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Prediction, Implications, and Management of Bleeding in Patients Undergoing Coronary Revascularisation

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A tutti coloro che
vivono di sogni
e di passioni.

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ABSTRACT (English version)

Coronary revascularisation, by either percutaneous or surgical procedures, is vital to prevent myocardial ischaemia and restore myocardial perfusion in patients with acute (ACS) or chronic (CCS) coronary syndrome. This is usually achieved by coronary stent implantation or preparation of coronary artery bypass grafts. Revascularisation procedures require the use of parenteral anticoagulation to reduce the risk of peri-procedural thrombosis. During or after the intervention, antiplatelet therapy is invariably initiated to prevent thrombotic events – with treatment type, intensity, and duration tailored to the clinical presentation, procedural features, and patients risk profile. For years, concerns about thrombosis and recurrent ischaemia have prevailed, prompting the use of potent antithrombotic therapies during and after coronary revascularisation. More recently, growing attention has been given to strategies targeting bleeding, especially in patients at higher bleeding risk. Bleeding can result from complications at vascular access site or at non-access sites, and is facilitated by the use of antithrombotic therapies. Solid evidence is currently available showing that the association between bleeding occurrences and subsequent adverse fatal and non-fatal events is important, possibly as much as the effect of ischaemic events (i.e., new or recurrent myocardial infarction). These considerations underscore the need to (i) standardise the definition of high bleeding risk (HBR) status, (ii) improve our capacity of predicting bleeding, and (iii) promote the adoption of effective strategies to mitigate bleeding burden after coronary revascularisation. The

data presented in this Thesis address some existing controversial issues in the definition, prediction, and implications of bleeding events after coronary revascularisation, with the aim to contribute to the contemporary understanding and management of bleeding in clinical practice.

ABSTRACT (Italian version)

La rivascolarizzazione coronarica, sia essa percutanea o chirurgica, è essenziale per prevenire l'ischemia e ripristinare la perfusione miocardica nei pazienti con sindrome coronarica acuta (ACS) o cronica (CCS). Tale obiettivo viene generalmente raggiunto mediante l'impianto di stent coronarici o la preparazione di bypass aorto-coronarici. Le procedure di rivascolarizzazione richiedono l'utilizzo di farmaci anticoagulanti parenterali per ridurre il rischio di eventi trombotici peri-procedurali. Durante la procedura o al suo termine, inoltre, un regime terapeutico antiaggregante viene iniziato in tutti i pazienti con l'obiettivo di prevenire eventi trombotici. La tipologia, l'intensità, e la durata del trattamento antiaggregante vengono generalmente adattati alla presentazione clinica, alle caratteristiche della procedura, ed al profilo di rischio del paziente. Per anni, le preoccupazioni legate al rischio di eventi trombotici ed ischemici ricorrenti hanno prevalso, determinando l'utilizzo di terapie antitrombotiche procedurali e post-rivascolarizzazione coronarica sempre più potenti. Più di recente, una crescente attenzione è stata posta nei confronti degli eventi emorragici e delle strategie che hanno l'obiettivo di ridurne il rischio, specialmente nei pazienti a più alto rischio. Gli eventi emorragici possono derivare da complicanze a livello del sito di accesso vascolare o in altre sedi, ed il loro verificarsi è favorito dall'utilizzo di terapie antitrombotiche. Le evidenze attualmente disponibili dimostrano una stretta associazione tra lo sviluppo di complicanze emorragiche e la prognosi a lungo termine dei pazienti rivascolarizzati, con un effetto almeno simile a quello

riportato per gli eventi ischemici (ad esempio, un infarto del miocardio). Queste considerazioni sottolineano la necessità di (i) standardizzare la definizione di alto rischio emorragico, (ii) migliorare la nostra capacità di predire il rischio complicanze emorragiche, e (iii) promuovere l'adozione di strategie efficaci per mitigare il rischio di sanguinamenti dopo rivascolarizzazione coronarica. I dati presentati in questa Tesi affrontano alcune delle questioni controverse attualmente esistenti circa la definizione, la capacità di predire, e le implicazioni degli eventi emorragici dopo rivascolarizzazione coronarica, con l'obiettivo di contribuire alla comprensione ed alla gestione terapeutica di tali complicanze nella pratica clinica contemporanea.

INTRODUCTION

Coronary revascularisation, by either percutaneous or surgical procedures, is vital to prevent myocardial ischaemia and restore myocardial perfusion in patients with acute (ACS) or chronic (CCS) coronary syndrome. This is usually achieved by coronary stents implantation or preparation of coronary artery bypass grafts. Revascularisation procedures require the use of parenteral anticoagulation to reduce the risk of peri-procedural thrombosis. During or after the intervention, antiplatelet therapy is invariably initiated to prevent thrombotic events – with treatment type, intensity, and duration tailored to the clinical presentation, procedural features, and patients risk profile. For years, concerns about thrombosis and recurrent ischaemia have prevailed, prompting the use of potent antithrombotic therapies during and after coronary revascularisation. More recently, growing attention has been given to strategies targeting bleeding, especially in patients at higher bleeding risk. Bleeding can result from complications at vascular access site or at non-access sites, and is facilitated by the use of antithrombotic therapies. Solid evidence is currently available showing that the association between bleeding occurrences and subsequent adverse fatal and non-fatal events is important, possibly as much as the effect of ischaemic events (i.e., new or recurrent myocardial infarction). These considerations underscore the need to (i) standardise the definition of high bleeding risk (HBR) status, (ii) improve our capacity to predict bleeding, and (iii) promote the adoption of effective strategies to mitigate bleeding burden after coronary revascularisation. The

data presented in this Thesis address some existing controversial issues in the definition, prediction, and implications of bleeding events after coronary revascularisation, with the aim to contribute to the contemporary understanding and management of bleeding in clinical practice.

PART I

Bleeding risk definition, prediction, and implications

Prognostic Implications of Declining Hemoglobin Content in Patients Hospitalized With Acute Coronary Syndromes.

Leonardi S[*], **Gragnano F[*],** Carrara G, Gargiulo G, Frigoli E, Vranckx P, Di Maio D, Spedicato V, Monda E, Fimiani L, Fioretti V, Esposito F, Avvedimento M, Magliulo F, Leone A, Chianese S, Franzese M, Scalise M, Schiavo A, Mazzone P, Esposito G, Andò G, Calabrò P, Windecker S, Valgimigli M.

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Prognostic Implications of Declining Hemoglobin Content in Patients Hospitalized With Acute Coronary Syndromes

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ABSTRACT

BACKGROUND Contemporary definitions of bleeding endpoints are restricted mostly to clinically overt events. Whether hemoglobin drop per se, with or without overt bleeding, adversely affects the prognosis of patients with acute coronary syndrome (ACS) remains unclear.

OBJECTIVES The aim of this study was to examine in the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial the incidence, predictors, and prognostic implications of in-hospital hemoglobin drop in patients with ACS managed invasively stratified by the presence of in-hospital bleeding.

METHODS Patients were categorized by the presence and amount of in-hospital hemoglobin drop on the basis of baseline and nadir hemoglobin values and further stratified by the occurrence of adjudicated in-hospital bleeding. Hemoglobin drop was defined as minimal (<3 g/dl), minor (≥3 and <5 g/dl), or major (≥5 g/dl). Using multivariate Cox regression, we modeled the association between hemoglobin drop and mortality in patients with and without overt bleeding.

RESULTS Among 7,781 patients alive 24 h after randomization with available hemoglobin data, 6,504 patients (83.6%) had hemoglobin drop, of whom 5,756 (88.5%) did not have overt bleeding and 748 (11.5%) had overt bleeding. Among patients without overt bleeding, minor (hazard ratio [HR]: 2.37; 95% confidence interval [CI]: 1.32 to 4.24; p = 0.004) and major (HR: 2.58; 95% CI: 0.98 to 6.78; p = 0.054) hemoglobin drop were independently associated with higher 1-year mortality. Among patients with overt bleeding, the association of minor and major hemoglobin drop with 1-year mortality was directionally similar but had wider CIs (minor: HR: 3.53 [95% CI: 1.06 to 11.79]; major: HR: 13.32 [95% CI: 3.01 to 58.98]).

CONCLUSIONS Among patients with ACS managed invasively, in-hospital hemoglobin drop ≥3 g/dl, even in the absence of overt bleeding, is common and is independently associated with increased risk for 1-year mortality. (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox; NCT01433627) (J Am Coll Cardiol 2021;77:375–88) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ACS = acute coronary syndrome(s)

BARC = Bleeding Academic Research Consortium

CI = confidence interval

eGFR = estimated glomerular filtration rate

HR = hazard ratio

OR = odds ratio

PCI = percutaneous coronary intervention

STEACS = ST-segment elevation acute coronary syndrome

Bleeding events have been extensively associated with higher mortality rates in patients with cardiovascular diseases, including patients with acute coronary syndromes (ACS) and those undergoing coronary revascularization (1,2); therefore, their accurate definition and quantification as endpoints are essential. In the context of cardiovascular randomized controlled trials, most contemporary classifications of bleeding endpoints have been restricted to clinically evident (i.e., overt) bleeding, using thresholds of 3 to 5 g/dl hemoglobin reductions to grade their severity (1–4).

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It is unclear, however, whether a hemoglobin reduction per se, in patients without overt bleeding, is independently associated with mortality and, if so, if this association is quantitatively similar to that observed in patients with overt bleeding. Using data from the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial of patients with ACS managed invasively (5,6), we examined the incidence, predictors, effects on randomized treatments, and prognostic implications of in-hospital hemoglobin drop in patients with and without adjudicated overt bleeding.

METHODS

MATRIX PROGRAM DESIGN. MATRIX (NCT01433627) was a program of 3 nested randomized controlled trials enrolling a total of 8,404 all-comer patients with ACS, with or without ST-segment elevation, receiving invasive management (7). The study protocol of the MATRIX trial was approved by the institutional ethics committees of participating institutions and the central regulatory body of each of the centers and was conducted according to the Declaration of Helsinki and Good Clinical Practice. Detailed study design, methods, and enrollment criteria have been previously published (7). In brief, the first study, MATRIX Access, randomized 8,404 patients with ACS to radial access or femoral access (5). The second study, MATRIX Antithrombin, randomized 7,213 patients comparing an antithrombotic strategy of bivalirudin versus unfractionated heparin (with optional glycoprotein IIb/IIIa inhibitors) (8). The third study, MATRIX Treatment Duration, randomized patients assigned to bivalirudin to receive extended bivalirudin administration after percutaneous coronary intervention (PCI) or short-term administration during PCI (8). Patients with ST-segment elevation ACS were eligible if they presented within 12 h of symptom onset or between 12 and 24 h with evidence of continuing ischemia or previous fibrinolytic treatment and if they had ST-segment elevation ≥1 mm in 2 or more contiguous electrocardiographic leads or a new left bundle branch block or true posterior myocardial infarction. Patients with non-ST-segment elevation ACS were eligible if they had histories consistent with new or worsening cardiac ischemia, occurring at rest or with minimal activity within 7 days before randomization and fulfilled at least 2 high-risk criteria among the following: age ≥60 years, elevation of cardiac biomarkers, electrocardiographic changes consistent with cardiac ischemia, and consideration as possible candidates for PCI after completion of coronary angiography (7).

STUDY PATIENTS AND DEFINITIONS. For this analysis, the study population included all patients enrolled in the MATRIX program who: 1) did not experience fatal events during the first 24 h after randomization, to minimize the risk for immortal time bias; and 2) had qualifying in-hospital hemoglobin information available, including values at baseline and nadir, which were prospectively collected in the electronic care report form. Baseline hemoglobin was the first hemoglobin value obtained at admission and prior to randomization. Nadir hemoglobin was the lowest value collected during hospitalization. All laboratory values, including in-hospital hemoglobin, were entered by the site and then locally monitored and centrally verified for quality using consistency checks. We defined patients as with hemoglobin drop those with positive differences between baseline and nadir hemoglobin values (i.e., the baseline was higher than the nadir). If this difference was zero or negative (i.e., the baseline was equal or lower than the nadir), patients were categorized into the no hemoglobin drop group. Patients with in-hospital hemoglobin drop were then further

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stratified on the basis of the presence or absence of an adjudicated overt bleeding during hospitalization. According to contemporary definitions of bleeding (3,4), thresholds of 3 and 5 g/dl were used to classify hemoglobin drop severity. A reduction was considered minimal if the difference between baseline and nadir hemoglobin concentrations was >0 and <3 g/dl, minor if this difference was ≥3 and <5 g/dl, and major if ≥5 g/dl.

STUDY ENDPOINTS. The primary endpoint for this analysis was all-cause mortality occurring from 24 h to 1 year from randomization. As secondary endpoint, all-cause mortality from 24 h to 30 days was also evaluated. An independent clinical events committee blinded to randomized treatment allocation adjudicated all suspected primary or secondary outcomes, including death and bleeding, by reviewing relevant medical records after site monitoring, and systematically identified potential bleeding events, either reported or not by the investigators, in patients with and without hemoglobin reduction. Specifically, all patients with in-hospital hemoglobin drop of at least 3 g/dl were centrally triggered, and source documentation was submitted to the clinical events committee for potential unreported bleeding events.

STATISTICAL ANALYSIS. Differences across groups were assessed using Student's *t*-test or the Wilcoxon-Mann-Whitney *U* test for continuous variables and the chi-square or Fisher exact test for categorical data. The incidence, distribution, and degree of hemoglobin reduction in the study population were assessed. Independent predictors of hemoglobin drop and Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding were selected with multivariate stepwise selection ($p < 0.01$), starting with forward selection and followed by backward selection. We applied a multivariate Cox proportional hazards model to evaluate the association of hemoglobin drops during index hospitalization (as a categorical and a continuous variable) with all-cause mortality from 24 h to 1 year from randomization in patients with and without overt bleeding. Patients without hemoglobin drop and no overt bleeding were the reference category to compute hazard ratios (HRs) for those with hemoglobin drop without overt bleeding. Patients without hemoglobin drop who bled were used as reference for the hemoglobin drop and overt bleeding group. Covariates tested in the model were chosen among the previously validated predictors of death in ACS populations, including those reported in the GRACE (Global Registry of Acute Coronary Events) risk score (9). The final multivariate model included the following covariates: age, heart rate, systolic blood pressure, estimated glomerular filtration rate, and baseline hemoglobin values as continuous variables; sex, diabetes, cardiac arrest on admission, Killip class, prior myocardial infarction, ST-segment elevation at presentation, and number of diseased coronary vessels (1, 2, or ≥3) as categorical variables. Continuous relation between hemoglobin drop and mortality was assessed using restricted cubic splines. The Kaplan-Meier method was used to estimate cumulative rates of events from 24 h to 30 days and 1 year of follow-up. Waterfall plots were used to graphically illustrate the distribution of hemoglobin drop in patients with and without overt bleeding. We performed an additional analysis according to the prespecified randomization subgroups to estimate possible effects of radial access versus femoral access and bivalirudin versus heparin on: 1) in-hospital bleeding and; 2) minor or major hemoglobin drop. We also evaluated the association of in-hospital hemoglobin drops with and without overt bleeding with blood transfusions as endpoint and sensitivity analyses in patients without known anemia at baseline. The analyses were done using Stata release 14.1 (StataCorp, College Station, Texas) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the 8,404 patients enrolled in the MATRIX trial, 568 (6.7%) were excluded because of incomplete hemoglobin values (baseline, nadir, or both) and 55 (0.6%) because they died within 24 h of randomization. Of the 7,781 patients alive at 24 h with complete hemoglobin information, 83.6% (n = 6,504) experienced hemoglobin drop during the index hospitalization, and 16.4% (n = 1,277) did not. Baseline characteristics, procedural data, and medications of patients with and without hemoglobin drop, as well as of those with missing hemoglobin values, are reported in Supplemental Tables 1 to 3. Unadjusted mortality rates of patients with or without qualifying hemoglobin values are shown in Supplemental Figure 1, indicating higher in-hospital mortality for patients with incomplete compared with complete hemoglobin information.

Of the 6,504 patients with in-hospital hemoglobin drop, 748 (11.5%) had at least 1 adjudicated overt bleeding event. Baseline characteristics, procedural data, and medications at discharge of patients with and without hemoglobin drop stratified by the presence or absence of overt bleeding are shown in **Table 1** and Supplemental Tables 4 and 5. Among patients with no hemoglobin reduction, patients who bled were older, more frequently had histories

TABLE 1 Baseline Characteristics of Patients With and Without Hemoglobin Drop Stratified by the Presence or Absence of Overt Bleeding

	Hemoglobin Drop Without Overt Bleeding (n = 5,756)	Hemoglobin Drop With Overt Bleeding (n = 748)	p Value	No Hemoglobin Drop Without Overt Bleeding (n = 1,178)	No Hemoglobin Drop With Overt Bleeding (n = 99)	p Value
Age, yrs	65.2 ± 11.7	68.4 ± 11.7	<0.001	66.2 ± 11.9	69.5 ± 11.3	0.007
≥75 yrs	1,368 (23.8)	273 (36.5)	<0.001	335 (28.4)	37 (37.4)	0.078
Male	4,298 (74.7)	509 (68.0)	<0.001	857 (72.8)	78 (78.8)	0.23
Weight, kg	77.6 ± 14	74.7 ± 13.7	<0.001	77.5 ± 13.2	74.3 ± 12.9	0.014
Body mass index, kg/m^2	27.1 ± 4.2	26.5 ± 4	<0.001	27.2 ± 4.1	26.5 ± 3.5	0.068
≥25 kg/m^2	3,865 (67.1)	460 (61.5)	0.002	814 (69.1)	65 (65.7)	0.55
Diabetes mellitus	1,279 (22.2)	181 (24.2)	0.24	293 (24.9)	17 (17.2)	0.11
Insulin dependent	310 (5.4)	46 (6.1)	0.20	72 (6.1)	4 (4.0)	0.092
Current smoking	2,101 (36.5)	219 (29.3)	<0.001	344 (29.2)	30 (30.3)	0.90
Hypercholesterolemia	2,535 (44.0)	330 (44.1)	>0.99	521 (44.2)	46 (46.5)	0.74
Hypertension	3,629 (63.0)	501 (67.0)	0.039	745 (63.2)	67 (67.7)	0.44
Family history of coronary artery disease	1,552 (27.0)	203 (27.1)	0.95	333 (28.3)	28 (28.3)	>0.99
Previous myocardial infarction	790 (13.7)	87 (11.6)	0.12	212 (18.0)	27 (27.3)	0.032
Previous PCI	812 (14.1)	80 (10.7)	0.013	197 (16.7)	20 (20.2)	0.45
Radial access	121 (2.1)	17 (2.3)	0.013	46 (3.9)	3 (3.0)	0.45
Femoral access	414 (7.2)	24 (3.2)		82 (7.0)	9 (9.1)	
Both radial and femoral access	50 (0.9)	2 (0.3)		16 (1.4)	2 (2.0)	
Access site unknown	227 (3.9)	37 (4.9)		53 (4.5)	6 (6.1)	
Previous CABG	150 (2.6)	24 (3.2)	0.40	62 (5.3)	9 (9.1)	0.17
Previous transient ischemic attack or stroke	265 (4.6)	47 (6.3)	0.053	68 (5.8)	5 (5.1)	0.94
Peripheral vascular disease	442 (7.7)	101 (13.5)	<0.001	112 (9.5)	12 (12.1)	0.50
Chronic obstructive pulmonary disease	357 (6.2)	57 (7.6)	0.15	72 (6.1)	10 (10.1)	0.18
Renal failure	70 (1.2)	10 (1.3)	0.91	17 (1.4)	2 (2.0)	0.65
Dialysis	4 (0.1)	1 (0.1)	0.45	3 (0.3)	0 (0.0)	>0.99
Cardiac arrest	108 (1.9)	26 (3.5)	0.006	21 (1.8)	0 (0.0)	0.40
Killip class			<0.001			0.40
I	5,238 (91)	643 (86)		1,077 (91.4)	89 (89.9)	
II	372 (6.5)	65 (8.7)				
III	109 (1.9)	22 (2.9)		1,077 (91.4)	89 (89.9)	
IV	37 (0.6)	18 (2.4)				
Previous lytic therapy	152 (2.6)	10 (1.3)	0.043	22 (1.9)	2 (2.0)	0.70
STEACS	2,915 (50.6)	420 (56.1)	0.005	367 (31.2)	33 (33.3)	0.73
NSTEACS	2,841 (49.4)	328 (43.9)	0.005	811 (68.8)	66 (66.7)	
NSTEACS, troponin negative	323 (5.6)	29 (3.9)	0.059	97 (8.2)	6 (6.1)	0.56
Systolic arterial pressure, mm Hg	139 ± 25.3	141.4 ± 29.5	0.038	138.2 ± 24.6	134.3 ± 26.4	0.22
Heart rate, beats/min	76.4 ± 16.6	77.4 ± 18.5	0.15	74.7 ± 16.1	74.4 ± 15.8	0.84
Left ventricular ejection fraction, %	51.2 ± 9.5	49.8 ± 10.5	0.001	51.2 ± 9.6	49.9 ± 10.9	0.28
Hemoglobin, g/dl	14.2 ± 1.7	13.9 ± 1.9	<0.001	13 ± 1.8	13 ± 2	0.83
eGFR, ml/min/1.73 m^2	84 ± 25.3	78.6 ± 24.9	<0.001	85.5 ± 26.5	80.3 ± 23.6	0.07
<60 ml/min/1.73 m^2	929 (16.2)	175 (23.5)	<0.001	198 (16.8)	23 (23.2)	0.14
<30 ml/min/1.73 m^2	55 (1.0)	7 (0.9)	>0.99	13 (1.1)	0 (0.0)	0.61

Continued on the next page

of myocardial infarction, and more often received intra-aortic balloon pump support than patients without overt bleeding. Compared with patients without hemoglobin drop or overt bleeding, patients with both hemoglobin drop and bleeding were older, had more comorbidities and cardiovascular risk factors at presentation (i.e., higher risk profile), and more often received clopidogrel at discharge. Baseline, procedural, and treatment characteristics of patients stratified by hemoglobin drop levels are detailed in Supplemental Tables 6 to 8. The distribution of hemoglobin drop in patients with and without overt bleeding is presented in Supplemental Figure 2. The proportion of patients with minor or major hemoglobin drop was higher among those with overt bleeding (15.1% and 3.5%, respectively) compared with those without overt bleeding (4.7% and 1.1%, respectively; $p < 0.001$) (**Figure 1, Table 2**). In contrast, a minor or major hemoglobin drop without overt bleeding was observed in 399 patients compared with 158 patients with the same level of hemoglobin drop and concomitant overt bleeding

TABLE 1 Continued

	Hemoglobin Drop Without Overt Bleeding (n = 5,756)	Hemoglobin Drop With Overt Bleeding (n = 748)	p Value	No Hemoglobin Drop Without Overt Bleeding (n = 1,178)	No Hemoglobin Drop With Overt Bleeding (n = 99)	p Value
Medications administered before catheterization						
Aspirin	5,428 (94.3)	713 (95.3)	0.29	1,097 (93.1)	96 (97.0)	0.20
Clopidogrel	2,706 (47)	336 (44.9)	0.29	625 (53.1)	56 (56.6)	0.57
Prasugrel	703 (12.2)	97 (13.0)	0.59	94 (8.0)	10 (10.1)	0.58
Ticagrelor	1,331 (23.1)	194 (25.9)	0.097	301 (25.6)	25 (25.3)	>0.99
Enoxaparin	866 (15.0)	122 (16.3)	0.39	283 (24.0)	31 (31.3)	0.13
Fondaparinux	561 (9.7)	72 (9.6)	0.96	163 (13.8)	17 (17.2)	0.44
ACE inhibitors	1,659 (28.8)	210 (28.1)	0.70	427 (36.2)	39 (39.4)	0.60
Angiotensin II receptor blockers	592 (10.3)	87 (11.6)	0.28	146 (12.4)	16 (16.2)	0.35
Statins	2,416 (42.0)	293 (39.2)	0.15	611 (51.9)	54 (54.5)	0.68
Beta-blockers	2,292 (39.8)	267 (35.7)	0.033	575 (48.8)	47 (47.5)	0.88
Warfarin	89 (1.5)	12 (1.6)	>0.99	25 (2.1)	2 (2.0)	>0.99
Proton pump inhibitors	2,896 (50.3)	385 (51.5)	0.57	683 (58.0)	63 (63.6)	0.32
Unfractionated heparin	1,742 (30.3)	265 (35.4)	0.005	288 (24.4)	25 (25.3)	0.95
Bivalirudin	3 (0.1)	0 (0.0)	>0.99	0 (0.0)	0 (0.0)	>0.99
Glycoprotein IIb/IIIa inhibitors	10 (0.2)	2 (0.3)	0.64	1 (0.1)	1 (1.0)	0.14

Values are mean ± SD or n (%). The chi-square or Fisher exact test was used for categorical variables; Student's *t*-test or the Wilcoxon test was used for continuous variables.

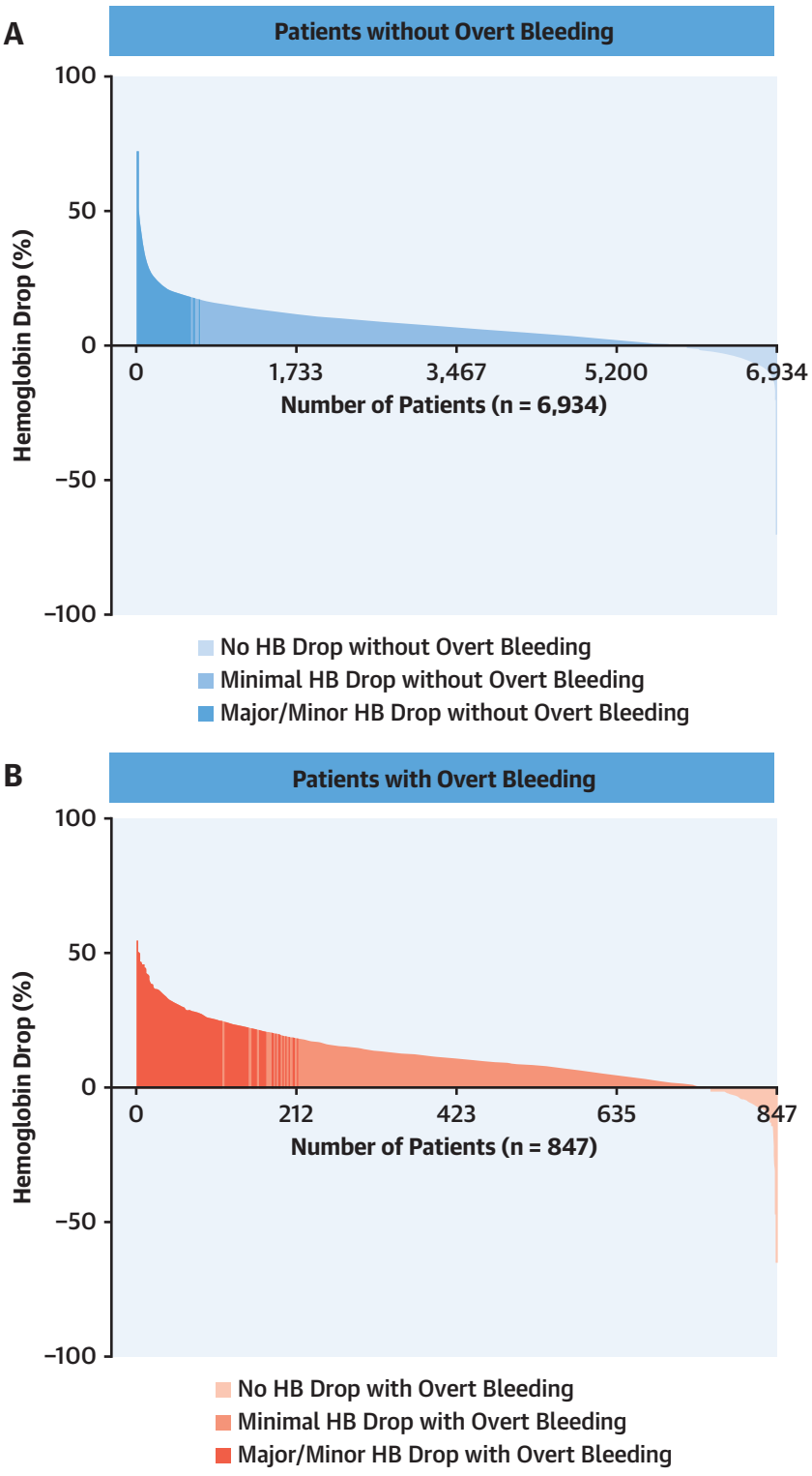
ACE = angiotensin-converting-enzyme; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; NSTEACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEACS = ST-segment elevation acute coronary syndrome.

(**Table 2**). Among patients with overt bleeding, 36.8% had BARC type 2 bleeding, while 16.4% had BARC type 3 or 5 bleeding (Supplemental Table 9). The percentage changes in hemoglobin levels in patients with overt bleeding stratified by BARC type severity (type 1 or 2 vs. type 3, 4, or 5) is reported in Supplemental Figure 3.

PREDICTORS OF MAJOR OR MINOR HEMOGLOBIN DROP AND BARC TYPE 3 OR 5 BLEEDING. To comprehensively characterize the potential use of hemoglobin drop as surrogate, multivariate predictors at baseline of major or minor hemoglobin drop as well as of BARC type 3 or 5 type bleeding were assessed (**Table 3**). Predictors of major or minor hemoglobin drop included age, female sex, body mass index, diabetes, non-ST-segment elevation ACS presentation, heart rate, clopidogrel on admission, and Killip class at presentation. Notably, baseline hemoglobin independently predicted both major or minor hemoglobin drop and BARC type 3 or 5 bleeding but with a directionally opposite association.

MULTIVARIATE ASSOCIATION OF HEMOGLOBIN DROP WITH ALL-CAUSE MORTALITY. Kaplan-Meier event curves showed a higher cumulative incidence of mortality from 24 h to 1 year in patients with major or minor hemoglobin drop compared with those with minimal or no hemoglobin drop, with a similar pattern in patients with and without overt bleeding (**Figure 2**). Multivariate association of hemoglobin drop with 30-day and 1-year mortality in patients with and without overt bleeding is reported in **Table 4** and displayed in **Figure 3** and the **Central Illustration**. In general, hemoglobin drop in patients with and without overt bleeding was independently associated with a graded association with mortality, which was higher for patients with overt bleeding compared with those without overt bleeding. Yet patients without overt bleeding had a higher risk for 1-year mortality after a minor (HR: 2.37; 95% confidence interval [CI]: 1.32 to 4.24; p = 0.004) or a major (HR: 2.58; 95% CI: 0.98 to 6.78, p = 0.054) hemoglobin drop, respectively, compared with those without hemoglobin drop and without overt bleeding. Among patients with overt bleeding, the hazard of 1-year mortality for minor and major hemoglobin drop, compared with patients without hemoglobin drop, was directionally similar but had wider CIs (minor: HR: 3.53 [95% CI: 1.06 to 11.79; p = 0.040]; major: HR: 13.32 [95% CI: 3.01 to 58.98; p = 0.001]). The multivariate 1-year HR for mortality of hemoglobin drop modeled as a continuous variable was 1.18 per g/dl decrease in hemoglobin for patients without overt bleeding (95% CI: 1.04 to 1.34; p = 0.010) and 1.41 for patients with overt bleeding (95% CI: 1.19 to 1.67; p < 0.001). Results were directionally similar at 30 days as well as restricting the population to those without known anemia at baseline (excluding 1,536 patients with baseline anemia) (Supplemental Table 10).

FIGURE 1 Waterfall Plot for the Percentage Change in Hemoglobin Level During Hospitalization



(A) Patients without overt bleeding. **(B)** Patients with overt bleeding. Data are shown for patients alive 24 h after randomization who had no hemoglobin (Hb) reduction **(light blue and light red)**, minimal hemoglobin reduction **(blue and red)**, and major or minor hemoglobin reduction **(dark blue and dark red)**. The y-axis shows percentage of hemoglobin drop. The x-axis shows absolute number of patients per group.

EFFECTS OF RANDOMIZED TREATMENTS ON HEMOGLOBIN DROP WITH OR WITHOUT BLEEDING. The effect of randomized treatments on in-hospital overt bleeding and in-hospital minor or major hemoglobin drop is reported in Table 5. The use of radial over femoral access was associated with a lower risk for in-hospital bleeding complications (odds ratio [OR]: 0.51; 95% CI: 0.44 to 0.59; p < 0.001) and a numerically lower risk for minor or major hemoglobin reduction (OR: 0.85; 95% CI: 0.71 to 1.01; p = 0.065). The use of bivalirudin was associated with a significantly reduced risk for in-hospital bleeding (OR: 0.77; 95% CI: 0.67 to 0.89; p < 0.001) and minor or major hemoglobin reduction (OR: 0.78; 95% CI: 0.64 to 0.94; p = 0.010) compared with unfractionated heparin. The rates and proportions of patients with and without hemoglobin reduction receiving blood transfusions are reported in Supplemental Table 11.

TABLE 2 Grade of Hemoglobin Drop in Patients With and Without Overt Bleeding

	Patients Without Overt Bleeding (n = 6,934)	Patients With Overt Bleeding (n = 847)	p Value
No hemoglobin drop	1,178 (17)	99 (11.7)	<0.001
Minimal hemoglobin drop (<3 g/dl)	5,357 (77.3)	590 (69.7)	
Minor hemoglobin drop (≥3 and <5 g/dl)	325 (4.7)	128 (15.1)	
Major hemoglobin drop (≥5 g/dl)	74 (1.1)	30 (3.5)	

Values are n (%). The chi-square or Fisher exact test was used for categorical variable; Student's *t*-test or the Wilcoxon test was used for continuous variables.

DISCUSSION

In the present analysis, we comprehensively assessed, in an all-comer population of patients with ACS managed invasively, the epidemiology, predictors, and association with outcome of in-hospital hemoglobin drop, with and without overt bleeding. The main findings are the following.

First, an in-hospital hemoglobin drop of ≥3 g/dl, even in the absence of adjudicated overt bleeding, showed a continuous, direct association with increased 1-year mortality. No independent association between minimal (<3 g/dl) hemoglobin drop and mortality was observed.

Second, patients with hemoglobin reduction ≥3 g/dl were proportionally more common (19% vs. 6%) in the group with adjudicated bleeding. Yet the prevalence of hemoglobin reduction ≥3 g/dl in patients without adjudicated bleeding was far higher than among patients with adjudicated bleeding (n = 158 vs. n = 399).

Third, randomized bleeding minimization strategies tested in MATRIX (i.e., radial access and bivalirudin use) were associated with a lower risk for incurring in-hospital hemoglobin drop compared with their control (i.e., femoral access on unfractionated heparin).

POSSIBLE CAUSES AND CONSEQUENCES OF HEMOGLOBIN REDUCTIONS IN PATIENTS WITH ACS. In patients with ACS, multiple mechanisms may be responsible for in-hospital hemoglobin drop. Overt bleeding can

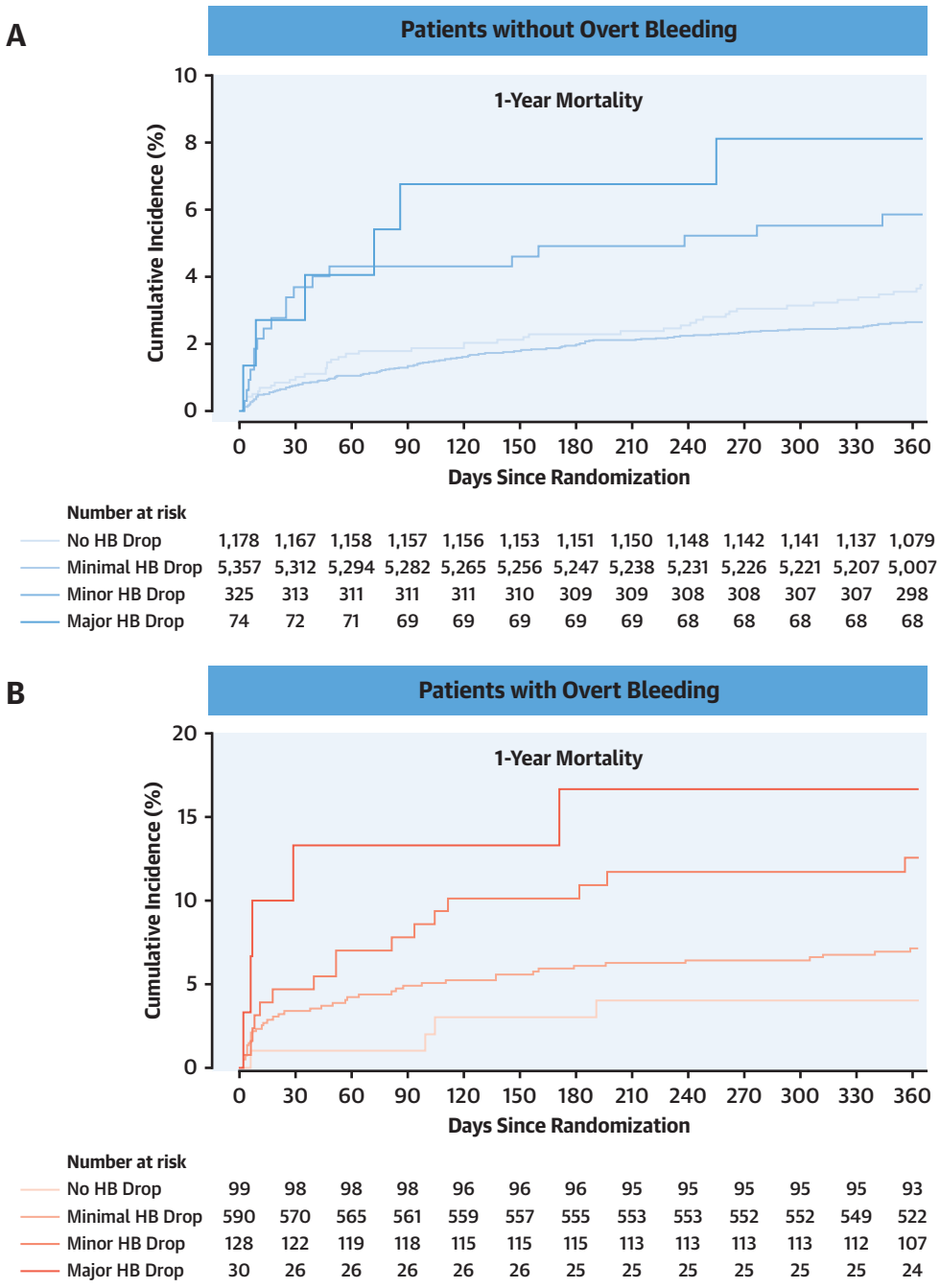
TABLE 3 Multivariate Predictors of Major or Minor Hemoglobin Drop and BARC Type 3 or 5 Bleeding

	Major/Minor HB Drop*		BARC Type 3 or 5 Bleeding*	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (for each increase of 10 yrs)	1.31 (1.20–1.42)	<0.001	1.54 (1.29–1.83)	<0.001
Female sex	1.52 (1.22–1.90)	<0.001	–	–
Body mass index (for each increase of 1 kg/m^2)	0.96 (0.94–0.99)	0.001	–	–
Peripheral vascular disease	–	–	2.46 (1.58–3.82)	<0.001
Diabetes mellitus	1.28 (1.01–1.63)	0.047	–	–
Insulin-dependent diabetes mellitus	2.10 (1.48–2.98)	<0.001	–	–
Killip class II (vs. class I)	1.45 (1.07–1.99)	0.020	–	–
Killip class III (vs. class I)	1.43 (0.83–2.48)	0.17	–	–
Killip class IV (vs. class I)	3.43 (1.83–6.43)	<0.001	–	–
NSTEACS on admission	0.63 (0.52–0.76)	<0.001	0.49 (0.34–0.70)	<0.001
Troponin-negative NSTEACS	0.43 (0.22–0.82)	0.011	–	–
Hemoglobin at baseline (for each increase of 1 g/dl)	1.51 (1.41–1.60)	<0.001	0.82 (0.75–0.90)	<0.001
Heart rate (for each increase of 10 beats/min)	1.11 (1.06–1.17)	<0.001	–	–
Clopidogrel on admission	0.76 (0.63–0.92)	0.005	0.57 (0.39–0.83)	0.003

*Multivariate analysis included all patients with complete hemoglobin data (n = 7,806).

BARC = Bleeding Academic Research Consortium; CI = confidence interval; HB = hemoglobin; NSTEACS = non-ST-segment elevation acute coronary syndrome; OR = odds ratio.

FIGURE 2 1-Year Mortality in Patients With and Without Overt Bleeding



Kaplan-Meier event curves for all-cause mortality stratified by hemoglobin (Hb) drop from 24 h to 1 year. **(A)** Patients without overt bleeding. **(B)** Patients with overt bleeding.

complicate hospital course as a consequence of pharmacological as well as invasive procedures (10,11). Besides evident blood loss, subtle bleeding can also occur because of the aggressive antithrombotic burden, with the primary source of bleeding remaining masked if not investigated appropriately. Also, a decline in hemoglobin after ACS can be caused by blood loss during the index procedure, intense inflammatory status (12), stress polycythemia on admission (13), hemodilution secondary to volume

TABLE 4 Multivariate Association With 30-Day and 1-Year All-Cause Mortality of In-Hospital Hemoglobin Reduction With and Without Overt Bleeding

	30-Day Mortality HR (95% CI)	p Value	1-Year Mortality HR (95% CI)	p Value
Patients without overt bleeding				
No hemoglobin drop*	Reference	—	Reference	—
Minimal hemoglobin drop (<3 g/dl)	0.78 (0.40–1.56)	0.48	0.85 (0.60–1.22)	0.39
Minor hemoglobin drop (≥3 and <5 g/dl)	4.30 (1.71–10.78)	0.002	2.37 (1.32–4.24)	0.004
Major hemoglobin drop (≥5 g/dl)	3.39 (0.68–16.85)	0.13	2.58 (0.98–6.78)	0.054
Continuous hemoglobin drop (for each increase of 1 g/dl)†	1.41 (1.16–1.70)	0.001	1.18 (1.04–1.34)	0.010
Patients with overt bleeding				
No hemoglobin drop‡	Reference	—	Reference	—
Minimal hemoglobin drop (<3 g/dl)	4.19 (0.52–34.04)	0.18	2.41 (0.82–7.08)	0.11
Minor hemoglobin drop (≥3 and <5 g/dl)	3.22 (0.33–31.63)	0.31	3.53 (1.06–11.79)	0.040
Major hemoglobin drop (≥5 g/dl)	33.8 (2.84–402.35)	0.005	13.32 (3.01–58.98)	0.001
Continuous hemoglobin drop (for each increase of 1 g/dl)†	1.44 (1.13–1.84)	0.003	1.41 (1.19–1.67)	<0.001

*The reference group consisted of patients without hemoglobin drop and without overt bleeding. †If reduction <0 g/dl, consider 0 g/dl. ‡The reference group consisted of patients without hemoglobin drop and with overt bleeding.
CI = confidence interval; HR = hazard ratio.

repletion (14), or impaired bone marrow activity due to clinical factors (15).

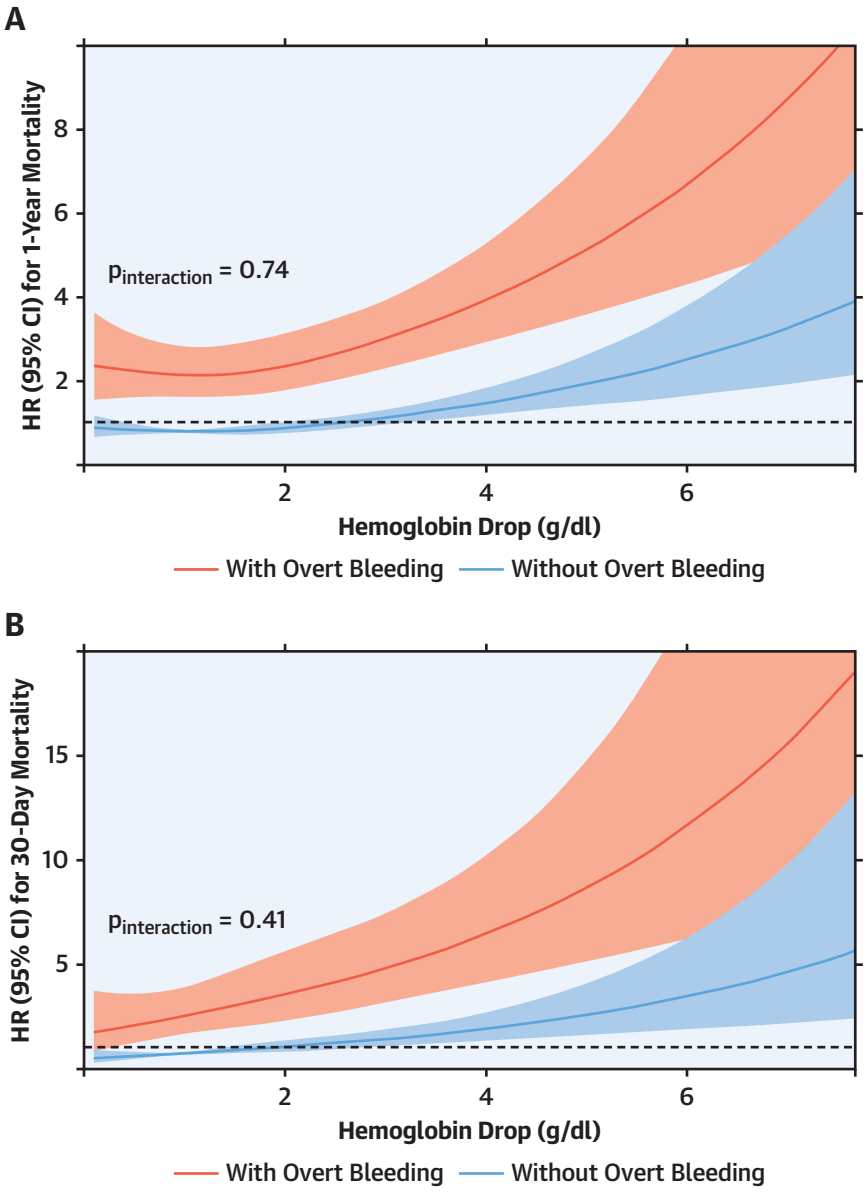
In the early phase of ACS, anemia has been consistently associated with bleeding complications (16,17). However, its prognostic impact can also extend to nonbleeding outcomes and mortality (18–20), possibly by worsening myocardial ischemic insult (i.e., decreasing the oxygen supply to the jeopardized myocardium) (21), increasing myocardial oxygen demand (i.e., need for higher cardiac output to maintain an adequate systemic oxygen delivery) (22), and inducing abnormal neurohormonal activation and cardiac remodeling (23). Previous studies showed that the presence of low hemoglobin levels before and/or after PCI is a powerful and independent predictor of future cardiovascular events (18–20). In a large pooled population of 39,922 patients with ACS, baseline hemoglobin level <11 g/dl was associated with excess mortality of more than 4-fold compared with higher values (18).

Evidence also indicates an adverse prognostic impact for in-hospital hemoglobin changes in this setting. Among 7,608 patients undergoing successful PCI from the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) registry (51.7% presenting with ACS), in-hospital hemoglobin reduction ≥4.0 g/dl in the presence of overt bleeding was associated with considerably increased risk for dying (24). In a prospective study involving 1,390 patients with myocardial infarction (15), in-hospital hemoglobin drop and nadir showed a significant and independent association with 2-year mortality. A relevant proportion of patients showed decreases in hemoglobin levels during hospitalization in the absence of bleeding, with a more than doubled proportion of patients having anemia at discharge (36.1%) than on admission (17.8%). In the TRIUMPH registry (25), including 2,909 patients with ACS and normal hemoglobin levels on admission, up to 45% of patients developed anemia during hospitalization, which if moderate to severe (<11 g/dl in 26% of cases) was associated with worse mortality and health status at 1 year. Among patients who developed in-hospital anemia, 86% did not have overt bleeding. Finally, post-PCI drop in hemoglobin levels has been associated with acute kidney injury (26), which in turn has demonstrated to be a relevant driver of mortality in the setting of ACS (27,28).

However, no previous study addressed the prognostic impact of hemoglobin reduction per se (i.e., without concomitant overt bleeding) in the setting of ACS.

PROGNOSTIC EFFECT OF HEMOGLOBIN REDUCTIONS IN PATIENTS WITH ACS WITHOUT OVERT BLEEDING AND IMPLICATIONS FOR BLEEDING ENDPOINT CLASSIFICATIONS. The present analysis extends previous evidence by examining the incidence and prognostic relevance of hemoglobin drop, with and without concomitant overt bleeding, in a large contemporary ACS population. In line with previous findings (15,25), the incidence of hemoglobin reduction was high in our population. In patients without adjudicated bleeding, a heightened risk for mortality was apparent at a hemoglobin threshold of approximately 3 g/dl. Thus, in the absence of overt bleeding, a minor (between 3 and 5 g/dl) or major (more than 5 g/dl) hemoglobin drop was associated with an increase in the risk for dying of about 2.5-fold at 1 year, which was independent of

FIGURE 3 Spline Functions of 1-Year and 30-Day Mortality in Patients With and Without Overt Bleeding According to In-Hospital Hemoglobin Drop

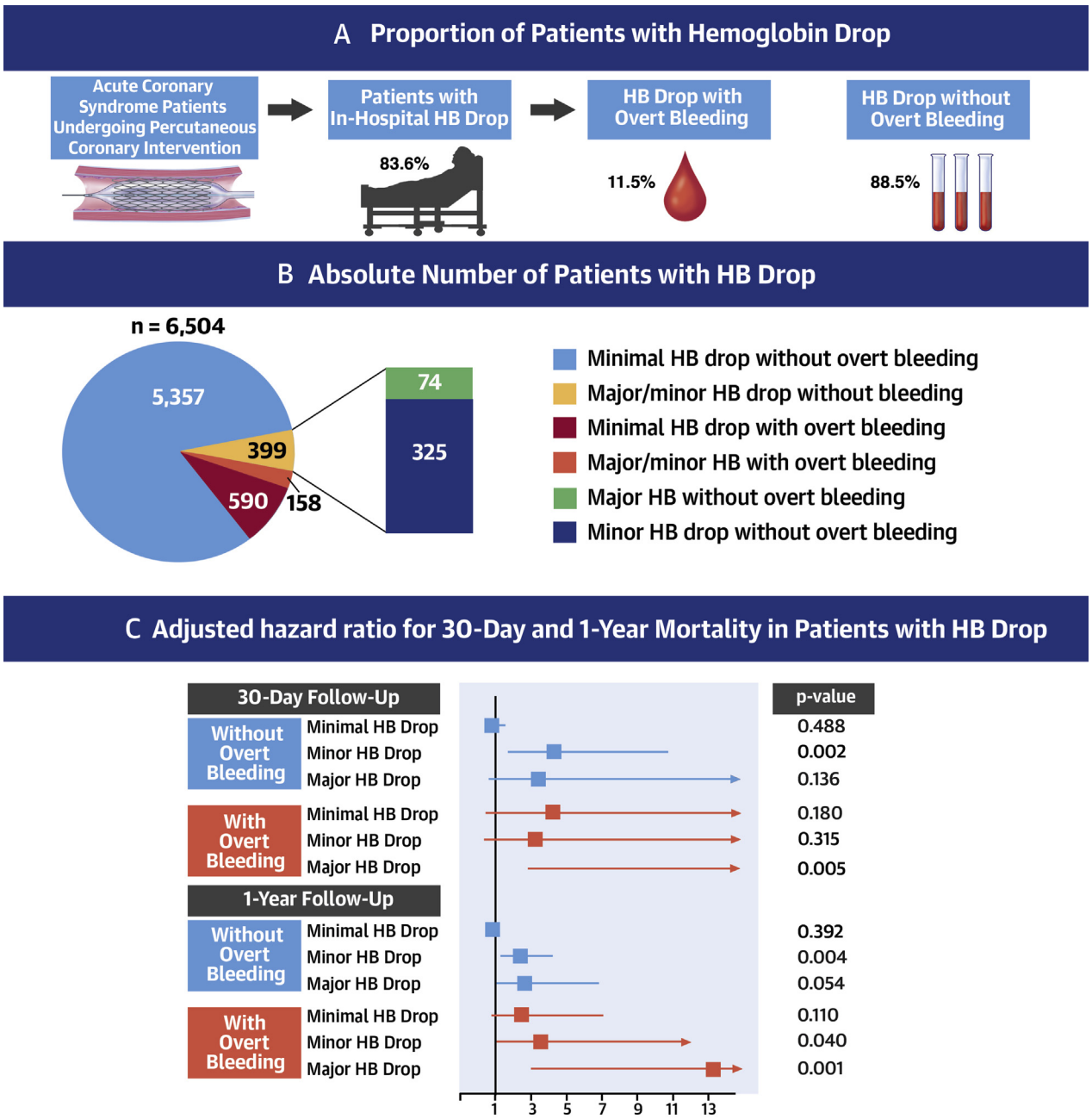


(A) Adjusted mortality risk from 24 h to 1 year. **(B)** Adjusted mortality risk from 24 h to 30 days. **Red** indicates patients with overt bleeding; **blue** indicates patients without overt bleeding. CI = confidence interval; HR = hazard ratio.

several covariates, including clinical and procedural factors and, importantly, baseline hemoglobin concentrations. Conversely, a minimal hemoglobin reduction (<3 g/dl) was not associated with mortality. In contrast, life-threatening bleeding such as intracranial hemorrhage or cardiac tamponade may occur with modest blood loss. This might in part explain why, in patients with adjudicated bleeding, an increase in the risk for mortality in multivariate analysis (although nonsignificant) was apparent even for minimal hemoglobin drop.

Adjudication of bleeding endpoints in most randomized controlled trials according to contemporary definitions mandates the presence of overt bleeding (29,30). This modern approach deviates from historical frameworks, which considered a decrease in hemoglobin as a minor hemorrhagic event even in the absence of overt bleeding (i.e., blood loss with no site

CENTRAL ILLUSTRATION **In-Hospital Hemoglobin Drop in Patients With and Without Overt Bleeding in Acute Coronary Syndrome**



Leonardi, S. et al. J Am Coll Cardiol. 2021;77(4):375–88.

(A) Approximately 8 in 10 patients invasively managed for acute coronary syndrome (ACS) can develop hemoglobin (HB) drop during the index hospitalization. In 7 of these 8 patients, hemoglobin reduction is observed in the absence of overt bleeding. **(B)** Although patients without overt bleeding frequently have a minimal hemoglobin drop (<3 g/dl), in view of the millions of individuals with ACS undergoing invasive management worldwide, a substantial number of patients can experience minor (≥3 g/dl) or major (≥5 g/dl) hemoglobin drop. **(C)** Patients with hemoglobin drop ≥3 g/dl showed doubled risk for 1-year mortality, even in the absence of overt bleeding. HR = hazard ratio; PCI = percutaneous coronary intervention.

TABLE 5 Effect of Radial Versus Femoral Access and of Bivalirudin Versus Unfractionated Heparin on In-Hospital Overt Bleeding and In-Hospital Minor or Major Hemoglobin Drop

	In-Hospital Overt Bleeding OR (95% CI) (n = 8,349)	p Value	In-Hospital Minor or Major Hemoglobin Drop OR (95% CI) (n = 7,781)	p Value
Radial access vs. femoral access	0.51 (0.44–0.59)	<0.001	0.85 (0.71–1.01)	0.065
Bivalirudin vs. unfractionated heparin	0.77 (0.67–0.89)	<0.001	0.78 (0.64–0.94)	0.010

Abbreviations as in Table 3.

identified) (31). Notably, most studies do not require systematic investigation of potential sources of hemoglobin loss. Thus, in clinical practice as well as in clinical research, many potential bleeding events may remain occult. Moreover, bleeding events considered prognostically relevant (such as BARC type 3 to 5) are relatively infrequent (29,30), limiting study power (32).

The observation of a direct, continuous, independent association with long-term mortality as well as a measurable treatment effect on established bleeding minimization strategies supports the concept that a threshold of in-hospital hemoglobin reduction higher than 3 g/dl may serve as a valid surrogate endpoint (33). As such, this level of hemoglobin reduction could complement contemporary definitions of bleeding endpoints and be easily implemented because of the simple, reliable, and inexpensive measurement.

Finally, a strength of this study is the inclusion of baseline hemoglobin as a covariate. The directionally inverse association of baseline hemoglobin with major or minor hemoglobin drop in patients without overt bleeding (vs. those with adjudicated bleeding) likely reflects the definition of hemoglobin drop (i.e., the higher the baseline value, the more likely a hemoglobin drop is observed) and supports the inclusion of baseline hemoglobin in the multivariate model with death as outcome (Table 4).

Therefore, regardless of baseline hemoglobin, a hemoglobin drop ≥3 g/dl, even in the absence of detectable bleeding, appears prognostically relevant.

STUDY LIMITATIONS. This was a post hoc analysis from a prospective, randomized controlled trial, which was not powered to explore outcome differences across hemoglobin reduction subgroups of patients. As such, the results should only be considered hypothesis generating. Qualifying hemoglobin values were missing in 7.1% of patients. Although the reason for this was not captured, the high early mortality rate of these patients indicates that an early fatal event prevented the collection of hemoglobin values in many of them. Specific conditions associated with or predisposing to chronic anemia were not assessed in detail in the study population and might have influenced our results. Another possible limitation is that some misclassification of hemoglobin reduction severity occurred in patients who received blood transfusions during the hospital stay. Finally, in the MATRIX trial, data on hemoglobin at follow-up were not collected. Thus, we were not able to analyze the prognostic impact of transient (i.e., in-hospital only) versus persistent (i.e., after discharge) anemia.

CONCLUSIONS

In patients with ACS managed invasively, in-hospital decreases in hemoglobin levels ≥3 g/dl, even in the absence of overt bleeding events, were common and independently associated with an increased risk for all-cause mortality at 1 year. If confirmed, these results may help the identification of higher risk patients and inform contemporary bleeding definitions.

AUTHOR DISCLOSURES

The MATRIX trial was sponsored by Società Italiana di Cardiologia Invasiva (a nonprofit organization), which received grant support from The Medicines Company and Terumo. This substudy did not receive any direct or indirect funding. Dr. Leonardi has received grants and personal fees from AstraZeneca, Bristol Myers Squibb/Pfizer, and Chiesi; and has received personal fees from Bayer outside the submitted work. Dr. Gragnano has received research grant support from the European Society of Cardiology outside the submitted work. Dr. Gargiulo has received consultant fees from Daiichi-Sankyo outside the submitted work. Dr. Vranckx has received personal fees from AstraZeneca, Terumo, CSL Behring, Daiichi-Sankyo, and Bayer Health Care outside the submitted work. Dr. Frigoli is affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in the design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest, visit the University of Bern Web site (and see Research, Declaration of Interest). Dr. Windecker has received research and educational grants to the institution from Abbott, Amgen, Bristol Myers Squibb, Bayer, Boston Scientific,

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In invasively managed patients with ACS, a decrease in hemoglobin content of ≥3 g/dl is associated with 1-year mortality even in the absence of overt bleeding.

TRANSLATIONAL OUTLOOK:

A declining hemoglobin level may be a useful surrogate for other bleeding-related endpoints in clinical trials investigating treatment strategies for patients with ACS undergoing invasive management.

REFERENCES

1. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J 2017;38:804–10.

2. Généreux P, Giustino G, Witzenbichler B, et al. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. J Am Coll Cardiol 2015;66:1036–45.

3. Mega J, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet 2009;374:29–38.

4. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials. Circulation 2011;123:2736–47.

5. Valgimigli M, Gagnor A, Calabró P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: A randomised multicentre trial. Lancet 2015;385:2465–76.

6. Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet 2018;392:835–48.

7. Valgimigli M, Gagnor A, Calabrò P, et al. Design and rationale for the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox program. Am Heart J 2014;168:838–45.

8. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. N Engl J Med 2015;373:997–1009.

9. Fox KAA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006;333:1091.

10. Suh JW, Mehran R, Claessen BE, et al. Impact of in-hospital major bleeding on late clinical outcomes after primary percutaneous coronary intervention in acute myocardial infarction. J Am Coll Cardiol 2011;58:1750–6.

11. Mehran R, Pocock SJ, Stone GW, et al. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. Eur Heart J 2009;30:1457–66.

12. James SK, Oldgren J, Lindbäck J, Johnston N, Siegbahn A, Wallentin L. An acute inflammatory reaction induced by myocardial damage is superimposed on a chronic inflammation in unstable coronary artery disease. Am Heart J 2005;149:619–26.

13. Jan KM, Chien S, Bigger JT. Observations on blood viscosity changes after acute myocardial infarction. Circulation 1975;51:1079–84.

14. Tahnk-Johnson ME, Sharkey SW. Impact of thrombolytic therapy on hemoglobin change after acute myocardial infarction. Am J Cardiol 1993;71:869–72.

15. Aronson D, Suleiman M, Agmon Y, et al. Changes in haemoglobin levels during hospital course and long-term outcome after acute myocardial infarction. Eur Heart J 2007;28:1289–96.

16. Moscucci M, Fox KAA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2003;24:1815–23.

17. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389:1025–34.

18. Sabatine MS, Morrow DA, Giugliano RP, et al. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 2005;111:2042–9.

19. Mahendiran T, Nanchen D, Gencer B, et al. Prognosis of patients with chronic and hospital-acquired anaemia after acute coronary syndromes. J Cardiovasc Transl Res 2020;13:618–28.

20. Nagao K, Watanabe H, Morimoto T, et al. Prognostic impact of baseline hemoglobin levels on long-term thrombotic and bleeding events after percutaneous coronary interventions. J Am Heart Assoc 2019;8:e013703.

21. Most AS, Ruocco NA, Gewirtz H. Effect of a reduction in blood viscosity on maximal myocardial oxygen delivery distal to a moderate coronary stenosis. Circulation 1986;74:1085–92.

22. Levy PS, Quigley RL, Gould SA. Acute dilutional anemia and critical left anterior descending coronary artery stenosis impairs end organ oxygen delivery. J Trauma Inj Infect Crit Care 1996;41:416–23.

23. Anand I, McMurray JJV, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation 2004;110:149–54.

24. Redfors B, Généreux P, Witzenbichler B, et al. Bleeding severity after percutaneous coronary intervention. Circ Cardiovasc Interv 2018;11:e005542.

25. Salisbury AC, Alexander KP, Reid KJ, et al. Incidence, correlates, and outcomes of acute, hospital-acquired anemia in patients with acute myocardial infarction. Circ Cardiovasc Qual Outcomes 2010;3:337–46.

26. Lee KH, Lee SR, Kang KP, et al. Periprocedural hemoglobin drop and contrast-induced nephropathy in percutaneous coronary intervention patients. Korean Circ J 2010;40:68.

27. Rothenbühler M, Valgimigli M, Odutayo A, et al. Association of acute kidney injury and bleeding events with mortality after radial or femoral access in patients with acute coronary syndrome undergoing invasive management: secondary analysis of a randomized clinical trial. Eur Heart J 2019;40:1226–32.

28. Andò G, Gragnano F, Calabrò P, Valgimigli M. Radial vs femoral access for the prevention of acute kidney injury (AKI) after coronary angiography or intervention: A systematic review and meta-analysis. Catheter Cardiovasc Interv 2018;92:E518–26.

29. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus

clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940–9.

30. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381:2032–42.

31. Rao AK, Pratt C, Berke A, et al. Thrombolysis In Myocardial Infarction (TIMI) trial-phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1–11.

32. Noordzij M, Tripepi G, Dekker FW, Zoccali C, Tanck MW, Jager KJ. Sample size calculations: basic principles and common pitfalls. Nephrol Dial Transplant 2010;25:1388–93.

33. Leonardi S, Thomas L, Neely ML, et al. Comparison of the prognosis of spontaneous and percutaneous coronary intervention-related myocardial infarction. J Am Coll Cardiol 2012;60:2296–304.

KEY WORDS acute coronary syndromes, bleeding, hemoglobin, percutaneous coronary intervention

APPENDIX For supplemental tables and figures, please see the online version of this paper.

Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk.

Corpataux N, Spirito A, **Gragnano F,** Vaisnora L, Galea R, Svab S, Gargiulo G, Zanchin T, Zanchin C, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Räber L, Capodanno D, Urban P, Pocock S, Heg D, Windecker S, Valgimigli M.

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CLINICAL RESEARCH

Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk

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Aims To validate the set of clinical and biochemical criteria proposed by consensus by the Academic Research Consortium (ARC) for High Bleeding Risk (HBR) for the identification of HBR patients. These criteria were categorized into *major and minor*, if expected to carry in isolation, respectively, ≥4% and <4% Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding risk within 1-year after percutaneous coronary intervention (PCI). High bleeding risk patients are those meeting at least 1 major or 2 minor criteria.

Methods and results All patients undergoing PCI at Bern University Hospital, between February 2009 and September 2018 were prospectively entered into the Bern PCI Registry (NCT02241291). Age, haemoglobin, platelet count, creatinine, and use of oral anticoagulation were prospectively collected, while the remaining HBR criteria except for planned surgery were retrospectively adjudicated. A total of 16 580 participants with complete ARC-HBR criteria were included. After assigning 1 point to each major and 0.5 point to each minor criterion, we observed for every 0.5 score increase a step-wise augmentation of BARC 3 or 5 bleeding rates at 1 year ranging from 1.90% among patients fulfilling no criterion, through 4.01%, 5.98%, 7.42%, 8.60%, 12.21%, 12.29%, and 17.64%. All major and five out of six minor criteria, conferred in isolation a risk for BARC 3 or 5 bleeding at 1 year exceeding 4% at the upper limit of the 95% confidence intervals.

Conclusion All major and the majority of minor ARC-HBR criteria identify in isolation patients at HBR.

Keywords Academic Research Consortium • Bleeding • Percutaneous coronary intervention • Validation

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Introduction

Over the last four decades, percutaneous coronary intervention (PCI) has reduced the risk of cardiac adverse events and improved quality of life among patients with coronary artery disease.[1] Yet, this benefit has come at expenses of higher peri- and post-procedural bleeding rates.[2] Mounting evidence indicates that bleeding events, even if *minor*, impact quality of life,[3] health care costs,[4] and mortality.[5–7]

In response to the lack of a widely accepted outline for computing bleeding risk among patients undergoing PCI, the Academic Research Consortium (ARC) for High Bleeding Risk (HBR) has recently offered a new framework for the identification of patients at HBR.[8] A set of clinical and biochemical criteria, which were previously shown to confer heightened bleeding risk, have been proposed by consensus.[8] These criteria were further categorized into *major*, if expected to carry in isolation at least 4% Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding risk within 12 months after PCI, or *minor*, if expected to confer lower than major bleeding risks.[8] Patients at HBR were defined as those meeting at least 1 major or 2 minor criteria.[8] Recent data from the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) registry cohort-2 indicate that ARC-HBR criteria identify an HBR population.[9] However, only a selected and sometimes modified set of criteria was investigated and no information is available on the contribution of each criterion on the incidence of BARC 3 or 5 bleeding at 1 year.[9] These criteria, generated in the context of a collaboration among leading research organizations, regulatory authorities, and physician–scientists from the USA, Asia, and Europe, are meant to inform patient selection for clinical practice or future clinical trials as well as the regulatory pathways for both drugs and devices.

We therefore sought to provide the first validation of the originally proposed ARC-HBR consensus definition in a large and unselected PCI cohort.

Methods

All consecutive patients undergoing PCI at Bern University Hospital, Switzerland, between February 2009 and September 2018 were prospectively entered into the CARDIOBASE Bern PCI Registry (ClinicalTrials.gov. Unique identifier: NCT02241291). The registry complied with the Declaration of Helsinki and was approved by the institutional ethics committee.[10] Dual antiplatelet therapy (DAPT) was initiated before, at the time, or immediately after the procedure. Prasugrel was introduced as of September 2009 and ticagrelor as of November 2011. The majority of patients with chronic coronary syndrome received clopidogrel. The routinely recommended DAPT duration was 12 months for all acute or chronic coronary syndrome patients until August 2017, unless high bleeding risk features were deemed present, including concomitant oral anticoagulation, which mandated DAPT not to exceed a duration of 6 months. From August 2017, the routinely recommended DAPT duration for chronic coronary syndrome patients became 6 months. Patients were contacted post-discharge during any unscheduled hospital visit, during planned hospital visits (e.g. staged procedure), and finally at 1 year after index PCI. Survival data were obtained from hospital records and municipal civil registries. A health questionnaire was sent to all living patients with questions on rehospitalization and adverse events, including bleeding occurrences, followed by telephone contact in case of missing response. General practitioners and referring cardiologists were contacted as necessary for additional information.

Clinical endpoints and definitions

The primary bleeding endpoint was the composite of BARC type 3 or 5 from intervention to 1 year.[11] Pre-specified secondary endpoints and endpoint definitions are in the Supplementary material online, *Appendix*. A clinical event committee blinded to outcome data adjudicated all events using original source documents (Supplementary material online, *Appendix*).

Academic Research Consortium for High Bleeding Risk criteria

The fulfilment of one or more originally proposed ARC-HBR criterion/a without adaptations was screened for each included patient (Supplementary material online, *Table S1*). Age, haemoglobin, platelet count, creatinine value, and anticipated use of long-term oral anticoagulation were prospectively collected in the database. All other HBR criteria except for planned surgery on DAPT were assessed retrospectively from electronic clinical records by trained study personnel, at variance with a prior report applying only some and largely modified criteria in a smaller sample of the Bern-PCI database.[12] For the generation of the ARC-HBR score, we assigned 1 point to each adjudicated major criterion and 0.5 point to each adjudicated minor criterion. In a random sample of 597 patients, ARC-HBR criteria were independently re-adjudicated by a different observer which provided at least 98% consistency (Supplementary material online, *Table S2*).

Statistical analysis

Baseline and procedural characteristics, medications, and ARC-HBR criteria are shown with means and standard deviations (SD) or counts with percentages (*P*-values from *t*-tests, Fisher's tests or chi-square tests as appropriate, comparing ACR-HBR vs. non-ARC-HBR patients). Time-to-event analyses were used for clinical outcomes. Patients were censored at 1-year follow-up or at the time of last contact if they withdrew consent or were lost to follow-up after hospital discharge. Cox regression and Kaplan–Meier cumulative event curves were used to compare ARC-HBR vs. non-ARC-HBR patients and single criteria vs. reference categories (Wald chi-square tests). A landmark at 30 days of follow-up time was used to compare event rates within 30 days and from 31 days to 1 year. Two-sided Z-tests were used to assess whether the cumulative incidences of 1-year BARC 3 or 5 bleeding did not include the major criteria threshold of 4%. Adjustment for the other ARC-HBR criteria using multivariable Cox's regression models was implemented to test whether the single criteria remain predictive for 4% BARC 3 or 5 bleeding. Competing risk with all-cause death time-to-event analyses were also conducted as sensitivity analyses. A random subsample of patients was re-assessed for ARC-HBR criteria and the agreement with the first assessor shown with the Gwet's agreement coefficients. Supplementary analyses were conducted using the Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding criteria and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) moderate or severe bleeding criteria as the outcome. Analyses were done in Stata Release 16.1 (StataCorp LP, College Station, TX).

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Results

Patient population

Between February 2009 and September 2018, 17 220 consecutive patients were included in the Bern PCI Registry and 16 580 participants had complete data for the ARC-HBR criteria and were included in the current analysis (Supplementary material online, *Table S3*). Mean age was 67.8 years (± 12.0), 74.5% were men and 9379 or 56.6% had an acute coronary syndrome at presentation (Supplementary material online, *Table S4*). The majority of patients received one or more drug-eluting stent at the time of intervention and 26.2% underwent multivessel PCI (Supplementary material online, *Table S5*). At discharge, DAPT, oral anticoagulation (OAC) plus a single antiplatelet agent or a combination of DAPT and OAC was implemented in 95.2%, 11.8%, and 10.0% of the patients, whereas at 1 year the corresponding figures were 65.4%, 13.7%, and 1.7%, respectively (Supplementary material online, *Table S6*). A total of 15 481 (93.4%) patients had 1-year complete information, whereas in the remaining 1099 patients, who refused further participation ($n = 524$ or 3.2%) or were lost to follow-up ($n = 575$ or 3.5%), the median follow-up was 2 (1–5) days.

Academic Research Consortium for High Bleeding Risk population

Altogether, 5752 (34.7%) patients were HBR as defined by ≥1 major ($n = 3876$ or 23.4%) or ≥2 ($n = 3109$ or 18.8%) minor criteria. Among the non-HBR population, 3364 (20.3%) and 7464 (45%) patients fulfilled a single minor or no criterion, respectively (Supplementary material online, *Table S1* and *Figure S1*).

High bleeding risk compared with non-HBR patients were on average 11 years older, less frequently males, had lower BMI and less frequently smokers, but more frequently history of hypertension, diabetes mellitus, myocardial infarction, PCI, and coronary artery bypass grafting and presented with lower left ventricular ejection fraction; they underwent more frequently intervention for left main or coronary artery bypass lesions and received more frequently intra-aortic balloon pump or left ventricular assist devices during PCI (Supplementary material online, *Tables S4* and *S5*).

Clinical outcomes

A total of 663 BARC 3 or 5 bleeding occurred, including 406 (7.9%) and 257 (2.5%) in HBR and non-HBR population, respectively (HR 3.18, 95%CI 2.72–3.72, $P < 0.001$), owing to higher rates of BARC 3 and BARC 5 instances in the former group (Supplementary material online, *Table S7*). At landmark analysis, a three-fold fold increase of BARC 3 or 5 bleeding rates was observed among HBR patients within 30 days (4.06% vs. 1.18%; HR 3.45, 95%CI 2.76–4.29, $P < 0.001$) and from 30 days to 1 year (3.96% vs. 1.36%; HR 2.95, 95%CI 2.36–3.68, $P < 0.001$) (Supplementary material online, *Table S7*). The rates of TIMI major or minor and GUSTO moderate to severe bleeding were also increased among HBR both within the first 30 days and thereafter up to 1 year (Supplementary material online, *Table S7*). Stratified analysis based on HBR category with respect to cardiovascular ischaemic or fatal endpoints provided consistent results (Supplementary material online, *Table S7*).

Academic Research Consortium for High Bleeding Risk score

The average ARC-HBR score was 0.66 (± 0.82) in the overall cohort, 1.61 (± 0.69) in the HBR and 0.16 (±0.23) in non-HBR populations.

There was a step-wise increase of BARC 3 or 5 bleeding rates as a function of the ARC-HBR score with event rates increasing from 1.90% at 1 year among patients fulfilling no criterion, through 4.01%, 5.98%, 7.42%, 8.60%, 12.21%, 12.29%, and 17.64% for every 0.5 increase (*Figures 1 and 2*), with an Harrell's C-index of 0.676 (95%CI 0.656–0.696). A consistent pattern was observed when only major criteria were cumulatively added (*Figure 1*). The rate of BARC 3 or 5 bleeding increased from 4.01% (95%CI 3.36–4.77) among patients with a single minor criterion to 6.16% (95%CI 4.95–7.65) among those with two minor criteria. These findings remained consistent when TIMI or GUSTO bleeding scales were appraised (Supplementary material online, *Figures S2* and *S3*).

Weight of major and minor criteria

BARC 3 or 5 bleeding

When assessed in isolation, all major and five out of six minor criteria, including advanced age, mild to moderate kidney dysfunction, mild anaemia, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) or steroids and remote stroke, conferred a BARC 3 or 5 bleeding risk which exceeded 4% at the upper limit of the 95% confidence intervals (*Take home figure*). The risk of BARC 3 or 5 bleeding was not computable for the minor category of remote prior bleeding. Results remained entirely consistent after exclusion of bleeding related to the access site (Supplementary material online, *Figure S4*). When each major or minor criteria was assessed at multivariable analysis, by adjusting for all ARC-HBR major or minor criteria but the one considered, all major and four minor criteria, including advanced age, mild to moderate kidney dysfunction, history of remote prior bleeding, and long-term use NSAIDs or steroids remained associated with a bleeding risk which included or exceeded 4% at the upper limit of the 95% confidence intervals (*Figure 3*). At competing risk modelling, all major and all minor criteria but prior bleeding—which was not computable—exceeded 4% at the upper limit of the 95% confidence intervals when tested in isolation (Supplementary material online, *Figure S5*). Finally, at competing risk model multivariable adjustment, the rates of BARC 3 exceeded 4% for all major and minor criteria (Supplementary material online, *Figure S6*). Results remained identical at a set of sensitivity analyses which only included 15 481 patients with 1-year complete information.

Discussion

The ARC-HBR initiative has provided a new framework for identifying HBR patients among those undergoing PCI on the basis of a literature review and clinical consensus.[8] The primary goal was advancing the consistency and quality of data collection and reporting, thereby supporting organizations tasked with making recommendations for clinical practice or regulatory decisions. The application of the 11 major and 6 minor proposed criteria requires an in-depth assessment of patient's medical history, which is not routinely collected among PCI databases. Therefore, only a selected and/or modified set of criteria has been so far analysed.[9,12] We provide the first

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	Nr of patients N=16580	BARC 3 or 5 events	Cumulative incidence [95% CI]	p-value vs score 0	p-value vs 4%
Score 0	**n=7464**	**134**	**1.90 [1.61 - 2.25]**	**[Ref.]**	**<0.001**
score 0.5	n=3364	123	4.01 [3.36 - 4.77]	<0.001	0.988
score 1	n=2342	128	5.98 [5.05 - 7.08]	<0.001	<0.001
score 1.5	n=1479	98	7.42 [6.13 - 8.98]	<0.001	<0.001
score 2	n=996	74	8.60 [6.90 - 10.69]	<0.001	<0.001
score 2.5	n=506	54	12.21 [9.47 - 15.66]	<0.001	<0.001
score 3	n=260	28	12.29 [8.62 - 17.36]	<0.001	<0.001
score >3	n=169	24	17.64 [12.11 - 25.30]	<0.001	<0.001
Minor criteria					
only 1 minor	n=3364	123	4.01 [3.36 - 4.77]	<0.001	0.988
only 2 minor	n=1423	78	6.16 [4.95 - 7.65]	<0.001	0.002
only >2 minor	n=453	22	5.58 [3.70 - 8.36]	<0.001	0.174
Major criteria					
only 1 major	n=919	50	5.74 [4.38 - 7.50]	<0.001	0.028
only 2 major	n=208	16	9.21 [5.73 - 14.62]	<0.001	0.018
only 3 major	n=50	7	17.40 [8.52 - 33.63]	<0.001	0.029
only >3 major	n=7	2	31.43 [8.79 - 78.72]	<0.001	0.141
Major and Minor criteria					
1 major + 1 minor	n=1069	79	8.23 [6.65 - 10.17]	<0.001	<0.001
1 major + 2 minor	n=746	55	8.45 [6.55 - 10.87]	<0.001	<0.001
2 major + 1 minor	n=310	36	13.40 [9.83 - 18.13]	<0.001	<0.001
2 major + 2 minor	n=184	18	11.10 [7.11 - 17.10]	<0.001	0.004
2 major + 3 minor	n=42	9	26.64 [14.70 - 45.33]	<0.001	0.003
3 major + 1 minor	n=67	6	10.07 [4.62 - 21.21]	<0.001	0.123
3 major + 2 minor	n=30	3	14.78 [4.78 - 40.67]	0.001	0.190
3 major + 3 minor	n=6	1	20.00 [3.08 - 79.62]	0.016	0.371
>3 major + 1 minor	n=11	2	27.08 [7.46 - 72.36]	<0.001	0.162

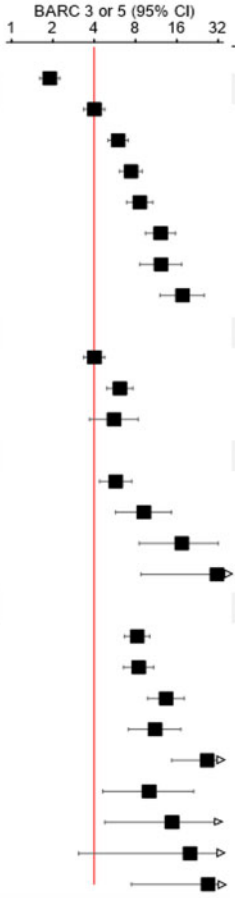


Figure 1 BARC 3 or 5 at 1 year according to ARC-HBR criteria (major = one point, minor = half point). BARC, bleeding academic research consortium; CI, confidence interval; Nr, number. The red line depicts 4% cut-point for a major criterion, corresponding to a score of 1.

comprehensive validation of the originally proposed ARC-HBR criteria and definition in the setting of a large all-comer PCI registry, based on prospectively adjudicated clinical endpoints.

Our key findings were as follows:

(1) Slightly more than one-third of an all-comer PCI population fulfilled HBR definition and incurred a three-fold greater risk of BARC 3 or 5 bleeding as a result of higher event rates within 30 days and from 30 days to 1 year after intervention. These observations were confirmed with TIMI or GUSTO bleeding scales.

(2) The risk of BARC 3 or 5 bleeding accrued progressively as a function of the number of major or minor criteria present with roughly a doubling of the risk for every single unit of ARC-HBR score increase.

(3) The 1-year BARC 3 or 5 bleeding risk exceeded 4% at the upper limit of the 95% confidence intervals for all major and five out of six minor criteria when assessed in isolation; for all major and four minor criteria, when assessed at multivariable analyses; for all major and five minor criteria, at competing risk modelling, and for all major and minor criteria at competing risk multivariable modelling.

Our results indicate that the ARC-HBR criteria identify a large population of PCI patients at high bleeding risk. There was also strong evidence that the risk of BARC 3 or 5 bleeding events was additive and increased linearly based on the number of fulfilled criteria. We, however, did not observe that the so-called *minor* criteria conferred lower bleeding risk than that provided by *major* criteria. Five or four out of six minor criteria conferred a BARC 3 or 5 bleeding risk exceeding the 4% cut-off at 1 year when analysed in isolation or at multivariable analysis, respectively. These findings were reinforced by the competing risk modelling, whereby either five, when assessed in isolation, or all six minor criteria, at multivariable analysis, were associated with ≥4% BARC 3 or 5 bleeding risks. Moreover, the BARC 3 or 5 bleeding risks associated with single major criteria were largely comparable with those observed among patients with single minor criteria. Minor criteria include advanced age, use of NSAIDs or steroids, conditions predisposing to bleeding which occurred more remotely from PCI than the major ones (e.g. a spontaneous bleeding requiring hospitalization or transfusion constitutes a major criterion if

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occurred within 6 months before PCI but a minor criterion if occurred within 6–12 months prior), mild anaemia or mild to moderate renal dysfunction. While some of these criteria were relatively infrequent (<2% e.g. prior stroke or bleeding or use of NSAIDs or steroids), advanced age, mild anaemia, and mild to moderate renal dysfunction were observed in 16.7%, 6.5%, and 4.8% of the patients among the non-HBR population and, in isolation, identified three patient subsets in whom the highest absolute number of bleeding instances occurred, namely 75, 23, and 14, respectively, corresponding to 65% (112/173) of overall bleeding events which occurred in isolation with each minor or major criterion. Our results are in keeping with our preliminary observations made for a selected set of ARC-HBR criteria in a smaller subset of patients in the BERN PCI registry,[12] and with the findings from the CREDO-Kyoto registry.[9] The rates of GUSTO moderate to severe bleeding equalled or exceeded 4% at 1 year among patients with a single minor criterion such as advanced age, mild anaemia, or moderate renal dysfunction and, among these three patient subsets, a total of 129 bleeding occurred as compared with overall 49 among patients who met in isolation the 6 major appraised criteria.[9] Hence, targeted interventions addressing bleeding risks in these three populations have the highest probability of success to mitigate overall bleeding occurrences among PCI patients.

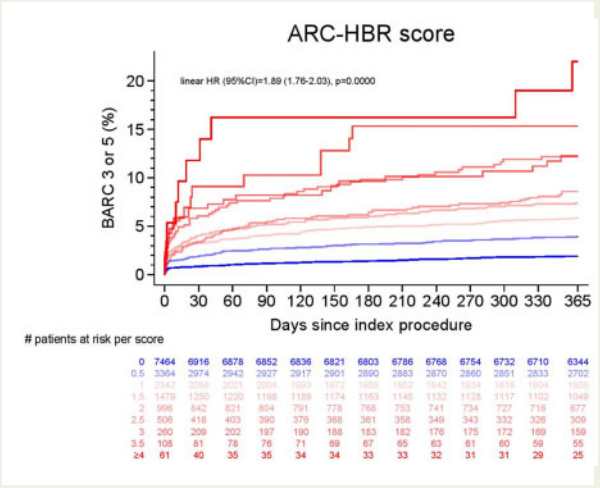
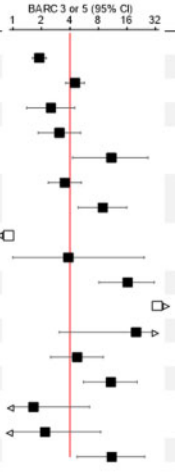


Figure 2 Kaplan-Meier curves for BARC 3 or 5 bleeding according to the ARC HBR score. ARC, academic research consortium; BARC, bleeding academic research consortium; CI, confidence interval; HBR, high bleeding risk; HR, hazard ratio.

Our results have important implications for practice, as question the originally proposed criteria qualification into major or minor. The belief that a single minor criterion would not confer similar bleeding risk as compared with a single major criterion could not be proven by our data. Moreover, at least some minor criteria were highly prevalent among PCI patients, allowing the identification of large groups of PCI patients at HBR. Hence, clinicians should value not only major but also minor criteria in isolation for the identification of HBR patients in view of implementing dedicated bleeding avoidance strategies.

Our results should be interpreted in view of several limitations. First, they arise from a single-centre albeit large cohort study and as such may suffer from limited generalizability. Yet, it is encouraging that our findings are consistent with a previous multicentre report among Asian patients.[9] Second, eight criteria needed retrospective adjudication which may have led to imprecision and underestimation of their true prevalence in our PCI population. However, in a random

Isolated risk factor present	Nr of patients N=16580	BARC 3 or 5 (%) events	Cumulative incidence [95% CI]	p-value vs score 0	p-value vs 4%
No criteria [score 0]	n=7464	134	1.90 [1.61 - 2.25]	[Ref.]	<0.001
Age ≥75 years [minor]	n=1804	75	4.53 [3.62 - 5.67]	<0.001	0.301
Oral anticoagulation [major]	n=452	11	2.52 [1.40 - 4.50]	0.344	0.048
Chronic kidney disease [minor]	n=522	14	3.10 [1.85 - 5.19]	0.081	0.272
Chronic kidney disease [major]	n=40	4	10.97 [4.25 - 26.74]	<0.001	0.180
Hemoglobin [minor]	n=708	23	3.53 [2.36 - 5.27]	0.006	0.517
Hemoglobin [major]	n=125	10	8.89 [4.88 - 15.92]	<0.001	0.069
Prior Bleeding [minor]	n=4	0			
Prior Bleeding [major]	n=26	1	3.85 [0.55 - 24.31]	0.468	0.967
Thrombocytopenia [major]	n=45	7	16.27 [8.09 - 31.19]	0.000	0.030
Chronic Bleeding Diathesis [major]	n=2	1	50.00 [8.96 - 99.40]	0.000	0.193
Liver Cirrhosis with portal hypertension [major]	n=5	1	20.00 [3.08 - 79.62]	0.018	0.371
Long-term use NSAIDs or Steroids [minor]	n=196	9	4.77 [2.51 - 8.97]	0.006	0.619
Active malignancy [major]	n=78	8	10.83 [5.57 - 20.50]	<0.001	0.059
Prior Stroke [minor]	n=130	2	1.65 [0.42 - 6.45]	0.832	0.043
Prior Stroke [major]	n=99	2	2.19 [0.55 - 8.46]	0.865	0.235
Surgery or Trauma within 30 days [major]	n=47	5	11.06 [4.75 - 24.61]	0.000	0.131



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	Nr of patients N=16580	BARC 3 or 5 (%) events	Adjusted Cumulative incidence [95% CI]	Adj BARC 3 or 5 (95% CI) 1 2 4 8 16 32	Adjusted p-value vs absence of risk factor	Adjusted p-value vs 4%
No criteria [score 0]	n=7464	134	1.90 [1.61 - 2.25]			<0.001
Age ≥75 years [minor]	n=5288	309	3.62 [3.09 - 4.25]		<0.001	0.199
Oral anticoagulation [major]	n=1908	132	3.74 [3.03 - 4.63]		<0.001	0.524
Chronic kidney disease [minor]	n=2797	199	4.34 [3.56 - 5.30]		<0.001	0.436
Chronic kidney disease [major]	n=491	47	5.24 [3.76 - 7.31]		<0.001	0.164
Hemoglobin [minor]	n=2446	132	3.20 [2.59 - 3.95]		0.018	0.021
Hemoglobin [major]	n=1132	112	4.66 [3.63 - 5.99]		<0.001	0.267
Prior Bleeding [minor]	n=33	4	4.73 [1.72 - 13.02]		0.216	0.766
Prior Bleeding [major]	n=282	35	4.96 [3.41 - 7.23]		<0.001	0.312
Thrombocytopenia [major]	n=233	31	6.86 [4.68 - 10.05]		<0.001	0.032
Chronic Bleeding Diathesis [major]	n=13	2	3.89 [0.93 - 16.28]		0.545	0.970
Liver Cirrhosis with portal hypertension [major]	n=25	4	5.62 [2.07 - 15.31]		0.113	0.572
Long-term use NSAIDs or Steroids [minor]	n=724	51	3.53 [2.61 - 4.77]		0.021	0.388
Active malignancy [major]	n=381	31	4.13 [2.84 - 6.01]		0.008	0.871
Prior Stroke [minor]	n=550	26	2.20 [1.46 - 3.32]		0.526	<0.001
Prior Stroke [major]	n=308	18	2.82 [1.72 - 4.61]		0.636	0.095
Surgery or Trauma within 30 days [major]	n=224	23	5.05 [3.28 - 7.79]		0.001	0.346

Figure 3 Rates of BARC 3 or 5 bleeding at 1 year according to isolated ARC-HBR criteria. First BARC 3 or 5 counted per patient (% from lifetable estimate). Only the single risk factor was present in isolation. The definition of every single ARC-HBR criteria are reported in the supplementary appendix. BARC, bleeding academic research consortium; CI, confidence interval; HR, hazard ratio; Nr, Number; NSAIDs, nonsteroidal anti-inflammatory drugs. The red line depicts 4% cut-point for a major criterion, corresponding to a score of 1.

cohort of 598 patients, the interobserver variability was ≥98%, which provides reassurance over the consistency of the retrospective adjudication process. Third, a single major criterion, namely non-deferrable major surgery on DAPT was not assessed as this condition may not have been known at the time of PCI and requires prospective data collection. Finally, a total of 650 (3.8%) patients had to be excluded from the analysis because of incomplete ARC-HBR criteria.

In conclusion, the ARC-HBR criteria identified roughly a third of PCI patients in whom BARC 3 or 5 bleeding or ICH risk was increased compared with non-HBR patients. A graded increase of bleeding risk as a function of the number of fulfilled criteria was observed for BARC 3 or 5 occurrences. All major and the majority of minor criteria met the 1-year major criteria performance goal of ≥4% BARC 3 or 5 bleeding. Sixty-five per cent of overall bleeding events, which occurred in isolation with each criterion, were observed among patients fulfilling only 1 among 3 minor criteria, including advanced age, moderate renal dysfunction, and mild anaemia. Our analysis, further corroborated by findings from the CREDO-Kyoto registry, supports the extension of bleeding avoidance strategies and future HBR trials to patients with single minor criteria.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *The Lancet* 2003;**361**:13–20.

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2. Vora AN, Rao SV. Temporal trends in bleeding among acute coronary syndrome patients: is it going up or down? Does it matter? Cardiology 2015;**132**:159–162.
3. Amin AP, Wang TY, Mccoy L, Bach RG, Effron MB, Peterson ED, Cohen DJ. Impact of bleeding on quality of life in patients on DAPT. J Am Coll Cardiol2016; **67**:59–65.
4. Rao SV, Kaul PR, Liao L, Armstrong PW, Ohman EM, Granger CB, Califf RM, Harrington RA, Eisenstein EL, Mark DB. Association between bleeding, blood transfusion, and costs among patients with non–ST-segment elevation acute coronary syndromes. Am Heart J 2008;**155**:369–374.
5. Vranckx P, Leonardi S, Tebaldi M, Biscaglia S, Parrinello G, Rao SV, Mehran R, Valgimigli M. Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial. Eur Heart J 2014;**35**: 2524–2529.
6. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, Van de Werf F, Harrington RA, Mahaffey KW, Tricoci P. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J 2017;**38**:804.10.1093/eurheartj/ehw525.
7. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi M J, Neumann F-J, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Yadav M, Francese DP, Palmerini T, Kirtane AJ, Litherland C, Mehran R, Stone GW. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. *J Am Coll Cardiol* 2015;**66**:1036–1045.
8. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Laschinger J, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice MC. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J* 2019;**40**:2632–2653.
9. Natsuaki M, Morimoto T, Shiomi H, Yamaji K, Watanabe H, Shizuta S, Kato T, Ando K, Nakagawa Y, Furukawa Y, Tada T, Nagao K, Kadota K, Toyofuku M, Kimura T. Application of the Academic Research Consortium high bleeding risk criteria in an all-comers registry of percutaneous coronary intervention. *Circ Cardiovasc Interv* 2019;**12**:e008307.10.1161/CIRCINTERVENTIONS.119.008307.
10. Koskinas KC, Raber L, Zanchin T, Pilgrim T, Stortecky S, Hunziker L, Blochlinger S, Billinger M, Gartwyl F, Moro C, Moschovitis A, Juni P, Heg D, Windecker S. Duration of triple antithrombotic therapy and outcomes among patients undergoing percutaneous coronary intervention. *JACC Cardiovasc Interv* 2016;**9**: 1473–1483.
11. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;**123**: 2736–2747.
12. Ueki Y, Bar S, Losdat S, Otsuka T, Zanchin C, Zanchin T, Gragnano F, Gargiulo G, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Heg D, Valgimigli M, Windecker S, Raber L. Validation of bleeding risk criteria (ARC-HBR) in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. *EuroIntervention* 2020 ; EIJ-D-20-00052. Ahead of print. 10.4244/EIJ-D-20-00052.

