

**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

Correspondence to: Marco Valgimigli, MD, PhD, Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Via Tesserete 48, 6900 Lugano, Switzerland.  
E-mail: marco.valgimigli@cardiocentro.org

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.021965>

For Sources of Funding and Disclosures, see page 10.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAH is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

## 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

<b>adjHR</b>	adjusted hazard ratio
<b>ARC</b>	Academic Research Consortium
<b>BARC</b>	Bleeding Academic Research Consortium
<b>HBR</b>	high bleeding risk

**B**leeding events after percutaneous coronary intervention (PCI) are associated with worse outcomes.<sup>1</sup> 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<sup>2,3</sup> and/or overall occurrences.<sup>4,5</sup> On the other hand, several studies did not find a similar association.<sup>6-8</sup> International recommendations on duration of dual antiplatelet therapy reflect this uncertainty, with female sex being included

among the bleeding risk factors in the American<sup>9</sup> but not the European guidelines.<sup>10</sup> Similarly, female sex accrues the predicted hemorrhagic hazard among some risk scores<sup>11,12</sup> but not in others.<sup>13,14</sup>

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.<sup>15</sup> The discriminatory performance of these criteria, as originally described without adaptations, was recently assessed,<sup>16</sup> 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.<sup>17</sup>

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.<sup>18,19</sup>

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 ( $2\times 2$  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 ( $72.1\pm 11.4$  versus  $66.4\pm 11.8$  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,

**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 <sup>2</sup>	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<sup>2</sup>, 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).