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Impact of Clinical Presentation on Bleeding Risk after Percutaneous Coronary Intervention and Implications for the ARC-HBR Definition

Short Title: Clinical presentation and bleeding risk after PCI

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ABSTRACT

Background: The identification of bleeding risk factors in patients undergoing percutaneous coronary intervention (PCI) is essential to inform subsequent management. Whether clinical presentation *per se* affects bleeding risk after PCI remains unclear.
Aims: We aimed to assess whether clinical presentation *per se* predisposes to bleeding in patients undergoing PCI and if the Academic Research Consortium (ARC)-high bleeding risk (HBR) criteria perform consistently among acute (ACS) and chronic (CCS) coronary syndrome patients.
Methods: Consecutive patients undergoing PCI from the Bern PCI Registry were stratified by clinical presentation. Bleeding events at 1 year were compared in ACS versus CCS patients, and the originally-defined ARC-HBR criteria were assessed.
Results: Among 16,821 patients, 9,503 (56.5%) presented with ACS. At 1 year, BARC 3 or 5 bleeding occurred in 4.97% and 3.60% of patients with ACS and CCS, respectively. After adjustment, ACS remained associated with higher BARC 3 or 5 bleeding risk (adjusted HR: 1.21; 95% CI: 1.01-1.43; p=0.034), owing to non-access site-related occurrences, which mainly accrued within the first 30 days after PCI. The ARC-HBR score had lower discrimination among ACS compared with CCS patients, and its performance slightly improved when ACS was computed as a minor criterion.
Conclusions: ACS presentation *per se* predicts 1-year major bleeding risk after PCI. The ARC-HBR score discrimination appeared lower in ACS than CCS, and its overall performance improved numerically when ACS was computed as an additional minor risk criterion.

Classifications: ACS / NSTE-ACS; NSTEMI; STEMI; Stable angina; Bleeding; Clinical research.

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Condensed abstract
We investigated the impact of clinical presentation on bleeding risk and the performance of the ARC-HBR framework among 16,821 all-comers patients undergoing PCI. After adjustment for confounders, ACS presentation *per se* remained associated with higher risk of BARC 3 or 5 bleeding than CCS. The excessive bleeding risk in ACS was driven by non-access site-related events, which mainly accrued within the first 30 days, and was highest among STEMI patients. The ARC-HBR score discrimination on bleeding risk prediction was lower in ACS compared with CCS, and its performance numerically improved when ACS was computed as an additional minor risk criterion.

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List of Abbreviations

ACS: Acute Coronary Syndrome
ARC-HBR: Academic Research Consortium-High Bleeding Risk
BARC: Bleeding Academic Research Consortium
CCS: Chronic Coronary Syndrome
CI: Confidence Intervals
CKD: Chronic Kidney Disease
DAPT: Dual Antiplatelet Therapy
GUSTO: Global Use of Strategies to Open Occluded Arteries
HR: Hazard Ratio
NSAIDs: Nonsteroidal Anti-Inflammatory Drugs
NSTEMI: Non-ST-Segment Elevation Myocardial Infarction
OAC: Oral Anticoagulation
PCI: Percutaneous Coronary Intervention
PH: Portal Hypertension
STEMI: ST-Elevation Myocardial Infarction
TIMI: Thrombolysis in Myocardial Infarction

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INTRODUCTION

Patients undergoing percutaneous coronary intervention (PCI) for either acute (ACS) or chronic (CCS) coronary syndrome are at risk for haemorrhagic complications due to the invasive nature of the procedure and mandated use of antithrombotic therapy [1,2]. As bleeding events adversely affect patients' outcomes, the identification of factors predisposing to heightened bleeding risk after PCI is essential for appropriate treatment selection [3,4].

The bleeding risk might differ according to the clinical presentation. Patients undergoing PCI for ACS are known to experience a higher crude incidence of bleeding complications compared with CCS [5,6]. However, whether ACS presentation *per se* – rather than differences in clinical and procedural characteristics and antithrombotic medications – is associated with an excess of bleeding remains controversial [1]. The higher bleeding risk in ACS patients might be due to a pro-inflammatory state causing a transient impairment of haemostasis [7], but also result from differences in patients' management and pharmacotherapy [2,8]. While some studies suggested that acute presentation might independently associate with bleeding [5,6,9,10], this association has not been confirmed in other reports [11,12]. On this basis, international guidelines recommend to rely on clinical presentation for ischaemic but not bleeding risk stratification purposes [2,8]. Also, the recent framework proposed by the Academic Research Consortium (ARC) for High Bleeding Risk (HBR) did not assign incremental bleeding risk to ACS patients under the premises that the more aggressive antithrombotic therapy prescribed more than the acute presentation *per se* might explain previous findings [1]. To date, no validation of the ARC-HBR criteria in separately appraised ACS and CCS patients exists.

We therefore investigated – in a large cohort of contemporary all-comers PCI patients – whether ACS presentation *per se* associates with higher bleeding risk and whether the ARC-HBR criteria provide a consistent risk stratification framework in patients presenting with or without ACS.

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METHODS

Study design and participants

All consecutive patients undergoing PCI at Bern University Hospital between February 2009 and December 2018 were prospectively entered in the Bern PCI Registry (NCT02241291). No exclusion criterion was applied. Participants provided written informed consent. Clinical characteristics and outcomes up to 1 year were collected prospectively. The prescription of dual antiplatelet therapy (DAPT) followed the recommendations of international guidelines. Detailed information on data collection is available in the **Supplementary Materials**. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee.

Assessment of ARC-HBR criteria

The fulfillment of each ARC-HBR criterion was assessed systematically according to the originally proposed definition (**Supplementary Table 1**). Age, haemoglobin, creatinine, platelet count, and anticipated use of long-term oral anticoagulation were collected prospectively. All other ARC-HBR criteria but nondeferrable major surgery on DAPT were evaluated retrospectively from electronic clinical records by trained investigators blinded to clinical outcomes. The ARC-HBR score was calculated by assigning 1 point to each adjudicated major criterion and 0.5 point to each adjudicated minor criterion. The inter-observer variability among different readers, as previously reported, indicated an excellent agreement for ARC-HBR criteria adjudication [4].

Clinical endpoints

The primary study endpoint was Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding, which was further stratified by (i) bleeding location (i.e., access site and non-access

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site-related), (ii) time of onset (i.e., early and late events with landmark at 30 days), and (iii) presence (i.e., CCS vs. ACS) and type of ACS (unstable angina, non-ST-segment elevation myocardial infarction [NSTEMI], and ST-elevation myocardial infarction [STEMI]). Secondary endpoints included BARC 2, 3 or 5, Thrombolysis In Myocardial Infarction (TIMI)-defined, and Global Use of Strategies to Open Occluded Arteries (GUSTO)-defined bleeding. A clinical event committee adjudicated endpoint events against original source documents. Outcomes were defined in accordance with standardised definitions of the Academic Research Consortium.

Statistical analysis

Baseline characteristics are reported as means (standard deviations) or counts and percentages. For the ACS versus CCS comparison, p-values were obtained using t-test, Fisher's test or chi-square test as appropriate. Time-to-event analyses and Kaplan-Meier event curves were used for outcomes. Analyses were performed at 1 year and with landmark at 30 days. Univariate and multivariate Cox regression was done to investigate the association of clinical presentation and other clinical and treatment characteristics with bleeding. A p-value <0.2 was used to select variables for the multivariable model. We assessed the unadjusted incidence of BARC 3 or 5 events at 1 year associated with each ARC-HBR criterion in ACS and CCS, and the incidence for each ARC-HBR criterion adjusted for the absence of all other criteria. Harrell's c-index was computed to evaluate the performance of the ARC-HBR criteria to predict BARC 3 or 5 bleeding. The discrimination of the ARC-HBR score after including ACS as an additional minor risk criterion was assessed. All analyses were performed using Stata Release 16.1 (StataCorp LP, Texas).

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RESULTS

Population characteristics

A total of 17,339 consecutive patients were prospectively entered into the Bern PCI Registry. Overall, 518 participants were excluded because of incomplete haemoglobin (n=459) or creatinine (n=59) values, with a final study population of 16,821 patients, of whom 9,503 (56.5%) presented with ACS and 7,318 (43.5%) with CCS.

Compared with CCS, ACS patients were on average 3 years younger (66.5±12.8 vs. 69.6±10.5 years), were more often active smokers, presented less frequently with cardiovascular risk factors such as hypertension and diabetes, and were less likely to have a history of myocardial infarction, coronary revascularisation, peripheral artery disease, and atrial fibrillation (**Table 1**). ACS patients underwent more frequently femoral access, invasive haemodynamic support, and staged PCI, but less often left main, bypass graft, or multivessel intervention (**Supplementary Table 2**). The ACS cohort was more likely to receive potent P2Y12 inhibitors, glycoprotein IIb/IIIa antagonists, and proton pump inhibitors but less likely to receive oral anticoagulants or triple antithrombotic therapy (**Supplementary Table 3**).

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Clinical outcomes at 1-year follow-up

At 1 year, BARC 3 or 5 bleeding occurred in 427 (4.97%) patients with ACS and 248 (3.60%) patients with CCS (unadjusted hazard ratio [HR]: 1.41; 95% confidence interval [CI]: 1.20-1.64; p<0.001) (**Table 2 and Figure 1**). At multivariable analysis, after adjusting for clinical, procedural, and treatment imbalances, ACS presentation remained independently associated with a higher risk of BARC 3 or 5 bleeding at 1 year (adjusted HR [adjHR]: 1.21; 95% CI: 1.01-1.43; p=0.034) (**Table 2**).

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BARC 2, 3 or 5 bleeding events at 1 year occurred in 657 (7.65%) ACS and 363 (5.28%) CCS patients (unadjusted HR: 1.49; 95% CI: 1.31-1.69; p<0.001), and were independently predicted by ACS presentation after adjustment (adjHR: 1.25; 95% CI: 1.08-1.44; p=0.003) (**Table 2**).

At sensitivity analyses, performed by adding "years of PCI" (i.e., 2009, 2010, etc.) as covariate in the multivariable model to explore a possible time-effect on outcomes, the results remained largely consistent for both BARC type 3 or 5 (adjHR: 1.27; 95% CI: 1.07-1.51; p=0.007) and type 2, 3 or 5 bleeding events (adjHR: 1.22; 95% CI: 1.02-1.45; p=0.016).

ACS patients bled more than CCS patients also when the TIMI and the GUSTO scales were assessed (**Supplementary Table 4**). The incidence of intracranial or fatal bleeding did not differ. The rates of death, ischaemic, and composite outcomes are reported in **Supplementary Table 4**. Other bleeding risk factors at univariate and multivariate analyses are shown in **Supplementary Tables 5-8**.

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Bleeding events stratified by location, time of onset, and ACS sub-types

The 1-year incidence of access site and non-access site-related BARC 3 or 5 bleeding was 0.62% and 4.40% in the ACS group and 0.49% and 3.18% in the CCS group, respectively (**Table 2**). The corresponding figures for BARC 2, 3 or 5 bleeding were 0.73%, 7.02%, 0.52%, and 4.83%, respectively. After adjustment, ACS presentation remained independently associated with greater non-access site-related type 2, 3 or 5 bleeding (adjHR: 1.23; 95% CI: 1.07-1.43; p=0.005), but with limited and inconclusive evidence for non-access site-related type 3 or 5 occurrences (adjHR: 1.19; 95% CI: 0.99-1.43; p=0.063). Clinical presentation did not emerge as an independent predictor of access site-related bleeding (**Table 2**).

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At landmark analysis, the excess of BARC bleeding among ACS patients occurred mainly within the first 30 days after PCI but not thereafter, and was largely driven by a 2-fold higher risk of non-access site-related events (**Table 3**).

After adjustment, we found a gradient of BARC 3 or 5 bleeding risks across ACS sub-types, being the highest among STEMI patients (adjHR: 1.92; 95% CI: 1.59-2.31; p<0.001), intermediate among NSTEMI patients (adjHR: 1.26; 95% CI: 1.04-1.53; p=0.019), and negligible in unstable angina patients (adjHR: 1.10; 95% CI: 0.74-1.66; p=0.63) (**Figure 2**). A similar graded-risk profile was noted for BARC 2, 3 or 5 bleeding. Clinical characteristics, procedural factors, and medications in patients presenting with unstable angina, NSTEMI, and STEMI are detailed in Supplementary Tables 9-11.

ARC-HBR criteria in patients with ACS and CCS

Thirty-one percent (n=3,020) of ACS and 39% (n=2,869) of CCS patients qualified as HBR defined by the presence of at least one major or two minor ARC-HBR criteria. The risk of BARC-defined bleeding was significantly higher in patients who fulfilled versus those who did not fulfill the ARC-HBR definition for both ACS and CCS groups (**Figure 1**).

Severe anemia, thrombocytopenia, and recent surgery or trauma were more frequently met criteria among ACS patients, whereas advanced age, oral anticoagulants, chronic kidney disease (CKD), mild anemia, prior stroke, and use of nonsteroidal inflammatory drugs or corticosteroids were more common in CCS (**Supplementary Figure 1A**).

The unadjusted risks of BARC 3 or 5 bleeding for each ARC-HBR criterion by clinical presentation are displayed in **Supplementary Figure 2**. At multivariate analysis, after adjusting for each ARC-HBR criterion but the one considered, greater BARC 3 or 5 bleeding risk was found among ACS compared with CCS patients with no ARC-HBR criterion as well as those

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with moderate CKD, or recent spontaneous bleeding and also trended higher in patients with advanced age (**Figure 3**).

ARC-HBR score in patients with ACS and CCS

Mean ARC-HBR score was lower among ACS than CCS patients (0.61±0.81 vs. 0.73±0.84; p<0.001), and distributed differently between study groups (**Supplementary Figure 1B**). For each 0.5-point increase in the ARC-HBR score from 0 to ≥2.5 points, a step-wise increase in the risk of 1-year BARC 3 or 5 events was observed in both groups (**Figure 4 and Supplementary Figure 3**). Compared with CCS, the incidence of BARC 3 or 5 events was higher among ACS patients with a score ≤1, but not for higher score values (**Figure 4**).

The discrimination of the ARC-HBR score was lower among ACS compared with CCS patients with respect to BARC 3 or 5 bleeding (c-indexes: 0.666 [95% CI: 0.641-0.691] vs. 0.716 [95% CI: 0.685-0.747]; p=0.014). In the overall study population, the ARC-HBR score showed moderate discrimination to predict BARC 3 or 5 events (c-index: 0.679 [95% CI: 0.659-0.698], which slightly increased when ACS was included as an additional minor risk criterion (c-index: 0.692 [95% CI: 0.673-0.711]) (**Figure 4**). On the other hand, the ARC-HBR score performance significantly diminished when the originally proposed binary ARC-HBR definition was adopted (c-index: 0.639 [95% CI: 0.621-0.658]).

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DISCUSSION

We investigated the impact of clinical presentation on centrally-adjudicated and prospectively collected bleeding events at 1 year and the ARC-HBR stratified performance in bleeding risk prediction in a large and unselected population of 16,821 PCI patients. The main findings can be summarised as follows (**central illustration**):

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1) ACS presentation *per se*, after extensive multivariable adjustment, remained associated with greater BARC type 3 or 5 and type 2, 3 or 5 bleeding risks;
2) The excess of bleeding among ACS patients was driven by non-access site-related events, which mainly accrued within the first 30 days and was highest among STEMI patients, intermediate among NSTEMI, and minimal for unstable angina patients;
3) Compared with CCS, ACS patients were less likely to qualify as high bleeding risk according to the ARC-HBR definition and presented lower ARC-HBR score mainly due to less frequent fulfillment of the advanced age and oral anticoagulation criteria;
4) ACS patients bled more than CCS patients across multiple ARC-HBR criteria. After multivariate adjustment, based on all ARC-HBR criteria but the one considered, ACS patients continued to show higher BARC 3 or 5 bleeding risk if fulfilled none, moderate CKD or recent bleeding criteria among the ARC-HBR criteria as well as if their ARC-HBR score was ≤1.
5) The ARC-HBR score discrimination was lower among ACS compared with CCS patients. The inclusion of ACS as an additional minor risk criterion slightly improved the performance of the score in the overall study cohort.

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Clinical presentation is deemed critical to guide ischaemic risk stratification by international guidelines in view of the higher risk of coronary events following ACS and the potential benefit accrued with intensified and prolonged antithrombotic therapy compared with CCS [2,8]. However, whether it should also inform bleeding risk assessment and encourage the adoption of bleeding avoidance strategies remains unclear.

Our analysis from a large contemporary cohort of consecutive PCI patients provides evidence that ACS presentation *per se* carries enhanced major and actionable bleeding risks within 1 year

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after PCI. The higher hazard associated with ACS was largely due to bleeding events unrelated to vascular access. As shown here, and consistently with many previous observations, non-access site-related bleeding events are much more prevalent than access-site related occurrences after PCI and have been associated with roughly 2-fold greater mortality risk compared with access site bleeding [13]. Therefore, our novel findings carry major implications for clinical practice.

Previous studies of PCI populations consistently reported a higher crude rate of bleeding complications – ranging from 2- to 4-fold – in ACS versus CCS patients [5,6,9–12,14]. However, when potential confounders were adjusted for, ACS presentation emerged as an independent predictor of bleeding in some studies [5,6,9,10] but not in others [11,12]. This apparent inconsistency might be due to relevant differences among studies in terms of patient characteristics, follow-up duration (i.e., in-hospital, 30-day, or long-term), antithrombotic regimen (i.e., extensive versus selective use of glycoprotein IIb/IIIa antagonists), as well as bleeding definition, location, and severity [5,6,9–12]. The relatively low number of patients and/or events in some studies may have hampered extensive multivariable adjustment.

Our analysis of a large, unselected, and contemporary PCI cohort shows that ACS presentation *per se* represents an independent determinant of spontaneous bleeding. Compared with CCS patients, the bleeding hazard in ACS was driven by an excess of events occurring in the first 30 days after the intervention. This observation might partly explain why clinical presentation emerged as an independent predictor of events in scores modeling short-term bleeding risk after PCI (i.e., REPLACE-2/ACUITY/HORIZONS, NCDR-CathPCI Registry 1, NCDR-CathPCI Registry 2)[6,9] but not in those focusing on long-term occurrences (i.e., PARIS, PRECISE-DAPT)[15,16].

Our analysis also suggests the existence of a graded risk across ACS sub-types. Compared with CCS, the risk of bleeding was not different in patients presenting with unstable angina, whereas

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an NSTEMI or STEMI presentation conferred a 26% and 92% increase in the adjusted hazard, respectively. These findings are consistent with previous algorithms including cardiac biomarkers and/or ST-segment changes as independent predictors of post-PCI bleeding [3,5,6,9,17,18]. Acute presentation is a well-established determinant of ischaemic risk after PCI [2,8]. Our data add to this evidence that patients with ACS are also more prone to bleed, and should be therefore carefully screened and managed to mitigate the concomitant high risk of ischaemic and bleeding complications. Provided that the use of potent antithrombotic therapies is essential in ACS to prevent recurrent coronary events [2], every effort should be made to identify and act promptly on modifiable bleeding risk factors (i.e., anemia, falls/trauma, use of NSAIDs or corticosteroids) in the acute setting – particularly within the first 30 days after STEMI.

This is the first study validating the ARC-HBR criteria in ACS and CCS patients separately. The ARC-HBR consensus did not include the acute presentation among the HBR criteria because the increased bleeding risk associated with ACS was deemed related to the more aggressive antiplatelet therapy and inconsistent evidence from the literature. Our analysis suggests that the ARC-HBR score discrimination was lower in ACS compared with CCS, mainly because of an underestimation of the bleeding risk among patients at lower score. After extensive adjustment including type and duration of antithrombotic therapy, ACS presentation appears to independently affect bleeding risk by acting somewhat as a minor HBR criterion. This consideration derives from the observation that the risk of bleeding is higher in ACS than CCS patients but still below the proposed 4% risk threshold for 1-year major bleeding when assessed in isolation. Of note, this effect seems to dissipate at scores ≥1.5, when the presence of multiple HBR criteria might prevail on the risks associated with ACS *per se*.

Our previous analysis showed that most of the so-called minor criteria identify in isolation patients at HBR and should be regarded as major more than minor criteria [4]. Our current

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analysis adds to the previous one by suggesting that ACS might qualify as a truly minor criterion in future iterations of the proposed ARC-HBR nomenclature. This consideration is further supported by the observation that the discrimination ability of the ARC-HBR score slightly increases when ACS is included as an additional minor risk criterion.

The causes underlying a higher bleeding risk in ACS patients can only be speculated upon. Inflammation and haemostasis are known to be tightly intertwined as platelets, leukocytes, and interleukins are involved in both mechanisms [7,19]. The development of a pro-inflammatory state in ACS patients might lead to a pro-haemorrhagic state, which could partly explain the excess in bleeding complications – the so-called inflammatory bleeding [7]. This hypothesis potentially matches our findings showing a more pronounced effect in the early post-PCI phase and in STEMIs – both featured by a more prominent inflammatory response [19]. The possible role of inflammation is also supported by prior studies reporting an independent association between white-blood-cells count and bleeding risk after PCI [16,20]. Differences in patients' management may also partly account, despite multivariable adjustments, for bleeding predisposition in ACS. As prompt mechanical reperfusion is critical in ACS [2,8], bleeding risk assessment is usually incomplete before or shortly after the intervention (i.e., laboratory values not yet available). In addition, even if bleeding risk factors are known upfront, a timely PCI remains mandatory in ACS, giving a few if no chances to adequately address concomitant risk conditions. Conversely, in CCS patients, careful assessment of bleeding risk is feasible, and PCI can be postponed pending the correction of modifiable factors predisposing to bleed. Our analysis supports these considerations, showing that severe anemia and history of recent trauma/surgery were less prevalent in the CCS than ACS cohort.

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Altogether, our findings lend support to the concept that clinical presentation might integrate the bleeding risk stratification in addition to other validated risk factors such as those included in the ARC-HBR document, carrying yet a truly *minor* impact on risk prediction.

LIMITATIONS

Our results have several limitations. First, this is a single-center study and may suffer from limited generalisability. Yet, clinical characteristics of our study groups and the incidence of bleeding are consistent with those reported in multicenter cohorts [3,6,9,12]. Despite extensive adjustment, which was made possible by the large number of bleeding events accrued, we cannot exclude the effect of residual confounders, including more intense antithrombotic therapies in ACS than CCS patients. Therefore, replication of our findings in other datasets remains desirable. Proton pump inhibitors were prescribed in about 40% of patients in our cohort. Yet, the prescription rate is overall consistent with other large contemporary registries of patients treated with DAPT for coronary artery disease [21]**.** Among the ARC-HBR criteria, eight were adjudicated retrospectively, which may potentially result in an underestimation of their prevalence. Finally, one single major ARC-HBR criterion, planned post-PCI surgery, was not evaluated.

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CONCLUSION

ACS presentation *per se* confers higher bleeding risk compared with CCS, largely owing to non-access site complications that mainly occur in the first 30 days and seem more pronounced among STEMI patients. The ARC-HBR framework performed less well among ACS patients due to bleeding risk underestimation among those with no, one, or two minor criteria or a single

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major criterion. Yet, ACS presentation did not confer in isolation an HBR status and might therefore qualify as a *minor* criterion in future iterations of the ARC-HBR framework.

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Impact on daily practice

Acute coronary syndrome presentation *per se* predisposes to excessive bleeding risk after PCI compared with chronic coronary syndrome, even after adjusting for clinical and procedural factors. The higher risk of bleeding in acute coronary syndrome patients largely owns to non-access site complications occurring mainly in the first 30 days, which seems more pronounced in the setting of STEMI. Clinical presentation can affect the risk of bleeding events after PCI and should therefore inform risk stratification and clinical decision-making in daily practice.

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References

1. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Laschinger J, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao S V., Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice MC. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J*. 2019;40:2632–53.
2. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, ESC Scientific Document Group, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European. *Eur Heart J*. 2018;39:213–60.
3. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzenbichler B, Guagliumi G, Lansky AJ, Stone GW. A Risk Score to Predict Bleeding in Patients With Acute Coronary Syndromes. *J Am Coll Cardiol*. 2010;55:2556–66.
4. Corpataux N, Spirito A, Gragnano F, Vaisnora L, Galea R, Svab S, Gargiulo G, Zanchin T, Zanchin C, Siontis G, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Räber L, Capodanno D, Urban P, Pocock S, Heg D, Windecker S, Valgimigli M. Validation of high

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bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. *Eur Heart J*. 2020;41:3743–9.

5. Loh JP, Pendyala LK, Torguson R, Chen F, Satler LF, Pichard AA, Waksman R. Incidence and correlates of major bleeding after percutaneous coronary intervention across different clinical presentations. *Am Heart J*. 2014;168:248–55.
6. Mehran R, Pocock S, Nikolsky E, Dangas GD, Clayton T, Claessen BE, Caixeta A, Feit F, Manoukian SV, White H, Bertrand M, Ohman EM, Parise H, Lansky AJ, Lincoff AM, Stone GW. Impact of Bleeding on Mortality After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*. 2011;4:654–64.
7. Ho-Tin-Noé B, Boulaftali Y, Camerer E. Platelets and vascular integrity: how platelets prevent bleeding in inflammation. *Blood*. 2018;131:277–88.
8. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020:ehaa575.
9. Mehta SK, Frutkin AD, Lindsey JB, House JA, Spertus JA, Rao S V., Ou F-S, Roe MT, Peterson ED, Marso SP. Bleeding in Patients Undergoing Percutaneous Coronary Intervention. *Circ Cardiovasc Interv*. 2009;2:222–9.
10. Patel NJ, Pau D, Nalluri N, Bhatt P, Thakkar B, Kanotra R, Agnihotri K, Ainani N, Patel N, Patel N, Shah S, Kadavath S, Arora S, Sheikh A, Badheka AO, Lafferty J, Alfonso C, Cohen M. Temporal Trends, Predictors, and Outcomes of In-Hospital Gastrointestinal Bleeding Associated With Percutaneous Coronary Intervention. *Am J Cardiol*.

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2016;118:1150–7.

11. Ko DT, Yun L, Wijeysundera HC, Jackevicius CA, Rao S V., Austin PC, Marquis J-F, Tu J V. Incidence, Predictors, and Prognostic Implications of Hospitalization for Late Bleeding After Percutaneous Coronary Intervention for Patients Older Than 65 Years. *Circ Cardiovasc Interv*. 2010;3:140–7.
12. Feit F, Voeltz MD, Attubato MJ, Lincoff AM, Chew DP, Bittl JA, Topol EJ, Manoukian S V. Predictors and Impact of Major Hemorrhage on Mortality Following Percutaneous Coronary Intervention from the REPLACE-2 Trial. *Am J Cardiol*. 2007;100:1364–9.
13. Verheugt FWA, Steinhubl SR, Hamon M, Darius H, Steg PG, Valgimigli M, Marso SP, Rao SV, Gershlick AH, Lincoff AM, Mehran R, Stone GW. Incidence, Prognostic Impact, and Influence of Antithrombotic Therapy on Access and Nonaccess Site Bleeding in Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*. 2011;4:191–7.
14. Subherwal S, Peterson ED, Dai D, Thomas L, Messenger JC, Xian Y, Brindis RG, Feldman DN, Senter S, Klein LW, Marso SP, Roe MT, Rao SV. Temporal Trends in and Factors Associated With Bleeding Complications Among Patients Undergoing Percutaneous Coronary Intervention. *J Am Coll Cardiol*. 2012;59:1861–9.
15. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents. *J Am Coll Cardiol*. 2016;67:2224–34.
16. Gragnano F, Heg D, Franzone A, McFadden EP, Leonardi S, Piccolo R, Vranckx P, Branca M, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurakowski A, Diletti R, Dominici M, Huber K, Slagboom T, Buszman P, Bolognese L, Tumscitz C,

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Bryniarski K, Aminian A, Vrolix M, Petrov I, Garg S, Naber C, Prokopczuk J, Hamm C, Steg PG, Jüni P, Windecker S, Valgimigli M. PRECISE-DAPT score for bleeding risk prediction in patients on dual or single antiplatelet regimens: insights from the GLOBAL LEADERS and GLASSY. *Eur Hear J - Cardiovasc Pharmacother*. 2020:pvaa106.

17. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB, Ohman EM, Stone GW. Impact of Major Bleeding on 30-Day Mortality and Clinical Outcomes in Patients With Acute Coronary Syndromes. *J Am Coll Cardiol*. 2007;49:1362–8.
18. Mathews R, Peterson ED, Chen AY, Wang TY, Chin CT, Fonarow GC, Cannon CP, Rumsfeld JS, Roe MT, Alexander KP. In-Hospital Major Bleeding During ST-Elevation and Non–ST-Elevation Myocardial Infarction Care: Derivation and Validation of a Model from the ACTION Registry®-GWTG™. *Am J Cardiol*. 2011;107:1136–43.
19. Crea F, Libby P. Acute Coronary Syndromes. *Circulation*. 2017;136:1155–66.
20. Palmerini T, Généreux P, Mehran R, Dangas G, Caixeta A, Riva D Della, Mariani A, Xu K, Stone GW. Association Among Leukocyte Count, Mortality, and Bleeding in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes (from the Acute Catheterization and Urgent Intervention Triage StrategY [ACUITY] Trial). *Am J Cardiol*. 2013;111:1237–45.
21. Sehested TSG, Carlson N, Hansen PW, Gerds TA, Charlot MG, Torp-Pedersen C, Køber L, Gislason GH, Hlatky MA, Fosbøl EL. Reduced risk of gastrointestinal bleeding associated with proton pump inhibitor therapy in patients treated with dual antiplatelet therapy after myocardial infarction. *Eur Heart J*. 2019;40:1963–70.

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FIGURE LEGENDS

Figure 1. Kaplan-Meier event curves for BARC-defined bleeding at 1 year by clinical presentation. BARC 3 or 5 and BARC 2, 3 or 5 events in ACS (red) vs. CCS (blue)(A, B), and further stratified by the ARC-HBR definition (C, D). ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium Criteria; CCS: chronic coronary syndrome; HR: hazard ratio.

Figure 2. Adjudicated BARC-defined bleeding at 1 year by ACS sub-types. Unadjusted (left) and adjusted (right) hazard ratio for BARC 3 or 5 and BARC 2, 3 or 5. CCS is the reference. BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

Figure 3. Adjusted incidence of BARC 3 or 5 bleeding at 1 year for minor and major ARC-HBR criteria in ACS (red) and CCS (blue). Depicted are the estimates of the main effects model, adjusted cumulative incidence in case all other criteria are set to absent. Dotted line: 4% bleeding incidence expected in the presence of a major ARC-HBR criterion. ACS: acute coronary syndrome; ADj: adjusted; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; CKD: chronic kidney disease; NSAIDs: nonsteroidal anti-inflammatory drugs; OAC: oral anticoagulation; PH: portal hypertension.

Figure 4. Adjudicated BARC 3 or 5 bleeding at 1 year by ARC-HBR score. Incidence of BARC 3 or 5 bleeding for score values from 0 to ≥2.5 in ACS (red) and CCS (blue) patients. The dotted line indicates a 4% incidence of bleeding, expected in the presence of one major or two

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minor ARC-HBR criteria (A). Harrell's C-index of the ARC-HBR score for the prediction of BARC 3 or 5 bleeding (B). ACS: acute coronary syndrome; AUC: area under the curve; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; CI: confidence interval.

Central illustration. Clinical presentation and bleeding risk after PCI. ACS presentation per se predisposes to excessive bleeding risk compared with CCS (A) that is largely driven by non-access site complications occurring mainly in the first 30 days. The bleeding risk was highest among STEMI, intermediate among NSTEMI, and minimal in unstable angina. ACS per se might qualify as a minor criterion in future iterations of the ARC-HBR framework (B). ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; HR: hazard ratio; NSTEMI: non-ST-segment elevation myocardial infarction; OAC: oral anticoagulation; STEMI: ST-segment elevation myocardial infarction.

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Table 1. Baseline characteristics stratified by clinical presentation.

	All patients (n=16,821)	ACS (n=9,503)	CCS (n=7,318)	p-value
Age (years)	67.8±12.0	66.5±12.8	69.6±10.5	<0.001
Females	4,307 (25.6%)	2,415 (25.4%)	1,892 (25.9%)	0.52
BMI (kg/m²)	27.3±4.7	27.2±4.6	27.6±4.7	<0.001
Current smoker	4,488 (27.1%)	3,104 (33.4%)	1,384 (19.0%)	<0.001
Hypertension	11,577 (69.3%)	5,869 (62.4%)	5,708 (78.3%)	<0.001
Diabetes mellitus	3,893 (23.2%)	1,892 (20.0%)	2,001 (27.4%)	<0.001
Hypercholesterolemia	10,741 (64.5%)	5,144 (54.9%)	5,597 (76.8%)	<0.001
Family history of CAD	4,323 (25.9%)	2,147 (22.8%)	2,176 (29.9%)	<0.001
Previous myocardial infarction	2,976 (17.8%)	1,348 (14.3%)	1,628 (22.3%)	<0.001
Previous PCI	3,989 (23.8%)	1,553 (16.5%)	2,436 (33.4%)	<0.001
Previous CABG	1,701 (10.1%)	643 (6.8%)	1,058 (14.5%)	<0.001
Previous TIA or stroke	1,237 (7.4%)	545 (5.8%)	692 (9.5%)	<0.001
Peripheral artery disease	1,448 (8.7%)	636 (6.7%)	812 (11.1%)	<0.001
History of malignancy	1,810 (10.8%)	907 (9.6%)	903 (12.4%)	<0.001
Renal failure	3,329 (20.7%)	1,811 (20.4%)	1,518 (21.1%)	0.26
Renal failure on dialysis	193 (1.2%)	94 (1.0%)	99 (1.4%)	0.034
History of atrial fibrillation/flutter	1,450 (12.2%)	564 (8.3%)	886 (17.4%)	<0.001
Chronic obstructive lung disease	1,113 (6.6%)	545 (5.8%)	568 (7.8%)	<0.001
History of spontaneous bleeding	729 (4.3%)	377 (4.0%)	352 (4.8%)	0.008
Left ventricular function (%)	52.3±13.7	49.0±13.4	57.1±12.5	<0.001
Haemoglobin before PCI (g/L)	136.5±18.1	136.8±19.4	136.2±16.5	0.036
Haemoglobin nadir (g/L)	127.0±20.6	124.3±20.6	131.5±19.9	<0.001
Leucocytes before PCI (g/L)	8.9±4.3	10.3±4.8	7.5±3.2	<0.001
Thrombocytes before PCI (g/L)	228.4±72.3	235.4±77.6	220.7±65.0	<0.001
ARC-HBR score	0.66±0.83	0.61±0.81	0.73±0.84	<0.001
Clinical indication for PCI	n=16,821	n=9,503	n=7,318	
CCS	7,318 (43.5%)	0 (0.0%)	7,318 (100.0%)	-
Unstable angina	783 (4.7%)	783 (8.2%)	0 (0.0%)	-
STEMI	4,218 (25.1%)	4,218 (44.4%)	0 (0.0%)	-
STEMI	4,502 (26.8%)	4,502 (47.4%)	0 (0.0%)	-
Killip class	n=16,780	n=9,477	n=7,303	<0.001
Killip I	13,936 (83.1%)	7,334 (77.4%)	6,602 (90.4%)	
Killip II	1,668 (9.9%)	1,091 (11.5%)	577 (7.9%)	
Killip III	496 (3.0%)	398 (4.2%)	98 (1.3%)	
Killip IV	680 (4.1%)	654 (6.9%)	26 (0.4%)	

ACS: acute coronary syndrome; ARC-HBR: Academic Research Consortium for High Bleeding Risk; BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCS: chronic coronary syndrome; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TIA: transient ischaemic attack.

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Table 2. Adjudicated bleeding outcomes at 1 year stratified by clinical presentation.

	ACS (n=9,503)	CCS (n=7,318)	Unadjusted hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
BARC type 3 or 5						
Overall	427 (4.97%)	248 (3.60%)	1.41 (1.20-1.64)	<0.001	1.21 (1.01-1.43)	0.034
Access site	56 (0.62%)	35 (0.49%)	1.25 (0.82-1.91)	0.29	1.12 (0.69-1.81)	0.65
Non-access site	375 (4.40%)	218 (3.18%)	1.41 (1.19-1.67)	<0.001	1.19 (0.99-1.43)	0.063
BARC type 2, 3 or 5						
Overall	657 (7.65%)	363 (5.28%)	1.49 (1.31-1.69)	<0.001	1.25 (1.08-1.44)	0.003
Access site	67 (0.73%)	37 (0.52%)	1.42 (0.95-2.12)	0.090	1.19 (0.78-1.82)	0.42
Non-access site	599 (7.02%)	331 (4.83%)	1.49 (1.31-1.71)	<0.001	1.23 (1.07-1.43)	0.005

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome.

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Table 3. Adjudicated bleeding outcomes at 30 days and with landmark from 30 days to 1-year follow-up in ACS and CCS patients.

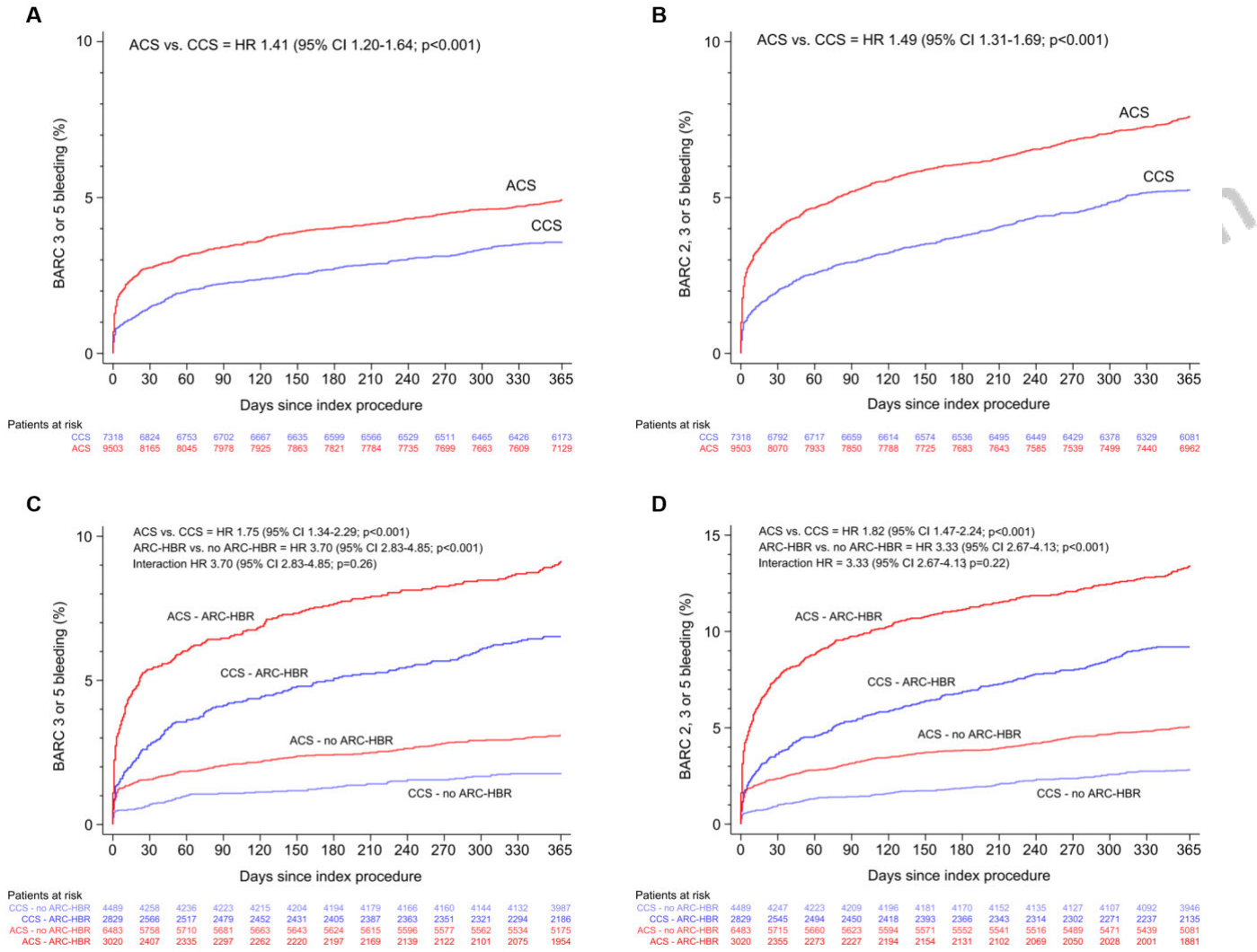
	ACS (n=9,503)	CCS (n=7,318)	Adjusted hazard ratio (95% CI)	p-value	p-interaction
BARC type 3 or 5					<0.001
At 30 days	249 (2.77%)	106 (1.50%)	1.87 (1.49-2.34)	<0.001	
From 31 days to 1 year	178 (2.26%)	142 (2.14%)	1.06 (0.85-1.32)	0.63	
Non-access site BARC 3 or 5					<0.001
At 30 days	201 (2.25%)	77 (1.09%)	2.08 (1.60-2.70)	<0.001	
From 31 days to 1 year	174 (2.20%)	141 (2.11%)	1.04 (0.83-1.30)	0.74	
Access site BARC 3 or 5					0.88
At 30 days	51 (0.55%)	32 (0.45%)	1.25 (0.81-1.95)	0.31	
From 31 days to 1 year	5 (0.06%)	3 (0.04%)	1.39 (0.33-5.82)	0.65	
BARC 2, 3 or 5					<0.001
At 30 days	361 (4.02%)	143 (2.02%)	2.02 (1.66-2.45)	<0.001	
From 31 days to 1 year	296 (3.78%)	220 (3.32%)	1.14 (0.96-1.36)	0.13	
Non-access site BARC 2, 3 or 5					<0.001
At 30 days	305 (3.42%)	113 (1.60%)	2.16 (1.74-2.68)	<0.001	
From 31 days to 1 year	294 (3.73%)	218 (3.28%)	1.14 (0.96-1.36)	0.13	
Access site BARC 2, 3 or 5					0.63
At 30 days	62 (0.67%)	33 (0.46%)	1.48 (0.97-2.25)	0.070	
From 31 days to 1 year	5 (0.06%)	4 (0.06%)	1.04 (0.28-3.89)	0.94	

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; HR: hazard ratio.

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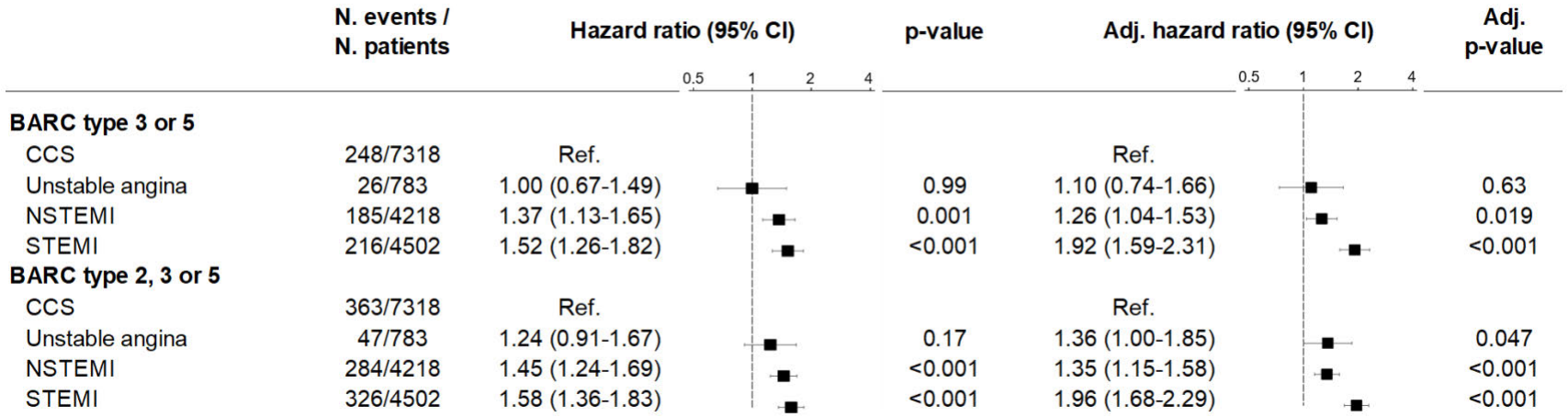
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Figure 1



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Figure 2

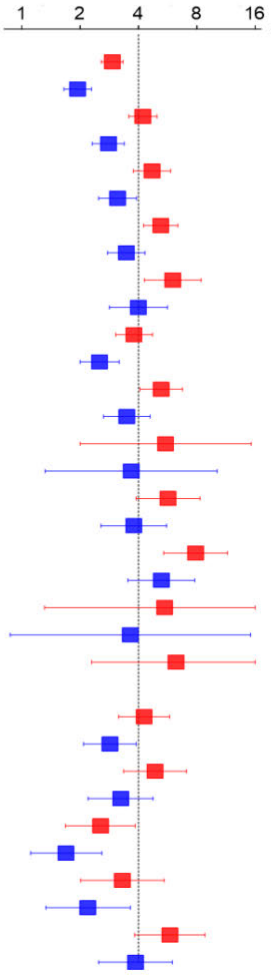


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Figure 3

Clinical presentation	ARC-HBR criteria	N. patients	BARC 3 or 5 events	Cumulative incidence (%) (95% CI)	Adj. BARC 3 or 5 (95% CI)	ACS vs. CCS Adj. p-value
ACS	No ARC-HBR criteria	n=4581	104	2.93 (2.57-3.33)		<0.001
CCS	No ARC-HBR criteria	n=2964	33	1.94 (1.65-2.29)		
ACS	ARC-HBR Age ≥75 years (minor)	n=2842	176	4.21 (3.56-4.98)		0.054
CCS	ARC-HBR Age ≥75 years (minor)	n=2534	137	2.80 (2.31-3.38)		
ACS	ARC-HBR OAC (major)	n=811	57	4.70 (3.76-5.86)		0.81
CCS	ARC-HBR OAC (major)	n=1132	79	3.12 (2.49-3.91)		
ACS	ARC-HBR CKD (minor)	n=1547	124	5.21 (4.25-6.38)		0.006
CCS	ARC-HBR CKD (minor)	n=1290	81	3.46 (2.77-4.32)		
ACS	ARC-HBR CKD (major)	n=275	30	6.01 (4.29-8.41)		0.078
CCS	ARC-HBR CKD (major)	n=236	17	3.99 (2.83-5.64)		
ACS	ARC-HBR Anemia (minor)	n=1253	68	3.79 (3.05-4.72)		0.40
CCS	ARC-HBR Anemia (minor)	n=1238	66	2.52 (2.00-3.18)		
ACS	ARC-HBR Anemia (major)	n=716	74	5.24 (4.07-6.74)		0.15
CCS	ARC-HBR Anemia (major)	n=440	40	3.48 (2.64-4.59)		
ACS	ARC-HBR Previous bleeding (minor)	n=18	2	5.52 (2.00-15.26)		-
CCS	ARC-HBR Previous bleeding (minor)	n=15	2	3.67 (1.32-10.19)		
ACS	ARC-HBR Previous bleeding (major)	n=152	25	5.68 (3.89-8.31)		0.023
CCS	ARC-HBR Previous bleeding (major)	n=134	10	3.78 (2.56-5.58)		
ACS	ARC-HBR Thrombocytopenia (major)	n=155	23	7.89 (5.40-11.52)		0.45
CCS	ARC-HBR Thrombocytopenia (major)	n=80	9	5.25 (3.53-7.80)		
ACS	ARC-HBR Chronic bleeding diathesis (major)	n=4	1	5.46 (1.31-22.87)		>0.99
CCS	ARC-HBR Chronic bleeding diathesis (major)	n=9	1	3.63 (0.87-15.15)		
ACS	ARC-HBR Liver cirrhosis with PH (major)	n=14	4	6.25 (2.29-17.07)		-
CCS	ARC-HBR Liver cirrhosis with PH (major)	n=12	0	-		
ACS	ARC-HBR Long-term use NSAIDs or steroids (minor)	n=367	27	4.28 (3.16-5.79)		0.60
CCS	ARC-HBR Long-term use NSAIDs or steroids (minor)	n=377	26	2.85 (2.08-3.89)		
ACS	ARC-HBR Active malignancy (major)	n=207	16	4.87 (3.35-7.08)		0.77
CCS	ARC-HBR Active malignancy (major)	n=179	16	3.24 (2.20-4.76)		
ACS	ARC-HBR History of stroke (minor)	n=255	14	2.55 (1.68-3.85)		0.43
CCS	ARC-HBR History of stroke (minor)	n=303	12	1.69 (1.11-2.59)		
ACS	ARC-HBR History of stroke (major)	n=141	9	3.30 (2.01-5.43)		0.38
CCS	ARC-HBR History of stroke (major)	n=173	9	2.19 (1.33-3.63)		
ACS	ARC-HBR Recent surgery or trauma (major)	n=176	18	5.81 (3.82-8.81)		0.56
CCS	ARC-HBR Recent surgery or trauma (major)	n=53	7	3.86 (2.49-5.98)		

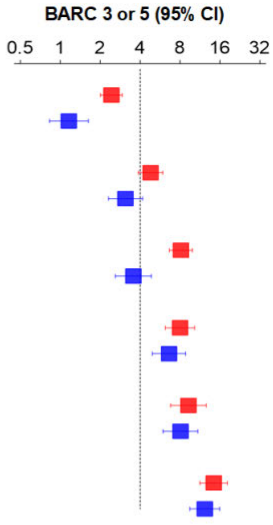


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Figure 4

A

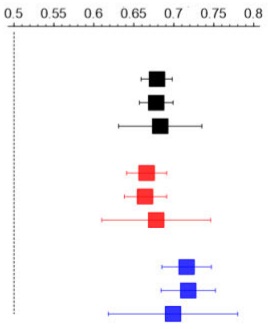
Clinical presentation	ARC-HBR score	N. patients	BARC 3 or 5 events	Cumulative incidence (%) (95% CI)	p-value
ACS	Score 0	n=4581	104	2.43 (2.01-2.93)	<0.001
CCS	Score 0	n=2964	33	1.16 (0.83-1.63)	
ACS	Score 0.5	n=1902	82	4.80 (3.88-5.93)	0.011
CCS	Score 0.5	n=1525	44	3.10 (2.31-4.17)	
ACS	Score 1	n=1250	90	8.12 (6.64-9.92)	<0.001
CCS	Score 1	n=1125	38	3.56 (2.60-4.86)	
ACS	Score 1.5	n=796	55	8.00 (6.19-10.31)	0.31
CCS	Score 1.5	n=703	43	6.61 (4.94-8.81)	
ACS	Score 2	n=485	37	9.26 (6.79-12.58)	0.49
CCS	Score 2	n=533	39	8.07 (5.96-10.89)	
ACS	Score ≥2.5	n=489	59	14.36 (11.28-18.18)	0.31
CCS	Score ≥2.5	n=468	51	12.30 (9.47-15.90)	



B

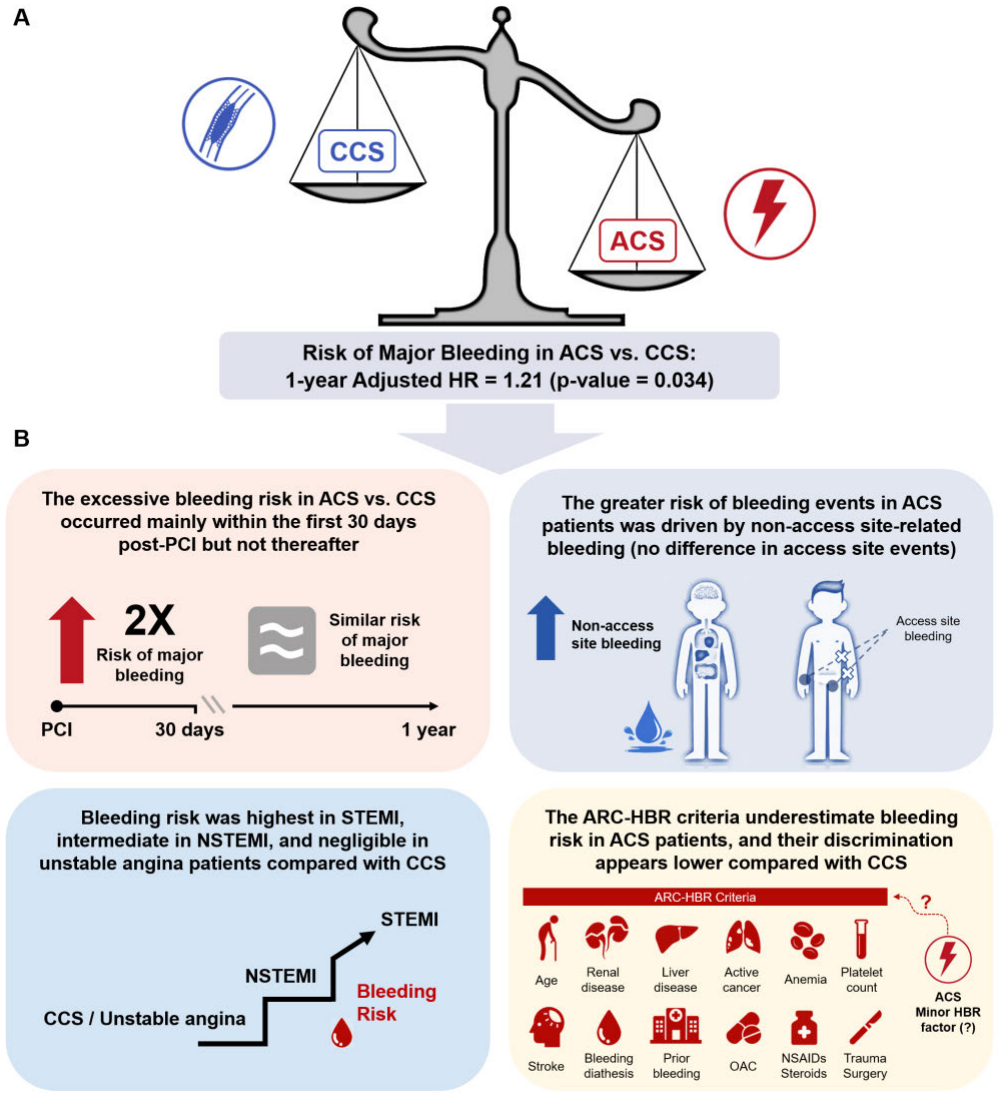
Outcomes at 1-year follow-up	Harrell's c-index (95% CI)	p-value (vs. c-index 0.5)
All patients		
BARC type 3 or 5 overall	0.679 (0.659-0.698)	<0.001
BARC type 3 or 5 non-access site	0.678 (0.657-0.699)	<0.001
BARC type 3 or 5 access site	0.683 (0.631-0.735)	<0.001
ACS		
BARC type 3 or 5 overall	0.666 (0.641-0.691)	<0.001
BARC type 3 or 5 non-access site	0.664 (0.638-0.691)	<0.001
BARC type 3 or 5 access site	0.678 (0.610-0.746)	<0.001
CCS		
BARC type 3 or 5 overall	0.716 (0.685-0.747)	<0.001
BARC type 3 or 5 non-access site	0.718 (0.684-0.752)	<0.001
BARC type 3 or 5 access site	0.699 (0.618-0.780)	<0.001

BARC 3 or 5 overall - ACS vs. CCS: c-index, p=0.014
BARC 3 or 5 non-access site - ACS vs. CCS: c-index, p=0.013
BARC 3 or 5 access site - ACS vs. CCS: c-index, p=0.68



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Central Illustration



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Sex-Based Differences in Bleeding Risk After Percutaneous Coronary Intervention and Implications for the Academic Research Consortium High Bleeding Risk Criteria.

Spirito A, **Gragnano F,** Corpataux N, Vaisnora L, Galea R, Svab S, Gargiulo G, Siontis GCM, Praz F, Lanz J, Billinger M, Hunziker L, Stortecky S, Pilgrim T, Capodanno D, Urban P, Pocock S, Mehran R, Heg D, Windecker S, Räber L, Valgimigli M.

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Journal of the American Heart Association

ORIGINAL RESEARCH

Sex-Based Differences in Bleeding Risk After Percutaneous Coronary Intervention and Implications for the Academic Research Consortium High Bleeding Risk Criteria

Alessandro Spirito, MD; Felice Gragnano, MD; Noé Corpataux, MD; Lukas Vaisnora, MD; Roberto Galea, MD; Stefano Svab, MD; Giuseppe Gargiulo, MD, PhD; George C. M. Siontis, MD, PhD; Fabien Praz, MD; Jonas Lanz, MD; Michael Billinger, MD; Lukas Hunziker, MD; Stefan Stortecky, MD; Thomas Pilgrim, MD; Davide Capodanno, MD, PhD; Philip Urban, MD; Stuart Pocock, PhD; Roxana Mehran, MD; Dik Heg, PhD; Stephan Windecker, MD; Lorenz Räber, MD, PhD; Marco Valgimigli, MD, PhD

BACKGROUND: Female sex was not included among the high bleeding risk (HBR) criteria by the Academic Research Consortium (ARC) as it remains unclear whether it constitutes an HBR condition after percutaneous coronary intervention. We investigated whether female sex associates with HBR and assessed the performance of ARC HBR criteria separately in women and men.

METHODS AND RESULTS: Among all consecutive patients undergoing percutaneous coronary intervention between 2009 and 2018, bleeding occurrences up to 1 year were prospectively collected and centrally adjudicated. All but one of the originally defined ARC HBR criteria were assessed, and the ARC HBR score generated accordingly. Among 16 821 patients, 25.6% were women. Compared with men, women were older and had lower creatinine clearance and hemoglobin values. After adjustment, female sex was independently associated with access-site (adjusted hazard ratio, 2.14; 95% CI, 1.22–3.74; *P*=0.008) but not with overall or non–access-site 1-year Bleeding Academic Research Consortium 3 or 5 bleeding. This association remained consistent when the femoral but not the radial approach was chosen. The ARC HBR score discrimination, using the original criteria, was lower among women than men (c-index 0.644 versus 0.688; *P*=0.048), whereas a revised ARC HBR score, in which age, creatinine clearance, and hemoglobin were modeled as continuous rather than dichotomized variables, performed similarly in both sexes.

CONCLUSIONS: Female sex is an independent predictor for access-site bleeding but not for overall bleeding events at 1 year after percutaneous coronary intervention. The ARC HBR framework shows an overall good performance in both sexes, yet is lower in women than men, attributable to dichotomization of age, creatinine clearance, and hemoglobin values, which are differently distributed between sexes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02241291.

Key Words: Academic Research Consortium ■ bleeding ■ female sex ■ percutaneous coronary intervention ■ vascular access

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For Sources of Funding and Disclosures, see page 10.

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CLINICAL PERSPECTIVE

What Is New?

- Female sex per se was associated with greater access-site bleeding, especially from the femoral artery, but not with overall or non-access site type 3 or 5 occurrences at 1 year, according to Bleeding Academic Research Consortium classification.
- The Academic Research Consortium high bleeding risk framework appears to be a suitable risk stratification tool for bleeding risk assessment in both sexes, provided women are considered at high bleeding risk for access-site events irrespective of high bleeding risk criteria and age, and creatinine clearance and hemoglobin are counted as continuous instead as dichotomous variables.

What Are the Clinical Implications?

- Strategies aiming at mitigating access-site bleeding risk among women, irrespective of high bleeding risk status and including radial access-site selection, should be adopted.
- The overall and non–access-site bleeding risk after percutaneous coronary intervention should not be assessed on the basis of sex but on the other validated bleeding predictors included in the Academic Research Consortium high bleeding risk criteria, which need be assessed in a continuous rather than dichotomized fashion.

Nonstandard Abbreviations and Acronyms

adjHR	adjusted hazard ratio
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
HBR	high bleeding risk

Bleeding events after percutaneous coronary intervention (PCI) are associated with worse outcomes.[1] As a result, the appropriate identification and management of high bleeding risk factors is recommended for all patients undergoing PCI.

Among the clinical factors predisposing to a heightened bleeding risk, the role of sex remains unclear. Evidence suggests that female sex per se confers higher bleeding risks, as it relates to in-hospital[2,3] and/or overall occurrences.[4,5] On the other hand, several studies did not find a similar association.[6–8] International recommendations on duration of dual antiplatelet therapy reflect this uncertainty, with female sex being included among the bleeding risk factors in the American[9] but not the European guidelines.[10] Similarly, female sex accrues the predicted hemorrhagic hazard among some risk scores[11,12] but not in others.[13,14]

The Academic Research Consortium (ARC) for high bleeding risk (HBR) has recently proposed by consensus a set of clinical and biochemical criteria, among which sex is not included, for the identification of patients with HBR.[15] The discriminatory performance of these criteria, as originally described without adaptations, was recently assessed,[16] but no independent assessment of this new framework in men and women exists. Inappropriate estimation of the bleeding risk could lead to erroneous therapeutic management among female patients only on the basis of sex.[17]

We sought therefore to investigate, in a large cohort of consecutive patients undergoing PCI, whether female sex is *independently* associated with higher bleeding occurrences and whether the recent ARC HBR criteria and definitions provide a consistent risk stratification tool in both men and women.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

All consecutive patients undergoing PCI at Bern University Hospital, Switzerland, between February 2009 and December 2018 were prospectively entered into the Bern PCI Registry (ClinicalTrials.gov: NCT02241291), which complies with the Declaration of Helsinki and was approved by the institutional ethics committee. All patients providing informed consent were included without formal exclusion criteria. Demographic, clinical, and procedural characteristics; laboratory values; hospital outcomes; and bleeding and ischemic events occurring up to 1 year after PCI were prospectively collected. The fulfillment of all but one (planned surgery) ARC HBR criteria were systematically screened for each patient according to the originally proposed definitions without adaptations (Table S1). We excluded patients for whom ≥1 ARC HBR criteria could not be assessed because of missing information (except for planned surgery).

Clinical End Points

The primary end point was the composite of Bleeding Academic Research Consortium (BARC) type 3 or 5, further stratified into non–access-site and access-site related. Secondary end points included BARC 2, 3 or 5 bleeding and according to the Thrombolysis in Myocardial Infarction and Global Strategies for Opening Occluded Coronary Arteries scales. Ischemic and fatal outcomes were also reported according to ARC standardized definitions.[18,19]

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Further details about methods can be found in Data S1.

Statistical Analysis

Baseline and procedural characteristics and medications are shown as means and SDs or counts with percentages; *P* values for comparisons of women versus men were obtained for continuous variables using *t* tests, for categorical variables using Fisher's tests (2×2 comparisons) or chi-square tests. Time-to-event analyses and Kaplan-Meier cumulative event curves were used for clinical outcomes. Univariable and multivariable Weibull time-to-event analyses were used to assess the association of sex and other clinical characteristics with the bleeding outcomes specified above. Multiple imputation of missing risk factors (other than ARC HBR criteria) was performed. The 20 generated data sets were used to derive predictors of BARC 3 or 5 bleeding and estimates were combined using Rubin's rule. Predictors with a *P* value below 0.2 were retained in the final models. Models were robustified by year of PCI. Unadjusted and adjusted rates of BARC 3 or 5 were additionally calculated after stratification of women and men by vascular access. Interaction effects between female sex and each adjusted ARC HBR criterion to predict BARC 3 or 5 bleeding was estimated.

Harrell's c-index (concordance statistic) was calculated to assess whether the ARC HBR score predicted BARC 3 or 5 bleeding in the overall population, as well as in women and men separately. The ARC HBR criteria age, hemoglobin, and estimated glomerular filtration rate using creatinine (estimated glomerular filtration rate) were also fitted as continuous risk factors to explore whether some differences between women and men might be attributable to dichotomization of these risk factors.

Analyses were done in Stata Release 16.1 (StataCorp LP, College Station, TX).

RESULTS

Population Characteristics

Between February 2009 and December 2018, 17 339 consecutive patients were included in the Bern PCI Registry. After excluding 518 patients with incomplete hemoglobin (n=459) or creatinine (n=59) data, the final study population comprised 16 821 patients. Follow-up was complete in 15 708 of 16 821 patients (93.4%); for 531 (3.1%) only information about vital status was available, and 582 (3.5%) were lost to follow-up. In the final study population, mean age was 67.9 years, 4307 (25.6%) were women, 9503 (56.5%) presented with acute coronary syndrome, and 16.9% had a Killip class >1 at presentation (Table 1).

Compared with men, female patients were on average 6 years older (72.1±11.4 versus 66.4±11.8 years); had a lower body mass index and hemoglobin values; were more likely to suffer from hypertension, diabetes mellitus, chronic kidney disease (CKD), and malignancy; and were more likely to have a non–ST-segment–elevation acute coronary syndrome as well as acute heart failure at presentation. Men were more frequently smokers and more frequently had a history of coronary disease and chronic obstructive lung disease (Table 1). Femoral access was more frequently used among women than men (70.4% versus 65.3%; *P*<0.001). Women had a lower number of treated coronary lesions, better Thrombolysis in Myocardial Infarction flow before PCI (Thrombolysis in Myocardial Infarction flow 0–1: 21.3% versus 24.1%) and fewer high-risk features such as in-stent restenosis, thrombotic lesions, or chronic total occlusion (Table S2). Other procedural and discharge medications are available in Table S3.

Clinical Outcomes

At 1-year follow-up, 217 (5.5%) overall BARC 3 or 5 bleeding events occurred among women, of which 176 (4.5%) were unrelated and 44 (1.1%) were related to the access site; among men, the corresponding occurrences attained at 458 (4.0%), 417 (3.6%), and 47 (0.4%), respectively. Women as compared with men had an increased unadjusted risk of overall (hazard ratio [HR], 1.41; 95% CI, 1.20–1.66; *P*<0.001), non–access-site (HR, 1.25; 95% CI, 1.05–1.49; *P*=0.013) and access-site (HR, 2.76; 95% CI, 1.83–4.16; *P*<0.001) BARC 3 or 5 bleeding (Table 2). Crude event rates of BARC 2, intracranial or coronary artery bypass grafting–related bleeding did not differ between sexes (Table S4). The results remained largely consistent when the Global Strategies for Opening Occluded Coronary Arteries and Thrombolysis in Myocardial Infarction bleeding scales were appraised (Table S4). Other factors associated with BARC 3 or 5 bleeding at unadjusted analyses are shown in Table S5. Mortality and ischemic outcomes are reported in Table 2.

At multivariate analysis, after adjusting for baseline, procedural, and treatment imbalances, female sex was no longer associated with higher risk of overall (adjusted hazard ratio [adjHR], 1.01; 95% CI, 0.81–1.27; *P*=0.918) or non–access-site (adjHR, 0.89; 95% CI, 0.73–1.07; *P*=0.244) BARC 3 or 5 bleeding. However, access-site–related BARC 3 or 5 events remained 2-fold higher among women compared with men (adjHR, 2.14; 95% CI, 1.22–3.74; *P*=0.008) (Figure 1A and Table S6). When the composite of BARC 2, 3, or 5 bleeding was appraised, female sex remained associated with greater access-site (adjHR 2.15; 95% CI,

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Table 1. Baseline Characteristics According to Sex

	All Patients (N=16 821)	Men (n=12 514)	Women (n=4307)	*P* Value
Age, y	n=16 821, 67.9±12.0	n=12 514, 66.4±11.8	n=4307, 72.1±11.4	<0.001
BMI, kg/m^2	n=16 182, 27.4±4.7	n=12 066, 27.5±4.4	n=4116, 26.9±5.5	<0.001
Current smoker	n=16 575, 4488 (27.1)	n=12 335, 3609 (29.3)	n=4240, 879 (20.7)	<0.001
Hypertension	n=16 694, 11 577 (69.3)	n=12 416, 8330 (67.1)	n=4278, 3247 (75.9)	<0.001
Diabetes mellitus	n=16 757, 3893 (23.2)	n=12 464, 2837 (22.8)	n=4293, 1056 (24.6)	0.014
Hypercholesterolemia	n=16 665, 10 741 (64.5)	n=12 393, 8028 (64.8)	n=4272, 2713 (63.5)	0.138
Family history of coronary artery disease	n=16 684, 4323 (25.9)	n=12 404, 3159 (25.5)	n=4280, 1164 (27.2)	0.027
Previous myocardial infarction	n=16 743, 2976 (17.8)	n=12 453, 2425 (19.5)	n=4290, 551 (12.8)	<0.001
Previous PCI	n=16 741, 3989 (23.8)	n=12 449, 3168 (25.4)	n=4292, 821 (19.1)	<0.001
Previous CABG	n=16 759, 1701 (10.1)	n=12 463, 1435 (11.5)	n=4296, 266 (6.2)	<0.001
Previous TIA or stroke	n=16 750, 1237 (7.4)	n=12 456, 914 (7.3)	n=4294, 323 (7.5)	0.685
Peripheral arterial disease	n=16 738, 1448 (8.7)	n=12 448, 1064 (8.5)	n=4290, 384 (9.0)	0.413
History of malignancy	n=16 746, 1810 (10.8)	n=12 455, 1303 (10.5)	n=4291, 507 (11.8)	0.014
Renal failure*	n=16 098, 3329 (20.7)	n=12 008, 2074 (17.3)	n=4090, 1255 (30.7)	<0.001
History of atrial fibrillation/atrial flutter	n=11 845, 1450 (12.2)	n=8810, 1055 (12.0)	n=3035, 395 (13.0)	0.131
Chronic obstructive lung disease	n=16 747, 1113 (6.6)	n=12 455, 887 (7.1)	n=4292, 226 (5.3)	<0.001
History of spontaneous bleeding	n=16 819, 729 (4.3)	n=12 513, 539 (4.3)	n=4306, 190 (4.4)	0.762
History of gastrointestinal bleeding	n=16 744, 368 (2.2)	n=12 452, 274 (2.2)	n=4292, 94 (2.2)	1.000
Left ventricular function (%)	n=15 122, 52.3±13.7	n=11 261, 51.9±13.5	n=3861, 53.5±14.0	<0.001
Hemoglobin before PCI, g/L	n=14 853, 136.54±18.11	n=11 059, 139.82±17.49	n=3794, 127.00±16.44	<0.001
Hemoglobin nadir, g/L	n=14 003, 126.97±20.64	n=10 358, 130.42±20.04	n=3645, 117.16±19.10	<0.001
ARC HBR score	n=16 821, 0.66±0.83	n=12 514, 0.60±0.80	n=4307, 0.82±0.86	<0.001
Clinical indication for PCI	n=16 821	n=12 514	n=4307	<0.001
Stable CAD	7318 (43.5)	5426 (43.4)	1892 (43.9)	0.521
Unstable angina	783 (4.7)	576 (4.6)	207 (4.8)	0.586
NSTEMI	4218 (25.1)	3056 (24.4)	1162 (27.0)	0.001
STEMI	4502 (26.8)	3456 (27.6)	1046 (24.3)	<0.001
Killip class II, III or IV	n=16 780, 2844 (16.9)	n=12 486, 2042 (16.4)	n=4294, 802 (18.7)	<0.001

Data are presented as absolute numbers and percentage or mean±SD. ARC indicates Academic Research Consortium; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; HBR, high bleeding risk; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIA, transient ischemic attack.

* Renal failure: <60 estimated glomerular filtration rate mL/min/1.73 m^2, using the Modification of Diet in Renal Disease formula.

1.34–3.43; *P*=0.001) but not with overall occurrences (adjHR, 0.89; 95% CI, 0.74–1.06; *P*=0.195), and even appeared protective toward non–access-site (adjHR, 0.78; 95% CI, 0.65–0.94; *P*=0.008) events (Figure 1A and Tables S7 and S8).

Bleeding Outcomes Stratified by Access Site

Among patients in whom the femoral access was used, the crude rate of 1-year BARC 3 or 5 bleeding in women and men reached 7.3% and 5.1% for overall, 6.2% and 4.7% for non–access-site, and 1.3% and 0.5% for access-site occurrences, conferring to women as compared with men an increased unadjusted risk of overall, non–access-site and access-site 1-year BARC 3 or 5 bleeding (Figure S1A). Conversely, when the radial approach was chosen, there were no differences between women and men for overall (crude rate 4.3% versus 4.4%), non–access-site (3.8% versus 4.1%) or access-site (0.5% versus 0.3%) 1-year BARC 3 or 5 bleeding events (Figure S1B).

At adjusted analysis, when the femoral access was attempted, female sex conferred an increased risk of access-site bleeding very close to statistical significance (adjHR, 1.99; 95% CI, 0.96–4.11; *P*=0.063) but not of overall and non–access-site bleeding (Figure S1A). By choosing the radial approach, female sex did not associate with a higher risk of access-site bleeding complications (adjHR, 1.12; 95% CI, 0.43–2.96; *P*=0.811) and resulted even protective in regard to overall and non–access-site occurrences (Figure S1B). These results remained consistent when also BARC 2 bleeding events were taken into account (Figure S1A and S1B).

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Table 2. Bleeding and Ischemic Events at 1 Year According to Sex

	Men (n=12 514)	Women (n=4307)	Hazard Ratio (95% CI)	*P* Value
Bleeding BARC 3 or 5	458 (4.0)	217 (5.5)	1.41 (1.20–1.66)	<0.001
Access site	47 (0.4)	44 (1.1)	2.76 (1.83–4.16)	<0.001
Non–access site	417 (3.6)	176 (4.5)	1.25 (1.05–1.49)	0.013
Bleeding BARC 2, 3, or 5	724 (6.3)	296 (7.5)	1.22 (1.06–1.39)	0.005
Access site	53 (0.4)	51 (1.2)	2.83 (1.93–4.16)	<0.001
Non–access site	681 (5.9)	249 (6.4)	1.08 (0.94–1.25)	0.288
Death	855 (7.2)	340 (8.4)	1.17 (1.04–1.33)	0.012
Cardiac death	601 (5.1)	244 (6.1)	1.20 (1.03–1.39)	0.018
Vascular (noncardiac) death	59 (0.5)	30 (0.8)	1.50 (0.97–2.33)	0.070
Noncardiovascular death	195 (1.7)	66 (1.7)	1.00 (0.76–1.33)	0.977
Myocardial infarction	514 (4.4)	187 (4.7)	1.07 (0.91–1.27)	0.413
Target vessel myocardial infarction	377 (3.2)	142 (3.5)	1.11 (0.91–1.34)	0.296
Revascularization (any)	900 (8.0)	292 (7.6)	0.96 (0.84–1.09)	0.522
Target lesion revascularization	462 (4.1)	156 (4.1)	1.00 (0.83–1.20)	0.981
Target vessel revascularization	663 (5.9)	213 (5.5)	0.95 (0.81–1.11)	0.505
Definite stent thrombosis	153 (1.3)	42 (1.0)	0.81 (0.57–1.13)	0.215
CVE (stroke and TIA)	221 (1.9)	82 (2.1)	1.10 (0.85–1.41)	0.479
Stroke (any)	178 (1.6)	70 (1.8)	1.16 (0.88–1.53)	0.288
Stroke (ischemic stroke)	135 (1.2)	47 (1.2)	1.03 (0.74–1.43)	0.875
Stroke (intracerebral hemorrhage)	38 (0.3)	21 (0.6)	1.64 (0.96–2.79)	0.070
Stroke (unclear etiology)	5 (0.0)	2 (0.1)	1.18 (0.23–6.08)	0.844
TIA	44 (0.4)	12 (0.3)	0.80 (0.42–1.52)	0.504
NACCE	1662 (13.9)	675 (16.5)	1.21 (1.11–1.32)	<0.001

Data are presented as absolute numbers and percentage (%). BARC indicates Bleeding Academic Research Consortium; CVE, cerebrovascular event; NACCE, net adverse cardiac and cerebrovascular event; and TIA, transient ischemic attack.

ARC HBR Criteria Stratified by Sex

Forty-three percent of women and 32% of men qualified as HBR, defined by the presence of at least 2 minor or 1 major ARC HBR criterion. Advanced age, CKD, anemia, and use of nonsteroidal anti-inflammatory drugs or corticosteroids were more common among women, while a history of active malignancy was more frequent among men (Figure S2A). The remaining ARC HBR criteria were similarly distributed between sexes. The unadjusted risks of BARC 3 or 5 bleeding for each ARC HBR criterion among men or women are shown in Figure S3. At multivariable analysis, in which each ARC HBR criterion was adjusted for all major or minor criteria but the one considered, no significant interaction was found between sex and each criterion in the likelihood of BARC 3 or 5 bleeding, except for CKD (*P* interaction for sex=0.035) (Figure 2). When age, creatinine clearance, and hemoglobin were entered into the model as continuous rather than dichotomized variables, as suggested by the ARC HBR, interaction testing between sex and ARC HBR criteria became consistently negative (Figure 3A).

ARC HBR Score Stratified by Sex

The ARC HBR score was higher among women than men (0.82±0.86 versus 0.60±0.80; *P*<0.001) and differently distributed in the 2 groups (Figure S2B). For each 0.5-point increase of the ARC HBR score from 0 to ≥2.5, there was a stepwise increase of BARC 3 or 5 bleeding rates at 1 year in both groups, with event rates increasing from 2.89% to 14.16% among women and from 1.77% to 12.92% among men. The incidence of BARC 3 or 5 bleeding was similar in the 2 sexes for each point of the score ≥1. For score values <1, women showed a significantly higher bleeding risk compared with men (Figure 1B), mainly attributable to an excess of access-site occurrences (Figure S4).

The ARC HBR score discrimination, in terms of Harrell's c-index with respect to BARC 3 or 5 bleeding, was lower among women compared with men (0.644; 95% CI, 0.607–0.680 versus 0.688; 95% CI, 0.664–0.712; *P*=0.048) (Figure 1C). When age, creatinine clearance, and hemoglobin were entered into the model as continuous rather than dichotomized variables, as

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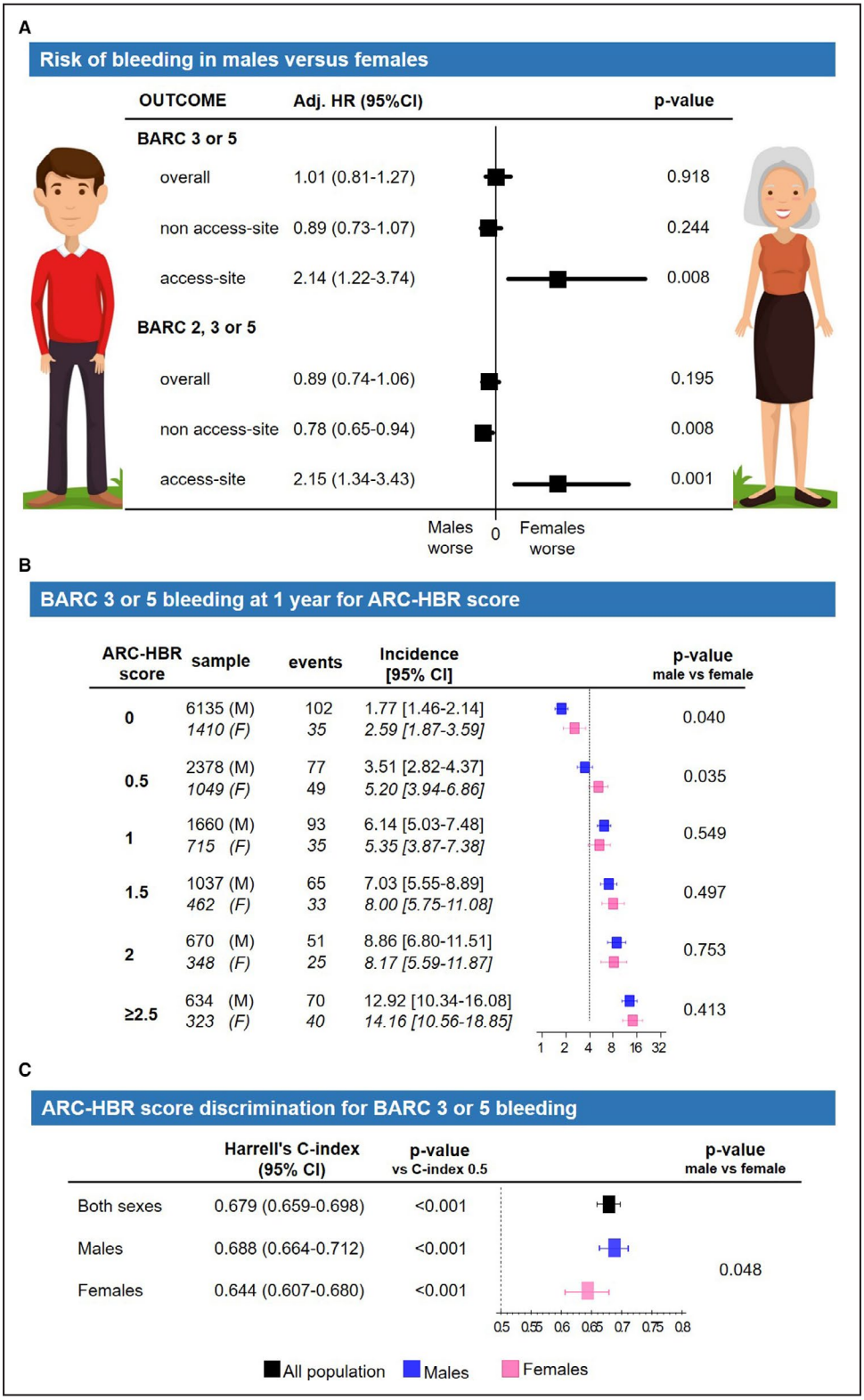


Figure 1. BARC 3 or 5 bleeding at 1 year and ARC HBR criteria in female (F) vs male patients (M). Adjusted (Adj) hazard ratio for overall, non–access-site and access-site bleeding (**A**). ARC HBR criteria modeled as a score (1 point for major criterion, 0.5 for minor): bleeding incidence for score values from 0 to ≥2.5 (**B**) and score discrimination using Harrell's c-index (**C**). The dotted line indicates a 4% incidence of bleeding, expected in presence of a major ARC HBR criterion (definition in Table S1). ARC indicates Academic Research Consortium; BARC, Bleeding Academic Research Consortium; and HBR, high bleeding risk.

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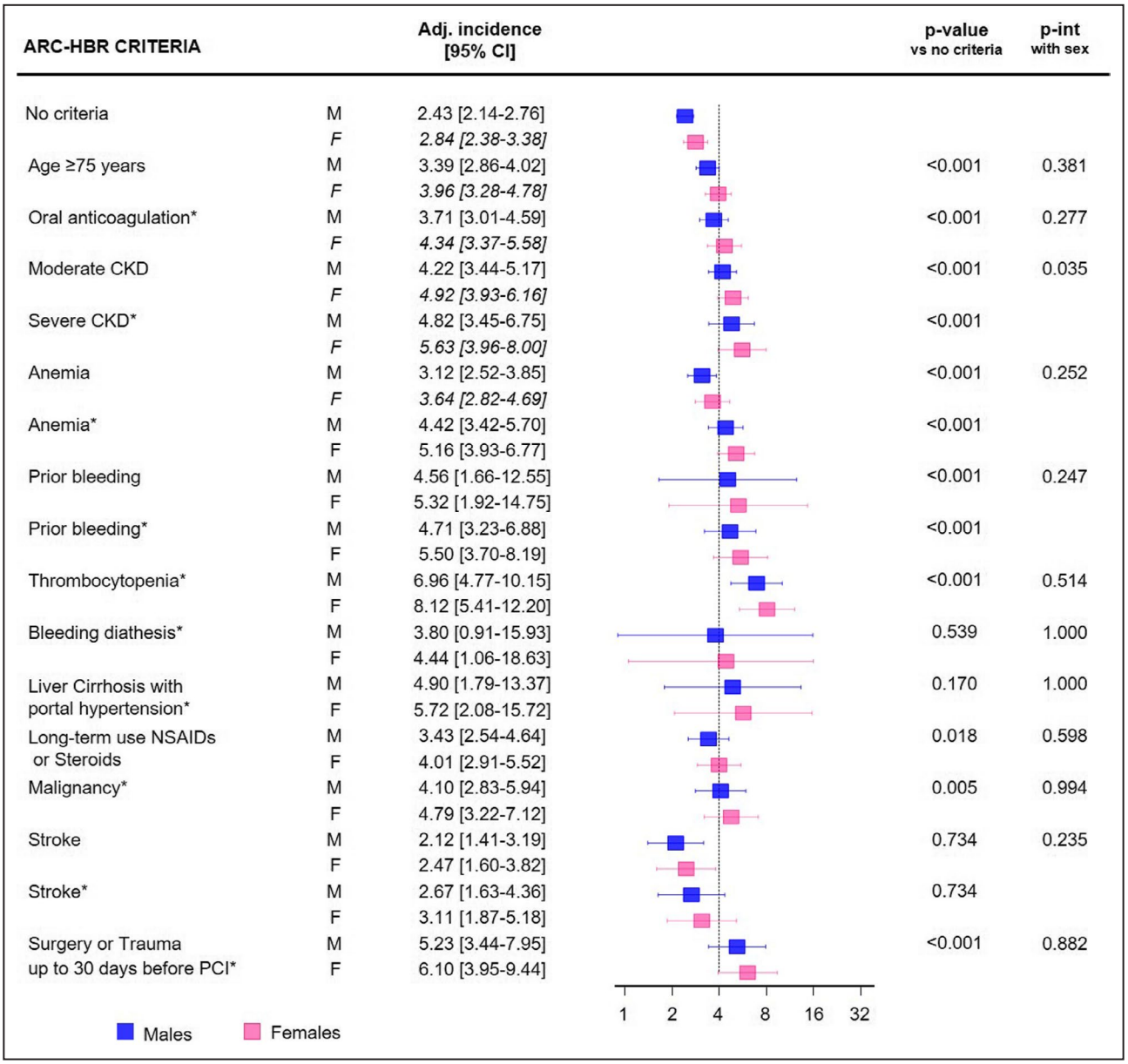


Figure 2. Adjusted (Adj) incidence of BARC 3 or 5 bleedings at 1 year for minor and major (*) ARC HBR criteria in male (M) and female patients (F).

Interaction between sex and each ARC HBR criterion is reported (*P* interaction [int] with sex). The dotted line indicates a 4% incidence of bleeding, expected in presence of a major ARC HBR criterion (definition in Table S1). ARC indicates Academic Research Consortium; BARC, Bleeding Academic Research Consortium; CKD, chronic kidney disease; HBR, high bleeding risk; and PCI, percutaneous coronary intervention.

suggested by the ARC HBR, the ARC HBR score discrimination significantly improved among female patients to the extent that it no longer differed between sexes (Figure 3B).

DISCUSSION

We aimed at addressing the conundrum between bleeding risk and female sex in patients undergoing PCI and ascertained whether the ARC HBR definition performs consistently across both sexes in a prospective all-comer cohort of 16 821 consecutive patients undergoing PCI, who underwent central event adjudication.

Our findings can be summarized as follows:

1. Female patients had higher crude risk of BARC 3 or 5 bleeding at 1 year compared with male patients; after adjustment, female sex per se remained independently associated with access-site–related

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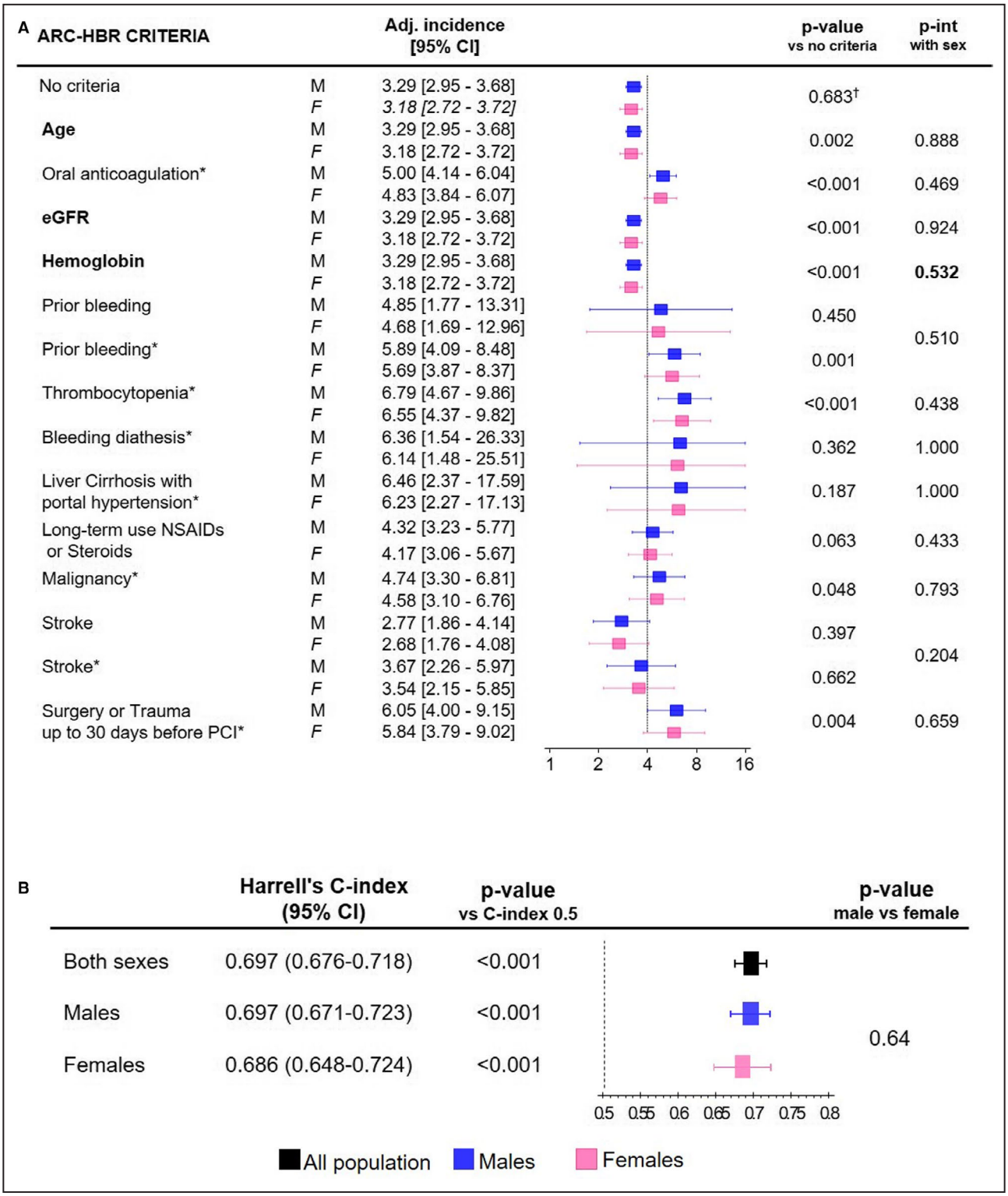


Figure 3. Modified ARC HBR criteria and BARC 3 or 5 bleedings at 1 year.
Modified ARC HBR criteria (age, creatinine clearance, and hemoglobin analyzed as continuous variables) to predict BARC 3 or 5 bleedings at 1 year in males (M) and females (F): adjusted (Adj) bleeding incidence for minor and major (*) ARC-HBR criteria (**A**) and score discrimination using Harrell's c-index (**B**). Bold risk factors: cumulative incidence calculated for the mean of that risk factor. The dotted line indicates a 4% incidence of bleeding, expected in presence of a major ARC HBR criterion (definition in Table S1). ARC indicates Academic Research Consortium; BARC, Bleeding Academic Research Consortium; eGFR, glomerular filtration rate according to Modification of Diet in Renal Disease formula; HBR, high bleeding risk; int, interaction; and PCI, percutaneous coronary intervention. †*P* value for female vs male sex after adjustment for all other modified ARC-HBR criteria.

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but not overall or non–access-site–related BARC 3 or 5 bleeding.
2. These results remained consistent when considering only patients in whom the femoral access was used, while there was no unadjusted and adjusted sex differences in terms of bleeding (overall, not related and related to access site) when the radial approach was chosen.
3. Compared with men, women were more likely to qualify as HBR according to the ARC HBR criteria and presented higher ARC HBR scores, mainly attributable to more frequent fulfillment of advanced age, CKD, or anemia criteria.
4. In a multivariate adjusted model, among the ARC HBR criteria, CKD showed a significant interaction with sex, suggesting higher risk of BARC 3 or 5 bleeding among women than men.
5. The performance of the ARC HBR score in terms of bleeding risk discrimination showed an overall good performance in both sexes, yet lower in women than men.
6. When age, hemoglobin, and creatinine clearance were forced into the model as continuous rather than dichotomized variables, interaction testing with sex was no longer significant, and the ARC HBR score performed consistently across sexes.

Women have an apparent biological protection from coronary artery disease, which translates to a decade-long delay in the onset of coronary artery disease and a different presentation profile and comorbid burden as compared with men. It remains unclear whether female sex per se affects the bleeding risk after PCI. Our analysis addresses this important knowledge gap by showing that after extensive adjustments for several characteristics that differ between women and men, like age, prevalence of CKD or anemia, female sex does not confer a higher risk of overall or non–access-site major bleeding events at 1 year, but remains associated with higher prevalence of major access-site complications, especially if the femoral access was used. These findings are consistent with previous studies, showing that use of radial access reduces significantly the rate of bleeding in both sexes,[20–23] with a possible greater benefit among women.[21,22]

A smaller reference diameter of the common femoral artery have been investigated as possible cause of increased predisposition to access-site bleeding in women in whom the femoral approach was chosen.[24]

Moreover, we observed that when any actionable bleeding events were appraised (ie, BARC 2, 3, or 5), female sex emerged as a protective factor for non–access-site–related occurrences, consistent with prior findings.[25,26]

In 8 of 20 contemporary studies reporting an adjusted sex-related risk of bleeding at >6 months after PCI (Table S9), female sex emerged as an independent predictor of bleeding. Yet a sensitivity analysis excluding periprocedural bleeding was performed in only 1 study,[4] which demonstrated that female sex was no longer a predictor of bleeding at 1 year when only postdischarge major bleeding was appraised. Furthermore, in 2 other studies,[27,28] the increased bleeding risk among female patients was largely driven by nonactionable occurrences (BARC 1), and in some other studies,[29] the low number of bleeding events may have hampered extensive multivariable adjustments.

Our results are supported by the observation that female sex appears in scores conceived to predict in-hospital or short-term bleedings (ie, ACUITY [Acute Catheterization and Urgent Intervention Triage Strategy][11] or CRUSADE [Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines] score[12]), but not across scores developed to predict only spontaneous (eg, PRECISE-DAPT [Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual AntiPlatelet Therapy][14]) or long-term bleeding occurrences (eg, PARIS [Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients][13]).

The recently proposed ARC HBR states that sex differences in bleeding risk should be considered in trial design and the interpretation of study outcomes but did not include female sex among risk factors for HBR.[15] No study has so far assessed this new framework separately in both male and female patients. Our analysis supports the ARC consensus decision not to include sex as an independent criterion for HBR and suggests that this novel HBR definition allows a good prediction of bleeding risk in both sexes. Nevertheless, we observed a lower performance of ARC HBR score among female as compared with male patients attributable to increased age and lower creatinine clearance and hemoglobin values among women. A revised HBR model, in which age, renal function, and hemoglobin values are analyzed as continuous instead of dichotomous variables, provides a more consistent bleeding risk prediction in both sexes.

Our results support the adoption of strategies aiming at mitigating access-site bleeding risk among women, irrespective of HBR status, including radial access-site selection.[21]

Strengths and Limitations

To our knowledge, this is the first study assessing the risk of bleeding at 1 year in female versus male patients stratified by the originally proposed ARC HBR

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criteria without adaptations. Our results have several limitations. First, they arise from a single-center albeit large cohort study and, as such, may suffer from limited generalizability. Yet the distribution of baseline characteristics between sexes as well as the incidence of bleeding and ischemic outcomes are consistent with those of previous multicenter cohorts.[3–5] Eight ARC HBR criteria were retrospectively adjudicated, which may have led to imprecision and underestimation of their true prevalence in our PCI population, but it is reassuring that after independent readjudication of ARC HBR criteria by a different observer in a random sample of 597 patients, the agreement with the first observer attained 98%.

The ARC HBR criteria were not originally conceived as a point-based score. Nevertheless, the creation of an ARC HBR score allowed a more precise bleeding risk stratification.

Finally, a single major ARC HBR criterion, namely, nondeferrable major surgery was not assessed.

CONCLUSIONS

Female sex after PCI is an independent risk factor for access-site but not for overall or non–access-site–related (ie, spontaneous) bleeding at 1 year when the femoral approach is adopted. The ARC HBR framework shows a slightly lower discrimination performance in female as compared with male patients but appears a suitable risk stratification tool for bleeding risk assessment in both sexes, provided female patients are considered at HBR for access-site events, and greater age and lower creatinine clearance and hemoglobin values are accounted for.

ARTICLE INFORMATION

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Supplementary Material

Data S1
Tables S1–S9
Figures S1–S4

REFERENCES

1. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the thrombin receptor antagonist for clinical event reduction in acute coronary syndrome (TRACER) randomized trial. *Eur Heart J*. 2017;38:804–810.
2. Mehran R, Chandrasekhar J, Urban P, Lang IM, Windhoevel U, Spaulding C, Copt S, Stoll HP, Morice MC; Investigators LF. Sex-based outcomes in patients with a high bleeding risk after percutaneous coronary intervention and 1-month dual antiplatelet therapy: a secondary analysis of the LEADERS FREE randomized clinical trial. *JAMA Cardiol*. 2020;5:939–947. DOI: 10.1001/jamacardio.2020.0285.
3. Potts J, Sirker A, Martinez SC, Gulati M, Alasnag M, Rashid M, Kwok CS, Ensor J, Burke DL, Riley RD, et al. Persistent sex disparities in clinical outcomes with percutaneous coronary intervention: insights from 6.6 million PCI procedures in the United States. *PLoS One*. 2018;13:e0203325. DOI: 10.1371/journal.pone.0203325.
4. Hess CN, McCoy LA, Duggirala HJ, Tavris DR, O'Callaghan K, Douglas PS, Peterson ED, Wang TY. Sex-based differences in outcomes after percutaneous coronary intervention for acute myocardial infarction: a

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report from TRANSLATE-ACS. *J Am Heart Assoc*. 2014;3:e000523. DOI: 10.1161/JAHA.113.000523.
5. Yu J, Mehran R, Grinfeld L, Xu KE, Nikolsky E, Brodie BR, Witzenbichler B, Kornowski R, Dangas GD, Lansky AJ, et al. Sex-based differences in bleeding and long term adverse events after percutaneous coronary intervention for acute myocardial infarction: three year results from the HORIZONS-AMI trial. *Catheter Cardiovasc Interv*. 2015;85:359–368. DOI: 10.1002/ccd.25630.
6. Anderson ML, Peterson ED, Brennan JM, Rao SV, Dai D, Anstrom KJ, Piana R, Popescu A, Sedrakyan A, Messenger JC, et al. Short- and long-term outcomes of coronary stenting in women versus men: results from the National Cardiovascular Data Registry Centers for Medicare & Medicaid services cohort. *Circulation*. 2012;126:2190–2199.
7. Chandiramani R, Cao D, Claessen BE, Sorrentino S, Guedeney P, Blum M, Goel R, Roumeliotis A, Krucoff M, Kozuma K, et al. Sex-related differences in patients at high bleeding risk undergoing percutaneous coronary intervention: a patient-level pooled analysis from 4 postapproval studies. *J Am Heart Assoc*. 2020;9:e014611. DOI: 10.1161/JAHA.119.014611.
8. Husted S, James SK, Bach RG, Becker RC, Budaj A, Heras M, Himmelmann A, Horrow J, Katus HA, Lassila R, et al. The efficacy of ticagrelor is maintained in women with acute coronary syndromes participating in the prospective, randomized, platelet inhibition and patient outcomes (PLATO) trial. *Eur Heart J*. 2014;35:1541–1550.
9. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2016;68:1082–1115. DOI: 10.1016/j.jacc.2016.03.513.
10. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39:213–260.
11. Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Della Riva D, Fahy M, Xu K, Stone GW. A new score for risk stratification of patients with acute coronary syndromes undergoing percutaneous coronary intervention: the ACUITY-PCI (acute catheterization and urgent intervention triage strategy-percutaneous coronary intervention) risk score. *JACC Cardiovasc Interv*. 2012;5:1108–1116.
12. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, et al. Baseline risk of major bleeding in non–ST-segment–elevation myocardial infarction: the CRUSADE (can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) bleeding score. *Circulation*. 2009;119:1873–1882. DOI: 10.1161/CIRCULATIONAHA.108.828541.
13. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from Paris. *J Am Coll Cardiol*. 2016;67:2224–2234.
14. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389:1025–1034.
15. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation*. 2019;140:240–261.
16. Corpataux N, Spirito A, Gragnano F, Vaisnora L, Galea R, Svab S, Gargiulo G, Zanchin T, Zanchin C, Siontis GCM, et al. Validation of high bleeding risk criteria and definition as proposed by the Academic Research Consortium for high bleeding risk. *Eur Heart J*. 2020;41:3743–3749. DOI: 10.1093/eurheartj/ehaa671.
17. Redfors B, Angerås O, Råmunddal T, Petursson P, Haraldsson I, Dworeck C, Odenstedt J, Ioaness D, Ravn-Fischer A, Wellin P, et al. Trends in gender differences in cardiac care and outcome after acute myocardial infarction in Western Sweden: a report from the Swedish web system for enhancement of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *J Am Heart Assoc*. 2015;4:e001995. DOI: 10.1161/JAHA.115.001995.
18. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es G-A, Gabriel Steg P, Morel MA, Mauri L, Vranckx P, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351. DOI: 10.1161/CIRCULATIONAHA.106.685313.
19. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel M-A, van Es G-A, Zuckerman B, et al. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. *Circulation*. 2018;137:2635–2650. DOI: 10.1161/CIRCULATIONAHA.117.029289.
20. Chester RC, Mina SA, Lewis B, Zhang N, Butterfield R, Yang EH. Radial artery access is under-utilized in women undergoing PCI despite potential benefits: Mayo Clinic PCI Registry. *Catheter Cardiovasc Interv*. 2020;95:675–683. DOI: 10.1002/ccd.28341.
21. Gargiulo G, Ariotti S, Vranckx P, Leonardi S, Frigoli E, Ciociano N, Tumscitz C, Tomassini F, Calabrò P, Garducci S, et al. Impact of sex on comparative outcomes of radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: data from the randomized MATRIX-Access trial. *JACC Cardiovasc Interv*. 2018;11:36–50. DOI: 10.1016/j.jcin.2017.09.014.
22. Pandie S, Mehta SR, Cantor WJ, Cheema AN, Gao P, Madan M, Niemela K, Rao SV, Schwalm JD, Valentin V, et al. Radial versus femoral access for coronary angiography/intervention in women with acute coronary syndromes: insights from the RIVAL trial (radial vs femoral access for coronary intervention). *JACC Cardiovasc Interv*. 2015;8:505–512.
23. Rao SV, Hess CN, Barham B, Aberle LH, Anstrom KJ, Patel TB, Jorgensen JP, Mazzaferri EL Jr, Jolly SS, Jacobs A, et al. A registry-based randomized trial comparing radial and femoral approaches in women undergoing percutaneous coronary intervention: the SAFE-PCI for women (study of access site for enhancement of PCI for women) trial. *JACC Cardiovasc Interv*. 2014;7:857–867. DOI: 10.1016/j.jcin.2014.04.007.
24. Ahmed B, Lischke S, De Sarno M, Holterman LA, Straight F, Dauerman HL. Gender related differences in predictors of vascular complications: role of vessel size and BMI. *J Thromb Thrombolysis*. 2013;36:84–90. DOI: 10.1007/s11239-012-0847-y.
25. Clemmensen P, Roe MT, Hochman JS, Cyr DD, Neely ML, McGuire DK, Cornel JH, Huber K, Zamoryakhin D, White HD, et al. Long-term outcomes for women versus men with unstable angina/non–ST-segment elevation myocardial infarction managed medically without revascularization: insights from the targeted platelet inhibition to clarify the optimal strategy to medically manage acute coronary syndromes trial. *Am Heart J*. 2015;170:695–705.e695. DOI: 10.1016/j.ahj.2015.06.011.
26. Ko DT, Yun L, Wijeysundera HC, Jackevicius CA, Rao SV, Austin PC, Marquis JF, Tu JV. Incidence, predictors, and prognostic implications of hospitalization for late bleeding after percutaneous coronary intervention for patients older than 65 years. *Circ Cardiovasc Interv*. 2010;3:140–147.
27. Xanthopoulou I, Davlouros P, Deftereos S, Hamilos M, Sitafidis G, Kanakakis I, Vavouranakis M, Goudevenos J, Lekakis J, Alexopoulos D. Gender-related differences in antiplatelet treatment patterns and outcome: insights from the GReekAntiPlatElet Registry. *Cardiovasc Ther*. 2017;35:e12270. DOI: 10.1111/1755-5922.12270.
28. Xu N, Tang XF, Zhao XY, Chen J, Gao Z, Qiao SB, Yang YJ, Gao RL, Xu B, Yuan JQ. Sex-based differences in bleeding and long-term adverse events after percutaneous coronary intervention in older patients with coronary artery disease. *J Interv Cardiol*. 2018;31:345–352. DOI: 10.1111/joic.12500.
29. Shin J-S, Tahk S-J, Yang H-M, Yoon M-H, Choi S-Y, Choi B-J, Lim H-S, Lee Y-H, Seo K-W, Park S-J, et al. Impact of female gender on bleeding complications after transradial coronary intervention (from the Korean Transradial Coronary Intervention registry). *Am J Cardiol*. 2014;113:2002–2006. DOI: 10.1016/j.amjcard.2014.03.042.

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Validation of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores



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KEYWORDS

- ACS/NSTE-ACS
- bleeding
- coronary artery disease
- stable angina

Abstract

Aims: The Academic Research Consortium for High Bleeding Risk (ARC-HBR) defined consensus-based criteria for patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI). We aimed to validate the ARC-HBR criteria for the bleeding outcomes using a large cohort of patients undergoing PCI.

Methods and results: Between 2009 and 2016, patients undergoing PCI were prospectively included in the Bern PCI Registry. Patients were considered to be at HBR if at least one major criterion or two minor criteria were met. The primary endpoint was Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding at one year; ischaemic outcomes were assessed using the device-oriented composite endpoints (DOCE) of cardiac death, target vessel myocardial infarction, and target lesion revascularisation. Among 12,121 patients, those at HBR (n=4,781, 39.4%) had an increased risk of BARC 3 or 5 bleeding (6.4% vs 1.9%; p<0.001) and DOCE (12.5% vs 6.1%; p<0.001) compared with those without HBR. The degree of risk and prognostic value were related to the risk factors composing the criteria. The ARC-HBR criteria had higher sensitivity than the PRECISE-DAPT score and the PARIS bleeding risk score (63.8%, 53.1%, 31.9%), but lower specificity (62.7%, 71.3%, 86.5%) for BARC 3 or 5 bleeding.

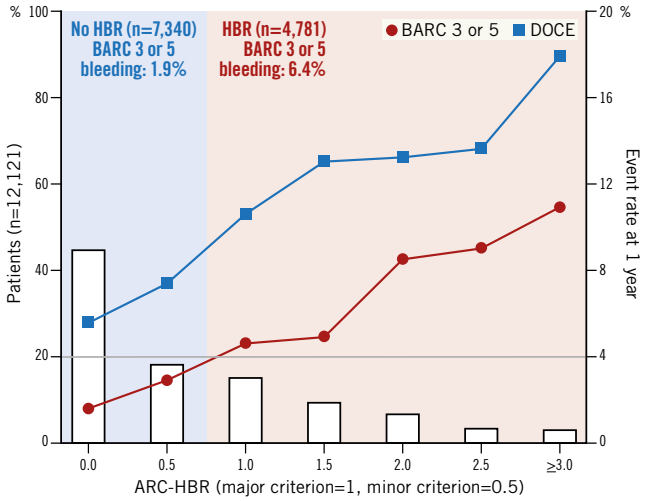
Conclusions: Patients at HBR defined by the ARC-HBR criteria had a higher risk of BARC 3 or 5 bleeding as well as DOCE. The bleeding risk was related to its individual components. The ARC-HBR criteria were more sensitive for identifying patients with future bleedings than other contemporary risk scores at the cost of specificity. ClinicalTrials.gov Identifier: NCT02241291

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Visual summary. *According to the ARC-HBR criteria, 40% of patients undergoing PCI were at HBR. Compared with patients without HBR, those at HBR had an increased risk of BARC 3 or 5 bleeding (6.4% vs 1.9%, p<0.001). There was a gradual risk increase for BARC 3 or 5 bleeding and DOCE as a function of the ARC-HBR score. BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoints; HBR: high bleeding risk.*

Abbreviations

ARC-HBR	Academic Research Consortium for High Bleeding Risk
BARC	Bleeding Academic Research Consortium
CCS	chronic coronary syndrome
CKD	chronic kidney disease
DAPT	dual antiplatelet therapy
DOCE	device-oriented composite endpoints
eGFR	estimated glomerular filtration rate
HBR	high bleeding risk
ICH	intracranial haemorrhage
MI	myocardial infarction
NACE	net adverse composite endpoints
OAC	oral anticoagulant
PCI	percutaneous coronary intervention
ST	stent thrombosis
TLR	target lesion revascularisation
TVR	target vessel revascularisation

Introduction

Following percutaneous coronary intervention (PCI), the impact of major bleeding on prognosis is at least as pronounced as that of myocardial infarction[1,2]. Dual antiplatelet therapy (DAPT) reduces the risk of stent- and non-stent-related ischaemic adverse events in patients undergoing PCI; however, this benefit is offset (at least in part) in patients at high bleeding risk (HBR) and is directly related to the duration of DAPT. A recent study demonstrated that patients at HBR did not gain benefit from long-term DAPT irrespective of the underlying ischaemic risk, suggesting that the characterisation of bleeding risk outweighs ischaemic risk (i.e., PCI complexity) in terms of optimal DAPT duration[3].

Although several bleeding prediction scores are currently available and received a Class IIb (level A) recommendation in the 2017 European Society of Cardiology Focused Update on DAPT to characterise patients undergoing PCI[4], they afford a modest discrimination ability with an average C-statistic of approximately 0.7 to predict bleeding[5,6]. In the clinical trial setting, heterogeneous definitions of HBR have been applied across numerous studies, which may limit the interpretation and generalisability of reported data[7-9]. Against this background, the Academic Research Consortium for High Bleeding Risk (ARC-HBR), a collaboration among leading research organisations, regulatory authorities, and physician-scientists from the USA, Asia, and Europe focusing on PCI-related bleeding, developed a consensus-based definition of patients at HBR in May 2019[10]. HBR was arbitrarily defined as one-year risk of ≥4% for a Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding or ≥1% for intracranial haemorrhage (ICH). To date, data on the applicability of the ARC-HBR criteria in the real-world setting are scarce. Therefore, we validated the ARC-HBR criteria to predict bleeding outcomes using prospective data from a large cohort of unselected, consecutive patients undergoing PCI.

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Methods

PATIENT POPULATION

All consecutive patients undergoing PCI at Bern University Hospital, Switzerland, were prospectively enrolled into the Bern PCI Registry (NCT02241291) between January 2009 and December 2016. For the present study, patients undergoing balloon angioplasty alone or implantation of bioresorbable scaffolds and those in whom ARC-HBR criteria could not be completely ascertained were excluded. The registry was approved by the institutional ethics committee. All patients provided written informed consent.

ARC-HBR CRITERIA

Some of the ARC-HBR criteria needed to be modified or were not available due to the data availability in the registry, as summarised in **Supplementary Table 1**. Major and minor ARC-HBR criteria applied in the current study are as follows: age ≥75 years (minor); oral anticoagulant or novel oral anticoagulant at discharge (major); estimated glomerular filtration rate (eGFR) <30 ml/min (major) and eGFR ≥30, <60 ml/min (minor); baseline haemoglobin <11 g/dL (major), and 11-12.9 g/dL for men and 11-11.9 g/dL for women (minor); spontaneous non-intracranial bleeding requiring hospitalisation or transfusion (major); thrombocytes at index PCI <100×10^9/L (major); non-steroidal anti-inflammatory drugs (NSAIDS) at discharge (minor); cancer history within one year prior to index PCI and/or ongoing treatment, excluding non-melanoma skin cancer (major); previous intracranial bleeding or previous stroke (major); any ischaemic stroke at any time not meeting the major criterion (minor). Definitions of the ARC-HBR criteria are provided in **Supplementary Appendix 1**. Patients were considered to be at HBR if at least one major criterion or two minor criteria were met[10]. The ARC-HBR score was calculated by adding 1 point for any major criterion and 0.5 for any minor criterion.

PROCEDURE

PCI was performed according to current guidelines[11]. Heparin (at least 5,000 IU or an initial bolus of 100 IU per kg body weight) was used for procedural anticoagulation with the aim of maintaining an activated clotting time >250 msec. The periprocedural use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. DAPT consisting of acetylsalicylic acid and a $P2Y_{12}$ inhibitor was initiated before, at the time of, or immediately after the procedure. Prasugrel was introduced as of September 2009, and ticagrelor as of November 2011. The majority of patients with chronic coronary syndrome (CCS) received clopidogrel. The routinely recommended DAPT duration was 12 months[12].

CLINICAL ENDPOINTS

The primary bleeding endpoint was bleeding defined as Bleeding Academic Research Consortium (BARC) 3 or 5[13]. Secondary endpoints, definitions, and patient follow-up are provided in **Supplementary Appendix 2**.

STATISTICAL ANALYSIS

Continuous variables were summarised as mean±standard deviation or median and interquartile range, and compared with the Student's t-test or the Mann-Whitney U test. Binary and categorical variables were calculated as frequencies (percentages) and were compared with the chi-square test or Fisher's exact test. Kaplan-Meier cumulative event curves were constructed for time-to-event variables and compared using the log-rank test. Subhazard ratio was obtained from a competing risk survival regression based on Fine and Gray's proportional subhazard model. Discrimination of the bleeding risk score was assessed by the C-statistic. Calibration was assessed by comparing predicted probabilities with the observed frequency of BARC 3 or 5 bleeding. Cox regression analysis was performed to test the prognostic significance of each component of the ARC-HBR criteria for BARC 3 or 5 bleeding and device-oriented composite endpoints (DOCE). Each component of the ARC-HBR criteria was adjusted by all components of the ARC-HBR criteria and clinically important variables reported by previous studies. For BARC 3 or 5 bleeding, female gender, body mass index, current smoker, hypertension, peripheral artery disease, acute coronary syndrome, and potent $P2Y_{12}$ at discharge, and for DOCE, age, female gender, current smoker, hypertension, peripheral artery disease, previous myocardial infarction, previous revascularisation (PCI and/or coronary artery bypass graft [CABG]), left ventricular ejection fraction, stent type (bare metal stent, first-generation drug-eluting stent), were entered into a multivariate model[5,6,14,15]. P-values were two-tailed and a value under 0.05 was considered statistically significant in all analyses. Statistical analyses were performed with R, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

PATIENTS

Of 13,748 patients enrolled into the Bern PCI Registry between January 2009 and December 2016, 12,121 patients were analysed for the present study with complete follow-up available in 11,314 (93.3%) patients at one year. Patients were excluded in case of balloon angioplasty without stent implantation (n=496), implantation of bioresorbable scaffolds (n=60), or if not all of the ARC-HBR criteria were assessable (n=1,071: missing haemoglobin [n=437], missing eGFR [n=710], missing thrombocytes [n=564], missing data on NSAIDs [n=152]).

BASELINE CHARACTERISTICS

Clinical and procedural characteristics and medication status are summarised in **Table 1**, **Supplementary Table 2** and **Supplementary Table 3**. Patients at HBR (n=4,781, 39.4%) were older and more commonly female, had more risk factors for atherosclerotic cardiovascular disease, comorbidities, CCS as an indication for PCI, and had higher PRECISE-DAPT scores compared with those without. Among HBR patients, PCI was more frequently performed in the anatomical setting of the left main and saphenous vein bypass grafts. New-generation drug-eluting stents were used in 93.4% of all patients with a lower frequency in patients at HBR. The use of potent $P2Y_{12}$ inhibitors was less frequent in patients at HBR.

ARC-HBR CRITERIA

The prevalence of ARC-HBR criteria is summarised in **Figure 1**. Age ≥75 years (31.9%), anaemia (26.4%), chronic kidney disease (CKD) (25.5%), oral anticoagulation (10.5%), and previous ICH or stroke (8.0%) were the leading ARC-HBR criteria in decreasing order. Prior spontaneous non-ICH bleeding (2.8%), thrombocytopaenia (1.3%), NSAIDS (1.7%), and active malignancy (1.9%) were rarely observed. Major CKD, major anaemia, and spontaneous non-ICH bleeding frequently overlapped with other criteria, as illustrated in **Supplementary Figure 1**. The ARC-HBR score had a C-statistic of 0.69 (95% CI: 0.66-0.71) for BARC 3 or 5 bleeding and showed

Table 1. Patient characteristics.

		HBR (n=4,781)	Non-HBR (n=7,340)	*p*-value
Age, years		75.5±10.0	62.8±10.4	<0.001
Age ≥75 years		3,026 (63.3%)	843 (11.5%)	<0.001
Female		1,644 (34.4%)	1,505 (20.5%)	<0.001
Body mass index, kg/m^2		26.7±4.9	27.8±4.5	<0.001
Current smoker		765 (16.0%)	2,502 (34.1%)	<0.001
Hypertension		3,780 (79.1%)	4,607 (62.8%)	<0.001
Diabetes mellitus		1,347 (28.2%)	1,430 (19.5%)	<0.001
Dyslipidaemia		3,125 (65.4%)	4,700 (64.0%)	0.060
Family history of coronary artery disease		972 (20.3%)	2,199 (30.0%)	<0.001
Previous myocardial infarction		932 (19.5%)	1,028 (14.0%)	<0.001
Previous PCI		1,127 (23.6%)	1,418 (19.3%)	<0.001
Previous CABG		677 (14.2%)	518 (7.1%)	<0.001
Peripheral artery disease		609 (12.7%)	361 (4.9%)	<0.001
Prior spontaneous non-ICH bleeding requiring hospitalisation or transfusion		338 (7.1%)	0 (0%)	<0.001
Active malignancy (excluding non-melanoma skin cancer) within past 12 months		234 (4.9%)	0 (0%)	<0.001
Previous ICH or previous stroke		146 (3.2%)	0 (0%)	<0.001
Any ischaemic stroke at any time not meeting the major criterion		965 (20.2%)	0 (0%)	<0.001
Left ventricular ejection fraction, %		50.6±14.9	54.2±12.3	<0.001
eGFR, ml/min/1.73 m^2		62.4±30.1	101±32.3	<0.001
eGFR ≥30, <60 ml/min/1.73 m^2		2,344 (49.0%)	314 (4.3%)	<0.001
eGFR <30 ml/min/1.73 m^2		434 (9.1%)	0 (0%)	<0.001
Haemoglobin, g/dL		12.5±2.0	14.3±1.3	<0.001
Haemoglobin 11.0-12.9 g/dL (males) or 11.0-11.9 g/dL (females)		1,362 (28.5%)	739 (10.1%)	<0.001
Haemoglobin ≤11.0 g/dL		1,095 (22.9%)	0 (0%)	<0.001
Thrombocytes × 10^9/L		226±84.8	228±63.1	<0.001
Thrombocytes <100×10^9/L		155 (3.2%)	0 (0%)	<0.001
Clinical indication for PCI				
Chronic coronary syndrome		2,356 (49.3%)	2,995 (40.8%)	<0.001
Acute coronary syndrome	Unstable angina	209 (4.4%)	380 (5.2%)	<0.001
	Non-ST-elevation myocardial infarction	1,286 (26.9%)	1,731 (23.6%)	
	ST-elevation myocardial infarction	930 (19.5%)	2,234 (30.4%)	
PRECISE-DAPT score		27.6 (11.4)	13.7 (7.4)	<0.001
Medication at discharge				
Aspirin		4,466 (93.4%)	7,187 (97.9%)	<0.001
Clopidogrel		3,449 (72.1%)	3,417 (46.6%)	<0.001
Potent P2Y$_{12}$ (prasugrel or ticagrelor)		1,180 (24.7%)	3,857 (52.5%)	<0.001
Any DAPT		4,413 (92.3%)	7,155 (97.5%)	<0.001
OAC or NOAC		1,271 (26.6%)	0 (0%)	<0.001
Any DAPT and OAC/NOAC		1,079 (22.6%)	0 (0%)	<0.001
NSAIDS		117 (2.5%)	86 (1.2%)	<0.001

Values are n (%) or mean±SD. CABG: coronary artery bypass graft; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; HBR: high bleeding risk; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention

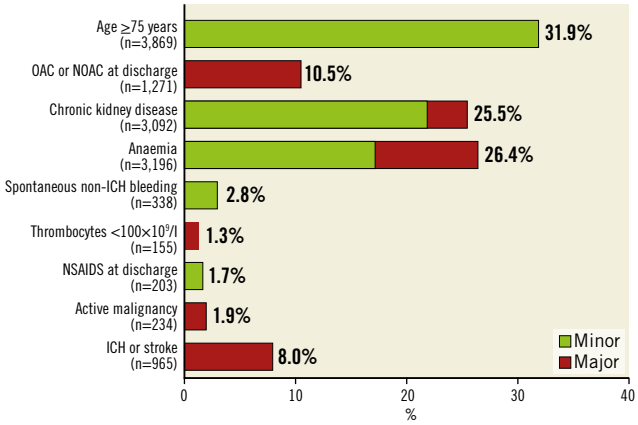
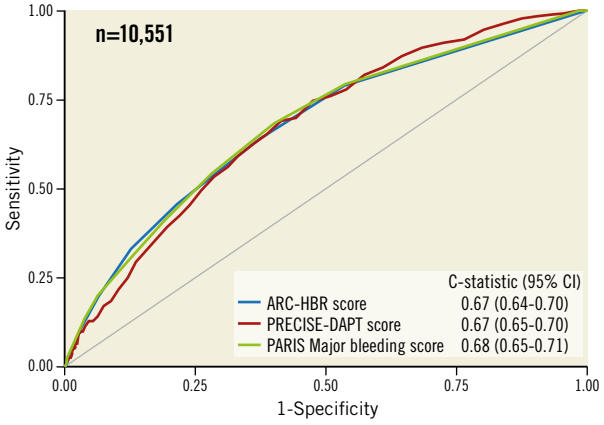


Figure 1. *Distribution of the ARC-HBR criteria. DAPT: dual antiplatelet therapy; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention*

accurate calibration **(Supplementary Figure 2)**. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the ARC-HBR score ≥1 (i.e., equivalent to one major or two minor ARC-HBR criteria) for BARC 3 or 5 bleeding at one year were 68.5%, 61.7%, 6.4%, 98.1%, and 61.9%, respectively. As an explanatory analysis, we compared the diagnostic ability and C-statistics among the ARC-HBR score, PRECISE-DAPT score, and PARIS bleeding score in patients in whom all three scores were available (n=10,551) **(Figure 2)**. The ARC-HBR criteria had higher sensitivity compared with other bleeding risk scores at the cost of lower specificity.



%	Sn	Sp	PPV	NPV	Accuracy
ARC-HBR score (≥1)	63.8	62.7	5.6	98.0	62.8
PRECISE-DAPT score (≥25)	53.1	71.3	6.0	97.8	70.7
PARIS Major bleeding score (≥8)	31.9	86.5	7.6	97.3	84.7

Figure 2. *ROC curves and diagnostic ability of bleeding prediction systems for one-year BARC 3 or 5 bleeding. BARC: Bleeding Academic Research Consortium; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; ROC: receiver operating characteristic; Sn: sensitivity; Sp: specificity*

CLINICAL OUTCOMES

Clinical outcomes at one year are summarised in **Table 2**. Compared to patients without HBR, those at HBR had an increased risk of BARC 3 or 5 bleeding (6.4% vs 1.9%, p<0.001) and DOCE (12.5% vs 6.1%, p<0.001) as well as other secondary endpoints including net adverse composite endpoints, all-cause death, cardiac death, myocardial infarction, target lesion revascularisation, definite stent thrombosis, stroke, and each BARC component. Patients at HBR had an increased risk of BARC 3 or 5 bleeding after considering all-cause death as a competing risk (hazard ratio 3.44, 95% CI: 2.80 to 4.17; p<0.001). There was a gradual risk increase for BARC 3 or 5 bleeding (0, 0.5: 1.9%, 1: 4.6%, and ≥1.5: 7.6%, p<0.001) and DOCE (0, 0.5: 6.1%, 1: 10.6%, and ≥1.5: 13.9%, p<0.001) as a function of the ARC-HBR score **(Figure 3)**. The frequency of BARC 3 or 5 bleeding and DOCE for each ARC-HBR score was: 0: 1.6% and 5.6%, 0.5: 2.9% and 7.4%, 1: 4.6% and 10.6%, 1.5: 4.9% and

Table 2. Event rates at one year.

	HBR (n=4,781)	Non-HBR (n=7,340)	*p*-value
Primary endpoint			
BARC 3 or 5 bleeding	304 (6.4%)	140 (1.9%)	<0.001
Secondary endpoints			
DOCE (cardiac death, TV-MI, TLR)	600 (12.5%)	446 (6.1%)	<0.001
NACE (cardiac death, TV-MI, TLR, BARC 3 or 5 bleeding)	923 (19.3%)	642 (8.8%)	<0.001
All-cause death	529 (11.1%)	120 (1.6%)	<0.001
Cardiac death	330 (6.9%)	92 (1.3%)	<0.001
Myocardial infarction	288 (6.0%)	270 (3.7%)	<0.001
Target vessel myocardial infarction	209 (4.4%)	210 (2.9%)	<0.001
Spontaneous myocardial infarction	156 (3.3%)	126 (1.7%)	<0.001
Any revascularisation	339 (7.1%)	522 (7.1%)	0.497
Target lesion revascularisation	191 (4.0%)	228 (3.1%)	0.002
Target vessel revascularisation	247 (5.2%)	365 (5.0%)	0.272
Non-target vessel revascularisation	148 (3.1%)	272 (3.7%)	0.209

	HBR (n=4,781)	Non-HBR (n=7,340)	*p*-value
Secondary endpoints			
Stent thrombosis (definite)	68 (1.4%)	67 (0.9%)	0.007
Acute (≤24 hours)	27 (0.6%)	29 (0.4%)	0.181
Subacute (>24 hours to 30 days)	20 (0.4%)	25 (0.3%)	0.460
Late (>30 days to 1 year)	21 (0.4%)	13 (0.2%)	0.006
Stroke	105 (2.2%)	50 (0.7%)	<0.001
Any bleeding	413 (8.6%)	229 (3.1%)	<0.001
BARC (2, 3, 5) bleeding	409 (8.6%)	219 (3.0%)	<0.001
BARC (2) bleeding	138 (3.0%)	93 (1.3%)	<0.001
BARC (3) bleeding	285 (6.2%)	135 (1.8%)	<0.001
BARC (4) bleeding	6 (0.1%)	12 (0.2%)	0.646
BARC (5) bleeding	19 (0.4%)	5 (0.1%)	<0.001

Values are n (%). BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoints; NACE: net adverse composite endpoints; TLR: target lesion revascularisation; TV-MI: target vessel myocardial infarction

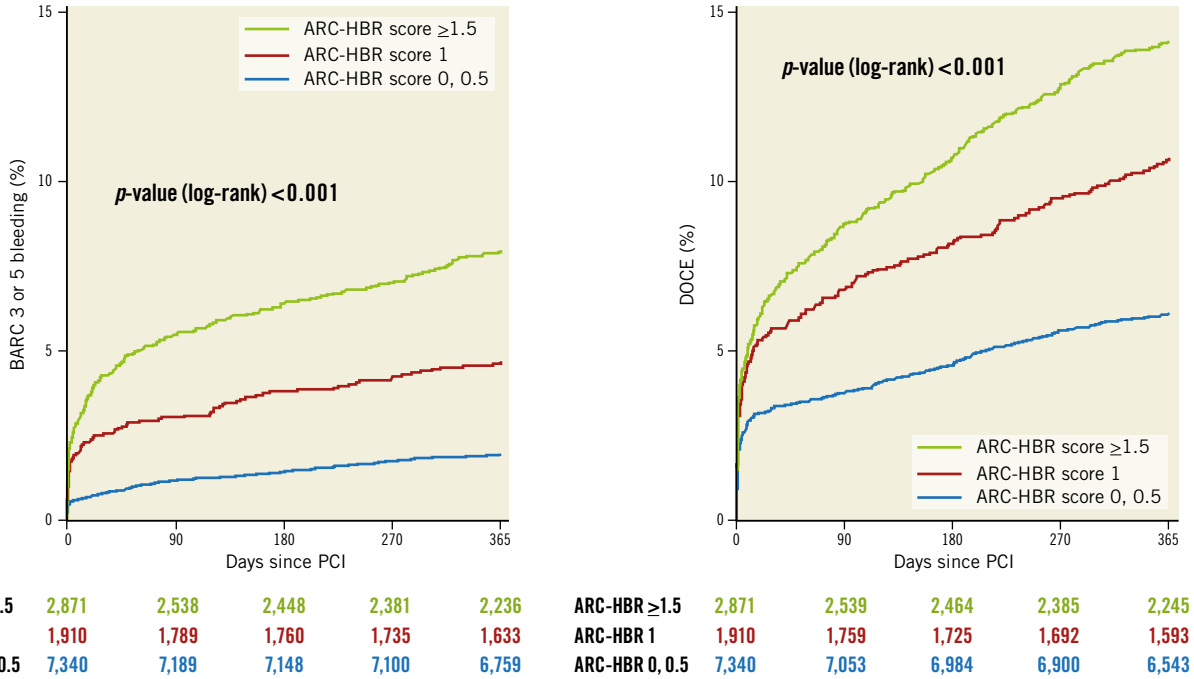


Figure 3. *Kaplan-Meier cumulative event curves for BARC 3 or 5 bleeding and DOCE at one year stratified by the ARC-HBR score. BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoints; PCI: percutaneous coronary intervention*

13.0%, 2: 8.5% and 13.2%, 2.5: 9.0% and 13.6%, ≥3: 10.9% and 17.9%, respectively **(Figure 4)**. Each ARC-HBR criterion except for NSAIDS at discharge was associated with a BARC 3 or 5 bleeding risk of ≥4% **(Figure 5)**, while the bleeding risk associated with an ARC-HBR score of 0.5 or 1 was dependent on the individual criteria of the score **(Table 3)**.

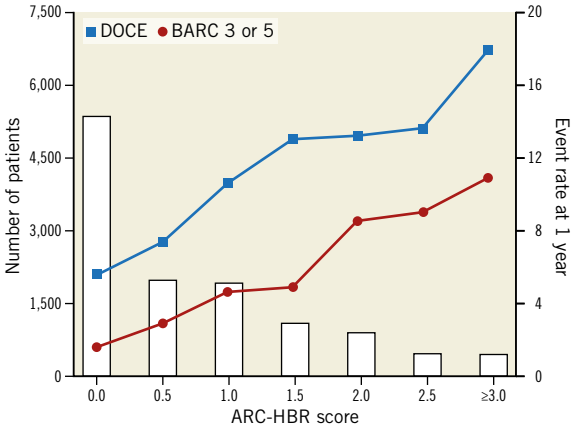


Figure 4. *Event rates according to the ARC-HBR score. BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoints*

Table 3. BARC 3 or 5 bleeding rates in patients with an ARC-HBR score 1 and 0.5.

Criteria		BARC 3 or 5 bleeding
ARC-HBR score=1 (n=1,910)		
Major criteria	OAC or NOAC at discharge (n=284)	7 (2.5%)
	CKD (major) (n=13)	2 (15.4%)
	Anaemia (major) (n=151)	12 (8.0%)
	Spontaneous non-ICH bleeding (n=52)	1 (1.9%)
	Thrombocytes <100×10^9/l (n=16)	3 (18.8%)
	Active malignancy within past 12 months (n=40)	3 (7.5%)
	ICH or stroke (n=243)	7 (2.9%)
Combination of minor criteria	Age ≥75 years+CKD (minor) (n=750)	38 (5.1%)
	Age ≥75 years+anaemia (minor) (n=213)	8 (3.8%)
	Age ≥75 years+NSAIDS at discharge (n=15)	0 (0%)
	CKD (minor)+anaemia (minor) (n=106)	6 (5.7%)
	CKD (minor)+NSAIDS at discharge (n=6)	0 (0%)
	Anaemia (minor)+NSAIDS at discharge (n=21)	0 (0%)
ARC-HBR score=0.5 (n=1,982)		
Minor criteria	Age ≥75 years (n=843)	27 (3.2%)
	CKD (minor) (n=314)	15 (4.8%)
	Anaemia (minor) (n=739)	15 (2.0%)
	NSAIDS at discharge (n=86)	0 (0%)

Values are n (%). BARC: Bleeding Academic Research Consortium; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; DOCE: device-oriented composite endpoints; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention

COX REGRESSION ANALYSIS

The unadjusted and adjusted risks of individual components of the ARC-HBR criteria for BARC 3 or 5 bleeding and DOCE at one year are presented in **Table 4** and **Supplementary Table 4**, respectively. An oral anticoagulant (OAC) or novel oral anticoagulant (NOAC) at discharge and prior spontaneous non-ICH bleeding emerged as independent predictors for BARC 3 or 5 bleeding at one year, while CKD and anaemia were associated with both BARC 3 or 5 bleeding and DOCE.

Discussion

The implementation of bleeding avoidance strategies is considered relevant as bleeding contributes substantially to adverse outcomes including mortality[1,2]. Guidelines support the use of bleeding risk scores (class IIb, level A) to predict bleeding and potentially tailor antithrombotic therapies. However, these scores depend on the characteristics of patients included in the derivation cohort and are not necessarily applicable to routine clinical practice. The ARC-HBR criteria represent a new and pragmatic consensus-based approach to predict bleeding. Our study aimed to evaluate in detail the ARC-HBR criteria using an unselected PCI population consecutively enrolled at a large tertiary care centre.

Patients at HBR according to the ARC-HBR criteria were frequent (≈40%). The criteria including age ≥75 years, CKD, anaemia, oral anticoagulation, and previous ICH or stroke were frequently observed in the real-world PCI population, in line with inclusion criteria applied in previous HBR studies[7,9], while prior spontaneous non-ICH bleeding, thrombocytopaenia, NSAIDS, and active malignancy were relatively rare.

Patients at HBR had a higher risk (6.4%) of bleeding at one year as defined by BARC 3 or 5, exceeding the anticipated threshold of 4.0%. The rate of BARC 3 or 5 bleeding of 1.9% at one year in patients without HBR was comparable with results obtained from previous DAPT trials (i.e., <3.0%) with systematic exclusion of HBR patients[10]. It is noteworthy that patients fulfilling one minor criterion carried a twofold higher bleeding risk as compared with patients without HBR (2.9% vs 1.6%). Further studies should investigate whether "intermediate-risk" patients (i.e., one minor criterion) and "truly low-risk" (i.e., no criterion) should be treated equally in terms of DAPT intensity and duration.

Although the bleeding risk increased proportionally with increasing number of ARC-HBR criteria, importantly the degree of risk and prognostic value varied considerably among the ARC-HBR criteria. In the ARC-HBR consensus document, a major criterion is defined as any criterion that, in isolation, confers a BARC 3 or 5 bleeding risk of ≥4% at one year, and a minor criterion is defined as any criterion that, in isolation, confers increased bleeding risk with a BARC 3 or 5 bleeding rate of <4% at one year[10]. Although this analysis includes only a limited number of patients with each criterion being present in isolation, not all criteria met the expectation of predicting a BARC 3 or 5 bleeding risk ≥4% (major) or <4% (minor). Patients who fulfilled only "anticipated long-term use of an oral anticoagulant" (major criterion) had a BARC 3 or 5 bleeding rate of 2.5%,

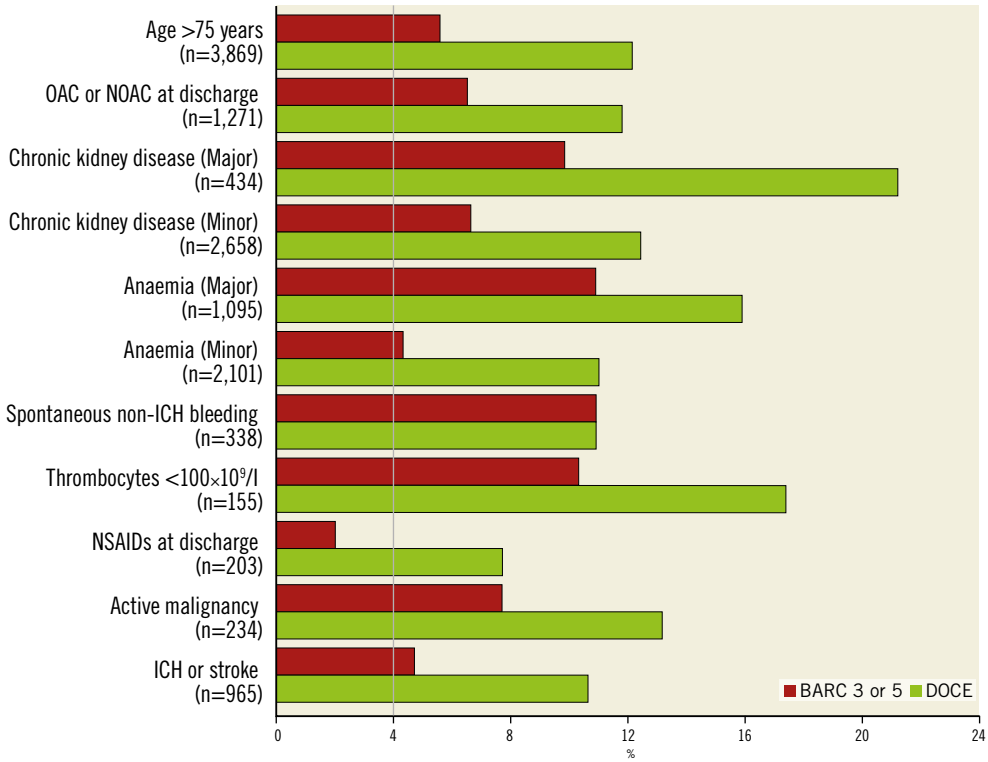


Figure 5. *Event rates at one year according to ARC-HBR criteria. BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; DOCE: device-oriented composite endpoints; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention*

while patients with "eGFR ≥30, <60 ml/min/1.73 m²" (minor criterion) had a bleeding risk of 4.8% at one year. Our data suggest that the bleeding risk associated with an ARC-HBR score 0.5 or 1 was dependent on the individual criteria composing the score. Physicians should note that an individualised approach based on the applied criteria may be needed in patients with an ARC-HBR score 0.5 or 1.

Table 4. Cox analysis for BARC 3 or 5 bleeding.

		Univariate		Multivariate model 1		Multivariate model 2	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age ≥75 years		2.15 (1.79-2.59)	<0.001	1.82 (1.47-2.26)	<0.001	1.20 (0.95-1.53)	0.125
OAC or NOAC at discharge		2.06 (1.62-2.61)	<0.001	2.14 (1.65-2.77)	<0.001	1.87 (1.44-2.43)	<0.001
Chronic kidney disease	eGFR ≥60 ml/min/1.73 m²	reference		reference		reference	
	eGFR ≥30, <60 ml/min/1.73 m²	2.80 (2.29-3.40)	<0.001	2.52 (2.01-3.17)	<0.001	1.82 (1.41-2.36)	<0.001
	eGFR <30 ml/min/1.73 m²	4.47 (3.22-6.19)	<0.001	3.88 (2.70-5.59)	<0.001	1.98 (1.33-2.95)	0.001
Anaemia	≥13.0 g/dL (males) or 12.0 g/dL (females)	reference		reference		reference	
	11.0-12.9 g/dL (males) or 11.0-11.9 g/dL (females)	1.69 (1.33-2.16)	<0.001	1.58 (1.23-2.04)	<0.001	1.32 (1.02-1.71)	0.036
	≤11.0 g/dL	4.60 (3.69-5.74)	<0.001	3.89 (3.04-4.97)	<0.001	2.64 (2.01-3.47)	<0.001
Spontaneous non-ICH bleeding		3.33 (2.38-4.66)	<0.001	2.94 (2.07-4.19)	<0.001	1.89 (1.31-2.73)	0.001
Thrombocytes <100×10⁹/l		3.30 (2.00-5.43)	<0.001	2.62 (1.47-4.66)	0.001	1.53 (0.85-2.75)	0.154
NSAIDS at discharge		0.53 (0.20-1.41)	0.202	0.42 (0.14-1.31)	0.136	0.47 (0.15-1.47)	0.197
Active malignancy within past 12 months		2.31 (1.44-3.70)	0.001	2.20 (1.35-3.59)	0.001	1.49 (0.90-2.42)	0.127
ICH or stroke		1.32 (0.97-1.80)	0.074	1.16 (0.83-1.61)	0.382	0.96 (0.69-1.33)	0.785

Of the study patients, 96.4% (11,689/12,121) were entered into the multivariable model for BARC 3 or 5 bleeding. In model 1, each criterion was adjusted by the following variables. In model 2, each criterion was adjusted by the following variables and all components of the ARC-HBR criteria. Variables: female gender, body mass index, current smoker, hypertension, peripheral artery disease, acute coronary syndrome, potent $P2Y_{12}$ at discharge. BARC: Bleeding Academic Research Consortium; CI: confidence interval; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ICH: intracranial haemorrhage; NOAC: novel oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention

Consistent with previous analyses[16], HBR patients incurred an increased risk not only of bleeding but also of multiple ischaemic events including cardiac death, myocardial infarction and stent thrombosis. HBR patients had more frequent risk factors correlating with atherosclerotic disease burden such as diabetes mellitus and previous revascularisation, explaining in part the excess in ischaemic events. The dilemmatic dual impact of certain clinical characteristics such as renal failure was consistent with one of our previous analyses on the same cohort[16] as well as previous studies[6,17]. Although many operators are still reluctant to use newer-generation DES in HBR patients, there was only a small difference between groups in this cohort (92.0% vs 94.3%), which may not be applied as an explanation for an increased risk of ischaemic events. Patients categorised as HBR may represent a frailer population, a characteristic that was not specifically assessed in the Bern PCI Registry, i.e., a notion supported by a higher frequency of non-cardiac mortality (4.2% vs 0.3%).

The ARC-HBR criteria categorised approximately 40% of an unselected PCI population as HBR, while fewer patients were identified as HBR by other bleeding risk scores. Specifically, 26.9% of patients fulfilled the PRECISE-DAPT score ≥25 and 14.5% fulfilled the PARIS bleeding score ≥8. Accordingly, the ARC-HBR criteria were more sensitive than others (ARC-HBR score ≥1: 63.8% vs PRECISE-DAPT score ≥25: 53.1% vs PARIS bleeding score ≥8: 31.9%) at the cost of specificity (62.7% vs 71.3% vs 86.5%). The C-statistics were comparable among the three bleeding prediction systems. In contrast to the consistently high negative predictive value, a limited positive predictive value represents a common limitation of clinical bleeding prediction tools, although an impact of a relatively low rate of bleeding events on positive predictive value needs to be considered. In light of a limited performance of bleeding prediction systems and the large overlap with ischaemic events in HBR patients, it remains of the utmost importance to conduct randomised controlled trials (RCTs) investigating the impact of score-based treatment strategies.

To date, only one study has attempted to validate the ARC-HBR criteria: it suggested that patients at HBR had a higher bleeding rate and that each individual ARC-HBR criterion was associated with a major bleeding risk >4% at one year[18]. However, the analysis did not include BARC bleeding as endpoints and was carried out in an Asian (Japanese) population. In the present study, we confirmed consistent results with the BARC bleeding definition using a large PCI data set of an European population.

Limitations

First, the single-centre design of this study may limit the generalisability of our findings. Second, four ARC-HBR criteria were not applicable and three needed to be substantially modified due to the data availability in the registry, which might hinder a complete review of criteria and precise estimates of the bleeding risk for each HBR criterion in isolation as well as potential cumulative effects, although missing criteria in the present study appear to be rare. Lastly, DAPT duration and intensity cannot be considered due to the nature of the observational study design. The results need to be interpreted against the background of a routine 12-month DAPT duration determined by operator's discretion in most patients, while bleeding risk associated with oral anticoagulation might be underestimated due to the shortened duration of DAPT in patients with triple therapy (i.e., DAPT and OACs).

Conclusions

Patients at HBR defined by the ARC-HBR criteria were as frequent as 40% and had a higher risk not only of BARC 3 or 5 bleeding but also of ischaemic events. The bleeding risk was proportional to the risk score and related to its individual components. The low positive predictive value of the ARC-HBR criteria for BARC 3 or 5 bleeding remains a notable limitation.

Impact on daily practice

The application of the ARC-HBR criteria to identify BARC 3 or 5 bleeding at one year in patients undergoing PCI carries a high negative but low positive predictive value. The bleeding risk was related to its individual components. Physicians should note that an individualised approach may be needed based on the applied criteria.

Conflict of interest statement

Y. Ueki reports personal fees from Infraredex, outside the submitted work. S. Bär reports grants from Medis medical imaging systems, outside the submitted work. S. Stortecky reports grants from Edwards Lifesciences, Medtronic and Abbott Vascular, grants and personal fees from Boston Scientific, and personal fees from BTG, outside the submitted work. T. Pilgrim reports grants and personal fees from Biotronik and Symetis/Boston Scientific, and grants from Edwards Lifesciences, outside the submitted work. M. Valgimigli reports grants and personal fees from Terumo, Abbott and AstraZeneca, grants from Medicure, personal fees from Chiesi, Bayer, Daiichi Sankyo, Amgen, Alvimedica, and Biosensors, outside the submitted work. S. Windecker reports grants from Abbott, Amgen, Bayer, Boston Scientific, Biotronik, BMS, Edwards Lifesciences, Medtronic, Sinomed, and Polares, outside the submitted work. L. Räber reports grants and personal fees from Abbott Vascular, Biotronik, Sanofi and Regeneron, personal fees from Amgen, AstraZeneca, Bayer, CSL Behring and Occlutech, and grants from HeartFlow, outside the submitted work. The other authors have no conflicts of interest to declare.

References

1. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Yadav M, Francese DP, Palmerini T, Kirtane AJ, Litherland C, Mehran R, Stone GW. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2015;66:1036-45.

2. Baber U, Dangas G, Chandrasekhar J, Sartori S, Steg PG, Cohen DJ, Giustino G, Ariti C, Witzenbichler B, Henry TD, Kini AS, Krucoff MW, Gibson CM, Chieffo A, Moliterno DJ, Weisz G, Colombo A, Pocock S, Mehran R. Time-Dependent Associations Between Actionable Bleeding,

Coronary Thrombotic Events, and Mortality Following Percutaneous Coronary Intervention: Results From the PARIS Registry. *JACC Cardiovasc Interv.* 2016; 9:1349-57.

3. Costa F, Van Klaveren D, Feres F, James S, Raber L, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; PRECISE-DAPT Study Investigators. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. *J Am Coll Cardiol.* 2019;73:741-54.

4. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018;39:213-60.

5. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet.* 2017;389:1025-34.

6. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. *J Am Coll Cardiol.* 2016;67: 2224-34.

7. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iniguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC; LEADERS FREE Investigators. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *N Engl J Med.* 2015;373:2038-47.

8. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrié D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, Helft G, Diaz Fernandez JF, Brugaletta S, Pinar-Bermudez E, Mauri Ferre J, Commeau P, Teiger E, Bogaerts K, Sabate M, Morice MC, Sinnaeve PR; SENIOR investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet.* 2018;391:41-50.

9. Ariotti S, Adamo M, Costa F, Patialiakas A, Briguori C, Thury A, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Ferlini M, Vranckx P, Valgimigli M; ZEUS Investigators. Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?: A Pre-Specified Analysis From the ZEUS Trial. *JACC Cardiovasc Interv.* 2016;9:426-36.

10. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Laschinger J, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice MC. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J.* 2019;40:2632-53.

11. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-619.

12. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J.* 2010;31:2501-55.

13. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011; 123:2736-47.

14. Yeh RW, Kereiakes DJ, Steg PG, Cutlip DE, Croce KJ, Massaro JM, Mauri L; DAPT Study Investigators. Lesion Complexity and Outcomes of Extended Dual Antiplatelet Therapy After Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2017;70:2213-23.

15. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J.* 2015;36:3258-64.

16. Ueki Y, Karagiannis A, Zanchin C, Zanchin T, Stortecky S, Koskinas KC, Siontis GCM, Praz F, Otsuka T, Hunziker L, Heg D, Moschovitis A, Seiler C, Billinger M, Pilgrim T, Valgimigli M, Windecker S, Räber L. Validation of High-Risk Features for Stent-Related Ischemic Events as Endorsed by the 2017 DAPT Guidelines. *JACC Cardiovasc Interv.* 2019;12:820-30.

17. Kwok CS, Tiong D, Pradhan A, Andreou AY, Nolan J, Bertrand OF, Curzen N, Urban P, Myint PK, Zaman AG, Loke YK, Mamas MA. Meta-Analysis of the Prognostic Impact of Anemia in Patients Undergoing Percutaneous Coronary Intervention. *Am J Cardiol.* 2016;118:610-20.

18. Natsuaki M, Morimoto T, Shiomi H, Yamaji K, Watanabe H, Shizuta S, Kato T, Ando K, Nakagawa Y, Furukawa Y, Tada T, Nagao K, Kadota K, Toyofuku M, Kimura T. Application of the Academic Research Consortium High Bleeding Risk Criteria in an All-Comers Registry of Percutaneous Coronary Intervention. *Circ Cardiovasc Interv.* 2019;12:e008307.

Supplementary data

Supplementary Appendix 1. Clinical endpoints and definitions.

Supplementary Appendix 2. Patient follow-up.

Supplementary Figure 1. Overlap of ARC-HBR criteria.

Supplementary Figure 2. Calibration plot of the ARC-HBR score for BARC 3 or 5 bleeding at one year.

Supplementary Table 1. Comparison of definitions between the ARC-HBR criteria and the present study.

Supplementary Table 2. Procedural characteristics.

Supplementary Table 3. Medication at one year.

Supplementary Table 4. Cox analysis for DOCE.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00052

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ORIGINAL ARTICLE
Interventional cardiology

PRECISE-DAPT score for bleeding risk prediction in patients on dual or single antiplatelet regimens: insights from the GLOBAL LEADERS and GLASSY

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Aims The five-item PRECISE-DAPT, integrating age, haemoglobin, white-blood-cell count, creatinine clearance, and prior bleeding, predicts bleeding risk in patients on dual antiplatelet therapy (DAPT) after stent implantation. We sought to assess whether the bleeding risk prediction offered by the PRECISE-DAPT remains valid among patients receiving ticagrelor monotherapy from 1 month onwards after coronary stenting instead of standard DAPT and having or not having centrally adjudicated bleeding endpoints.

Methods and results The PRECISE-DAPT was calculated in 14 928 and 7134 patients from GLOBAL LEADERS and GLASSY trials, respectively. The ability of the score to predict Bleeding Academic Research Consortium 3 or 5 bleeding was assessed and compared among patients on ticagrelor monotherapy (experimental strategy) or standard DAPT (reference strategy) from 1 month after drug-eluting stent implantation. Bleeding endpoints were investigator-reported or centrally adjudicated in GLOBAL LEADERS and GLASSY, respectively. At 2 years, the *c*-indexes for

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the score among patients treated with the experimental or reference strategy were 0.67 [95% confidence interval (CI): 0.63–0.71] vs. 0.63 (95% CI: 0.59–0.67) in GLOBAL LEADERS ($P = 0.27$), and 0.67 (95% CI: 0.61–0.73) vs. 0.66 (95% CI: 0.61–0.72) in GLASSY ($P = 0.88$). Decision curve analysis showed net benefit using the PRECISE-DAPT to guide bleeding risk assessment under both treatment strategies. Results were consistent between investigator-reported and adjudicated endpoints and using the simplified four-item PRECISE-DAPT.

Conclusion The PRECISE-DAPT offers a prediction model that proved similarly effective to predict clinically relevant bleeding among patients on ticagrelor monotherapy from 1 month after coronary stenting compared with standard DAPT and appears to be unaffected by the presence or absence of adjudicated bleeding endpoints.

Keywords Dual antiplatelet therapy • Ticagrelor • Aspirin • Bleeding • Percutaneous coronary intervention

Introduction

Dual antiplatelet therapy (DAPT) reduces the risk of stent-related and spontaneous ischaemic events in patients undergoing percutaneous coronary intervention (PCI).[1–4] This benefit comes with an increased risk of bleeding, which can offset the ischaemic benefit and adversely impact prognosis.[3,4] Therefore, the assessment of bleeding risk after PCI is crucial to guide clinicians' decisions with respect to antiplatelet therapies.[1,5] The PRECISE-DAPT is a five-item score that has been developed to predict bleeding risk during DAPT[6] and was endorsed by a Class IIB recommendation to identify high bleeding risk patients (i.e. score ≥25), in whom the benefits of shorter DAPT (i.e. 3–6 months) can outweigh the risks of extended treatment duration.[1,7] Since its generation, the performance of the score has been tested in contemporary PCI cohorts treated with standard DAPT consisting of aspirin plus a P2Y12 inhibitor (i.e. 6–12 months) followed by aspirin monotherapy.[8–10] Recently, several trials have challenged current DAPT paradigm and provided evidence that early discontinuation of aspirin followed by the continuation of potent P2Y12 inhibitors is able to reduce overall bleeding risks without an apparent trade-off in efficacy.[11–14] Whether PRECISE-DAPT score retains consistent bleeding risk prediction capability in patients receiving potent P2Y12 inhibitor monotherapy is unclear. Moreover, no study so far has assessed whether the PRECISE-DAPT performance might be affected by the presence or absence of centrally adjudicated bleeding endpoints, which carries relevant implications for practice.

The GLOBAL LEADERS trial[11] and its Adjudication Sub-Study (GLASSY)[15] randomized patients to receive 1-month DAPT followed by 23-month ticagrelor monotherapy or 12-month DAPT followed by aspirin alone after new-generation drug-eluting stenting.

We sought to assess the performance of PRECISE-DAPT score to predict bleeding risk in patients receiving either ticagrelor 90 mg twice daily monotherapy from 1 month after PCI or standard DAPT in the setting of GLOBAL LEADERS, based on investigator-reported endpoints, and GLASSY, based on centrally adjudicated endpoints.

Methods

Study design and participants

GLOBAL LEADERS (NCT01813435) is a multicenter randomized trial investigating two antiplatelet strategies in all-comer patients receiving drug-eluting stent for acute coronary syndromes (ACS) or stable coronary artery disease (CAD).[11] After coronary angiography, 15 991 patients were randomized (1:1) using a web-based-system stratified by centre and clinical presentation. The experimental strategy consisted of 1-month DAPT (aspirin 75–100 mg plus ticagrelor 90 mg b.i.d.) followed by 23-month ticagrelor 90 mg b.i.d. monotherapy. The reference strategy consisted of standard 12-month DAPT (aspirin 75–100 mg plus clopidogrel 75 mg if stable CAD or ticagrelor 90 mg b.i.d. if ACS) followed by aspirin alone for 12 months.

GLASSY (NCT03231059) is a sub-study of the GLOBAL LEADERS including adjudicated events from all 7585 patients enrolled at the 20 highest recruiting sites, whereby investigator-reported events and triggered potential unreported events were centrally adjudicated by an independent Clinical Events Committee (CEC) blinded to treatment groups.[15]

All participants provided written informed consent. The protocols were approved by ethic committees of participating institutions.

PRECISE-DAPT score calculation

The PRECISE-DAPT is a five-item bleeding risk score, which has been generated for the prediction of thrombosis in myocardial infarction (TIMI) out-of-hospital bleeding in patients on DAPT using age, creatinine clearance, white-blood-cell count, haemoglobin, and history of bleeding at baseline.[6] The PRECISE-DAPT has the potential to inform clinicians' decision with respect to the optimal DAPT duration post PCI, selecting high bleeding risk patients (score ≥25) for a shorter treatment (i.e. 3–6 months) and non-high-risk patients for prolonged treatment (i.e. ≥12 months). A simplified four-item version of the score, lacking white-blood-cells count, has also been developed and validated.[16] In the present analysis, PRECISE-DAPT was calculated and assigned to each participant as in the development cohort. The simplified four-item version of the score was also computed.[6] All data for score calculations were prospectively collected.

Study endpoints

The primary endpoint was bleeding type 3 or 5 defined according to the Bleeding Academic Research Consortium (BARC) scale,[17] which was investigator-reported in GLOBAL LEADERS and CEC-adjudicated in GLASSY. The primary endpoint was analysed in the overall populations and separately in the experimental and control groups, and across 2 years or with landmark at 1 year.

Statistical analysis

The PRECISE-DAPT score was calculated using data collected at index PCI. Patients were stratified into four groups according to study treatment and PRECISE-DAPT (≥25 vs. <25). Continuous variables are expressed as mean (standard deviation) or median (interquartile range),

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and categorical variables as numbers and percentages. Differences were calculated using *t*-test and Wilcoxon test for continuous data and χ^2 or Fisher's tests for categorical data. Kaplan–Meier method was used to estimate cumulative event rates and log-rank test to examine differences across score strata. The association between the primary endpoint and risk categories was calculated as hazard ratios (HR), considering very-low risk patients as reference. Discrimination was assessed using Harrell's *c*-statistic, and compared through treatment strategies using a nonparametric test. Calibration was assessed by Grønnesby–Borgan χ^2 test and plotted as observed vs. predicted outcomes using Arjas plots. Continuous relation between the risk (as HR) and incidence of BARC 3 or 5 bleeding at follow-up and PRECISE-DAPT was assessed using restricted cubic splines. Net clinical benefit was determined by means of decision curve analyses.[18] All analyses were performed at 2 years and with landmark at 1 year. A two-sided $P < 0.05$ was considered statistically significant. Analyses were performed using STATA 16.1 (Stata Corp., College Station, TX, USA).

Results

Study patients

Of the 15 991 and 7585 patients enrolled in GLOBAL LEADERS and GLASSY, the PRECISE-DAPT was available in 14 928 (93.3%) and 7134 (94.0%), respectively. The mean score was 16.5 ± 8.8 in the parental trial and 16.5 ± 8.7 in the adjudication sub-study, while the median score was 15.0 (interquartile range: 10.0–21.0) in both studies (*Tables 1* and *2*). A total of 2483 (16.6%) patients in GLOBAL LEADERS and 1180 (16.5%) in GLASSY had a PRECISE-DAPT score ≥25. Score distribution was similar in the experimental and control groups (*Figure 1*).

In both studies, baseline characteristics were well balanced between the experimental and control group within PRECISE-DAPT strata (*Tables 1* and *2* and Supplementary material online). Patients with high vs. non-high PRECISE-DAPT differed for the 5 score covariates and were more frequently female, had lower body-mass index and higher rates of cardiovascular risk factors, prior myocardial infarction, coronary revascularization, and stroke; they also received less frequent radial access, single lesion intervention, or direct stenting.

Bleeding risk stratification by PRECISE-DAPT score

The risk of bleeding as estimated by Kaplan–Meier event curves differed significantly according to PRECISE-DAPT score with similar stratification effect for the experimental and reference strategy (*Figure 2*). At 2 years, GLOBAL LEADERS patients with

Table 1 Baseline characteristics of the GLOBAL LEADERS population stratified by PRECISE-DAPT

	PRECISE-DAPT ≥25			PRECISE-DAPT <25			
	Experimental group (*n* = 1248)	Control group (*n* = 1235)	*P*-value	Experimental group (*n* = 6210)	Control group (*n* = 6235)	*P*-Value	*P*-value ≥25 vs. <25
Age (years)	74.9 ± 8.0	75.0 ± 7.9	0.58	62.5 ± 9.5	62.5 ± 9.5	0.93	<0.001
Females	499 (40.0%)	470 (38.1%)	0.34	1261 (20.3%)	1241 (19.9%)	0.57	<0.001
Body mass index (kg/m^2)	28.0 ± 4.5	27.9 ± 4.7	0.59	28.2 ± 4.6	28.3 ± 4.6	0.69	0.001
Diabetes mellitus	465 (37.3%)	432 (35.0%)	0.22	1463 (23.6%)	1446 (23.2%)	0.62	<0.001
Insulin-dependent diabetes mellitus	174 (14.0%)	176 (14.3%)	0.86	389 (6.3%)	402 (6.5%)	0.68	<0.001
Hypertension	1092 (87.6%)	1019 (82.7%)	0.001	4475 (72.3%)	4486 (72.2%)	0.87	<0.001
Hypercholesterolaemia	847 (70.3%)	854 (70.8%)	0.82	4167 (69.5%)	4253 (70.5%)	0.23	0.55
Current smoker	160 (12.8%)	154 (12.5%)	0.80	1776 (28.6%)	1830 (29.4%)	0.36	<0.001
Previous myocardial infarction	309 (24.8%)	332 (27.0%)	0.23	1408 (22.7%)	1450 (23.3%)	0.45	0.002
Previous PCI	433 (34.8%)	461 (37.4%)	0.18	2013 (32.4%)	2008 (32.2%)	0.81	<0.001
Previous coronary artery by-pass graft	107 (8.6%)	127 (10.3%)	0.15	307 (4.9%)	342 (5.5%)	0.18	<0.001
Previous stroke	57 (4.6%)	60 (4.9%)	0.77	142 (2.3%)	138 (2.2%)	0.80	<0.001
Peripheral vascular disease	125 (10.1%)	130 (10.6%)	0.74	324 (5.3%)	365 (5.9%)	0.12	<0.001
Previous major bleeding	43 (3.5%)	47 (3.8%)	0.66	0 (0.0%)	0 (0.0%)	—	<0.001
Impaired renal function	721 (57.8%)	694 (56.2%)	0.44	329 (5.3%)	322 (5.2%)	0.74	<0.001
Chronic obstructive pulmonary disease	104 (8.4%)	103 (8.4%)	1.00	278 (4.5%)	293 (4.7%)	0.54	<0.001
Clinical presentation							
Stable coronary artery disease	619 (49.6%)	637 (51.6%)	0.33	3255 (52.4%)	3255 (52.2%)	0.81	0.11
Acute coronary syndrome	629 (50.4%)	598 (48.4%)	0.33	2955 (47.6%)	2980 (47.8%)	0.81	0.11
Unstable angina	161 (12.9%)	148 (12.0%)	0.50	813 (13.1%)	842 (13.5%)	0.50	0.25
Non-STEMI	272 (21.8%)	301 (24.4%)	0.12	1329 (21.4%)	1323 (21.2%)	0.81	0.05
STEMI	196 (15.7%)	149 (12.1%)	0.009	813 (13.1%)	815 (13.1%)	0.97	0.28
PRECISE-DAPT							
Mean score	31.4 ± 6.6	31.0 ± 6.3	0.11	13.6 ± 5.8	13.6 ± 5.8	0.96	
Median score	29.0 (27.0–34.0)	29.0 (27.0–33.0)	0.28	14.0 (9.0–18.0)	14.0 (9.0–18.0)	0.95	

Sample sizes (*n*), counts (%), means (±standard deviations), or medians (25–75% interquartile range).
PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

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Table 2 Baseline characteristics of the GLASSY population stratified by PRECISE-DAPT

	PRECISE-DAPT score ≥25			PRECISE-DAPT score <25			
	Experimental group (*n* = 607)	Control group (*n* = 573)	*P*-Value	Experimental group (*n* = 2956)	Control group (*n* = 2998)	*P*-Value	*P*-Value ≥25 vs. <25
Age (years)	75.5 ± 7.7	75.9 ± 7.6	0.48	62.8 ± 9.4	62.7 ± 9.5	0.62	<0.001
Females	256 (42.2%)	225 (39.3%)	0.31	606 (20.5%)	603 (20.1%)	0.72	<0.001
Body mass index (kg/m^2)	27.8 ± 4.3	27.5 ± 4.4	0.32	28.0 ± 4.6	28.0 ± 4.5	0.75	0.02
Diabetes mellitus	213 (35.1%)	195 (34.0%)	0.71	656 (22.2%)	663 (22.1%)	0.95	<0.001
Insulin-dependent diabetes mellitus	80 (13.2%)	75 (13.1%)	1.00	166 (5.6%)	175 (5.8%)	0.73	<0.001
Hypertension	525 (86.5%)	473 (82.5%)	0.06	2117 (71.6%)	2146 (71.6%)	1.00	<0.001
Hypercholesterolaemia	397 (65.4%)	379 (66.1%)	0.89	1897 (64.2%)	2002 (66.8%)	0.02	0.72
Current smoker	96 (15.8%)	83 (14.5%)	0.57	932 (31.5%)	962 (32.1%)	0.65	<0.001
Previous myocardial infarction	149 (24.5%)	165 (28.8%)	0.09	666 (22.5%)	683 (22.8%)	0.85	0.004
Previous PCI	204 (33.6%)	234 (40.8%)	0.01	950 (32.1%)	984 (32.8%)	0.58	0.002
Previous coronary artery by-pass graft	39 (6.4%)	55 (9.6%)	0.05	154 (5.2%)	170 (5.7%)	0.45	0.001
Previous stroke	33 (5.4%)	25 (4.4%)	0.42	62 (2.1%)	66 (2.2%)	0.79	<0.001
Peripheral vascular disease	79 (13.0%)	74 (12.9%)	1.00	165 (5.6%)	207 (6.9%)	0.03	<0.001
Previous major bleeding	25 (4.1%)	18 (3.1%)	0.43	0 (0.0%)	0 (0.0%)	–	<0.001
Impaired renal function	349 (57.5%)	315 (55.0%)	0.41	142 (4.8%)	152 (5.1%)	0.67	<0.001
Chronic obstructive pulmonary disease	53 (8.7%)	56 (9.8%)	0.61	136 (4.6%)	139 (4.6%)	0.95	<0.001
Clinical presentation							
Stable coronary artery disease	260 (42.8%)	268 (46.8%)	0.17	1449 (49.0%)	1488 (49.6%)	0.64	0.004
Acute coronary syndrome	347 (57.2%)	305 (53.2%)	0.17	1507 (51.0%)	1510 (50.4%)	0.64	0.004
Unstable angina	83 (13.7%)	67 (11.7%)	0.33	392 (13.3%)	418 (13.9%)	0.45	0.42
Non-STEMI	138 (22.7%)	148 (25.8%)	0.22	588 (19.9%)	559 (18.6%)	0.22	<0.001
STEMI	126 (20.8%)	90 (15.7%)	0.02	527 (17.8%)	533 (17.8%)	0.97	0.67
PRECISE-DAPT							
Mean score	31.3 ± 6.7	30.6 ± 5.9	0.68	13.6 ± 5.7	13.6 ± 5.8	0.65	
Median score	29.0 (26.0–34.0)	29.0 (26.0–33.0)	0.27	14.0 (9.0–18.0)	14.0 (9.0–18.0)	0.69	

Sample sizes (*n*), counts (%), means (±standard deviations), or medians (25–75% interquartile range).
PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

PRECISE-DAPT ≥25 had significantly increased risk of BARC 3 or 5 bleeding in both the experimental group [HR: 4.37; 95% confidence interval (CI): 2.64–7.23; $P < 0.001$] and control group (HR: 3.81; 95% CI: 2.30–6.30; $P < 0.001$) compared with the reference (score ≤10). In GLASSY, patients with high PRECISE-DAPT showed an HR of 4.71 in the experimental group (95% CI: 2.44–9.07; $P < 0.001$) and of 3.39 in the control group (95% CI: 1.78–6.57; $P < 0.001$). Results were consistent in the overall study populations (Supplementary material online, *Figure S1*).

The PRECISE-DAPT showed a continuous association with the risk (in terms of HR) as well as the incidence of BARC 3 or 5 bleeding at 1 and 2 years, which was consistent between the experimental and control groups (*Figure 3* and Supplementary material online, *Figures S2 and S3*).

PRECISE-DAPT performance for bleeding prediction

PRECISE-DAPT was effective to predict BARC 3 or 5 bleeding in patients receiving either the experimental or reference strategy (*Tables* 3 and 4 and Supplementary material online, *Figures S4 and S5*).

In GLOBAL LEADERS, the score showed moderate discrimination with *c*-index of 0.67 (95% CI: 0.63–0.71) in the experimental group vs. 0.63 (95% CI: 0.59–0.67) in the control group at 2 years ($P = 0.27$). In GLASSY, the *c*-index was 0.67 (95% CI: 0.61–0.73) in the experimental group and 0.66 (95% CI: 0.61–0.72) in the control group ($P = 0.88$). The score was moderately calibrated in both treatment strategies, although the predicted and observed probability approximated more closely in GLOBAL LEADERS than GLASSY.

Results were consistent at landmark analysis. In GLOBAL LEADERS, *c*-index estimates during the first and second year of follow-up were 0.68 and 0.64 in the experimental group, and 0.62 and 0.66 in the control group, respectively. Similarly, in GLASSY, *c*-index values before and after the 1-year landmark were 0.69 and 0.61 in the experimental arm, and 0.64 and 0.75 in the control arm (*Tables 3* and 4 and Supplementary material online, *Figure S5*).

Discriminative ability of the four-item PRECISE-DAPT was similar to the score including white-blood-cell count and consistent with respect to randomized treatment strategies, although this score iteration appeared less well calibrated (*Tables 3* and 4 and Supplementary material online, *Figure S6*).

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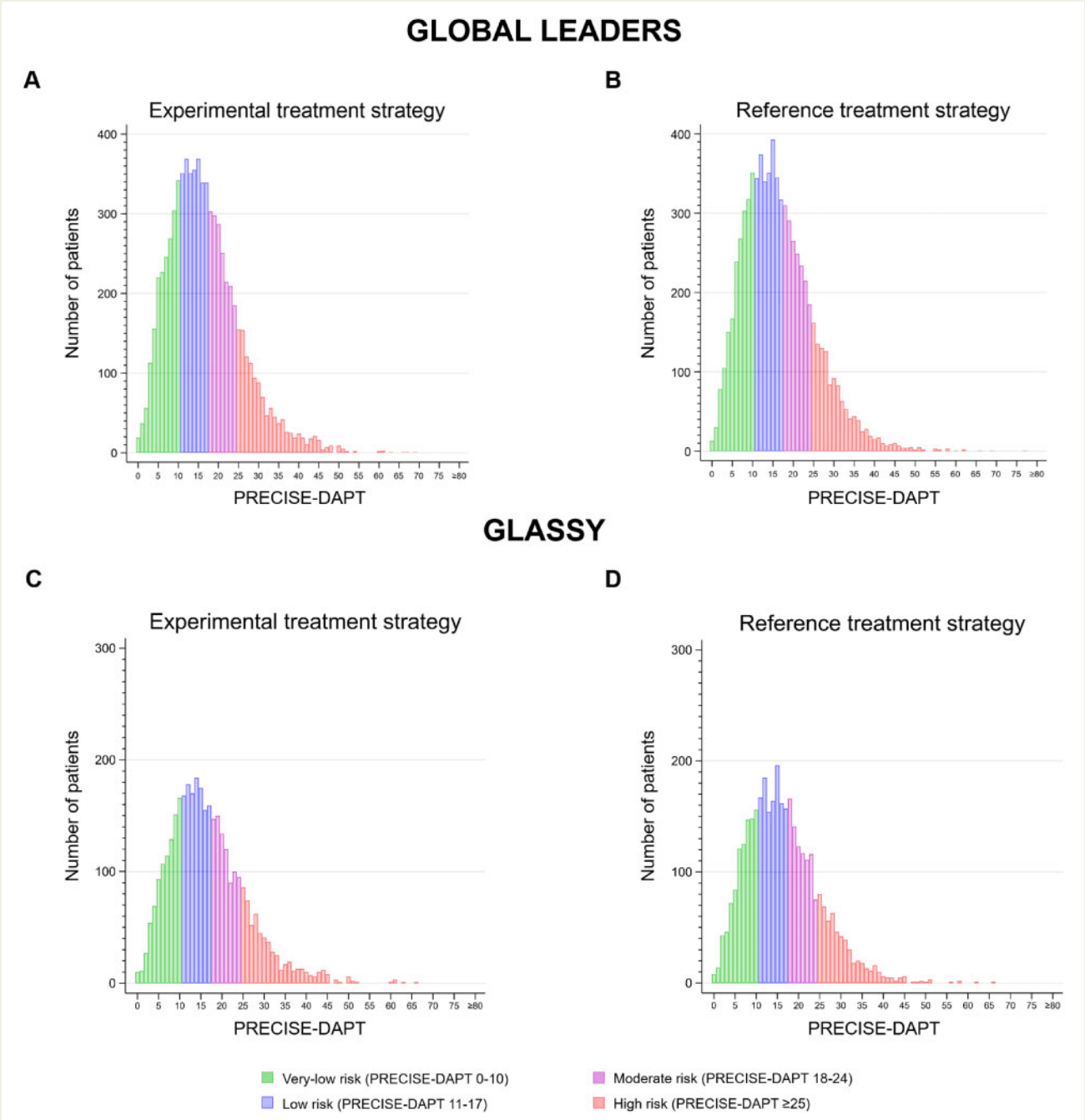


Figure 1 PRECISE-DAPT score distribution in GLOBAL LEADERS and GLASSY according to the treatment strategy. Experimental and control groups in GLOBAL LEADERS (*A* and *B*) and GLASSY (*C* and *D*).

Net clinical benefit

Figure 4 compares the decision curves to classify individuals using PRECISE-DAPT and its four-item version assuming that all patients will bleed (i.e., all are at high risk of bleeding) or that no patient will bleed (i.e., all are at low risk of bleeding). For BARC 3 or 5 bleeding, decision curves showed that both scores were superior to the scenario of 'not using scores' for risk thresholds from 1% to 8% in all study groups (*Figure 2* and Supplementary material online, *Figure S4*). For instance, in the experimental group of GLOBAL LEADERS, applying a risk threshold of 3% for BARC 3 or 5 events, the use of PRECISE-DAPT would result in a net benefit gain of +0.27% (+0.32% for the four-item score) and of +1.12% (1.17% for the four-item score) compared with the scenario of 'assuming all as high-risk' (Supplementary material online, *Table S3*). In other words, the net benefit of using the PRECISE-DAPT score leads to 37.3 (39 for the four-item score) and 9 (10.6 for the four-item score) more

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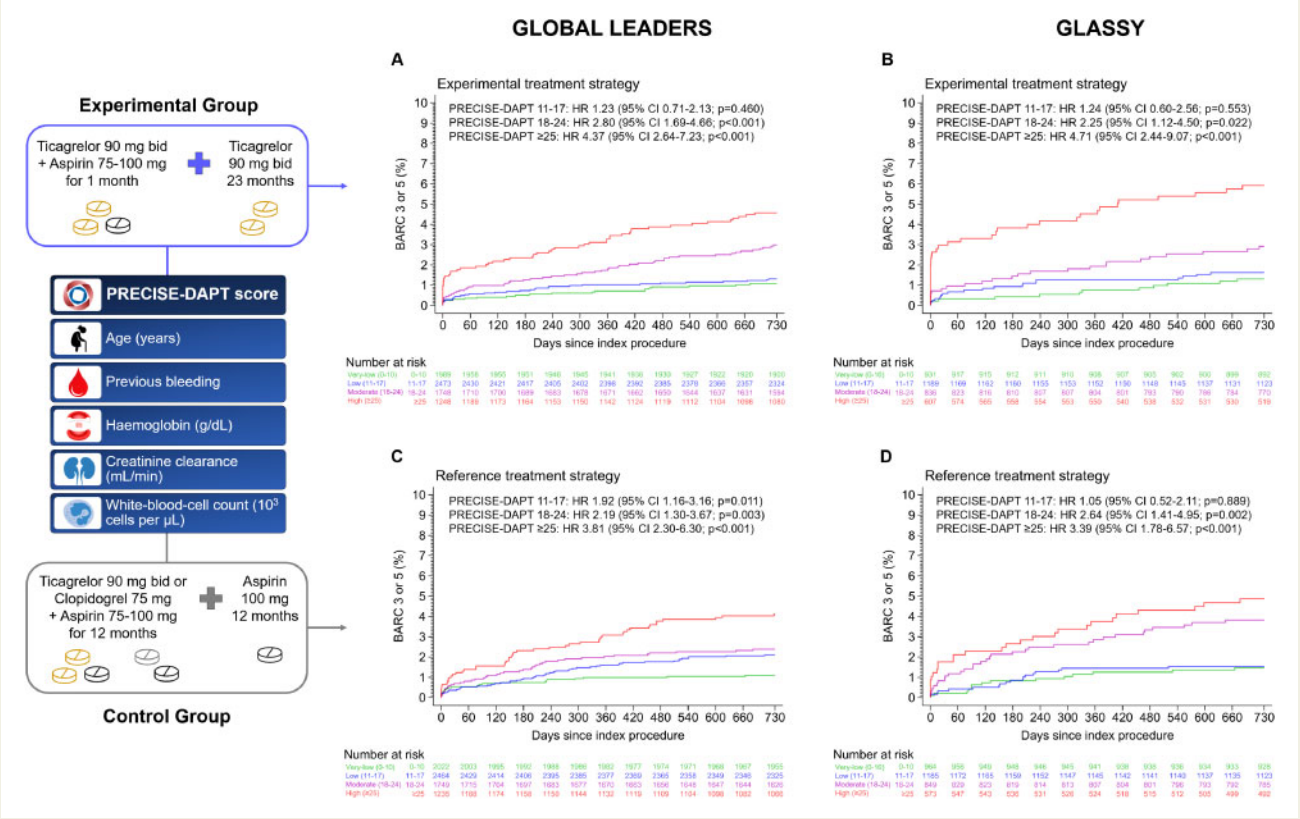


Figure 2 BARC 3 or 5 bleeding at 2 years in GLOBAL LEADERS and GLASSY stratified by PRECISE-DAPT score. Kaplan–Meier event curves for BARC 3 or 5 bleeding at 2 years. Experimental and control groups in GLOBAL LEADERS (*A* and *C*) and GLASSY (*B* and *D*). BARC, Bleeding Academic Research Consortium Criteria; HR, hazard ratio.

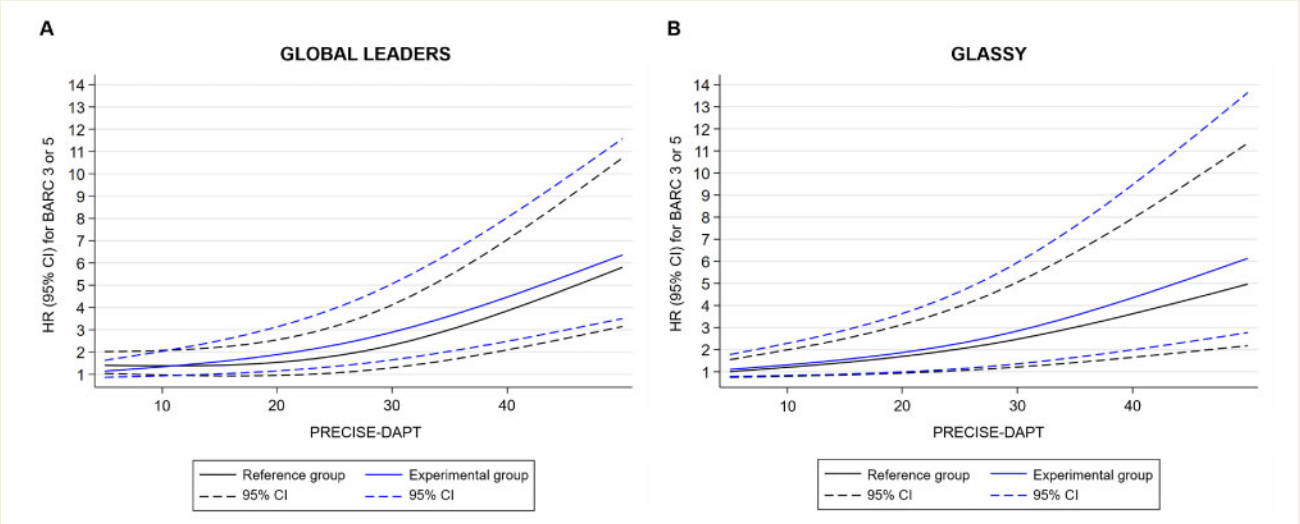


Figure 3 Spline functions of BARC 3 or 5 bleeding risk at 2 years according to PRECISE-DAPT. Experimental and control groups in GLOBAL LEADERS (*A*) and GLASSY (*B*). BARC, Bleeding Academic Research Consortium Criteria; CI, confidence interval; HR, hazard ratio.

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Table 3 Harrell's c-indexes and goodness-of-fit for BARC 3 or 5 bleeding in GLOBAL LEADERS

	Overall				Experimental group				Control group				
	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	P-Value c-Index Experimental vs. control
At 1 year													
PRECISE-DAPT	244/14 928	0.65 (0.61–0.68)	2.3	0.79	113/7458	0.68 (0.63–0.73)	1.5	0.91	131/7470	0.62 (0.58–0.67)	2.6	0.75	0.27
Four-item PRECISE-DAPT		0.63 (0.60–0.67)	10.2	0.07		0.68 (0.62–0.73)	9.8	0.08		0.60 (0.55–0.65)	5.2	0.39	0.14
At 2 years													
PRECISE-DAPT	322/14 928	0.65 (0.62–0.68)	2.7	0.75	159/7458	0.67 (0.63–0.71)	2.3	0.81	163/7470	0.63 (0.59–0.67)	2.8	0.73	0.27
Four-item PRECISE-DAPT		0.65 (0.61–0.67)	7.8	0.16		0.68 (0.64–0.72)	11	0.05		0.61 (0.57–0.65)	5.2	0.39	0.14
Landmark 1–2 years													
PRECISE-DAPT	78/14 302	0.65 (0.59–0.71)	1.2	0.94	46/7145	0.64 (0.56–0.72)	2.5	0.77	32/7157	0.66 (0.57–0.76)	2.6	0.75	0.83
Four-item PRECISE-DAPT		0.67 (0.62–0.73)	4.5	0.48		0.69 (0.61–0.76)	3.2	0.67		0.66 (0.57–0.75)	13.6	0.01	0.74

BARC, Bleeding Academic Research Consortium; CI, confidence interval.

Table 4 Harrell's c-indexes and goodness-of-fit for BARC 3 or 5 bleeding in GLASSY

	Overall				Experimental group				Control group				
	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	BARC 3 or 5/n. patients	c-Index (95% CI)	Grønnesby–Borgan LR χ^2	P-Value	P-Value c-Index Experimental vs. control
At 1 year													
PRECISE-DAPT	140/7134	0.66 (0.62–0.71)	4.3	0.51	66/3563	0.69 (0.62–0.75)	5.1	0.40	74/3571	0.64 (0.58–0.71)	6.5	0.26	0.50
Four-item PRECISE-DAPT		0.66 (0.61–0.70)	6.6	0.25		0.70 (0.63–0.76)	5.1	0.40		0.63 (0.57–0.69)	4.7	0.45	0.30
At 2 years													
PRECISE-DAPT	181/7134	0.67 (0.63–0.71)	4.5	0.48	90/3563	0.67 (0.61–0.73)	5.9	0.31	91/3571	0.66 (0.61–0.72)	7.3	0.19	0.88
Four-item PRECISE-DAPT		0.67 (0.63–0.71)	9.5	0.09		0.69 (0.63–0.74)	7.4	0.19		0.65 (0.60–0.71)	5.6	0.34	0.51
Landmark 1–2 years													
PRECISE-DAPT	41/6827	0.67 (0.58–0.76)	5.6	0.34	24/3412	0.61 (0.49–0.73)	3.2	0.66	17/3415	0.75 (0.64–0.87)	2.9	0.71	0.42
Four-item PRECISE-DAPT		0.70 (0.62–0.78)	7.3	0.19		0.66 (0.55–0.77)	5.3	0.37		0.74 (0.62–0.86)	9.3	0.09	0.30

BARC, Bleeding Academic Research Consortium; CI, confidence interval.