**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.

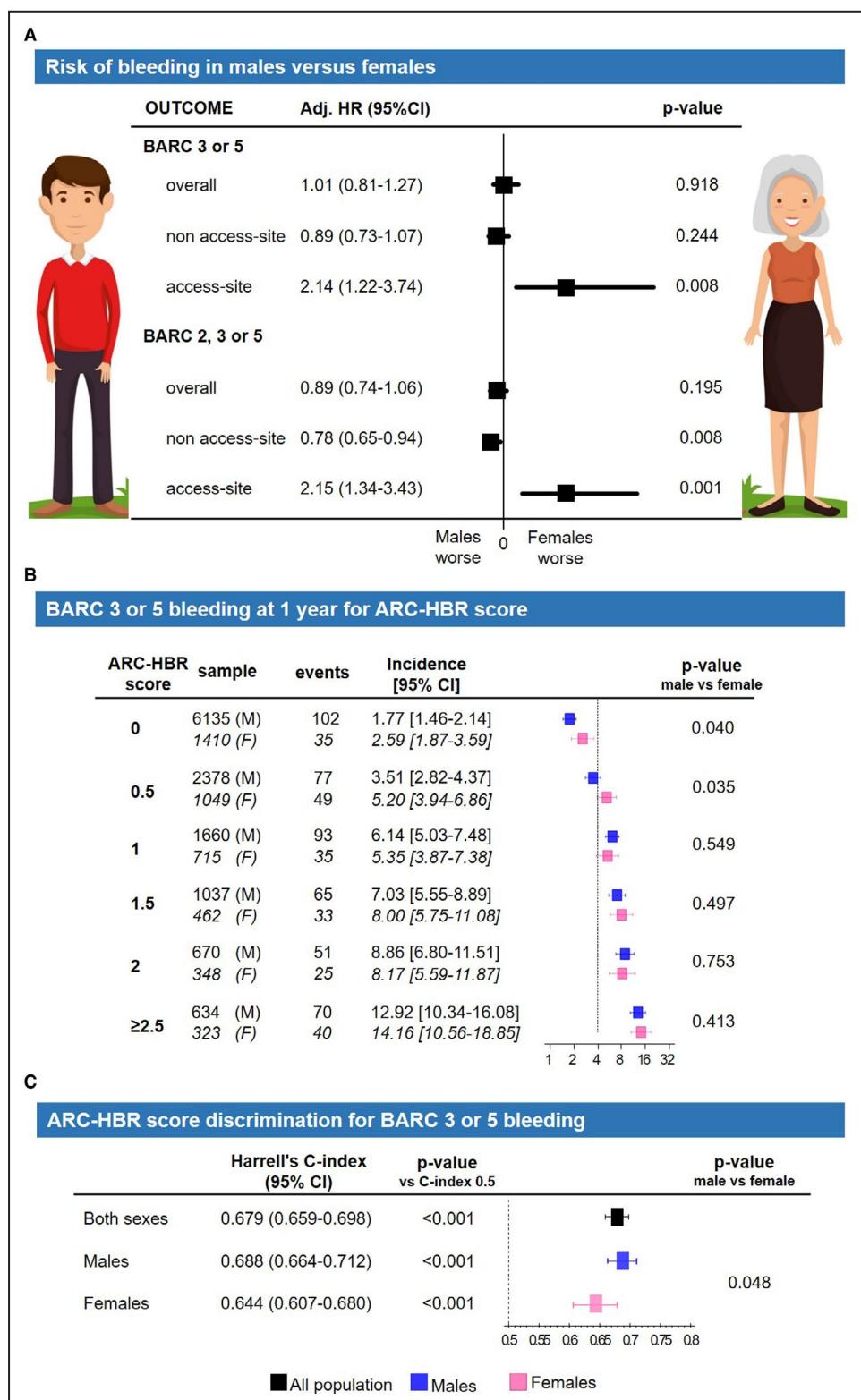
## ARC HBR Criteria Stratified by Sex

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).