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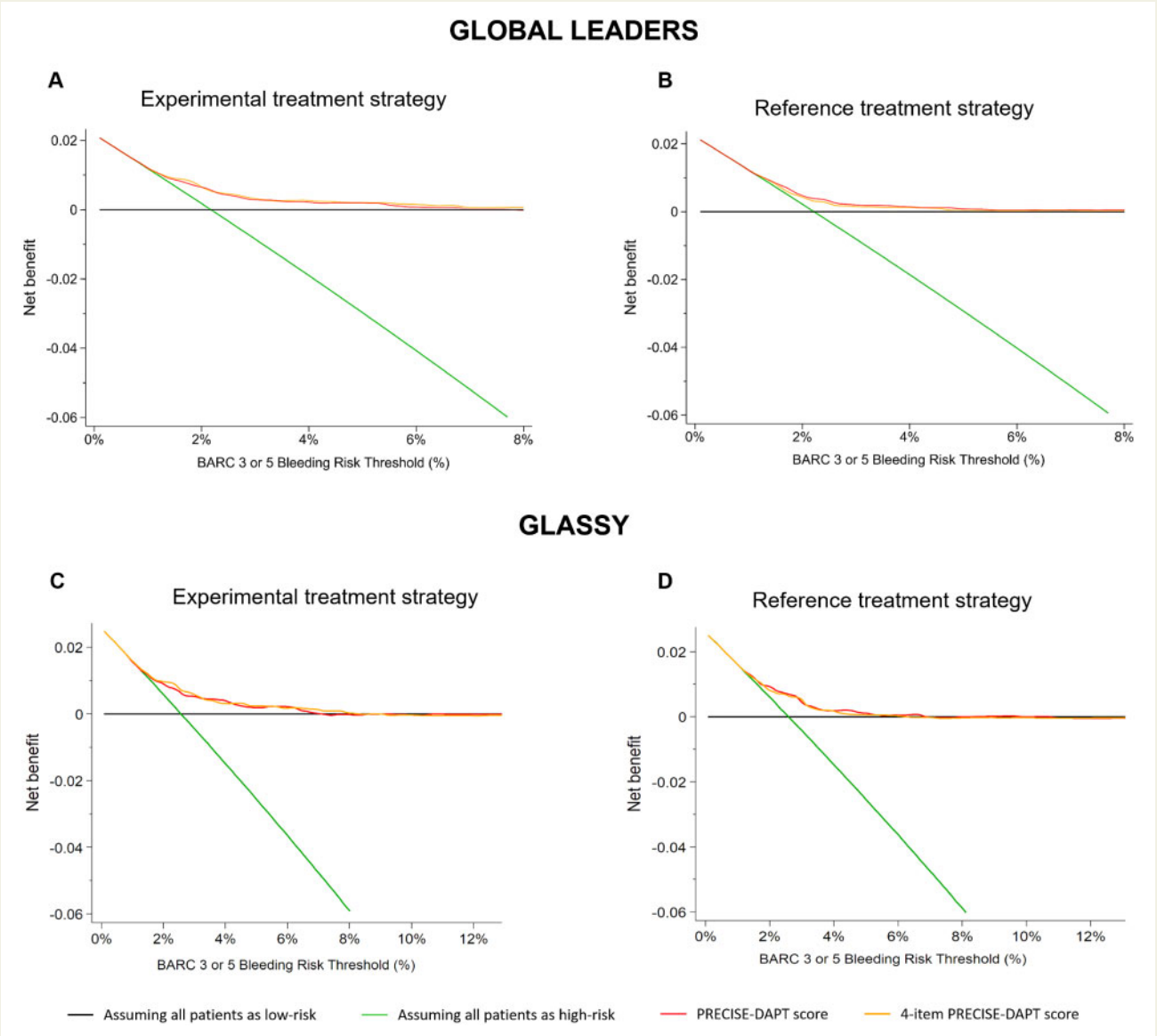


Figure 4 Decision curves showing net benefit of using the PRECISE-DAPT or the four-item PRECISE-DAPT for predicting BARC 3 or 5 bleeding at 2 years. Experimental and control groups in GLOBAL LEADERS (*A* and *B*) and GLASSY (*C* and *D*). Black horizontal line: treat all assuming at low risk of bleeding. Green line: treat all assuming at high-risk of bleeding. Red curve: PRECISE-DAPT. Yellow curve: four-item PRECISE-DAPT. Decision curves are drawn by plotting net benefit (*y*-axis) at different risk thresholds (*x*-axis) to visually estimate and compare the benefit offered by different strategies. BARC, Bleeding Academic Research Consortium Criteria.

true-positive cases per 100 patients without additional false-positives (i.e., 'net' true-positives) compared with 'assuming all as high-risk' and 'assuming all as low-risk', respectively. Additional case examples are reported in Supplementary material online, *Tables S4–S6*.

Discussion

In the current analysis, which included >14 000 participants of the GLOBAL LEADERS trial and its GLASSY sub-study, we evaluated the performance of PRECISE-DAPT score in patients having or not adjudicated bleeding endpoints and treated with ticagrelor plus aspirin for 1 month followed by 23-month ticagrelor monotherapy or standard 12-month DAPT followed by aspirin monotherapy after PCI. The main findings are the following:

- The PRECISE-DAPT score was able to stratify bleeding risk to a similar extent in patients with or without DAPT, consisting of a 12 month combination of aspirin and ticagrelor or aspirin and clopidogrel followed by 12-month aspirin monotherapy or 23-month ticagrelor monotherapy from 1 month after coronary stenting.
- The score provided modest but consistent discrimination and good calibration for the prediction of BARC-defined bleeding in both study arms, with a net benefit compared with the scenario of not using risk scores.

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- The score performance remained consistent for bleeding prediction within the first year, where mainly ticagrelor monotherapy was compared with a DAPT regimen, as well as during the second year, where ticagrelor monotherapy was compared with aspirin monotherapy.
- The score performance remained comparable when investigator-reported bleeding, within GLOBAL LEADERS, or centrally adjudicated bleeding endpoints, within GLASSY, were separately appraised.
- The four-item PRECISE-DAPT score appeared very similar to the five-item iteration, offering a credible option for bleeding risk assessment if white-blood-cell count is not available.

Current guidelines recommend with a class IIB—pending prospective validation—the use of bleeding prediction models to individualize DAPT duration in patients undergoing PCI.[1,6] The PRECISE-DAPT score was developed in a large PCI-treated population receiving standard antiplatelet treatment, typically consisting of DAPT for 6–12 months followed by aspirin alone after P2Y12 inhibitors discontinuation.[3,6] Multiple studies have assessed the score performance showing a consistent ability to predict bleeding among patients receiving standard DAPT.[8–10]

Yet, recent studies have challenged current DAPT paradigm by investigating the potential of early aspirin discontinuation after PCI. The GLOBAL LEADERS[11] and its Adjudication Sub-study GLASSY[15] pioneered this approach and provided reassuring data on the safety and efficacy of ticagrelor monotherapy, but failed to show its superiority over standard DAPT. In the STOPDAPT-2[12] and SMART-CHOICE,[13] P2Y12 monotherapy—principally clopidogrel—after 1 or 3 months of DAPT was associated with a lower incidence of bleeding than 12-month DAPT, without an apparent difference in ischaemic endpoints. The TWILIGHT[14] and TICO[19] trials provided additional support by demonstrating lower bleeding risks with ticagrelor monotherapy (after 3-month DAPT) over conventional treatment while preserving ischaemic efficacy.

Whether the PRECISE-DAPT score retains its potential to reasonably forecast bleeding in patients undergoing treatment with a single antiplatelet agent, including a potent P2Y12 inhibitor or aspirin, remains unclear. In addition, PRECISE-DAPT was generated and externally validated in the context of centrally adjudicated bleeding endpoints, and it remained unclear if its performance might be affected by investigator-reported endpoints.

We showed that PRECISE-DAPT, as well as its four-item simplified version, retains a similar capacity to stratify bleeding risk in PCI patients on ticagrelor monotherapy after 1-month DAPT as among those on standard DAPT. Regardless of the assigned treatment, the higher the score, the higher the risk of clinically relevant bleeding, which increased by a factor of more than two in patients with 18–24 points and more than four-fold in those with ≥25 points. In GLASSY, a PRECISE-DAPT score of 25 conferred a 1-year risk of adjudicated BARC 3 or 5 bleeding that ∼4% at the upper limit of the 95% CI—a threshold that has been recently proposed to select high bleeding risk patients by the Academic Research Consortium for High Bleeding Risk.[5] The lower rate of BARC 3 or 5 events in GLOBAL LEADERS compared with GLASSY might be explained by the under-reporting of clinical events due to the use of investigator-reported vs. centrally adjudicated endpoints, respectively. In addition, the use of PRECISE-DAPT was consistently better than 'not using risk scores' at decision curve analysis, irrespective of the implemented antiplatelet treatment. Indeed, under both treatment strategies, we observed a net benefit in terms of fewer false-positive cases across a wide range of bleeding risk thresholds, in the absence of any potential drawbacks. Of note, despite the pragmatic study design, the proportion of patients with score ≥25 in GLOBAL LEADERS and GLASSY was ∼16% and relatively low compared with previous studies.[6,9]

During ticagrelor monotherapy, similarly to standard DAPT, PRECISE-DAPT was reasonably accurate to distinguish patients who would have bled from those who would have not (discrimination) and predicted the level of risk subsequently observed in reality (calibration). We noticed a slightly better score calibration in the parental trial, while the *c*-index estimates were slightly higher but less precise (in terms of 95% CI) in GLASSY. The evaluation of scores performance requires appropriate sample size of preferably ≥100 events, whereas a lower number of events can negatively affect calibration and (to a lesser extent) *c*-index estimates.[20] GLASSY included about half of patients and events included in the parent trial, and this may reasonably account for the less precise calibration and *c*-index estimates observed in this cohort, with a less apparent effect on the latter.

No other risk score has been so far tested for bleeding risk prediction with ticagrelor monotherapy. Several risk scores have been designed to predict in-hospital or 30-day bleeding (i.e., CRUSADE, ACUITY). At variance from these models, PRECISE-DAPT predicts long-term bleeding risk and therefore appears more suited for patients on ticagrelor monotherapy after a short course of DAPT. The comparative performance of PRECISE-DAPT vs. other bleeding risk scores remains unclear.

We also observed that score performance remained consistent among patients receiving aspirin monotherapy (i.e., reference group during the second year). Though interesting, these data should be interpreted cautiously considering the low number of events in this Subgroup.

Applying the score to GLOBAL LEADERS and GLASSY gave us the opportunity to test the score in the context of investigator-reported or adjudicated bleeding events. Our data showed the ability of PRECISE-DAPT to offer consistent bleeding prediction inside and outside the context of CEC-adjudication, which carries relevant implications for practice.

In the present analysis, PRECISE-DAPT performance was reasonable in both GLOBAL LEADERS and GLASSY (*c*-index of 0.65 and 0.67, respectively), but somewhat lower than that reported in the derivation and PLATO cohorts (*c*-index of 0.73 and 0.70, respectively).[6] The relative performance of the score in different studies can be explained, at least in part, by differences in bleeding definitions and patients' characteristics. At variance with our analysis, which included all post-PCI bleeding graded by BARC scale, the score has been developed to predict out-of-hospital bleeding according to TIMI scale.[6] Noteworthy, when the score had been tested in its derivation cohort to predict all post-PCI bleeding (rather than out-of-hospital events), its discriminative ability for TIMI major or minor occurrences was slightly lower (*c*-index of 0.68) and closer to our estimates. Moreover, when BARC 3 or 5 bleeding has been used as endpoint, the score has shown a *c*-index of 0.69 and 0.65 for post-PCI and

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post-discharge bleeding, respectively, in contemporary PCI registries,[6,10] in line with our findings. A recent study of 904 PCI patients showed a c-index of 0.81 for BARC ≥3a.[8] However, the retrospective design, small sample size, the exclusive inclusion of Asian patients, and much higher than expected BARC ≥3a bleeding (17% at 1 year) potentially limit data generalizability.[8] Higher score performance for predicting BARC 3 or 5 bleeding (c-index of 0.73) has also been reported in 1926 ACS patients.[9] Yet, differences in bleeding characterization (out-of-hospital events assessed through medical records), population's characteristics, and study design can possibly account for these discrepancies [9].

Our study has several limitations. First, this analysis was prespecified, yet the results should be considered hypothesis-generating. Second, the PRECISE-DAPT was not available in ∼6% of patients that were excluded. Third, differences in bleeding definition used as compared with the derivation cohort may have affected the score performance. Finally, ∼20% of GLOBAL LEADERS and GLASSY patients were non-adherent to study treatment. Prior on- vs. off-treatment analyses suggested higher score performance for the former compared with the latter.

Conclusions

The PRECISE-DAPT consistently predicts bleeding risk in patients on ticagrelor monotherapy after 1-month DAPT or on aspirin monotherapy after 12-month DAPT when compared with patients on standard DAPT after drug-eluting stent implantation. Our analysis also suggests that the score performance is unaffected by the presence or absence of adjudicated bleeding endpoints, which carries relevant implications for practice.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–260.
2. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
3. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting. *Circulation* 2012;**125**:2015–2026.
4. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand S-LT, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Lee P, Ver Rinaldi MJ, Massaro JM. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;**371**:2155–2166.
5. Ueki Y, Bär S, Losdat S, Otsuka T, Zanchin C, Zanchin T, Gragnano F, Gargiulo G, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Heg D, Valgimigli M, Windecker S, Räber L. Validation of bleeding risk criteria (ARC-HBR) in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. *Eurointervention* 2020;**16**:371–379.
6. Costa F, Klaveren D, van James S, Heg D, Räber L, Feres F, Pilgrim T, Hong M-KK, Kim H-SS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet

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therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;**389**:1025–1034.
7. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
8. Choi SY, Kim MH, Cho Y-R, Sung Park J, Min Lee K, Park T-H, Yun S-C. Performance of PRECISE-DAPT score for predicting bleeding complication during dual antiplatelet therapy. *Circ Cardiovasc Interv* 2018;**11**:e006837.
9. Abu-Assi E, Raposeiras-Roubin S, Cobas-Paz R, Caneiro-Queija B, Martínez-Reglero C, Rodríguez-Rodríguez JM, Baz A, Íñiguez-Romo A. Assessing the performance of the PRECISE-DAPT and PARIS risk scores for predicting one-year out-of-hospital bleeding in acute coronary syndrome patients. *Eurointervention* 2018;**13**:1914–1922.
10. Bianco M, D'ascenzo F, Raposeiras Roubin S, Kinnaird T, Peyracchia M, Ariza-Solé A, Cerrato E, Manzano-Fernández S, Gravinese C, Templin C, Destefanis P, Velicki L, Luciano A, Xanthopoulou I, Rinaldi M, Rognoni A, Varbella F, Boccuzzi G, Omedè P, Montabone A, Bernardi A, Taha S, Rossini R, Durante A, Gili S, Magnani G, Autelli M, Grosso A, Blanco PF, Giustetto C, Garay A, Quadri G, Queija BC, Srdanovic I, Paz RC, Fernández MC, Pousa IM, Gallo D, Morbiducci U, Dominguez-Rodriguez A, Lopez-Cuenca Á, Cequier A, Alexopoulos D, Iñiguez-Romo A, Pozzi R, Assi EA, Valgimigli M. Comparative external validation of the PRECISE-DAPT and PARIS risk scores in 4424 acute coronary syndrome patients treated with prasugrel or ticagrelor. *Int J Cardiol* 2020;**301**:200–206.
11. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Möllmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018;**392**:940–949.
12. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, Hata Y, Yagi M, Suematsu N, Yokomatsu T, Takamisawa I, Doi M, Noda T, Okayama H, Seino Y, Tada T, Sakamoto H, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Hanaoka KI, Morino Y, Kozuma K, Kadota K, Furukawa Y, Nakagawa Y, Kimura T.; for the STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI. *JAMA* 2019;**321**:2414.
13. Hahn J-Y, Song Y, Bin Oh J-H, Chun WJ, Park YH, Jang WJ, Im E-S, Jeong J-O, Cho BR, Oh SK, Yun KH, Cho D-K, Lee J-Y, Koh Y-Y, Bae J-W, Choi JW, Lee WS, Yoon HJ, Lee SU, Cho JH, Choi WG, Rha S-W, Lee JM, Park TK, Yang JH, Choi J-H, Choi S-H, Lee SH, Gwon H-C; for the SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention. *Jama* 2019;**321**:2428.
14. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Džavík V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han Y-L, Pocock S, Gibson CM. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 2019;**381**:2032–2042.
15. Franzone A, McFadden E, Leonardi S, Piccolo R, Vranckx P, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurakowski A, Diletti R, Dominici M, Huber K, Slagboom T, Buszman P, Bolognese L, Tumscitz C, Bryniarski K, Aminian A, Vrolix M, Petrov I, Garg S, Naber C, Prokopczuk J, Hamm C, Steg PG, Heg D, Jüni P, Windecker S, Valgimigli M. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. *J Am Coll Cardiol* 2019;**74**:2223–2234.
16. Costa F, van Klaveren D, Colombo A, Feres F, Räber L, Pilgrim T, Hong M-K, Kim HS, Windecker S, Steyerberg EW, Valgimigli M. A 4-item PRECISE-DAPT score for dual antiplatelet therapy duration decision-making. *Am Heart J* 2020;**223**:44–47.
17. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials. *Circulation* 2011;**123**:2736–2747.
18. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Mak* 2006;**26**:565–574.
19. Jang Y. Ticagrelor with or without aspirin in acute coronary syndrome after PCI (TICO). *American College of Cardiology Annual Scientific Session*, 2020.
20. Collins GS, Ogundimu EO, Altman DG. size considerations for the external validation of a multivariable prognostic model: a resampling study. *Stat Med* 2016;**35**:214–226.

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The benefit and harm of treating STEMI:
Between ischemia, bleeding, and reperfusion injury.

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The benefit and harm of treating STEMI: Between ischemia, bleeding, and reperfusion injury

Marco Valgimigli[1,2] and Felice Gragnano[1]

Prompt referral for mechanical reperfusion with primary percutaneous coronary intervention (pPCI) is a pivotal step in the current treatment of ST-segment elevation myocardial infarction (STEMI).[1] The 'early open artery theory' has inspired and guided seminal trials and clinical practice over the last 30 years, and its application reduces in-hospital mortality after STEMI from 15% to approximately 3.5%.[2] Yet, what are the next steps to further improve STEMI outcomes? Percutaneous myocardial reperfusion is of unquestionable benefit, yet the ischemic relief provided by this intervention comes with some drawbacks. Bleeding complications related to access site negatively affect short- and long-term outcomes.[3,4] Thus, their risk should be minimised. Moreover, myocardial reperfusion after temporary coronary occlusion injuries the surviving myocardium – the so-called ischemia/reperfusion (I/R) injury – and effective strategies for its assessment and/or prevention lack in practice. Two reports in the *Journal* offer new data on these issues that still hamper the contemporary management of STEMI (Figure 1).

Radial access to reduce bleeding and mortality after STEMI

Using data from more than 44,000 individuals undergoing pPCI from the nationwide SWEDEHEART registry, Dworeck et al.[5] evaluated the effect of radial versus femoral access on in-hospital and 30-day outcomes. The number of radial interventions increased by 35% per year during the study period, rising from 12.3% in 2005 to 85.8% in 2016.[5] At outcome analysis after effective propensity score-adjustment, radial access was independently associated with 30% lower risk of 30-day mortality, and a more than 50% reduction in the risk of clinically relevant in-hospital bleeding and cardiogenic shock.[5] These results from a large unselected STEMI cohort are consistent with those from randomised trials[3,4] and complement available evidence by confirming the benefit of radial access in patients undergoing pPCI in current practice. Given the robustness of data, radial access should remain the default approach,[1] and more efforts should be directed to increase its adoption and ensure proficiency with the procedure. The use of vascular closure devices do not mitigate the risk of femoral complications,[6] and radial access provides benefits which extend beyond access site-related bleeding.[7]

Pentraxin 3 as a novel marker of myocardial reperfusion injury

Pentraxin 3 (PTX3) is an acute-phase inflammatory protein playing a primary role in ischemic cardiac disease by exerting a number of cardio-protective effects.[8] The deficiency of PTX3 increases no-reflow area and exacerbates myocardial I/R injury by enhancing neutrophils infiltration and reactive-oxygen-species production.[8] Butt et al.[9] investigated the kinetic of PTX3 as well as its correlation with inflammatory biomarkers and infarct size in 161 patients undergoing pPCI from the MITOCARE trial. PTX3 showed a steep increase in the early phase of STEMI (first 12 hours after admission) followed by a gradual decrease from 12 to 72 hours, therefore mimicking interleukin-6 and cardiac markers of necrosis, at variance from high-sensitive C-reactive protein (which continuously increased after 72 hours). PTX3 levels at 12 hours showed a significant

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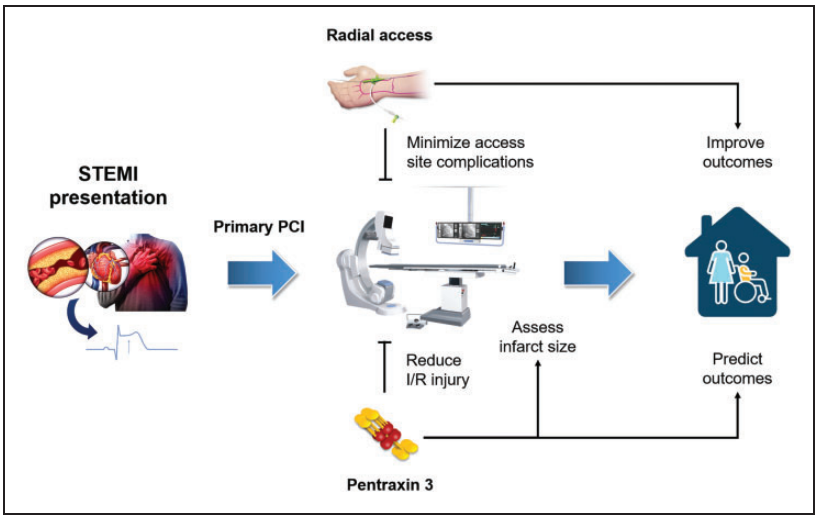


Figure 1. Radial access and pentraxin 3 in the management of STEMI. In patients undergoing pPCI, radial access reduces the risk of bleeding and mortality. Pentraxin 3 is a novel marker of ischemia-reperfusion injury and a candidate target for therapy. I/R: ischemia/reperfusion; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction.

correlation with infarct size (as assessed by troponin and CK-MB), suggesting a possible role for this novel marker in the detection of irreversible myocardial damage and, ultimately, in the prediction of outcomes. PTX3 is also a candidate target for therapies.[8] Exogenous PTX3 showed the potential to attenuate ischemia and I/R injury in myocardial infarction models.[10] Also, by increasing PTX3 levels, subcutaneous transplantation of mesenchymal stem cells showed a protective effect against myocardial I/R injury, mitigating inflammation and promoting cell survival.[11]

Targeting ischemia, bleeding, and reperfusion injury in STEMI

Ischemia, bleeding, and I/R injury shape a paradigmatic triad in STEMI. The time is now to address the continuum of STEMI care through its complexity, focusing on these three interacting factors. Since the relevance of each mechanism is likely to differ among patients, a targeted approach addressing all mechanisms is likely needed to reduce the burden of STEMI in the community.

Conflict of interest

MV received grants/personal fees from Abbott, Chiesi, Bayer, Daiichi Sankyo, Amgen; from Terumo, Alvimedica, Medicure, Astrazeneca, Biosensors, Idorsia, outside the submitted work.

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References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019; 40: 87–165.
2. Braunwald E. The treatment of acute myocardial infarction: the past, the present, and the future. *Eur Heart J Acute Cardiovasc Care* 2012; 1: 9–12.
3. Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet* 2018; 392: 835–848.
4. Dworeck C, Redfors B, Volz S, et al. Radial artery access is associated with lower mortality in patients undergoing primary PCI: a report from the SWEDEHEART registry. *Eur Heart J Acute Cardiovasc Care*, Epub ahead of print 2020.
5. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet* 2011; 377: 1409–1420.
6. Gragnano F, Manavifar N, Gargiulo G, et al. Femoral access with or without vascular closure device or radial access in acute coronary syndrome. *JACC Cardiovasc Interv* 2019; 12: 2116–2118.
7. Andò G, Cortese B, Russo F, et al. Acute kidney injury after radial or femoral access for invasive acute coronary

syndrome management: AKI-MATRIX. *J Am Coll Cardiol* 2017; 69: 2592–2603.
8. Casula M, Montecucco F, Bonaventura A, et al. Update on the role of pentraxin 3 in atherosclerosis and cardiovascular diseases. *Vascul Pharmacol* 2017; 99: 1–12.
8. Butt N, Bache-Mathiesen LK, Ushakova A, et al. Pentraxin 3 in primary percutaneous coronary intervention for ST-elevation myocardial infarction is associated with early irreversible myocardial damage: Kinetic profile, relationship to interleukin 6 and infarct size. *Eur Heart J Acute Cardiovasc Care*, Epub ahead of print 14 May 2020. DOI: 10.1177/2048872620923641.
10. Salio M, Chimenti S, De Angelis N, et al. Cardioprotective function of the long pentraxin PTX3 in acute myocardial infarction. *Circulation* 2008; 117: 1055–1064.
11. Preda MB, Rønningen T, Burlacu A, et al. Remote transplantation of mesenchymal stem cells protects the heart against ischemia-reperfusion injury. *Stem Cells* 2014; 32: 2123–2134.

Part II

Antiplatelet therapy in patients undergoing coronary revascularisation

P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials.

Valgimigli M,* **Gragnano F,*** Branca M, Franzone A, Baber U, Jang Y, Kimura T, Hahn JY, Zhao Q, Windecker S, Gibson CM, Kim BK, Watanabe H, Song YB, Zhu Y, Vranckx P, Mehta S, Hong SJ, Ando K, Gwon HC, Serruys PW, Dangas GD, McFadden EP, Angiolillo DJ, Heg D, Jüni P, Mehran R.

*Valgimigli and Gragnano contributed equally and are co-first authors.

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P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials

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ABSTRACT

OBJECTIVE

To assess the risks and benefits of $P2Y_{12}$ inhibitor monotherapy compared with dual antiplatelet therapy (DAPT) and whether these associations are modified by patients' characteristics.

DESIGN

Individual patient level meta-analysis of randomised controlled trials.

DATA SOURCES

Searches were conducted in Ovid Medline, Embase, and three websites (www.tctmd.com, www.escardio.org, www.acc.org/cardiosourceplus) from inception to 16 July 2020. The primary authors provided individual participant data.

ELIGIBILITY CRITERIA

Randomised controlled trials comparing effects of oral $P2Y_{12}$ monotherapy and DAPT on centrally adjudicated endpoints after coronary revascularisation in patients without an indication for oral anticoagulation.

MAIN OUTCOME MEASURES

The primary outcome was a composite of all cause death, myocardial infarction, and stroke, tested for non-inferiority against a margin of 1.15 for the hazard ratio. The key safety endpoint was Bleeding Academic Research Consortium (BARC) type 3 or type 5 bleeding.

RESULTS

The meta-analysis included data from six trials, including 24 096 patients. The primary outcome occurred in 283 (2.95%) patients with $P2Y_{12}$ inhibitor monotherapy and 315 (3.27%) with DAPT in the per protocol population (hazard ratio 0.93, 95% confidence interval 0.79 to 1.09; P=0.005 for non-inferiority; P=0.38 for superiority; τ^2=0.00) and in 303 (2.94%) with $P2Y_{12}$ inhibitor monotherapy and 338 (3.36%) with DAPT in the intention to treat population (0.90, 0.77 to 1.05; P=0.18 for superiority; τ^2=0.00). The treatment effect was consistent across all subgroups, except for sex (P for interaction=0.02), suggesting that $P2Y_{12}$ inhibitor monotherapy lowers the risk of the primary ischaemic endpoint in women (hazard ratio 0.64, 0.46 to 0.89) but not in men (1.00, 0.83 to 1.19). The risk of bleeding was lower with $P2Y_{12}$ inhibitor monotherapy than with DAPT (97 (0.89%) *v* 197 (1.83%); hazard ratio 0.49, 0.39 to 0.63; P<0.001; τ^2=0.03), which was consistent across subgroups, except for type of $P2Y_{12}$ inhibitor (P for interaction=0.02), suggesting greater benefit when a newer $P2Y_{12}$ inhibitor rather than clopidogrel was part of the DAPT regimen.

CONCLUSIONS

$P2Y_{12}$ inhibitor monotherapy was associated with a similar risk of death, myocardial infarction, or stroke, with evidence that this association may be modified by sex, and a lower bleeding risk compared with DAPT.

REGISTRATION

PROSPERO CRD42020176853.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Aggregate data meta-analyses comparing P2Y12 inhibitor monotherapy with dual antiplatelet therapy (DAPT) in patients undergoing coronary revascularisation have been conducted

They generally showed similar risks of ischaemic events and lower risks of bleeding with P2Y12 inhibitor monotherapy than with DAPT

Previous meta-analyses did not account for the initial DAPT phase, usually common to both experimental and control groups, and almost invariably failed to provide information on subgroups of interest

WHAT THIS STUDY ADDS

P2Y12 inhibitor monotherapy was associated with a similar risk of fatal and ischaemic events and lower rates of major bleeding compared with DAPT

P2Y12 inhibitor monotherapy may be particularly beneficial among female patients, owing to an association with lower cardiovascular mortality

Aspirin cessation from one to three months after coronary revascularisation and continuation with P2Y12 inhibitor monotherapy may be warranted instead of continuation of DAPT, especially in women

Introduction

Inhibition of platelet $P2Y_{12}$ receptor signalling plays a central role in the secondary prevention of cardiac or cerebrovascular thrombotic complications.[1-3] Oral $P2Y_{12}$ inhibitors have mainly been investigated in combination with aspirin after coronary revascularisation.[2-4] In this context, robust evidence shows that dual antiplatelet therapy (DAPT), consisting of aspirin and an oral $P2Y_{12}$ inhibitor, mitigates the incidence of ischaemic events but increases the risk of major bleeding compared with aspirin alone.[1 2] A few studies have assessed oral $P2Y_{12}$ inhibitor monotherapy as an alternative to conventional DAPT.[5-10] However, none was powered to assess whether withdrawal of aspirin and continuation with an

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oral $P2Y_{12}$ inhibitor preserves the treatment effect of the latter in combination with aspirin.[11] Previous aggregate data meta-analyses of oral $P2Y_{12}$ inhibitor monotherapy studies included events occurring during the initial DAPT phase, which was identical in both experimental and control regimens in most studies, and have therefore not conclusively ascertained the risks and benefits of aspirin withdrawal; nor did they explore the consistency of treatment effects across subgroups.[12-14] Therefore, concerns remain that removal of aspirin after a short course of DAPT may, from that moment onwards, be associated with a higher risk of ischaemic events, especially among patients with high risk features.[3] As a reflection of the residual uncertainties about the trade-off between risks and benefits of aspirin withdrawal in this setting, the 2020 European Society of Cardiology guidelines for the management of acute coronary syndromes in patients presenting without ST segment elevation state that discontinuation of aspirin after a three to six month course of DAPT, and continuation with $P2Y_{12}$ inhibitor monotherapy, should be considered depending on the balance between ischaemic risk and bleeding risk.[15] The American Heart Association/American College of Cardiology guidelines have not yet issued a formal recommendation for this treatment option.[1]

We did a systematic review and individual participant data meta-analysis of all randomised trials that compared $P2Y_{12}$ inhibitor monotherapy with DAPT among patients who underwent coronary revascularisation, with a focus on the preservation of the treatment effect after aspirin removal, and investigated its consistency across predefined subgroups.

Methods

We conducted a systematic review and individual participant data meta-analysis to answer the following PICOS question: in patients who have undergone percutaneous or surgical revascularisation for stable or unstable coronary artery disease, is $P2Y_{12}$ inhibitor monotherapy at least similarly effective for a composite of fatal and cardiovascular ischaemic endpoints and, if so, safer for bleeding endpoints, compared with DAPT among randomised trials that reported centrally adjudicated outcome data?

We excluded trials including patients with a concomitant indication for oral anticoagulation under the rationale that concomitant oral anticoagulation further increases the risk of bleeding and mitigates the risk of ischaemic recurrences after aspirin withdrawal, and long term DAPT is no longer considered a valid standard of care in this setting.[16] We implemented no further restrictions for study selection, such as the number of participants or duration of follow-up. Methods and reporting follow the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD).[17] The study protocol was prospectively registered on PROSPERO (international prospective register of systematic reviews) and is available online (www.crd.york.ac.uk/prospero, CRD42020176853).

Search strategy

Two investigators (MV, FG) determined trial eligibility criteria; a third investigator (RM) was involved in case of disagreement. Randomised trials were identified by a search in Ovid Medline, Embase, and three websites (www.tctmd.com, www.escardio.org, www.acc.org/cardiosourceplus). Reference lists of retrieved articles were hand searched. We imposed no language restrictions. The search strategy is provided in the appendix.

Outcome measures

The pre-specified primary efficacy endpoint was the composite of all cause death, myocardial infarction, and stroke throughout the duration of the randomised comparison of protocol mandated $P2Y_{12}$ inhibitor monotherapy versus DAPT. The key safety endpoint was Bleeding Academic Research Consortium (BARC) type 3 or type 5 bleeding.[18] Other secondary endpoints are shown in the appendix. The outcome definitions were largely consistent among the included trials (supplementary methods).

Data extraction and quality assessment

We contacted the principal investigators of the eligible trials, requesting individual participant data to be provided in an anonymised electronic dataset (supplementary methods). We checked data for completeness and consistency and compared them with the results of the original publications. We contacted the principal investigators of the included trials in case of missing data or when queries emerged during the integrity checks. Once queries had been resolved, the clean data were uploaded to the main study dataset. For one trial,[10] 587 (8.2%) patients were excluded from this analysis owing to the lack of approval to share the data from the country's legal and regulatory authorities. Two investigators (MV, FG) independently assessed the quality of included trials by using the Cochrane Collaboration's tool for assessing the risk of bias 2 (supplementary table D).[19] Disagreements were resolved first by discussion and then by consulting a third investigator (RM) for arbitration. Each trial had been approved by its local medical ethics committee, and all patients had provided written informed consent.

Data synthesis

We pre-specified a one step approach to model the data from all trials simultaneously using a mixed effect Cox regression model with baseline hazards stratified by trial and a random intercept to account for variation between trials in treatment effect. Treatment effects were derived as hazard ratios and 95% confidence intervals. We quantified the heterogeneity of the treatment effect between trials by using the variance of the random slope τ^2. Pre-specified sensitivity analyses were based on a two step approach using a DerSimonian-Laird random effects model to combine trial level estimates. We used I^2 to estimate between trial heterogeneity for the two step model.

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All primary analyses were conducted with censoring of events that occurred during the initial DAPT phase, if present, common to both experimental and treatment groups, and included only events occurring after the time when the protocol specified the change from DAPT to $P2Y_{12}$ inhibitor monotherapy in the experimental group. Data were analysed up to the longest available time point with protocol specified $P2Y_{12}$ inhibitor monotherapy in the experimental group and DAPT in the control group.

We first tested the non-inferiority of $P2Y_{12}$ inhibitor monotherapy compared with DAPT on the primary efficacy endpoint at a one sided α of 0.05 and a non-inferiority margin of 1.15 on the hazard ratio scale. Under the rationale that aspirin was omitted in the experimental arm of $P2Y_{12}$ inhibitor monotherapy, while being continued in the DAPT group, we chose this non-inferiority margin because it represents 50% of the treatment effect of aspirin compared with placebo or standard care observed by the Antithrombotic Trialists' Collaboration in patients with previous myocardial infarction for the composite endpoint of vascular death, myocardial infarction, and stroke.[11] If non-inferiority was met, we pre-specified testing of the superiority of $P2Y_{12}$ inhibitor monotherapy at a two sided α of 0.05. We did superiority analyses in the intention to treat population and the non-inferiority analysis in the per protocol population. We reported the one sided P value for non-inferiority only for the primary per protocol analysis; for all remaining analyses, we reported two sided P values for superiority and two sided 95% confidence intervals to allow conventional interpretation of the results. The per protocol population was pre-specified and excluded ineligible patients (that is, those violating inclusion/exclusion criteria) and/or those who never received allocated treatment strategy. We pre-specified a set of subgroup analyses for the primary efficacy endpoint and the key safety endpoint according to age, sex, clinical presentation, diabetes mellitus, history of chronic kidney disease, peripheral artery disease, bleeding risk, complexity of percutaneous coronary intervention, left main or left anterior descending percutaneous intervention, type of revascularisation (percutaneous or surgical), type of $P2Y_{12}$ inhibitor in the comparator and experimental therapies, use of proton pump inhibitor, and geographical region, accompanied by tests of interaction. Further details on data analysis are reported in the appendix.

Patient and public involvement

Patients and public were not directly involved in this individual participant data meta-analysis. However, we acknowledge their contribution in performing included clinical trials and disseminating research findings.

Results

Study selection

We screened 13 240 unique citations. Of these, 820 were judged potentially eligible during screening of titles and abstracts, and six were deemed eligible after full text review (supplementary figure A). We sought and obtained individual participant data for all eligible trials. The appendix describes trial characteristics and patient populations (supplementary tables A and B). The definitions used for outcomes were largely consistent across trials (supplementary table C), and the risk of bias assessment identified some concerns for five of six trials related to the open label allocation of the treatment assignment (supplementary table D). All six studies were sponsored by academic organisations.

We considered 24 096 participants for the primary analysis, of whom 12 037 (50%) were randomly allocated to $P2Y_{12}$ inhibitor monotherapy and 12 059 (50%) to DAPT. We excluded 788 (3.3%) patients owing to premature study termination or death before the time point at which each study protocol specified the implementation of $P2Y_{12}$ inhibitor monotherapy in the experimental group (four trials) or owing to lack of approval to share the data from the Chinese legal and regulatory authorities for 8.2% of the patients recruited in one trial. Therefore, 23 308 patients were available for the intention to treat analysis, including 11 634 (49.9%) patients assigned to P2Y12 inhibitor monotherapy (clopidogrel in 2586 (22.2%), prasugrel in 92 (0.8%), ticagrelor in 8956 (77.0%)) and 11 674 (50.1%) to DAPT (aspirin and clopidogrel 4297 (36.8%), aspirin and prasugrel 140 (1.2%), aspirin and ticagrelor 7237 (62.0%)). A total of 1347 (5.8%) participants were excluded from the per protocol population (supplementary figure B). The median treatment duration was 334 days (range 9-12 months).

Patient characteristics

Baseline clinical characteristics were balanced between groups (table 1 and supplementary table E). The mean age was 65 years, and 5423 (23.3%) patients were female. A total of 7419 (31.8%) patients had a history of diabetes, and 3823 (16.6%) had chronic kidney failure. History of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery was noted in 4438 (19.0%), 6959 (30.3%), and 1250 (5.4%) patients, respectively. At presentation, most patients (13 966; 59.9%) had an acute coronary syndrome. Procedural characteristics are shown in supplementary tables E and F.

Efficacy endpoints

The composite endpoint of all cause death, myocardial infarction, and stroke occurred in 283 (2.95%) patients with $P2Y_{12}$ inhibitor monotherapy and 315 (3.27%) patients with DAPT in the per protocol population, fulfilling non-inferiority (P=0.005 for non-inferiority with one sided α of 5%), but not superiority (hazard ratio 0.93, 95% confidence interval 0.79 to 1.09; P=0.38), with no between trial heterogeneity (τ^2=0.00) (table 2). The same composite endpoint occurred in 303 (2.94%) and 338 (3.36%) patients with $P2Y_{12}$ inhibitor monotherapy and DAPT, respectively, in the intention to treat population (hazard ratio 0.90, 0.77

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Table 1 | Baseline characteristics. Values are numbers (percentages) unless stated otherwise

Characteristics	Primary study population (n=23 308)	$P2Y_{12}$ inhibitor (n=11 634)	Aspirin + $P2Y_{12}$ inhibitor (n=11 674)	Difference (95% CI)	P value
Study ID:					
DACAB	334 (1.4)	166 (1.4)	168 (1.4)	0.0% (−0.3% to 0.3%)	0.95
GLASSY	7509 (32.2)	3753 (32.3)	3756 (32.2)	0.1% (−1.1% to 1.3%)	0.90
SMART-CHOICE	2926 (12.6)	1455 (12.5)	1471 (12.6)	−0.1% (−0.9% to 0.8%)	0.84
STOPDAPT-2	3003 (12.9)	1496 (12.9)	1507 (12.9)	−0.1% (−0.9% to 0.8%)	0.92
TICO	3004 (12.9)	1499 (12.9)	1505 (12.9)	−0.0% (−0.9% to 0.9%)	>0.99
TWILIGHT	6532 (28.0)	3265 (28.1)	3267 (28.0)	0.1% (−1.1% to 1.2%)	0.89
Mean (SD) age, years	64.8 (10.6) (n=23 308)	64.8 (10.6) (n=11 634)	64.9 (10.6) (n=11 674)	−0.1 (−0.3 to 0.2)	0.58
Age ≥65 years	12 194 (52.3)	6094 (52.4)	6100 (52.3)	0.1% (−1.2% to 1.4%)	0.85
Female sex	5423 (23.3)	2717 (23.4)	2706 (23.2)	0.2% (−0.9% to 1.3%)	0.75
Mean (SD) height, m	1.7 (0.1) (n=22 951)	1.7 (0.1) (n=11 455)	1.7 (0.1) (n=11 496)	0.0 (−0.0 to 0.0)	0.32
Mean (SD) weight, kg	76.6 (17.3) (n=22 958)	76.7 (17.3) (n=11 461)	76.5 (17.2) (n=11 497)	0.2 (−0.3 to 0.6)	0.42
Mean (SD) body mass index	26.9 (4.8) (n=22 948)	26.9 (4.8) (n=11 455)	26.9 (4.8) (n=11 493)	0.0 (−0.1 to 0.1)	0.79
Geographical region:					0.99
Asia	10 318 (44.3)	5146 (44.2)	5172 (44.3)	−0.1% (−1.3% to 1.2%)	0.91
North America	2972 (12.8)	1484 (12.8)	1488 (12.7)	0.0% (−0.8% to 0.9%)	0.98
Western Europe	7848 (33.7)	3917 (33.7)	3931 (33.7)	−0.0% (−1.2% to 1.2%)	>0.99
Eastern Europe	2170 (9.3)	1087 (9.3)	1083 (9.3)	0.1% (−0.7% to 0.8%)	0.87
Diabetes mellitus	7419/23 304 (31.8)	3744/11 630 (32.2)	3675/11 674 (31.5)	0.7% (−0.5% to 1.9%)	0.24
Insulin treated diabetes	1543/21 104 (7.3)	746/10 547 (7.1)	797/10 557 (7.5)	−0.5% (−1.2% to 0.2%)	0.18
Current cigarette smoker	6271/23 299 (26.9)	3134/11 630 (26.9)	3137/11 669 (26.9)	0.1% (−1.1% to 1.2%)	0.91
Hypercholesterolaemia	14 695/23 030 (63.8)	7298/11 494 (63.5)	7397/11 536 (64.1)	−0.6% (−1.9% to 0.6%)	0.32
Hypertension	16 005/23 286 (68.7)	7985/11 624 (68.7)	8020/11 662 (68.8)	−0.1% (−1.3% to 1.1%)	0.90
Liver disease	33/20 048 (0.2)	21/10 013 (0.2)	12/10 035 (0.1)	0.1% (−0.0% to 0.2%)	0.11
Peripheral artery disease	1323/20 267 (6.5)	633/10 114 (6.3)	690/10 153 (6.8)	−0.5% (−1.2% to 0.1%)	0.12
Previous myocardial infarction	4438/23 297 (19.0)	221/11 626 (19.1)	2217/11 671 (19.0)	0.1% (−0.9% to 1.1%)	0.83
Previous PCI	6959/22 966 (30.3)	3440/11 464 (30.0)	3519/11 502 (30.6)	−0.6% (−1.8% to 0.6%)	0.33
Previous CABG	1250/23 300 (5.4)	606/11 629 (5.2)	644/11 671 (5.5)	−0.3% (−0.9% to 0.3%)	0.29
Previous stroke	733/23 298 (3.1)	343/11 626 (3.0)	390/11 672 (3.3)	−0.4% (−0.8% to 0.1%)	0.09
Previous bleeding	265/23 291 (1.1)	132/11 623 (1.1)	133/11 668 (1.1)	0.0% (−0.3% to 0.3%)	0.97
History of chronic kidney disease	3823/23 031 (16.6)	1892/11 491 (16.5)	1931/11 540 (16.7)	−0.3% (−1.2% to 0.7%)	0.58
Chronic lung disease	826/17 238 (4.8)	403/8609 (4.7)	423/8629 (4.9)	−0.2% (−0.9% to 0.4%)	0.49
Clinical presentation:	(n=23 305)	(n=11 633)	(n=11 672)		0.53
Chronic coronary syndrome	9339 (40.1)	4685 (40.3)	4654 (39.9)	0.4% (−0.9% to 1.7%)	0.53
Acute coronary syndrome	13 966 (59.9)	6948 (59.7)	7018 (60.1)	−0.4% (−1.7% to 0.9%)	0.53
Unstable angina	5579 (39.9)	2752 (39.6)	2827 (40.3)	−0.7% (−2.3% to 1.0%)	0.41
Non-STEMI	5122 (36.7)	2543 (36.6)	2579 (36.7)	−0.1% (−1.7% to 1.5%)	0.86
STEMI	3265 (23.4)	1653 (23.8)	1612 (23.0)	0.8% (−0.6% to 2.2%)	0.25
Aspirin on admission	13 182/20 301 (64.9)	6581/10 137 (64.9)	6601/10 164 (64.9)	0.0% (−1.3% to 1.3%)	0.97
Mean (SD) PRECISE-DAPT score*	16.7 (9.7) (n=22 018)	16.7 (9.6) (n=10 972)	16.8 (9.7) (n=11 046)	−0.1 (−0.3 to 0.2)	0.55
PRECISE-DAPT score ≥25	3928/22 018 (17.8)	1941/10 972 (17.7)	1987/11 046 (18.0)	−0.3% (−1.3% to 0.7%)	0.56
Median (IQR) creatinine clearance (MDRD), mL/min	84.4 (70.0-100.0) (n=22 961)	84.7 (70.1-100.2) (n=11 455)	84.2 (69.7-99.8) (n=11 506)	0.2 (−2.2 to 2.6)	0.19
Mean (SD) haemoglobin, g/dL	19.8 (27.3) (n=22 639)	19.8 (26.9) (n=11 295)	19.9 (27.6) (n=11 344)	−0.1 (−0.8 to 0.6)	0.74
Mean (SD) LVEF, %	56.4 (11.1) (n=13 742)	56.3 (11.0) (n=6851)	56.4 (11.2) (n=6891)	−0.1 (−0.5 to 0.3)	0.64

ACS=acute coronary syndrome; CABG=coronary artery bypass grafting; CCS=chronic coronary syndrome; LVEF=left ventricular ejection fraction; MDRD=Modification of Diet in Renal Disease; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction.
*Includes five items: age, creatinine clearance, white blood cell count, haemoglobin, and history of bleeding.

to 1.05; P=0.18), with no between trial heterogeneity (τ^2=0.00) (table 2; fig 1).

$P2Y_{12}$ inhibitor monotherapy was not associated with a lower risk of all cause death (0.98% with monotherapy versus 1.40% with DAPT; hazard ratio 0.80, 0.62 to 1.03), but the risk of cardiovascular death was lower with $P2Y_{12}$ inhibitor monotherapy (0.57% *v* 0.90%; 0.69, 0.50 to 0.95), with no between trial heterogeneity (τ^2=0.00). The risks of myocardial infarction (1.64% with monotherapy versus 1.79% with DAPT; hazard ratio 0.93, 0.75 to 1.14), stroke (0.51% *v* 0.41%; 1.10, 0.73 to 1.64), definite stent thrombosis (0.24% *v* 0.28%; 0.85, 0.48 to 1.50), and definite or probable stent thrombosis (0.27% *v* 0.34%; 0.81, 0.49 to 1.37) did not differ (table 2).

The treatment effect for the primary ischaemic endpoint was consistent across most of the pre-defined subgroups, in both intention to treat and per protocol analyses (fig 2). We observed a treatment-by-subgroup interaction with sex (P for interaction=0.02), suggesting that $P2Y_{12}$ inhibitor monotherapy lowers the risk of the primary ischaemic endpoint in women (hazard ratio 0.64, 0.46 to 0.89) but not in men (1.00, 0.83 to 1.19) (fig 2). This corresponded to a number needed to treat to benefit of 72 (95% confidence interval 42 to 250) in women but no benefit in men. These findings remained consistent in the per protocol analysis (supplementary figure C). When the components of the primary efficacy endpoint were stratified by sex, a treatment-by-sex interaction existed

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Table 2 | Clinical outcomes in intention to treat and per protocol populations. Values are number of events/number of patients at risk (% cumulative incidence) unless stated otherwise

	Intention to treat population					Per protocol population				
Outcome	$P2Y_{12}$ inhibitor (n=11 634)	Aspirin + $P2Y_{12}$ inhibitor (n=11 674)	Hazard ratio (95% CI)	τ^2	P value	$P2Y_{12}$ inhibitor (n=10 766)	Aspirin + $P2Y_{12}$ inhibitor (n=11 195)	Hazard ratio (95% CI)	τ^2	P value
Death, MI, or stroke*	303 (2.94)	338 (3.36)	0.90 (0.77 to 1.05)	0.00	0.18	283 (2.95)	315 (3.27)	0.93 (0.79 to 1.09)	0.00	0.38
Death or MI	259 (2.49)	299 (3.0)	0.87 (0.74 to 1.03)	0.00	0.10	245 (2.53)	287 (2.99)	0.88 (0.74 to 1.05)	0.00	0.15
Death:										
All cause	107 (0.98)	137 (1.40)	0.80 (0.62 to 1.03)	0.00	0.08	107 (1.05)	128 (1.36)	0.88 (0.68 to 1.15)	0.01	0.35
Cardiovascular	61 (0.57)	90 (0.90)	0.69 (0.50 to 0.95)	0.00	0.03	61 (0.61)	83 (0.86)	0.77 (0.56 to 1.08)	0.00	0.13
Non-cardiovascular	42 (0.38)	42 (0.46)	1.03 (0.67 to 1.58)	0.15	0.89	42 (0.40)	41 (0.46)	1.10 (0.71 to 1.70)	0.19	0.66
MI	167 (1.64)	181 (1.79)	0.93 (0.75 to 1.14)	0.01	0.47	153 (1.61)	177 (1.81)	0.89 (0.72 to 1.10)	0.01	0.28
Stroke:										
Any	51 (0.51)	45 (0.41)	1.10 (0.73 to 1.64)	0.09	0.65	45 (0.48)	34 (0.32)	1.32 (0.84 to 2.08)	0.00	0.22
Ischaemic	38 (0.39)	36 (0.33)	1.01 (0.63 to 1.60)	0.07	0.98	35 (0.39)	27 (0.26)	1.27 (0.76 to 2.11)	0.00	0.35
Haemorrhagic	6 (0.05)	2 (0.02)	2.53 (0.49 to 13.0)	0.00	0.26	5 (0.05)	2 (0.02)	2.21 (0.40 to 12.09)	0.00	0.36
Stent thrombosis:										
Definite	23 (0.24)	26 (0.28)	0.85 (0.48 to 1.50)	0.00	0.56	17 (0.20)	25 (0.28)	0.72 (0.38 to 1.33)	0.00	0.29
Probable	6 (0.05)	7 (0.06)	0.72 (0.23 to 2.26)	0.00	0.57	4 (0.04)	7 (0.06)	0.51 (0.13 to 2.06)	0.00	0.34
Possible	27 (0.26)	48 (0.52)	0.56 (0.35 to 0.90)	0.00	0.02	27 (0.28)	47 (0.53)	0.59 (0.37 to 0.94)	0.00	0.03
Definite or probable	27 (0.27)	32 (0.34)	0.81 (0.49 to 1.37)	0.00	0.43	21 (0.23)	31 (0.34)	0.68 (0.38 to 1.19)	0.00	0.17
Any	52 (0.52)	79 (0.85)	0.65 (0.46 to 0.92)	0.00	0.02	47 (0.51)	77 (0.86)	0.61 (0.42 to 0.88)	0.00	0.008
BARC bleeding:										
2, 3, or 5	295 (2.91)	493 (4.76)	0.59 (0.51 to 0.69)	0.00	<0.001	277 (2.93)	475 (4.76)	0.60 (0.52 to 0.70)	0.00	<0.001
3 or 5	97 (0.89)	197 (1.83)	0.49 (0.39 to 0.63)	0.03	<0.001	91 (0.90)	176 (1.71)	0.53 (0.41 to 0.69)	0.03	<0.001
5	3 (0.03)	5 (0.06)	0.67 (0.11 to 4.02)	0.00	0.66	3 (0.04)	5 (0.06)	0.69 (0.11 to 4.12)	0.00	0.68
TIMI bleeding:										
Major	44 (0.45)	93 (0.94)	0.47 (0.33 to 0.68)	0.29	<0.001	44 (0.48)	82 (0.87)	0.55 (0.38 to 0.79)	0.20	0.001
Minor	136 (1.43)	242 (2.4)	0.56 (0.45 to 0.69)	0.00	<0.001	132 (1.48)	230 (2.37)	0.57 (0.46 to 0.71)	0.00	<0.001
Major or minor	179 (1.88)	331 (3.33)	0.53 (0.45 to 0.64)	0.04	<0.001	175 (1.96)	309 (3.25)	0.56 (0.47 to 0.68)	0.04	<0.001
NACE	384 (3.69)	504 (4.94)	0.76 (0.67 to 0.87)	0.02	<0.001	359 (3.71)	460 (4.71)	0.81 (0.70 to 0.93)	0.01	0.002

BARC=Bleeding Academy Research Consortium; MI=myocardial infarction; NACE=net adverse clinical events, defined as composite of all cause death, myocardial infarction, stroke, and BARC type 3 or type 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.
*P value for non-inferiority=0.005 in per protocol population; non-inferiority testing was performed on one sided α of 5% corresponding to 90% CIs; other P values are two sided for superiority; 95% CIs are shown.

for all cause death (P for interaction=0.02) attributable to cardiovascular death (P for interaction=0.02), which was markedly reduced among women (hazard ratio 0.31, 0.15 to 0.65) but not men (0.86, 0.59 to 1.25) with $P2Y_{12}$ inhibitor monotherapy (fig 3). The treatment effects for the primary efficacy endpoint or its components were consistent with respect to clopidogrel or newer $P2Y_{12}$ inhibitors, consisting of mainly ticagrelor, in the experimental arm (fig 4). In an analysis restricted to trials with monotherapy with newer $P2Y_{12}$ inhibitors, the effect of monotherapy was consistent across subgroups except for sex (P for interaction=0.02) (supplementary figure D). In an analysis restricted to trials with monotherapy with clopidogrel, the effect of monotherapy was consistent across all subgroups (supplementary figure E).

Safety endpoints

We found strong evidence for a reduction in the risk of BARC type 3 or type 5 bleeding among patients randomly allocated to $P2Y_{12}$ inhibitor monotherapy compared with DAPT (0.89% *v* 1.83%; hazard ratio 0.49, 0.39 to 0.63; P<0.001; τ^2=0.03), for a number needed to treat to benefit of 111 (77 to 200) over a median treatment duration of 334 days (table 2; fig 5). The treatment effect was consistent across pre-defined subgroups (supplementary figure F), with the exception of a treatment-by-subgroup interaction for type of $P2Y_{12}$ inhibitor in the control group (hazard ratio 0.77 (0.50 to 1.18) for clopidogrel and 0.41 (0.30 to 0.55) for newer $P2Y_{12}$ inhibitors; P for interaction=0.02) (supplementary figure F). The use of a newer $P2Y_{12}$ inhibitor was associated with treatment-by-subgroup interactions for clinical presentation (acute versus chronic coronary syndrome) and type of $P2Y_{12}$ inhibitor in the control group (supplementary figure G). Clopidogrel monotherapy provided consistent treatment effects across pre-defined subgroups (supplementary figure H). The rates of other bleeding endpoints or net adverse clinical events were reduced with $P2Y_{12}$ inhibitor monotherapy (table 2).

Pre-specified sensitivity analyses

Sensitivity analyses including the initial DAPT phase after randomisation, which was identical in both treatment groups in four trials, yielded no difference for the composite ischaemic endpoint, with attenuated absolute and relative bleeding benefits with $P2Y_{12}$ inhibitor monotherapy (supplementary table H). Additional sensitivity analyses excluding patients who experienced non-fatal ischaemic events (supplementary tables I and J), bleeding events (supplementary tables K and L), or any of these events (supplementary table M) during the initial DAPT phase provided consistent findings. All cause death occurred in 144 (0.98%) patients with $P2Y_{12}$ inhibitor

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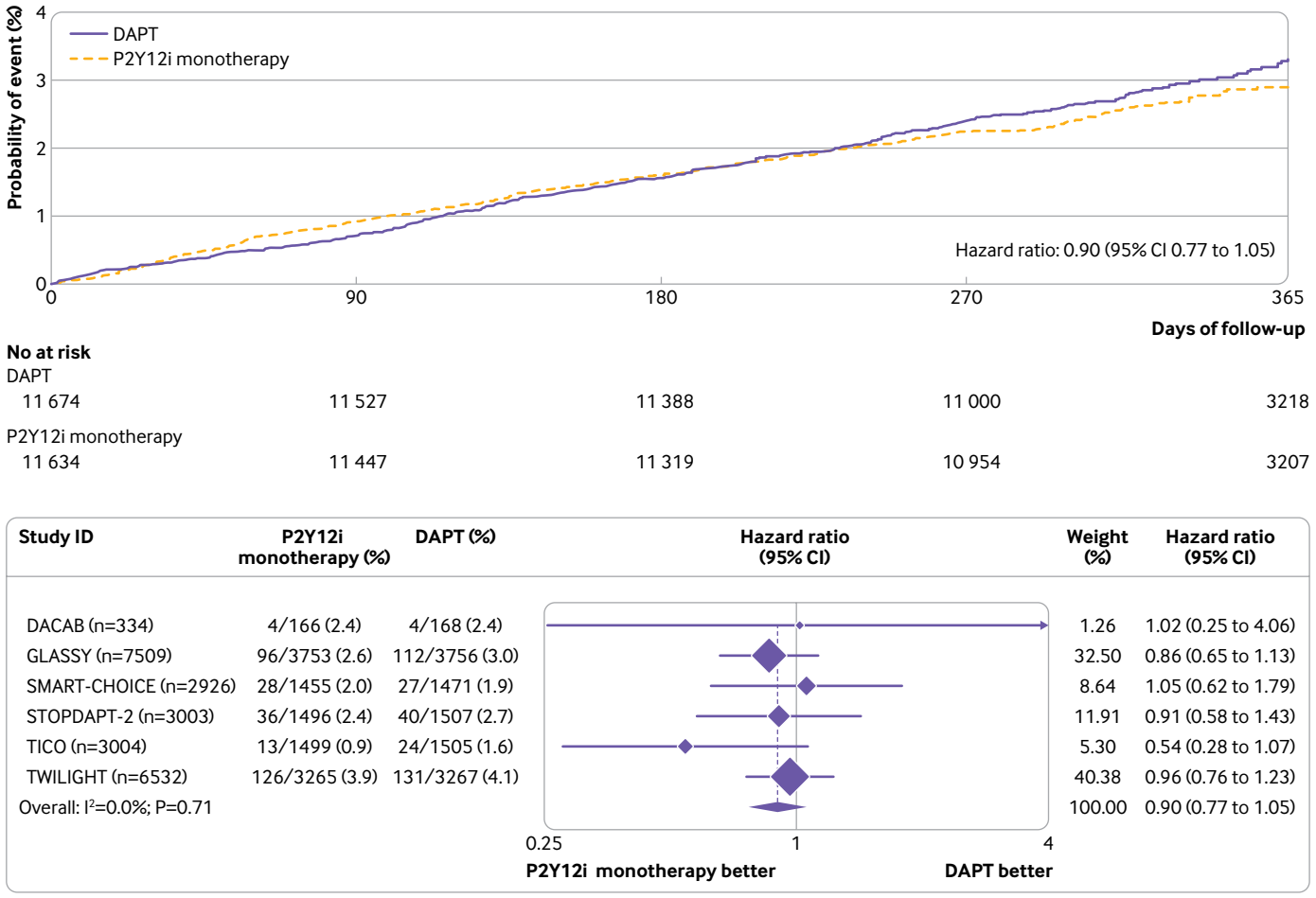


Fig 1 | Hazard ratios for individual trials and for pooled population and Kaplan-Meier estimates for primary endpoint of all cause death, myocardial infarction, or stroke in intention to treat population. Kaplan-Meier curves and hazard ratios from one step, fixed effect meta-analysis (top) and two step, fixed effect meta-analysis (bottom). DAPT=dual antiplatelet therapy; P2Y12i=$P2Y_{12}$ inhibitor monotherapy

monotherapy and 173 (1.31%) with DAPT (hazard ratio 0.85, 0.68 to 1.06; P=0.14; τ^2=0.00) when GLOBAL LEADERS instead of GLASSY was pooled with the other trials. An on-treatment analysis, excluding one trial due to lack of information,[9] showed no excess of ischaemic events and lower bleeding risk with $P2Y_{12}$ inhibitor monotherapy (supplementary table N).

Additional post hoc analyses

The composite endpoint of all-cause death, myocardial infarction, and stroke, censoring events that occurred nine months after the start of $P2Y_{12}$ inhibitor monotherapy in the experimental arm (to achieve a uniform length of follow-up across trials), occurred in 259 (2.28%) and 240 (2.28%) patients with $P2Y_{12}$ inhibitor monotherapy and in 284 (2.49%) and 262 (2.39%) with DAPT in the intention to treat (hazard ratio 0.92, 0.77 to 1.08; P=0.31 for superiority) and per protocol (0.95, 0.80 to 1.13; P=0.58 for superiority) populations, respectively, with no between trial heterogeneity (τ^2=0.00) (supplementary table O). We observed no treatment-by-subgroup interaction with body weight for the primary efficacy endpoint when both sexes were appraised separately, suggesting consistent benefit with $P2Y_{12}$ inhibitor monotherapy among women but not men, irrespective of body weight (supplementary figure I). The treatment-by-sex interaction testing for the primary outcome in each included study is shown in supplementary figure J.

Discussion

Our individual participant data meta-analysis of the totality of available randomised studies investigating $P2Y_{12}$ inhibitor monotherapy after revascularisation, including 24 096 patients mainly after percutaneous coronary intervention, provides strong evidence that $P2Y_{12}$ inhibitor monotherapy is non-inferior to DAPT. We chose a non-inferiority margin that preserved half of the treatment effect of aspirin observed in the historical aspirin trials,[11] under the rationale that the experimental arm consists of aspirin withdrawal and that the treatment effect of DAPT versus placebo is not known. $P2Y_{12}$ inhibitor monotherapy was associated with a lower risk of major bleeding and net adverse clinical events compared with DAPT. The main findings were corroborated by all sensitivity analyses. Our analysis suggests that female patients may derive particular benefit from $P2Y_{12}$ inhibitor monotherapy

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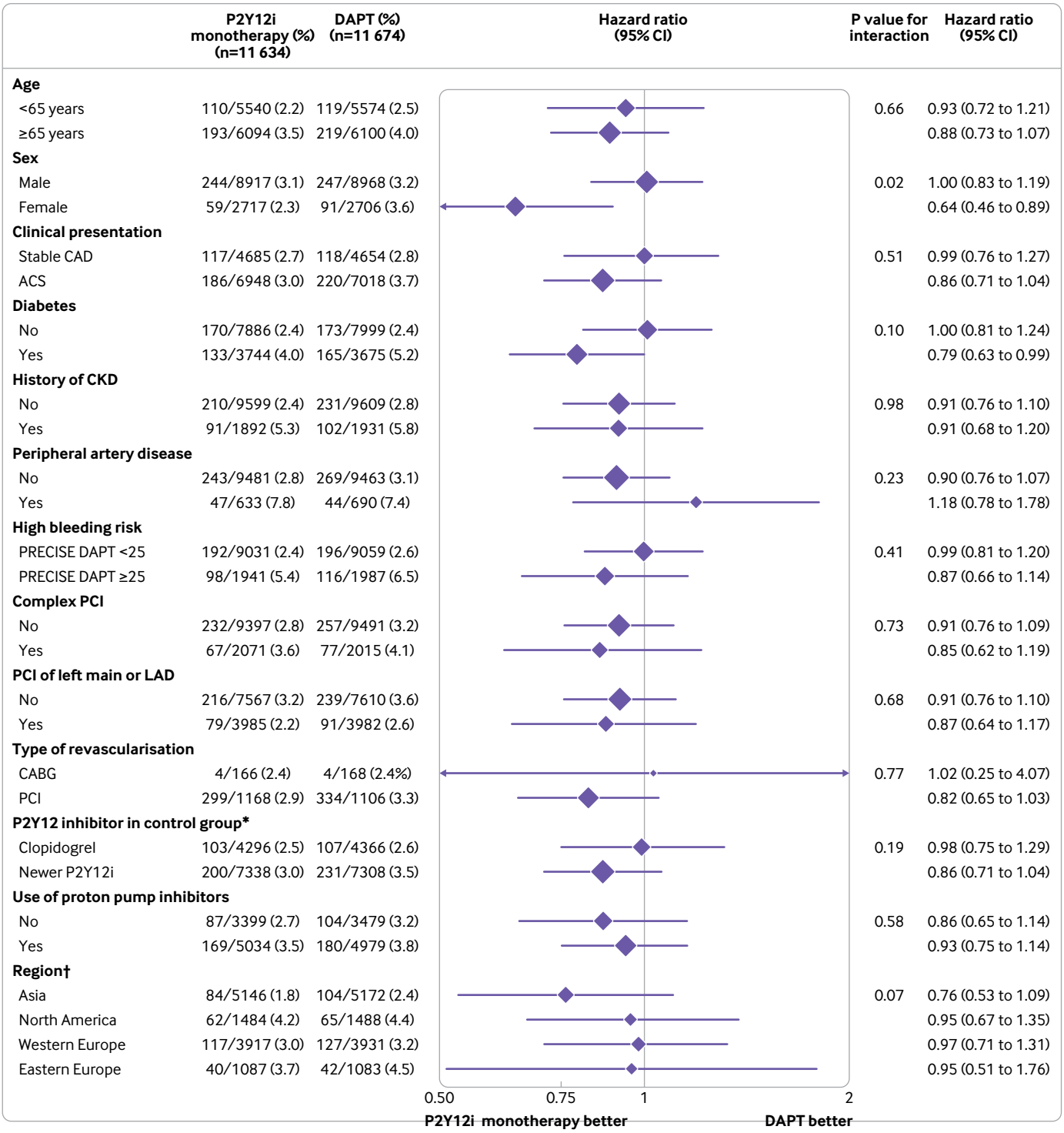


Fig 2 | Subgroup analyses for primary endpoint of all cause death, myocardial infarction, or stroke in intention to treat population. High bleeding risk was defined on basis of PRECISE-DAPT score ≥25. *P value obtained by merging within study and across study interactions (owing to design of trials). †European regions pooled together and within study and across study interactions merged owing to trial designs. ACS=acute coronary syndrome; CABG=coronary artery bypass grafting; CAD=coronary artery disease; CKD=chronic kidney disease; DAPT=dual antiplatelet therapy; LAD=left anterior descending artery; P2Y12i=$P2Y_{12}$ inhibitor monotherapy; PCI=percutaneous coronary intervention

owing to the lower risk of major adverse cardiovascular events, largely driven by a reduction in cardiovascular death. $P2Y_{12}$ inhibitor monotherapy was associated with lower bleeding rates consistently across subgroups, although the magnitude of this treatment effect varied by the potency of the $P2Y_{12}$ inhibitor in the experimental and control groups, which has important implications for practice.

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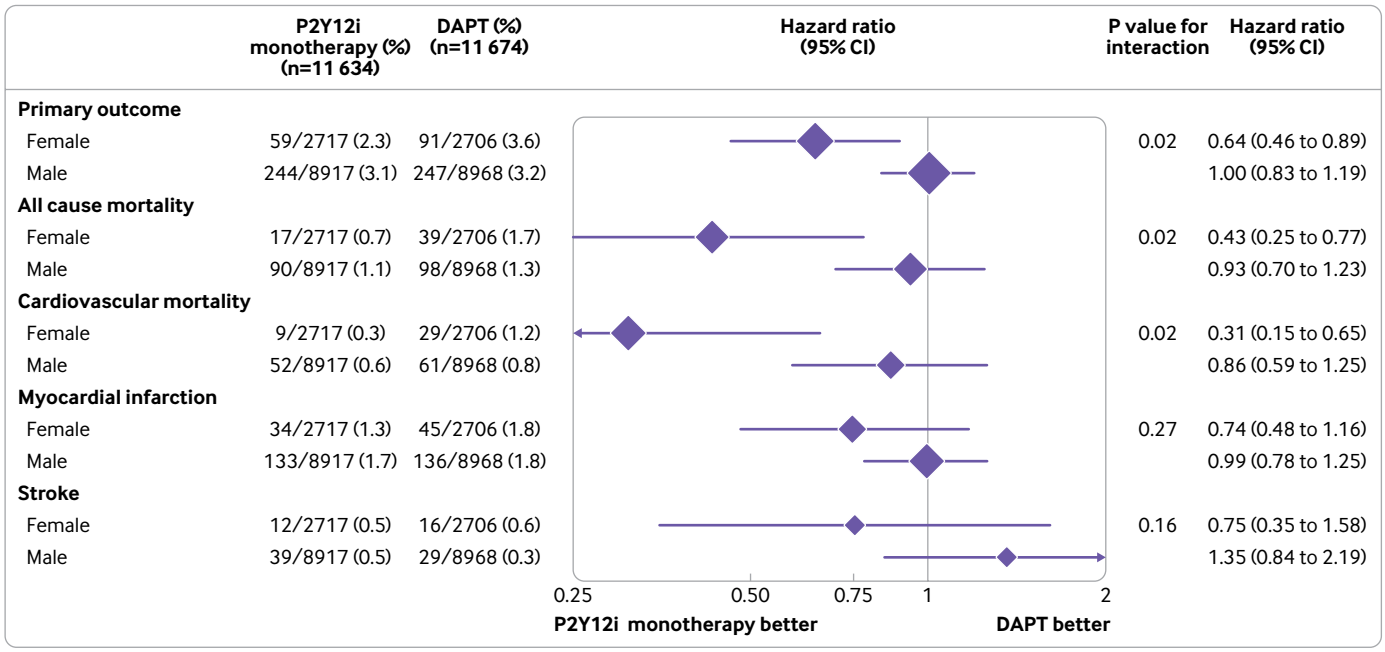


Fig 3 | Sex stratified analysis for primary endpoint, all cause death, cardiovascular death, myocardial infarction, or stroke in intention to treat population. DAPT=dual antiplatelet therapy; P2Y12i=$P2Y_{12}$ inhibitor monotherapy

Rationale for $P2Y_{12}$ inhibitor monotherapy after coronary revascularisation

A six to 12 month DAPT regimen is endorsed with a class I recommendation after percutaneous coronary intervention, irrespective of the clinical presentation or revascularisation techniques, and after coronary artery bypass grafting in patients with myocardial infarction.[12] This reflects the robust evidence indicating lower ischaemic risk with DAPT compared with aspirin monotherapy. However, DAPT invariably confers a heightened risk of major bleeding affecting mortality and morbidity,[2 20 21] and its use requires careful assessment of the trade-off between risks and anticipated benefits. An individualised approach to the DAPT regimen, modulating the duration of $P2Y_{12}$ inhibition on a background of aspirin therapy, has gained consensus.[1 2 4 22] However, this approach is poorly standardised and lacks prospective validation.[1 2] An alternative approach consists of early aspirin withdrawal and continuation with $P2Y_{12}$ inhibitor monotherapy up to 12 months after percutaneous coronary intervention or direct initiation of $P2Y_{12}$ inhibitor monotherapy after coronary artery bypass grafting.[5-10] Trials examining this approach were generally powered for non-inferiority with respect to ischaemic endpoints,[6 7 10] based on arbitrary non-inferiority margins, and/or superiority with respect to bleeding or net adverse clinical events, including a combination of ischaemic and bleeding endpoints.[6 9 10] They mostly showed no excess of ischaemic events and lower bleeding rates with $P2Y_{12}$ inhibitor monotherapy instead of DAPT. However, the imprecisions around the composite or individual ischaemic endpoint estimates entailed the loss of the entire treatment effect observed in historical aspirin trials.[11]

Comparison with previous meta-analyses on aggregate data and implications for clinicians

Previous aggregate data meta-analyses have not conclusively quantified the risks and benefits of aspirin withdrawal in comparison with DAPT after coronary revascularisation, because they included events occurring during the initial DAPT phase, which was identical in both experimental and control regimens and might have biased treatment estimates towards the null.[12 14] Both ischaemic events and bleeding events are known to cluster within the first month after revascularisation.[23-25] In our analysis, we censored 30.6% of all primary composite endpoints, 44.4% of cardiovascular deaths, 77.5% of definite stent thromboses, and 52.0% of BARC type 3 or type 5 bleeding events in the included trials. These events had occurred during the initial DAPT phase, which was identical in both treatment groups. In addition, our individual participant data enabled us to investigate the consistency of treatment effects across subgroups of interest. Specifically, we collected in our assembled dataset patient and procedural characteristics affecting ischaemic and/or bleeding outcomes aiming at determining whether $P2Y_{12}$ inhibitor monotherapy could be associated with potential harm in high ischaemic risk subsets or whether the bleeding benefit was confined to patients at high risk of bleeding.

Our individual participant data meta-analysis provides confidence that aspirin withdrawal one to three months after percutaneous coronary intervention and continuation with $P2Y_{12}$ inhibitor monotherapy also consistently preserves ischaemic protection compared with DAPT in patients at higher ischaemic risk, such as those with diabetes or acute coronary syndromes or receiving a complex intervention or an

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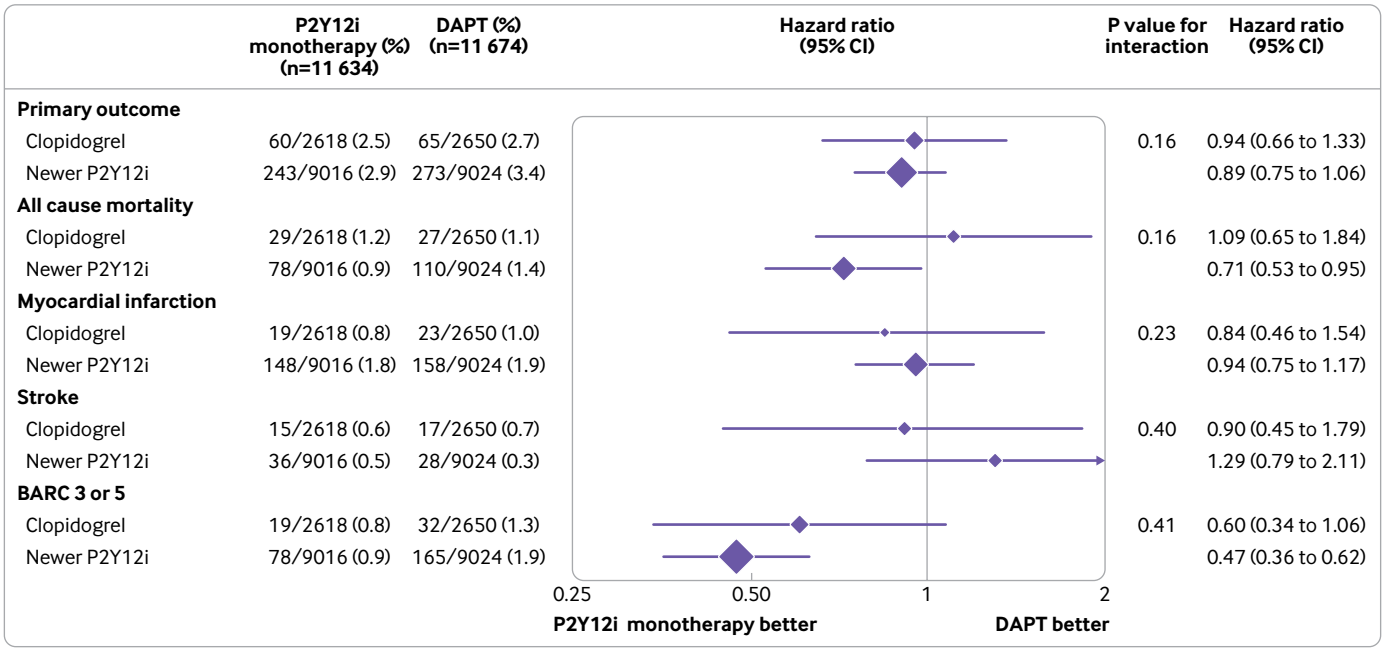


Fig 4 | Primary endpoint or its components and key safety endpoint stratified by use of clopidogrel or newer $P2Y_{12}$ inhibitors in experimental arm of intention to treat population. BARC=Bleeding Academy Research Consortium; DAPT=dual antiplatelet therapy

intervention in critical coronary segments, such as left main or left anterior descending coronary arteries. The treatment effect was consistent irrespective of the choice of $P2Y_{12}$ inhibitor monotherapy. However, ticagrelor was over-represented and prasugrel was under-represented among the newer $P2Y_{12}$ inhibitors, and clopidogrel monotherapy was tested only in Asian populations in comparison with a combination of aspirin and clopidogrel. We ran several sensitivity analyses, which suggested that the observed overall treatment effect was robust and reproducible despite the inclusion or exclusion of patients who experienced non-fatal events during the initial DAPT phase. We also did confirmatory analyses in the per protocol and on-treatment populations, which were either previously not conducted or conducted inconsistently across trials. The observation of a possible benefit of $P2Y_{12}$ inhibitor monotherapy on cardiovascular mortality, apparently confined to female patients, deserves attention. Given the number of pre-specified subgroups of interest and the lack of correction for multiplicity, this finding remains hypothesis generating. Each of the six included trials observed lower hazards of the composite ischaemic endpoint with $P2Y_{12}$ inhibitor monotherapy compared with DAPT in female rather than male patients, even though none of them individually showed a positive treatment-by-sex interaction. The effect on mortality does not seem to be explained by a reduction in major bleeding events with $P2Y_{12}$ inhibitor monotherapy, as both relative and absolute risk reductions for major bleeding were entirely consistent across sexes. Whether between sex disparity in bleeding management, as previously observed,[26] may contribute to explaining our findings remains to be investigated. Given that the risks and benefits of aspirin may be affected by weight,[27] its role was separately appraised in men and women. Our data do not support the hypothesis that weight accounts for the observed heterogeneity in the treatment benefit across sexes.

The treatment effect with $P2Y_{12}$ inhibitor monotherapy on bleeding varied in magnitude according to the potency of $P2Y_{12}$ inhibitor in the experimental and/or control groups and was apparently null when monotherapy with a newer $P2Y_{12}$ inhibitor was compared with aspirin and clopidogrel. However, confidence intervals were large for this comparison, including both benefit and harm. $P2Y_{12}$ inhibitor monotherapy therefore seems particularly appealing when newer $P2Y_{12}$ inhibitors, rather than clopidogrel, are clinically favoured. In all other subgroup analyses, we found benefits with respect to major bleeding events irrespective of baseline risks and across the entire spectrum of included patients. Taken together, this suggests that the recent guideline statements that $P2Y_{12}$ inhibitor monotherapy should be considered after a short course of DAPT, depending on the balance between the ischaemic and bleeding risk, is therefore no longer supported by the totality of evidence.[15]

Our findings are poorly informative on the choice of antithrombotic treatment after coronary artery bypass grafting.[5] Firstly, only a small trial powered for angiographic endpoints was available for inclusion. Secondly, limited and controversial evidence is available on the value of DAPT after surgical revascularisation in patients with chronic coronary syndrome.[1 2 28] Despite supportive evidence from subgroups of large trials after acute coronary syndrome for clopidogrel or ticagrelor,[29 30] a DAPT regimen remains inconsistently implemented in practice.[1 2]

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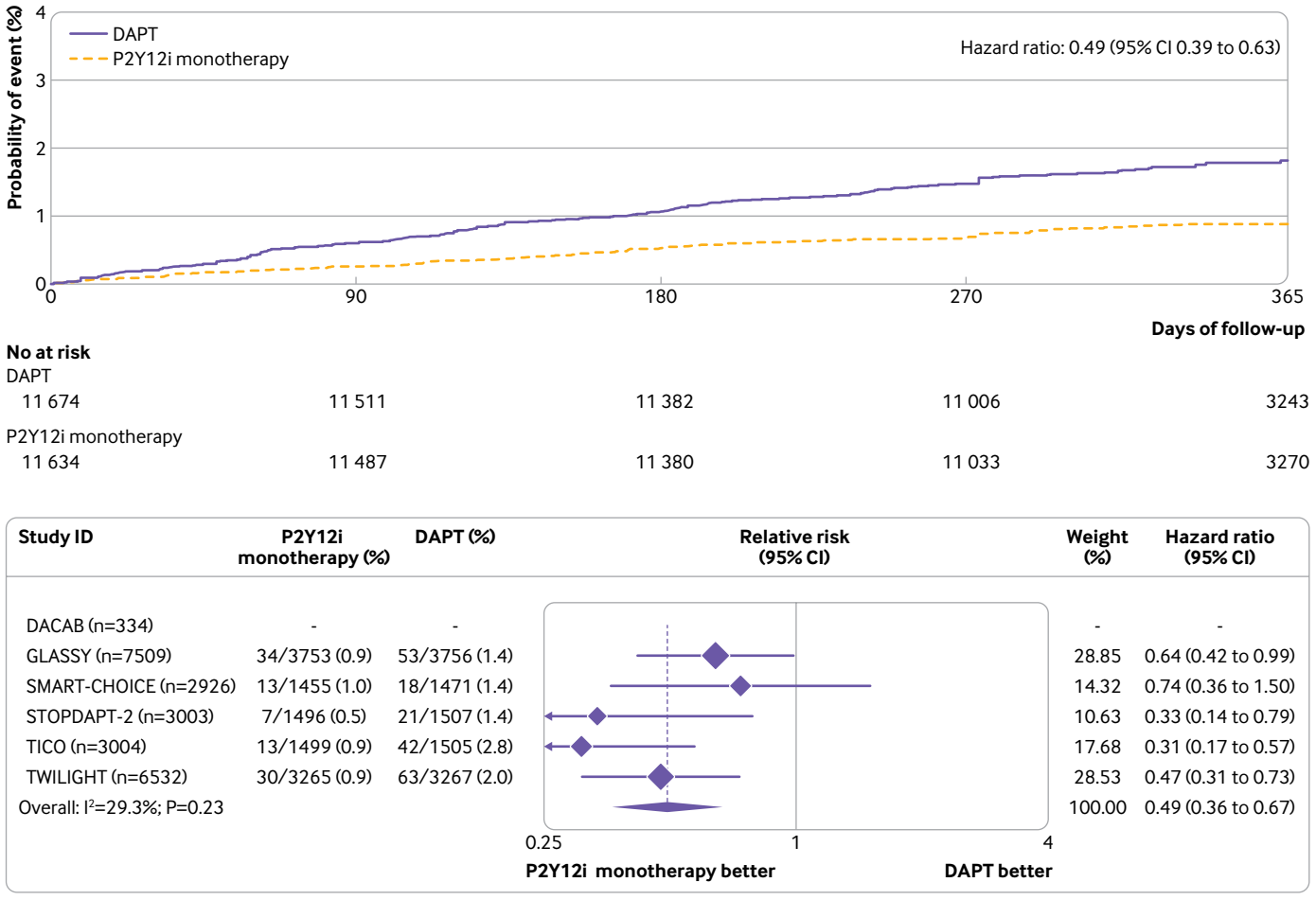


Fig 5 | Hazard ratios for individual trials and for pooled population and Kaplan-Meier estimates for key safety endpoint of Bleeding Academic Research Consortium (BARC) type 3 or type 5 bleeding in intention to treat population. Kaplan-Meier curves and hazard ratios from one step, fixed effect meta-analysis (top) and two step, fixed effect meta-analysis (bottom). DAPT=dual antiplatelet therapy

Limitations of study

The results of this individual participant data meta-analysis should be interpreted in view of several limitations. The analysis is subject to the shortcomings of the original trials, including an open label design in five of the six studies.[5-9] However, all studies implemented blinded central endpoint adjudication,[31] and endpoint definitions were largely consistent across trials. Cardiac instead of cardiovascular death was analysed in one trial because vascular death was not independently adjudicated.[9] We excluded events occurring while randomised groups received identical DAPT regimens in four trials.[6-9] However, sensitivity analyses including the initial DAPT phase following randomisation provided consistent results. No correction for multiple testing was pre-specified. Therefore, the lower risk of composite ischaemic endpoints with $P2Y_{12}$ inhibitor monotherapy in women is exploratory and needs prospective validation. The choice of $P2Y_{12}$ inhibitor monotherapy requires further investigation. Prasugrel monotherapy was used in a few patients within one trial and as protocol deviations in another.[7 8] Four trials mandated the use of ticagrelor monotherapy,[5 6 9 10] one study mandated clopidogrel monotherapy,[8] and only one trial allowed and stratified randomisation for all three oral $P2Y_{12}$ inhibitors.[7] The duration of $P2Y_{12}$ inhibitor monotherapy ranged from nine to 12 months across the included trials. However, findings were consistent after censoring of events that occurred beyond nine months. Finally, six rather than 12 month DAPT is recommended after percutaneous coronary intervention in patients with chronic coronary syndrome. However, 12 month DAPT remains the standard of care in many centres across the world in patients with chronic coronary syndrome,[32] and the results remained largely consistent for either ischaemic or bleeding endpoints when stratified on the basis of clinical presentation.

Conclusions

$P2Y_{12}$ inhibitor monotherapy was associated with similar risks of death, myocardial infarction, or stroke and lower risks of major bleeding compared with DAPT. We found evidence that these associations may be modified by sex and type of $P2Y_{12}$ inhibitor, respectively. The data on $P2Y_{12}$ inhibitor monotherapy compared with DAPT after coronary artery bypass grafting is limited to a single trial and requires further

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investigation. Our results, based on the totality of the available evidence, support a paradigm shift in antithrombotic management and question the central role of DAPT beyond one to three months after percutaneous coronary intervention.

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Ethical approval: Not needed.

Data sharing: Requests for data sharing should be sent to the corresponding author at marco.valgimigli@cardiocentro.org.

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The authors will disseminate the study results through their social media outlets, including Twitter, Facebook, and LinkedIn. They will run dedicated #hashtag campaigns (#SIDNEY2, #MonoP2Y12, #monoTx) to promote the main findings. The results will be also disseminated through scientific meetings and webinars. Press releases will be prepared for public engagement via general medicine and cardiology blogs and websites on request.

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1 Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016;134:e123-55.
2 Valgimigli M, Bueno H, Byrne RA, et al, ESC Scientific Document Group. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2018;53:34-78. doi:10.1093/ejcts/ezx334
3 Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M. A Critical Appraisal of Aspirin in Secondary Prevention: Is Less More?*Circulation* 2016;134:1881-906. doi:10.1161/CIRCULATIONAHA.116.023952
4 Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018;15:480-96. doi:10.1038/s41569-018-0049-1
5 Zhao Q, Zhu Y, Xu Z, et al. Effect of Ticagrelor Plus Aspirin, Ticagrelor Alone, or Aspirin Alone on Saphenous Vein Graft Patency 1 Year After Coronary Artery Bypass Grafting: A Randomized Clinical Trial. *JAMA* 2018;319:1677-86. doi:10.1001/jama.2018.3197
6 Franzone A, McFadden E, Leonardi S, et al, GLASSY Investigators. Ticagrelor Alone Versus Dual Antiplatelet Therapy From 1 Month After Drug-Eluting Coronary Stenting. *J Am Coll Cardiol* 2019;74:2223-34. doi:10.1016/j.jacc.2019.08.1038
7 Hahn JY, Song YB, Oh JH, et al, SMART-CHOICE Investigators. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. *JAMA* 2019;321:2428-37. doi:10.1001/jama.2019.8146
8 Watanabe H, Domei T, Morimoto T, et al, STOPDAPT-2 Investigators. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. *JAMA* 2019;321:2414-27. doi:10.1001/jama.2019.8145
9 Kim BK, Hong SJ, Cho YH, et al, TICO Investigators. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. *JAMA* 2020;323:2407-16. doi:10.1001/jama.2020.7580
10 Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med* 2019;381:2032-42. doi:10.1056/NEJMoa1908419
11 Collaboration AT, Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. doi:10.1136/bmj.324.7329.71
12 O'Donoghue ML, Murphy SA, Sabatine MS. The Safety and Efficacy of Aspirin Discontinuation on a Background of a $P2Y_{12}$ Inhibitor in Patients After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. *Circulation* 2020;142:538-45. doi:10.1161/CIRCULATIONAHA.120.046251
13 Giacoppo D, Matsuda Y, Fovino LN, et al. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2021;42:308-19. doi:10.1093/eurheartj/ehaa739
14 Kuno T, Ueyama H, Takagi H, Bangalore S. P2Y12 inhibitor monotherapy versus aspirin monotherapy after short-term dual antiplatelet therapy for percutaneous coronary intervention: Insights from a network meta-analysis of randomized trials. *Am Heart J* 2020;227:82-90. doi:10.1016/j.ahj.2020.06.008
15 Collet JP, Thiele H, Barbato E, et al, ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42:1289-367. doi:10.1093/eurheartj/ehaa575
16 Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J* 2019;40:3757-67. doi:10.1093/eurheartj/ehz732
17 Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA* 2015;313:1657. doi:10.1001/jama.2015.3656
18 Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736-47. doi:10.1161/CIRCULATIONAHA.110.009449
19 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi:10.1136/bmj.l4898
20 Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J* 2017;38:804-10.
21 Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC Cardiovasc Interv* 2011;4:654-64. doi:10.1016/j.jcin.2011.02.011
22 Costa F, Van Klaveren D, Feres F, et al, PRECISE-DAPT Study Investigators. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. *J Am Coll Cardiol* 2019;73:741-54. doi:10.1016/j.jacc.2018.11.048
23 Valgimigli M, Patialiakas A, Thury A, et al, ZEUS Investigators. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. *J Am Coll Cardiol* 2015;65:805-15. doi:10.1016/j.jacc.2014.11.053
24 Valgimigli M, Campo G, Monti M, et al, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012;125:2015-26. doi:10.1161/CIRCULATIONAHA.111.071589
25 Stone GW, Witzenbichler B, Weisz G, et al, ADAPT-DES Investigators. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 2013;382:614-23. doi:10.1016/S0140-6736(13)61170-8
26 Wang WT, James SK, Wang TY. A review of sex-specific benefits and risks of antithrombotic therapy in acute coronary syndrome. *Eur Heart J* 2017;38:165-71.

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27 Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet* 2018;392:387-99. doi:10.1016/S0140-6736(18)31133-4
28 Neumann FJ, Sousa-Uva M, Ahlsson A, et al, ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87-165. doi:10.1093/eurheartj/ehy394
29 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. doi:10.1056/NEJMoa010746
30 Wallentin L, Becker RC, Budaj A, et al, PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57. doi:10.1056/NEJMoa0904327
31 Leonardi S, Branca M, Franzone A, et al. Comparison of Investigator-Reported and Clinical Event Committee-Adjudicated Outcome Events in GLASSY. *Circ Cardiovasc Qual Outcomes* 2021;14:e006581. doi:10.1161/CIRCOUTCOMES.120.006581
32 De Luca L, Temporelli PL, Riccio C, et al, START Investigators. Clinical outcomes, pharmacological treatment, and quality of life of patients with stable coronary artery diseases managed by cardiologists: 1-year results of the START study. *Eur Heart J Qual Care Clin Outcomes* 2019;5:334-42. doi:10.1093/ehjqcco/qcz002

Web appendix: Supplementary materials

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Cangrelor, Tirofiban, and Chewed or Standard Prasugrel Regimens in Patients With ST-Segment-Elevation Myocardial Infarction: Primary Results of the FABOLUS-FASTER Trial.

Gargiulo G, Esposito G, Avvedimento M, Nagler M, Minuz P, Campo G, **Gragnano F,** Manavifar N, Piccolo R, Tebaldi M, Cirillo P, Hunziker L, Vranckx P, Leonardi S, Heg D, Windecker S, Valgimigli M.

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ORIGINAL RESEARCH ARTICLE

Cangrelor, Tirofiban, and Chewed or Standard Prasugrel Regimens in Patients With ST-Segment–Elevation Myocardial Infarction

Primary Results of the FABOLUS-FASTER Trial

BACKGROUND: Standard administration of newer oral $P2Y_{12}$ inhibitors, including prasugrel or ticagrelor, provides suboptimal early inhibition of platelet aggregation (IPA) in patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention. We aimed to investigate the effects of cangrelor, tirofiban, and prasugrel, administered as chewed or integral loading dose, on IPA in patients undergoing primary percutaneous coronary intervention.

METHODS: The FABOLUS-FASTER trial (Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel: A Multicenter Randomized Open-Label Trial in Patients with ST-Elevation Myocardial Infarction Referred for Primary Percutaneous Intervention) is an investigator-initiated, multicenter, open-label, randomized study. A total of 122 $P2Y_{12}$-naive patients with ST-segment–elevation myocardial infarction were randomly allocated (1:1:1) to cangrelor (n=40), tirofiban (n=40) (both administered as bolus and 2-hour infusion followed by 60 mg of prasugrel), or 60-mg loading dose of prasugrel (n=42). The latter group underwent an immediate 1:1 subrandomization to chewed (n=21) or integral (n=21) tablets administration. The trial was powered to test 3 hypotheses (noninferiority of cangrelor compared with tirofiban using a noninferiority margin of 9%, superiority of both tirofiban and cangrelor compared with chewed prasugrel, and superiority of chewed prasugrel as compared with integral prasugrel, each with α=0.016 for the primary end point, which was 30-minute IPA at light transmittance aggregometry in response to 20 µmol/L adenosine diphosphate.

RESULTS: At 30 minutes, cangrelor did not satisfy noninferiority compared with tirofiban, which yielded superior IPA over cangrelor (95.0±8.9 versus 34.1±22.5; *P*<0.001). Cangrelor or tirofiban were both superior to chewed prasugrel (IPA, 10.5±11.0; *P*<0.001 for both comparisons), which did not provide higher IPA over integral prasugrel (6.3±11.4; *P*=0.47), despite yielding higher prasugrel active metabolite concentration (ng/mL; 62.3±82.6 versus 17.1±43.5; *P*=0.016).

CONCLUSIONS: Cangrelor provided inferior IPA compared with tirofiban; both treatments yielded greater IPA compared with chewed prasugrel, which led to higher active metabolite concentration but not greater IPA compared with integral prasugrel.