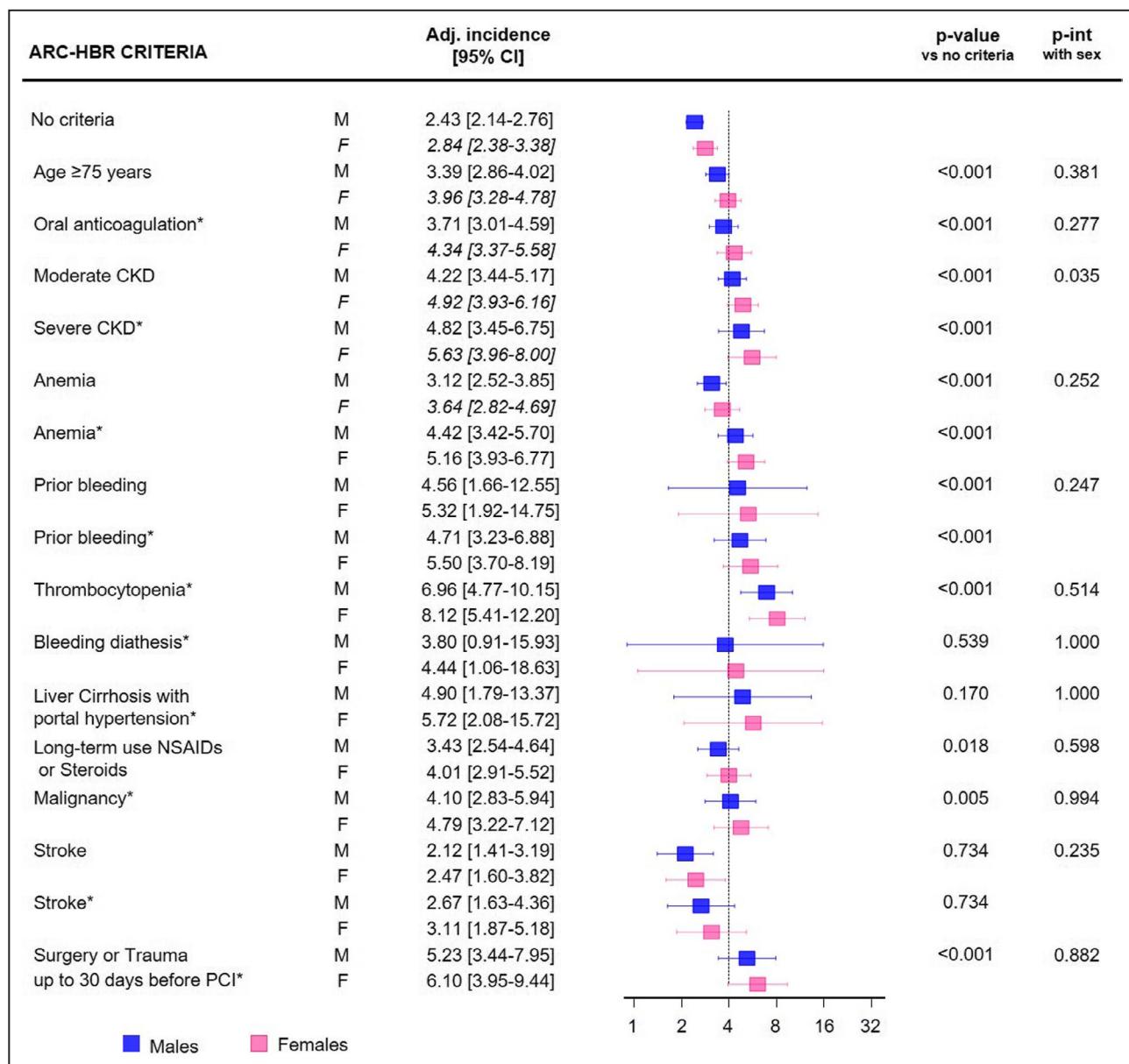
## ARC HBR Score Stratified by Sex

The ARC HBR score was higher among women than men ( $0.82 \pm 0.86$  versus  $0.60 \pm 0.80$ ;  $P < 0.001$ ) and differently distributed in the 2 groups (Figure S2B). For each 0.5-point increase of the ARC HBR score from 0 to  $\geq 2.5$ , 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  $\geq 1$ . 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



**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  $\geq 2.5$  (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.



**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).

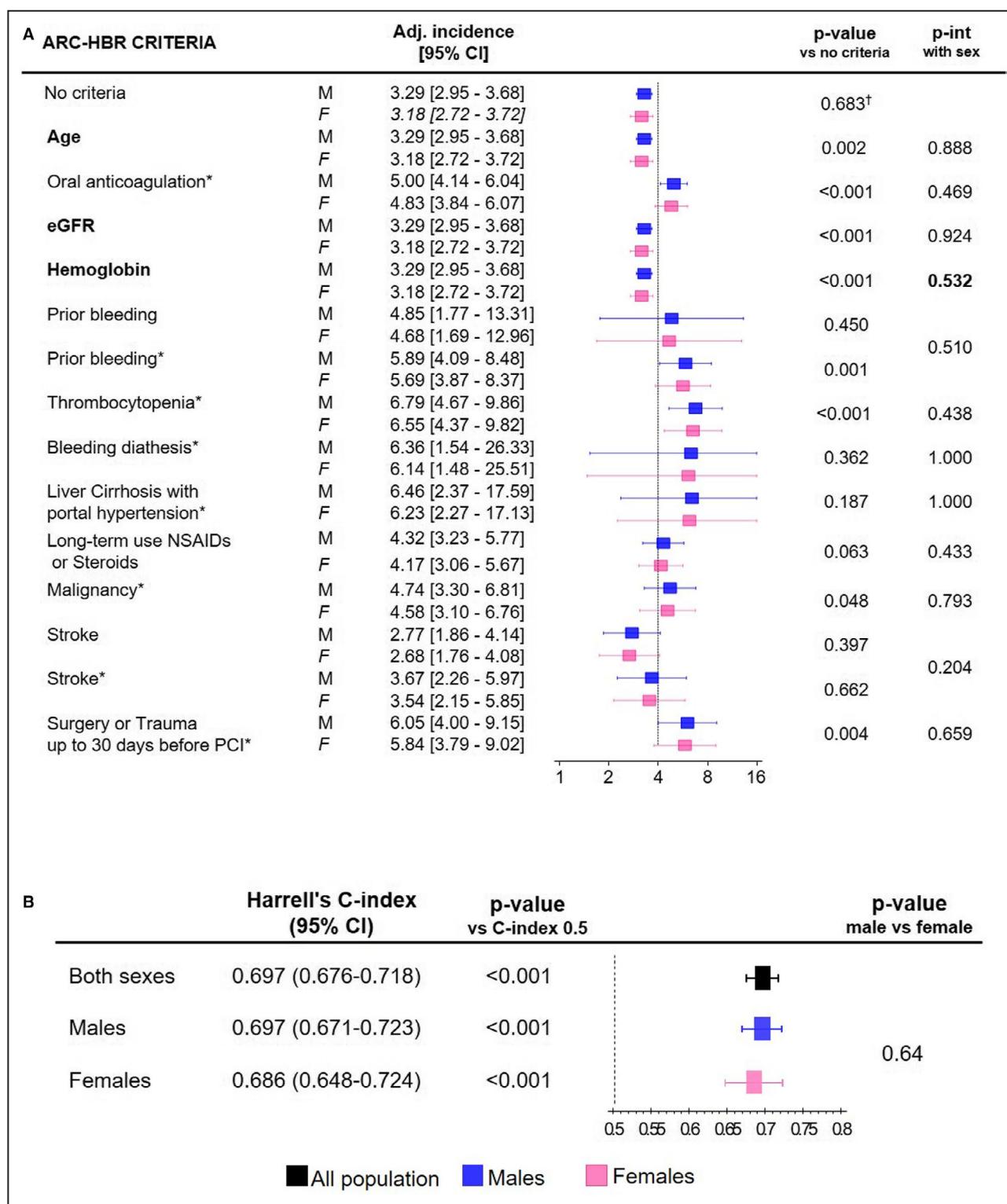
## DISCUSSION

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

**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. <sup>†</sup>P value for female vs male sex after adjustment for all other modified ARC-HBR criteria.

- 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,<sup>20–23</sup> with a possible greater benefit among women.<sup>21,22</sup>

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.<sup>24</sup>

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.<sup>25,26</sup>

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,<sup>4</sup> 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,<sup>27,28</sup> the increased bleeding risk among female patients was largely driven by nonactionable occurrences (BARC 1), and in some other studies,<sup>29</sup> 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]<sup>11</sup> or CRUSADE [Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines] score<sup>12</sup>), 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]<sup>14</sup>) or long-term bleeding occurrences (eg, PARIS [Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients]<sup>13</sup>).

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.<sup>15</sup> 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.<sup>21</sup>

## 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

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.<sup>3-5</sup> 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

Received April 6, 2021; accepted April 29, 2021.

### Affiliations

Department of Cardiology, Bern University Hospital, Bern, Switzerland (A.S., F.G., N.C., L.V., R.G., S. Svab, G.C.M.S., F.P., J.L., M.B., L.H., S. Stortecky, T.P., S.W., L.R., M.V.); Division of Cardiology, Department of Translational Medicine, University of Campania "Luigi Vanvitelli," Caserta, Italy (F.G.); Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy (G.G.); Division of Cardiology, Azienda Ospedaliero Universitaria "Policlinico-Vittorio Emanuele" University of Catania, Catania, Italy (D.C.); La Tour Hospital, Geneva, Switzerland (P.U.); London School of Hygiene and Tropical Medicine, London, United Kingdom (S.P.); Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY (R.M.); Clinical Trial Unit Bern, University of Bern, Switzerland (D.H.); and Istituto Cardiocentro Ticino, Ente Ospedaliero Cantonale, Lugano, Switzerland (M.V.).

### Acknowledgments

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Sources of Funding

This study was supported by the Department of Cardiology at Bern University Hospital, Bern, Switzerland.