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Clinical Perspective

What Is New?

- The FABOLUS-FASTER trial (Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel: A Multicenter Randomized Open-Label Trial in Patients with ST-Elevation Myocardial Infarction Referred for Primary Percutaneous Intervention) is the first study comparing the pharmacodynamic effects of cangrelor, a direct parenteral $P2Y_{12}$ inhibitor, with tirofiban, a glycoprotein IIb/IIIa inhibitor, as well as the pharmacodynamic and pharmacokinetic effects of a 60-mg chewed or integral pill intake of prasugrel, an oral indirect $P2Y_{12}$ inhibitor among patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention.
- Cangrelor did not reach noninferiority with tirofiban at adenosine diphosphate–induced platelet aggregation; the latter showed superior platelet inhibition at 30 minutes as well as at all other time points.
- Chewed prasugrel led to higher active metabolite concentration but not greater inhibition of platelet aggregation compared with integral prasugrel.

What Are the Clinical Implications?

- This study supports the use of parenteral drugs to achieve immediate inhibition of platelet aggregation and to bridge the initial gap in platelet inhibition observed with oral $P2Y_{12}$ inhibitors.
- Cangrelor, unlike tirofiban, was associated with modest reductions of platelet reactivity during the drug infusion and during the transition toward oral $P2Y_{12}$ inhibitors.
- Tirofiban, by exerting more potent and consistent inhibition of platelet aggregation, may be more effective than cangrelor in reducing the risks of acute ischemic complications, which need to be ascertained in the context of studies powered for clinical end points.

Antithrombotic therapy, including oral or parenteral antiplatelet and anticoagulation agents, or both, mitigates the ischemic risks in patients with ST-segment–elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).[1–4] New-generation oral inhibitors of adenosine diphosphate (ADP)–activated platelet $P2Y_{12}$ receptor (prasugrel or ticagrelor) are recommended, but their administration does not abrogate high residual platelet reactivity (HRPR) up to 4 or 6 hours after standard loading dose.[5–7] Strategies to increase the bioavailability of oral $P2Y_{12}$ inhibitors, such as crushing or chewing tablets, have been investigated, but pharmacokinetic and pharmacodynamic data remain limited.[8–11] Parenteral antiplatelet agents, including tirofiban or cangrelor, have been shown to provide more rapid and sustained inhibition of platelet aggregation (IPA) as compared with prasugrel or ticagrelor. Pharmacodynamic data on cangrelor showed that it is able to achieve very high degrees (>80%) of platelet inhibition,[12] suggesting that its effect could be equivalent to that of tirofiban; however, no comparative data on IPA are available between tirofiban or cangrelor in patients undergoing primary PCI, and it remains unclear how these treatment options compare with chewed prasugrel instead of standard administration of integral tablets.

We conducted the FABOLUS-FASTER trial (Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel: A Multicenter Randomized Open-Label Trial in Patients with ST-Elevation Myocardial Infarction Referred for Primary Percutaneous Intervention) to investigate the acute pharmacodynamic effects of cangrelor, tirofiban, or prasugrel, administered at standard 60 mg loading dose as integral or chewed tablets, in patients with STEMI undergoing primary PCI.

METHODS

Study Design and Patient Population

The FABOLUS-FASTER trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02978040; URL: https://www.clinicaltrialsregister.eu; EudraCT 2017-001065-24) is an investigator-initiated, multicenter, open-label, randomized trial.

The study rationale and design have been reported previously.[13] Briefly, patients with suspected STEMI arriving to the catheterization laboratory with indication for coronary angiography were screened for eligibility. After informed consent was obtained, and coronary angiography confirmed the diagnosis, $P2Y_{12}$-naive patients undergoing primary PCI (within 12 hours, or 24 hours if ongoing ischemia was demonstrated) were enrolled at 3 centers (Bern University Hospital, Switzerland; University Hospital Federico II, Naples, Italy; and University Hospital of Ferrara, Italy). The main exclusion criteria were inability to provide informed consent or to adhere with study protocols (prasugrel pills chewing or ingestion); contraindications or known hypersensitivity or allergy to aspirin, prasugrel, intravenous unfractionated heparin (UFH), cangrelor, or tirofiban; contraindications to the PCI procedure; recent (<7 days) treatment with study drugs (glycoprotein IIb/IIIa inhibitor [GPI] or $P2Y_{12}$ inhibitors or cangrelor); dialysis; recent (<15 days) or ongoing major bleeding; recent (<15 days) major surgery; fibrinolytics administration (<30 days); oral anticoagulation therapy; prior stroke or transient ischemic attack; concomitant disease affecting life expectancy (<6 months); pregnant or breastfeeding; and recent (<30 days) recruitment in alternative trials on investigational drugs.

Patients were randomly allocated (1:1:1) to standard regimen of tirofiban (bolus + 2-hour infusion, followed by 60 mg loading dose prasugrel at the infusion discontinuation time), standard regimen of cangrelor (bolus + 2-hour infusion, followed by 60 mg loading dose prasugrel at the infusion discontinuation time), or prasugrel 60 mg (integral or chewed tablets) at PCI initiation. Patients in the prasugrel

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group immediately underwent a subrandomization (1:1) to chewed or integral tablets of prasugrel oral loading dose. Randomization was concealed and stratified according to center and to time from symptom onset to PCI (<3 hours, 3 to 6 hours, >6 hours) with randomly alternating blocks of 3 or 6 in the first randomization, and stratified according to center with randomly alternating blocks of 2 or 4 in the second randomization. The electronic data capture system delivered by AdvicePharma was used. The study complied with the Declaration of Helsinki and Good Clinical Practice and was approved by national agencies and local ethics committees. Further details are reported in the Data Supplement.

The data that support the findings of this study are available from the corresponding author on reasonable request.

Medications and Procedures

Aspirin was administered to all patients before primary PCI (150 to 300 mg orally or 80 to 150 mg intravenously, then 81 to 325 mg daily). Tirofiban was administered at a 25 µg/kg bolus + 0.15 µg/kg per minute infusion for 2 hours (or infusion at 0.075 µg/kg per minute if creatinine clearance was <30 mL/min). Cangrelor was administered at a 30 µg/kg bolus + 4 µg/kg per minute infusion for 2 hours. In both tirofiban and cangrelor arms, patients received integral pills of 60 mg loading dose prasugrel at the time of infusion discontinuation with a following maintenance dose of 10 mg daily (5 mg daily if body weight <60 kg or age >75 years). Patients in the prasugrel group had not to have received parenteral antiplatelet agents and received prasugrel (integral or chewed) at an identical loading dose of 60 mg, with a following maintenance dose of 10 mg daily (5 mg daily if body weight <60 kg or age >75 years). Patients in the chewed prasugrel group had to chew prasugrel tablets for at least 10 to 15 seconds and then swallow with water (≈150 mL) as described.[10]

UFH was used as an anticoagulant with an initial bolus of 50 to 70 UI/kg in tirofiban- and cangrelor-treated patients or 70 to 100 UI/kg bolus in prasugrel-treated patients, eventually followed by further boluses to reach an intraprocedural activated clotting time of at least 250 seconds. Protocol recommended to stop UFH at the end of PCI in the absence of strict clinical indications.

Blood samples were collected before study drug initiation (baseline), as well as at 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, and between 4 and 6 hours after study drug administration (bolus completion or oral pills ingestion).

Pharmacodynamic and Pharmacokinetic Assessment

Pharmacodynamic assessments were performed using light transmittance aggregometry (LTA).[14] Blood samples were collected in sodium citrate anticoagulated tubes. Platelet-rich plasma was stimulated with 5 and 20 µmol/L ADP and 5 and 15 µmol/L thrombin receptor agonist peptide (TRAP). Platelet aggregation (maximal percent of platelet aggregation after agonist stimulation) was collected and used to calculate IPA.[7] The percent of late platelet aggregation was also collected.

Multiple electrode aggregometry (Multiplate, Roche Diagnostics, Switzerland) was also performed at 2 centers (Bern and Naples).[15] Whole blood samples were collected in hirudin-anticoagulated tubes, then diluted with saline (1:2 with 0.9% NaCl) and stimulated with agonists (ADP or TRAP), and platelet aggregation was recorded continuously for 6 minutes. The area under the aggregation curve (AUC) value was used to express platelet inhibition.

A pharmacokinetic assessment was implemented within the prasugrel arm after 10 patients had already been included on request from the Italian Medicines Agency to compare integral versus chewed prasugrel. Prasugrel active metabolite (PAM) was measured at each time point by using precooled ethylenediaminetetraacetic acid tubes treated with 25 µL of 500 mM 3′-methoxyphenacyl bromide in acetonitrile within 30 seconds after collection to derivatize and stabilize the PAM as described previously.[9,16] Plasma samples were centrifuged (2800 rpm for 15 minutes at 4°C) within 30 minutes and stored in polypropylene tubes at –20°C/–80°C. The analysis was performed at a central laboratory (University Hospital of Verona) through validated liquid chromatography methods and tandem mass spectrometric detection.

Study End Points

The primary end point was the 30-minute percentage of IPA (%IPA) assessed with LTA after stimulation of platelet-rich plasma with ADP 20 µmol/L. %IPA is defined as follows: 100% × (Baseline Platelet Aggregation – Platelet Aggregation at Time *t*)/Baseline Platelet Aggregation.

Secondary end points were LTA %IPA after TRAP (5 and 15 µmol/L), ADP (5 µmol/L) stimulation at all time frames, and ADP (20 µmol/L) at 15 minutes, 1 hour, 2 hours, 3 hours, and 4 to 6 hours.

Additional secondary end points were AUC values (residual platelet reactivity) measured by Multiplate after stimulation with ADP and TRAP at all time points.

HRPR was defined as percent of patients with platelet reactivity >59% after ADP 20 µmol/L or >46% after ADP 5 µmol/L or >46 U at Multiplate ADPtest as described previously.[14,17,18]

For pharmacokinetic assessment, the time to maximum plasma concentration, maximum observed plasma concentration, and the area under the plasma concentration versus time curve from time 0 to various times ($AUC_{0\text{ to }30\text{ minutes}}$, $AUC_{0\text{ to }1\text{ hour}}$, $AUC_{0\text{ to }2\text{ hours}}$, $AUC_{0\text{ to }4\text{ hours}}$) were analyzed.

Adverse clinical outcomes within 30 days were collected including all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, transient ischemic attack, definite or probable stent thrombosis, urgent target vessel revascularization, unplanned revascularization, bleeding occurrences, and net adverse clinical events. Events were blindly adjudicated by an independent clinical event committee. All deaths were categorized as cardiovascular or noncardiovascular. Cardiovascular death was defined as death resulting from an acute MI, sudden cardiac death, death from heart failure, death from stroke, death (immediate) from cardiovascular procedures, death from cardiovascular hemorrhage, and death from other cardiovascular causes. Noncardiovascular death was defined as any death not thought to be from a cardiovascular cause. MI was defined according to the fourth universal definition of MI.[19] Stroke, categorized as ischemic or hemorrhagic or unknown, was defined as an acute episode of focal or global neurologic dysfunction caused by central nervous system (brain, spinal cord, and retina) vascular injury

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as a result of hemorrhage or infarction. Transient ischemic attack was defined as a new transient episode of neurologic dysfunction (usually 1 to 2 hours), always within 24 hours, caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. Stent thrombosis was defined according to the Academic Research Consortium.[20] Urgent target vessel revascularization was defined as an urgent coronary revascularization in a target coronary vessel (ie, a vessel treated during the index PCI), and unplanned revascularization as any revascularization that was not prespecified or staged after index PCI. Bleeding events were defined according to BARC (Bleeding Academic Research Consortium),[21] TIMI (Thrombolysis in Myocardial Infarction),[22] and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries)[23] classifications. Net adverse clinical events were defined as the composite of death, nonfatal MI, definite or probable stent thrombosis, nonfatal stroke, and BARC 2, 3, or 5 bleeding.

Statistical Analysis

All analyses were performed at the Clinical Trials Unit of Bern according to the prespecified statistical analysis plan. The sample size calculation was based on testing the noninferiority of cangrelor compared with tirofiban, superiority of both tirofiban and cangrelor compared with chewed prasugrel, and superiority of chewed compared with integral prasugrel.

The sample size estimation, which is partly based on previous evidence,[7] followed these considerations (3 primary end points, each with α of 0.05/3=0.016): assuming at least 94% IPA with ADP 20 µmol/L 30 minutes after parenteral drug administration, 8% as SD, 9% as noninferiority margin (this margin was considered a clinically meaningful reduction in the %IPA to refute noninferiority), and 0.016 α, 40 patients per arm would provide a power of 99% to demonstrate noninferiority of cangrelor compared with tirofiban. If noninferiority of cangrelor was not met, then the superiority of tirofiban over cangrelor was tested (prespecified secondary end point); assuming 55% IPA with ADP 20 µmol/L 30 minutes after chewed prasugrel, a 24% SD, and 0.016 as α, the study power would be 100% to demonstrate superiority of tirofiban (n=40) compared with chewed prasugrel (n=20) and superiority of cangrelor (n=40) compared with chewed prasugrel (n=20); and assuming 55% IPA with ADP 20 µmol/L 30 minutes after chewed prasugrel, a 24% SD, and 0.016 as α, 20 patients per arm would provide a power of 82% to demonstrate superiority of chewed compared with integral prasugrel.

Clinical characteristics, procedural data, and medication use were summarized using means with SDs and counts with percentages, *P* values from *t* tests, Fisher exact tests, and χ^2 tests. Pairwise mean differences in platelet inhibition (difference in %IPA) with 95% CIs were calculated (cangrelor versus tirofiban, cangrelor versus chewed prasugrel, tirofiban versus chewed prasugrel, chewed versus integral prasugrel; based on generalized mixed models, including data on all time points after drug administration, and random effects of patient as appropriate), and a *z* test was used to test noninferiority. Generalized mixed models (including data on all time points after drug administration) were used to test superiority (%IPA at LTA or AUC unit on Multiplate, as continuous variables or random effects of patient, as appropriate). *P* values are interpreted with a Bonferroni post hoc correction. Generalized mixed models used the appropriate link function according to the type of primary or secondary outcomes measured (continuous or binary) and adjusted for time point (minutes to hours after drug administration) and the interaction between randomized arm and time point, with random effects added of site and patient as appropriate. Wald χ^2 test was used to compare event rates. Hazard ratios were estimated by fitting a Cox proportional hazards model (proportional hazards were tested and nonsignificant). The α used to claim statistical significance is 0.016 for the primary end point. Secondary end points were analyzed with a 2-sided α set at 0.05 to allow conventional interpretation of results. Statistical analyses were performed with Stata version 16.1.

RESULTS

Between July 4, 2017, and August 26, 2019, we enrolled 122 patients with STEMI intended for primary PCI (cangrelor, n=40; tirofiban, n=40; prasugrel, n=42 [chewed, n=21; integral, n=21]) across 3 centers in Switzerland and Italy. Patient disposition is summarized in Figure 1.

Baseline and procedural characteristics were well balanced across groups (Tables 1 and 2 and Tables I and II in the Data Supplement). Patients were predominantly male (76%), mean age was 64 years, 20% had diabetes mellitus, and 52% presented within 3 hours from symptom onset. Most patients presented in sinus rhythm, 27% had Killip class >1, 4% previously had cardiac arrest, and 4% required continuous infusion of vasopressors. Also, 21 (17%) patients were on chronic aspirin at the time of presentation and 115 (94%) received aspirin loading dose, administered mainly intravenously, whereas all patients received UFH. The radial was the primarily attempted access site in 84% of the patients, and 98% of the patients had TIMI flow 3 at the end of the procedure. Clinical outcomes at 30 days are shown in Table III in the Data Supplement.

Pharmacodynamic Assessment

Light Transmittance Aggregometry

At baseline, there were no differences across groups in ADP- or TRAP-induced platelet aggregation. Figure 2 and Table IV in the Data Supplement show IPA with LTA ADP 20 µmol/L. At 30 minutes, cangrelor did not reach noninferiority with tirofiban, which, in turn, achieved superior IPA over cangrelor (IPA, 95.0±9.0 versus 34.1±22.5; *P*<0.001), cangrelor or tirofiban were both superior to chewed prasugrel (IPA, 10.5±11.0; *P*<0.001 for both comparisons), and chewed prasugrel did not reach superior IPA over integral prasugrel (6.3±11.4; *P*=0.47). At secondary analyses, tirofiban provided greater IPA at all time points compared with cangrelor or chewed prasugrel. Cangrelor provided

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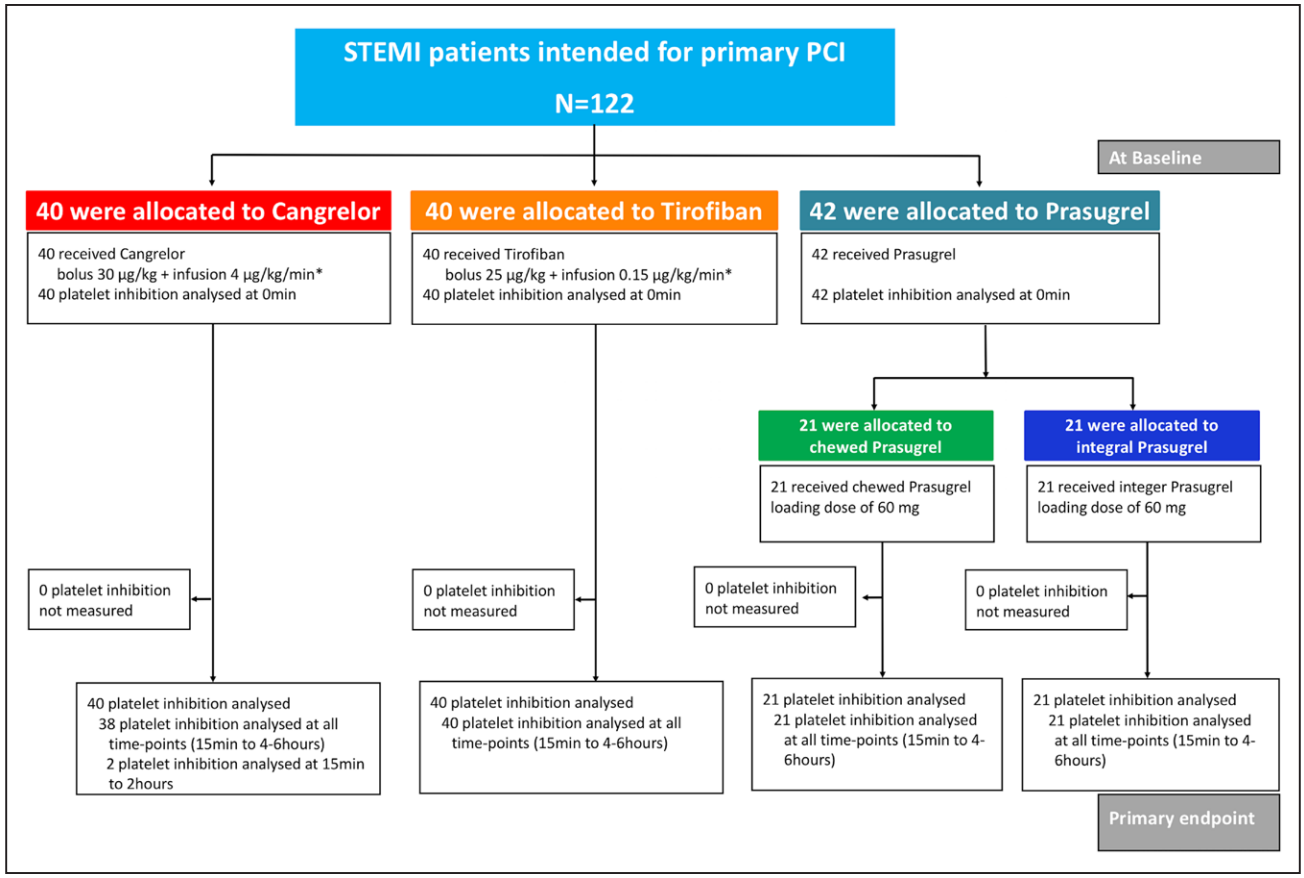


Figure 1. Flow chart of the FABOLUS-FASTER trial.
*For 2 hours or to the end of the PCI. FABOLUS-FASTER indicates Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel: A Multicenter Randomized Open-Label Trial in Patients with ST-Elevation Myocardial Infarction Referred for Primary Percutaneous Intervention; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

greater IPA up to 1 hour compared with chewed prasugrel, but IPA did not differ at 2 hours and it became higher with chewed prasugrel compared with cangrelor at 3 and 4 to 6 hours. The proportions of patients with IPA >80% or 90% were consistently higher with tirofiban compared with cangrelor or chewed or integral prasugrel (Figure 2B and 2C). No patient with tirofiban had HRPR within the first 2 hours, whereas HRPR rates ranged from 50% to 58% during cangrelor infusion (Figure 3 and Table V in the Data Supplement). Cangrelor, in turn, provided significantly lower HRPR rates compared with chewed prasugrel at 15 and 30 minutes but not at 1 and 2 hours; at 3 hours and 4 to 6 hours, chewed prasugrel was associated with lower HRPR rates compared with cangrelor. HRPR rates trended lower with chewed versus integral prasugrel for up to 2 hours without reaching statistical significance. The primary end point for chewed versus integral prasugrel remained consistent when stratified by patients receiving opioids or not ($P_{interaction}$=0.226; Table VI in the Data Supplement).

The kinetics of platelet inhibition were consistent after 5 µmol/L ADP (Figure 4A and Tables V and VII in the Data Supplement).

Tirofiban was also associated with higher inhibition of 15 or 5 µmol/L TRAP-induced platelet aggregation at all time points compared with cangrelor or chewed prasugrel (Figure 4B and 4C and Table VII in the Data Supplement). IPA after 15 µmol/L TRAP was higher with cangrelor compared with chewed prasugrel at 15 minutes but not thereafter up to 2 hours, whereas at 3 and 4 to 6 hours chewed prasugrel was associated with greater IPA as compared with cangrelor. IPA after 5 µmol/L TRAP did not differ between cangrelor and chewed prasugrel up to 3 hours but was greater in the latter group at the 4 to 6 hours assessment.

Results remained consistent when the 2 prasugrel arms were analyzed as a single group against tirofiban or cangrelor or when IPA was calculated using late instead of maximal aggregation.

Multiplate

ADP-induced platelet aggregation was lower in tirofiban-treated patients compared with cangrelor or chewed prasugrel up to 2 hours, and in turn lower with cangrelor compared with chewed prasugrel from 15 minutes to 2 hours, but higher thereafter with cangrelor compared with chewed or integral prasugrel (Figure

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Table 1. Baseline Clinical Characteristics

Variable	Cangrelor (n=40)	Tirofiban (n=40)	Chewed Prasugrel (n=21)	Integral Prasugrel (n=21)
Age, y	65.6±12.2	62.9±13.0	64.7±11.7	60.6±10.8
Male sex	29 (73)	31 (78)	19 (90)	14 (67)
Body mass index, kg/m^2	27.2±4.7	27.7±4.3	27.4±5.2	26.5±3.2
Diabetes mellitus	7 (18)	9 (23)	3 (14)	5 (24)
Oral treated	5 (71)	5 (56)	3 (100)	3 (60)
Insulin treated	0 (0)	2 (22)	0 (0)	0 (0)
Hypertension	18 (45)	19 (48)	12 (57)	8 (38)
Dyslipidemia	18 (45)	19 (48)	8 (38)	13 (62)
Family history of coronary artery disease	8 (20)	13 (33)	3 (14)	6 (29)
Current smoker	16 (40)	23 (57)	12 (57)	11 (52)
Peripheral arterial disease	1 (3)	2 (5)	1 (5)	1 (5)
Carotid artery disease	2 (5)	2 (5)	1 (5)	1 (5)
Chronic kidney disease, estimated glomerular filtration rate <60 mL/min	7 (18)	4 (10)	3 (14)	1 (5)
Heart failure	0 (0)	0 (0)	1 (5)	0 (0)
Previous myocardial infarction	6 (15)	6 (15)	2 (10)	2 (10)
Previous percutaneous coronary intervention	6 (15)	6 (15)	2 (10)	1 (5)
Previous coronary artery bypass graft	0 (0)	2 (5)	0 (0)	1 (5)
Previous bleeding requiring medical attention	2 (5)	3 (8)	1 (5)	0 (0)
Chronic obstructive pulmonary disease	4 (10)	4 (10)	0 (0)	3 (14)
Symptom onset to percutaneous coronary intervention, h				
<3	23 (57)	19 (48)	9 (43)	12 (57)
3 to 6	6 (15)	7 (18)	5 (24)	3 (14)
>6	11 (28)	14 (35)	7 (33)	6 (29)
Baseline medications				
Aspirin, daily dose ≤100 mg	6 (15)	9 (23)	4 (19)	2 (10)
Oral anticoagulants	0 (0)	0 (0)	0 (0)	0 (0)
Statins	10 (25)	10 (25)	4 (19)	5 (24)
Other lipid-lowering drug	3 (8)	0 (0)	1 (5)	1 (5)
Angiotensin-converting enzyme inhibitor	5 (13)	9 (23)	1 (5)	1 (5)
Angiotensin II antagonist	5 (13)	4 (10)	6 (29)	5 (24)
β-Blocker	7 (18)	8 (20)	3 (14)	2 (10)
Amiodarone	0 (0)	0 (0)	1 (5)	0 (0)
Calcium antagonist	5 (13)	6 (15)	3 (14)	2 (10)
Nitrates	0 (0)	0 (0)	0 (0)	0 (0)
Diuretics	7 (18)	4 (10)	7 (33)	2 (10)
Insulin	0 (0)	2 (5)	0 (0)	0 (0)
Oral antidiabetic	5 (13)	5 (13)	3 (14)	3 (14)
Nonsteroidal anti-inflammatory drug	2 (5)	2 (5)	0 (0)	1 (5)
Antidepressant drug	0 (0)	3 (8)	2 (10)	2 (10)
Proton pump inhibitor	5 (13)	8 (20)	3 (14)	4 (19)

Data are mean±SD or n (%).

I and Table VII in the Data Supplement). Chewed prasugrel was associated with lower platelet aggregation than integral prasugrel at 30 minutes and 1 hour. Tirofiban was associated with higher TRAP-induced platelet aggregation compared with cangrelor or chewed prasugrel (P<0.001 at any time point for both comparisons) whereas there was no difference between cangrelor and chewed prasugrel or between the 2 prasugrel groups.

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Table 2. Clinical Presentation and Catheterization Laboratory Data

Variable	Cangrelor (n=40)	Tirofiban (n=40)	Chewed Prasugrel (n=21)	Cangrelor vs Tirofiban, *P* Value	Cangrelor vs Chewed Prasugrel, *P* Value	Tirofiban vs Chewed Prasugrel, *P* Value	Integral Prasugrel (n=21)	Integral Prasugrel vs Chewed Prasugrel, *P* Value
Presentation								
Systolic arterial pressure, mm Hg	140.0±29.0	141.1±32.9	149.4±27.2	0.877	0.223	0.323	142.2±37.9	0.481
Diastolic arterial pressure, mm Hg	81.5±17.2	83.9±19.8	83.0±13.8	0.555	0.718	0.857	78.7±11.6	0.271
Heart rate, beats/min	76.5±15.9	80.1±16.1	75.9±12.9	0.311	0.893	0.307	73.7±14.3	0.606
Killip class				0.524	0.715	0.569		0.078
I	28 (70)	26 (65)	16 (76)	0.812	0.766	0.561	20 (95)	0.184
II	11 (28)	13 (33)	5 (24)	0.808	1.000	0.564	1 (5)	0.184
III	1 (3)	0 (0)	0 (0)	1.000	1.000		0 (0)	
IV	0 (0)	1 (3)	0 (0)	1.000		1.000	0 (0)	
Left ventricular ejection fraction, %	46.4±9.1	45.0±9.9	44.7±10.0	0.527	0.524	0.918	48.5±9.7	0.242
Cardiac arrest	1 (3)	3 (8)	0 (0)	0.615	1.000	0.545	1 (5)	1.000
≥2 Episodes of chest pain in the past 24 h	13 (33)	12 (30)	7 (33)	1.000	1.000	0.780	6 (29)	1.000
Rhythm				0.122	0.164	0.696		0.311
Sinus rhythm	40 (100)	36 (90)	20 (95)	0.116	0.344	0.651	21 (100)	1.000
Atrial fibrillation	0 (0)	3 (8)	1 (5)	0.241	0.344	1.000	0 (0)	1.000
Other rhythm	0 (0)	1 (3)	0 (0)	1.000		1.000	0 (0)	
Intraventricular conduction defects	3 (8)	7 (18)	2 (10)	0.311	1.000	0.479	2 (10)	1.000
Left bundle branch block	1 (3)	5 (13)	1 (5)	0.201	1.000	0.654	1 (5)	1.000
Right bundle branch block	2 (5)	1 (3)	1 (5)	1.000	1.000	1.000	1 (5)	1.000
Other conduction defect	0 (0)	1 (3)	0 (0)	1.000		1.000	0 (0)	
Vasopressor (continuous infusion)	2 (5)	2 (5)	0 (0)	1.000	0.541	0.541	1 (5)	1.000
Catheterization								
First arterial access				0.762	0.881	0.685		0.679
Femoral	7 (18)	6 (15)	4 (19)	1.000	1.000	0.725	3 (14)	1.000
Radial	33 (83)	34 (85)	17 (81)	1.000	1.000	0.725	18 (86)	1.000
Shift to other access site				0.590	0.691	0.696		1.000
Not needed	38 (95)	36 (90)	20 (95)	0.675	1.000	0.651	20 (95)	1.000
To femoral	1 (3)	3 (8)	1 (5)	0.615	1.000	1.000	1 (5)	1.000
To radial	1 (3)	1 (3)	0 (0)	1.000	1.000	1.000	0 (0)	

Data are expressed as mean±SD (*P* values from *t* tests) or n (%; *P* values from Fisher exact tests or χ^2 tests).

Pharmacokinetic Assessment

Chewed prasugrel, compared with integral prasugrel, was associated with higher PAM levels at 15, 30, and 60 minutes, but not thereafter. Maximum observed plasma concentration, time to maximum plasma concentration, $AUC_{0\ to\ 2\ hours}$ and $AUC_{0\ to\ 4\ hours}$ did not differ between the 2 prasugrel groups. $AUC_{0\ to\ 30\ minutes}$ and $AUC_{0\ to\ 1\ hour}$ were both significantly higher with chewed compared with integral prasugrel (Figure 5 and Table 3).

DISCUSSION

To our knowledge, our study is the first to compare the pharmacodynamic effects of cangrelor, a direct parenteral $P2Y_{12}$ inhibitor, with tirofiban, a GPI, as well as the pharmacodynamic and pharmacokinetic effects of a 60-mg chewed or integral pill intake of prasugrel, an oral indirect $P2Y_{12}$ inhibitor. The following are the main findings of the study (Figure 6):

- Cangrelor did not reach noninferiority with tirofiban at ADP-induced platelet aggregation; the latter showed superior platelet inhibition at 30 minutes as well as at all other time points.
- Cangrelor and tirofiban provided superior inhibition of platelet aggregation after ADP compared with chewed prasugrel at 30 minutes. Tirofiban remained associated with higher inhibition of ADP-induced platelet aggregation at all time points.

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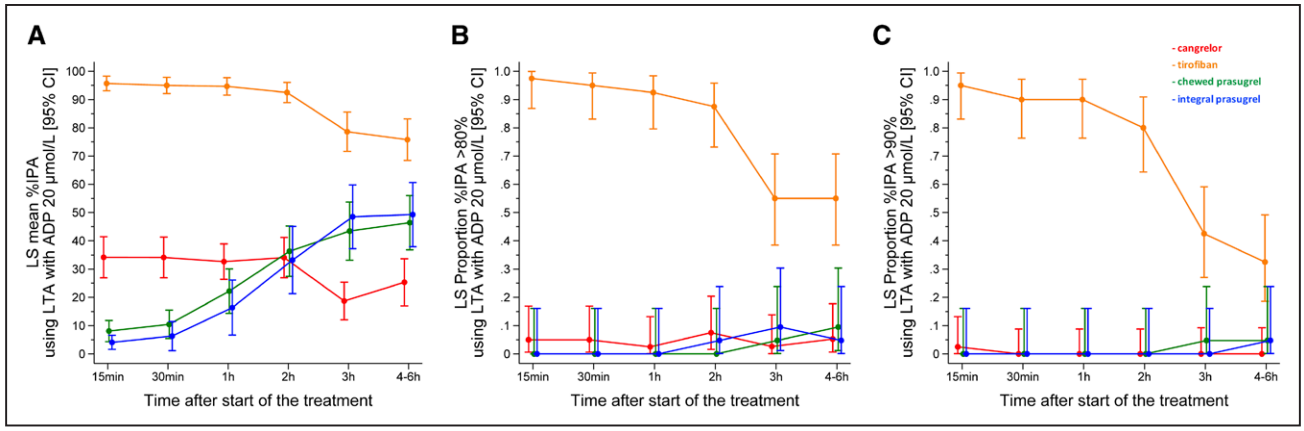


Figure 2. Pharmacodynamic effects of drugs measured by LTA after ADP 20 µmol/L stimulation.
A, Percentage of inhibition of platelet aggregation (IPA). **B**, IPA >80%. **C**, IPA >90%. ADP indicates adenosine diphosphate; CI, confidence interval; LS, least square; and LTA, light transmittance aggregometry.

Cangrelor, on the other hand, proved superior to chewed prasugrel at ADP-induced platelet aggregation test up to 1 hour from drug administration, but it provided similar treatment effect at 2 hours and lower IPA at later assessments.

- Chewed prasugrel, compared with integral prasugrel, did not provide greater ADP-induced IPA despite providing greater active metabolite bioavailability up to 1 hour after drug administration.
- TRAP-induced platelet aggregation was profoundly inhibited by tirofiban infusion whereas it was mildly affected by cangrelor or chewed or integral prasugrel at peak effects (ie, early after bolus administration for cangrelor and at 3 hours and 4 to 6 hours for both prasugrel arms).

On-treatment residual platelet reactivity measured at the time of intervention with LTA in response to ADP or at other platelet function assays correlates with myocardial damage, ST-segment–elevation resolution, procedural success, and clinical outcomes among patients with STEMI.[24,25] Standard loading dose of newer $P2Y_{12}$ inhibitors, even when administered at first medical contact, provides only limited IPA at the time of intervention,[5,7] which led to the investigation of alternative treatment strategies aiming at enhancing early suppression of platelet reactivity, procedural success, and potentially improved outcomes among patients with STEMI.

Numerous studies have formed the basis for the currently approved cangrelor regimen.[12,13] Yet, none of them included patients with STEMI and the majority of them evaluated multiple maintenance cangrelor regimens administered for several hours while omitting an initial bolus regimen. Among 14 patients with unstable angina or non–Q-wave MI, treated with aspirin, UFH, and cangrelor infusion at 4 µg/kg/min for up to 69 hours, mean IPA was 98.7±2.1% at 24

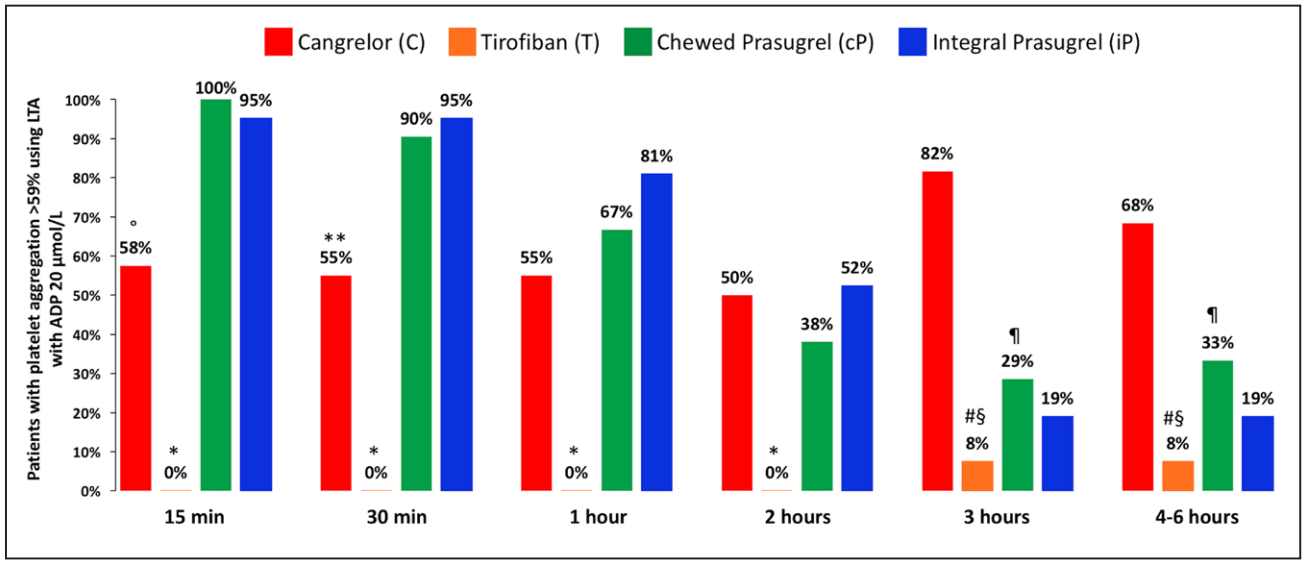


Figure 3. Rates of high residual platelet reactivity defined by platelet aggregation >59% at LTA after ADP 20 µmol/L stimulation.
°*P*<0.001 versus cP; **P*<0.001 versus C and cP; ***P*<0.05 versus cP; #*P*<0.001 versus C; §*P*<0.05 versus cP; ¶*P*<0.01 versus C. ADP indicates adenosine diphosphate; and LTA, light transmittance aggregometry.

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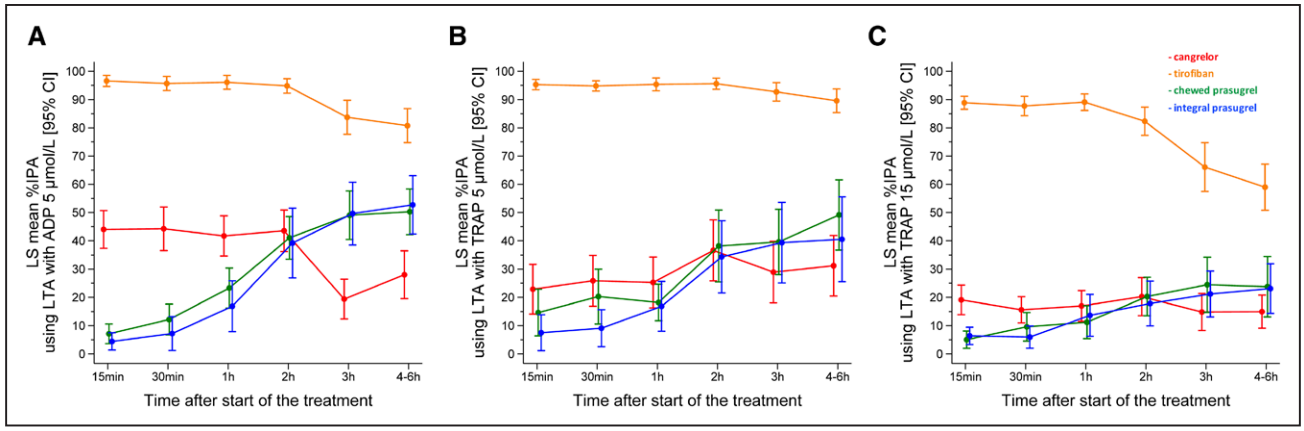


Figure 4. Pharmacodynamic effects of drugs measured by LTA.
Pharmacodynamic effects of drugs measured by LTA after stimulation with ADP 5 µmol/L (**A**) and TRAP 15 (**B**) and 5 (**C**) µmol/L. ADP indicates adenosine diphosphate; CI, confidence interval; IPA, inhibition of platelet aggregation; LS, least square; LTA, light transmittance aggregometry; and TRAP, thrombin receptor agonist peptide.

hours measured through whole blood impedance aggregometry and using ADP 3 µmol/L as agonist.[26] In another randomized trial (composed of 2 parts) including overall 399 patients undergoing elective or urgent PCI, but excluding patients with STEMI, the mean %IPA measured with impedance aggregometry in heparinized blood in response to ADP 3 µmol/L was 99% for those receiving cangrelor infusion at 4 µg/kg/min.[27] During part 2, the mean platelet inhibition was 100% before the end of infusion for both cangrelor 4 µg/kg/min and abciximab groups with 95% and 100% of patients achieving 100% platelet inhibition, respectively.[27]

Across these pivotal dose-finding studies, response to 3 µmol/L of ADP was chosen because this concentration was found to produce maximal or just submaximal activation when testing with impedance aggregometry in heparinized blood and a degree of activation similar

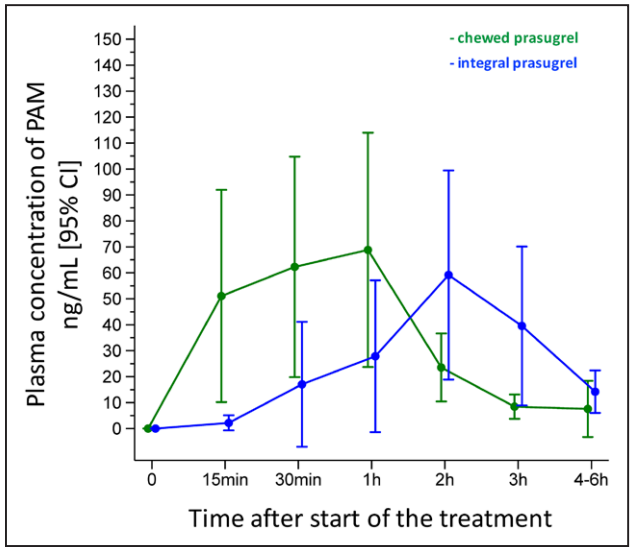


Figure 5. Pharmacokinetic analysis comparing PAM concentrations between chewed and integral prasugrel groups.
CI indicates confidence interval; and PAM, prasugrel active metabolite.

to that seen with 5 to 20 µmol/L of ADP when using optical aggregometry in citrated platelet-rich plasma.[27]

We therefore anticipated a nearly maximal IPA in response to 20 µmol/L of ADP at optical aggregometry in citrated platelet-rich plasma and powered the study for noninferiority based on a stringent noninferiority margin. Our findings show that cangrelor provides a quicker onset of action among patients with STEMI as compared with prasugrel, administered with either chewed or integral pill loading dose. Yet, cangrelor yielded lower than expected and inferior IPA than tirofiban throughout the study duration as well as than prasugrel at 3 hours or 4 to 6 hours after drug administration. This latter finding likely reflects the fast recovery of platelet function at the end of cangrelor infusion and the time needed for prasugrel to provide sufficient IPA once cangrelor infusion is terminated. IPA in response to 5 or 20 µmol/L ADP was lower with cangrelor during drug infusion as compared with prasugrel peak effect at 3 hours or 4 to 6 hours. Patients with STEMI have higher platelet reactivity,[28] have higher expression of $P2Y_{12}$ receptor,[29] and require greater concentration of antiplatelet agents to achieve similar IPA as compared with healthy subjects or patients without ongoing myocardial ischemia undergoing elective coronary artery disease.[30] It was previously observed that, among patients with type 2 diabetes mellitus, in whom enhanced platelet $P2Y_{12}$ receptor expression occurs, cangrelor yields lower IPA compared with nondiabetic patients.[31] Whether an increased cangrelor regimen is required to yield greater IPA among STEMI, and in a similar order of magnitude as previously observed in patients undergoing elective procedures, remains speculative. The CANTIC study (Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) assessed pharmacodynamic effects of standard cangrelor regimen versus placebo as $P2Y_{12}$ reaction units (PRUs) by VerifyNow and platelet reactivity index by vasodilator-stimulated

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Table 3. Pharmacokinetic Analysis Comparing Prasugrel Active Metabolite Concentrations Between Chewed and Integral Prasugrel Groups

Prasugrel Active Metabolite	Chewed Prasugrel (n=17)	Integral Prasugrel (n=15)	Chewed Prasugrel vs Integral Prasugrel Least Square Mean Difference or Mean Difference (95% CI)	Integral Prasugrel vs Chewed Prasugrel, *P* Value
Baseline	0.000±0.000	0.000±0.000		
15 min	51.066±79.488	2.184±5.252	48.9 (12.1 to 85.7)	0.009
30 min	62.289±82.626	17.052±43.453	45.2 (8.4 to 82.1)	0.016
1 h	68.836±87.797	27.861±52.841	41.0 (4.2 to 77.8)	0.029
2 h	23.518±25.491	59.164±72.739	−35.6 (−72.5 to 1.2)	0.058
3 h	8.446±9.127	39.544±55.248	−31.1 (−67.9 to 5.7)	0.098
4 to 6 h	7.582±20.270	14.208±14.777	−5.7 (−43.0 to 31.6)	0.766
Tmax	1.441±1.316	1.933±1.033	−0.5 (−1.3 to 0.3)	0.244
Cmax	98.795±86.493	94.634±79.108	4.2 (−53.6 to 61.9)	0.888
$AUC_{0\ to\ 4\ h}$	124.787±117.474	136.219±104.129	−11.4 (−88.8 to 65.9)	0.772
$AUC_{0\ to\ 2\ h}$	101.286±112.093	60.029±68.782	41.3 (−24.3 to 106.8)	0.217
$AUC_{0\ to\ 1\ h}$	55.106±67.246	16.525±33.094	38.6 (1.0 to 76.1)	0.044
$AUC_{0\ to\ 30\ min}$	9.214±13.664	0.758±1.341	8.5 (1.5 to 15.4)	0.017

Data are expressed as least square mean±SD (*P* values from mixed models) for 15 min to 4 to 6 h (in ng/mL) and mean±SD for time for the maximum plasma concentration (Tmax), maximum observed plasma concentration (Cmax; in ng/mL), and area under the plasma concentration vs time curve (AUC) mean units (*P* values from separate general linear models). In 1 patient randomized to chewed prasugrel, the assessment at 4 to 6 h was not available.

phosphoprotein in patients with STEMI undergoing PCI concomitantly treated with crushed ticagrelor.[32] In the cangrelor plus ticagrelor arm, median PRU value was 63, with an interquartile range of 32 to 93. No patient with cangrelor had a PRU higher than 208 U during drug infusion. Yet, this cutoff value for defining nonresponsiveness to $P2Y_{12}$ inhibitors was generated for the prediction of out-of-hospital events among patients who underwent elective PCI and it remains unclear whether it applies to patients with STEMI undergoing emergency treatment.[33] It is interesting that 3 out of 22 patients remained nonresponders to cangrelor at vasodilator-stimulated phosphoprotein assay during drug infusion.[32] Alexopoulos et al[34] reported that HRPR was 6.7% at 15 minutes and 0% at 1 hour (using VerifyNow and a cutoff of PRU >208) in 15 patients with STEMI receiving cangrelor (pretreated with ticagrelor; none of them received morphine). Ubaid et al[35] reported an HRPR rate of 10% (using VerifyNow and a cutoff of PRU >208) at the time of balloon inflation in 50 cangrelor-treated patients with STEMI. In Buchtele et al,[36] 16 cardiac arrest survivors with STEMI, who were treated with targeted temperature management, received cangrelor, and none had HRPR (using Multiplate Analyzer, platelet function had a median 18 U, interquartile range 10 to 25; <46 U was used as the cutoff). Our results show a much higher rate of HRPR during cangrelor infusion (50% to 58%) at LTA test after 20 µmol/L ADP stimulation, whereas HRPR ranged from 8.6% at 15 minutes to ≈14% at 30 minutes and 2 hours at Multiplate testing. Therefore, whereas the rates of HRPR varied across STEMI studies, most likely reflecting different platelet function tests and test-specific HRPR cutoffs, almost all STEMI studies have identified some degree of hyporesponsiveness to cangrelor.

Unlike cangrelor and prasugrel, tirofiban exerts a downstream IPA by blocking the glycoprotein IIb/IIIa receptor. This explains our observations on TRAP-induced platelet aggregation, which was profoundly inhibited by tirofiban but not with cangrelor or prasugrel. In keeping with previous observations,[7] our results confirm that $P2Y_{12}$ inhibition exerts a mild yet measurable effect on TRAP-induced platelet aggregation.

A strategy to crush a standard loading dose of ticagrelor or prasugrel has resulted in greater drug bioavailability and higher IPA in the first few hours after drug administration compared with whole tablets in patients with STEMI.[11,13] However, crushing tablets requires available dedicated point-of-care devices. Recently, chewed ticagrelor resulted in a more rapid platelet inhibition compared with crushed or whole tablets among patients undergoing coronary angiography for stable angina.[10] No study had so far examined whether chewed prasugrel increases PAM bioavailability and allows a more rapid IPA among patients with STEMI. In our study, chewed compared with integral prasugrel was associated with higher PAM levels up to 1 hour after drug administration. Despite numeric higher IPA with chewed prasugrel, at no time point was IPA significantly greater than integral prasugrel at LTA measurements. At Multiplate testing, IPA was greater with chewed as compared with integral prasugrel at 30 and 60 minutes. Yet, this assay was performed in only 2 out of 3 centers participating in the study and thus was available in a subset of patients (n=108).

Our results are consistent with previous observations suggesting that crumbling $P2Y_{12}$ inhibitor tablets

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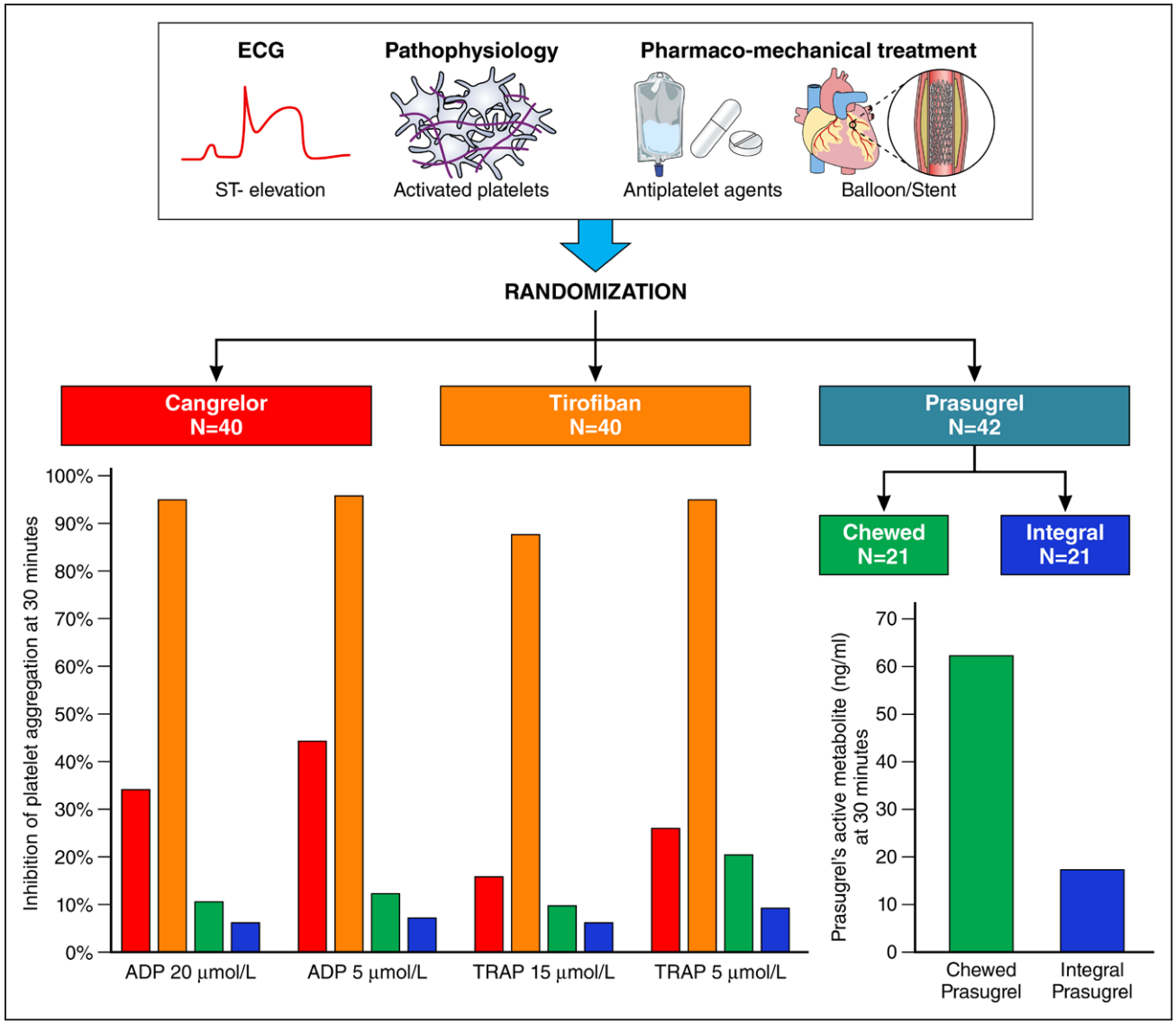


Figure 6. Pharmacodynamic and pharmacokinetic effects of cangrelor, tirofiban, and prasugrel (chewed or integral) in patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention 30 minutes after drug administration.
ADP indicates adenosine diphosphate; and TRAP, thrombin receptor agonist peptide.

increases early drug availability. However, in the setting of our multicenter study, chewed tablets resulted in only a mild and lower than anticipated IPA increase in the first hour after drug administration.

Our study might have important clinical implications. First, the comparative efficacy data of intravenous agents with chewed prasugrel reinforces the superiority notion of parenteral over oral antiplatelet medications in the acute phase of STEMI treatment. Second, among parenteral drugs, tirofiban demonstrated superior efficacy than cangrelor, which in turn was associated with relatively high HRPR rates, suggesting that GPI might be preferable over cangrelor to minimize the risk of acute ischemic complications. A recent large retrospective study suggested that a short regimen of GPI was protective against stent thrombosis risk in morphine-treated patients with STEMI (who are potentially exposed to increased risk of acute stent thrombosis owing to delayed absorption of oral $P2Y_{12}$ inhibitors).[37] In recent years, the use of GPI has declined, mainly because of the perception that the ischemic benefits are counterbalanced by bleeding risks.[3] Yet, clinical data on GPI are mainly based on prolonged post-bolus drug infusion and femoral access site at the time of intervention. Large-scale trials reassessing the comparative risks and benefits of short infusion of parenteral platelet inhibitors such as cangrelor or GPI compared with newer oral $P2Y_{12}$ receptor blockers alone in contemporary primary PCI practice remain desirable.

Limitations

Our study was mechanistic in nature and was not powered for clinical end points. Whereas multiple prior studies have shown an association between low residual platelet

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reactivity and better ischemic outcomes during and after PCI among patients undergoing elective procedures as well as patients with STEMI, the comparative efficacy and safety profile of cangrelor, tirofiban, or prasugrel in patients undergoing primary PCI remain to be established in an adequately powered clinical trial. A single study has suggested that prasugrel can be given at the start of cangrelor infusion, without evidence of drug–drug interaction.[38] Whether this evidence applies to patients with STEMI is unknown and this treatment strategy remains off-label. Applicability to ticagrelor loading, which is mostly used in clinical practice at the beginning of cangrelor infusion or before primary PCI,[39,40] cannot be claimed. However, on the basis of our observation that cangrelor followed by prasugrel associates with a rebound of platelet activation at 2 to 4 hours and on previous data showing some HRPR during and after cangrelor infusion,[32,34] one could speculate that when cangrelor is used, ticagrelor might be the preferred oral $P2Y_{12}$ inhibitor. It remains unclear whether the test-specific cutoffs used to define HRPR rates retain prognostic implications for the acute treatment of STEMI, considering that they were generated mainly for stable or stabilized patients receiving oral $P2Y_{12}$ inhibitors.

Conclusions

Among patients with STEMI undergoing primary PCI, cangrelor provided inferior IPA compared with tirofiban; both parenteral treatment strategies yielded superior IPA during drug infusion compared with chewed prasugrel, which, despite achieving early higher active metabolite concentrations, did not lead to greater IPA compared with integral prasugrel.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement Tables I–VII
Data Supplement Figure I
Study Protocols (Swiss and Italian versions)
Statistical Analysis Plan

REFERENCES

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119–177. doi: 10.1093/eurheartj/ehx393
2. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol.* 2016;67:1235–1250. doi: 10.1016/j.jacc.2015.10.005
3. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87–165. doi: 10.1093/eurheartj/ehy394
4. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, et al; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018;39:213–260. doi: 10.1093/eurheartj/ehx419
5. Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, Koutsogiannis N, Damelou A, Tsigkas G, Davlouros P, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv.* 2012;5:797–804. doi: 10.1161/CIRCINTERVENTIONS.112.972323
6. Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, Carrabba N, Santini A, Gensini GF, Abbate R, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs)

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primary PCI study. *J Am Coll Cardiol.* 2013;61:1601–1606. doi: 10.1016/j.jacc.2013.01.024
7. Valgimigli M, Tebaldi M, Campo G, Gambetti S, Bristot L, Monti M, Parrinello G, Ferrari R; FABOLUS PRO Investigators. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation Through Aggrastat By Dropping or Shortening Infusion Line in Patients With ST-Segment Elevation Myocardial Infarction Compared to or on Top of Prasugrel Given at Loading Dose) trial. *JACC Cardiovasc Interv.* 2012;5:268–277. doi: 10.1016/j.jcin.2012.01.006
8. Parodi G, Xanthopoulou I, Bellandi B, Gkizas V, Valenti R, Karanikas S, Migliorini A, Angelidis C, Abbate R, Patsilinakos S, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. *J Am Coll Cardiol.* 2015;65:511–512. doi: 10.1016/j.jacc.2014.08.056
9. Rollini F, Franchi F, Hu J, Kureti M, Aggarwal N, Durairaj A, Park Y, Seawell M, Cox-Alomar P, Zenni MM, et al. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study. *J Am Coll Cardiol.* 2016;67:1994–2004. doi: 10.1016/j.jacc.2016.02.045
10. Venetsanos D, Sederholm Lawesson S, Swahn E, Alfredsson J. Chewed ticagrelor tablets provide faster platelet inhibition compared to integral tablets: the inhibition of platelet aggregation after administration of three different ticagrelor formulations (IPAAD-Tica) study, a randomised controlled trial. *Thromb Res.* 2017;149:88–94. doi: 10.1016/j.thromres.2016.10.013
11. Serenelli M, Pavasini R, Vitali F, Tonet E, Bilotta F, Parodi G, Campo G. Efficacy and safety of alternative oral administrations of P2Y12-receptor inhibitors: systematic review and meta-analysis. *J Thromb Haemost.* 2019;17:944–950. doi: 10.1111/jth.14434
12. Ferreiro JL, Ueno M, Angiolillo DJ. Cangrelor: a review on its mechanism of action and clinical development. *Expert Rev Cardiovasc Ther.* 2009;7:1195–1201. doi: 10.1586/erc.09.101
13. Gargiulo G, Esposito G, Cirillo P, Nagler M, Minuz P, Campo G, Gragnano F, Manavifar N, Piccolo R, Avvedimento M, et al. Facilitation through aggrastat or cangrelor bolus and infusion over prasugrel: a Multicenter Randomized Open-Label Trial in Patients With ST-Elevation Myocardial Infarction Referred for Primary Percutaneous Intervention (FABOLUS-FASTER) trial: design and rationale: the FABOLUS-FASTER trial [published online February 24, 2020]. *J Cardiovasc Transl Res*. doi: 10.1007/s12265-020-09969-4. https://link.springer.com/article/10.1007%2Fs12265-020-09969-4
14. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, Collet JP, Cuisset T, Franchi F, Gross L, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2019;12:1521–1537. doi: 10.1016/j.jcin.2019.03.034
15. Sibbing D, Braun S, Morath T, Mehilli J, Vogt W, Schömig A, Kastrati A, von Beckerath N. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. *J Am Coll Cardiol.* 2009;53:849–856. doi: 10.1016/j.jacc.2008.11.030
16. Farid NA, McIntosh M, Garofolo F, Wong E, Shwajch A, Kennedy M, Young M, Sarkar P, Kawabata K, Takahashi M, et al. Determination of the active and inactive metabolites of prasugrel in human plasma by liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom.* 2007;21:169–179. doi: 10.1002/rcm.2813
17. Aradi D, Storey RF, Komócsi A, Trenk D, Gulba D, Kiss RG, Husted S, Bonello L, Sibbing D, Collet JP, et al; Working Group on Thrombosis of the European Society of Cardiology. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. *Eur Heart J.* 2014;35:209–215. doi: 10.1093/eurheartj/eht375
18. Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, Becker R, Bhatt DL, Cattaneo M, Collet JP, Cuisset T, et al; Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol.* 2010;56:919–933. doi: 10.1016/j.jacc.2010.04.047
19. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol.* 2018;72:2231–2264. doi: 10.1016/j.jacc.2018.08.1038
20. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, et al; Academic Research Consortium. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium–2 consensus document. *Circulation.* 2018;137:2635–2650. doi: 10.1161/CIRCULATIONAHA.117.029289
21. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449
22. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial: phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol.* 1988;11:1–11. doi: 10.1016/0735-1097(88)90158-1
23. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673–682. doi: 10.1056/NEJM199309023291001
24. Campo G, Valgimigli M, Gemmati D, Percoco G, Tognazzo S, Cicchitelli G, Catozzi L, Malagutti P, Anselmi M, Vassanelli C, et al. Value of platelet reactivity in predicting response to treatment and clinical outcome in patients undergoing primary coronary intervention: insights into the STRATEGY study. *J Am Coll Cardiol.* 2006;48:2178–2185. doi: 10.1016/j.jacc.2005.12.085
25. Frossard M, Fuchs I, Leitner JM, Hsieh K, Vlcek M, Losert H, Domanovits H, Schreiber W, Laggner AN, Jilma B. Platelet function predicts myocardial damage in patients with acute myocardial infarction. *Circulation.* 2004;110:1392–1397. doi: 10.1161/01.CIR.0000141575.92958.9C
26. Storey RF, Oldroyd KG, Wilcox RG. Open multicentre study of the P2T receptor antagonist AR-C69931MX assessing safety, tolerability and activity in patients with acute coronary syndromes. *Thromb Haemost.* 2001;85:401–407.
27. Greenbaum AB, Grines CL, Bittl JA, Becker RC, Kereiakes DJ, Gilchrist IC, Clegg J, Stankowski JE, Grogan DR, Harrington RA, et al. Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: results from a 2-part, phase II, multicenter, randomized, placebo- and active-controlled trial. *Am Heart J.* 2006;151:689.e1–689.e10. doi: 10.1016/j.ahj.2005.11.014
28. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med.* 2007;357:2482–2494. doi: 10.1056/NEJMra071014
29. Liverani E, Kilpatrick LE, Tsygankov AY, Kunapuli SP. The role of $P2Y_{12}$ receptor and activated platelets during inflammation. *Curr Drug Targets.* 2014;15:720–728. doi: 10.2174/1389450115666140519162133
30. Kabbani SS, Aggarwal A, Terrien EF, DiBattiste PM, Sobel BE, Schneider DJ. Suboptimal early inhibition of platelets by treatment with tirofiban and implications for coronary interventions. *Am J Cardiol.* 2002;89:647–650. doi: 10.1016/s0002-9149(01)02319-0
31. Hu L, Chang L, Zhang Y, Zhai L, Zhang S, Qi Z, Yan H, Yan Y, Luo X, Zhang S, et al. Platelets express activated P2Y12 receptor in patients with diabetes mellitus. *Circulation.* 2017;136:817–833. doi: 10.1161/CIRCULATIONAHA.116.026995
32. Franchi F, Rollini F, Rivas A, Wali M, Briceno M, Agarwal M, Shaikh Z, Nawaz A, Silva G, Been L, et al. Platelet inhibition with cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation.* 2019;139:1661–1670. doi: 10.1161/CIRCULATIONAHA.118.038317
33. Campo G, Fileti L, de Cesare N, Meliga E, Furgieri A, Russo F, Colangelo S, Brugaletta S, Ferrari R, Valgimigli M; 3T/2R Investigators. Long-term clinical outcome based on aspirin and clopidogrel responsiveness status after elective percutaneous coronary intervention: a 3T/2R (tailoring treatment with tirofiban in patients showing resistance to aspirin and/or resistance to clopidogrel) trial substudy. *J Am Coll Cardiol.* 2010;56:1447–1455. doi: 10.1016/j.jacc.2010.03.103
34. Alexopoulos D, Pappas C, Sfantou D, Xanthopoulou I, Didagelos M, Kikas P, Ziakas A, Tziakas D, Karvounis H, Iliodromitis E. Cangrelor in ticagrelor-loaded STEMI patients undergoing primary percutaneous coronary intervention. *J Am Coll Cardiol.* 2018;72:1750–1751. doi: 10.1016/j.jacc.2018.07.041
35. Ubaid S, Ford TJ, Berry C, Murray HM, Wrigley B, Khan N, Thomas MR, Armesilla AL, Townend JN, Khogali SS, et al. Cangrelor versus ticagrelor in patients treated with primary percutaneous coronary intervention: impact on platelet activity, myocardial microvascular function and infarct size: a randomized controlled trial. *Thromb Haemost.* 2019;119:1171–1181. doi: 10.1055/s-0039-1688789

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36. Buchtele N, Herkner H, Schorgenhofer C, Merrelaar A, Laggner R, Gelbenegger G, Spiel AO, Domanovits H, Lang I, Jilma B, et al. High platelet reactivity after transition from cangrelor to ticagrelor in hypothermic cardiac arrest survivors with ST-segment elevation myocardial infarction. *J Clin Med*. 2020;9:E583. doi: 10.3390/jcm9020583
37. Zwart B, Yazdani M, Ow KW, Richardson JD, Iqbal J, Gunn JP, Storey RF. Use of glycoprotein IIb/IIIa antagonists to prevent stent thrombosis in morphine-treated patients with ST-elevation myocardial infarction. *Platelets*. 2020;31:174–178. doi: 10.1080/09537104.2019.1665642
38. Hochholzer W, Kleiner P, Younas I, Valina CM, Löffelhardt N, Amann M, Bömicke T, Ferenc M, Hauschke D, Trenk D, et al. Randomized comparison of oral P2Y12-receptor inhibitor loading strategies for transitioning from cangrelor: the ExcelsiorLOAD2 trial. *JACC Cardiovasc Interv*. 2017;10:121–129. doi: 10.1016/j.jcin.2016.10.004
39. Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, Sibbing D, So DYF, Trenk D, Alexopoulos D, et al. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. *Circulation*. 2017;136:1955–1975. doi: 10.1161/CIRCULATIONAHA.117.031164
40. Grimfjärd P, Lagerqvist B, Erlinge D, Varenhorst C, James S. Clinical use of cangrelor: nationwide experience from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J Cardiovasc Pharmacother*. 2019;5:151–157. doi: 10.1093/ehjcvp/pvz002

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Clopidogrel versus ticagrelor in high-bleeding risk patients presenting with acute coronary syndromes: insights from the multicenter START-ANTIPLATELET registry

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Abstract

Optimal dual antiplatelet therapy (DAPT) strategy in high-bleeding risk (HBR) patients presenting with acute coronary syndrome remains debated. We sought to investigate the use of clopidogrel versus ticagrelor in HBR patients with acute coronary syndrome and their impact on ischemic and bleeding events at 1 year. In the START-ANTIPLATELET registry (NCT02219984), consecutive patients with ≥ 1 HBR criteria were stratified by DAPT type in clopidogrel versus ticagrelor groups. The primary endpoint was net adverse clinical endpoints (NACE), defined as a composite of all-cause death, myocardial infarction, stroke, and major bleeding. Of 1209 patients with 1-year follow-up, 553 were defined at HBR, of whom 383 were considered eligible for the study as on DAPT with clopidogrel (174 or 45.4%) or ticagrelor (209 or 54.6%). Clopidogrel was more often administered in patients at increased ischemic and bleeding risk, while ticagrelor in those undergoing percutaneous coronary intervention. Mean DAPT duration was longer in the ticagrelor group. At 1 year, after multivariate adjustment, no difference in NACEs was observed between patients on clopidogrel versus ticagrelor (19% vs. 11%, adjusted hazard ratio 1.27 [95% CI 0.71–2.27], $p = 0.429$). Age, number of HBR criteria, and mean DAPT duration were independent predictors of NACEs. In a real-world registry of patients with acute coronary syndrome, 45% were at HBR and frequently treated with clopidogrel. After adjustment for potential confounders, the duration of DAPT, but not DAPT type (stratified by clopidogrel vs. ticagrelor), was associated with the risk of ischemic and bleeding events at 1 year.

Keywords Bleeding · Dual antiplatelet therapy · Clopidogrel · Ticagrelor · Percutaneous coronary intervention

Introduction

Dual antiplatelet therapy (DAPT) represents the cornerstone of treatment in patients presenting with acute coronary syndromes (ACS), with a proven benefit in terms of recurrent ischemic events [1]. Current guidelines recommend potent P2Y12 inhibitors as ticagrelor over clopidogrel as part of the DAPT after ACS, irrespective of final management strategy [1–3]. In the PLATO trial [4], ticagrelor significantly reduced the rate of composite ischemic endpoints after ACS compared with clopidogrel. However, the ischemic benefit came with an increased risk of major bleeding, which has been shown to adversely affect prognosis [5, 6].

The proper definition as well as invasive and pharmacological management of patients with coronary artery disease and deemed at high bleeding risk (HBR) remains

Drs. Felice Gragnano and Elisabetta Moscarella equally contributed to the manuscript and are joint first author.

The list of the START-ANTIPLATELET Collaborators are given in Acknowledgements.

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a clinical conundrum [7–11]. While assessing the individual risk of bleeding is of major importance to guide a tailored DAPT duration [7, 8], current guidelines do not recommend to prefer (the less potent) clopidogrel in HBR patients with ACS [1]. Nevertheless, data from real-world registries showed that ACS patients with factors predisposing to hemorrhagic complications are more likely to be treated with clopidogrel rather than ticagrelor compared with those without [12–15]. However, whether a clopidogrel-based strategy entails potential benefit or harm in HBR patients with ACS remains debated.

In this background, we sought to investigate the use of clopidogrel versus ticagrelor in consecutive ACS patients deemed at HBR enrolled in the real-world START-ANTIPLATELET registry and their impact on 1-year incidence of ischemic and bleeding events.

Methods

Study design and population

The START-ANTIPLATELET is a branch of the investigators-driven, non-sponsored, START registry (Survey on anticoagulated pAtients RegisTer, ClinicalTrials.gov: NCT02219984). Study design and results have already been reported elsewhere [16–18]. Briefly, the START-ANTIPLATELET is an all-comers, prospective, multicenter Italian real-world registry which enrolled consecutive patients admitted for ACS, with or without ST-segment elevation, since January 2014. No explicit exclusion criteria were applied. Each center identified two fixed days for enrolment during the week, and all consecutive patients admitted in those 2 days were included in the registry. All patients underwent clinical assessment during in-hospital stay for the index event (baseline), and subsequently at 6 months and 1 year. In the present study, a sub-group analysis was performed in high-bleeding risk patients (HBR group). Patients were considered at HBR if at least one of the following criteria was present: (1) clinical indication for long-term oral anticoagulation; (2) previous bleeding requiring medical attention and/or hospitalization; (3) age ≥ 75 years; (4) platelet count $< 100{,}000/mm^3$; (5) documented anemia defined as repeated hemoglobin levels < 11 g/dL; (6) history of chronic or recent transfusion (within 1 month before inclusion in the registry); (7) history of previous stroke; (8) severe or end-stage renal impairment (creatinine clearance < 30 mL/min); and (9) PRECISE-DAPT ≥ 25 [19]. Patients on oral anticoagulation therapy (in whom ticagrelor-based DAPT is discouraged by international guidelines) and those on prasugrel were excluded from this analysis.

Definition of clinical endpoints

One-year outcomes analysis comparing HBR patients treated with clopidogrel versus ticagrelor was performed. The primary endpoint was the occurrence of net adverse clinical endpoints (NACE) defined as a composite of all-cause death, myocardial infarction, stroke, and major bleeding events at 1 year. The secondary endpoints were major adverse cardiac and cerebral events (MACE), defined as a composite of all-cause death, myocardial infarction and stroke, each individual component of NACE and MACE, and target vessel revascularization. Myocardial infarction and all-cause death were defined according to the Academic Research Consortium criteria [20]. Coronary revascularization was defined as either percutaneous coronary intervention (PCI) or coronary artery bypass surgery. Stroke was defined as an abrupt onset of a focal neurologic deficit, generally distributed in the territory of a single brain artery, lasting more than 24 h [21]. Major bleeding was classified according to the Thrombolysis in Myocardial Infarction (TIMI) scale, as intracranial bleeding or overt bleeding associated with a decrease in hemoglobin > 5 g/dL [22].

Statistical analysis

Data are shown as mean and standard deviation or median and interquartile range in the case of continuous variables, and number and percentage for categorical variables. The normal distribution was preliminarily assessed through a Kolmogorov–Smirnov Goodness-of-Fit K–S test. Categorical data were compared using either the Pearson Chi-square test (with Mantel–Haenszel common odds ratio estimate) or Fisher exact test when indicated, and continuous variables by non-parametric Mann–Whitney *U* test or Kruskal–Wallis test, as appropriate. In case of a percentage of either row or column < 5 events, the Yates correction of continuity was also applied. Among HBR patients, all analyses were performed according to the treatment group (clopidogrel versus ticagrelor). Cumulative event rates were estimated by the Kaplan–Meier method and compared using the log-rank test. Hazard ratios and 95% confidence intervals (CI) were also calculated. A multivariable Cox regression model for NACE was performed, correcting for those clinical variables significantly different between groups. All variables significant at the univariate analysis were entered in a multivariable logistic regression model using a backward stepwise selection approach with a threshold set at 0.1, with a final adjustment model including age, PCI, smoking status, creatinine clearance, previous myocardial infarction, number of HBR criteria,

and DAPT duration. A p value < 0.05 was considered as statistically significant. All analyses were performed with the SPSS software (IBM, Armonk, New York), version 24, and STATA 14.0 software (StataCorp. 2015. College Station, TX: StataCorp LP).

Results

Among patients included in the START-ANTIPLATELET registry, 1209 patients enrolled between January 2014 and June 2018 completed the 1-year follow-up and were assessed for the present analysis. Of those, 553 (45%) patients were defined at HBR (Supplementary Tables 1 and 2), of whom 393 (71%) had ≥ 2 criteria. HBR patients had a significantly higher risk of NACEs and MACEs as compared with the non-HBR (Supplementary Table 3). After excluding patients on oral anticoagulants or prasugrel, the final study population consisted of 383 HBR patients, of whom 174 (45.4%) were on clopidogrel while 209 (54.6%) were on ticagrelor. Baseline characteristics are shown in Table 1.

Risk profile in HBR patients treated with clopidogrel or ticagrelor

Compared with HBR patients on ticagrelor, those treated with clopidogrel were more likely to be at increased ischemic risk (as expressed by a higher rate of previous myocardial

Table 1 Baseline and procedural characteristics in HBR patients on clopidogrel versus ticagrelor

	Clopidogrel ($n = 174$)	Ticagrelor ($n = 209$)	p-value
Age (years), mean (SD)	80.2 ± 9.9	78.5 ± 8.4	0.061
Male sex, *n* (%)	111 (63.8)	129 (61.7)	0.67
BMI (kg/m^2), mean (SD)	26 ± 4.1	26.3 ± 3.8	0.50
Hypertension, *n* (%)	137 (78.7)	170 (81.3)	0.52
Current smoker, *n* (%)	51 (29.3)	83 (39.7)	**0.034**
Hypercholesterolemia, *n* (%)	94 (54.0)	109 (52.2)	0.71
Diabetes, *n* (%)	69 (39.7)	67 (32.1)	0.12
Ejection fraction, mean (SD)	47.8 ± 10.8	47.3 ± 10.6	0.69
Family history of CVD, *n* (%)	36 (20.7)	54 (25.8)	0.23
Previous MI, *n* (%)	52 (29.9)	37 (17.7)	**0.005**
Previous PCI, *n* (%)	62 (35.6)	39 (18.7)	**< 0.001**
Multivessel CAD, *n* (%)	21 (12.1)	34 (16.3)	0.24
Prior bleeding, *n* (%)	5 (2.9)	4 (1.9)	0.78*
Type of bleeding, *n* (%)			0.38
Cerebral	2 (40.0)	3 (60.0)	
Gastrointestinal	3 (60.0)	1 (25.0)	
Genitourinary	0 (–)	1 (25.0)	
Prior TIA, *n* (%)	11 (6.3)	5 (2.4)	**0.056**
Prior ischemic stroke, *n* (%)	14 (8)	9 (4.3)	0.12
Peripheral artery disease, *n* (%)	2 (1.2)	8 (3.9)	0.10
History of heart failure, *n* (%)	3 (1.8)	10 (4.9)	0.099
Hemoglobin (g/dL), mean (SD)	12.2 ± 2.1	12.9 ± 2.0	**0.001**
Hematocrit (%), mean (SD)	37 ± 6.2	38.8 ± 5.7	**0.003**
Platelets (10^3), mean (SD)	215 ± 88.7	223.8 ± 67.1	0.26
Creatinine clearance, mean (SD)	52.5 ± 27.1	64.6 ± 25.9	**< 0.001**
PRECISE-DAPT score, mean (SD)	36.3 ± 13.4	29.2 ± 11.1	**< 0.001**
Clinical presentation, *n* (%)			0.066
STEMI	75 (43.1)	111 (53.1)	
NSTEMI	78 (44.8)	84 (40.2)	
Unstable angina	21 (12.1)	14 (6.7)	

Statistically significant differences (p value < 0.05) are reported in bold

BMI Body Mass Index, *CAD* coronary artery disease, *MI* myocardial infarction, *NSTEMI* non-ST-elevation myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST-elevation myocardial infarction, *SD* standard deviation, *TIA* transient ischemic attack

*Yates correction was applied due to the reduced number of events

infarction and previous PCI) and bleeding risk (as expressed by a more frequent diagnosis of anemia, thrombocytopenia, and severe chronic kidney disease, a higher PRECISE DAPT score, and a higher rate of ≥ 2 HBR criteria) (Figs. 1 and 2). Moreover, clopidogrel was more likely to be administered in medically managed patients, while ticagrelor in those receiving PCI. Mean DAPT duration was longer in the ticagrelor group (9.35 ± 5.4 months versus 10.40 ± 4.29 months; *p*-value = 0.035) (Table 2).

Clinical outcomes in HBR patients treated with clopidogrel versus ticagrelor

At 1-year follow-up, unadjusted risk of NACEs (19% vs. 11%, HR 1.82 [95% CI 1.07–3.09], $p = 0.028$) and MACEs (16.1% vs. 9.6%, HR 1.83 [95% CI 1.04–3.24], $p = 0.038$) was significantly higher in the clopidogrel than ticagrelor group (Fig. 3 and Table 3) mainly driven by a higher rate of death; while, no difference was observed in terms of major bleeding, stroke, or revascularization.

After multivariate adjustment, DAPT type stratified by the use of clopidogrel or ticagrelor was not associated with NACEs (adjusted HR 1.27 [95% CI 0.71–2.27], $p = 0.429$), MACEs (adjusted HR 1.19 [95% CI 0.63–2.24], $p = 0.592$), nor with any of the individual secondary endpoints (Fig. 3 and Table 3). Advanced age (adjusted HR 1.06 [95% CI 1.02–1.10], $p = 0.006$), total number of HBR criteria (adjusted HR 1.38 [95% CI 1.02–1.87], $p = 0.035$), and shorter DAPT duration (adjusted HR 0.76 [95% CI 0.71–0.81], $p < 0.001$) revealed independent predictors of NACEs in the HBR patients.

Discussion

The main findings of our analysis are the following. First, in real-world HBR ACS patients, clopidogrel is often preferred over ticagrelor as part of DAPT, especially in those with high ischemic and bleeding risk. Second, no difference was observed in terms of bleeding or ischemic events between

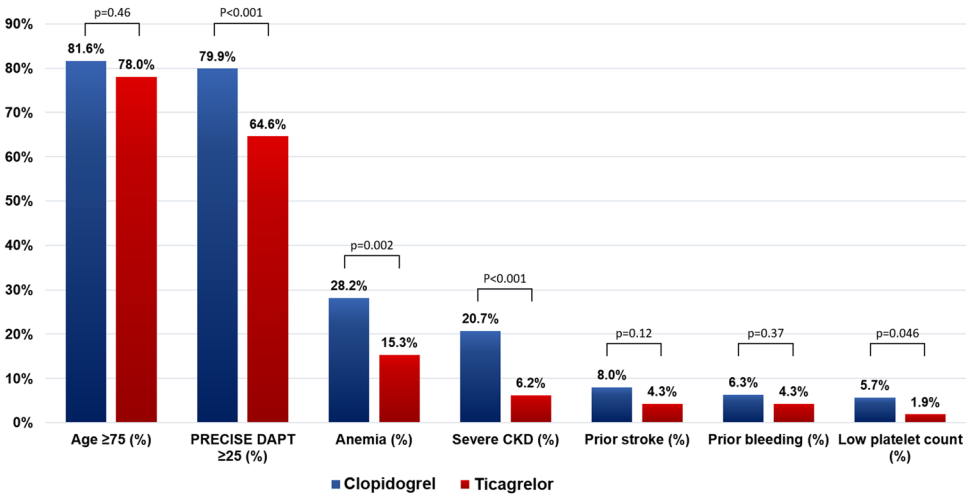


Fig. 1 HBR criteria distribution in patients on clopidogrel or ticagrelor. *CKD* chronic kidney disease

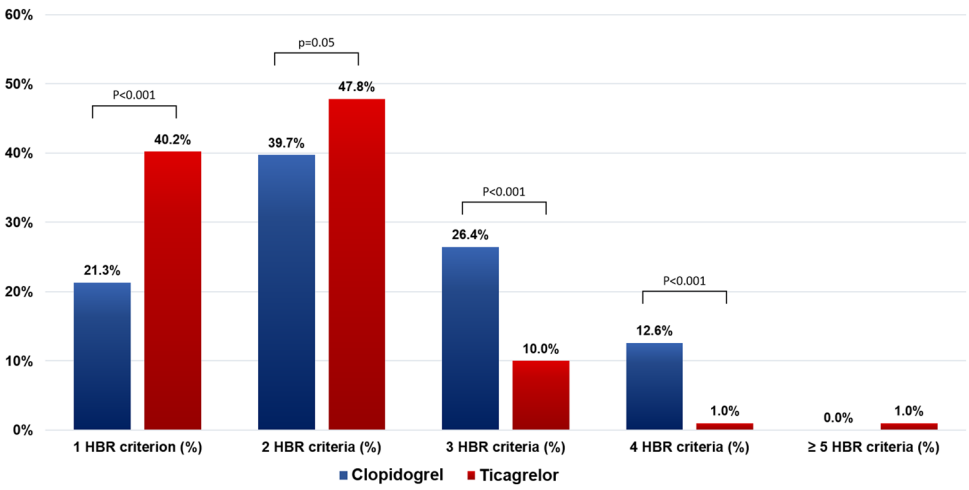


Fig. 2 Number of HBR criteria in patients on clopidogrel or ticagrelor. *HBR* high bleeding risk

Table 2 Revascularization strategy and medical therapy at discharge in HBR patients on clopidogrel versus ticagrelor

	Clopidogrel ($n=174$)	Ticagrelor ($n=209$)	p-value
Revascularization strategy			
PCI	130 (74.7)	193 (92.3)	**< 0.001**
Stent	117 (90.0)	184 (95.3)	0.062
Drug-eluting stent	112 (86.2)	176 (91.2)	0.21
Coronary artery bypass grafting, *n* (%)	4 (2.3)	3 (1.4)	0.53
Medical therapy, *n* (%)	42 (24.1)	12 (5.7)	**< 0.001**
Pharmacological therapy			
Proton pump inhibitors, *n* (%)	171 (98.3)	204 (97.6)	0.64
ACE-i/ARBs, *n* (%)	104 (59.8)	142 (67.9)	0.097
Beta blockers, *n* (%)	112 (64.4)	146 (69.9)	0.25
CCBs, *n* (%)	6 (14.3)	5 (6.3)	0.14
Diuretic, *n* (%)	72 (41.4)	68 (32.5)	0.074
Nitrates, *n* (%)	26 (14.9)	17 (8.1)	**0.036**
Statins, *n* (%)	165 (94.8)	204 (97.6)	0.14
Aspirin, *n* (%)	172 (98.9)	205 (98.1)	0.54
DAPT duration			**0.023**
Never done	5 (2.9)	3 (1.4)	
≤ 30 days	12 (6.9)	5 (2.4)	
> 30 days and < 6 months	15 (8.6)	6 (2.9)	
≥ 6 months and < 1 year	35 (20.1)	55 (26.3)	
= 1 year	95 (54.6)	124 (59.3)	
> 1 year	12 (6.9)	16 (7.7)	
DAPT ≥ 1 year	107 (61.5)	140 (67)	0.26
Total DAPT duration (months), mean ± SD	9.35 ± 5.4	10.40 ± 4.2	**0.035**

Statistically significant differences (p value < 0.05) are reported in bold

ACE-i/ARBs angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, *CCBs* calcium channel blockers, *DAPT* dual antiplatelet therapy, *PCI* percutaneous coronary intervention

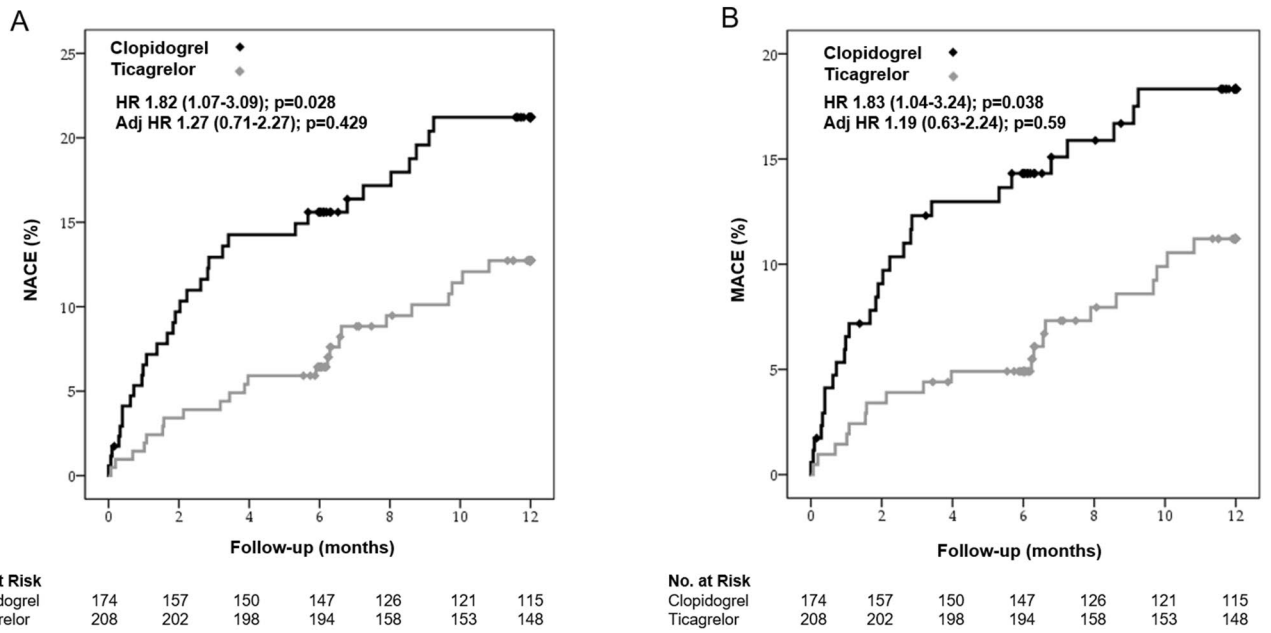


Fig. 3 Kaplan–Meier event curves for **a** NACE and **b** MACE at 1-year follow-up in HBR patients with acute coronary syndrome receiving either clopidogrel or ticagrelor. *Adj* adjusted for age, PCI, smoke, creatinine clearance, previous MI, number of HBR criteria, DAPT duration; *HR* hazard ratio

Table 3 Adjusted and unadjusted Cox multivariable regression model at 1 year for the study outcomes

	Clopidogrel ($n=174$)	Ticagrelor ($n=209$)	HR (CI 95%)	p-value
NACE	33 (18.96)	23 (11.00)	1.82 (1.07–3.09)	**0.028**
			1.27 (0.71–2.27)*	0.42*
MACE	28 (16.09)	20 (9.56)	1.83 (1.04–3.24)	**0.038**
			1.19 (0.63–2.24)*	0.59*
Myocardial infarction	8 (4.59)	7 (3.34)	1.45 (0.53–3.99)	0.47
			1.16 (0.38–3.54)*	0.79*
Target vessel revascularization	1 (0.57)	4 (1.91)	0.32 (0.04–2.86)	0.30
			0.32 (0.04–2.86)*	0.30*
Stroke	2 (1.14)	1 (0.47)	2.56 (0.23–28.23)	0.44
			2.11 (0.17–26.52)*	0.56*
Death	24 (13.79)	17 (8.13)	1.78 (0.96–3.32)	0.068
			1.13 (0.57–2.22)*	0.73*
Major bleeding	5 (2.87)	4 (1.91)	1.62 (0.43–6.02)	0.47
			1.59 (0.42–6.04)*	0.49*

Clopidogrel group was selected as reference

Statistically significant differences (p value < 0.05) are reported in bold

HR hazard ratio, *MACE* major adverse cardiac and cerebral events, *NACE* net adverse clinical events

*Adjusted for age, percutaneous coronary intervention, smoking status, creatinine clearance, previous myocardial infarction, number of high bleeding risk criteria, dual antiplatelet therapy duration

ticagrelor and clopidogrel after correction for potential confounders. Third, age, total number of HBR criteria, and DAPT duration revealed as independent predictors of NACEs in the HBR population.

In patients with ACS, 12-month DAPT with potent P2Y12 inhibitors, as ticagrelor, is strongly recommended over clopidogrel to reduce the risk of ischemic recurrences, irrespective of the treatment strategy [1]. However, the effective ischemic protection offered by stronger P2Y12 inhibition is potentially counterbalanced by an increased risk of bleeding [4]. Recently, increased attention has been focused on preventing bleeding complications in patients on DAPT, based on evidence showing that the risk of death after major bleeding is equal to (if not higher than) that following myocardial infarction [5, 6]. Although current guidelines do not recommend the use of clopidogrel over ticagrelor in HBR patients presenting with ACS [1], several registries have shown that clopidogrel is frequently preferred by clinicians in this setting (especially, in complex high-risk patients), a phenomenon also known as "treatment paradox" [12–14]. Moreover, prospective real-world registries have questioned the benefit of ticagrelor in high-risk ACS patients undergoing contemporary drug-eluting stenting [23–25]. For instance, subgroup analyses of the CHANGE DAPT study and SCOPE registry showed an increased risk of major bleeding in HBR patients treated with ticagrelor without any improvement in ischemic outcomes [23–25].

In the present sub-analysis of the START-ANTIPLATELET registry, we investigated the use of clopidogrel versus ticagrelor in consecutive ACS patients at HBR and their impact on ischemic and bleeding outcomes at 1 year. In line with previous reports [14, 25, 26], our study confirms the frequent use of clopidogrel in real-world practice, especially in ACS patients with high ischemic and/or bleeding risk. Indeed, we found that clopidogrel-treated patients had a higher prevalence of prior myocardial infarction and PCI, paired with a higher bleeding risk (higher rate of anemia, thrombocytopenia, severe chronic kidney disease, and PRECISE DAPT score and almost 80% had > 1 HBR criteria). In addition, our findings suggest that an increase in the number of HBR criteria is associated with an increase in the risk of NACE, in line with previous reports [8]. In our study, the lower rate of NACEs and death observed in ticagrelor-treated patients is likely to be due to confounding factors rather than ticagrelor per se. Of note, unlike the CHANGE DAPT HBR sub-study [24], we did not observe an excess of bleeding in HBR patients receiving ticagrelor. Such a finding may be due to several factors. First, gastric protection treatment was not optimized in the CHANGE DAPT HBR sub-study. It has been shown that half of the major bleeds in patients on antiplatelet therapy aged 75 years or older are upper gastrointestinal, but this risk can be cut by 70–90% by proton-pump inhibitors use [27, 28]. In our study, gastrointestinal bleeding represented three out of five major bleeding events in the clopidogrel group, and three out of four in the ticagrelor group, confirming the relevance of these events in HBR patients. However, only two-thirds of patients in CHANGE DAPT were discharged on proton-pump inhibitors versus almost all (98%) in our study.

Second, the use of radial rather femoral access in PCI is associated with a significant reduction in major bleeding complications [29–31]. However, while radial access in CHANGE DAPT study was quite low (28%), all centers enrolling patients in the START-ANTIPLATELET registry are high-volume radial centers, and more extensive use of radial might have affected bleeding outcomes. Moreover, DAPT duration was longer in CHANGE DAPT study compared to our study (at 1 year 80% of patients still on DAPT, while 60% in our study), which may also have affected bleeding outcomes. Also, our findings suggest that a shorter rather than prolonged DAPT might be of benefit in HBR patients with ACS, which is in line with current guidelines recommendations [1, 32].