## Disclosures

Dr Gargiulo reports personal fees from Daiichi Sankyo. Dr Praz reports personal fees from Edwards Lifesciences. Dr Stortecky reports grants from Edwards Lifesciences, Medtronic, Abbott Vascular, and Boston Scientific; and personal fees from Boston Scientific/British Technology Group and Teleflex. Dr Pilgrim reports grants and personal fees from Biotronik and Boston Scientific, and personal fees from HighLife Société par actions simplifiée (SAS; English: simplified joint-stock company). Dr Capodanno reports personal fees from AstraZeneca, Bayer, Daiichi Sankyo, Sanofi, and Boehringer. Dr Urban reports other fees from Cardiovascular European Research Center (CRO [Contract Research Organization] in Massy, France) and MedAlliance, and personal fees from Edwards Lifesciences and Biosensors. Dr Mehran reports grants from Abbott Laboratories, Abiomed, Applied Therapeutics, AstraZeneca, Bayer, Beth Israel Deaconess, Bristol-Myers Squibb, CERC, Chiesi, Concept Medical, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, and OrbusNeich; personal fees from Abbott Laboratories, Boston Scientific, CardiaWave, Janssen Scientific Affairs, Medscape/WebMD, Roviant Services, Sanofi, Siemens Medical Solutions, Medtelligence (Janssen Scientific Affairs), American College of Cardiology, American Medical Association, and Chiesi; nonfinancial support and other from Idorsia Pharmaceuticals Ltd. and Regeneron Pharmaceuticals; and other from Abbott Laboratories, Abiomed, Bristol-Myers Squibb, Merck, The Medicines Company, Spectranetics/Philips/Volcano Corp, Watermark Research Partners, Claret Medical, and Elixir Medical. Dr Windecker reports research and educational grants to the institution from Abbott, Amgen, Bristol Myers Squibb, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson & Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, and Sinomed; Dr Windecker serves as an unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Polares, Sinomed, V-Wave, and Xeltis but has not received personal payments by any pharmaceutical company or device manufacturer. He is also member of the steering/executive committee group of several investigated-initiated trials that receive funding by industry without impact on his personal remuneration. Dr Räber reports grants and personal fees from Abbott and Sanofi Aventis; personal fees from Amgen, Astra Zeneca, Biotronik, and CSL Behring. Dr Valgimigli reports personal fees from Astra Zeneca, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Opsens, Bayer, CoreFLOW, Idorsia Pharmaceuticals Ltd, Universität Basel | Dept. Klinische Forschung, Vifor, Bristol Myers Squib SA, iVascular, and Medscape; and grants and personal fees from Terumo. All the declared financial disclosures occurred outside the submitted work. The remaining authors have no disclosures to report.

## 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

- 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, Horowicz 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, Kohl 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, Vainsora 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/euroheartj/eaa671.
  17. Redfors B, Angerås O, Råmunddal T, Petrusson P, Haraldsson I, Dworeck C, Odenskjöld 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, Calabro 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, Valentini 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, Wijeyesundara 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/jic.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.

# **SUPPLEMENTAL MATERIAL**

## Data S1.

### SUPPLEMENTAL METHODS

#### *Data collection during follow-up*

Throughout 1 year, patients were systematically contacted after discharge in case of any unscheduled hospital visit due to bleeding or ischemic complications (death, myocardial infarction, stroke) in order to collect details about the event and concomitant medical treatment; they were contacted as well in case of staged procedure. At 1 year after index PCI all living patients received a form containing questions about adverse events, including bleeding occurrences, and in case of missing response they were contacted by telephone. General practitioners, referring cardiologists and other medical institutions were reached as necessary in order to collect discharge letters, coronary angiography documentation or any other relevant medical records, which were reviewed and used to adjudicate the events.

Survival data were obtained from hospital records and municipal civil registries.

#### *DAPT Duration*

The prescription of DAPT after PCI, consisting of acetylsalicylic acid and a P2Y<sub>12</sub> inhibitor, followed the recommendations of international guidelines. Dual antiplatelet therapy (DAPT) consisting of acetylsalicylic acid and a P2Y12 inhibitor 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, in agreement with existing European and American guidelines.

#### *Clinical endpoints*

All bleeding, ischemic and fatal events were adjudicated against original source documents by one trained physician and verification was carried out by a second one; disagreements were resolved through a third part adjudication.

Definitions of BARC 2, 3 or 5 bleeding are provided below:

- BARC Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
- BARC Type 3a: Overt bleeding plus hemoglobin drop of 3 to  $<5$  g/dL\* (provided hemoglobin drop is related to bleed) or any transfusion with overt bleeding
- BARC Type 3b: Overt bleeding plus hemoglobin drop  $\geq 5$  g/dL\* (provided hemoglobin drop is related to bleed) or cardiac tamponade or bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) or bleeding requiring intravenous vasoactive agents
- BARC Type 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) or subcategories confirmed by autopsy or imaging or lumbar puncture or intraocular bleed compromising vision
- BARC Type 4 (CABG-related bleeding): Perioperative intracranial bleeding within 48 h or reoperation after closure of sternotomy for the purpose of controlling bleeding or transfusion of  $\geq 5$  U whole blood or packed red blood cells within a 48-h period or chest tube output  $\geq 2$ L within a 24-h period
- BARC Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
- BARC Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

**Table S1. Definition of High bleeding risk (HBR) criteria according to academic research consortium (ARC) consensus.**

	Major	Minor
<b>Advanced age</b>		Age $\geq$ 75 years
<b>Oral anticoagulation</b>	Anticipated use of long-term oral anticoagulation	
<b>Chronic kidney disease (CKD)</b>	Severe or end-stage CKD (eGFR $<30$ mL/min)	Moderate CKD (eGFR 30–59 mL/min)
<b>Anaemia</b>	Hemoglobin $<11$ g/dL	11–12.9 g/dL for men 11–11.9 g/dL for women
<b>Prior bleeding</b>	Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion
<b>Thrombocytopenia</b>	Moderate or severe baseline thrombocytopenia (platelet count $<100 \times 10^9/L$ )	
<b>Chronic bleeding diathesis</b>	Inherited or acquired conditions known to be associated with increased bleeding risk such as platelet dysfunction, von Willebrand disease, inherited or acquired clotting factor deficiencies (including factors VII, VIII [hemophilia A], IX [hemophilia B], and XI), or acquired antibodies to clotting factors, among others	
<b>Liver cirrhosis</b>	Liver cirrhosis with portal hypertension	
<b>NSAIDs or steroids</b>		Long-term use of oral NSAIDs or steroids
<b>Active malignancy</b>	Diagnosis within the previous 12 months or ongoing active treatment, excluding non-melanoma skin cancer	
<b>Prior stroke</b>	Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 months Presence of a brain arteriovenous malformation Moderate or severe ischemic stroke within the past 6 months	Any ischemic stroke at any time not meeting the major criterion
<b>Planned surgery</b>	Nondeferrable major surgery on dual antiplatelet therapy*	
<b>Prior surgery or trauma</b>	Recent major surgery or major trauma within 30 days before PCI	

CKD= chronic kidney disease; eGFR= glomerular filtration rate according to MDRD formula; ICH= intracranial haemorrhage; PCI= percutaneous coronary intervention; NSAIDs= nonsteroidal anti-inflammatory drugs;