A recent analysis, including over 25,000 patients from 5 real-world nation-wide registries, also investigated the impact of prasugrel or ticagrelor versus clopidogrel in terms of ischemic and bleeding outcomes [26]. After propensity score matching, novel P2Y12 inhibitors showed a favorable effect on ischemic outcomes without increasing the risk of bleeding when compared with clopidogrel, suggesting potential net clinical benefit in real-world high-risk patients [26]. In line with these data, our findings provide further evidence in the real-world setting, showing the absence of an increased risk of bleeding with ticagrelor in HBR patients while confirming the importance of a tailored (short) DAPT duration in this sub-group to prevent the occurrence of major bleeding complications.

Limitations

This study has several limitations. The observational design of the study limits our conclusions. Also, as the enrollment was limited to 2 days per week, a selection bias might have occurred. Patients were included in the HBR group in the presence of at least one HBR criteria. However, several clinical data such as chronic medical therapy with nonsteroidal anti-inflammatory drug/corticosteroids as well as other conditions at higher bleeding risk (i.e., coagulation disorders) were not considered, as these data were not collected in our registry. Our database did not provide information on the access site used, which would have added important data to our analysis. Also, we only used TIMI classification for defining major bleeding, since other definitions were not implemented in the registry. Despite multiple adjustment for differences in baseline characteristics between treatment groups, unmeasured confounders influencing outcomes cannot be excluded. Finally, although DAPT duration was systematically collected at follow-up visits, reasons for DAPT discontinuation were not recorded in the dataset.

Conclusions

In conclusion, our study confirms that clopidogrel, rather than potent P2Y12 inhibitors, is frequently used of as part of DAPT in real-world HBR patients presenting with ACS. After adjustment for confounders, no difference for ischemic and bleeding events was observed in HBR patients on clopidogrel versus ticagrelor. Our findings suggest that DAPT duration, more than DAPT type, might impact on clinical outcomes in HBR patients and should be appropriately tailored according to patients' risk profile.

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Author contributions FG and PC designed the work. FG and EM drafted the manuscript. FG, EM, PC, and PCP worked to the acquisition, analysis, and interpretation of data. All authors revised data critically for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest FG: Research grant from the European Society of Cardiology (ESC). GP: speaker/consultant/advisory board for Amgen, Sanofi, Bayer, Boehringer-Ingelheim, BMS-Pfizer, Daiichi Sankyo, Astra Zeneca, Sigma-Tau, Malesci, PIAM and MSD. IC: speaker for BMS-Pfizer, AstraZeneca, and Boeringher-Ingelheim. Other Authors have no conflicts of interest to disclose.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement of human and animal rights The study protocol was approved by the local ethics committees and was conducted in accordance with the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Informed consent was obtained from all individual participants included in the study.

Availability of data and material All study data are available on request to the principal investigator.

Code availability Statistical analysis plan and data analysis are available on request to the principal investigator.

References

1. Valgimigli M, Bueno H, Byrne RA et al (2018) 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur Heart J 39:213–254
2. Neumann F-J, Sousa-Uva M, Ahlsson A et al (2018) 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 40:87–165
3. Crisci M, Gragnano F, Di Maio M et al (2019) Improving adherence to Ticagrelor in patients after acute coronary syndrome: results from the PROGRESS trial. Curr Vasc Pharmacol 18:294–301
4. Wallentin L, Becker RC, Budaj A et al (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361:1045–1057
5. Eikelboom JW, Mehta SR, Anand SS et al (2006) Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 114:774–782
6. Valgimigli M, Costa F, Lokhnygina Y et al (2017) Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J 38:804–810
7. Urban P, Mehran R, Colleran R et al (2019) Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. Eur Heart J 40:2632–2653
8. Ueki Y, Bär S, Losdat S, et al (2020) Validation of bleeding risk criteria (ARC-HBR) in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. EuroIntervention EIJ-D-20-00052
9. Gragnano F, Cattano D, Calabrò P (2018) Perioperative care of cardiac patient's candidate for non-cardiac surgery: a critical appraisal of emergent evidence and international guidelines. Intern Emerg Med 13:1185–1190
10. Prisco D (2018) A focus on direct oral anticoagulants: "old" and possible new indications and efforts for a better clinical management. Intern Emerg Med 13:985–988
11. Testa S, Ageno W, Antonucci E et al (2018) Management of major bleeding and outcomes in patients treated with direct oral anticoagulants: results from the START-Event registry. Intern Emerg Med 13:1051–1058
12. Alexopoulos D, Xanthopoulou I, Deftereos S et al (2016) Contemporary antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: 1-year outcomes from the GReek AntiPlatElet (GRAPE) Registry. J Thromb Haemost 14:1146–1154
13. Beigel R, Iakobishvili Z, Shlomo N et al (2017) Real-world use of novel P_2Y_{12} inhibitors in patients with acute myocardial infarction: a treatment paradox. Cardiology 136:21–28
14. Sahlén A, Varenhorst C, Lagerqvist B et al (2016) Contemporary use of ticagrelor in patients with acute coronary syndrome: insights from Swedish web system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Eur Hear J Cardiovasc Pharmacother 2:5–12
15. Gragnano F, Fimiani F, Di Maio M et al (2019) Impact of lipoprotein(a) levels on recurrent cardiovascular events in patients with premature coronary artery disease. Intern Emerg Med 14:621–625
16. Patti G, Cavallari I, Antonucci E et al (2017) Prevalence and predictors of dual antiplatelet therapy prolongation beyond one year in patients with acute coronary syndrome. PLoS ONE 12:e0186961
17. Calabrò P, Moscarella E, Gragnano F et al (2019) Effect of body mass index on ischemic and bleeding events in patients presenting with acute coronary syndromes (from the START-ANTIPLATELET Registry). Am J Cardiol 124:1662–1668
18. Calabrò P, Gragnano F, Di Maio M et al (2018) Epidemiology and management of patients with acute coronary syndromes in contemporary real-world practice: evolving trends from the EYESHOT study to the START-ANTIPLATELET registry. Angiology 69:795–802
19. Costa F, van Klaveren D, James S et al (2017) Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 389:1025–1034
20. Garcia-Garcia HM, McFadden EP, Farb A et al (2018) Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. Circulation 137:2635–2650
21. Sacco RL, Kasner SE, Broderick JP et al (2013) An updated definition of stroke for the 21st century. Stroke 44:2064–2089
22. Jolly SS, Cairns JA, Yusuf S et al (2015) Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med 372:1389–1398
23. Zocca P, Van Der Heijden LC, Kok MM et al (2017) Clopidogrel or ticagrelor in acute coronary syndrome patients treated with newer-generation drug-eluting stents: CHANGE DAPT. EuroIntervention 13:1168–1176
24. Zocca P, Kok MM, van der Heijden LC et al (2018) High bleeding risk patients with acute coronary syndromes treated with contemporary drug-eluting stents and Clopidogrel or Ticagrelor: insights from CHANGE DAPT. Int J Cardiol 268:11–17
25. De Luca L, De Servi S, Musumeci G, Bolognese L (2018) Is ticagrelor safe in octogenarian patients with non-ST elevation acute coronary syndromes? Eur Heart J Cardiovasc Pharmacother 4:12–14
26. De Luca L, Zeymer U, Claeys MJ, et al (2020) Comparison of P2Y12 receptor inhibitors in patients with ST-elevation myocardial infarction in clinical practice: a propensity score analysis of five contemporary European registries. Eur Heart J Cardiovasc Pharmacother 22; pvaa002
27. Li L, Geraghty OC, Mehta Z, Rothwell PM (2017) Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 390:490–499
28. Porta L, Baorda F, Fusco A, Gruppo di Autoformazione Metodologica (GrAM) (2018) Is proton pump inhibitors' prophylaxis indicated for patients on antiplatelet therapy? Intern Emerg Med 13:585–587
29. Valgimigli M, Frigoli E, Leonardi S et al (2018) Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet 392:835–848
30. Bianchi R, D'Acierno L, Crisci M et al (2017) From femoral to radial approach in coronary intervention. Angiology 68:281–287
31. Gragnano F, Manavifar N, Gargiulo G et al (2019) Femoral access with or without vascular closure device or radial access in acute coronary syndrome. JACC Cardiovasc Interv 12:2116–2118

32. Gragnano F, Calabrò P, Valgimigli M (2019) Is triple antithrombotic therapy, or rather its duration and composition, the true culprit for the excess of bleeding events observed in patients with atrial fibrillation undergoing coronary intervention? Eur Heart J 40:216–217

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Part III

Anticoagulation in patients undergoing percutaneous coronary intervention

Is triple antithrombotic therapy, or rather its duration and composition, the true culprit for the excess of bleeding events observed in patients with atrial fibrillation undergoing coronary intervention?

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DISCUSSION FORUM

Is triple antithrombotic therapy, or rather its duration and composition, the true culprit for the excess of bleeding events observed in patients with atrial fibrillation undergoing coronary intervention?

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This commentary refers to 'Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials' by H.B. Golwala *et al.* doi: 10.1093/eurheartj/ehy162.

Golwala *et al.*[1] claimed that dual (DAT) and triple antithrombotic therapy (TAT) are equally effective in preventing cardiovascular events with DAT being safer by approximately halving bleeding risk.[1] We do not concur with the conclusive statement that these 'findings support the concept that DAT may be a better option than TAT in many patients with atrial fibrillation (AF) following percutaneous coronary intervention (PCI)'. Triple antithrombotic therapy duration amongst the included studies exceeded 6-months in a relevant proportion of patients. In the WOEST and PIONEER-AF PCI, 66% and 25% of patients received TAT for 12-months, respectively (*Figure 1*). In the RE-DUAL PCI, in which TAT was assigned for a maximum of 3-months, almost one-third of patients continued TAT, reaching up to 12-months in 14% of cases. The ISAR-TRIPLE, in which TAT was discontinued in all patients at 6-months, found no bleeding excess vs.

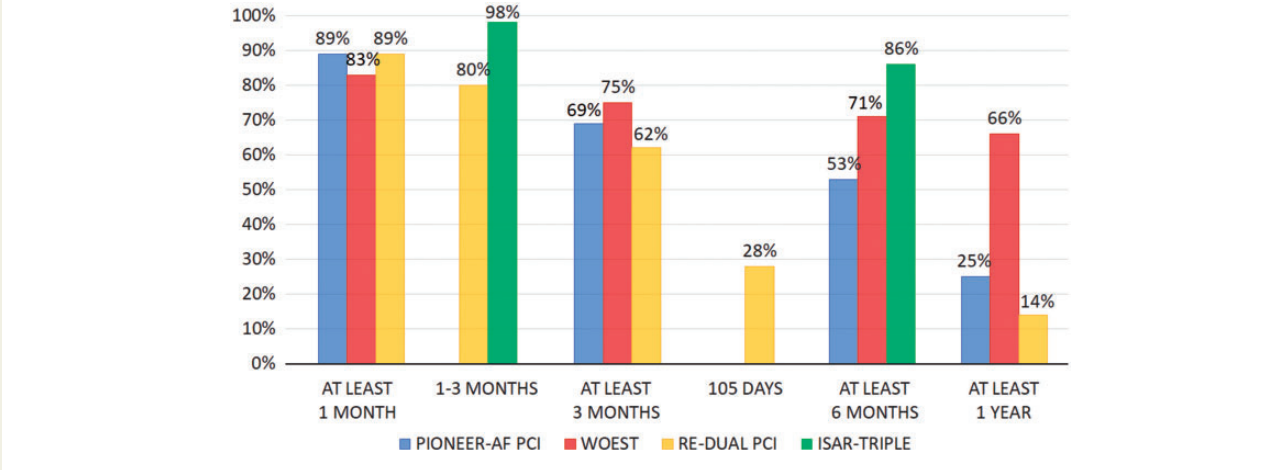


Figure 1 Percentage of patients on actual triple antithrombotic therapy in four randomized trials.

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1-month therapy. By inspecting the upper boundary of the 95% confidence interval, DAT can double myocardial infarction risks compared to TAT. This raises concerns given the trade-off of ischaemic vs. bleeding events on the actual net clinical benefit[2] and should be openly discussed with patients. Finally, TAT composition [vitamin K antagonists (VKAs) vs. direct oral anticoagulant (DOAC)] varied significantly amongst study groups, limiting definite conclusions. The 2017 ESC focused update on dual antiplatelet therapy[3] recommended not to routinely skip TAT, rather keep it short and preferentially use DOAC. The safety and efficacy of 1-month vs. a more prolonged TAT duration, while allowing DOAC to be used in both study groups, is being investigated in the MASTER DAPT (NCT03023020). We thus believe that further studies are needed to clarify whether TAT *per se*, or rather its duration and/or composition, should be blamed for the excess of bleeding complications observed across the few available studies.

Conflict of interest: none declared.

References

1. Golwala HB, Cannon CP, Steg PG, Doros G, Qamar A, Ellis SG, Oldgren J, Ten Berg JM, Kimura T, Hohnloser SH, Lip GYH, Bhatt DL. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2018;**39**:1726–1735a.
2. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, Van de Werf F, Harrington RA, Mahaffey KW, Tricoci P. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J* 2017;**38**:804–810.
3. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, Badimon L, Vranckx P, Agewall S, Andreotti F, Antman E, Barbato E, Bassand J-P, Bugiardini R, Cikirikcioglu M, Cuisset T, De Bonis M, Delgado V, Fitzsimons D, Gaemperli O, Galiè N, Gilard M, Hamm CW, Ibanez B, Iung B, James S, Knuuti J, Landmesser U, Leclercq C, Lettino M, Lip G, Piepoli MF, Pierard L, Schwerzmann M, Sechtem U, Simpson IA, Uva MS, Stabile E, Storey RF, Tendera M, Van de Werf F, Verheugt F, Aboyans V, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh T, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Zamorano JL, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh T, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Zamorano JL, Roithinger FX, Aliyev F, Stelmashok V, Desmet W, Postadzhiyan A, Georghiou GP, Motovska Z, Grove EL, Marandi T, Kiviniemi T, Kedev S, Gilard M, Massberg S, Alexopoulos D, Kiss RG, Gudmundsdottir IJ, McFadden EP, Lev E, De Luca L, Sugraliyev A, Haliti E, Mirrakhimov E, Latkovskis G, Petrauskiene B, Huijnen S, Magri CJ, Cherradi R, Ten Berg JM, Eritsland J, Budaj A, Aguiar CT, Duplyakov D, Zavatta M, Antonijevic NM, Motovska Z, Fras Z, Montoliu AT, Varenhorst C, Tsakiris D, Addad F, Aydogdu S, Parkhomenko A, Kinnaird T. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–260.

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Antithrombotic Therapy in Patients Taking Oral Anticoagulants and Undergoing Percutaneous Coronary Intervention: Time to Be Bold and Wise.

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Antithrombotic Therapy in Patients Taking Oral Anticoagulants and Undergoing Percutaneous Coronary Intervention: Time to Be Bold and Wise

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This Commentary relates to the article by Tanner et al on pages 501–507.

Finding the optimal antithrombotic therapy in patients undergoing percutaneous coronary intervention (PCI) with an indication for long-term oral anticoagulants remains a challenge.[1] The ultimate goal is to find the best antithrombotic regimen—the right drugs, at the right doses, for the right duration—to prevent ischemic events while minimizing bleeding. Clinical decision-making requires therefore consideration of ischemic and bleeding risk, whether assessed intuitively or by risk score, taking into account clinical presentation (acute or chronic coronary syndrome), comorbidities (ie, diabetes and renal impairment), coronary anatomy, and other factors.[2,3]

Patients with atrial fibrillation (AF) treated with coronary stenting account for most of these cases. In this scenario, based on large randomized trials and meta-analyses,[4] most recent European guidelines endorse—with the highest class of recommendation—a short course of triple antithrombotic therapy (≤1 week) followed by a dual therapy with a nonvitamin K antagonist oral anticoagulant (NOAC) and a P2Y12 inhibitor (preferably clopidogrel).[5,6] An alternative regimen consisting of prolonged triple therapy (ie, up to 1 month) is deemed as reasonable in patients at high ischemic and low bleeding risk, but it is based primarily on "expert opinion" rather than evidence.[5,6] Noteworthy, a non-negligible proportion of patients undergoing PCI receive a combination of anticoagulant and antiplatelet agents for reasons other than AF, such as mechanical valve prostheses, venous thromboembolism, and ventricular thrombosis. In this setting, the evidence is less robust,[5,7] and the management remains poorly standardized.

Given the difficulty of treating these patients, a nonuniform prescription of antithrombotic regimens persists for both type and duration. Therefore, data from real-world are welcome and useful to understand if and how clinicians integrate novel evidence and follow guidelines recommendations in daily practice.

In this issue of the *Journal of Cardiovascular Pharmacology*, Tanner et al[8] presented the results of a real-world retrospective study investigating patients undergoing PCI and having an indication for oral anticoagulation because of various clinical conditions from an Irish high-volume PCI center. Over a 1-year period, 133 of 1650 (or 8.1%) consecutive patients treated with PCI were discharged with a combination of oral antiplatelet and anticoagulant agents,[8] which is in line with contemporary cohorts from other European real-world registries.[3,9]

Most patients had a diagnosis of AF, were discharged on triple antithrombotic therapy, and received a NOAC in preference of vitamin K antagonists as currently advised.[5,6] The mean duration of triple therapy was 6 weeks that is—particularly in the case of AF—longer than what guidelines recommend (1-week duration as default strategy), but somewhat justifiable considering that 80% of stent thrombosis in patients with early aspirin discontinuation occurs within the first month after PCI.[10]

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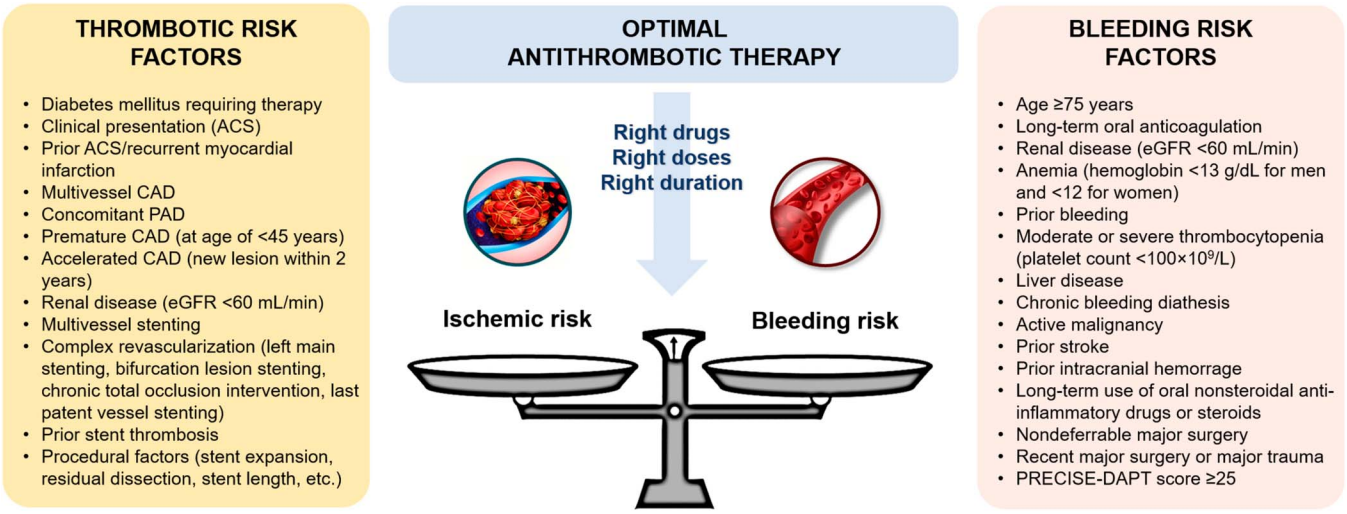


FIGURE 1. Finding the optimal antithrombotic therapy in patients taking oral anticoagulants and undergoing percutaneous coronary intervention. ACS, acute coronary syndrome; CAD, coronary artery disease; PAD, peripheral artery disease.

Approximately the same number of patients were discharged on dual antithrombotic therapy with either clopidogrel or aspirin (about 9% in both groups). This approach deviates from guidelines recommendations, which support the use of clopidogrel over aspirin in combination with oral anticoagulants[5,6] and reflects the enduring belief that aspirin is a "must-have" drug after PCI. Concerns for possible clopidogrel resistance can also partly explain this attitude. However, clinically meaningful events (ie, stent thrombosis) remain rare even in patients with apparent poor responsiveness to clopidogrel.[11] Accordingly, the use of platelet function or genetic testing to guide antithrombotic therapy remains debated and should be considered in selected patients only.[5,12]

It is also worth noting that Tanner et al[8] reported infrequent use of intracoronary imaging at their institution (less than 1%). Considering the importance of a high-quality PCI to reduce the risk of stent-related complications,[5] a more extensive use of intracoronary imaging remains desirable for stent optimization, especially in patients planned for early aspirin discontinuation.

At a glance, the study reveals a substantial heterogeneity in the combination as well as the duration of antithrombotic agents prescribed at discharge, which reflects the complexity of the clinical scenario and uncertainty of clinicians in deciding which therapy represents the optimum for each individual patient. In such struggling situations, the clinical judgment might benefit from validated tools to stratify the risk and guide decision-making. However, in this real-world study, the decision to adopt a more intense and/or prolonged antithrombotic therapy seemed decoupled from the thrombotic and bleeding risk predicted by risk scores (ie, CHA_2DS_2-VASc and HAS-BLED), meaning that the prescription was based on the discretion of the treating physicians and confirming a sort of disaffection of clinicians for risk scores. As a note, the HAS-BLED score, which is currently recommended by guidelines for bleeding risk prediction, has been generated from vitamin K antagonists–treated patients and might be less practical in the contemporary NOACs era. In this context, the recently proposed and validated Academic Research Consortium for High Bleeding Risk criteria should be preferred for bleeding risk stratification after PCI.[2,3] Among other prediction models, the PRECISE-DAPT score, which has been previously validated in patients on single and dual antiplatelet therapy,[13] has been recently proposed to predict the risk of bleeding and select the optimal antithrombotic strategy in AF patients treated with PCI.[14]

Altogether, data presented by Tanner et al[8] reinforce the concept that an individualized approach in patients with recent coronary stenting and an indication for long-term oral anticoagulation is critical. Bleeding and ischemic risk factors have continuous and dynamic interactions with each therapeutic intervention and need to be comprehensively taken into account to select the optimal treatment (Fig. 1).[2,3] The exercise of carefully assessing clinical, laboratory, and procedural factors remains essential to guide decision-making in this conundrum.

The time has come to be bold and wise in choosing the antithrombotic therapy in patients taking an oral anticoagulant and undergoing PCI. We have to be bold in trusting evidence that early cessation of aspirin (1 week or shortly after) is safe and warranted in most cases. We have to be wise in recognizing that in the subset of patients in whom concerns about ischemic risk prevail (ie, acute presentation, high thrombotic burden, and/or complex PCI), continuing aspirin for 1 month (or slightly more) should be advised, and triple therapy duration tailored to the patient's need.

REFERENCES

1. Gragnano F, Calabro P, Valgimigli M. Is triple antithrombotic therapy, or rather its duration and composition, the true culprit for the excess of bleeding events observed in patients with atrial fibrillation undergoing coronary intervention? *Eur Heart J.* 2019;40:216–217.
2. Ueki Y, Bär S, Losdat S, et al. Validation of bleeding risk criteria (ARC-HBR) in patients undergoing percutaneous coronary intervention and

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comparison with contemporary bleeding risk scores. *EuroIntervention*. 2020;16:371–379.
3. Corpataux N, Spirito A, Gragnano F, et al. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. *Eur Heart J.* 2020;41:3743–3749.
4. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J.* 2019;40:3757–3767.
5. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2020;10:ehaa575.
6. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2020;10:ehaa612.
7. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381:1107–1115.
8. Tanner R, Cronin M, Macken L, et al. Real world experience with anti-platelet agents after percutaneous coronary intervention in patients with an indication for an oral anticoagulant. *J Cardiovasc Pharmacol.* 2020;45:645–656.
9. Calabrò P, Gragnano F, Di Maio M, et al. Epidemiology and management of patients with acute coronary syndromes in contemporary real-world practice: evolving trends from the EYESHOT study to the START-ANTIPLATELET registry. *Angiology*. 2018;69:795–802.
10. Lopes RD, Leonardi S, Wojdyla DM, et al. Stent thrombosis in patients with atrial fibrillation undergoing coronary stenting in the AUGUSTUS trial. *Circulation*. 2020;141:781–783.
11. Legrand V, Cuisset T, Chenu P, et al. Platelet reactivity and cardiovascular events after percutaneous coronary intervention in patients with stable coronary artery disease: the Stent Thrombosis in Belgium (STIB) trial. *EuroIntervention.* 2014;10:204–211.
12. Cattano D, Altamirano AV, Kaynak HE, et al. Perioperative assessment of platelet function by Thromboelastograph Platelet Mapping in cardiovascular patients undergoing non-cardiac surgery. *J Thromb Thrombolysis.* 2013;35:23–30.
13. Gragnano F, Heg D, Franzone A, et al. PRECISE-DAPT score for bleeding risk prediction in patients on dual or single antiplatelet regimens: insights from the GLOBAL LEADERS and GLASSY. *Eur Heart J Cardiovasc Pharmacother.* 2020;10:pvaa106.
14. Costa F, Valgimigli M, Steg PG, et al. Antithrombotic therapy according to baseline bleeding risk in patients with atrial fibrillation undergoing percutaneous coronary intervention: applying the PRECISE-DAPT score in RE-DUAL PCI. *Eur Heart J Cardiovasc Pharmacother.* 2020;10:pvaa135.

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Acute kidney injury in patients with acute coronary syndrome undergoing invasive management treated with bivalirudin vs. unfractionated heparin: Insights from the MATRIX trial.

Landi A, Branca M, Andò G, Russo F, Frigoli E, Gargiulo G, Briguori C, Vranckx P, Leonardi S, **Gragnano F,** Calabrò P, Campo G, Ambrosio G, Santucci A, Varbella F, Zaro T, Heg D, Windecker S, Jüni P, Pedrazzini G, Valgimigli M.

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ORIGINAL SCIENTIFIC PAPER
Acute Coronary Syndromes

Acute kidney injury in patients with acute coronary syndrome undergoing invasive management treated with bivalirudin vs. unfractionated heparin: insights from the MATRIX trial

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Aims Acute kidney injury (AKI) is a critical complication among patients with acute coronary syndrome (ACS) undergoing invasive management. The value of adjunctive antithrombotic strategies, such as bivalirudin or unfractionated heparin (UFH) on the risk of AKI is unclear.

Methods and results Among 7213 patients enrolled in the MATRIX-Antithrombin and Treatment Duration study, 128 subjects were excluded due to incomplete information on serum creatinine (sCr) or end-stage renal disease on dialysis treatment. The primary endpoint was AKI defined as an absolute (>0.5 mg/dL) or a relative (>25%) increase in sCr. AKI occurred in 601 patients (16.9%) treated with bivalirudin and 616 patients (17.4%) treated with UFH [odds ratio (OR): 0.97; 95% confidence interval (CI): 0.85–1.09; $P = 0.58$]. A >25% sCr increase was observed in 597 patients (16.8%) with bivalirudin and 616 patients (17.4%) with UFH (OR: 0.96; 95% CI: 0.85–1.08; $P = 0.50$), whereas a >0.5 mg/dL absolute sCr increase occurred in 176 patients (5.0%) with bivalirudin vs. 189 patients (5.4%) with UFH (OR: 0.92; 95% CI: 0.75–1.14; $P = 0.46$). By implementing the Kidney Disease Improving Global Outcomes (KDIGO) criteria, the risk of AKI was not significantly different between bivalirudin and UFH groups (OR: 0.88; 95% CI: 0.72–1.07; $P = 0.21$). Subgroup analyses of the primary endpoint suggested a benefit with bivalirudin in patients randomized to femoral access.

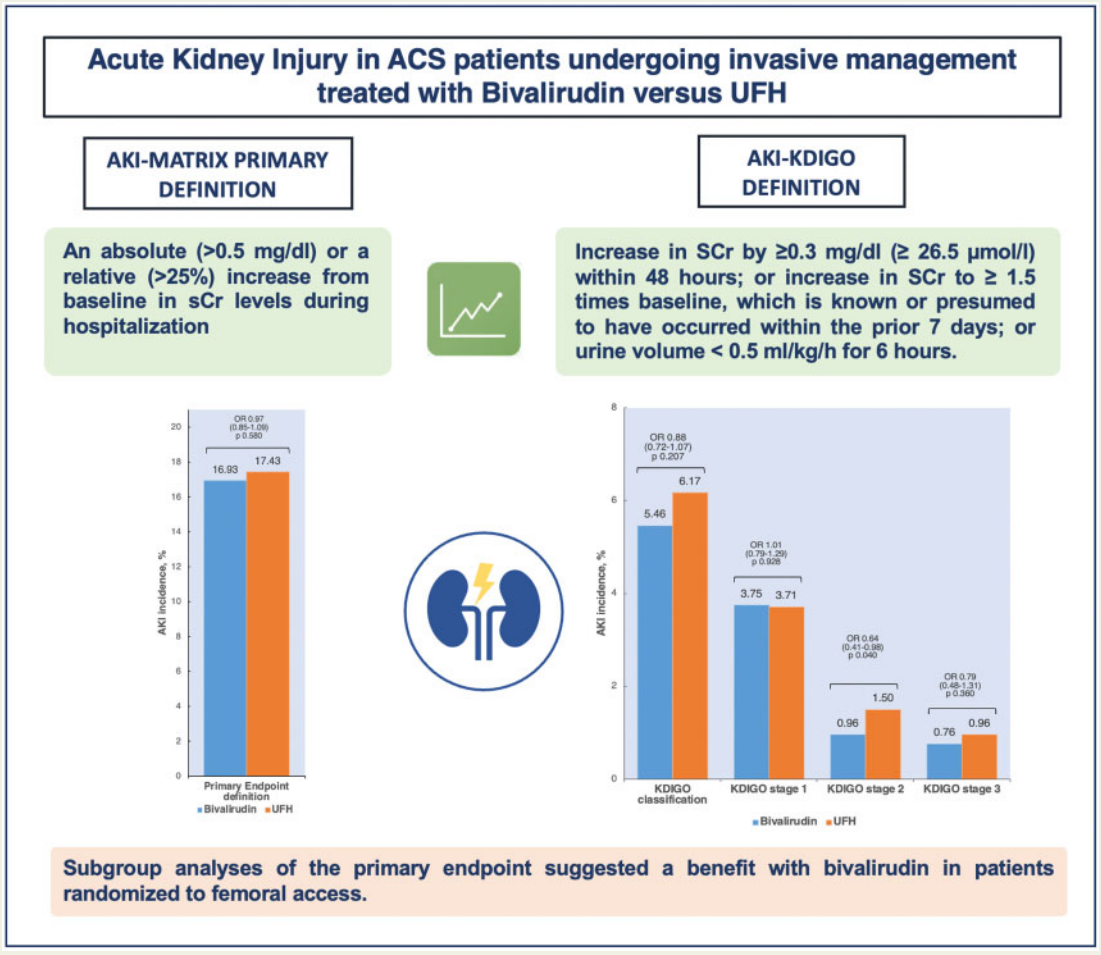
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Conclusion Among ACS patients undergoing invasive management, the risk of AKI was not significantly lower with bivalirudin compared with UFH.

Trial registration clinicaltrials.gov NCT01433627.

Graphical Abstract



Keywords Bivalirudin • Unfractionated heparin • Acute kidney injury • Acute coronary syndromes

Introduction

Among patients undergoing interventional procedures, acute kidney injury (AKI) prolongs hospital stay and is associated with worse clinical outcomes.[1,2] The incidence of AKI ranges from 3% to 13% following percutaneous coronary intervention (PCI)[3] and it is especially high in complex PCI procedures or patients presenting with the acute coronary syndrome (ACS) undergoing urgent revascularization.[3] Larger volume of contrast medium or insufficient time to perform renal prophylactic measures are recognized contributing factors for AKI in patients with ACS. Alongside these, other factors, such as haemodynamic instability, left ventricular (LV) dysfunction resulting in impaired systemic or renal perfusion and cholesterol embolization have been advocated as potential mechanisms of AKI in ACS patients undergoing invasive management.[4] Nonetheless, effective strategies for AKI prevention and improving outcomes of ACS patients at risk for AKI are still limited in clinical practice.

There is evidence suggesting that the route of vascular access for PCI plays an important role in the risk of AKI.[5–7] In the *Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX)* Access trial, radial access (RA) was associated with lower bleeding, AKI, and all-cause mortality

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compared with femoral access (FA) in patients with ACS undergoing invasive management.[6,8,9] Whether the mortality benefit of RA is related to the lower incidence of bleeding, AKI, or both has been disentangled in a recent report, which identified AKI prevention as the major, independent determinant.[10] Despite these beneficial effects, the rate of AKI in ACS patients undergoing PCI through RA remains substantial (nearly 15% in the MATRIX Access trial), emphasizing the need for further approaches for AKI prevention.

Multiple trials have shown that bivalirudin reduces the risk of major bleeding,[9,11–13] which may in turn influence the occurrence of AKI. However, no prospective appraisal of the incidence of AKI has been carried out in randomized studies of ACS patients receiving bivalirudin vs. unfractionated heparin (UFH). We pre-specified a prospective assessment of whether bivalirudin compared with UFH reduces the incidence of AKI in subjects with ACS, including patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing invasive management.

Methods

Study design and population

MATRIX was a programme of three independent randomized controlled, multicentre, superiority trials (NCT01433627) in patients with ACS undergoing invasive management.[14] The first trial (MATRIX-Access) compared radial vs. femoral access in 8404 patients with ACS[8,9] and the effects of access site on AKI (AKI-MATRIX substudy) have been previously reported.[6] MATRIX-Antithrombin compared bivalirudin with UFH [use of glycoprotein IIb/IIIa inhibitors (GPI) was left to the discretion of the investigator] in 7213 ACS patients in whom PCI was planned. MATRIX Treatment Duration compared prolonged bivalirudin administration with a post-PCI infusion vs. short-term bivalirudin administration without a post-PCI infusion in 3610 patients assigned to receive bivalirudin.

Patients with NSTE-ACS were eligible if they had a history consistent with new or worsening cardiac ischemia that occurred while they were at rest or with minimal activity within 7 days before randomization and met at least two high-risk criteria among the following: (i) age of 60 years or older, the elevation of cardiac biomarkers, or electrocardiographic changes compatible with ischaemia; and (ii) if they were considered to be candidates for PCI after completion of coronary angiography. Patients with STEMI were eligible if they presented within 12 h of the onset of symptoms or between 12 and 24 h after symptom onset if there was evidence of continued ischaemia or previous fibrinolytic treatment. The main inclusion and exclusion criteria were previously reported.[8,15]

All patients enrolled in MATRIX Antithrombin and the MATRIX Treatment Duration were eligible for this study, except those with incomplete serum creatinine (sCr) data or those who had an end-stage renal disease that required dialysis. The trial was approved by the institutional review board at each participating site, and all patients gave written informed consent.

Study protocol and randomization

Patients were randomly assigned, in a 1:1 ratio, to receive bivalirudin or UFH, and those assigned to the bivalirudin group were subsequently randomized, in a 1:1 ratio, to receive a post-PCI bivalirudin infusion or no post-PCI infusion. The randomization sequence was computer-generated, blocked, and stratified by the type of ACS (i.e. with ST-segment elevation vs. without ST-segment elevation), intended for or ongoing use of a P2Y12 inhibitor (clopidogrel vs. ticagrelor or prasugrel), and study site. All interventions were administered in an open-label fashion. Bivalirudin was given according to the product labelling, with a bolus of 0.75 mg/kg of body weight, followed immediately by an infusion of 1.75 mg/kg/h until completion of PCI. Receiving a post-PCI bivalirudin infusion or no post-PCI infusion was randomly determined (MATRIX treatment duration). In those assigned to bivalirudin prolongation, the choice between two regimens (full dose for up to 4 h or reduced dose of 0.25 mg/kg/h for at least 6 h) was made at the discretion of the treating physicians. UFH was administered at a dose of 70–100 U or 50–70 U/kg in patients who did not receive or received GPI, respectively. Subsequent UFH dose adjustment based on the activated clotting time was left to the discretion of the treating physicians.

Outcomes

The outcomes of the MATRIX-Antithrombin and MATRIX-Treatment Duration have been previously reported.[9,15] The primary endpoint of this substudy was the incidence of AKI, defined as either an absolute (>0.5 mg/dL) or a relative (>25%) increase from baseline in sCr levels during hospitalization in the intention-to-treat population.[16,17] Furthermore, the incidence of AKI was evaluated by implementing the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Sensitivity analyses were also performed in patients proceeding to PCI after diagnostic coronary angiography (i.e. excluding patients who received only an angiogram and no further PCI).

Statistical analysis

All analyses were performed according to the intention-to-treat principle. Differences across groups were assessed using the Student's *t*-test in case of continuous variables and the χ^2 or Fisher's exact test in case of categorical data. The differences at the lesion level considered the nested structure of lesions within individuals and then were analysed using multilevel general or generalized mixed models, as appropriate. We applied multivariable logistic regression models to evaluate the association of AKI during index hospitalization with randomized access site, the individual components of the Mehran's score, bleeding, and measures of bleeding severity in the two study groups. We performed stratified logistic regressions by subgroups, including diabetes at baseline, estimated glomerular filtration rate (eGFR), age, clinical presentation, LV ejection fraction, Killip class, Mehran's score, contrast media volume, and randomized access site. The analyses were done using Stata release 16.1 (StataCorp LLC, College Station, TX, USA).

Results

Among 7213 patients enrolled in the MATRIX-Antithrombin trial from 78 centres in Italy, The Netherlands, Spain, and Sweden between October 2011 and July 2014, 128 patients (1.8%) were excluded due to incomplete sCr data or because they suffered from the end-stage renal disease on dialysis treatment. Among the 7085 patients included in the analysis, 3550 subjects were allocated to bivalirudin and 3535 to UFH.

Baseline characteristics

Baseline demographics, medical history, clinical presentation, and procedural characteristics were well matched between bivalirudin and UFH groups (*Table 1*). Baseline characteristics of subjects

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Table 1 Baseline and procedural characteristics

	Bivalirudin (*N* = 3550)	UFH (*N* = 3535)	*P*-value
Clinical characteristics			
Age (years)	65.4 ± 11.9	65.4 ± 11.8	0.82
≥75 years	890 (25.1)	880 (24.9)	0.86
Male sex	2689 (75.7)	2715 (76.8)	0.30
Hypotension[a]	22 (0.6)	35 (1.0)	0.08
Anaemia[b]	671 (18.9)	679 (19.2)	0.74
Diabetes	812 (22.9)	770 (21.8)	0.27
Creatinine >1.5 mg/dL	175 (4.9)	168 (4.8)	0.73
Killip class III or IV	109 (3.1)	92 (2.6)	0.24
STEMI	1986 (55.9)	1966 (55.6)	0.78
NSTE-ACS	1564 (44.1)	1569 (44.4)	0.78
NSTE-ACS, troponin negative	161 (4.5)	158 (4.5)	0.89
NSTE-ACS, troponin positive	1403 (39.5)	1411 (39.9)	0.73
NSTE-ACS with ST-segment deviation	730 (20.6)	726 (20.5)	0.98
NSTE-ACS with T Wave inversion	441 (12.4)	499 (14.1)	0.04
EF ≤35%	316 (9.2)	295 (8.7)	0.40
Systolic arterial pressure (mmHg)	138.7 ± 26.0	138.3 ± 25.8	0.59
Hb at baseline	14.0 ± 1.9	14.0 ± 2.0	0.38
Glucose at baseline	140.7 ± 65.7	138.2 ± 61.4	0.11
Statins before cath-lab	1442 (40.6)	1428 (40.4)	0.85
ACE inhibitors before cath-lab	986 (27.8)	1007 (28.5)	0.51
Angiotensin II receptor antagonist before cath-lab	366 (10.3)	347 (9.8)	0.49
Procedural characteristics			
Radial access	1770 (49.9)	1771 (50.1)	0.84
Any cross-over during index hospitalization	262 (7.4)	258 (7.3)	0.89
Total amount of contrast used during index hospitalization—mL	199.8 ± 108.5	196.5 ± 104.8	0.20
No PCI attempted after coronary angiography during index hospitalization	195 (5.5)	178 (5.0)	0.39
CABG	21 (0.6)	19 (0.5)	0.76
Patient with significant lesion and medical treatment	143 (4.0)	118 (3.3)	0.12
Patient without significant lesion	31 (0.9)	44 (1.2)	0.13
At least one PCI attempted	3355 (94.5)	3357 (95.0)	0.39
Died during PCI	1 (0.0)	0 (0.0)	1.00
At least one PCI completed during index hospitalization	3354 (94.5)	3357 (95.0)	0.36
Medications administered in and after the catheterization laboratory			
Aspirin	236 (6.6)	265 (7.5)	0.16
Clopidogrel	242 (6.8)	284 (8.0)	0.05
Prasugrel	309 (8.7)	312 (8.8)	0.86
Ticagrelor	394 (11.1)	373 (10.6)	0.46
Bailout GPI	167 (4.7)	152 (4.3)	0.41
≥1 intra-aortic balloon pump	79 (2.2)	85 (2.4)	0.62
≥1 PCI completed	(*N* = 3354)	(*N* = 3357)	
TIMI 3 flow in all treated lesions during whole index hospitalization	3172 (94.6)	3203 (95.4)	0.12
Coronary stenosis <30% in all treated lesions	3189 (95.1)	3195 (95.2)	0.86
Procedural success in all treated lesions	3088 (92.1)	3112 (92.7)	0.33
Duration of procedure (min)	60.9 ± 36.4	60.2 ± 37.4	0.43
Amount of contrast used	205.2 ± 108.4	201.7 ± 104.1	0.19
Treated vessel(s) per patient			
Left main coronary artery	174 (5.2)	154 (4.6)	0.26
Left anterior descending artery	1848 (55.1)	1808 (53.9)	0.32
Left circumflex artery	1063 (31.7)	1033 (30.8)	0.42
Right coronary artery	1225 (36.5)	1246 (37.1)	0.60

Continued

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Table 1 *Continued*

	Bivalirudin (*N* = 3550)	UFH (*N* = 3535)	*P*-value
Bypass graft	33 (1.0)	25 (0.7)	0.29
At least two vessels treated	831 (24.8)	765 (22.8)	0.06
Lesions treated per patient (interquartile range)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.46
One lesion	2288 (68.2)	2333 (69.5)	
Two lesions	753 (22.5)	737 (22.0)	
Three or more lesions	313 (9.3)	285 (8.5)	
At least one complex lesion	1800 (53.7)	1842 (54.9)	0.31
Median number of stents per patient (interquartile range)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.89
Overall stent length per patient—mm	66.8 ± 53.7	66.8 ± 53.6	0.97
Lesions			
Number of lesions with PCI	(*N* = 5030)	(*N* = 4947)	
Lesions stented	4407 (91.2)	4345 (91.1)	0.91
At least one drug-eluting stent	3300 (68.3)	3212 (67.4)	0.27
At least one bare-metal stent	1107 (22.9)	1133 (23.8)	0.33
Lesions not stented	427 (8.8)	422 (8.9)	0.91
TIMI flow pre-procedure			
0 or 1	1700 (35.2)	1599 (33.6)	0.09
2	571 (11.8)	553 (11.6)	0.78
3	2562 (53.0)	2612 (54.8)	0.06
TIMI flow post-procedure			
0 or 1	77 (1.6)	73 (1.5)	0.80
2	119 (2.5)	90 (1.9)	0.09
3	4637 (95.9)	4601 (96.6)	0.15
Coronary stenosis <30%	4653 (96.3)	4582 (96.2)	0.89
Procedural success	4541 (93.9)	4494 (94.3)	0.52
Number of lesions stented	(*N* = 4407)	(*N* = 4345)	
Total stent length per lesion—mm	26.2 ± 14.6	26.5 ± 15.0	0.30
Average stent diameter per lesion—mm	3.0 ± 0.5	3.0 ± 0.5	0.84
At least one direct stenting	975 (22.1)	925 (21.3)	0.31
Post-dilation	2021 (45.9)	2021 (46.5)	0.57

Values are mean ± SD, *n* (%), *n*, or median (interquartile range).
ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; EF, ejection fraction; GPI, glycoprotein IIb/IIIa inhibitors; Hb, haemoglobin; NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin.
[a]Systolic blood pressure <80 mmHg.
[b]<12 g/dL for women, <13 g/dL for men.

randomly allocated to receive or not post-PCI bivalirudin infusion are presented in Supplementary material online, *Table S1*.

AKI occurred in 1213 patients (17.1%) as defined by a relative (>25%) increase in sCr and 365 patients (5.2%) according to an absolute increase in sCr of >0.5 mg/dL. Patients who developed AKI were older, more frequently men with multiple comorbidities (including anaemia or diabetes), and received higher amounts of contrast volume (Supplementary material online, *Table S2*); they were more likely to present STEMI with advanced Killip class and required 4-times greater use of intra-aortic balloon pump. AKI patients presented more commonly complex coronary lesions involving the left coronary system, requiring prolonged procedural time. In addition, procedural success was lower in patients who developed AKI compared with non-AKI patients (Supplementary material online, *Table S2*).

Endpoints according to antithrombotic therapy

Before randomization, sCr and the estimated glomerular filtration rate (eGFR) were comparable between the two groups (*Table 2*). Peak sCr after intervention or at discharge did not differ in the bivalirudin vs. UFH group, as nadir eGFR during hospitalization (78.39 ± 24.92 mL/min/1.73 m^2 in the bivalirudin group vs. 78.89 ± 26.14 mL/min/1.73 m^2 in the UFH group; $P = 0.41$) or eGFR at hospital discharge (83.69 ± 25.59 mL/min/1.73 m^2 in the bivalirudin group vs. 84.15 ± 26.73 mL/min/1.73 m^2 in the UFH group, $P = 0.46$).

The primary outcome of AKI occurred in 601 patients (16.9%) in the bivalirudin group and 616 patients (17.4%) in the UFH group [odds ratio (OR) 0.97; 95% confidence interval (CI): 0.85–1.09; $P = 0.58$; *Figure 1*, *Table 3*]. Both components of the AKI primary

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Table 2 Renal function

	Randomized to Bivalirudin (*N* = 3550)	Randomized to UFH (*N* = 3535)	*P*-value
Creatinine, mg/dL			
Pre-PCI	0.98 ± 0.35	0.98 ± 0.34	0.54
Post-PCI	1.08 ± 0.55	1.08 ± 0.57	0.64
At hospital discharge	1.00 ± 0.43	1.01 ± 0.47	0.40
Creatinine clearance/eGFR, mL/min/1.73 m^2 (MDRD formula)			
Pre-PCI	83.61 ± 24.98	84.61 ± 25.69	0.10
Post-PCI	78.39 ± 24.92	78.89 ± 26.14	0.41
At hospital discharge	83.69 ± 25.59	84.15 ± 26.73	0.46

Values are expressed as mean ± SD.
eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; PCI, percutaneous coronary intervention.

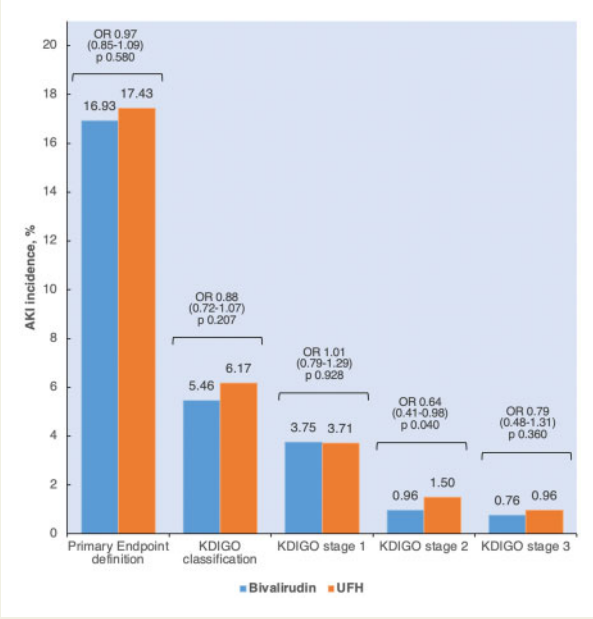


Figure 1 Incidence of AKI in patients randomized to bivalirudin vs. UFH and assessed according to primary endpoint definition and KDIGO classification. AKI, acute kidney injury; KDIGO, kidney disease improving global outcomes; OR, odds ratio; UFH, unfractionated heparin.

endpoint definition were not significantly different in patients randomized to bivalirudin. Specifically, a >25% increase in sCr was observed in 597 patients (16.8%) with bivalirudin and 616 patients (17.4%) with UFH (OR: 0.96; 95% CI: 0.85–1.08; $P = 0.50$), and a >0.5 mg/dL absolute increase in sCr occurred in 176 patients (5%) with bivalirudin and 189 patients (5.4%) with UFH (OR: 0.92; 95% CI: 0.75–1.14; $P = 0.46$). Among patients who underwent PCI after coronary angiography during the index hospitalization ($n = 6612$), the risk of AKI did not significantly differ between the two randomized groups (*Table 3*).

By implementing the KDIGO criteria, AKI occurred in 194 patients (5.5%) with bivalirudin and 218 patients (6.2%) with UFH (OR: 0.88; 95% CI: 0.72–1.07; $P = 0.21$). Stage 1 or 3 AKI was not reduced in the bivalirudin group (*Figure 1*, *Table 3*), but Stage 2 was lower with bivalirudin compared with UFH (1.0 vs. 1.5%; $P = 0.04$).

Study outcomes according to randomization to post-PCI bivalirudin infusion (MATRIX Treatment Duration) were not significantly different and are presented in Supplementary material online, *Table S3*.

Subgroups analyses and multivariate modelling

The effect of antithrombotic therapy on AKI occurrence was largely consistent across subgroups, including diabetes, eGFR, age, clinical presentation, LV dysfunction, Killip class, Mehran score, and contrast media volume (*Figure 2*). Positive quantitative interaction testing was noted between the randomized antithrombotic therapy and access site, suggesting a benefit with bivalirudin compared with UFH in patients allocated to FA.

At multivariate modelling, random allocation to radial access was associated with a significantly lower risk of AKI in patients randomized to UFH (Supplementary material online, *Table S4*), while the treatment effect of the randomized access-site on AKI was not observed in those treated with bivalirudin (Supplementary material online, *Table S5*).

Discussion

The MATRIX trial is one of the largest randomized studies comparing bivalirudin with UFH in ACS patients and the only randomized trial comparing post-PCI vs. no post-PCI bivalirudin infusion. The study failed to demonstrate that bivalirudin as compared to UFH with provisional use of GPI reduces major adverse cardiovascular events or net adverse clinical events, and post-PCI bivalirudin infusion did not demonstrate adjunctive benefit compared with no post-PCI infusion.[9] However, in secondary endpoint analyses, bivalirudin consistently reduced major bleeding, including fatal and non-access site-related events as well as transfusion rates in both randomly allocated access sites.[9]

The main finding of the present analysis is that a regimen of bivalirudin monotherapy did not reduce the occurrence of AKI compared with UFH with or without GPI. These results remained consistent by implementing the KDIGO criteria, which revealed a much lower risk of AKI in the overall population and a numerically lower incidence of

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Table 3 Acute kidney injury

All patients receiving an angiography and/or PCI	Randomized to Bivalirudin (*N* = 3550)	Randomized to UFH (*N* = 3535)	Odds Ratio (95% CI)	*P*-value
AKI according to primary endpoint definition	601 (16.9)	616 (17.4)	0.97 (0.85–1.09)	0.58
AKI 25% increase	597 (16.8)	616 (17.4)	0.96 (0.85–1.08)	0.50
AKI 0.5 increase	176 (5.0)	189 (5.4)	0.92 (0.75–1.14)	0.46
AKI related to index procedure only	566 (15.9)	582 (16.5)	0.96 (0.85–1.09)	0.55
AKI 25% increase	562 (15.8)	581 (16.4)	0.96 (0.84–1.09)	0.49
AKI 0.5 increase	171 (4.8)	184 (5.2)	0.92 (0.74–1.14)	0.45
AKI related to staged procedure only	81 (2.3)	83 (2.4)	0.97 (0.71–1.32)	0.85
AKI 25% increase	80 (2.3)	81 (2.3)	0.98 (0.72–1.34)	0.91
AKI 0.5 increase	21 (0.6)	22 (0.6)	0.95 (0.52–1.73)	0.87
KDIGO criteria	194 (5.5)	218 (6.2)	0.88 (0.72–1.07)	0.21
Stage 1	133 (3.8)	131 (3.7)	1.01 (0.79–1.29)	0.93
Stage 2	34 (1.0)	53 (1.5)	0.64 (0.41–0.98)	0.04
Stage 3	27 (0.8)	34 (1.0)	0.79 (0.48–1.31)	0.36
Dialysis during index hospitalization	1 (0.03)	0 (0.0)	1.00 (1.00–1.00)	
Only patients who underwent index PCI[a]	(*N* = 3315)	(*N* = 3297)		
AKI during hospitalization	564 (17.0)	562 (17.1)	1.00 (0.88–1.13)	0.97
AKI 25% increase	560 (16.9)	562 (17.1)	0.99 (0.87–1.12)	0.87
AKI 0.5 increase	156 (4.7)	172 (5.2)	0.90 (0.72–1.12)	0.34

Values are expressed as *n* or *n* (%) unless otherwise indicated.
PCI, percutaneous coronary intervention; UFH, unfractionated heparin.
[a]Excluding patients who underwent angiography only.

AKI in favour of bivalirudin, albeit not statistically significant. The study results were also mainly consistent across the pre-defined study subgroups. However, in the subpopulation of patients who entered the access-site randomization, we found a significant interaction with the type of allocated access site at the time of PCI. Bivalirudin reduced the incidence of AKI compared to UFH in patients randomized to FA, whereas no such effect was observed in those randomized to RA. These results are specular to what was observed for radial vs. femoral access site, in which the treatment effect for radial was mainly observed in the UFH but not in the bivalirudin group.[8]

Our overall study results are consistent with previous findings from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI),[18] which did not observe a lower risk of AKI with bivalirudin (16.8%) vs. UFH plus GPI (15.5%). Yet, the results of the HORIZONS-AMI study referred solely to a selected population of STEMI patients undergoing primary PCI mainly through FA while only a minority using RA. This analysis extends these findings to a contemporary, all-comers ACS population with randomly allocated access site, including both STEMI and NSTE-ACS undergoing invasive management.

Previous *post-hoc* analyses of randomized studies comparing bivalirudin with UFH in ACS patients undergoing PCI do support a beneficial effect of bivalirudin on bleeding in patients with chronic kidney disease (CKD), a subset of patients at high risk for AKI.[19,20] In the *Second Randomized Evaluation in PCI Linking Bivalirudin to Reduced Clinical Events* (REPLACE-2) trial, bivalirudin use was associated with lower TIMI major or minor bleeding (3.2% vs. 7.1%, $P = 0.009$) compared with UFH plus a GPI in a sub-population of 886 patients with CKD.[19] The *Acute Catheterization and Urgent Intervention Triage strategy* (ACUITY) demonstrated a remarkable reduction of 30-day non-coronary artery bypass graft (CABG) major bleeding (including access site and non-access site bleeding events) in patients with CKD treated with bivalirudin compared with those treated with heparin plus a GPI (6.2% vs. 9.8%, $P = 0.008$).[20] A recent report from the National Cardiovascular Data Registry CathPCI Registry demonstrated a lower rate of in-hospital bleeding with bivalirudin compared with UFH (7.0% vs. 9.5%; adjusted OR: 0.82; 95% CI: 0.76–0.87) in 71 675 patients with end-stage renal disease undergoing PCI.[21] One would expect that the more pronounced benefit of bivalirudin in reducing access site and non-access site bleeding events in patients with CKD would translate into a potential reduction of AKI compared with patients treated with UFH. We did not find an advantage of bivalirudin on the risk of AKI in the overall population or the subgroup of CKD patients.

RA has been shown to reduce the risk of AKI compared with FA, especially among patients at higher risk for AKI.[6] However, a beneficial effect of RA for AKI prevention was not observed in another smaller and most likely underpowered randomized controlled trial comparing the two access sites.[22] The advocated mechanisms through which RA may reduce AKI occurrence might include the avoidance of direct passage of catheters in the proximity of renal arteries (with potential impact on embolization into renal circulation),[23] the reduction of bleeding events,[8] or a combination of both. The effect of bleeding prevention achieved with the use of bivalirudin as opposed to UFH[15] was greater than the one observed with RA vs. FA in the MATRIX trial.[9] Therefore, our results suggest that bleeding avoidance strategies do not necessarily translate into an effect on AKI

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AKI during index procedure	Randomized to Bivalirudin	Randomized to UFH	Odds Ratio (95% CI)	p Value	p Value for interaction
Diabetes					0.35
Yes	183/812	166/770	1.06 (0.83-1.34)	0.64	
No	418/2738	450/2765	0.93 (0.80-1.07)	0.30	
Estimated glomerular filtration rate (eGFR)					0.52
<60 mL/min	140/580	134/574	1.04 (0.80-1.37)	0.75	
≥ 60 mL/min	461/2961	482/2952	0.94 (0.82-1.09)	0.43	
Age					0.38
≥ 75 years	236/890	253/880	0.89 (0.73-1.10)	0.29	
<75 years	365/2660	363/2655	1.00 (0.86-1.17)	0.96	
Clinical presentation					0.64
STEMI	376/1986	376/1966	0.99 (0.84-1.16)	0.88	
NSTEACS	225/1564	240/1569	0.93 (0.76-1.13)	0.47	
LVEF under 40%					0.18
< 40%	134/378	110/344	1.17 (0.86-1.59)	0.32	
≥ 40%	453/3044	486/3065	0.93 (0.81-1.07)	0.29	
Killip class					0.97
Killip class III or IV	39/109	34/92	0.95 (0.53-1.69)	0.86	
Killip class I or II	562/3441	582/3443	0.96 (0.85-1.09)	0.52	
Mehran score					0.73
> 10 points	88/248	92/241	0.89 (0.62-1.29)	0.54	
≤ 10 points	499/3237	520/3240	0.95 (0.83-1.09)	0.48	
Contrast media volume					0.39*
0-99 ml	47/420	272/426	0.75 (0.50-1.13)	0.17	
100-199 ml	291/1833	272/1857	1.10 (0.92-1.32)	0.30	
200-299 ml	177/953	178/905	0.93 (0.74-1.17)	0.55	
300-399 ml	58/254	79/265	0.70 (0.47-1.03)	0.072	
≥ 400 ml	28/90	26/82	0.97 (0.51-1.85)	0.93	
Randomized Access					0.018
Radial	300/1770	271/1771	1.13 (0.94-1.35)	0.18	
Femoral	301/1780	345/1764	0.84 (0.71-0.99)	0.041	

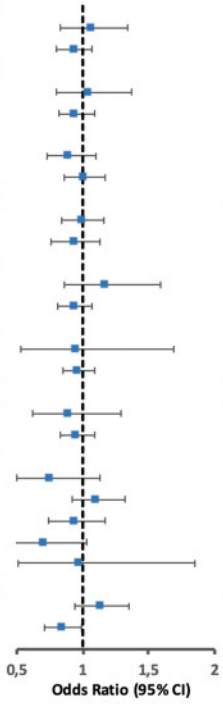


Figure 2 Subgroup analysis of the primary endpoint. AKI, acute kidney injury; CI, confidence interval; LVEF, left ventricle ejection fraction; NSTEACS, non-ST segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin. **P*-value for trend across ordered groups.

prevention. The reasons why RA but not bivalirudin was associated with a lower occurrence of AKI remain speculative but lend support to the role of embolization into the renal circulation.

The observation that bivalirudin may exert a beneficial effect on AKI prevention only among patients who received FA may be a spurious finding. Yet, it may also suggest that a bleeding prevention strategy may mitigate the consequences of renal embolization in a possible two-hit hypothesis whereby renal under-perfusion may be especially detrimental if micro-embolization into the renal district has concomitantly occurred.

Study limitations

Some limitations of this analysis should be considered. Firstly, the independent clinical events committee did not adjudicate AKI events and AKI occurrence relied solely on measurements of sCr values. Since the results of the primary endpoints were negative, differential effects across subgroups of the randomized treatments should be considered hypothesis-generating. As in the AKI-MATRIX study, the intensity of peri-procedural hydration, type of used contrast media, or nephrotoxic drugs discontinuation were not systematically collected in the study case report form.[6] Thus, we were not able to adjust study outcomes according to these variables. In addition, the time and date of sCr peak during index hospitalization and after discharge were not collected. Finally, MATRIX Antithrombin and Treatment Duration compared two antithrombotic strategies (bivalirudin with bailout GPI vs. UFH with the planned use of GPI), so the different use of GPI in both treatment arms may represent a potential confounder on study outcomes.

Conclusions

This study demonstrated that the risk of post-procedural AKI was not significantly lower with bivalirudin compared with UFH and discretionary use of GPI among ACS patients undergoing invasive management.

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care* online.

Data availability

The data generated in this research will be shared on reasonable request to the corresponding author.

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References

1. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, Kosiborod M, Amin AP, Messenger JC, Rumsfeld JS, Spertus JA. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI Registry. *JACC Cardiovasc Interv* 2014;**7**:1–9.
2. Valle JA, McCoy LA, Maddox TM, Rumsfeld JS, Ho PM, Casserly IP, Nallamothu BK, Roe MT, Tsai TT, Messenger JC. Longitudinal risk of adverse events in patients with acute kidney injury after percutaneous coronary intervention. *Circ Cardiovasc Interv* 2017;**10**:e004439.
3. Azzalini L, Kalra S. Contrast-induced acute kidney injury – definitions, epidemiology, and implications. *Interv Cardiol Clin* 2020;**9**:299–309.
4. Marenzi G, Cosentino N, Bartorelli AL. Acute kidney injury in patients with acute coronary syndromes. *Heart* 2015;**101**:1778–1785.
5. Steinvil A, Garcia-Garcia HM, Rogers T, Koifman E, Buchanan K, Alraies MC, Torguson R, Pichard AD, Satler LF, Ben-Dor I, Waksman R. Comparison of propensity score-matched analysis of acute kidney injury after percutaneous coronary intervention with transradial versus transfemoral approaches. *Am J Cardiol* 2017;**119**:1507–1511.
6. Andò G, Cortese B, Russo F, Rothenbühler M, Frigoli E, Gargiulo G, Briguori C, Vranckx P, Leonardi S, Guiducci V, Belloni F, Ferrari F, de la Torre Hernandez JM, Curello S, Liistro F, Perkan A, De Servi S, Casu G, Dellavalle A, Fischetti D, Micari A, Loi B, Mangiacapra F, Russo N, Tarantino F, Saia F, Heg D, Windecker S, Jüni P, Valgimigli M; MATRIX Investigators. Acute kidney injury after radial or femoral access for invasive acute coronary syndrome management: AKI-MATRIX. *J Am Coll Cardiol* 2017;**69**:2592–2603.
7. Andò G, Gragnano F, Calabrò P, Valgimigli M. Radial vs femoral access for the prevention of acute kidney injury (AKI) after coronary angiography or intervention: a systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2018;**92**:E518–E526.
8. Valgimigli M, Gagnor A, Calabró P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Andò G, Repetto A, Limbruno U, Cortese B, Sganzerla P, Lupi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbühler M, Vranckx P, Jüni P; MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015;**385**:2465–2476.
9. Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, Varbella F, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andó G, Ferrario M, Limbruno U, Garbo R, Sganzerla P, Russo F, Nazzaro M, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Ferrante G, Santarelli A, Sardella G, de Cesare N, Tosi P, van 't Hof A, Omerovic E, Brugaletta S, Windecker S, Heg D, Jüni P; MATRIX Investigators. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet* 2018;**392**:835–848.
10. Rothenbühler M, Valgimigli M, Odutayo A, Frigoli E, Leonardi S, Vranckx P, Turturo M, Moretti L, Amico F, Uguccioni L, Contarini M, Gómez-Hospital JA, Mainar V, Creaco M, Petronio AS, Cremonesi A, Tamburino C, Fresco C, Bonmassari R, Díaz Fernández JF, Romagnoli E, Beyersmann J, Heg D, Jüni P. Association of acute kidney injury and bleeding events with mortality after radial or femoral access in patients with acute coronary syndrome undergoing invasive management: secondary analysis of a randomized clinical trial. *Eur Heart J* 2019;**40**:1226–1232.
11. Steg PG, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell' Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 2013;**369**:2207–2217.
12. Zeymer U, van't Hof A, Adgey J, Nibbe L, Clemmensen P, Cavallini C, ten Berg J, Coste P, Huber K, Deliargyris EN, Day J, Bernstein D, Goldstein P, Hamm C, Steg PG. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial. *Eur Heart J* 2014;**35**:2460–2467.
13. Han Y, Guo J, Zheng Y, Zang H, Su X, Wang Y, Chen S, Jiang T, Yang P, Chen J, Jiang D, Jing Q, Liang Z, Liu H, Zhao X, Li J, Li Y, Xu B, Stone GW. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA* 2015;**313**:1336–1346.
14. Valgimigli M; MATRIX investigators. Design and rationale for the Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX program. *Am Heart J* 2014;**168**:838–845.e6.
15. Valgimigli M, Frigoli E, Leonardi S, Rothenbühler M, Gagnor A, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andò G, Repetto A, Limbruno U, Garbo R, Sganzerla P, Russo F, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Presbitero P, Santarelli A, Sardella G, Varbella F, Tresoldi S, de Cesare N, Rigattieri S, Zingarelli A, Tosi P, van't Hof A, Boccuzzi G, Omerovic E, Sabaté M, Heg D, Jüni P, Vranckx P; MATRIX Investigators. Bivalirudin or unfractionated heparin in acute coronary syndromes. *N Engl J Med* 2015;**373**:997–1009.
16. Slocum NK, Grossman PM, Moscucci M, Smith DE, Aronow HD, Dixon SR, Share D, Gurm HS. The changing definition of contrast-induced nephropathy and its clinical implications: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). *Am Heart J* 2012;**163**:829–834.
17. Andò G, Cortese B, Frigoli E, Gagnor A, Garducci S, Briguori C, Rubartelli P, Calabrò P, Valgimigli M; MATRIX Investigators. Acute kidney injury after percutaneous coronary intervention: rationale of the AKI-MATRIX (Acute Kidney Injury-Minimizing Adverse hemorrhagic events by TRansradial access site and systemic Implementation of angioX) sub-study. *Catheter Cardiovasc Interv* 2015;**86**:950–957.
18. Narula A, Mehran R, Weisz G, Dangas GD, Yu J, Genereux P, Nikolsky E, Brener SJ, Witzenbichler B, Guagliumi G, Clark AE, Fahy M, Xu K, Brodie BR, Stone GW. Contrast-induced acute kidney injury after primary percutaneous

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coronary intervention: results from the HORIZONS-AMI substudy. *Eur Heart J* 2014;**35**:1533–1540.
19. Chew DP, Lincoff AM, Gurm H, Wolski K, Cohen DJ, Henry T, Feit F, Topol EJ. *Bivalirudin* versus *heparin* and glycoprotein IIb/IIIa inhibition among patients with renal impairment undergoing percutaneous coronary intervention (a subanalysis of the REPLACE-2 trial). *Am J Cardiol* 2005;**95**:581–585.
20. Mehran R, Nikolsky E, Lansky AJ, Kirtane AJ, Kim Y-H, Feit F, Manoukian S, Moses JW, Ebrahimi R, Ohman EM, White HD, Pocock SJ, Dangas GD, Stone GW. Impact of chronic kidney disease on early (30-day) and late (1-year) outcomes of patients with acute coronary syndromes treated with alternative antithrombotic treatment strategies: an ACUITY (Acute Catheterization and Urgent Intervention Triage strategY). *JACC Cardiovasc Interv* 2009;**2**:748–757.
21. Washam JB, Kaltenbach LA, Wojdyla DM, Patel MR, Klein AJ, Abbott JD, Rao SV. Anticoagulant use among patients with end-stage renal disease undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 2018;**11**:e005628.
22. Marbach JA, Wells G, Santo PD, So D, Chong A-Y, Russo J, Labinaz M, Dick A, Froeschl M, Glover C, Hibbert B, Marquis J-F, MacDougall A, Kass M, Paddock V, Quraishi AUR, Chandrasekhar J, Ghosh N, Bernick J, Le May M. Acute kidney injury after radial or femoral artery access in ST-segment elevation myocardial infarction: AKI-SAFARI. *Am Heart J* 2021;**234**:12–22.
23. Scolari F, Ravani P, Gaggi R, Santostefano M, Rollino C, Stabellini N, Colla L, Viola BF, Maiorca P, Venturelli C, Bonardelli S, Faggiano P, Barrett BJ. The challenge of diagnosing atheroembolic renal disease. *Circulation* 2007;**116**:298–304.

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Part IV

Radial versus femoral access for coronary revascularisation

Prediction of radial crossover in acute coronary syndromes: derivation and validation of the MATRIX score.

Gragnano F, Jolly SS, Mehta SR, Branca M, van Klaveren D, Frigoli E, Gargiulo G, Leonardi S, Vranckx P, Di Maio D, Monda E, Fimiani L, Fioretti V, Chianese S, Andò G, Esposito G, Sangiorgi GM, Biondi-Zoccai G, Heg D, Calabrò P, Windecker S, Romagnoli E, Valgimigli M.

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Prediction of radial crossover in acute coronary syndromes: derivation and validation of the MATRIX score

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KEYWORDS

- access site
- ACS/NSTE-ACS
- femoral
- NSTEMI
- radial
- STEMI

Abstract

Background: The radial artery is recommended by international guidelines as the default vascular access in patients with acute coronary syndromes (ACS) managed invasively. However, crossover from radial to femoral access is required in 4-10% of cases and has been associated with worse outcomes. No standardised algorithm exists to predict the risk of radial crossover.

Aims: We sought to derive and externally validate a risk score to predict radial crossover in patients with ACS managed invasively.

Methods: The derivation cohort consisted of 4,197 patients with ACS undergoing invasive management via the randomly allocated radial access from the MATRIX trial. Using logistic regression, we selected predictors of radial crossover and developed a numerical risk score. External validation was accomplished among 3,451 and 491 ACS patients managed invasively and randomised to radial access from the RIVAL and RIFLE-STEACS trials, respectively.

Results: The MATRIX score (age, height, smoking, renal failure, prior coronary artery bypass grafting, ST-segment elevation myocardial infarction, Killip class, radial expertise) showed a c-index for radial crossover of 0.71 (95% CI: 0.67-0.75) in the derivation cohort. Discrimination ability was modest in the RIVAL (c-index: 0.64; 95% CI: 0.59-0.67) and RIFLE-STEACS (c-index: 0.66; 95% CI: 0.57-0.75) cohorts. A cut-off of ≥41 points was selected to identify patients at high risk of radial crossover.

Conclusions: The MATRIX score is a simple eight-item risk score which provides a standardised tool for the prediction of radial crossover among patients with ACS managed invasively. This tool can assist operators in anticipating and better addressing difficulties related to transradial procedures, potentially improving outcomes.

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Abbreviations

ACS	acute coronary syndrome
CABG	coronary artery bypass graft
MATRIX	Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
OR	odds ratio
PCI	percutaneous coronary intervention
RIFLE-STEACS	Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome
RIVAL	RadIal Vs femorAL access for coronary intervention with ACS undergoing an invasive management
STEMI	ST-segment elevation myocardial infarction
TRIPOD	transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

Introduction

Vascular access for coronary diagnostic and interventional procedures is typically obtained via the radial or femoral artery. Radial access is currently recommended by European and American professional societies as the default approach[1,2] in view of substantial evidence showing advantages over femoral access in terms of clinical outcomes, quality of life, and costs[3-6]. In a non-negligible proportion of cases, however, transradial intervention may be hampered by unfavourable upper limb and aortic arch anatomy, resulting in a more demanding procedure and ultimately in the decision to switch to femoral access – radial crossover. In contemporary acute coronary syndrome (ACS) cohorts, radial crossover has been reported in approximately 8% of cases[7-9], though this rate varies according to patient characteristics and the centres' expertise[3-5,9-14]. The occurrence of radial crossover is undesirable since it has been associated with patient discomfort, increased radiation exposure, delayed revascularisation, and worse outcomes compared with successful radial access – particularly in ST-elevation myocardial infarction (STEMI) where prompt reperfusion is warranted[7-11]. Additionally, radial access failure and subsequent crossover to femoral access have been shown to abolish the bleeding benefit offered by the radial over the femoral artery, underlining the importance of initial access-site selection[7,15]. The upfront identification of patients at high risk of radial crossover could allow operators to anticipate, prevent, and/or overcome technical difficulties, and ultimately improve patient care and outcomes[15]. Two risk scores have been developed to predict radial crossover in patients undergoing elective and/or urgent percutaneous coronary intervention (PCI) from a single high-radial-volume centre[9,12]. However, these algorithms cannot be applied in centres with low-to-intermediate radial expertise, and their generalisability remains unclear since they have not been externally validated. Thus, no standardised and validated tool exists to predict the risk of radial crossover in patients invasively managed for ACS.

We created a novel risk score for the prediction of radial crossover in patients with ACS undergoing invasive management from the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) trial. The score was externally validated in two independent ACS cohorts from two large randomised trials.

Methods

STUDY DESIGN AND POPULATION

MATRIX (ClinicalTrials.gov, NCT01433627) was a programme of three nested, randomised, multicentre trials[4]. The MATRIX-Access trial compared radial versus femoral access in 8,404 patients with ACS, with or without ST-segment elevation, who were about to undergo invasive management and where the interventional cardiologist was willing to proceed via radial or femoral access and was expert in both (i.e., at least 75 coronary interventions performed, and at least 50% of interventions in ACS via the radial access during the previous year) **(Supplementary Figure 1)**. Patients were randomised to radial or femoral access before starting coronary angiography using a web-based system. Access-site management was at the discretion of the treating physician[16]. Bivalirudin was infused consistently with approved labelling. Heparin was given at 70-100 units/kg or 50-70 units/kg if glycoprotein IIb/IIIa inhibitors were administered. All outcomes were centrally adjudicated by an independent clinical events committee blinded to treatment allocation. The trial was approved by the institutional review board at each centre, and patients gave written informed consent.

OUTCOMES

The primary endpoint was the occurrence of radial crossover at the index procedure. Radial crossover was defined as a failure to either start or complete coronary angiography or intervention via radial access and subsequent crossover to femoral or brachial access. All clinical and procedural variables included in the analysis were prospectively collected.

VALIDATION COHORTS

External validation of the score was done in two independent cohorts from the randomised multicentre RadIal Vs femorAL access for coronary intervention with ACS undergoing invasive management (RIVAL)[3] and Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS)[5] trials. The RIVAL trial (ClinicalTrials.gov, NCT01014273) randomised 7,021 ACS patients, with or without ST-segment elevation, to receive invasive management by radial (n=3,507) or femoral (n=3,514) access. In the RIFLE-STEACS trial (ClinicalTrials.gov, NCT01420614), 1,001 patients with ST-segment elevation ACS were randomised to radial (n=500) or femoral (n=501) access for primary/rescue PCI. Enrolment criteria are listed in **Supplementary Figure 1**. In the validation cohorts, the score was calculated in all patients with complete information for score variables and assigned to each participant in a similar manner to the derivation cohort. Patients from the derivation and validation cohorts were enrolled in 240 sites from 33 countries **(Supplementary Figure 2)**. To compare the novel score with previously proposed algorithms,

we calculated the score proposed by Abdelaal et al[12] (female sex, previous coronary artery bypass graft [CABG], cardiogenic shock) and the WRIST-CASE score[9] (age, weight, creatinine, hypertension, prior PCI, cardiogenic shock, intra-aortic balloon pump, operator's proportion of femoral interventions, intubation) **(Supplementary Table 1)**. The primary endpoint for the score validation was the occurrence of radial crossover at the index procedure. Data in the validation cohorts were prospectively collected. The study protocols were approved by ethics committees in all participating institutions. Patients provided written informed consent.

STATISTICAL ANALYSIS

We studied the associations between possible predictors and radial crossover at index procedure with logistic regression in patients randomised to radial access from the MATRIX trial. Potential predictors of radial crossover were identified by consensus based on previous studies, clinical judgement, and prompt availability in the catheterisation laboratory, and selected at univariable analysis ($p<0.10$). Independent predictors were selected with multivariable backward selection ($p<0.10$). Linear predictor values were scaled and rounded to a score with integer values between 0 and 100. Discrimination was quantified by Harrell's c-index[17], and calibration was assessed comparing predicted and observed risks using calibration plots[18]. A cut-off point to identify patients at high versus low risk of radial crossover was selected to maximise the Youden index. C-indices, integrated discrimination improvement (IDI), and continuous net reclassification improvement (NRI)[19] were computed to compare the performance of the MATRIX score with the score by Abdelaal et al and the WRIST-CASE score. Sensitivity analyses were performed to evaluate the score discrimination (i) after excluding patients in whom the randomly assigned radial access was not attempted by the operator in the derivation cohort, and (ii) using operator's instead of centre's proportion of radial intervention in the RIVAL trial, in which both operator's and centre's proportions of radial PCI were prospectively collected. The analyses were performed in accordance with the TRIPOD statement **(Supplementary Table 2)**[20]. Data were analysed using Stata 16.1 (StataCorp, College Station, TX, USA).

Results

Between October 2011 and November 2014, 8,404 patients were randomised in the MATRIX trial to receive radial (n=4,197) or femoral (n=4,207) access. Of those assigned to radial access, 183 (4.4%) underwent radial crossover at the index procedure, comprising 178 to femoral access and 5 to brachial access. Crossover occurred in 169 of 3,712 patients with initial right radial access and 14 of 485 patients with initial left radial access. Difficulties in establishing radial access accounted for 20.8% of cases. Radial failure occurred during coronary angiography or intervention in 50.3% and 13.1% of cases, respectively, mainly because of tortuosity or vasospasm. In 15.8% of patients, the operator did not attempt the randomly allocated radial access **(Figure 1)**.

PREDICTORS OF RADIAL CROSSOVER AND SCORE DERIVATION

The derivation cohort included all 4,197 patients randomised to radial access in the MATRIX trial. Among potential predictors of radial crossover, those with a p-value of less than 0.10 at univariable analysis were included in the multivariable model. Eight independent predictors remained in the final model at a p-value of less than 0.10 **(Table 1, Supplementary Appendix 1)**. From the final multivariable model, we developed an eight-item risk score (age, height, history of renal failure, previous CABG, current smoker, STEMI at presentation, Killip class, centre's proportion of radial interventions – the MATRIX score), assigning points to each factor based on the magnitude of association of each predictor with radial crossover **(Table 1, Supplementary Figure 3)**. The distribution of the MATRIX score in the derivation cohort,

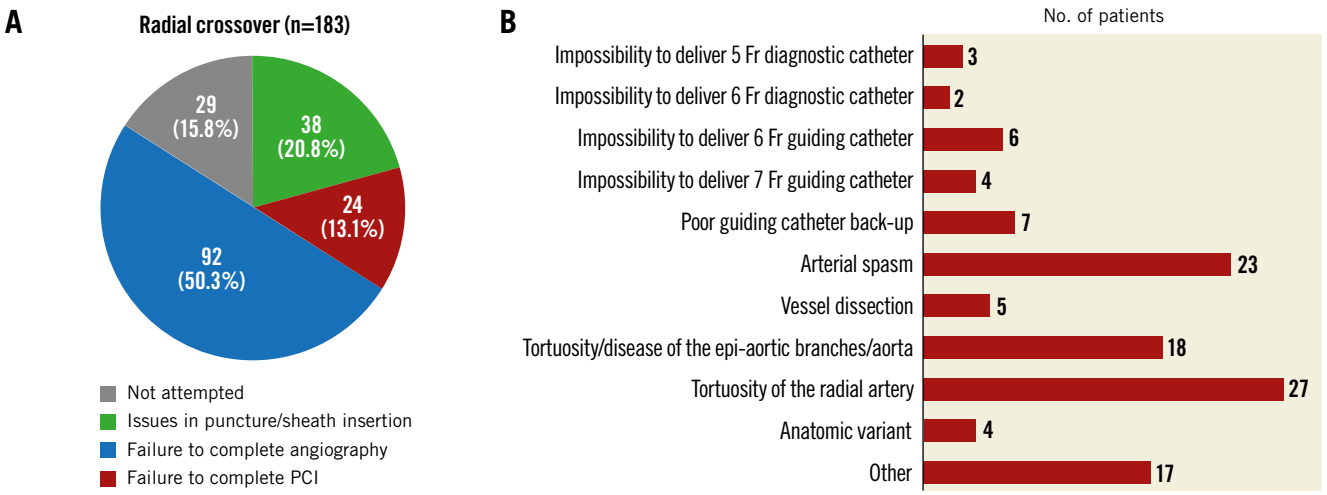


Figure 1. *Radial crossover characteristics in the MATRIX trial. A) Reasons for radial crossover. B) Access-site issues causing radial crossover after successful sheath insertion. PCI: percutaneous coronary intervention*

Table 1. Univariable and multivariable analysis for radial crossover predictors selected at *α* level of 0.1.

		Univariable analysis		Multivariable analysis	
		Rate ratio (95% CI)	*p*-value	Rate ratio (95% CI)	*p*-value
Age (for each increase of 10 years)		1.37 (1.21-1.55)	<0.001	1.28 (1.11-1.47)	0.001
Male sex		0.70 (0.52-0.95)	0.021	–	–
Height (for each increase of 25 cm)		0.64 (0.45-0.91)	0.014	0.71 (0.52-0.99)	0.043
Body mass index, kg/m^2		1.00 (0.96-1.03)	0.87	–	–
Current smoker		0.54 (0.39-0.76)	<0.001	0.68 (0.46-1.01)	0.055
Hypertension		1.36 (1.00-1.85)	0.052	–	–
Previous percutaneous coronary intervention		1.34 (0.93-1.93)	0.11	–	–
Previous radial access		1.57 (0.79-3.11)	0.19	–	–
Previous coronary artery bypass graft		2.35 (1.32-4.20)	0.004	2.12 (1.08-4.17)	0.029
Previous transient ischaemic attack or stroke		1.83 (1.10-3.05)	0.020	–	–
Peripheral arterial disease		1.16 (0.71-1.88)	0.55	–	–
History of renal failure		4.13 (2.16-7.87)	<0.001	3.39 (1.47-7.81)	0.004
ST-elevation myocardial infarction		1.35 (1.02-1.80)	0.038	1.61 (1.18-2.19)	0.003
Night-time arrival in cath lab (from 8 pm to 8 am)		1.17 (0.80-1.70)	0.42	–	–
Cardiac arrest at presentation		1.36 (0.57-3.22)	0.48	–	–
Systolic arterial pressure (for each increase of 1 mmHg)		1.00 (0.99-1.00)	0.093	–	–
Killip class ≥II		2.01 (1.39-2.90)	<0.001	1.63 (1.07-2.48)	0.022
Centre's proportion of radial percutaneous coronary intervention	Low (14.9-64.4%)	Ref.		Ref.	
	Intermediate (65.4-79.0%)	0.56 (0.40-0.78)	0.001	0.53 (0.37-0.75)	<0.001
	High (80.0-98.0%)	0.44 (0.30-0.64)	<0.001	0.37 (0.25-0.55)	<0.001

Age was truncated above 100 years and below 20 years. Height was truncated above 2.00 metres and below 1.35 metres. History of renal failure was defined as a clinical history of renal impairment (i.e., creatinine value higher than 200 µmol or 2.26 mg/dl) preceding the index event hospitalisation. Centre's proportion of radial percutaneous coronary intervention was defined as low, intermediate, or high based on tertiles of radial procedure performed among enrolling centres. CI: confidence interval

the risk of radial crossover by total score points, and a nomogram for score calculation are presented in the **Central illustration**. A web calculator is available online (www.matrixscore.org).

The MATRIX score showed a c-index of 0.71 (95% confidence interval [CI]: 0.67-0.75) for radial crossover and was well calibrated as indicated by the good agreement between predicted and actual risks **(Figure 2)**. A cut-off of 41 points was selected to discriminate between patients at high versus low risk of crossover. Among patients randomised to radial access, 1,279 (30.5%) had a score ≥41 points and experienced a more than threefold higher risk of crossover compared with those at a lower score, showing an odds ratio (OR) of 3.67 (95% CI: 2.71-4.97; p<0.001) **(Figure 3)**. These results remained consistent when right radial access (OR 3.90, 95% CI: 2.84-5.36; p<0.001]) and left radial access (OR 2.30, 95% CI: 0.77-6.61; p=0.14) were appraised separately. At very high score values (MATRIX score ≥70 points), patients had a predicted risk of radial crossover of 31% **(Central illustration)**.

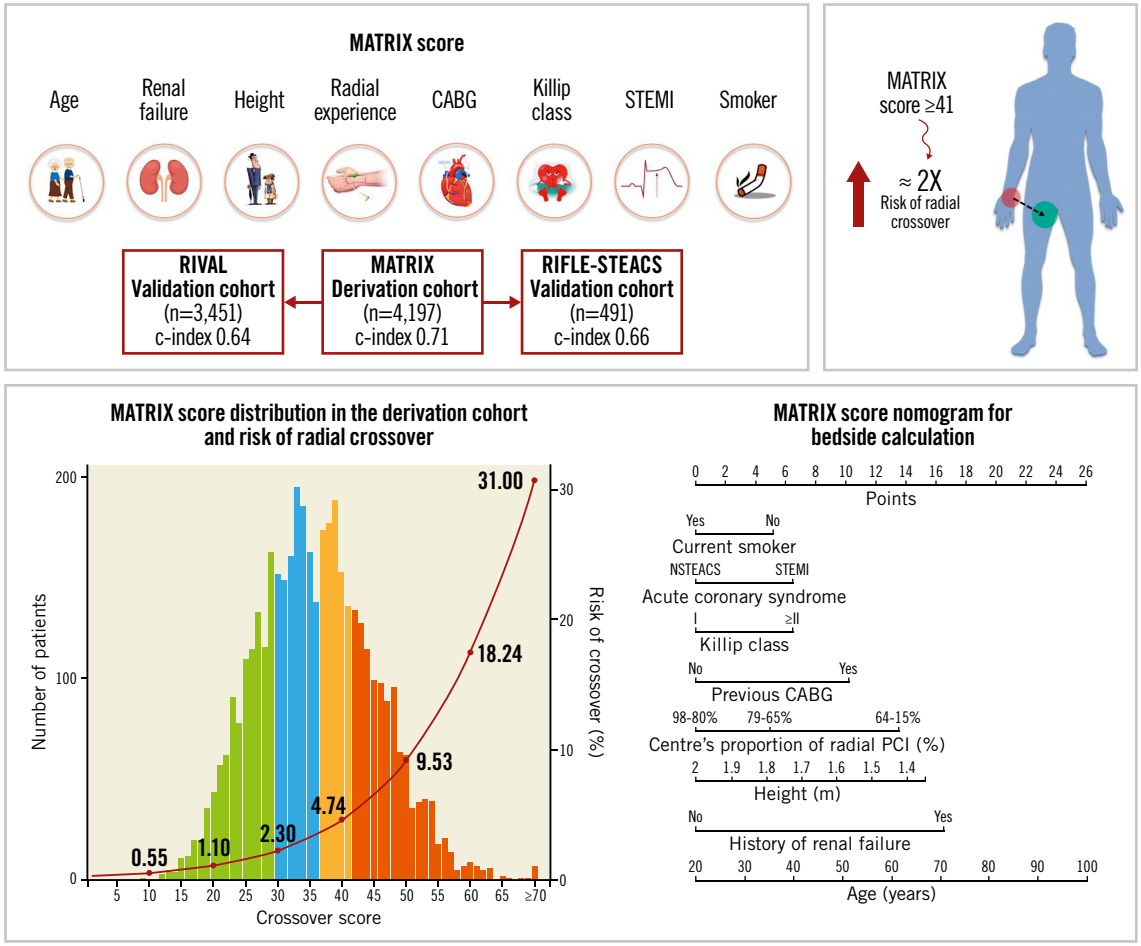
EXTERNAL VALIDATION IN THE RIVAL AND RIFLE-STEACS TRIAL COHORTS

The MATRIX score was validated in 98.4% (n=3,451) and 98.2% (n=491) of the patients randomised to radial access with complete information for score calculation in the RIVAL and RIFLE-STEACS trials, respectively. The rate of radial crossover was 7.7% (265 events) in the RIVAL cohort and 9.6% (47 events) in the RIFLE-STEACS cohort. The c-index for radial crossover was 0.64 (95% CI: 0.59-0.67) in the RIVAL cohort, and 0.66 (95% CI: 0.57-0.75) in the RIFLE-STEACS cohort. The score maintained a consistent association between predicted probabilities and observed frequencies in the validation cohorts, although crossover risk was systematically underestimated in both external study cohorts **(Table 2, Figure 2)**. At a cut-off ≥41, the score identified 1,304 patients (37.2%) in the RIVAL and 204 patients (40.8%) in the RIFLE-STEACS cohorts at increased crossover risk compared with those at a lower score (OR 1.71, 95% CI: 1.32-2.20; p<0.0001, and OR 2.70, 95% CI: 1.45-5.01; p=0.0029, respectively) **(Figure 3)**.

PERFORMANCE COMPARED WITH PREVIOUS RISK SCORES

The score by Abdelaal et al showed a c-index for radial crossover of 0.57 (95% CI: 0.53-0.61) in the MATRIX, 0.58 (95% CI: 0.55-0.61) in the RIVAL, and 0.62 (95% CI: 0.53-0.70) in the RIFLE-STEACS cohorts. The c-index of the WRIST-CASE score was 0.60 (95% CI: 0.56-0.65), 0.55 (95% CI: 0.51-0.58), and 0.64 (95% CI: 0.56-0.72) in the MATRIX, RIVAL, and RIFLE-STEACS cohorts, respectively **(Table 2)**.

The MATRIX score showed a superior discriminative ability according to the c-index compared with the score proposed by Abdelaal et al, with a non-significant effect in the RIVAL (p=0.11)



Central illustration. *The MATRIX score for the prediction of radial crossover. The MATRIX score is a simple eight-item score to predict the risk of radial crossover in patients with ACS undergoing invasive management. A nomogram for bedside calculation is provided. The histogram refers to the MATRIX score distribution in the derivation cohort: green bars, the first score quartile of risk; blue bars, the second score quartile; yellow bars, the third score quartile; and orange bars, the fourth score quartile. The risk curve refers to the risk of radial crossover. At a cut-off of ≥41, the MATRIX score can select patients at higher risk of radial crossover compared with a lower score. ACS: acute coronary syndrome; CABG: coronary artery bypass graft; NSTEACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction*

Table 2. Prediction of radial access crossover in the derivation and validation cohorts.