\* not adjudicated in the current analysis

**Table S2. Procedural characteristics in male and female patients.**

	All patients N = 16821	Male	Female	p-value
		N = 12514	N = 4307	
Access site	n = 11879, 3964 (33.4%) 7912 (66.6%) 3 (0.0%)	n = 8833, 3065 (34.7%) 5767 (65.3%) 1 (0.0%)	n = 3046, 899 (29.5%) 2145 (70.4%) 2 (0.1%)	<0.001
Coronary arteries treated				
Left main artery	n = 16821, 809 (4.8%)	n = 12514, 622 (5.0%)	n = 4307, 187 (4.3%)	0.099
Left anterior descending artery	n = 16821, 8677 (51.6%)	n = 12514, 6298 (50.3%)	n = 4307, 2379 (55.2%)	<0.001
Left circumflex artery	n = 16821, 5354 (31.8%)	n = 12514, 4119 (32.9%)	n = 4307, 1235 (28.7%)	<0.001
Right coronary artery	n = 16821, 6104 (36.3%)	n = 12514, 4514 (36.1%)	n = 4307, 1590 (36.9%)	0.321
Bypass graft	n = 16821, 556 (3.3%)	n = 12514, 487 (3.9%)	n = 4307, 69 (1.6%)	<0.001
Number of lesions	n = 16821, 1 2 ≥3	n = 12514, 7135 (57.0%) 3559 (28.4%) 1820 (14.5%)	n = 4307, 2632 (61.1%) 1143 (26.5%) 532 (12.4%)	<0.001
Multivessel treatment (2-3 vessels)	n = 16821, 4398 (26.1%)	n = 12514, 3307 (26.4%)	n = 4307, 1091 (25.3%)	0.159
IABP (prior or during PCI)	n = 16813, 210 (1.2%)	n = 12507, 152 (1.2%)	n = 4306, 58 (1.3%)	0.524
Percutaneous left ventricular assist device	n = 15448, 128 (0.8%)	n = 11489, 99 (0.9%)	n = 3959, 29 (0.7%)	0.478
Staged PCI performed	n = 16821, 2714 (16.1%)	n = 12514, 2120 (16.9%)	n = 4307, 594 (13.8%)	<0.001
Access site of first Staged PCI	n = 2147, radial femoral	n = 1682, 780 (46.4%) 902 (53.6%)	n = 465, 195 (41.9%) 270 (58.1%)	0.089 0.092 0.092
Nr of lesions treated	N = 27085	N = 20370	N = 6715	
Lesion type				
Restenotic lesion	n = 27051, 1576 (5.8%)	n = 20341, 1268 (6.2%)	n = 6710, 308 (4.6%)	<0.001
Evidence of thrombus	n = 26980, 3883 (14.4%)	n = 20293, 3065 (15.1%)	n = 6687, 818 (12.2%)	<0.001
Chronic total occlusion	n = 27085, 830 (3.1%)	n = 20370, 661 (3.2%)	n = 6715, 169 (2.5%)	0.005
Stenting				
Any DES	n = 25096, 23887 (95.2%)	n = 18802, 17895 (95.2%)	n = 6294, 5992 (95.2%)	0.950

Any Bare-metal stent	n = 25096, 1064 (4.2%)	n = 18802, 802 (4.3%)	n = 6294, 262 (4.2%)	0.793
Any Absorbable scaffold*	n = 25096, 79 (0.3%)	n = 18802, 54 (0.3%)	n = 6294, 25 (0.4%)	0.200
Mix of types of stents	n = 27085, 42 (0.2%)	n = 20370, 31 (0.2%)	n = 6715, 11 (0.2%)	0.834
Only DES stents used per patient	n = 27085, 24959 (92.2%)	n = 20370, 18755 (92.1%)	n = 6715, 6204 (92.4%)	0.400
Total number of stents implanted in this lesion	n = 25096, 1.32 ± 0.61	n = 18802, 1.32 ± 0.60	n = 6294, 1.32 ± 0.63	0.971
Total stent length (mm)	n = 25090, 27.76 ± 17.36	n = 18799, 27.98 ± 17.40	n = 6291, 27.09 ± 17.20	0.001
Mean stent diameter (mm)	n = 25089, 2.94 ± 0.59	n = 18798, 2.97 ± 0.62	n = 6291, 2.87 ± 0.46	<0.001
Treatment of a bifurcation	n = 27031, 3750 (13.9%)	n = 20330, 2827 (13.9%)	n = 6701, 923 (13.8%)	0.543
Baseline TIMI flow	n = 26607,	n = 20021,	n = 6586,	0.002
0 or 1	6239 (23.4%)	4834 (24.1%)	1405 (21.3%)	
2	4210 (15.8%)	3136 (15.7%)	1074 (16.3%)	
3	16157 (60.7%)	12050 (60.2%)	4107 (62.4%)	
Post TIMI flow	n = 26727,	n = 20115,	n = 6612,	0.606
0 or 1	184 (0.7%)	137 (0.7%)	47 (0.7%)	
2	387 (1.4%)	298 (1.5%)	89 (1.3%)	
3	26156 (97.9%)	19680 (97.8%)	6476 (97.9%)	

DES= drug eluting stent; IABP= intra-aortic balloon pump; PCI= percutaneous coronary intervention

\*Polymer or metal absorbable.