		No. of crossover / No. of patients	c-index (95% CI)	*p*-value	IDI	*p*-value	cNRI	*p*-value
Derivation cohort (MATRIX)	MATRIX score	183/4,197	0.71 (0.67-0.75)	<0.001*	0.024*	<0.001*	0.435*	<0.001*
				<0.001#	0.012#	0.035#	0.376#	<0.001#
	Abdelaal et al (2013)		0.57 (0.53-0.61)	Ref.*	Ref.*	–	Ref.*	–
	WRIST-CASE (2016)		0.60 (0.56-0.65)	Ref.#	Ref.#	–	Ref.#	–
Validation cohort 1 (RIVAL)	MATRIX score	265/3,451	0.64 (0.59-0.67)	0.11*	0.009*	0.003*	0.200*	0.001*
				<0.001#	0.017#	0.001#	0.080#	0.21#
	Abdelaal et al (2013)		0.58 (0.55-0.61)	Ref.*	Ref.*	–	Ref.*	–
	WRIST-CASE (2016)		0.55 (0.51-0.58)	Ref.#	Ref.#	–	Ref.#	–
Validation cohort 2 (RIFLE-STEACS)	MATRIX score	47/491	0.66 (0.57-0.75)	0.22*	0.056*	0.044*	0.502*	0.001*
				0.96#	0.039#	0.084#	0.318#	0.035#
	Abdelaal et al (2013)		0.62 (0.53-0.70)	Ref.*	Ref.*	–	Ref.*	–
	WRIST-CASE (2016)		0.64 (0.56-0.72)	Ref.#	Ref.#	–	Ref.#	–

The score by Abdelaal et al (*) and the WRIST-CASE score (#) were used as reference to test c-indices, IDI, and continuous NRI compared with the MATRIX score. CI: confidence interval; cNRI: continuous net reclassification index; IDI: integrated discrimination improvement

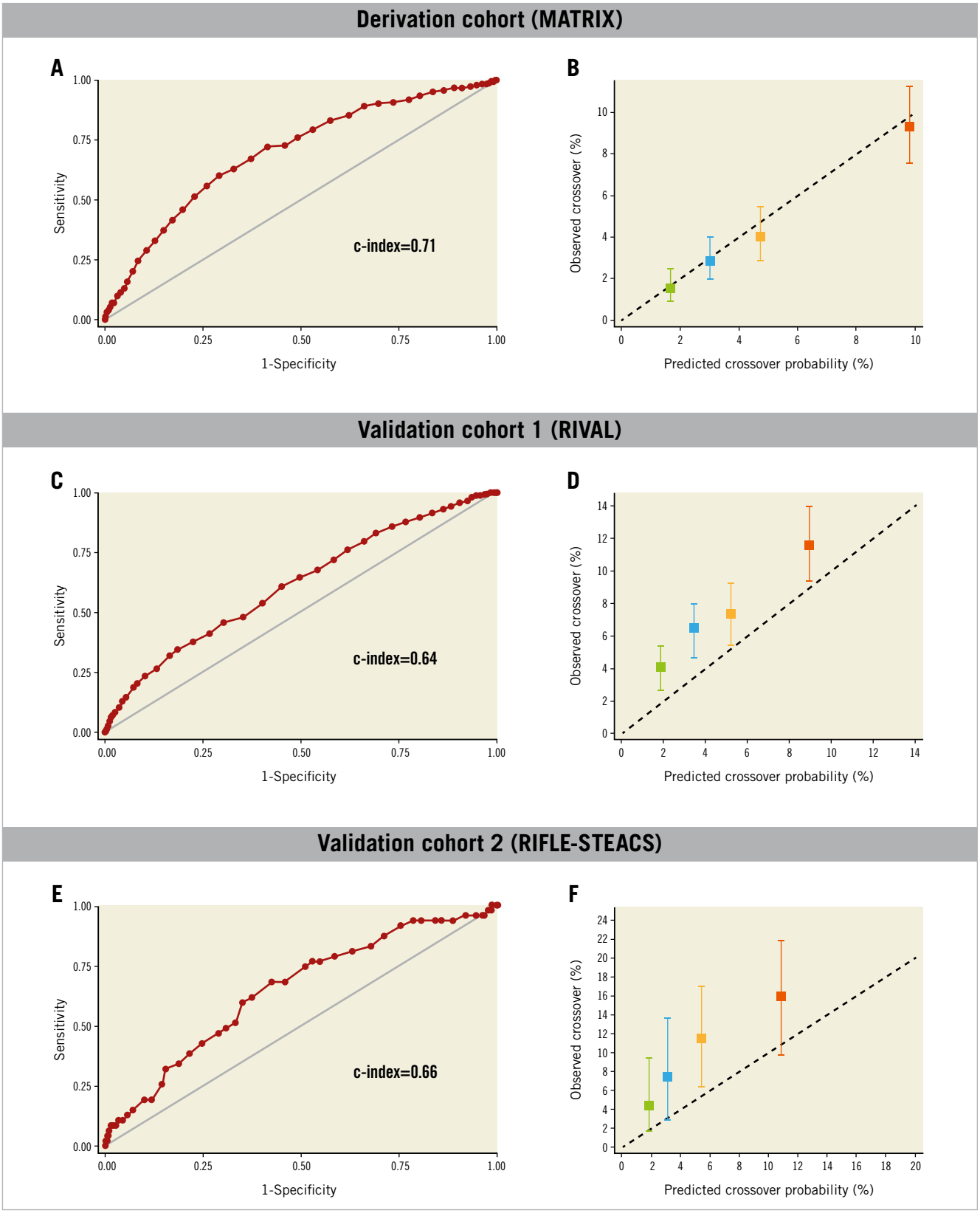


Figure 2. *Receiver operating characteristic curve and calibration plot of the MATRIX score for the prediction of radial crossover in the derivation and validation cohorts. Receiver operating characteristic curves (A, C, & E). Calibration plots (B, D, & F). Quartiles of the patients by score are depicted including confidence intervals of risk estimates. The black dotted 45° line indicates perfect calibration (i.e., predictive value of the model perfectly matches patient's actual risk). Any deviation above or below the 45° line indicates under- or over-prediction, respectively.*

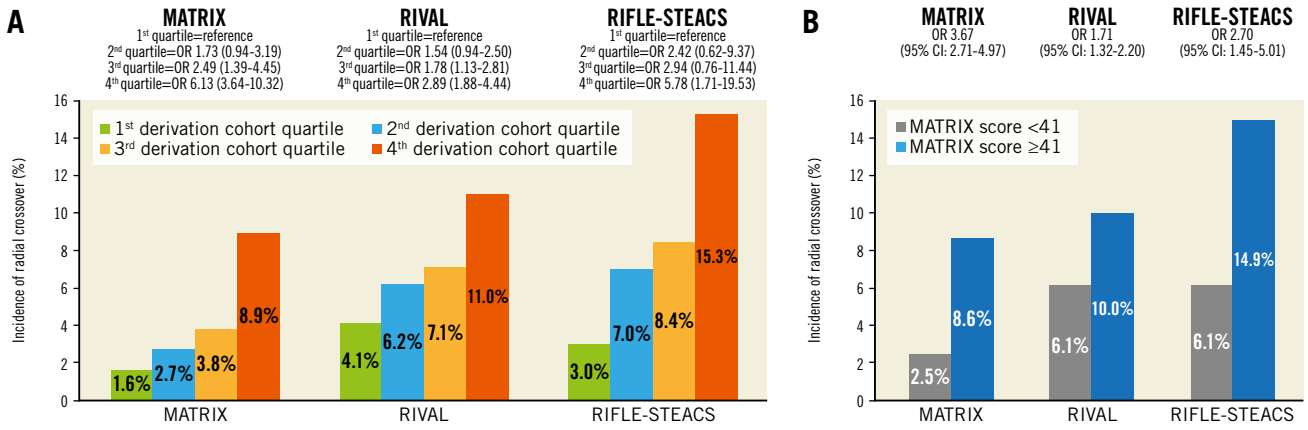


Figure 3. *Cumulative incidence and odds ratio of radial crossover according to the MATRIX score in the derivation and validation cohorts. A) Risk of radial crossover stratified by MATRIX score in the derivation and validation cohorts using as cut-off points those separating quartiles in the derivation cohort. B) Risk of radial crossover stratified by MATRIX score at a cut-off point of 41 in the derivation and validation cohorts. CI: confidence interval; OR: odds ratio*

and RIFLE-STEACS (p=0.22) cohorts. The discrimination offered by the MATRIX score was significantly superior to that provided by the WRIST-CASE score in the RIVAL (p<0.001), but not in the RIFLE-STEACS cohort (p=0.96) **(Table 2)**.

The IDI and continuous NRI analysis showed improved risk stratification with the MATRIX score compared with previous scores, although differences were not always significant versus the WRIST-CASE score **(Table 2)**.

SENSITIVITY ANALYSES

In the MATRIX trial, the randomly assigned radial access was not attempted by the operator in 29 cases. The median MATRIX score in these patients was 44 (interquartile range 38-48). After excluding these cases, the performance of the score in the derivation cohort remained consistent (c-index 0.69, 95% CI: 0.65-0.73). When the score c-index was computed using operator's instead of centre's proportion of radial intervention in the RIVAL trial, the discrimination ability remained almost identical (c-index 0.63, 95% CI: 0.60-0.66).

Discussion

We developed the first externally validated score to predict the risk of crossover from radial access to mainly femoral access among ACS patients managed invasively. It consists of eight readily available items, namely age, height, smoking status, history of renal failure, prior CABG, Killip class, STEMI at presentation, and radial expertise. The generation data set consisted of the largest randomised trial comparing radial versus femoral access. The validation data sets included the second-largest trial with randomised vascular access and one of the largest randomised data sets focusing on STEMI[3,5]. The score ranges from zero to 100 arbitrary points and identifies – at a cut-off point of 41 – a sizeable proportion of patients, approximating 30% of the study cohorts, in whom crossover risk seems at least doubled and close to 10% in absolute terms. The MATRIX score is meant to assist operators in anticipating and potentially addressing difficulties in performing transradial procedures.

Our study does not offer insights into whether a primary femoral approach might be associated with similar or even improved outcomes compared to radial access in patients at high crossover risk. However, it provides for the first time a standardised tool to quantify crossover risks and inform operators, serving as a basis for future research. For instance, patients at high predicted risk of radial failure may be considered for more extensive use of ultrasound-guided radial artery cannulation to prevent issues in arterial puncture or sheath insertion (accounting for 20% of radial crossover cases in our cohorts). Also, before attempting radial access, a careful examination of the femoral arteries appears desirable if a high risk of crossover exists in order to plan safe alternative vascular access. Additionally, the upfront selection and/or prompt availability of procedural materials that can facilitate vascular navigation, reduce the need for catheter exchanges, and address possible transradial difficulties (e.g., hydrophilic sheaths, guidewires, and catheters, dedicated radial shapes)[21] may be warranted in these cases. The MATRIX score may also serve as a benchmark and quality measure for centres and operators during and after the adoption of transradial interventions in daily practice. A stepwise approach to learning may be proposed based on the predicted risk of radial crossover, and patients with an increasing score may be treated gradually via the radial artery. The highest level of radial competency for institutions and operators may be established when patients at a high score and requiring complex procedures can be managed with timely and technically proficient control of coronary interventions. Finally, estimating the risk of crossover to the femoral access upfront may provide a unique asset during patient counselling and the informed consent process, especially for the growing number of patients who explicitly request radial access. Whether radial access should still be preferable in patients

at high risk for radial crossover remains unclear and should be prospectively investigated in clinical studies.

The use of individual factors and risk scores to identify patients at risk of radial crossover has been proposed previously. However, prior studies have been flawed by several limitations, undermining the applicability of their conclusions, including small sample size and the absence of external validation[9-13]. The MATRIX score showed modest performance in two large independent validation cohorts of ACS patients. The higher discriminative ability in the RIFLE-STEACS trial compared with the RIVAL trial may reflect differences in study populations. For instance, in the RIVAL trial, patients with cardiogenic shock were excluded, and those with STEMI and advanced Killip class were more likely enrolled in high-radial-volume centres[3]. The score discrimination ability in terms of the c-index was relatively modest but at least similar to (or numerically higher than) previously proposed algorithms for radial crossover risk[9,12] and other widely adopted cardiovascular and non-cardiovascular prediction models[22,23]. The c-index is a widespread measure of discrimination, which is however well known to be insensitive for assessing the clinical implications of prediction models[24]. As such, reliance on the c-index alone has significant limitations; other measures – such as calibration – should be considered. In this respect, the MATRIX score was well calibrated, as indicated by the good agreement between predicted and actual risks of radial crossover, and maintained a consistent effect in both validation cohorts.

The present analysis confirms the predictive value of well-known risk factors for radial failure, such as advanced age, previous CABG, and renal failure[9-13]. We featured the relevance of radial expertise, which emerged as a strong risk predictor in our model. Our findings are consistent with previous studies reporting an increase in the proficiency of radial access and a reduction in the rate of crossover as the radial expertise grows[11,14,25]. We observed that height has an independent association with radial crossover, which has been reported in some studies[26,27] but not by others[9-13]. The predictive value of this variable has a sound rationale since a short height (or height loss due to senescence) is known to predispose to vascular tortuosity of the upper limb arteries[28]. Moreover, in patients with short stature, a small aortic root or short ascending aorta can hamper stable coronary cannulation during radial intervention, therefore increasing the risk of failure. In contrast with previous reports suggesting more difficulties for radial intervention among women[11,12,21,27], female sex did not arise as an independent predictor of radial crossover in our model. Of note, two of the predictors included in the MATRIX score – advanced age and short height – frequently coexist in women[29] and may potentially underpin this misconception. Finally, the presence of ongoing cardiac ischaemia and haemodynamic compromise – marked by STEMI presentation and advanced Killip class – were independently associated with increased risk of radial crossover, which is in agreement with previous observations[9,12]. Of importance, all the variables included in the novel score are readily available to the interventional team and do not imply any delay for data collection (i.e., no laboratory data required), which is essential for any novel algorithm proposed to improve ACS management.

Two risk scores for the prediction of radial crossover have been developed previously in the context of a single-centre experience. A first score was derived from 1,654 patients undergoing PCI (77% for ACS)[12]. The same group of investigators developed the WRIST-CASE score from 2,020 STEMI patients undergoing primary PCI[9]. The need for creatinine on admission for score calculation, which is not generally available at the time of intervention, limits its use in clinical practice. Moreover, the exclusion of patients with prior CABG precludes the application of the algorithm in this subset. As both models were derived from a single high-radial-volume institution without external validation, it remained unclear whether they apply to centres with low-to-intermediate radial expertise, which might benefit more from these tools. With respect to crossover risk prediction, our score proved at least as good as both scores, showing c-indices consistently numerically, even if not always statistically, superior. In addition, our findings seem to reflect the relatively low number of crossover cases in the RIFLE-STEACS cohort in which the superiority of the MATRIX score over the WRIST-CASE score could not be confirmed – in contrast with the comparative data observed within the generation and RIVAL data sets. Finally, at variance from our algorithm, neither of the two previously available scores offered a cut-off point for selecting patients at higher risk of crossover. Interestingly, the Youden index analysis identified at 41 the best score trade-off between sensitivity and specificity, which is consistent with the boundary between the third and fourth quartiles in the generation data set.

Limitations

Our analysis has several limitations. The discrimination ability of our score was modest. Future investigations should assess whether enlarged or modified sets of baseline covariates might improve discrimination. Our findings suggest that access crossover remains a rather technical aspect that is difficult to predict accurately upfront. Information on coronary anatomy and the complexity of the required intervention is probably critical in the decision making for crossover. However, angiographic characteristics are unknown before access-site selection and are not useful to improve crossover prediction. The score was able to risk stratify patients when initial right and left radial accesses were appraised separately, although the low number of patients in the latter group precludes definite conclusions. Information on the type of CABG surgery was not collected in the trial data sets, preventing more granular analyses. A minority of crossover cases followed the operator's decision not to attempt radial access. Consistent with previous studies[9,12], these cases were included to avoid case selection, and results remained consistent at sensitivity analyses excluding these patients. Radial expertise was appraised in the derivation cohort based on the centre's experience. However, when the score c-index was computed using operator's rather than centre's proportion of radial PCI in the RIVAL trial, results remained entirely consistent, suggesting that such information can be used alternatively for the score

calculation. Our score underestimated the crossover risk in the validation cohorts, probably because of the higher crossover rates observed in these data sets compared with the derivation cohort. The MATRIX score was generated and validated using data from clinical trials. The derivation and validation cohorts included unselected high-risk patients, and their clinical characteristics are consistent with those reported in contemporary registries[30]. However, the study exclusion criteria (i.e., peripheral vascular disease, end-stage renal disease) may still limit the applicability of the score in some specific settings. Whether the routine use of the MATRIX score could reduce the rate of radial crossover and improve procedural and/or clinical outcomes remains to be determined.

Conclusions

We developed the MATRIX score, a simple eight-item tool to predict the risk of radial crossover in patients with ACS undergoing invasive management. It is well calibrated and has modest discrimination at external validation analysis. At a cut-off point of ≥41, the MATRIX score identifies patients with at least twofold higher risk of radial crossover compared with those at a lower score. The novel score may assist operators in anticipating and potentially better addressing issues with radial access in clinical practice and provides a new opportunity to investigate the risks and benefits of radial access versus direct femoral access in this high-risk patient subset.

Impact on daily practice

The MATRIX score is the first standardised tool to predict the risk of radial crossover in patients with ACS undergoing invasive management. The novel score can identify, at a cut-off of ≥41 points, patients at high risk of radial crossover, and assist operators in anticipating and potentially addressing issues associated with transradial interventions in daily practice. Patients at high risk of radial failure may be considered for the use of specific techniques and materials that can facilitate radial artery cannulation and navigation (e.g., ultrasound-guided radial access, hydrophilic sheaths, guidewires, and catheters, dedicated radial shapes). The MATRIX score may also serve as a benchmark and quality measure for centres and operators during and after the adoption of transradial interventions in clinical practice.

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Conflict of interest statement

S. Leonardi reports grants and personal fees from AstraZeneca, BMS/Pfizer, and Chiesi, and personal fees from Bayer, outside the submitted work. G. Gargiulo reports consultant fees from Daiichi Sankyo, outside the submitted work. P. Vranckx reports personal fees from AstraZeneca, Terumo, CSL Behring, Daiichi Sankyo, and Bayer Health Care outside the submitted work. E. Frigoli, D. Heg, and M. Branca are affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organisations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html. S. Windecker reports research and educational grants to the institution from Abbott, Abiomed, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, Cardiovalve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, and Sinomed. He serves as unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, V-Wave and Xeltis, but has not received personal payments by pharmaceutical companies or device manufacturers. He is also member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration. He is an unpaid member of the Pfizer Research Award selection committee in Switzerland. G. Biondi-Zoccai reports personal fees from InnovHeart, Meditrial, and Replycare, outside the submitted work. M. Valgimigli reports grants and personal fees from Abbott Vascular, personal fees from Chiesi, Bayer, CoreFlow, Opsens, Daiichi Sankyo, and Amgen, grants and personal fees from Terumo, personal fees from Alvimedica, grants from Medicure, grants and personal fees from AstraZeneca, personal fees from Biosensors, Idorsia, Bristol Myers Squibb, iVascular, Medscape and Vifor, outside the submitted work. G. Ando reports non-financial support from Terumo during the conduct of the study, personal fees and non-financial support from Bayer, Daiichi Sankyo, Bristol Myers Squibb-Pfizer, and Boehringer Ingelheim, personal fees from Menarini, AstraZeneca, Chiesi, and Biosensors, outside the submitted work. The other authors have no conflicts of interest to declare.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

2. Mason PJ, Shah B, Tamis-Holland JE, Bittl JA, Cohen MG, Safirstein J, Drachman DE, Valle JA, Rhodes D, Gilchrist IC; American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Peripheral Vascular Disease; and Council on Genomic and Precision Medicine. An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. *Circ Cardiovasc Interv.* 2018;11:e000035.

3. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, Budaj A, Niemelä M, Valentin V, Lewis BS, Avezum A, Steg PG, Rao SV, Gao P, Afzal R, Joyner CD,

Chrolavicius S, Mehta SR; RIVAL trial group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet.* 2011;377:1409-20.

4. Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, Varbella F, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andó G, Ferrario M, Limbruno U, Garbo R, Sganzerla P, Russo F, Nazzaro M, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Ferrante G, Santarelli A, Sardella G, de Cesare N, Tosi P, van't Hof A, Omerovic E, Brugaletta S, Windecker S, Heg D, Jüni P; MATRIX Investigators. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet.* 2018;392:835-48.

5. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, Summaria F, Patrizi R, Borghi A, Di Russo C, Moretti C, Agostoni P, Loschiavo P, Lioy E, Sheiban I, Sangiorgi G. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol.* 2012;60:2481-9.

6. Andò G, Gragnano F, Calabrò P, Valgimigli M. Radial vs femoral access for the prevention of acute kidney injury (AKI) after coronary angiography or intervention: A systematic review and meta-analysis. *Catheter Cardiovasc Interv.* 2018;92:E518-26.

7. Gragnano F, Branca M, Frigoli E, Leonardi S, Vranckx P, Di Maio D, Monda E, Fimiani L, Fioretti V, Chianese S, Esposito F, Franzese M, Scalise M, D'Angelo C, Scalise R, De Blasi G, Andò G, Esposito G, Calabrò P, Windecker S, Pedrazzini G, Valgimigli M; MATRIX Trial Investigators. Access-Site Crossover in Patients With Acute Coronary Syndrome Undergoing Invasive Management. *JACC Cardiovasc Interv.* 2021;14:361-73.

8. Le May M, Wells G, So D, Chong AY, Dick A, Froeschl M, Glover C, Hibbert B, Marquis JF, Blondeau M, Osborne C, MacDougall A, Kass M, Paddock V, Quraishi A, Labinaz M. Safety and Efficacy of Femoral Access vs Radial Access in ST-Segment Elevation Myocardial Infarction: The SAFARI-STEMI Randomized Clinical Trial. *JAMA Cardiol.* 2020;5:126-34.

9. Abdelaal E, MacHaalany J, Plourde G, Barria Perez A, Bouchard MP, Roy M, Déry JP, Déry U, Barbeau G, Larose É, Gleeton O, Noël B, Rodés-Cabau J, Roy L, Costerousse O, Bertrand OF. Prediction and impact of failure of transradial approach for primary percutaneous coronary intervention. *Heart.* 2016;102:919-25.

10. Azzalini L, Khan R, Al-Hawwas M, Hatem R, Fortier A, L'Allier PL, Ly HQ. Effect of radial-to-femoral access crossover on adverse outcomes in primary percutaneous coronary intervention. *Am J Cardiol.* 2014;114:1165-73.

11. Vink MA, Amoroso G, Dirksen MT, Van Der Schaaf RJ, Patterson MS, Tijssen JGP, Kiemeneij F, Slagboom T. Routine use of the transradial approach in primary percutaneous coronary intervention: procedural aspects and outcomes in 2209 patients treated in a single high-volume centre. *Heart.* 2011;97:1938-42.

12. Abdelaal E, Brousseau-Provencher C, Montminy S, Plourde G, MacHaalany J, Bataille Y, Molin P, Déry JP, Barbeau G, Roy L, Larose É, De Larochellière R, Nguyen CM, Proulx G, Costerousse O, Bertrand OF; Interventional Cardiologists at Quebec Heart-Lung Institute. Risk score, causes, and clinical impact of failure of transradial approach for percutaneous coronary interventions. *JACC Cardiovasc Interv.* 2013;6:1129-37.

13. Le J, Bangalore S, Guo Y, Iqbal SN, Xu J, Miller LH, Coppola J, Shah B. Predictors of Access Site Crossover in Patients Who Underwent Transradial Coronary Angiography. *Am J Cardiol.* 2015;116:379-83.

14. Jolly SS, Cairns J, Yusuf S, Niemela K, Steg PG, Worthley M, Ferrari E, Cantor WJ, Fung A, Valettas N, Rokoss M, Olivecrona GK, Widimsky P, Cheema AN, Gao P, Mehta SR; RIVAL Investigators. Procedural volume and outcomes with radial or femoral access for coronary angiography and intervention. *J Am Coll Cardiol.* 2014;63:954-63.

15. Hirshfeld JW, Faxon DP, Williams DO. Impact of Crossover: A Consideration for Initial Access Site Selection. *JACC Cardiovasc Interv.* 2021;14:374-7.

16. Gragnano F, Manavifar N, Gargiulo G, Sunnåker M, Galea R, Frigoli E, Calabrò P, Windecker S, Valgimigli M. Femoral Access With or Without Vascular Closure Device or Radial Access in Acute Coronary Syndrome. *JACC Cardiovasc Interv.* 2019;12:2116-8.

17. Harrell FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA.* 1982;247:2543-6.

18. Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW; Topic Group 'Evaluating diagnostic tests and prediction models' of the STRATOS initiative. Calibration: the Achilles heel of predictive analytics. *BMC Med.* 2019;17:230.

19. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med.* 2011;30:11-21.

20. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD Statement. *Ann Intern Med.* 2015;162:55-63.

21. Hamon M, Pristipino C, Di Mario C, Nolan J, Ludwig J, Tubaro M, Sabate M, Mauri-Ferré J, Huber K, Niemelä K, Haude M, Wijns W, Dudek D, Fajadet J, Kiemeneij F; European Association of Percutaneous Cardiovascular Interventions; Working Group on Acute Cardiac Care of the European Society of Cardiology; Working Group on Thrombosis on the European Society of Cardiology. Consensus document on the radial approach in percutaneous cardiovascular interventions: position paper by the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care** and Thrombosis of the European Society of Cardiology. *EuroIntervention.* 2013;8:1242-51.

22. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SLT, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L; DAPT Study Investigators. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. *JAMA.* 2016;315:1735-49.

23. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann Intern Med.* 2008;148:337-47.

24. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation.* 2007;115:928-35.

25. Bianchi R, D'Acierno L, Crisci M, Tartaglione D, Cappelli Bigazzi M, Canonico M, Albanese M, Gragnano F, Fimiani F, Russo M, Cirillo P, Calabrò P. From Femoral to Radial Approach in Coronary Intervention. *Angiology.* 2017;68:281-7.

26. Dehghani P, Mohammad A, Bajaj R, Hong T, Suen CM, Sharieff W, Chisholm RJ, Kutryk MJ, Fam NP, Cheema AN. Mechanism and predictors of failed transradial approach for percutaneous coronary interventions. *JACC Cardiovasc Interv.* 2009;2:1057-64.

27. Tröbs M, Achenbach S, Plank PM, Marwan M, Röther J, Klinghammer L, Blachutzik F, Schlundt C. Predictors of Technical Failure in Transradial Coronary Angiography and Intervention. *Am J Cardiol.* 2017;120:1508-13.

28. Ciurică S, Lopez-Sublet M, Loeys BL, Radhouani I, Natarajan N, Vikkula M, Maas AHEM, Adlam D, Persu A. Arterial Tortuosity. *Hypertension.* 2019;73:951-60.

29. Gargiulo G, Ariotti S, Vranckx P, Leonardi S, Frigoli E, Ciociano N, Tumscitz C, Tomassini F, Calabrò P, Garducci S, Crimi G, Andò G, Ferrario M, Limbruno U, Cortese B, Sganzerla P, Lupi A, Russo F, Garbo R, Ausiello A, Zavalloni D, Sardella G, Esposito G, Santarelli A, Tresoldi S, Nazzaro MS, Zingarelli A, Petronio AS, Windecker S, da Costa BR, Valgimigli M. Impact of Sex on Comparative Outcomes of Radial Versus Femoral Access in Patients With Acute Coronary Syndromes Undergoing Invasive Management; Data From the Randomized MATRIX-Access Trial. *JACC Cardiovasc Interv.* 2018;11:36-50.

30. Corpataux N, Spirito A, Gragnano F, Vaisnora L, Galea R, Svab S, Gargiulo G, Zanchin T, Zanchin C, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Räber L, Capodanno D, Urban P, Pocock S, Heg D, Windecker S, Valgimigli M. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. *Eur Heart J.* 2020;41:3743-9.

Supplementary data

Supplementary Appendix 1. Definitions of predictors of crossover.

Supplementary Figure 1. Population selection for the derivation and validation cohorts.

Supplementary Figure 2. Geographic distribution of the derivation and validation cohorts of the MATRIX score.

Supplementary Figure 3. Predictor effects for radial access crossover in the MATRIX score in the derivation cohort.

Supplementary Table 1. Variables included in previously proposed algorithms for the prediction of radial access crossover.

Supplementary Table 2. TRIPOD checklist for prediction model development and validation.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00441

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Access-Site Crossover in Patients With Acute Coronary Syndrome Undergoing Invasive Management

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ABSTRACT

OBJECTIVES The aim of this study was to assess the impact of access-site crossover in patients with acute coronary syndrome undergoing invasive management via radial or femoral access.

BACKGROUND There are limited data on the clinical implications of access-site crossover.

METHODS In the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox)-Access trial, 8,404 patients with acute coronary syndrome were randomized to radial or femoral access. Patients undergoing access-site crossover or successful access site were investigated. Thirty-day coprimary outcomes were a composite of death, myocardial infarction, or stroke (major adverse cardiovascular events [MACE]) and a composite of MACE or Bleeding Academic Research Consortium type 3 or 5 bleeding (net adverse clinical events [NACE]).

RESULTS Access-site crossover occurred in 183 of 4,197 patients (4.4%) in the radial group (mainly to femoral access) and 108 of 4,207 patients (2.6%) in the femoral group (mainly to radial access). In multivariate analysis, the risk for coprimary outcomes was not significantly higher with radial crossover compared with successful radial (MACE: adjusted rate ratio [adjRR]: 1.25; 95% confidence interval [CI]: 0.81 to 1.93; p = 0.32; NACE: adjRR: 1.40; 95% CI: 0.94 to 2.06; p = 0.094) or successful femoral access (MACE: adjRR: 1.17; 95% CI: 0.76 to 1.81; p = 0.47; NACE: adjRR: 1.26; 95% CI: 0.86 to 1.86; p = 0.24). Access site-related Bleeding Academic Research Consortium type 3 or 5 bleeding was higher with radial crossover than successful radial access. Femoral crossover remained associated with higher risks for MACE (adjRR: 1.84; 95% CI: 1.18 to 2.87; p = 0.007) and NACE (adjRR: 1.69; 95% CI: 1.09 to 2.62; p = 0.019) compared with successful femoral access. Results remained consistent after excluding patients with randomized access not attempted.

CONCLUSIONS Crossover from radial to femoral access abolishes the bleeding benefit offered by the radial over femoral artery but does not appear to increase the risk for MACE or NACE compared with successful radial or femoral access. (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox [MATRIX]; NCT01433627) (J Am Coll Cardiol Intv 2021;14:361-73) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

adjRR = adjusted rate ratio

BARC = Bleeding Academic Research Consortium

CI = confidence interval

MACE = major adverse cardiovascular event(s)

NACE = net adverse clinical event(s)

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

The radial artery is currently recommended by European and American professional societies as the default vascular access site for the invasive management of patients with acute coronary syndrome (ACS) (1,2). In randomized clinical trials and observational registries, radial access has been shown to reduce the risk for major bleeding, vascular complications, and all-cause mortality (3–6) and to improve quality of life and reduce health care costs (7) compared with femoral access. As a result, the adoption of radial access has steadily increased over time (8,9). However, in up to 10% of patients, technical difficulties related to radial intervention can preclude the use or cause the failure of radial access, requiring crossover to femoral access (3–6,10–14).

It remains unclear if access-site crossover from radial to femoral access negatively affects outcomes compared with primary successful femoral access, especially in the setting of ST-segment elevation myocardial infarction (STEMI), in which the bailout switch to a second vascular access site has been associated with delayed interventions (10,15). Similarly, no study has so far investigated the prognostic implications of crossover from femoral to radial access in invasively managed patients with ACS, which still occurs in up to 4% of cases (3–6).

We sought therefore to assess the incidence, characteristics, and prognostic implications of access-site crossover in patients with ACS undergoing invasive management by randomly allocated radial or femoral access from the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox)-Access trial.

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METHODS

STUDY DESIGN AND PARTICIPANTS. This was a prespecified subanalysis of MATRIX-Access, a randomized, multicenter, superiority trial comparing radial versus femoral access in patients with ACS, with or without ST-segment elevation, undergoing invasive management (NCT01433627). The rationale, design, and main results of the MATRIX program have been previously reported (4,5,16). In brief, patients were randomized (1:1) to radial or femoral access for diagnostic angiography and percutaneous coronary intervention (PCI) if indicated. Patients were eligible if they presented with ACS with or without ST-segment elevation, if they were about to receive invasive management, and if the interventional cardiologist was willing to proceed with either radial or femoral access with expertise for both, including at least 75 coronary interventions performed and at least 50% of interventions in patients with ACS via the radial artery during the previous year (4,16). Access-site management during and after the procedure was left to the discretion of the treating physician (16,17). The use of anticoagulant agents outside the MATRIX protocol was not allowed. Bivalirudin was administered according to the approved product labeling. Unfractionated heparin was dosed at 70 to 100 U/kg in patients not receiving glycoprotein IIb/IIIa inhibitors and 50 to 70 U/kg in patients receiving glycoprotein IIb/IIIa inhibitors. The use of all other medications was allowed per guidelines. The study protocol of the MATRIX trial was approved by institutional ethics committees of participating institutions and was conducted according to the Declaration of Helsinki and Good Clinical Practice.

ACCESS-SITE CROSSOVER DEFINITION. All participants in the MATRIX-Access trial were considered eligible for the present analysis. On the basis of the arterial access site used to perform coronary catheterization in the index procedure, patients were categorized into 4 groups: 1) radial crossover, if the operator failed to start or complete the procedure via the randomly assigned radial access and required crossover to femoral or brachial access; 2) femoral crossover, if the operator failed to start or complete the procedure via the randomly assigned femoral access and required crossover to radial or brachial access; and 3) successful radial or 4) successful femoral access, if the operator successfully performed the procedure via the randomly assigned access. Patients undergoing crossover from the radial to the ulnar artery, from the radial to the contralateral radial artery, or from the femoral to the contralateral femoral

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics of Radial and Femoral Groups

	Radial Crossover (n = 183)	Successful Radial (n = 4,014)	Femoral Crossover (n = 108)	Successful Femoral (n = 4,099)	p Value*	p Value†	p Value‡
Baseline characteristics							
Age, yrs	69.8 ± 11.3§	65.4 ± 11.8	65.5 ± 12.8	65.9 ± 11.8	<0.001	<0.001	0.68
≥75 yrs	69 (37.7)	1,004 (25.0)	30 (27.8)	1,079 (26.3)	<0.001	<0.001	0.73
Male	123 (67.2)	3,003 (74.8)	77 (71.3)	2,969 (72.4)	0.021	0.12	0.79
Body mass index, kg/m^2	27.0 ± 4.1§	27.1 ± 4.2	28.2 ± 5.7	27.0 ± 4.1	0.87	0.97	0.003
Diabetes mellitus	53 (29.0)	906 (22.6)	37 (34.3)	907 (22.1)	0.044	0.030	0.002
Insulin dependent	12 (6.6)§	197 (4.9)	15 (13.9)	242 (5.9)	0.31	0.71	<0.001
Current smoking	41 (22.4)	1,418 (35.3)	32 (29.6)	1,396 (34.1)	<0.001	0.001	0.33
Hypercholesterolemia	83 (45.4)	1,716 (42.8)	51 (47.2)	1,841 (44.9)	0.48	0.90	0.63
Hypertension	127 (69.4)	2,498 (62.2)	74 (68.5)	2,612 (63.7)	0.050	0.11	0.30
Previous myocardial infarction	39 (21.3)	546 (13.6)	22 (20.4)	596 (14.5)	0.003	0.011	0.091
Previous PCI	34 (18.6)	576 (14.3)	23 (21.3)	562 (13.7)	0.11	0.062	0.024
Previous CABG	11 (6.0)	100 (2.5)	4 (3.7)	142 (3.5)	0.003	0.069	0.89
Previous TIA or stroke	15 (8.2)	180 (4.5)	6 (5.6)	224 (5.5)	0.019	0.11	0.96
Peripheral vascular disease	17 (9.3)§	324 (8.1)	22 (20.4)	350 (8.5)	0.55	0.72	<0.001
Renal failure	8 (4.4)	38 (0.9)	3 (2.8)	56 (1.4)	<0.001	0.001	0.21
Dialysis	2 (1.1)	2 (0.1)	0 (0.0)	4 (0.1)	0.010	0.024	>0.99
Clinical presentation							
STEMI	101 (55.2)§	1,900 (47.3)	41 (38.0)	1,968 (48.0)	0.037	0.057	0.039
NSTE-ACS	82 (44.8)§	2,114 (52.7)	67 (62.0)	2,131 (52.0)			
NSTE-ACS, troponin positive	73 (39.9)§	1,881 (46.9)	64 (59.3)	1,868 (45.6)	0.064	0.13	0.004
Heart rate, beats/min	75.7 ± 15.9	76.3 ± 16.6	79.1 ± 18.7	75.9 ± 16.8	0.59	0.84	0.050
Systolic arterial pressure, mm Hg	135.4 ± 27.3	138.6 ± 25.4	139.0 ± 30.4	138.8 ± 25.5	0.095	0.078	0.94
Left ventricular ejection fraction, %	48.9 ± 11.0	51.4 ± 9.5	51.2 ± 9.8	50.8 ± 9.8	0.001	0.012	0.74
eGFR, ml/min/1.73 m^2	76.0 ± 27.4§	84.5 ± 25.3	84.7 ± 32.9	83.3 ± 25.3	<0.001	<0.001	0.57
eGFR <60 ml/min/1.73 m^2	49 (27.2)	651 (16.3)	24 (22.4)	691 (17.0)	<0.001	<0.001	0.13
Cardiac arrest at presentation	5 (2.7)	80 (2.0)	2 (2.0)	81 (2.0)	0.53	0.44	0.89
Killip class							
I	151 (82.5)	3,645 (90.8)	92 (85.2)	3,708 (90.5)			
II	20 (10.9)	248 (6.2)	11 (10.2)	290 (7.1)	<0.001	<0.001	0.27
III	2 (1.1)	86 (2.1)	4 (3.7)	75 (1.8)			
IV	10 (5.5)	35 (0.9)	1 (0.9)	26 (0.6)			
Medications before catheterization							
Lytic therapy	5 (2.7)	89 (2.2)	0 (0.0)	104 (2.5)	0.64	0.86	0.093
Aspirin	171 (93.4)	3,785 (94.3)	106 (98.1)	3,848 (93.9)	0.62	0.81	0.065
Clopidogrel	94 (51.4)	1,921 (47.9)	58 (53.7)	1,939 (47.3)	0.35	0.28	0.18
Prasugrel	18 (9.8)	467 (11.6)	10 (9.3)	458 (11.2)	0.45	0.57	0.53
Ticagrelor	42 (23.0)	936 (23.3)	19 (17.6)	1,010 (24.6)	0.90	0.60	0.092
Enoxaparin	22 (12.0)§	665 (16.6)	26 (24.1)	716 (17.5)	0.10	0.056	0.075
Fondaparinux	15 (8.2)§	413 (10.3)	17 (15.7)	451 (11.0)	0.36	0.23	0.12
ACE inhibitors	54 (29.5)	1,199 (29.9)	37 (34.3)	1,264 (30.8)	0.91	0.70	0.44
Angiotensin II receptor blocker	19 (10.4)	431 (10.7)	16 (14.8)	446 (10.9)	0.87	0.83	0.19
Statin	75 (41.0)	1,737 (43.3)	49 (45.4)	1,814 (44.3)	0.54	0.38	0.81
Beta-blocker	72 (39.3)	1,622 (40.4)	45 (41.7)	1,730 (42.2)	0.77	0.44	0.91
Warfarin	3 (1.6)	69 (1.7)	3 (2.8)	61 (1.5)	0.93	0.86	0.27
Proton pump inhibitor	92 (50.3)	2,066 (51.5)	59 (54.6)	2,133 (52.0)	0.75	0.64	0.59
Unfractionated heparin	54 (29.5)	1,185 (29.5)	22 (20.4)	1,215 (29.6)	0.99	0.96	0.036
Bivalirudin	0 (0)	4 (0.1)	0 (0.0)	2 (0.1)	>0.99	>0.99	>0.99
Glycoprotein IIb/IIIa inhibitor	0 (0)	8 (0.2)	0 (0.0)	6 (0.1)	>0.99	>0.99	>0.99

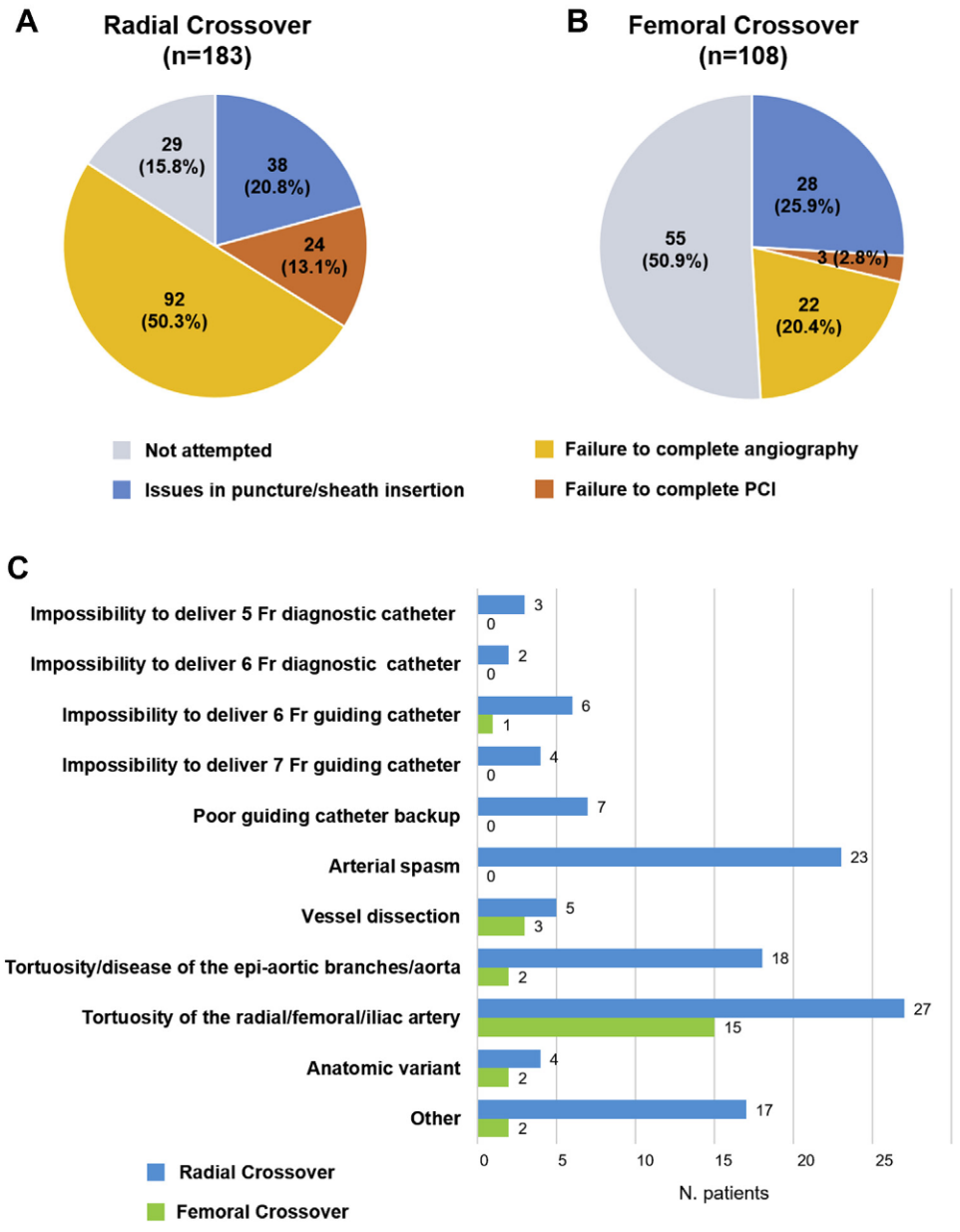
Values are mean ± SD or n (%). The p values were generated using the chi-square or Fisher exact test for categorical variables and Student's *t*-test or the Wilcoxon test for continuous variables. *For radial crossover versus successful radial access. †For radial crossover versus successful femoral access. ‡For femoral crossover versus successful femoral access. §p < 0.05, radial crossover group versus femoral crossover group.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

artery (internal crossover) were not considered crossover patients. Clinical and/or procedural reasons determining radial or femoral crossover were collected and categorized as follows: 1) access site not attempted, if the randomly allocated access was not chosen by the operator as initial access for any clinical reason; 2) issues in arterial puncture or sheath insertion; 3) failure to complete coronary angiography; and 4) failure to complete PCI.

FOLLOW-UP AND STUDY OUTCOMES. In the MATRIX program, the 2 coprimary outcomes at 30 days were major adverse cardiovascular events

FIGURE 1 Crossover Data for Radial and Femoral Groups



(A) Reasons for radial access crossover. **(B)** Reasons for femoral access crossover. **(C)** Access-site issues causing crossover after successful sheath insertion in patients undergoing radial or femoral crossover. PCI = percutaneous coronary intervention.

(MACE), defined as the composite of all-cause death, myocardial infarction, or stroke, and net adverse clinical events (NACE), defined as the composite of MACE or major bleeding not related to coronary artery bypass grafting (Bleeding Academic Research Consortium [BARC] type 3 or 5) (16). Secondary outcomes included each component of the coprimary outcomes, cardiovascular death, access site-related and non-access site-related bleeding events, and definite or probable stent thrombosis. Bleeding was defined according to the BARC, TIMI (Thrombolysis In Myocardial Infarction), and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator) scales. An independent clinical events committee, blinded to treatment allocation, adjudicated all adverse events.

STATISTICAL ANALYSIS. The MATRIX-Access trial was powered for superiority on the 2 coprimary outcomes at 30 days, expecting a rate reduction of 30% that corresponded to a rate ratio of 0.70. All analyses were performed following intention-to-treat principles, and clinical events at 30 days after randomization were considered. Primary and secondary outcomes were analyzed as time to first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding 2-sided p values. For the present analysis, to take into account differences in baseline characteristics among study groups, dedicated multivariate models were implemented to obtain adjusted outcomes, including as variables: 1) age, sex, diabetes, smoking, previous myocardial infarction, previous coronary artery bypass grafting, previous transient ischemic attack or stroke, type of ACS, ejection fraction, estimated glomerular filtration rate, Killip class, glycoprotein IIb/IIIa inhibitor use, intra-aortic balloon pump use, staged procedure, left main PCI, sheath size, post-procedural TIMI flow grade 3, and total contrast volume for the comparison between radial crossover and successful radial access; 2) age, diabetes, smoking, previous myocardial infarction, previous coronary artery bypass grafting, type of ACS, ejection fraction, estimated glomerular filtration rate, Killip class, glycoprotein IIb/IIIa inhibitor use, intra-aortic balloon pump use, staged procedure, left main PCI, sheath size, post-procedural TIMI flow grade 3, and total contrast volume for the comparison between radial crossover and successful femoral access; and 3) body mass index, diabetes, previous PCI, peripheral vascular disease, type of ACS, lytic therapy use, ticagrelor use before catheterization laboratory, unfractionated heparin use before catheterization laboratory, post-PCI bivalirudin regimen, sheath size, and total contrast volume for the comparison between femoral crossover and successful femoral access. Sensitivity analyses were conducted in patients undergoing access-site crossover after unsuccessful attempts via the randomly allocated access (i.e., excluding patients without initial attempts from the assigned access). Subgroups analysis according to the clinical presentation was performed to estimate possible interaction terms across comparisons. All analyses were performed using Stata version 15.1 (StataCorp, College Station, Texas).

RESULTS

STUDY POPULATION. The MATRIX-Access trial enrolled 8,404 patients, of whom 4,197 were randomized to radial access and 4,207 to femoral access. In the radial group, 4.4% of patients (n = 183) underwent crossover to femoral (n = 178) or brachial (n = 5) access, while in the femoral group, 2.6% (n = 108) of patients had crossover to radial (n = 107) or brachial (n = 1) access.

CLINICAL AND PROCEDURAL CHARACTERISTICS. Baseline and procedural characteristics of the study population are detailed in **Table 1** and Supplemental Table 1. Compared with patients undergoing successful radial access, patients with radial crossover were approximately 5 years older and more frequently women; more often had histories of myocardial infarction, coronary artery bypass grafting, and renal failure; presented more often with STEMI or advanced Killip class; and more frequently underwent left main coronary intervention, hemodynamic support, and unsuccessful PCI. Compared with patients undergoing successful femoral access, those with femoral crossover had higher body mass index, more often had histories of diabetes and peripheral vascular disease, and less frequently had diagnoses of STEMI on admission. Both crossover groups had a higher prevalence of diabetes and were exposed to higher contrast volumes and longer fluoroscopy and procedural times than patients undergoing successful access site. Compared with the femoral crossover group, patients with radial crossover were older, had lower body mass index and estimated glomerular filtration rates, presented more frequently with STEMI, and less often had TIMI flow grade 3 in all treated lesions after the intervention.

Access-site crossover characteristics are reported in **Figure 1**. In the radial group, difficulties in establishing radial access accounted for 20.8% of the crossover cases, whereas 50.3% of cases occurred during coronary angiography, mainly because of tortuosity or vasospasm.

CLINICAL OUTCOMES. Unadjusted outcomes at 30 days. Clinical outcomes at 30 days with respect to fatal, ischemic, and bleeding endpoints were seemingly worse in the radial and femoral crossover groups compared with patients undergoing successful radial or femoral access (**Tables 2 and 3,** Supplemental Tables 2 and 3).

Multivariate-adjusted outcomes at 30 days. ***Radial crossover versus successful radial access.*** After multivariate adjustment, the risks for MACE (adjusted rate ratio [adjRR]: 1.25; 95% confidence interval [CI]: 0.81 to 1.93; p = 0.32), NACE (adjRR: 1.40; 95% CI: 0.94 to 2.06; p = 0.090), and their individual components did not differ between patients undergoing radial crossover and those undergoing successful radial access. Yet radial crossover remained associated with a

TABLE 2 Coprimary and Main Secondary Adjusted and Unadjusted Outcomes in Patients With Radial Crossover Versus Successful Radial or Femoral Access

	Radial Crossover (n = 183)	Successful Radial (n = 4,014)	Successful Femoral (n = 4,099)	Unadjusted Rate Ratio (95% CI)*	p Value*	Adjusted Rate Ratio (95% CI)*	p Value*	Unadjusted Rate Ratio (95% CI)†	p Value†	Adjusted Rate Ratio (95% CI)†	p Value†
Death, myocardial infarction, or stroke	25 (13.7)	344 (8.6)	407 (10.0)	1.66 (1.08–2.53)	0.018	1.25 (0.81–1.93)	0.32	1.41 (0.93–2.16)	0.10	1.17 (0.76–1.81)	0.47
Death, myocardial infarction, stroke, BARC type 3 or 5 bleeding	32 (17.5)	378 (9.4)	463 (11.4)	1.98 (1.35–2.89)	<0.001	1.40 (0.94–2.06)	0.090	1.63 (1.12–2.37)	0.010	1.26 (0.86–1.86)	0.24
All-cause death	7 (3.8)	59 (1.5)	84 (2.1)	2.64 (1.20–5.79)	0.011	0.32 (0.10–1.02)	0.053	1.88 (0.87–4.08)	0.10	0.68 (0.22–2.07)	0.49
Myocardial infarction	18 (9.9)	281 (7.1)	316 (7.8)	1.45 (0.88–2.39)	0.13	1.34 (0.82–2.18)	0.23	1.31 (0.80–2.15)	0.28	1.28 (0.79–2.09)	0.31
Stroke	1 (0.6)	15 (0.4)	14 (0.3)	1.48 (0.20–11.24)	0.70	1.69 (0.15–19.17)	0.67	1.62 (0.21–12.32)	0.63	1.03 (0.11–9.61)	0.97
BARC type 3 or 5 bleeding	8 (4.4)	57 (1.5)	96 (2.4)	3.21 (1.52–6.75)	0.001	1.28 (0.47–3.49)	0.62	1.92 (0.93–3.97)	0.073	1.10 (0.46–2.63)	0.83
BARC type 3 or 5 bleeding, access site related	7 (3.9)	9 (0.2)	42 (1.1)	17.75 (6.56–47.98)	<0.001	9.65 (2.49–37.41)	0.001	3.84 (1.71–8.60)	<0.001	2.14 (0.79–5.76)	0.13
BARC type 3 or 5 bleeding, not access site related	1 (0.6)	48 (1.2)	54 (1.3)	0.46 (0.06–3.35)	0.43	0.19 (0.02–1.54)	0.11	0.42 (0.06–3.03)	0.37	0.27 (0.03–2.11)	0.21
BARC type 2, 3, or 5 bleeding	22 (12.1)	168 (4.2)	299 (7.4)	3.12 (1.98–4.93)	<0.001	1.80 (1.02–3.16)	0.041	1.75 (1.12–2.73)	0.013	1.26 (0.76–2.08)	0.37
BARC type 2, 3, or 5 bleeding, access site related	19 (10.5)	50 (1.2)	191 (4.7)	9.06 (5.26–15.62)	<0.001	6.65 (3.60–12.26)	<0.001	2.37 (1.46–3.85)	<0.001	1.87 (1.08–3.26)	0.026
BARC type 2, 3, or 5 bleeding, not access site related	3 (1.6)	119 (3.0)	113 (2.8)	0.56 (0.18–1.75)	0.30	0.28 (0.08–1.01)	0.051	0.60 (0.19–1.88)	0.37	0.41 (0.12–1.33)	0.13

Values are n (%), unless otherwise indicated. *For radial crossover versus successful radial access. †For radial crossover versus successful femoral access.
BARC = Bleeding Academic Research Consortium; CI = confidence interval.

significantly higher risk for bleeding—including access site-related BARC type 3 or 5 (adjRR: 9.65; 95% CI: 2.49 to 37.41; p = 0.001), overall BARC type 2, 3, or 5 (adjRR: 1.80; 95% CI: 1.02 to 3.16; p = 0.041), and access site-related BARC type 2, 3, or 5 events (adjRR: 6.65; 95% CI: 3.60 to 12.26; p < 0.001)—and surgical access site repair or transfusions (adjRR: 2.60; 95% CI: 1.01 to 6.67; p = 0.047) (**Central Illustration, Table 2**, and Supplemental Table 2).

Radial crossover versus successful femoral access. The adjusted risk for MACE (adjRR: 1.17; 95% CI: 0.76 to 1.81; p = 0.47), NACE (adjRR: 1.26; 95% CI: 0.86 to 1.86; p = 0.24), and their individual components did not differ between the radial crossover group and the successful femoral access group. The overall bleeding risk was also similar in the 2 groups, yet the risk for access site-related BARC type 2, 3, or 5 bleeding was higher in patients with radial crossover (adjRR: 1.87; 95% CI: 1.08 to 3.26; p = 0.026) (**Central Illustration, Table 2** and Supplemental Table 2).

Femoral crossover versus successful femoral access. Compared with successful femoral access, femoral crossover remained associated with a significantly increased risk for MACE (adjRR: 1.84; 95% CI: 1.18 to 2.87; p = 0.007) and NACE (adjRR: 1.69; 95% CI: 1.09 to 2.62; p = 0.019), as well as death, stroke, urgent target vessel revascularization, and definite or probable stent thrombosis after multivariate adjustment. Bleeding events did not differ between the 2 groups (**Central Illustration, Table 3** and Supplemental Table 3).

SENSITIVITY ANALYSIS. Sensitivity analyses showed consistent results in patients undergoing radial (n = 154) or femoral (n = 53) crossover after unsuccessful attempts. After excluding patients with assigned access sites not attempted, both crossover groups confirmed higher crude event rates than the successful access groups (**Table 4** and Supplemental Table 4). Compared with those undergoing successful radial access, patients with radial crossover showed a higher adjusted risk for NACE and bleeding events, related mainly to access site. The radial crossover group also showed an increased risk for access site-related BARC type 2, 3, or 5 bleeding compared with the successful femoral access group but no difference in terms of ischemic or fatal endpoints. Patients with femoral crossover had a significant and borderline increase in the risk for MACE, NACE, all-cause mortality, and BARC type 2, 3, or 5 bleeding (p = 0.049, p = 0.062, p = 0.057, and

p = 0.016, respectively) compared with those undergoing successful femoral access.

SUBGROUP ANALYSES. Subgroup analyses suggested that the type of presenting syndrome—with or without ST-segment elevation—affected the prognostic impact of access-site crossover so that the bleeding risk associated with radial crossover and the ischemic hazard associated with femoral crossover were both apparently magnified among patients with STEMI compared with patients in whom the allocated access site was successful, with positive interaction testing (Supplemental Figures 1 to 3).

DISCUSSION

To the best of our knowledge, this is the largest study investigating the incidence, characteristics, and prognostic implications of access-site crossover in patients with ACS undergoing invasive management via radial or femoral access. The key findings are the following.

First, crossover from radial to mainly femoral access occurred more frequently in patients presenting with advanced age, histories of coronary artery bypass grafting, STEMI, and more advanced Killip class. Compared with successful radial access, radial crossover was associated with a higher risk for access site-related major bleeding, which was particularly evident among patients with STEMI, to the extent that they did not differ compared with patients undergoing successful femoral access. Importantly, there was no signal of increased ischemic risk with radial crossover compared with successful radial or femoral access.

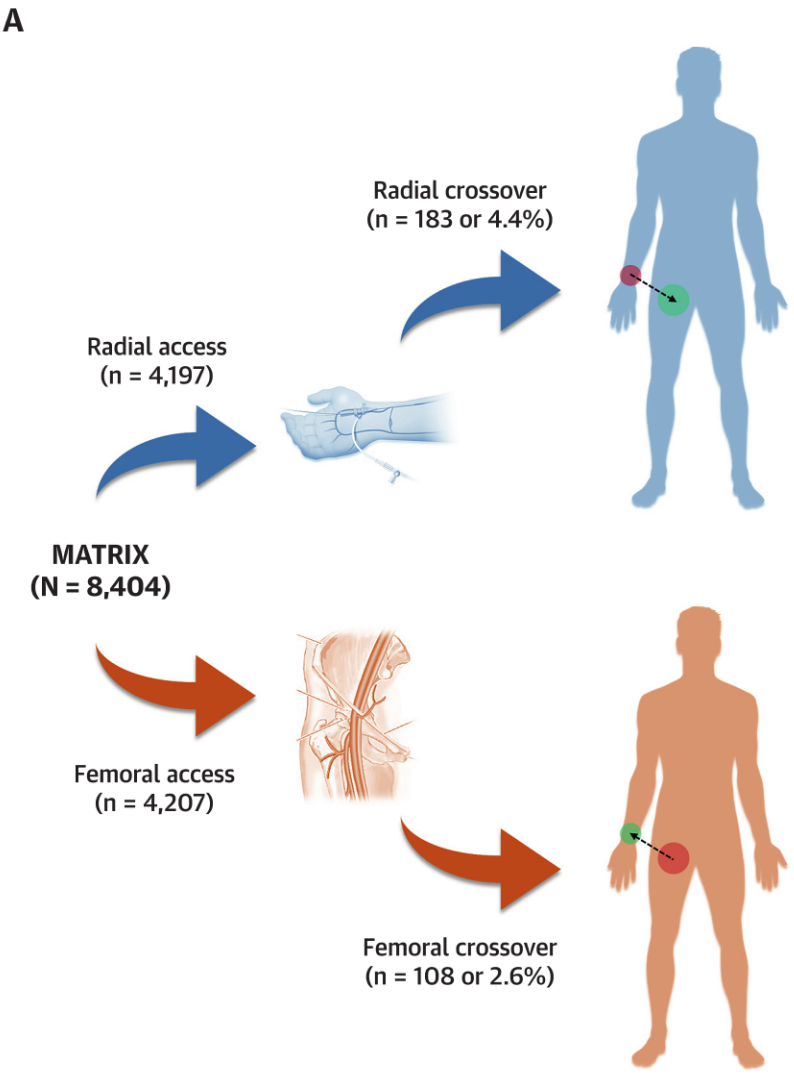
Second, crossover from femoral to mainly radial access occurred more frequently in patients with higher body mass index, established diabetes and/or peripheral artery disease, and non-ST-segment elevation ACS on admission. Femoral crossover was not associated with a higher risk for major bleeding. However, despite extensive multivariate adjustment, the risk for both coprimary endpoints, death, stroke, and stent thrombosis was higher with femoral crossover compared with successful femoral access. Subgroup analyses suggested that this risk was particularly pronounced among patients with STEMI.

European guidelines recommend the radial artery as the preferred vascular access site in patients with ACS undergoing invasive management (1). However, crossover from radial to femoral access remains a not uncommon occurrence even at highly experienced centers, and patients in whom crossover is undertaken incur a higher risk for ischemic and bleeding events (10,11,15). In this context, selecting up front the optimal access site remains essential to improving patients' management in the setting of ACS. Whether crossover is simply a marker of patient risk profile or whether it is causally related to impaired outcomes remains unclear. As a consequence, the threshold to cross over from radial to femoral access in more complex cases varies in clinical practice.

INCIDENCE AND CHARACTERISTICS OF ACCESS-SITE CROSSOVER. In contemporary PCI cohorts, radial crossover has been reported in up to 10% of cases, though this rate varies widely according patient characteristics, procedural aspects, and operator expertise (10–15,18,19). In the RIVAL (A Trial of Trans-Radial Versus Trans-Femoral Percutaneous Coronary Intervention [PCI] Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy) trial (3), enrolling 7,021 patients with ACS with and without ST-segment elevation, the incidence of crossover was 7.6% in patients randomized to radial access and 2.0% in those randomized to femoral access, while in the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) trial (6), including 1,001 patients with STEMI, the corresponding figures were 9.4% and 2.8%. In large observational studies, including patients undergoing elective or urgent coronary catheterization, access-site crossover has been reported in 4% to 8% of cases for radial access and in about 2% of cases for femoral access (10–15). In the MATRIX trial, access-site crossover occurred in 4.4% of patients randomized to radial access and 2.6% of those randomized to femoral access, and this rate did further decrease to 3.7% and 1.3%, respectively, after excluding patients in whom the randomly allocated access was not attempted by the operator. The relatively low rate of radial crossover in the MATRIX trial should be interpreted in the context of the high radial proficiency of each participating operator. Similar to previous reports, the principal reasons for crossover in our cohort were issues related to the arterial puncture or sheath insertion, vessel tortuosity, vasospasm, and the operator's decision not to attempt the randomized access (10–12).

IMPACT OF RADIAL ACCESS CROSSOVER ON PROCEDURAL AND CLINICAL OUTCOMES. A few studies have investigated procedural and clinical outcomes in patients with radial crossover compared with successful radial or femoral access (10–13,15). Among 241 patients with STEMI undergoing primary

CENTRAL ILLUSTRATION Summary of Ischemic and Bleeding Endpoints in Patients With Access-Site Crossover or Successful Access via the Radial or Femoral Artery



Gragnano, F. et al. J Am Coll Cardiol Intv. 2021;14(4):361–73.

(A) In the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox trial, radial crossover (mainly to femoral access) and femoral crossover (mainly to radial access) occurred in 4.4% and 2.6% of cases, respectively. **(B)** Radial crossover was associated with a higher risk for Bleeding Academic Research Consortium type 3 or 5 access-site bleeding compared with successful radial access. Radial crossover abolished the bleeding benefit of radial access over femoral access but did not expose patients to higher risks for major adverse cardiovascular events (MACE) or net adverse clinical events (NACE) compared with successful femoral access. Femoral crossover was associated with a higher risk for MACE and NACE than successful femoral access. BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiovascular event(s); MATRIX = Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox; NACE = net adverse clinical event(s).

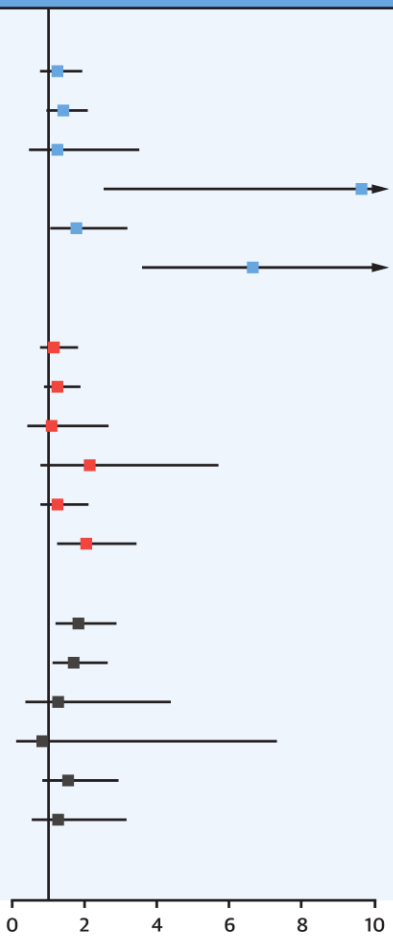
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PCI (15), radial crossover was associated with a slight but significant increase in time to gain vascular access and procedure duration compared with successful radial access (of approximately 6 and 14 min, respectively) or successful femoral access (of approximately 5 and 8 min, respectively). These results are in line with our findings, as we observed a significant, although modest, increase in total procedure time, fluoroscopy time, and contrast volume (of approximately 15 min, 5 min, and 25 ml,

CENTRAL ILLUSTRATION Continued

B

Outcomes	No. of Events (%)		Multivariate Adjusted Rate Ratio (95% Confidence Interval)	p Value
Radial Crossover vs. Successful Radial Access				
MACE	25 (13.7%)	344 (8.6%)	1.25 (0.81-1.93)	0.32
NACE	32 (17.5%)	378 (9.4%)	1.40 (0.94-2.06)	0.09
BARC 3 or 5	8 (4.4%)	57 (1.5%)	1.28 (0.47-3.49)	0.62
BARC 3 or 5 access site	7 (3.9%)	9 (0.2%)	9.65 (2.49-37.41)	0.001
BARC 2, 3, or 5	22 (12.1%)	168 (4.2%)	1.80 (1.02-3.16)	0.041
BARC 2, 3, or 5 access site	19 (10.5%)	50 (1.2%)	6.65 (3.60-12.26)	< 0.001
Radial Crossover vs. Successful Femoral Access				
MACE	25 (13.7%)	407 (10.0%)	1.17 (0.76-1.81)	0.47
NACE	32 (17.5%)	463 (11.4%)	1.26 (0.86-1.86)	0.24
BARC 3 or 5	8 (4.4%)	96 (2.4%)	1.10 (0.46-2.63)	0.83
BARC 3 or 5 access site	7 (3.9%)	42 (1.1%)	2.14 (0.79-5.76)	0.13
BARC 2, 3, or 5	22 (12.1%)	299 (7.4%)	1.26 (0.76-2.08)	0.37
BARC 2, 3, or 5 access site	19 (10.5%)	191 (4.7%)	1.87 (1.08-3.26)	0.026
Femoral Crossover vs. Successful Femoral Access				
MACE	22 (20.4%)	407 (10.0%)	1.84 (1.18-2.87)	0.007
NACE	23 (21.3%)	463 (11.4%)	1.69 (1.09-2.62)	0.019
BARC 3 or 5	3 (2.9%)	96 (2.4%)	1.27 (0.37-4.35)	0.69
BARC 3 or 5 access site	1 (0.9%)	42 (1.1%)	0.83 (0.09-7.29)	0.86
BARC 2, 3, or 5	12 (11.3%)	299 (7.4%)	1.55 (0.82-2.92)	0.17
BARC 2, 3, or 5 access site	6 (5.6%)	191 (4.7%)	1.26 (0.51-3.14)	0.61



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respectively) in the 2 crossover groups compared with the successful access groups.

With respect to clinical outcomes, Abdelaal et al. (10) recently reported the prognostic impact of radial access crossover in 2,020 patients with STEMI treated with primary PCI from a single high-volume radial center. Patients requiring radial crossover (7.7% of the study population) had a higher rate of major bleeding and vascular complications, as well as 30-day mortality compared with those undergoing PCI via successful radial access. In multivariate analysis, conversion to femoral access after radial failure remained associated with a 2-fold increase in the risk for mortality (10). More data from the same center (11) as well as other institutions (15) have consistently shown that radial crossover is associated with a higher incidence of ischemic and/or bleeding events compared with successful radial access. However, these studies were potentially limited by the single-center design, the small sample size, the nonrandom allocation of access site, and the absence of adjudicated events (10,11,15). In the present analysis, including 8,404 patients with ACS from 78 centers with randomly assigned access and adjudicated endpoints, ischemic and bleeding events at 30 days were seemingly worse in both crossover groups compared with patients who underwent successful intervention via the randomly assigned access site, either the radial or femoral artery. However, the risk profile of both crossover groups was significantly worse

TABLE 3 Coprimary and Main Secondary Adjusted and Unadjusted Outcomes in Patients With Femoral Crossover Versus Successful Femoral Access

	Femoral Crossover (n = 108)	Successful Femoral (n = 4,099)	Unadjusted Rate Ratio (95% CI)	p Value	Adjusted Rate Ratio (95% CI)	p Value
Death, myocardial infarction, or stroke	22 (20.4)	407 (10.0)	2.17 (1.39–3.39)	<0.001	1.84 (1.18–2.87)	0.007
Death, myocardial infarction, stroke, BARC type 3 or 5 bleeding	23 (21.3)	463 (11.4)	1.99 (1.29–3.08)	0.001	1.69 (1.09–2.62)	0.019
All-cause death	7 (6.5)	84 (2.1)	3.24 (1.50–7.03)	0.001	3.50 (1.42–8.65)	0.006
Myocardial infarction	14 (13.3)	316 (7.8)	1.75 (1.00–3.05)	0.045	1.43 (0.83–2.44)	0.19
Stroke	2 (1.9)	14 (0.3)	5.61 (1.27–24.72)	0.010	5.31 (1.31–21.55)	0.019
BARC type 3 or 5 bleeding	3 (2.9)	96 (2.4)	1.21 (0.38–3.82)	0.74	1.27 (0.37–4.35)	0.69
BARC type 3 or 5 bleeding, access site related	1 (0.9)	42 (1.1)	0.92 (0.13–6.67)	0.93	0.83 (0.09–7.29)	0.86
BARC type 3 or 5 bleeding, not access site related	2 (1.9)	54 (1.3)	1.44 (0.35–5.89)	0.61	1.57 (0.34–7.11)	0.56
BARC type 2, 3, or 5 bleeding	12 (11.3)	299 (7.4)	1.58 (0.88–2.85)	0.12	1.55 (0.82–2.92)	0.17
BARC type 2, 3, or 5 bleeding, access site related	6 (5.6)	191 (4.7)	1.21 (0.53–2.77)	0.64	1.26 (0.51–3.14)	0.61
BARC type 2, 3, or 5 bleeding not access site related	6 (5.7)	113 (2.8)	2.08 (0.91–4.76)	0.074	1.85 (0.74–4.61)	0.18

Values are n (%), unless otherwise indicated. Rate ratios and p values are for femoral crossover versus successful femoral access.
Abbreviations as in Table 2.

compared with the successful access site groups. After extensive adjustment for all measured confounders, radial crossover was no longer associated with higher ischemic risk compared with successful radial or femoral access. Yet radial crossover remained associated with a higher risk for access site-related major and minor bleeding compared with successful radial access to the extent that this subset of patients incurred at least the same risk for access site-related major bleeding compared with patients successfully treated via femoral access. These results remained consistent after excluding patients in whom the operator elected not to attempt the randomized access for clinical reasons. Our findings can be easily explained by the need to puncture a second femoral or brachial access site, and both alternatives

TABLE 4 Coprimary and Main Secondary Adjusted Outcomes in Patients With Access-Site Crossover After Initial Attempts Versus Successful Access

	Radial Crossover (n = 154)	Successful Radial (n = 4,014)	Femoral Crossover (n = 53)	Successful Femoral (n = 4,099)	Adjusted Rate Ratio (95% CI)*	p Value*	Adjusted Rate Ratio (95% CI)†	p Value†	Adjusted Rate Ratio (95% CI)‡	p Value‡
Death, myocardial infarction, or stroke	22 (14.3)	344 (8.6)	12 (22.6)	407 (10.0)	1.32 (0.83–2.08)	0.23	1.25 (0.79–1.98)	0.34	1.78 (1.01–3.16)	0.049
Death, myocardial infarction, stroke, BARC type 3 or 5 bleeding	29 (18.8)	378 (9.4)	13 (24.5)	463 (11.4)	1.53 (1.02–2.30)	0.037	1.38 (0.92–2.07)	0.11	1.71 (0.97–3.01)	0.062
All-cause death	6 (3.9)	59 (1.5)	3 (5.7)	84 (2.1)	0.42 (0.12–1.47)	0.17	1.08 (0.36–3.28)	0.88	3.22 (0.96–10.73)	0.057
Myocardial infarction	16 (10.5)	281 (7.1)	9 (17.3)	316 (7.8)	1.37 (0.81–2.31)	0.23	1.30 (0.76–2.20)	0.33	1.55 (0.80–2.99)	0.19
Stroke	1 (0.7)	15 (0.4)	1 (2.0)	14 (0.3)	1.83 (0.15–21.82)	0.63	1.41 (0.16–12.55)	0.75	4.24 (0.67–26.71)	0.12
BARC type 3 or 5 bleeding	8 (5.3)	57 (1.5)	2 (3.8)	96 (2.4)	1.81 (0.68–4.80)	0.23	1.34 (0.55–3.27)	0.52	1.50 (0.33–6.80)	0.60
BARC type 3 or 5 bleeding, access site related	7 (4.6)	9 (0.2)	1 (1.9)	42 (1.1)	13.16 (3.73–46.47)	0.0001	2.56 (0.92–7.12)	0.071	1.57 (0.17–14.19)	0.68
BARC type 3 or 5 bleeding, not access site related	1 (0.7)	48 (1.2)	1 (1.9)	54 (1.3)	0.25 (0.03–2.06)	0.19	0.34 (0.04–2.70)	0.30	1.37 (0.17–11.15)	0.77
BARC type 2, 3, or 5 bleeding	21 (13.8)	168 (4.2)	8 (15.3)	299 (7.4)	2.01 (1.13–3.57)	0.017	1.39 (0.82–2.35)	0.22	2.39 (1.18–4.88)	0.016
BARC type 2, 3, or 5 bleeding, access site related	19 (12.5)	50 (1.2)	5 (9.5)	191 (4.7)	7.76 (4.19–14.36)	<0.0001	2.20 (1.25–3.87)	0.0061	2.50 (0.98–6.37)	0.054
BARC type 2, 3, or 5 bleeding, not access site related	2 (1.3)	119 (3.0)	3 (5.7)	113 (2.8)	0.21 (0.05–1.01)	0.051	0.31 (0.07–1.30)	0.10	1.94 (0.62–6.07)	0.25

Values are n (%), unless otherwise indicated. *For radial crossover after initial attempts versus successful radial access. †For radial crossover after initial attempts versus successful femoral access. ‡For femoral crossover after initial attempts versus successful femoral access.
Abbreviations as in Table 2.

have been associated with a higher risk for bleeding compared with the radial artery (3–5,19). Altogether, our results are reassuring and support the concept of the radial-first strategy, considering that failure to complete the intervention via the radial artery requiring crossover to femoral access does not expose patients to heightened risks for ischemic outcomes, while understandably dissipating the bleeding benefit observed with radial access. In this context, the upfront identification of patients at high risk for radial crossover could allow operators to anticipate technical difficulties and select optimal access site in each individual patient. However, no standardized and validated tool exists to predict the risk for radial crossover and/or select specific patient cohorts that could be better treated via primary femoral access. Hence, future research addressing this issue remains desirable.

PROGNOSTIC IMPLICATIONS OF FEMORAL ACCESS CROSSOVER. No study has so far investigated the prognostic implications of femoral access crossover in invasively managed patients with ACS. Failure to accomplish a coronary procedure via the femoral access is relatively rare, and its frequency approximates 2% in large ACS cohorts (3,6,14), which is consistent with our data. In our study, patients undergoing femoral crossover were characterized by higher body mass index and more frequent histories of diabetes and peripheral artery disease compared with those with successful femoral intervention. The need for crossover from the femoral access identified a subset of patients in whom the crude incidence of composite ischemic and/or bleeding events at 30 days exceeded 20%, the highest among all study groups. After extensive adjustment, we observed an increased risk for nonfatal cardiovascular ischemic and fatal events in this group of patients compared with the successful femoral access group, which occurred mainly among patients with STEMIs. Patients with initial attempts for femoral access incurred greater ischemic risk as well as BARC type 2, 3, or 5 bleeding, attributable mainly to the originally attempted access site. Our study by design cannot prove causation, and it remains therefore unclear if and to what extent our findings reflect the presence of unmeasured confounders in this highly selected patient subset. Yet femoral crossover identified a high-risk patient population whose worse outcomes do not seem to be accounted for by baseline characteristics. Strategies to optimize femoral access management should be routinely implemented to minimize the risk for femoral access failure and subsequent complications.

STUDY LIMITATIONS. Although the present analysis is the largest evaluating patients undergoing radial or femoral access with and without crossover, MATRIX-Access was not powered to explore differences in outcomes across these subgroups. As such, the present analysis might be subject to type II error. In a non-negligible proportion of patients, especially in the femoral group, access-site crossover followed the operator's decision not to proceed via the randomly assigned access. Of note, study results remained largely consistent after excluding these cases, suggesting that our conclusions are valid and can be similarly applied to crossover patients with or without attempted access site. Access-site management was left to the discretion of the operator. Thus, all procedures related to patient preparation, puncture technique, medications (i.e., spasmolytic cocktail), and materials were used per local practice. This introduces a certain variability but reflects current practice, in which these procedures remain not standardized. Our data and conclusions apply to the context of the MATRIX trial, in which all participating centers were experienced with both radial and femoral access; therefore, similar results may not apply in centers with low radial or femoral expertise.

CONCLUSIONS

Radial access failure and subsequent crossover to femoral access abolishes the peri-procedural bleeding benefit associated with radial over femoral interventions but does not expose patients to a higher risk for MACE or NACE compared with successful radial or femoral access. In turn, femoral access failure and subsequent crossover to radial access remained associated with worse fatal and nonfatal ischemic outcomes, particularly among patients with STEMI, which could not be explained by measured patient characteristics. Although in a relevant proportion of patients undergoing femoral crossover, the randomly assigned access was not attempted by the operators, introducing potential bias, our findings remained consistent after excluding these cases in a sensitivity analysis. Our results lend further support to use of the radial artery as the default approach in patients with ACS.

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PERSPECTIVES

WHAT IS KNOWN? It remains unclear whether access-site crossover, which occurs in a sizable proportion of patients with ACS undergoing invasive management, adversely affects clinical outcomes compared with successful access.

WHAT IS NEW? Access-site crossover from radial to femoral access abolishes the bleeding benefit offered by the radial over the femoral artery but does not seem to increase the risk for MACE or NACE compared with primary successful radial or femoral access. Femoral access crossover remains associated with an increased adjusted risk for fatal events and nonfatal ischemic outcomes, particularly among patients with STEMIs.

WHAT IS NEXT? Prospective and adequately powered studies are needed to clarify the prognostic implications of access-site crossover in patients with ACS undergoing invasive management. Further research is needed to develop standardized algorithms or tools to predict the risk for access-site crossover, inform operators with respect to possible procedural difficulties, and ultimately improve access-site management and patient outcomes.

REFERENCES

1. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165.

2. Mason PJ, Shah B, Tamis-Holland JE, et al. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: a scientific statement from the American Heart Association. Circ Cardiovasc Interv 2018;11:e000035.

3. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377:1409–20.

4. Valgimigli M, Gagnor A, Calabró P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet 2015;385:2465–76.

5. Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet 2018;392:835–48.

6. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. J Am Coll Cardiol 2012;60:2481–9.

7. Amin AP, House JA, Safley DM, et al. Costs of transradial percutaneous coronary intervention. J Am Coll Cardiol Intv 2013;6:827–34.

8. Kopin D, Seth M, Sukul D, et al. Primary and secondary vascular access site complications associated with percutaneous coronary intervention: insights from BMC2. J Am Coll Cardiol Intv 2019;12:2247–56.

9. Valgimigli M, Gragnano F. The use of radial access for cardiac catheterization. J Am Coll Cardiol Intv 2019;12:2257–9.

10. Abdelaal E, MacHaalany J, Plourde G, et al. Prediction and impact of failure of transradial approach for primary percutaneous coronary intervention. Heart 2016;102:919–25.

11. Abdelaal E, Brousseau-Provencher C, Montminy S, et al. Risk score, causes, and clinical impact of failure of transradial approach for percutaneous coronary interventions. J Am Coll Cardiol Intv 2013;6:1129–37.

12. Vink MA, Amoroso G, Dirksen MT, et al. Routine use of the transradial approach in primary percutaneous coronary intervention: procedural aspects and outcomes in 2209 patients treated in a single high-volume centre. Heart 2011;97:1938–42.

13. Dehghani P, Mohammad A, Bajaj R, et al. Mechanism and predictors of failed transradial approach for percutaneous coronary interventions. J Am Coll Cardiol Intv 2009;2:1057–64.

14. Le May M, Wells G, So D, et al. Safety and efficacy of femoral access vs radial access in ST-segment elevation myocardial infarction. JAMA Cardiol 2020;5:126.

15. Azzalini L, Khan R, Al-Hawwas M, et al. Effect of radial-to-femoral access crossover on adverse outcomes in primary percutaneous coronary intervention. Am J Cardiol 2014;114:1165–73.

16. Valgimigli M, Gagnor A, Calabrò P, et al. Design and rationale for the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox program. Am Heart J 2014;168:838–45.

17. Gragnano F, Manavifar N, Gargiulo G, et al. Femoral access with or without vascular closure device or radial access in acute coronary syndrome. J Am Coll Cardiol Intv 2019;12:2116–8.

18. Jolly SS, Cairns J, Yusuf S, et al. Procedural volume and outcomes with radial or femoral access for coronary angiography and intervention. J Am Coll Cardiol 2014;63:954–63.

19. Kiemeneij F, Laarman GJ, Odekerken D, Slagboom T, Van Der Wieken R. A randomized comparison of percutaneous transluminal coronary angioplasty by the radial, brachial and femoral approaches: the Access study. J Am Coll Cardiol 1997;29:1269–75.

KEY WORDS acute coronary syndrome, crossover, femoral access, percutaneous coronary intervention, radial access

APPENDIX For supplemental tables and figures, please see the online version of this paper.

Femoral Access With or Without Vascular Closure Device or Radial Access in Acute Coronary Syndrome.

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This analysis demonstrates that TTVR in patients with CIED/RVL is feasible and results in comparable procedural success and TR reduction as in patients without RVL. Post-procedural device interrogation should be recommended as adaption of output might be required.

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REFERENCES

1. Chang JD, Manning WJ, Ebrille E, Zimetbaum PJ. Tricuspid valve dysfunction following pacemaker or cardioverter-defibrillator implantation. J Am Coll Cardiol 2017 9;69:2331–41.

2. Braun D, Orban M, Nabauer M, et al. Transcatheter treatment of severe tricuspid regurgitation using the edge-to-edge repair technique in the presence and absence of pacemaker leads. J Am Coll Cardiol Intv 2017;10:2014–6.

RESEARCH CORRESPONDENCE

Femoral Access With or Without Vascular Closure Device or Radial Access in Acute Coronary Syndrome

The superiority of vascular closure devices (VCDs) over manual compression in terms of femoral access complications is debated (1), and whether their use can narrow the gap in outcomes between radial and femoral access remains unclear (2,3).

In the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial (NCT01433627), 8,404 acute coronary syndrome (ACS) patients were randomly allocated to radial (n = 4,197) or femoral (n = 4,207) access. Access site closure strategy was at the discretion of the treating physician and any commercially available VCDs were permitted (4,5).

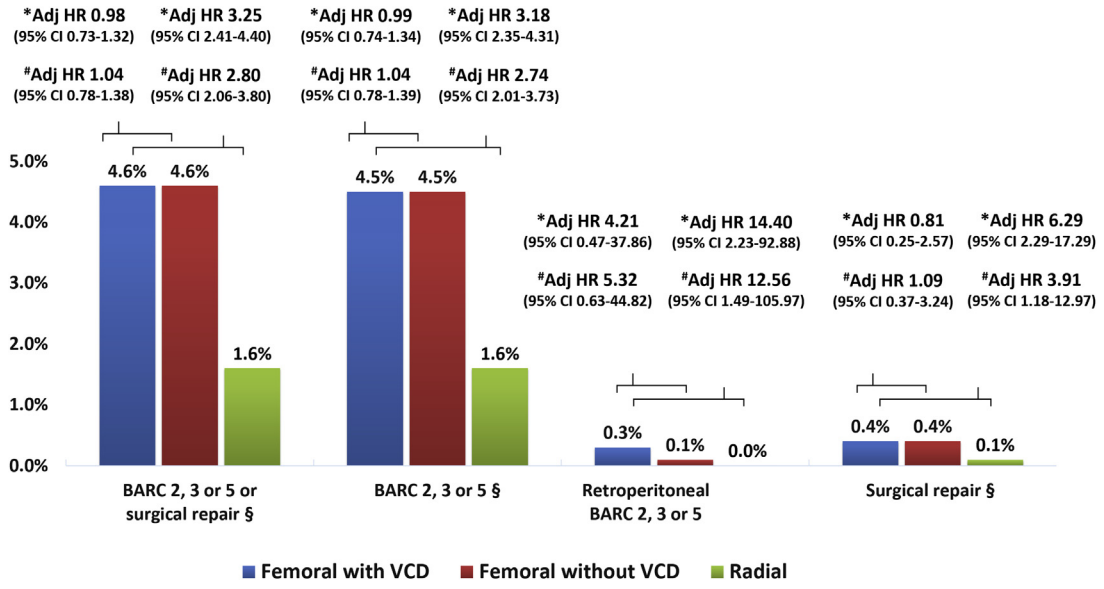
In the femoral group, 62 patients did not receive femoral access—it was either not attempted (n = 56) or failed (n = 6)—and information on access closure was missing in 35 patients. In the remaining 4,110 patients, VCDs were used in 2,133 (51.9%) and manual compression in 1,977 (48.1%). Angio-Seal (Terumo, Tokyo, Japan) was the most commonly used device (73.7%), followed by Proglide (Abbott Vascular, Santa Clara, California) (13.1%), Femoseal (Terumo). (10.8%), and others (2.4%). Failure of VCD was reported in 21 (1%) cases.

We appraised the incidence of 30-day access site-related complications, defined as the composite of access site bleeding (Bleeding Academic Research Consortium type 2, 3, or 5), or vascular injury requiring surgical repair, between femoral access with or without VCD groups and between femoral access with VCD and radial access.

Baseline and procedural characteristics differed across groups. To account for imbalances for each of the 2 comparisons, adjustments were made using nonparsimonious propensity score and multivariable logistic models including (but not limited to) age, sex, weight, ACS type, insulin-dependent diabetes, smoking, hypercholesterolemia, hypertension, peripheral arterial disease, renal failure, previous myocardial infarction, previous femoral access, previous coronary artery bypass grafting, cardiac arrest, Killip class, periprocedural anticoagulation, $P2Y_{12}$ inhibitors, glycoprotein IIb/IIIa inhibitors, femoral vein access, procedural success, procedure duration, sheath size, SYNTAX score, staged procedure, center's annual volume, and proportion of radial coronary interventions. The ability of propensity score to balance VCD versus non-VCD and VCD versus radial access comparisons was confirmed by the absence of residual differences in covariates across treatment groups after propensity weighting.

Access site-related complications occurred in 4.6% of the patients in both the femoral access with VCD group and femoral access without VCD group (unadjusted hazard ratio [HR]: 1.00; 95% confidence interval [CI]: 0.75 to 1.33; p = 0.98; propensity-adjusted HR: 0.98; 95% CI: 0.73 to 1.32; p = 0.90; multivariable-adjusted HR: 1.04; 95% CI: 0.78 to

FIGURE 1 Access Site Complications in VCD Versus Non-VCD and Radial Access Groups



It was assessed whether the use of VCD mitigated the incidence of 30-day access site complications in patients with acute coronary syndromes receiving invasive management. At propensity score and multivariable adjusted analysis, the use of femoral VCD did not reduce the incidence of access site complications compared with manual compression. Radial access significantly reduced the rate of access site complications compared with femoral access with VCD. § = access site; *Adj = propensity score adjusted; #Adj = multivariable adjusted; BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; VCD = vascular closure device.

1.38; p = 0.80) as compared with 1.6% in the radial arm (unadjusted HR: 2.78; 95% CI: 2.05 to 3.78; p < 0.001; propensity-adjusted HR: 3.25; 95% CI: 2.41 to 4.40; p < 0.001; multivariable-adjusted HR: 2.80; 95% CI: 2.06 to 3.80; p < 0.001 vs. femoral VCD group) (Figure 1). Radial access was associated with lower risks of access site complications, including retroperitoneal bleeding or vascular injury requiring surgical repair, as compared with femoral access with VCD (Figure 1). Bleeding Academic Research Consortium type 3 or 5 access site-related bleeding occurred equally in 1% of the femoral access with VCD and femoral access without VCD groups (unadjusted HR: 1.02; 95% CI: 0.55 to 1.90; p = 0.94; propensity-adjusted HR: 1.01; 95% CI: 0.54 to 1.88; p = 0.96; multivariable-adjusted HR: 1.02; 95% CI: 0.55 to 1.89; p = 0.95) as compared with 0.4% of the radial access arm (unadjusted HR: 2.58; 95% CI: 1.35 to 4.95; p = 0.004; propensity-adjusted HR: 3.35; 95% CI: 1.85 to 6.06; p < 0.001; multivariable-adjusted HR: 2.62; 95% CI: 1.36 to 5.05; p = 0.004). A per-protocol analysis, which excluded 67 patients of the radial group who did not receive radial access, showed even greater benefits for radial access versus femoral access with VCD.

Our findings suggest that in patients with ACS undergoing invasive management, the use of VCD does not reduce the risks of access site complications as compared with manual compression.

No study has so far compared the outcomes of radial access versus femoral access with VCD in terms of access site complications. Although VCD implementation was left to discretion of the operator in MATRIX trial, it was used in a large cohort of patients allocated to femoral access.

Our current findings are also consistent with results of a previous large randomized study in which VCDs did not mitigate the risk of access site complications, but did reduce hemostasis and ambulation time compared with manual compression after femoral artery puncture (1). Similar findings were observed in a systematic review and meta-analysis (2).

In conclusion, our analysis did not detect an effect of VCD on vascular or access site-related complications and did not support the hypothesis that routine use of VCD narrows the gap between radial and femoral access.

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REFERENCES

1. Schulz-Schüpke S, Helde S, Gewalt S, et al. Comparison of vascular closure devices vs manual compression after femoral artery puncture. JAMA 2014;312:1981–7.

2. Rigattieri S, Sciahbasi A, Ratib K, et al. Comparison between radial approach and femoral approach with vascular closure devices on the occurrence of access-site complications and periprocedural bleeding after percutaneous coronary procedures: a systematic review and meta-analysis. J Invasive Cardiol 2016;28:473–9.

3. Le May MR, Singh K, Wells GA. Reply: radial versus femoral: issues remain and questions need answers. J Am Coll Cardiol Intv 2016;9:979–80.

4. Valgimigli M, Gagnor A, Calabró P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: A randomised multicentre trial. Lancet 2015;385:2465–76.

5. Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet 2018;392:835–48.

Radial vs femoral access for the prevention of acute kidney injury (AKI) after coronary angiography or intervention: A systematic review and meta-analysis.

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ORIGINAL STUDIES

Radial vs femoral access for the prevention of acute kidney injury (AKI) after coronary angiography or intervention: A systematic review and meta-analysis

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Abstract

Objectives: We sought to investigate the impact of radial vs femoral access on the incidence of acute kidney injury (AKI) after coronary angiography or intervention.

Background: There is a growing recognition of the importance of access site selection as an adjudicative measure to mitigate the risk of renal impairment for patients with coronary artery disease undergoing angiography with or without percutaneous coronary intervention.

Methods: We conducted a systematic review of the literature and meta-analyzed available evidence comparing the rates of AKI with radial vs femoral access in patients undergoing coronary angiography or intervention. Studies reporting the incidence of AKI as a primary or secondary outcome were pooled in fixed- and random-effects meta-analyses and meta-regression techniques were used to account for across-study heterogeneity.

Results: Across data pooled from nine studies (n = 32 181), radial access was significantly associated with a reduction in the incidence of AKI (OR 0.57, 95% CI 0.50 to 0.66, P < 0.0001 with fixed-effects model, OR 0.55, 95% CI 0.45 to 0.67, P < 0.0001 with random-effects model) as compared to femoral. In the meta-regression model, the effect size of radial access effect was related to the number of centers in which studies were conducted.

Conclusions: Compared with the femoral approach, radial access was associated with a lower incidence of AKI after coronary angiography or intervention, although this benefit was less pronounced in multicenter than in single-center studies.

KEYWORDS

angiography, coronary, catheterization, brachial/radial/ulnar, coronary artery disease, percutaneous coronary intervention (PCI), renal disease, acute

1 | INTRODUCTION

Acute kidney injury (AKI) is consistently recognized as a relevant complication of percutaneous coronary angiography and intervention.[1] Although its course is usually transient, a subset of patients develops an irreversible organ injury leading to progressive renal dysfunction, which is associated with prolonged hospitalization, and short- and long-term adverse outcomes.[1,2] Strategies to avoid AKI in patients with coronary disease who are invasively managed include prophylactic venous hydration, renal replacement therapy, and contrast volume minimization.[3] Currently, the possibility of adopting and implementing preventive strategies is limited,[4] especially for acute coronary artery disease patients undergoing expedite coronary catheterization. Over the past decades, the transradial access (TRA) has gained more favor among interventional cardiologist as a safe and feasible strategy in patients managed invasively, either for stable or urgent settings.[5,6] In the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial,[5] TRA reduced major bleeding and all-cause mortality as compared to transfemoral access (TFA). Recently, evidence is emerging supporting the role of TRA for reducing renal complications.[7–9] Various mechanisms have been implicated for the nephroprotective

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potential of the radial over the femoral route, including the reduction of (a) access-related major bleeding,[5,10] (b) iatrogenic cholesterol embolization in renal circulation,[2,11] (c) episodes of hypotension, (d) and contrast medium use (especially for high experienced operators).[2,6] Several trials explored the effect of the arterial access on the renal outcomes in different subsets of patients, providing heterogeneous findings.[7,12–14] Previous meta-analyses performed to examine this issue have included only observational and nonrandomized studies, possibly introducing bias and confounders, despite forcing adjustment for baseline variables and risk factors.[9,15] In 2017, the effectiveness of TRA in reducing the incidence of AKI has been demonstrated for the first time within a prespecified subanalysis (AKI-MATRIX) of the randomized MATRIX program.[16] Hence, considering these emerging findings and their potential implications, it is useful to reconcile available data in the context of available evidence.

On this background, the scope of this systematic review and meta-analysis is to provide an updated quantitative assessment of the impact of vascular access on the incidence of AKI after coronary angiography or intervention.

2 | MATERIALS AND METHODS

We performed a systematic review and meta-analysis of contemporary studies to compare the effect of radial vs femoral access on the incidence of AKI in patients undergoing cardiac catheterization or percutaneous coronary intervention (PCI). The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards[17] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[18] The protocol has been registered in the PROSPERO International prospective register of systematic reviews CRD42018088519.

The full search string is: (((((((radial[all fields]) OR transradial[all fields]) AND femoral[all fields]) OR transfemoral[all fields]) AND coronary angiography[all fields]) OR percutaneous coronary intervention [all fields]) AND acute kidney injury[all fields]) OR contrast-induced nephropathy[all fields]).

MEDLINE, the Cochrane Library, and SCOPUS databases were searched using Internet-based engines with the search restricted for reports published in English, from January 1, 1990 until January 31st, 2018. Additional sources included www.clinicaltrials.gov and www.tctmd.com. We searched the reference lists of relevant studies and reviews, editorials, and letters to identify further citations. The most updated or inclusive data for a given study were chosen for abstraction.

We restricted our meta-analysis selecting studies that met all the following inclusion criteria: (1) study including patients undergoing either urgent or elective coronary angiography and/or PCI; (2) study reporting the incidence of AKI or contrast-induced nephropathy (CIN) as a primary or secondary outcome; (3) study comparing radial vs femoral vascular access. The final search was performed on January 31, 2018.

Two investigators (G.A. and F.G.) independently reviewed the studies, extracted data, and reported the results in a structured dataset. Disparities between investigators regarding the inclusion or exclusion of each study were resolved by consensus with a third independent investigator (P.C.).

Odds ratio (OR) with 95% confidence intervals (CI) was either directly abstracted or derived on the basis of the reported event rates. For nonrandomized studies reporting unadjusted, adjusted, or propensity-matched data, the highest quality estimate was used for the meta-analysis according to the following rank order: propensity-matched >adjusted >unadjusted. We initially planned to assess the risk of bias at the study level according to the Cochrane Collaboration.[19] However, given the higher prevalence of nonrandomized studies, the quality assessment was mainly based on the Newcastle–Ottawa Scale (NOS):[20] when a study included relevant information that could be associated with NOS, one point was considered. Studies with 7–9, 4–6, and 0–3 points were identified as good, satisfactory or unsatisfactory, respectively.

The results of all studies were pooled using the Mantel–Haenszel method and a DerSimonian-Laird random-effects model.[21] Statistical heterogeneity was assessed with Cochran's Q via a χ^2 test and graded using the I^2 statistic with I^2 < 25%, 25% to 50%, and I^2 > 50% representing mild, moderate, and severe heterogeneities, respectively.[22] The influence of individual studies on the pooled OR for each of the appraised outcome was assessed as sensitivity analysis to establish the impact of each individual trial on the effect size. Publication bias was assessed by visual inspection of funnel plots and by rank correlation.[23] In addition, the regression asymmetry test was performed to explore the potential publication bias further.[24]

In order to account for the observed heterogeneity, which means that the variance comes from real differences between studies and, as such, can potentially be explained by study-level covariates (moderators), weighted random-effects meta-regression modeling was used.[24] We regressed the log-transformed impact of radial access effect size (log OR) in each study, using the inverse of the variance of the log OR as weight, against several study-level variables: first, the log-transformed prevalence of STEMI (ST-segment elevation myocardial infarction) and incidence of major bleeding in each study, which are generic indicators of the underlying hemorrhagic risk of each population; second, the log-transformed prevalence of other clinical and procedural variables, which in turn are generic indicators of the risk of AKI; third the log-transformed number of centers in which the study itself had been conducted, thus mostly accounting for differences in centers' expertise in radial procedures.[25]

All tests were two-sided unless otherwise specified. Calculations were performed using R version 3.3.3 (The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

We identified 591 potentially relevant studies (Figure 1). After removing duplicates and unsuitable studies at the title/abstract level, 26 full-text studies were retrieved for eligibility and further 16 studies were excluded: three studies did not report the incidence of AKI as primary or secondary outcome, 11 studies did not report renal outcomes stratified by vascular access, one study was not in English language, and one study was mainly a review. Finally, 10 studies met

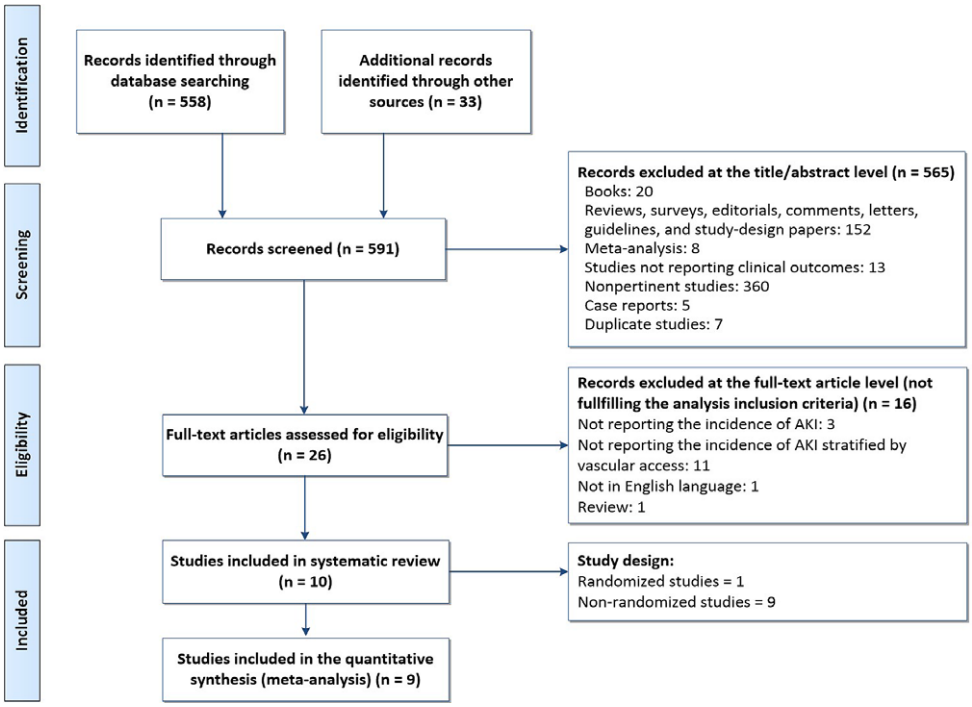


FIGURE 1 Selection process for studies to be included in the meta-analysis according to PRISMA standards. PRISMA: Preferred reporting items for systematic reviews and meta-analyses [Color figure can be viewed at wileyonlinelibrary.com]

the inclusion criteria and were included in this systematic review (Table 1). All the studies but AKI-MATRIX were observational and fulfilled satisfactory or good quality criteria according to NOS (Table 2). The AKI-MATRIX trial had a low risk of bias for five out of the seven domains of the Cochrane Collaboration's tool.[19] Five out of nine nonrandomized selected studies provided adjusted outcomes by propensity score matching, which were used for quantitative synthesis. The systematic review, therefore, reports data from 40 391 patients (Table 1 and Figure 2(A)). Importantly, the only randomized study, namely AKI-MATRIX, was not used to calculate pooled estimates altogether with nonrandomized ones, as this was deemed methodologically incorrect. AKI-MATRIX data are reported in the forest plot (Figure 2(A)) just to visually compare it with the effect size obtained in the meta-analysis of nonrandomized studies. The final analysis was therefore obtained by pooling data from 32 181 patients.

Compared with TFA, TRA was associated with a statistically significant lower occurrence of AKI (OR 0.57, 95% CI 0.50 to 0.66, $P < 0.0001$ with fixed-effects model, OR 0.55, 95% CI 0.45 to 0.67, $P < 0.0001$ with random-effects model) (Figure 2(B)). Hence, the risk of postprocedural AKI was approximately 45% lower with TRA. Removing individual studies did not result in significant deviation of the pooled OR (all $P < 0.0001$) for the occurrence of AKI. Subgroup analysis (Figure 2(B)) demonstrated a gradient in the impact of TRA according to study design, with higher benefit accrued in retrospective studies[14,26–28] than across studies with propensity-score matching,[8,12,29–31] as compared with the relatively lower treatment effect (namely 13%) observed in the randomized AKI-MATRIX trial.[16]

There was moderate heterogeneity across the studies included in the meta-analysis ($I^2 = 35\%$), indicating that a relevant percentage of the observed variance resulted from real differences existing between individual studies and, as such, could potentially be explained by study-level covariates.

According to meta-regression modeling, the impact of TRA effect size in reducing the incidence of AKI was inversely related ($z = 2.54$ $P = 0.01$, residual $I^2 = 0\%$) to the log-transformed number of centers in which studies have been conducted (Figure 3). No significant associations were found for STEMI presentation, incidence of major bleeding, or other clinical and procedural factors (data not shown).

The funnel plot appeared asymmetric at visual inspection (Figure 4). Rank correlation test was not consistent with the existence of funnel plot asymmetry ($z = 0.21$, $P = 0.83$) nor Egger's regression test ($t = -0.74$, $P = 0.49$), indicating no publication bias.

4 | DISCUSSION

This meta-analysis of contemporary randomized and nonrandomized studies suggested a significantly lower occurrence of AKI with TRA vs TFA in patients undergoing coronary angiography or intervention. The risk of postprocedural AKI was reduced by approximately 45% with TRA in comparison with TFA. However, our results indicated that the effect size of TRA as compared to TFA might be influenced by the design of the study, appearing more relevant in observational studies as compared to the treatment effect observed in the single randomized study published to date.[16] Accordingly, the higher the methodological quality of the studies, the lower is the magnitude of the benefit derived from TRA instead of TFA. Furthermore, meta-regression modeling showed that an inverse relationship exists between the effect size of TRA in lowering the incidence of AKI (log OR) and the number of involved centers across each study: the higher the number of the centers, the lower the magnitude of the benefit for TRA vs TFA

TABLE 1 Overview of studies evaluating the occurrence of AKI after cardiac catheterization and/percutaneous coronary intervention using trans-radial as compared to trans-femoral approach

	AKI definition	AKI time lapse	N. of patients	N. of centers	Radial (%)	Femoral (%)	Mean/median age (years)		Diabetes (%)		Chronic kidney disease (%)		Congestive heart failure (%)		Mean left ventricular ejection fraction (%)		STEMI (%)		Mean/median contrast volume (ml)		Major bleeding (%)		Incidence of AKI (%)	
							Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral
Cortese [30]	Creatinine increase >0.5 mg/dL or 25%	Within 72 hours	450 propensity matched	5	50	50	64	64	22	22	NR	NR	NR	NR	47	47	100	100	193	188	0.5[c]	3.0[c]	**8.4**	**16.9**
Kooiman [31]	Creatinine increase >0.5 mg/dL	Within 7 days[b]	17 714 propensity matched	47	50	50	64	64	39	39	20	21	14	14	NR	NR	8	8	NR	NR	0.9[c]	1.8[c]	**1.4**	**1.9**
Damluji[a] [14]	Creatinine increase >0.5 mg/dL or 50%	Within 72 hours	1374 propensity matched	1	61	39	62[c]	60[c]	32[c]	41[c]	16[c]	28[c]	12	15	NR	NR	NR	NR	180[c]	165[c]	NR	NR	**2.5**	**4.5**
Azzalini [26]	Creatinine increase of ≥0.3 mg/dL or 1.5- to 2-fold	NR	221	1	78	22	61	65	13	24	6	14	2	8	48	43	100	100	200	200	0.6	13	**3**	**10**
Steinvil [8]	Creatinine increase of ≥0.3 mg/dL or 1.5- to 2-fold	NR	1072 propensity matched	1	50	50	67	67	33	34	NR	NR	16	13	51	51	NR	NR	157	155	1.3	1.5	**4.3**	**10.4**
Kolte [29]	Creatinine increase >0.5 mg/dL or 25%	Within 48 hours	508 propensity matched	2	50	50	60	61	22	24	2	2	NR	NR	50	50	100	100	184	186	NR	NR	**5.5**	**8.3**
Gili [12]	Creatinine increase of ≥0.3 mg/dL or 1.5- to 2-fold	NR	354 propensity matched	5	50	50	69	71	38	29	NR	NR	NR	NR	NR	NR	12	12	NR	NR	NR	NR	**2.8**	**1.7**
Pancholy [28]	Creatinine increase >0.5 mg/dL or 25%	Within 48-72 hours	7529	1	29	71	62[c]	66[c]	32	33	NR	NR	10	9	NR	NR	83[d]	74[d]	190[c]	220[c]	1[c]	5[c]	**1.1**	**2.4**
Feldkamp [27]	Creatinine increase >0.3 mg/dL or 50%	Within 48 hours	2937	1	39	61	71[c]	73[c]	25[c]	29[c]	21[c]	29[c]	38[c]	43[c]	NR	NR	28[#]	19[#]	180	180	NR	NR	**10.1**	**15.9**
Andò [16]	Creatinine increase >0.5 mg/dL or 25%	Within hospitalisation	8210 randomized	78	50	50	65	65	22	22	NR	NR	9	8	NR	NR	48	48	183	183	NR	NR	**15.4**	**17.4**

AKI, acute kidney injury. NR, not reported. STEMI, ST-elevation myocardial infarction.
[a] Data are referred to the baseline characteristics of the population, before propensity matching.
[b] Peak postprocedural creatinine was the highest creatinine value obtained within 1 to 7 days of the procedure or the highest value in the first 30 days of hospitalization.
[c] Radial vs femoral $P < 0.05$.
[d] ACS presentation, Radial vs femoral $P < 0.05$.

TABLE 2 Study quality assessment based on the Newcastle–Ottawa scale (NOS) for cohort studies

	Selection				Comparability		Outcome			
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome not present at start of study	Control for main factor	Control for additional factor	Outcome assessment	Length of follow-up	Adequacy of follow up	TOTAL
Cortese [30]	*	*	*	*	*	*	*	*	*	**9**
Kooiman [31]	*	*	*	*	*	*	*		*	**8**
Damluji [14]	*		*	*			*	*	*	**6**
Azzalini [26]	*		*	*		*	*		*	**6**
Steinvil [8]	*	*	*	*	*	*	*		*	**8**
Kolte [29]	*	*	*	*	*	*	*	*	*	**9**
Gili [12]	*	*	*	*	*	*	*		*	**8**
Pancholy [28]	*		*	*	*		*	*	*	**7**
Feldkamp [27]	*		*	*			*	*	*	**6**
Andò [16]	*	*	*	*	*	*	*		*	**8**

on renal outcomes. Such results might be explained by differences in centers' expertise for radial procedures: the superiority of TRA is probably overestimated in studies including single or few expert centers (and operators), while a more realistic treatment effect is generally reported in large multi-center trials.[5,7,32] On the other hand, these findings might suggest that neutral (or even negative) results emerging from small studies to be underreported in the literature and, as an obvious consequence, not included in the meta-analysis. Although they have equal dignity, manuscripts reporting nonpositive results are less likely being submitted for publication by authors or accepted by journals.[33] This hypothesis is also consistent with the slight asymmetry observed in the funnel plot, although no formal publication bias was observed in this meta-analysis.

A previous meta-analysis, including 26 185 patients from six observational studies,[15] also examined the role access site in reducing the incidence of AKI in patients undergoing PCI. Although potentially biased by not negligible heterogeneity across studies (including different clinical presentation and AKI definition), this previous meta-analysis showed that TRA resulted in superior renal outcomes as compared to TFA, by halving the risk of AKI (OR 0.51, 95% CI 0.39 to 0.67, $P < 0.001$). In addition, a meta-regression analysis suggested a higher benefit in terms of AKI prevention favoring TRA in patients presenting with STEMI as contrasted to other clinical presentations.

The present meta-analysis, which analyzed a larger population and included more recent studies, confirmed the superiority of TRA over TFA for AKI prevention, providing an updated and hopefully more reproducible treatment effect.

The occurrence of AKI after coronary angiography and intervention is a multicausal phenomenon and derives from the complex interaction of multiple hemodynamic and nonhemodynamic factors. Importantly, the assessment of AKI should be limited to a specific time frame: measuring creatinine beyond strict temporal intervals (namely 48 to 72 hours) could lead to both underestimation and overestimation of AKI occurrence, possibly adjudicating as AKI a late increase in creatinine for other reasons. The primary risk factor for AKI is the presence of preprocedural renal dysfunction.[34] Also, other clinical (ie, age, sex, diabetes mellitus, heart failure, and volume status) and procedural (contrast volume, type and administration route, nephrotoxic drug use, and operator experience) features demonstrated an association with the incidence of postprocedural AKI.[34,35]

No effective treatment, apart from renal replacement therapy, is currently available in patients with AKI. Prophylactic venous hydration with isotonic saline is the only highly recommended preventive strategy in subjects at moderate to high risk.[3]

Recently, it has been suggested that TRA may positively impact on the occurrence of adverse renal outcomes[16] by favorably modulating different AKI determinants other than contrast media administration. Procedure-related major bleedings and vascular access site complications are established risk factors for the development of renal complications.[10] Potential determinants of impaired renal perfusion and function in these patients are blood loss, the presence (and worsening) of anemia, periprocedural hypotension (due to vasovagal responses in association with femoral sheath removal and access-site compression maneuver), transfusions, and hemodilution (possibly resulting by the intensive fluid replacement after hemorrhagic events).

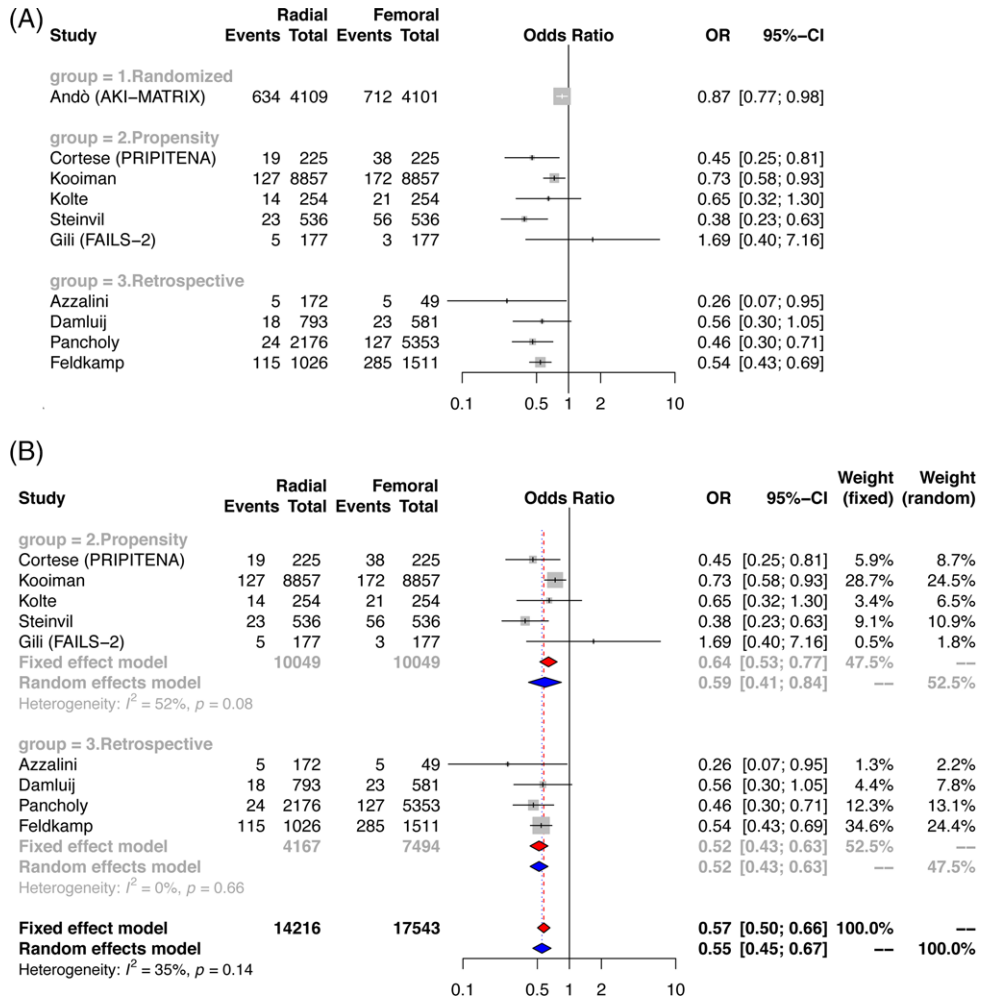


FIGURE 2 **A:** Forest plot displaying OR for AKI with radial versus femoral access in each of the studies included in the systematic review, stratified by study design. B: Forest plot displaying OR for AKI with radial versus femoral access with pooled effect estimates in nonrandomized studies (meta-analysis): TRA was associated with a significantly lower occurrence of AKI, compared with TFA. AKI, Acute kidney injury; OR, Odds ratio; TFA, Transfemoral access; TRA, Transradial access [Color figure can be viewed at wileyonlinelibrary.com]

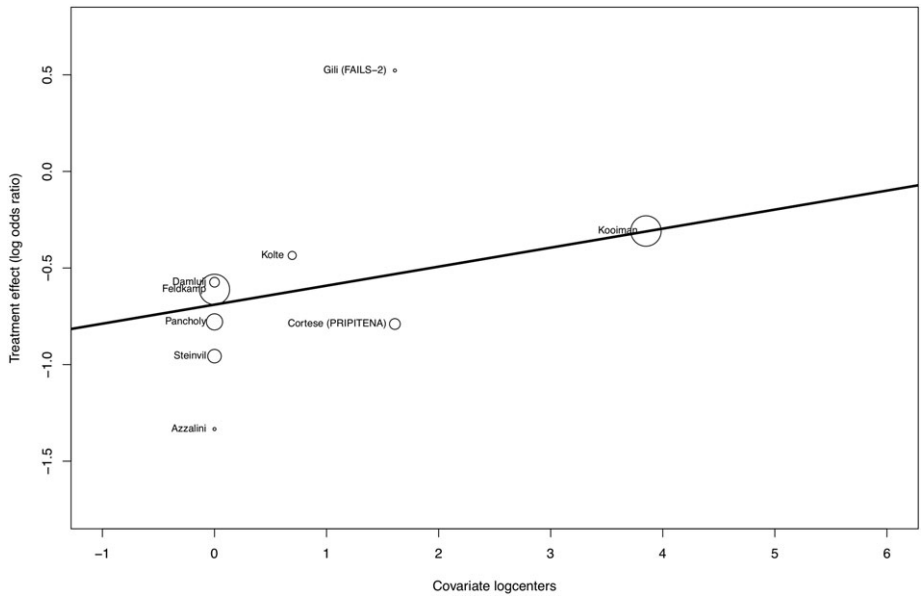


FIGURE 3 Bubble plot displaying log-transformed treatment effect (OR) for each study (y-axis) by the log-transformed number of centers in which the study itself has been conducted (x-axis). Bubble size is inversely proportional to the variance of the estimated treatment effect. OR, odds ratio

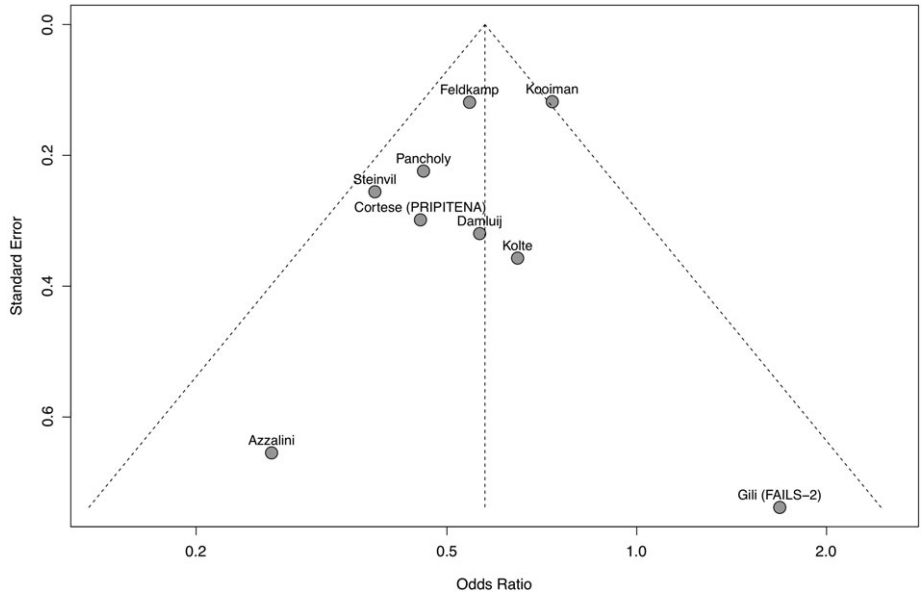


FIGURE 4 Funnel plot displaying SE (y-axis) by treatment effect (OR) for each study. Visual assessment of publication bias illustrates mild asymmetry in the funnel plot. However, formal tests yielded nonsignificant results. OR, odds ratio

In a recent prospective multicentre study conducted by Ohno et al.,[10] the risk of AKI was significantly higher in patients experiencing major bleeding (OR 2.23, 95% CI 1.37 to 3.63; $P = 0.001$) and correlated with the severity of the events. Of importance, most studies included in this meta-analysis have shown a significant reduction in the occurrence of bleeding events in the population managed with TRA. These findings suggested that the reported nephron-protective effects of TRA might be, at least in part, mediated by the reduced rate of major bleeding and access-site complications, potentially preventing renal hypoperfusion.[16]

A second possible mechanism explaining the renal advantage of radial over femoral access is represented by the reduction of iatrogenic cases of cholesterol embolism. Although largely underestimated in clinical practice, cholesterol embolization syndrome is a serious complication of cardiac catheterization, leading to end-stage renal failure in up to 30% of patients within 6 months.[11] TFA determines a greater catheter contact with thoracic and especially abdominal aortic atheroma, whereas TRA completely spares the abdominal and descending thoracic portions of the aorta, the sites of the largest quantity of plaque.[36] The aortic "scraping" during catheter advancement can disrupt atherosclerotic plaque material, and dislodge cholesterol emboli from the aortic wall to the renal vasculature.[11] TRA obviates to the need of close passage of catheters and wires to renal vessels, limiting renal atheroembolic episodes. However, the relative impact of cholesterol embolism on renal outcomes remains challenging to quantify.

Finally, as the volume of contrast media administered is an established determinant of AKI after coronary procedures, operators experience might influence the occurrence of renal outcomes. It is generally recommended to minimize as much as possible the amount of contrast media, for instance by using intracoronary ultrasound, and also by adapting contrast volume to baseline renal function.[35] In the literature, contrasting evidence reports the use of lower,[2] equal,[37] and higher[38] contrast volume in patients managed with TRA vs TFA. Therefore, contrast minimization by highly experienced radial operators might be considered a critical intervention to prevent renal sequelae, especially in patients with challenging arterial anatomies.[6,39] However, this hypothesis is not univocally confirmed, and results from the AKI-MATRIX showed no clear heterogeneity across sites and centers' experience for the occurrence of major bleeding or AKI.[16] Hence, the role of TRA in renal protection is probably only marginally influenced by operator proficiency, and primarily due to bleeding prevention that occurs at any stage of the learning curve.

5 | LIMITATIONS

The results of this meta-analysis are inherently limited by the nonrandomized design of all studies and by the use of multivariable adjustment techniques in many but not in all of them. Such issues always make the calculation of a single summary estimate of the effect of exposure to a grouping variable potentially misleading. Besides this, one major limitation of this study consists in the differences in AKI definitions across studies and, more specifically, in the inconsistency in AKI assessment time frame (Table 1). In other words, wide heterogeneity exists in the temporal assessment of the postprocedural increase in creatinine. In addition, data about patient hydration, which however is now used routinely in clinical practice, are lacking. We were not able to correct for all of these study-level covariates, but at meta-regression modeling, it was unlikely that clinical variables were the main source of variability between studies. Rather, meta-regression supported the idea that smaller retrospective studies from expert operators/centers[25] tended to overestimate the effect size of TRA; this was consistent with the observed funnel plot asymmetry, implying that some "small study effect" was present in our meta-analysis, and with the slightly larger estimate observed with random-effects model, which is known to overweight smaller studies.

6 | CONCLUSION

Radial access was associated with a lower occurrence of AKI after coronary angiography or intervention, as compared to femoral access. The renal benefits of TRA appeared to be consistent among studies included in the meta-analysis; however, the effect size seemed to be influenced by the study design and the number of involved centers across studies, with less pronounced treatment effect in multicenter than in single-center cohorts. The present meta-analysis supports the use of TRA as a renal-protective strategy in patients undergoing cardiac catheterization or PCI. However, since the AKI-MATRIX trial was the only available randomized study, our findings warrant further confirmation by additional randomized controlled trials.

DISCLOSURES

None.

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REFERENCES

1. Rihal CS. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;*105*:2259-2264.
2. Vuurmans T, Byrne J, Fretz E, et al. Chronic kidney injury in patients after cardiac catheterisation or percutaneous coronary intervention: A comparison of radial and femoral approaches (from the British Columbia cardiac and renal registries). *Heart*. 2010;*96*:1538-1542.
3. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. *EuroIntervention*. 2015;*10*:1024-1094.
4. Marenzi G, Ferrari C, Marana I, et al. Prevention of contrast nephropathy by furosemide with matched hydration: The MYTHOS (induced diuresis with matched hydration compared to standard hydration for contrast induced nephropathy prevention) trial. *JACC Cardiovasc Interv*. 2012;*5*:90-97.
5. Valgimigli M, Gagnor A, Calabró P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: A randomised multicentre trial. *Lancet*. 2015;*385*:2465-2476.
6. Bianchi R, D'Acierno L, Crisci M, Tartaglione D, Cappelli Bigazzi M, Canonico M, … Calabrò P. From femoral to radial approach in coronary intervention: Review of the literature and 6 years single-center experience. *Angiology*. 2017;*68*:281-287.
7. Andò G, Cortese B, Frigoli E, et al. Acute kidney injury after percutaneous coronary intervention: Rationale of the AKI-MATRIX (acute kidney injury-minimizing adverse hemorrhagic events by TRansradial access site and systemic implementation of angioX) sub-study. *Catheter Cardiovasc Interv*. 2015;*86*:950-957.
8. Steinvil A, Garcia-Garcia HM, Rogers T, et al. Comparison of propensity score–matched analysis of acute kidney injury after percutaneous coronary intervention with Transradial versus Transfemoral approaches. *Am J Cardiol*. 2017;*119*:1507-1511.
9. Andò G, Costa F, Boretti I, Trio O, Valgimigli M. Benefit of radial approach in reducing the incidence of acute kidney injury after percutaneous coronary intervention: A meta-analysis of 22,108 patients. *Int J Cardiol*. 2015;*179*:309-311.
10. Ohno Y, Maekawa Y, Miyata H, et al. Impact of Periprocedural bleeding on incidence of contrast-induced acute kidney injury in patients treated with percutaneous coronary intervention. *J Am Coll Cardiol*. 2013;*62*:1260-1266.
11. Scolari F, Ravani P, Gaggi R, et al. The challenge of diagnosing Atheroembolic renal disease: Clinical features and prognostic factors. *Circulation*. 2007;*116*:298-304.
12. Gili S, D'Ascenzo F, Di Summa R, Conrotto F, Cerrato E, Chieffo A, … Gaita F. Radial versus femoral access for the treatment of left Main lesion in the era of second-generation drug-eluting stents. *Am J Cardiol*. 2017;*120*:33-39.
13. Azzalini L, Jolicoeur EM. The use of radial access decreases the risk of vascular access-site-related complications at a patient level but is associated with an increased risk at a population level: The radial paradox. *EuroIntervention*. 2014;*10*:531-532.
14. Damluji A, Cohen MG, Smairat R, Steckbeck R, Moscucci M, Gilchrist IC. The incidence of acute kidney injury after cardiac catheterization or PCI: A comparison of radial vs. femoral approach. *Int J Cardiol*. 2014;*173*:595-597.
15. Andò G, Costa F, Trio O, Oreto G, Valgimigli M. Impact of vascular access on acute kidney injury after percutaneous coronary intervention. *Cardiovasc Revascularization Med*. 2016;*17*:333-338.
16. Andò G, Cortese B, Russo F, et al. Acute kidney injury after radial or femoral access for invasive acute coronary syndrome management: AKI-MATRIX. *J Am Coll Cardiol*. 2017;*69*:2592-2603.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ*. 2009;*339*:b2535.
18. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000;*283*:2008-2012.
19. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions. Chichester*. UK: Wiley-Blackwell; 2008.
20. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;*25*:603-605.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;*7*:177-188.
22. Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ*. 2003;*327*:557-560.
23. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;*50*:1088-1101.
24. Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? *Stat Med*. 2002;*21*:1559-1573.
25. Rao SV, Nolan J, Fraser DG, Mamas MA, Bertrand OF, Pancholy SB, … Valgimigli M. Efficacy of radial versus femoral access in the acute coronary syndrome: Is it the operator or the operation that matters? *JACC Cardiovasc Interv*. 2016;*979*:978.
26. Azzalini L, Khan R, Al-Hawwas M, Hatem R, Fortier A, L'Allier PL, Ly HQ. Effect of radial-to-femoral access crossover on adverse outcomes in primary percutaneous coronary intervention. *Am J Cardiol*. 2014;*114*:1165-1173.
27. Feldkamp T, Luedemann M, Spehlmann ME, Freitag-Wolf S, Gaensbacher J, Schulte K, … Luedde M. Radial access protects from contrast media induced nephropathy after cardiac catheterization procedures. *Clin Res Cardiol*. 2018;107(2):148-157.
28. Pancholy MS, Skelding K, Scott T, Blankenship J, Pancholy SB. Effect of access site choice on acute kidney injury after percutaneous coronary intervention. *Am J Cardiol*. 2017;*120*:2141-2145.
29. Kolte D, Spence N, Puthawala M, et al. Association of radial versus femoral access with contrast-induced acute kidney injury in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Cardiovasc Revascularization Med*. 2016;*17*:546-551.
30. Cortese B, Sciahbasi A, Sebik R, et al. Comparison of risk of acute kidney injury after primary percutaneous coronary interventions with the Transradial approach versus the Transfemoral approach (from the PRIPITENA urban Registry). *Am J Cardiol*. 2014;*114*:820-825.
31. Kooiman J, Seth M, Dixon S, et al. Risk of acute kidney injury after percutaneous coronary interventions using radial versus femoral vascular access insights from the blue cross blue shield of Michigan cardiovascular consortium. *Circ Cardiovasc Interv*. 2014;*7*:190-198.
32. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet*. 2011;*377*(9775):1409-1420.

33. Olson CM, Rennie D, Cook D, et al. Publication bias in editorial decision making. *JAMA*. 2002;*287*(21):2825-2828.
34. Wichmann JL, Katzberg RW, Litwin SE, et al. Contrast-induced nephropathy. *Circulation*. 2015;*132*:1931-1936.
35. Ando G, de Gregorio C, Morabito G, Trio O, Saporito F, Oreto G. Renal function-adjusted contrast volume redefines the baseline estimation of contrast-induced acute kidney injury risk in patients undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2014;*7*:465-472.
36. Roberts WC, Schussler JM. Frequency of plaque dislodgement and embolization in Transradial vs Transfemoral approaches for left-sided cardiac catheterization. *JAMA Cardiol*. 2018;*3*:551-552.
37. Pristipino C, Trani C, Nazzaro MS, et al. Major improvement of percutaneous cardiovascular procedure outcomes with radial artery catheterisation: Results from the PREVAIL study. *Heart*. 2009;*95*:476-482.
38. Jaffe R, Hong T, Sharieff W, et al. Comparison of radial versus femoral approach for percutaneous coronary interventions in octogenarians. *Catheter Cardiovasc Interv*. 2007;*69*:815-820.
39. Calabro P, Golia E, Crisci M. Radial versus femoral access for coronary angiography. *Angiology*. 2018;*69*:286-287.

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The Use of Radial Access for Cardiac Catheterization: Slowly, But Yet it Moves.

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EDITORIAL COMMENT

The Use of Radial Access for Cardiac Catheterization

Slowly, But Yet it Moves*

Marco Valgimigli, MD, PhD, Felice Gragnano, MD

"And yet it moves," was pronounced by the physicist and philosopher Galileo Galilei in 1633 after being forced to abjure his revised heliocentric theory. The embedded message was: despite any conviction or doctrine of men, the earth moves around the sun, rather than the converse. Yet, this maxim sounds as a sort of imperishable admonition implying that "no matter what you believe; there are facts."

Percutaneous coronary intervention (PCI) is a life-saving treatment in patients with acute coronary syndromes (1). A large body of evidence has been provided in favor of radial over femoral access as standard approach for PCI, given the reduced risk of major bleeding, vascular-access-site complications (VASC), and mortality. Two large randomized trials, RIVAL (RadIal Vs femorAL access for coronary intervention) and MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) (2-4), have tested the superiority of radial versus femoral access in patients with acute coronary syndrome receiving invasive management.

In line with the evidence, a "radial-first" strategy has been strongly endorsed by the American and European cardiology societies (1,5), followed by an increase in the use of radial access worldwide (6). However, the transition from femoral to radial approach in the United States remains slow, accompanied by a somewhat femoral inertia (5), that only recently has been overtaken.

As the enhancement of radial expertise is essential for modern interventional cardiologists, it is likewise important for all operators reaching and maintaining an adequate femoral skill in the current era of recommended default radial access. Performing femoral PCI safely remains of paramount importance when radial artery access fails or cannot support PCI demands (i.e., procedures requiring mechanical support). However, in the context of declining rates of femoral procedures, recent studies raised concerns that radial operators may lose their skills in managing femoral access, consequently increasing VASC rates that could narrow (or even nullify) the benefits of the diffusion of radial access (so-called Campeau Radial Paradox) (7).

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In this issue of *JACC: Cardiovascular Interventions*, Kopin et al. (8) analyze the trends in radial access adoption and VASC in Michigan. Using the BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Collaborative) registry, they investigated a cohort of 153,123 patients receiving PCI at 48 nonfederal hospitals between 2013 and 2017. The authors addressed 4 questions: 1) trends in radial use for PCI; 2) rates of VASC for radial and femoral access; 3) rates of secondary access use for PCI (and related VASC); and 4) impact of operators' radial experience on femoral and overall VASC. VASC was only clinically defined (and not systematically investigated by imaging), and laboratory analyses were not standardized among centers.

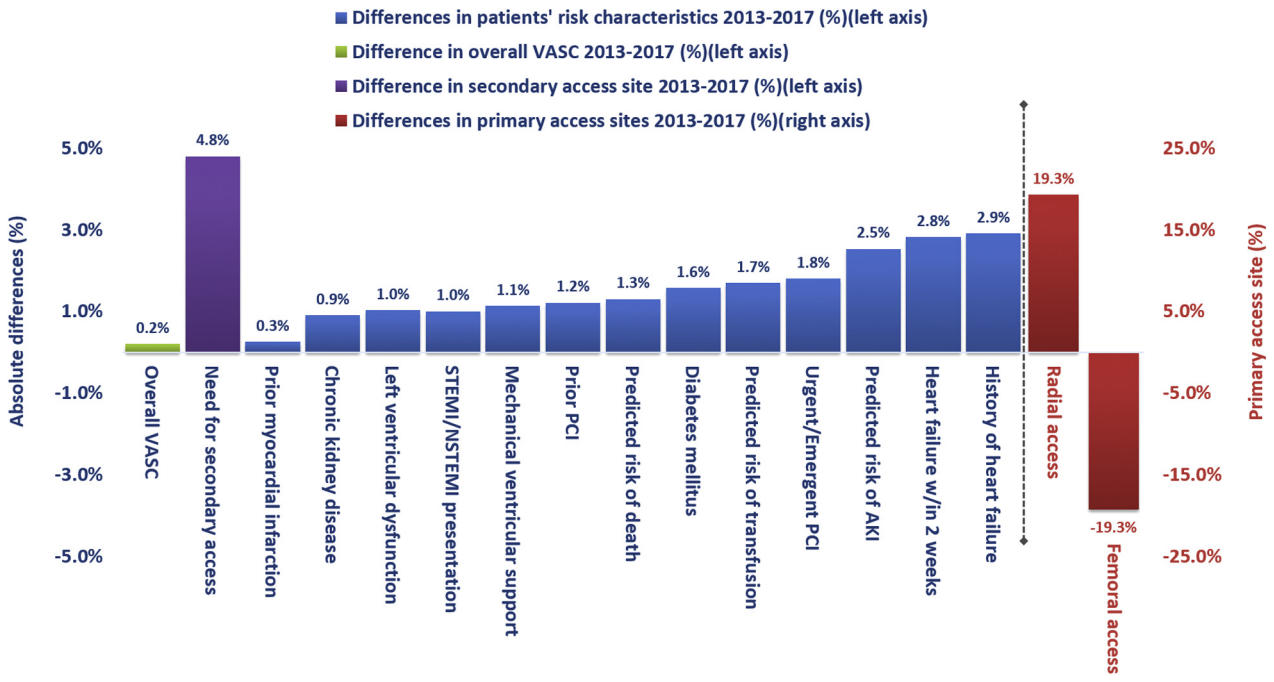
Femoral was the predominant access used for PCI (98,247 patients or 64.2% receiving femoral vs. 54,876 patients or 35.8% receiving radial), but a steep

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FIGURE 1 Differences in Patient Characteristics, Overall Vascular Access Site Complications, and Primary and Secondary Access Sites in BMC2 Between 2013 and 2017



AKI = acute kidney injury; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; VASC = vascular access site complications.

increase in radial access was observed over years, from 7,817 patients (or 25.9%) in 2013 to 14,023 patients (or 45.2%) in 2017.

Patients' characteristics showed increased clinical complexity and frailty over time (Figure 1). During the 5-year study period, VASC rates increased from 1.6% to 2.3% for femoral ($p < 0.001$), and from 0.2% to 0.4% for radial ($p = 0.019$). These results confirm that radial access is safe in a large real-world population with VASC rates 5 to 8 times lower with radial than femoral, which accounted for 80% to 85% of overall VASC. It is not surprising that the unadjusted rate of VASC increased in both groups, given the increase in patients' frailty over time, with yet greater absolute VASC increase in femoral (0.7%) than radial (0.2%) patients (Figure 1).

To investigate the impact of radial experience on VASC occurrence, operators were categorized on the basis of the proportion of radial cases in 2017. After adjusting for patients' characteristics, patients treated by middle or highest tertiles of radial use operators had 57% and 60% higher chance to experience femoral VASCs compared with those treated by operators from lowest tertile, respectively, indicating a potential relationship between radial expertise and femoral deskilling. A significant rising trend in the use of secondary vascular access in both femoral (5.6% to 12.9%) and radial (2.9% to 3.6%) cases was also reported, and its presence associated with a more than 5-fold increase in the risk of VASC. Of note, patients receiving secondary access for hemodynamic support were also included, potentially biasing toward the null the comparison between radial and femoral access.

Authors call for the Campeau (radial) paradox reporting that despite radial is associated with lower VASC risk and its use is increasing over time, benefits of radial access can be offset by a paradoxical increase in femoral VASC. However, results seem to act against these conclusions for several reasons.

First, the comparison between VASC rates in 2013 and 2017 was unadjusted. During this period, the authors described a net increase of patients with frailty and comorbidities, and procedural complexity (i.e., receiving 3 times more frequently hemodynamic support) (Figure 1). One may argue that radial use may have contributed to minimizing the overall VASC increase to only 0.2% in absolute terms. Second, patients treated by operators in highest radial tertile

had 38% less chance to experience any VASC compared with those treated by operators in the lowest tertile. Thus, the most experienced radial operators (suspected for being the most deskilled femoral operators) were solely able to concretely reduce the overall risk of VASC. Third, femoral access led to more complications considering that even for operators in the lowest tertile of radial use, the rate of VASC was higher for femoral (1.8%) than radial (0.4%). Finally, the more experienced the operator for radial access is, the more complex and highly selected are patients requiring crossovers to femoral access. Therefore, the fact that dedicated radial operators had a higher complication rate for secondary femoral access when compared with low-volume radial operators (or routine femoral patients) may speak for selection bias, more than for lack of femoral expertise. Unfortunately, the authors did not specifically address this point, and the analysis is nonconclusive in this regard.

Thus, is the Campeau a true paradox? Or does the true radial paradox (*para* ["contrary to"], *doxa* ["common opinion/evidence"]) consist of the fact that more than one-half of the procedures are performed using a potentially riskier (femoral) access, and that a large proportion of operators are not yet adequately experienced for radial?

Of importance, this study analyzed only VASC rates over time. Radial access entails clinical benefits that go beyond VASC, such as acute kidney injury prevention (9,10), proposed as the predominant responsible for mortality benefit of radial compared with femoral (11). Interestingly, a recent analysis of the BMC2 registry also observed a decline in acute kidney injury rates from 2010 to 2016 and whether the concomitant increase in radial access might also explain this finding remains unclear.

The best interventional cardiologists are those maintaining high expertise in both radial and femoral access, making individual access site decisions based on clinical variables and technical procedural considerations. The interventional cardiology community can best serve patients by having operators who are proficient with both the arm and the leg.

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REFERENCES

1. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2018;40:87–165.

2. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377:1409–20.

3. Valgimigli M, Gagnor A, Calabró P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet 2015; 385:2465–76.

4. Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet 2018;392:835–48.

5. Mason PJ, Shah B, Tamis-Holland JE, et al. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: a scientific statement from the American Heart Association. Circ Cardiovasc Interv 2018;11:e000035.

6. Waldo SW, Gokhale M, O'Donnell CI, et al. Temporal trends in coronary angiography and percutaneous coronary intervention. J Am Coll Cardiol Intv 2018;11:879–88.

7. Azzalini L, Tosin K, Chabot-Blanchet M, et al. The benefits conferred by radial access for cardiac catheterization are offset by a paradoxical increase in the rate of vascular access site complications with femoral access: the Campeau Radial Paradox. J Am Coll Cardiol Intv 2015;8: 1854–64.

8. Kopin D, Seth M, Sukul D, et al. Primary and secondary vascular access site complications associated with percutaneous coronary intervention: insights from the BMC2 registry. J Am Coll Cardiol Intv 2019;12:2247–56.

9. Andò G, Cortese B, Russo F, et al. Acute kidney injury after radial or femoral access for invasive acute coronary syndrome management: AKI-MATRIX. J Am Coll Cardiol 2017;69:2592–603.

10. Andò G, Gragnano F, Calabrò P, Valgimigli M. Radial vs femoral access for the prevention of acute kidney injury (AKI) after coronary angiography or intervention: a systematic review and meta-analysis. Catheter Cardiovasc Interv 2018; 92:e518–26.

11. Rothenbühler M, Valgimigli M, Odutayo A, et al. Association of acute kidney injury and bleeding events with mortality after radial or femoral access in patients with acute coronary syndrome undergoing invasive management: secondary analysis of a randomized clinical trial. Eur Heart J 2019;40:1226–32.

KEY WORDS femoral access, percutaneous coronary intervention, radial access

Part V

Bleeding and ischaemia: a COVID-19 perspective

Questions and Answers on Practical Thrombotic Issues in SARS-CoV-2 Infection: A Guidance Document from the Italian Working Group on Atherosclerosis, Thrombosis and Vascular Biology.

Patti G, Lio V, Cavallari I, **Gragnano F,** Riva L, Calabrò P, Di Pasquale G, Pengo V, Rubboli A; Italian Study Group on Atherosclerosis, Thrombosis, Vascular Biology.

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REVIEW ARTICLE

Questions and Answers on Practical Thrombotic Issues in SARS-CoV-2 Infection: A Guidance Document from the Italian Working Group on Atherosclerosis, Thrombosis and Vascular Biology

Giuseppe Patti[1] · Veronica Lio[1] · Ilaria Cavallari[2] · Felice Gragnano[3] · Letizia Riva[4] · Paolo Calabrò[3] · Giuseppe Di Pasquale[4] · Vittorio Pengo[5,6] · Andrea Rubboli[7] on behalf of the Italian Study Group on Atherosclerosis, Thrombosis, Vascular Biology

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Abstract

In patients with coronavirus disease 2019 (COVID-19), the prevalence of pre-existing cardiovascular diseases is elevated. Moreover, various features, also including pro-thrombotic status, further predispose these patients to increased risk of ischemic cardiovascular events. Thus, the identification of optimal antithrombotic strategies in terms of the risk–benefit ratio and outcome improvement in this setting is crucial. However, debated issues on antithrombotic therapies in patients with COVID-19 are multiple and relevant. In this article, we provide ten questions and answers on risk stratification and antiplatelet/anticoagulant treatments in patients at risk of/with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection based on the scientific evidence gathered during the pandemic.

Since December 2019, when the first cases of interstitial pneumonia were identified in the province of Wuhan, China, the infection due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly involved a large part of the population worldwide, reaching the global pandemic level. National health systems had to implement public health responses to protect their populations and limit viral diffusion. In patients with coronavirus disease 2019 (COVID-19), the high prevalence of cardiovascular comorbidities [1] and the increased incidence of thrombotic events, sustained by multiple factors (Fig. 1), made complex and, at the same time, crucial the optimization of antithrombotic treatments. Moreover, guideline recommendations in this setting should be followed, taking into account peculiar features related to the pandemic, in particular, the modalities of transmission and the high contagiousness of SARS-CoV-2, with the related need for use of appropriate personal protective equipment and the design of specific in-hospital diagnostic and therapeutic protocols.

Key Points

Patients with coronavirus disease-19 (COVID-19) have an elevated risk of thrombotic events due to a high prevalence of cardiovascular risk factors, previous cardiovascular diseases and a pro-thrombotic status.

In patients with COVID-19 the thrombotic risk outweighs the bleeding risk.

Diagnostic and therapeutic approaches for thrombotic events in patients with COVID-19 should take into account the risk of contagion, the baseline risk profile and possible drug interactions.

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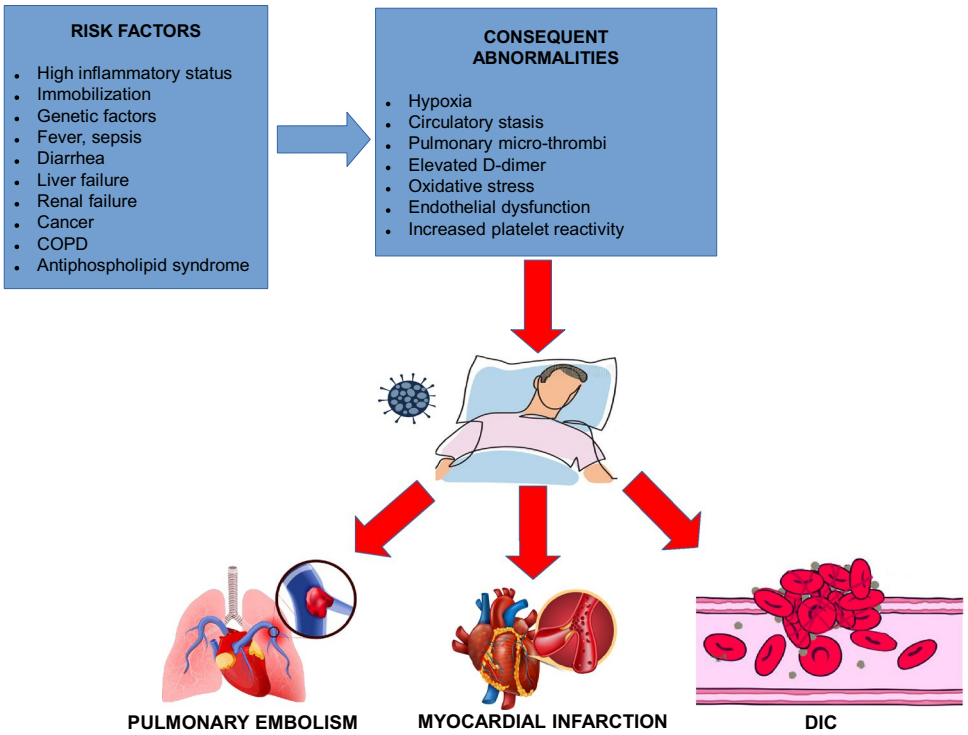


Fig. 1 Pathogenesis of prothrombotic status and thrombotic complications in patients with COVID-19. *COPD* chronic obstructive pulmonary disease, *COVID-19* coronavirus disease 2019, *DIC* disseminated intravascular coagulation

In this guidance document, we provide ten questions and answers on issues related to risk stratification and antithrombotic treatments in patients at risk of/with SARS-CoV-2 infection based on the scientific evidence gathered during the pandemic.

1 What Advice Should We Give to Patients on Chronic Anticoagulant Therapy at Risk of SARS-CoV-2 Infection or with Mild COVID-19 Maintained at Home?

In patients on oral anticoagulant therapy (OAC) who are at risk of contagion or have mild COVID-19 and are treated at home, anticoagulation should be individualized according to the patient's characteristics, clinical indication for OAC [atrial fibrillation (AF), venous thromboembolism (VTE), prosthetic heart valve], severity of infection, and therapies used for the viral infection. The duration of OAC for preventing AF-related thromboembolism is generally lifelong, based on the patient's CHA_2DS_2-VASc score (> 1 for males and > 2 for females) [2]. Patients with VTE usually receive OAC for 3–6 months after the event, but treatment is frequently prolonged in the presence of relapsing episodes or a high risk of recurrence (i.e., idiopathic thromboembolism, cancer, antiphospholipid syndrome, and severe congenital thrombophilias) [3]. Patients with mechanical valve prostheses are given OAC for their lifetime, whereas OAC duration is limited to 3 months post-implantation in the case of a biological prosthesis.

During the pandemic, lockdown measures reducing interindividual contacts were applied in several countries to contain viral diffusion; thus, the indication was to stay home to keep safe, which was especially addressed to patients with more advanced age or comorbidities. This should be specifically applied to patients with AF or VTE, who are often older and have a higher prevalence of previous cardiovascular diseases or cancer. Moreover, health systems worldwide dealt with an emergency never seen before and had to limit elective, non-urgent, ambulatory visits. Therefore, in this context, the management of patients receiving vitamin K antagonist anticoagulants (VKAs) for AF or VTE was even more problematic. For these patients, it became difficult to access the centers for international normalized ratio (INR) control, especially if more frequent monitoring was needed because of unstable INR values (which is not uncommon). Moreover, during the outbreak, public centers for INR control had a reduced number of staff members due to the redistribution of care workers for the emergency and re-addressed or limited the outpatient flow to contain the viral diffusion as much as possible. Finally, general practitioners were not able to immediately assist patients on VKAs in need of INR adjustments, as they were also fully involved in the management of COVID-19 patients.

Accordingly, in patients at risk for SARS-CoV-2 infection on VKAs and who have substantial "stability" in their INR

Table 1 Indications for patients at risk of/with SARS-CoV-2 infection maintained at home

Patients on VKAs at risk of SARS-CoV-2 infection
If INR values are stable (i.e., time in therapeutic range > 60%), a prolongation of the INR control intervals may be considered (every 4–8 weeks)
The use of portable coagulometer devices with self-measurement of INR is encouraged
Switching from VKAs to DOACs must be considered
In the case of unstable INR values, switching from VKAs to DOACs is recommended
Patients on VKAs with mild COVID-19 maintained at home
The use of portable coagulometer devices with self-measurement of INR is encouraged
Switching from VKAs to DOACs must be considered, taking into account possible drug interactions
In the case of unstable INR values, switching from VKAs to DOACs is recommended
Patients not on oral anticoagulant therapy with asymptomatic SARS-CoV-2 infection
No thromboprophylaxis is indicated
Patients not on oral anticoagulant therapy with mild COVID-19
Thromboprophylaxis with LMWH is indicated if multiple risk factors for VTE are present and bleeding risk is low

COVID-19 coronavirus disease 2019, *DOAC* direct oral anticoagulant, *INR* international normalized ratio, *LMWH* low-molecular weight heparin, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *VKA* vitamin K antagonist anticoagulant, *VTE* venous thromboembolism

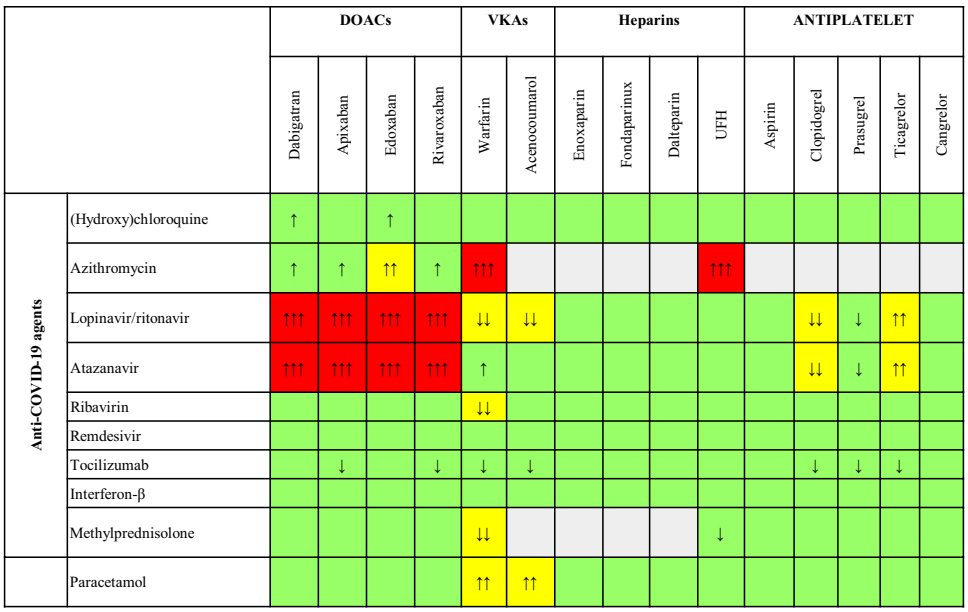


Fig. 2 Interactions between antithrombotic drugs and agents used for COVID-19. White*:* no data; green*:* no interaction; yellow*:* minor interaction, possibly requiring dose reduction of DOACs, additional INR controls (if VKA therapy) or functional monitoring of antiplatelet activity (in the case of $P2Y_{12}$ treatment); red*:* co-administration is contraindicated because of significant interaction. *Upward arrows:* increased activity of the antithrombotic drug, proportional to the number of arrows; *downward arrows*: decreased activity of the antithrombotic drug, proportional to the number of arrows. Adapted from ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic (https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance). *COVID-19* coronavirus disease 2019, *CV* cardiovascular, *DOAC* direct oral anticoagulant, *ESC* European Society of Cardiology, *INR* international normalized ratio, *UFH* unfractionated heparin, *VKA* vitamin K antagonist anticoagulant

values within the therapeutic range (i.e., time in therapeutic range > 60%), a prolongation of the INR control intervals may be considered (every 4–8 weeks) [4] (Table 1). The self-measurement of INR values by portable coagulometer devices is encouraged [5]. Switching from VKAs to direct oral anticoagulants (DOACs) must be considered [6].

In patients with mild COVID-19 treated at home who are on VKAs, the use of portable coagulometer devices should be implemented [7]. Moreover, switching from VKAs to DOACs has a clear indication. In fact, the duration of home isolation can be longer than 4 weeks; INR values are generally unstable during acute infection or illness; and paracetamol decreases the synthesis of vitamin K-dependent clotting factors [8], and therefore there is a major interaction between VKAs and this drug largely utilized for COVID-19-related fever (Fig. 2).

2 What are the Relevant Interactions Between Anticoagulant Drugs and Anti-SARS-CoV-2 Agents?

Treatment approaches in patients with COVID-19 include a combination of several drugs with virtually synergistic effects acting at different steps of the pathogenetic mechanisms of the disease [9]. Scientific evidence in this regard is currently limited but in continuous and rapid evolution [10]. In the first period of the SARS-CoV-2 pandemic, a widespread practice pattern was to treat with hydroxychloroquine both patients with mild COVID-19 kept at home and those with more severe disease requiring hospitalization. Notably, most recent data shifted the therapeutic paradigm from the initial enthusiasm to a rise of skepticism and uncertainty when more in-depth analyses of the use of hydroxychloroquine emerged [9–11]. In particular, the World Health Organization prematurely stopped the hydroxychloroquine arm of the Solidarity trial (NCT04330690), where no survival benefit had been observed in patients hospitalized for COVID-19. However, no significant interaction has been described between hydroxychloroquine and any antithrombotic agent (Fig. 2). The protease inhibitors lopinavir and atazanavir (either drug given in association with ritonavir or cobicistat) [12–15] have been largely utilized; however, accumulating data from recently published randomized studies and an interim analysis of the previously mentioned Solidarity trial, showed no reduction in mortality with the use of lopinavir/ritonavir in COVID-19 [16]. Furthermore, the nucleotide analog remdesivir [17–19] (developed for the treatment of Ebola and Marburg virus infections) showed favorable results in hospitalized patients with SARS-CoV-2 infection [20]. A less robust clinical benefit has been demonstrated with the nucleotide analog ribavirin [21], as well as with azithromycin [22], a macrolide often administered for COVID-19 in combination with hydroxychloroquine. In particular, the effects of the drug combination azithromycin plus hydroxychloroquine are controversial, given the limited evidence, the significant biases of available studies, and the pending results of randomized studies [22]. Interferon-β, currently authorized for the treatment of multiple sclerosis, was used in the treatment of Middle East respiratory syndrome coronavirus (MERS-CoV) infections with some positive preclinical results [14]; on this basis, it has been now included in anti-SARS-CoV-2 experimental protocols. Finally, due to recent encouraging clinical results, the use of glucocorticoids, mainly dexamethasone [23], and/or tocilizumab [24] (an interleukin-6 inhibitor) in patients with severe COVID-19 has increased. In asymptomatic or pauci-symptomatic patients with SARS-CoV-2 infection maintained at home, during the initial phases of the outbreak, treatment with hydroxychloroquine (with or without azithromycin) was generally performed, although the diffusion of this approach was greatly different across different countries.

There is no significant interaction between all agents used in COVID-19 and low-molecular weight heparins (LMWHs) or fondaparinux (Fig. 2) [25].

Ribavirin and lopinavir/ritonavir decrease the anticoagulant effects of VKAs, especially of warfarin, by interfering with cytochrome P450 3A4 (CYP3A4). Azithromycin significantly increases the anticoagulant action of warfarin; thus, co-administration should be avoided or at least INR monitoring must be intensified. Furthermore, azithromycin enhances the anticoagulant effects of unfractionated heparin (UFH) (Fig. 2).

DOACs, except dabigatran, are metabolized by CYP3A4. All DOACs are substrates of intestinal P-glycoprotein. In specific cases of uncertainty about possible drug interference, although not routinely recommended, a measurement of DOAC concentration could be considered. Macrolides inhibit the action of intestinal P-glycoprotein, resulting in a potential increase in the blood levels of DOACs and increased hemorrhagic risk. To date, no clinically relevant interference has been reported for dabigatran, rivaroxaban, or apixaban and azithromycin. There are no data on the interaction between azithromycin and edoxaban. Accordingly, the labeling of this agent does not recommend reducing the edoxaban dose in the case of co-administration. However, such interaction has to be considered plausible, similarly to what occurs for edoxaban with clarithromycin or erythromycin [25]. Indeed, in the randomized VTE-CANCER study [26], where edoxaban was compared to dalteparin in patients with cancer and VTE, the concomitant use of azithromycin required reduction of the DOAC dose (Fig. 2).

Some antiviral agents used for COVID-19 (lopinavir/ritonavir, atazanavir) are competitors of intestinal P-glycoprotein and inhibit CYP3A4 [9]. These agents significantly increase the bleeding risk of DOACs, due to an elevation in blood concentrations [27]. Thus, an absolute contraindication for co-administering the aforementioned antiviral substances with DOACs must be indicated (Fig. 2). Although dabigatran is not metabolized by CYP3A4, this

drug is a substrate of intestinal P-glycoprotein; therefore, the concomitant use of those antiviral agents and dabigatran should be reasonably prohibited. Accordingly, in COVID-19 patients on DOACs with an established indication for lopinavir/ritonavir or atazanavir, DOACs will be temporarily stopped and replaced with LMWH over the short term [25]. No significant interaction between DOACs and ribavirin is described.

No significant interference has been reported between VKAs or DOACs and interferon-ß or tocilizumab (Fig. 2). However, the use of this monoclonal antibody has been associated with hepatotoxicity [28]. Thus, close monitoring of liver function and coagulation indices is mandatory if tocilizumab is given in patients on anticoagulant treatment. Furthermore, as tocilizumab may cause an increase in the expression of CYP3A4, its co-administration can lead to a slight decrease in blood levels of anti-Xa agents (especially apixaban and rivaroxaban); therefore, close functional monitoring of coagulation parameters is indicated [25].

3 What to Do in Patients on Antithrombotic Agents Hospitalized for COVID-19?

Therapy with non-steroidal anti-inflammatory drugs (NSAIDs) was hypothesized to be a potential risk factor for a more serious clinical presentation of COVID-19, but these data have not been confirmed in the most recent series [29]. Aspirin at the "antiplatelet" daily dose of 75–100 mg has limited anti-inflammatory effects. Given its significant cardiovascular benefits, in patients on chronic therapy with aspirin for secondary prevention who are hospitalized or are maintained at home for COVID-19, this agent must be continued (Table 2), consistent with the recent recommendations by McCullough and colleagues [30]. Aspirin treatment for primary cardiovascular prevention should also be continued, unless contraindications have occurred during in-hospital stay (acute liver failure, severe renal failure, severe thrombocytopenia, documented drug interactions, planned invasive procedures). In patients hospitalized for COVID-19, dual antiplatelet therapy (aspirin plus oral $P2Y_{12}$ receptor inhibitor) must be continued in those who have recently undergone percutaneous coronary intervention (PCI) (within ≤ 3 months), unless hemorrhagic events are reported [25].

Regarding $P2Y_{12}$ receptor inhibitors, lopinavir/ritonavir and atazanavir reduce the antiplatelet effect of clopidogrel and prasugrel (the latter not significantly), while they increase blood concentrations of ticagrelor (Fig. 2) [9]. Thus, in this setting, the co-administration of aspirin plus prasugrel should be preferred. Indeed, the most recent evidence has indicated no clinical benefit of lopinavir/ritonavir, and the use of such antiviral drugs has progressively declined over the pandemic course [31]. However, in patients with COVID-19 who are candidates for lopinavir/ritonavir or atazanavir treatment and are on aspirin plus clopidogrel for a recent (≤ 3 months) PCI after chronic coronary syndrome, clopidogrel is continued, with blood cell count and ischemic event monitoring (Table 2). In patients with COVID-19 who are candidates for lopinavir/ritonavir or atazanavir and are on aspirin plus clopidogrel/ticagrelor for a recent (≤ 3 months) PCI after acute coronary syndrome (ACS), the replacement of clopidogrel/ticagrelor with prasugrel is indicated. If prasugrel is contraindicated, therapy with clopidogrel/ticagrelor is continued, with blood cell count and ischemic/bleeding event monitoring. There is no significant interference between clopidogrel/ticagrelor/prasugrel and the other agents used in COVID-19.

Table 2 Indications for patients receiving chronic antithrombotic treatments admitted for COVID-19

Patients on chronic antiplatelet therapy
Aspirin therapy for primary cardiovascular prevention should be continued, unless contraindications have arisen or there is need for venous thromboprophylaxis
Antiplatelet therapy for secondary cardiovascular prevention must be continued, considering possible drug interactions
Dual antiplatelet therapy in patients who have undergone PCI within ≤ 3 months must be continued unless hemorrhagic events are reported
In patients on aspirin plus clopidogrel/ticagrelor who have undergone a recent PCI (≤ 3 months) for ACS requiring treatment with lopinavir/ritonavir or atazanavir, switching from clopidogrel/ticagrelor to prasugrel is indicated. If prasugrel is contraindicated, therapy with clopidogrel/ticagrelor is continued, monitoring blood cell count and ischemic/bleeding events
In patients on aspirin plus clopidogrel who have undergone a recent PCI (≤ 3 months) for stable coronary syndrome requiring treatment with lopinavir/ritonavir or atazanavir, clopidogrel is continued, monitoring blood cell count and ischemic events
No significant interaction between clopidogrel/prasugrel/ticagrelor and the other agents used for COVID-19 are present
Patients on chronic OAC
If indication for OAC is adequate and no contraindication exists, short-term switching from OAC to LMWH is reasonable

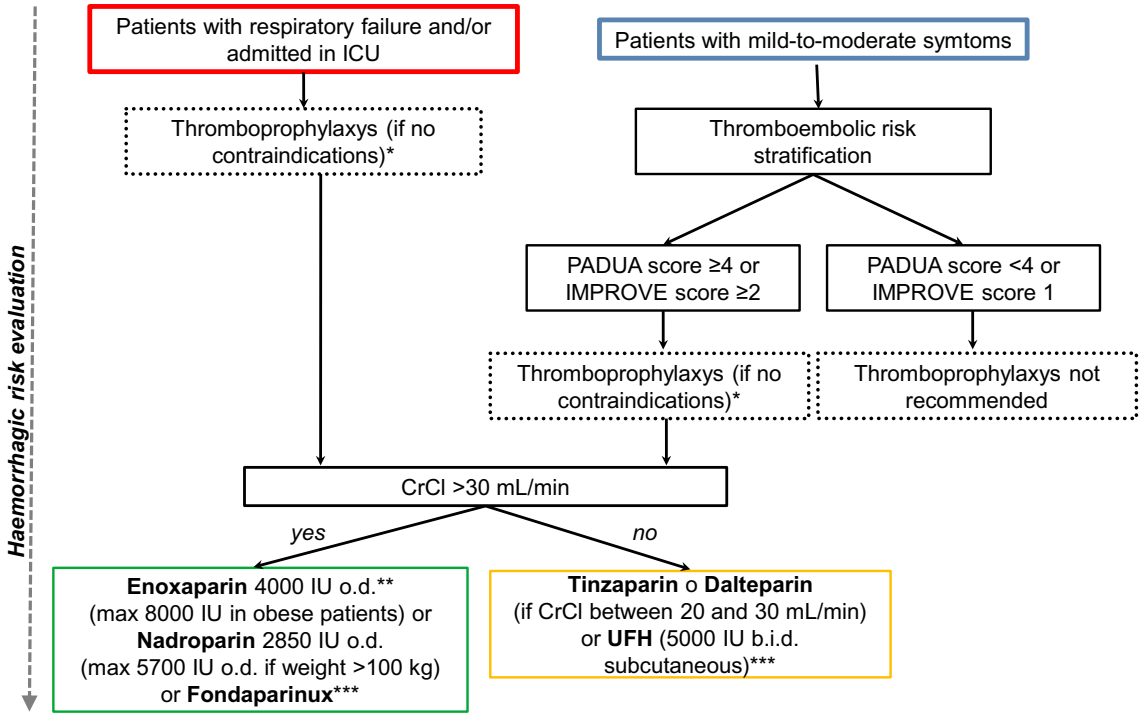
ACS acute coronary syndrome, *COVID-19* coronavirus disease 2019, *LMWH* low-molecular weight heparin, *OAC* oral anticoagulant therapy, *PCI* percutaneous coronary intervention

Finally, in patients on chronic OAC, if the indication for OAC is adequate and no contraindication exists, short-term switching from OAC to LMWH is reasonable (Table 2).

4 Antithrombotic Prophylaxis in Patients with SARS-CoV-2 Infection: When and How?

Thromboprophylaxis is not recommended in asymptomatic patients in whom a nasopharyngeal swab tested positive for molecular detection of SARS-CoV-2 RNA. In patients with mild COVID-19 maintained at home, thromboprophylaxis is indicated only if multiple risk factors for VTE and a low bleeding risk exist (Table 1) [25, 30].

In patients with more severe COVID-19, the release of pro-inflammatory mediators, platelet activation, oxidative stress, endothelial dysfunction [32], prolonged immobilization, hypoxia, circulatory stasis, the use of mechanical ventilation, liver dysfunction, central venous catheters, and nutritional deficit increase the risk of VTE (Fig. 1). Thus, these patients should be stratified upon hospitalization based on the clinical pattern and on the risk of thrombotic and bleeding complications. However, it is worth pointing out that this stratification is a dynamic process requiring a periodical reassessment according to clinical course and laboratory tests. Patients admitted to the intensive care unit (ICU), regardless of the need for mechanical ventilation, and those with acute respiratory insufficiency must be considered at high thromboembolic risk; thus, they require thromboprophylaxis [33, 34]. In patients with mild-to-moderate respiratory symptoms, with or without evidence of interstitial pneumonia, stratification based on the risk of VTE assessed using the PADUA Prediction Score [35] or the IMPROVE VTE score [36] is recommended (Fig. 3). A PADUA score of ≥ 4 identifies patients with an elevated risk of VTE; an IMPROVE score of 2–3 indicates an intermediate risk, whereas a value of ≥ 4 indicates a high risk. Following this stratification, thromboprophylaxis is not indicated in patients with a PADUA score of < 4 or an IMPROVE score of 1. In patients with a PADUA score indicating a high risk or an IMPROVE score indicating intermediate-to-high risk, thromboprophylaxis is needed, if contraindications do not exist.



* If pharmacological prophylaxys is contraindicated, it is possible to perform mechanical thromboprophylaxys by intermittent mechanical elasto-compression

** Due to recent reports showing in COVID-19 a pro-thrombotic *milieu* and high rates of venous thromboembolism, the use of higher-than-prophylactic doses of enoxaparin (e.g. 4000 IU BID) has been recently encouraged

*** In patients at high thrombotic risk (PADUA score ≥4 or IMPROVE score ≥4) and low bleeding risk, consider thromboprophylaxys up to 45 days after discharge

Fig. 3 Flowchart for thromboprophylaxis in patients with COVID-19. *COVID-19* coronavirus disease 2019, *CrCl* creatinine clearance, *BID/b.i.d.* twice a day *ICU* intensive care unit, *IU* international units, *o.d.* every day, *UFH* unfractionated heparin

The choice of agent for thromboprophylaxis should take into account renal function. In patients with creatinine clearance < 30 mL/min, UFH [5000 international units (IU) twice a day (BID) subcutaneously] can be used, whereas in those with creatinine clearance 20–30 mL/min, tinzaparin or dalteparin represents an option [25]. Notably, measurement of plasma anti-Xa activity is recommended in patients with renal failure, adjusting the dosage to maintain levels of 0.2–0.5 U anti-Xa/mL. In patients with creatinine clearance > 30 mL/min, enoxaparin is the first choice for thromboprophylaxis, with nadroparin or fondaparinux alternatively. Regarding the dosage of thromboprophylaxis drugs, there is an extensive debate. The World Health Organization expressed an orientation in favor of using a daily prophylactic dose of LMWH. A general indication is to give enoxaparin at a daily dose of 4000 IU (increased up to 8000 IU in obese patients) or nadroparin [37].

Notably, available data on the clinical benefit of thromboprophylaxis in patients with COVID-19 were initially based mainly on a single analysis of approximately 100 patients included in a retrospective study. Here, prophylaxis was associated with lower mortality only in patients having criteria for sepsis-induced coagulopathy or with D-dimer values sixfold higher than the reference limit [38]. Furthermore, data from a large United States cohort suggested that systemic anticoagulation (including oral, subcutaneous, or intravenous forms) may be associated with higher survival among patients hospitalized with COVID-19 [39]. Notably, in agreement with recent reports showing in such patients a pro-thrombotic *milieu* [32] and high rates of venous thromboembolic complications, the use of intermediate doses of enoxaparin (e.g., 4000 IU BID) for thromboprophylaxis has been recently encouraged, as prophylactic doses were considered insufficient for this aim [25]. However, specific studies are urgently needed to establish the optimal approach to thromboprophylaxis with LMWH in this setting, but, in the absence of robust evidence supporting higher dosing regimens, if thromboprophylaxis is indicated, it appears reasonable to utilize LMWH at prophylactic dosages. There are no specific data on the extension of thromboprophylaxis beyond hospitalization in patients with COVID-19; it is advisable to proceed individually and consider this extension up to a maximum of 45 days after discharge only in patients with a high VTE risk and a low risk of bleeding [25].

5 What is the Approach for Diagnosing Venous Thromboembolism in Patients with COVID-19?

The diagnosis of pulmonary embolism (PE) in patients with SARS-CoV-2 infection must be based on the integration of clinical, laboratory, and instrumental data (Table 3). D-dimer testing has a central role as a diagnostic marker for VTE; monitoring can allow an early diagnosis, but at the same time, it may be non-specific, if not contextualized. Indeed, over 50% of patients admitted for COVID-19 present elevated D-dimer values (in most cases < 1.0 mcg/mL), even without thrombotic complications [40]. Thus, in line with the diagnostic algorithms provided by pre-existing guidelines [41], D-dimer must be measured only in the presence of a clinical suspicion of VTE. Conversely, in the absence of concomitant clinical worsening, high levels of D-dimer should not guide diagnostic and therapeutic processes. PE is suspected if increased values of D-dimer are associated with clinical symptoms/signs of deep venous thrombosis (DVT), worsening hypoxemia disproportionate to the degree of respiratory involvement, and/or acute right ventricular dysfunction.

Table 3 Indications for the management of VTE in patients with COVID-19

In patients with a worsening clinical status, especially in those without anticoagulant treatment, a diagnosis of VTE must always be suspected
In patients with suspected VTE, the diagnostic and therapeutic workup must integrate clinical data, laboratory findings, and imaging test results
Measurement of D-dimer for diagnosing VTE must be performed only if a clinical suspect exists
Vascular/cardiac ultrasound imaging for diagnosing VTE should precede radiological imaging
Patients undergoing a *CT scan* for worsening respiratory status should receive angio-CT sequences to exclude PE
The use of LMWH for treating a VTE episode is preferred. UFH should be limited to patients with CrCl < 30 mL/min
An invasive "catheter"-based therapy for PE is indicated in selected cases with contraindication to anticoagulant drugs, recurrent events despite adequate anticoagulation, or when systemic fibrinolysis cannot be performed
For the risk stratification of patients with VTE, monitoring of the following parameters is useful: troponin, BNP, D-dimer, blood cell count, fibrinogen, prothrombin time, activated partial thromboplastin time, and degradation products of fibrin
After the initial approach, DOACs may represent an option for in-hospital treatment of a VTE episode in patients with clinical stability and decreasing inflammation
After a VTE episode, DOACs should represent the therapy of choice at discharge

BNP brain natriuretic peptide, *COVID-19* coronavirus disease 2019, *CrCl* creatinine clearance, *CT* computed tomography, *DOAC* direct oral anticoagulant, *LMWH* low-molecular weight heparin, *PE* pulmonary embolism, *UFH* unfractionated heparin, *VTE* venous thromboembolism

The use of imaging techniques in diagnosing a VTE episode is complex, because of the risk of viral transmission to other patients and to healthcare workers, and must be regulated by specific in-hospital protocols aimed at limiting such risk. Each imaging test must be subsequent to an integrated evaluation of clinical and laboratory data. Notably, vascular or cardiac ultrasound examination usually anticipates radiological imaging and requires appropriate personal protective equipment and specific methods for sanitizing the instruments. In view of the high rates of DVT in ICU patients, an extensive use of vascular ultrasound is advisable to assess broadly the diagnosis of DVT. Due to the higher risk of PE, patients with COVID-19 undergoing a lung computed tomography (CT) scan for worsening respiratory function should receive angio-CT sequences to optimize the diagnostic process [42]. In patients with acute respiratory distress syndrome (ARDS) and suspected PE, performing radiological tests is difficult because of patient's prone position and unstable clinical conditions. Here, echocardiographic evidence of deterioration of the right ventricular function or (more rarely) of transit thrombus represents a relevant finding justifying further diagnostic steps and on this basis the initiation of specific treatments.

6 How to Stratify the Prognosis of Patients with COVID-19?

Prognostic stratification of patients with COVID-19 is important and may guide treatment modalities. A higher inflammatory status (as identified by increased C-reactive protein levels or neutrophil/lymphocyte ratio) has been correlated with a poorer outcome, including lower survival [43]. The measurement of troponin and brain natriuretic peptide (BNP) is also useful, as an increase in these parameters indicates acute myocardial damage and hemodynamic overload [33, 41, 44]. Various abnormalities in the hemostatic parameters were associated with a higher risk of cardiovascular complications, mechanical ventilation, and mortality, in particular, thrombocytopenia (especially $< 50{,}000 \times 10^9$/L) and elevation of D-dimer (> 3 µg/mL), fibrinogen (> 1 g/L), or degradation products of fibrin. Recent studies suggested a relationship between severity in the clinical course of COVID-19 and spontaneous prothrombin time prolongation (> 3 s) or activated partial thromboplastin time prolongation (> 5 s) [33, 41, 45]. Accordingly, all the aforementioned hemostatic markers should be routinely monitored in these patients, with the aim to obtain a more accurate prognostic stratification.

7 How to Manage Antithrombotic Treatment in Patients with COVID-19 Complicated by Venous Thromboembolism?

In COVID-19 patients with VTE, the indications for treatment are based on pre-existing guidelines and should be integrated with specific assessments related to the SARS-CoV-2 infection [40]. As described above, the choice of the therapeutic regimen must also take into account considerations regarding the severity of clinical presentation, co-existence of renal disease, liver dysfunction and/or thrombocytopenia, and possible drug interactions with antiviral drugs [33]. The use of parenteral anticoagulants represents the best initial option, due to the greater manageability and the lower risk of drug interference (Table 3). LMWH at anticoagulant dosages (i.e., subcutaneous enoxaparin 1 mg/kg BID or nadroparin 86 IU/kg BID) should be preferred over UFH, which exposes healthcare workers to an increased risk of contagion, due to frequent blood samplings for dose adjustment. UFH should be used only in patients with creatinine clearance < 30 mL/min. An invasive catheter-based therapy for PE (locoregional thrombolytic therapy or embolectomy) is indicated in selected cases with contraindication to anticoagulant drugs, in those who experience recurrent events despite adequate anticoagulation, or when systemic fibrinolysis cannot be performed.

After the initial approach with LMWH, DOACs may represent an option for in-hospital treatment of a VTE episode only in patients with clinical stability and decreasing inflammation (Table 3). Unless contraindicated, DOACs should be preferred over VKAs, given they are easier to manage during the in-hospital stay and transition to the subsequent home regimen. However, as mentioned above, the choice of the OAC drug must consider possible interactions with anti-SARS-CoV-2 drugs [33, 39].

8 How to Manage Anticoagulant Therapy in Patients Hospitalized for COVID-19 Who Develop Atrial Fibrillation?

In patients with COVID-19, the onset or recurrence of AF is favored by fever, hypoxia, and adrenergic activation due to respiratory failure [46, 47]. Here, anticoagulant treatment for preventing thromboembolic events must be guided by the CHA_2DS_2-VASc score rather than the characteristics of the arrhythmic episodes (i.e., duration of the episodes, number of relapses). It is reasonable to initiate anticoagulation with LMWH and then switch to OAC during the hospitalization

Table 4 Criteria of the ISTH for the diagnosis of disseminated intravascular coagulation

Evaluation of the risk of DIC	Does the patient present a clinical condition consistent with DIC? No: do not proceed with the score Yes: proceed with the score
ISTH score	
Coagulation parameters	Prothrombin time, platelet count, D-dimer, degradation products of fibrin, fibrinogen
Diagnostic score	*Prolongation of prothrombin time*: ≤ 3 s = 0 points; > 3– ≤ 6 s = 1 point; > 6 s = 2 points
	Platelets: ≥ 100×10^9/L = 0 points; < 100×10^9/L = 1 point; < 50×10^9/L = 2 points
	D-DIMER, DEGRADATION PRODUCTS OF FIBRIN: normal = 0 points; moderately increased = 2 points; markedly increased = 3 points
	Fibrinogen: > 1 g/L = 0 points; ≤ 1 g/L = 1 point
ISTH score calculation	≥ 5 points: compatible with DIC
	< 5 points: non-suggestive for DIC

DIC disseminated intravascular coagulation, *ISTH* International Society on Thrombosis and Haemostasis

course, preferentially with a DOAC, taking into account possible drug interference.

9 How to Manage Patients with COVID-19 and Arterial Thrombosis?

Hospitalizations for ACS have apparently declined during the pandemic [48]. However, it was observed that 20–30% of patients hospitalized for COVID-19 have a history of cardiovascular disease [49]. As demonstrated in other viral inflammatory syndromes [50], an ACS due to coronary thrombosis can derive from destabilization of pre-existing lesions, as a result of the cytokine storm. Given the paucity of specific data, the pharmacological and interventional management of patients with COVID-19 and ACS should follow the pre-existing guidelines [51], using specific in-hospital protocols and appropriate measures for preventing the contagion infecting healthcare workers [52]. As previously indicated, in this setting, antiplatelet strategies play a crucial role. Aspirin can be used without specific additional concerns. In patients with COVID-19 and ACS on lopinavir/ritonavir or atazanavir treatment, the co-administration of aspirin and prasugrel after PCI should be preferred. If prasugrel is contraindicated, the use of clopidogrel or ticagrelor can be considered, possibly with testing of their antiplatelet efficacy [53]. The metabolism of cangrelor is independent of liver function. No drug interaction is expected between this agent and all drugs used in COVID-19.

Notably, in patients with COVID-19, a high incidence of ACS, with "ST-elevation myocardial infarction (STEMI)-like" presentation and without coronary lesions, has been reported [54]. In particular, recent data showed that approximately 40% of patients with COVID-19 and STEMI did not present culprit lesions at coronary angiography [55]. Possible pathogenetic mechanisms of this finding are acute myocarditis, type 2 myocardial infarction (due to mismatch between oxygen demand and supply), or "Takotsubo-like" myocardiopathy [52]. Thus, in patients with confirmed (or suspected) SARS-CoV-2 infection and "STEMI-like" presentation, fibrinolytic therapy should be considered only in selected cases, when coronary angiography and a possible percutaneous revascularization cannot be performed promptly and safely.

Regarding arterial thrombosis in non-coronary vessels, a recent observational investigation reported a 1.6% incidence of ischemic stroke among consecutive patients hospitalized for COVID-19 [56]. Moreover, there is evidence that patients with SARS-CoV-2 infection may have a more severe stroke presentation than non-infected patients [57]. Finally, cases of ischemic stroke associated with bilateral acute lower limbs ischemia in the context of antiphospholipid syndrome have been described [58].

10 How to Manage Patients Hospitalized for COVID-19 Developing Disseminated Intravascular Coagulation?

Disseminated intravascular coagulation (DIC) represents a possible complication in all patients admitted to the ICU with critical infectious diseases. In patients with COVID-19, a severe clinical course was associated with DIC in > 50% of cases [45]. Serial evaluation of platelet count, prothrombin time, D-dimer, and fibrinogen plays an important role in diagnosing DIC and monitoring its coagulation abnormalities (Table 4) [59]. The management of these patients includes the identification and treatment of the triggering causes and, in line with international recommendations, the initiation of specific treatments based on platelet transfusion, coagulation factors (fresh concentrated plasma), and fibrinogen (cryo-precipitate) in the presence of bleeding complications or, more rarely, on anticoagulant therapy with heparin, if a thromboembolic pattern is prevalent. In patients with DIC, treatment

with antiplatelet drugs should be limited to those with recent coronary stent implantation. With regard to patients on dual antiplatelet therapy, such treatment is continued if the platelet count is $\geq 50{,}000 \times 10^9$/L, whereas if the platelet count is 25,000–50,000 $\times 10^9$/L, an antiplatelet agent is stopped, and if the platelet count is $< 25{,}000 \times 10^9$/L, both antiplatelet drugs are withdrawn. However, the management of these patients must be individualized, balancing thrombotic and hemorrhagic risks.

Declarations

Conflict of interest Giuseppe Patti, Veronica Lio, Ilaria Cavallari, Felice Gragnano, Letizia Riva, Paolo Calabrò, Giuseppe Di Pasquale, Vittorio Pengo, and Andrea Rubboli declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

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References

1. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531–8.
2. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.
3. Kearon C, Akl EA, Camerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S–494S.
4. Porter AL, Margolis AR, Staresinic CE, et al. Feasibility and safety of a 12week INR follow-up protocol over 2 years in an anticoagulation clinic: a single-arm prospective cohort study. J Thromb Thrombolysis. 2019;47:200–8.
5. Plesch W, van den Besselaar AM. Validation of the international normalized ratio (INR) in a new point-of-care system designed for home monitoring of oral anticoagulation therapy. Int J Lab Hematol. 2009;31:20–5.
6. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955–62.
7. Meyer S, Frei CR, Kelly RD. Impact of a new method of warfarin management on patient satisfaction, time and cost. Pharmacotherapy. 2013;33:1147–55.
8. Mahé I, Bertrand N, Drouet L, et al. Interaction between paracetamol and warfarin in patients: a double-blind, placebo-controlled, randomized study. Haematologica. 2006;91:1621–7.
9. European Society of Cardiology. ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic. Bruxelles: European Society of Cardiology; 2020.
10. Misra S, Nath M, Hadda V, Vibha D. Efficacy of various treatment modalities for nCOV-2019: a systematic review and meta-analysis. Eur J Clin Invest. 2020;e13383.
11. Sattui SE, Liew JW, Graef ER, et al. Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19. Expert Rev Clin Immunol. 2020;16:659–66.
12. de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother. 2014;58:4875–84.
13. Chan JF, Yao Y, Yeung ML, et al. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERSCoV infection in a nonhuman primate model of common marmoset. J Infect Dis. 2015;212:1904–13.
14. Arabi YM, Alothman A, Balkhy HH, et al. Treatment of Middle East respiratory syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. Trials. 2018;19:81.
15. Park SY, Lee JS, Son JS, et al. Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. J Hosp Infec. 2019;101:42–6.
16. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382(19):1787–99.
17. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9:eaa13653.

18. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci USA. 2020;117:6771–6.
19. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11:222.
20. 20Jiang Y, Chen D, Cai D, Yi Y, Jiang S. Effectiveness of remdesivir for the treatment of hospitalized Covid-19 persons: a network meta-analysis. J Med Virol. 2020.
21. Khalili JS, Zhu H, Mak NSA, Yan Y, Zhu Y. Novel coronavirus treatment with ribavirin: groundwork for evaluation concerning COVID-19. J Med Virol. 2020;92:740–6.
22. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis. 2020;S1201–9712(20):30534–8.
23. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2021436.
24. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol. 2020;92(7):814–8.
25. Patti G, Lio V, Cavallari I, et al. Antithrombotic treatments in patients with SARS-CoV-2 infection: from current evidence to reasonable recommendations—a position paper from the Italian Working Group on Atherosclerosis, Thrombosis and Vascular Biology. G Ital Cardiol (Rome). 2020;21(7):489–501.
26. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med. 2018;378:615–24.
27. Testa S, Prandoni P, Paoletti O, et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: the Cremona experience. J Thromb Haemost. 2020;18(6):1320–3.
28. Mahamid M, Mader R, Safadi R. Hepatotoxicity of tocilizumab and anakinra in rheumatoid arthritis: management decisions. Clin Pharmacol. 2011;3:39–433.
29. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancermedicalscience. 2020;14:1023.
30. McCullough PA, Kelly RJ, Ruocco G, et al. Pathophysiological basis and rationale for early outpatient treatment of SARS-CoV-2 (COVID-19) Infection. Am J Med. 2020;S0002–9343(20):30673–82.
31. Ford N, Vitoria M, Rangaraj A, Norris SL, Calmy A, Doherty M. Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment. J Int AIDS Soc. 2020;23(4):e25489.
32. Singhania N, Bansal S, Nimmatoori DP, et al. Current overview on hypercoagulability in COVID-19. Am J Cardiovasc Drugs. 2020;1–11.
33. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol. 2020;75(23):2950–73.
34. Zhai Z. Prevention and treatment of venous thromboembolism associated with coronavirus disease 2019 infection: a consensus statement before guidelines. Thromb Haemost. 2020;120(6):937–48.
35. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010;8:2450–7.
36. Rosenberg D, Eichorn A, Alarcon M, McCullagh L, McGinn T, Spyropoulos AC. External validation of the risk assessment model of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) for medical patients in a tertiary health system. J Am Heart Assoc. 2014;3:e001152.
37. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019nCoV) infection is suspected. Interim guidance. 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed 31 July 2020.
38. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094–9.
39. Paranjpe I, Fuster V, Lala A, Russak A, Glicksberg BS, Levin MA, Charney AW, Narula J, Fayad ZA, Bagiella E, Zhao S, Nadkarni GN. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020;76:122–4.
40. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
41. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543–603.
42. Rotzinger DC, Beigelman-Aubry C, von Garnier C, Qanadli SD. Pulmonary embolism in patients with COVID-19: time to change the paradigm of computed tomography. Thromb Res. 2020;190:58–9.
43. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020;58:1131–4.
44. Stefanini GG, Chiarito M, Ferrante G, et al. Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. Heart. 2020;106:1512–8.
45. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844–7.
46. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. Circulation. 2020;141:1648–55.
47. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323:1775–6.
48. De Filippo O, D'Ascenzo F, Angelini F, et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in Northern Italy. N Engl J Med. 2020;383:88–9.
49. Kang Y, Chen T, Mui D. Cardiovascular manifestations and treatment considerations in covid-19. Heart. 2020;106:1132–41.
50. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med. 2018;378:2540–1.
51. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87–165.
52. Scotto di Uccio F, Valente S, Colivicchi F, et al. Position paper ANMCO: Organizzazione della Rete per il trattamento dei pazienti con sindrome coronarica acuta durante emergenza pandemica COVID-19. G Ital Cardiol. 2020;21:332–5.
53. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. J Am Coll Cardiol. 2020;75:2352–71.
54. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan. China. JAMA Cardiol. 2020;5:802–10.

55. Stefanini GG, Montorfano M, Trabattoni D, et al. ST-elevation myocardial infarction in patients with COVID-19: Clinical and angiographic outcomes. Circulation. 2020;141:2113–6.
56. Bilaloglu S, Aphinyanaphongs Y, Jones S, et al. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA. 2020;324:799–801.
57. Escalard S, Chalumeau V, Escalard C, et al. Early brain imaging shows increased severity of acute ischemic strokes with large vessel occlusion in COVID-19 Patients. Stroke. 2020. https://doi.org/10.1161/STROKEAHA.120.031011.
58. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020;382:e38.
59. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. Br J Haematol. 2009;145:24–33.

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