**Table S3. Medications in male and female patients.**

	All patients N = 16821	Male N = 12514	Female N = 4307	p-value
<b>Procedure medications, no.(%)</b>				
Loading procedure	n = 16821,	n = 12514,	n = 4307,	<0.001
No loading dose	1387 (8.2%)	1020 (8.2%)	367 (8.5%)	0.441
Only loading Clopidogrel	8060 (47.9%)	5818 (46.5%)	2242 (52.1%)	<0.001
Only loading Prasugrel	1908 (11.3%)	1564 (12.5%)	344 (8.0%)	<0.001
Only loading Ticagrelor	4605 (27.4%)	3409 (27.2%)	1196 (27.8%)	0.513
Loading Clopidogrel and Prasugrel	681 (4.0%)	571 (4.6%)	110 (2.6%)	<0.001
Loading Clopidogrel and Ticagrelor	154 (0.9%)	109 (0.9%)	45 (1.0%)	0.308
Loading Prasugrel and Ticagrelor	26 (0.2%)	23 (0.2%)	3 (0.1%)	0.117
Unfract. Heparin	n = 16808, 16452 (97.9%)	n = 12507, 12244 (97.9%)	n = 4301, 4208 (97.8%)	0.806
Fondaparinux	n = 15460, 1685 (10.9%)	n = 11501, 1231 (10.7%)	n = 3959, 454 (11.5%)	0.183
LMWH	n = 16803, 307 (1.8%)	n = 12502, 223 (1.8%)	n = 4301, 84 (2.0%)	0.468
Bivalirudin	n = 16803, 302 (1.8%)	n = 12502, 236 (1.9%)	n = 4301, 66 (1.5%)	0.143
Glycoprotein IIb/IIIa inhibitors	n = 16807, 1497 (8.9%)	n = 12506, 1202 (9.6%)	n = 4301, 295 (6.9%)	<0.001
Thrombolytic therapy	n = 15455, 48 (0.3%)	n = 11498, 35 (0.3%)	n = 3957, 13 (0.3%)	0.868
<b>Discharge medications, no.(%)</b>				
Aspirin	n = 16415, 15881 (96.7%)	n = 12215, 11834 (96.9%)	n = 4200, 4047 (96.4%)	0.107
Clopidogrel	n = 16415, 8850 (53.9%)	n = 12215, 6380 (52.2%)	n = 4200, 2470 (58.8%)	<0.001
Prasugrel	n = 16415, 2721 (16.6%)	n = 12215, 2232 (18.3%)	n = 4200, 489 (11.6%)	<0.001
Ticagrelor	n = 16415, 4539 (27.7%)	n = 12215, 3376 (27.6%)	n = 4200, 1163 (27.7%)	0.952
Any DAPT	n = 16415, 15623 (95.2%)	n = 12215, 11639 (95.3%)	n = 4200, 3984 (94.9%)	0.278
Any OAC	n = 16412, 1943 (11.8%)	n = 12214, 1460 (12.0%)	n = 4198, 483 (11.5%)	0.455
Novel oral anticoagulants	n = 11600, 689 (5.9%)	n = 8630, 515 (6.0%)	n = 2970, 174 (5.9%)	0.857
Any DAPT and OAC/NOAC	n = 16412, 1655 (10.1%)	n = 12214, 1266 (10.4%)	n = 4198, 389 (9.3%)	0.043
Statin	n = 16412, 14924 (90.9%)	n = 12214, 11264 (92.2%)	n = 4198, 3660 (87.2%)	<0.001
PPI	n = 12425, 5036 (40.5%)	n = 9294, 3567 (38.4%)	n = 3131, 1469 (46.9%)	<0.001
<b>One year follow-up medications, no.(%)</b>				
Aspirin*	n = 14355, 12898 (89.9%)	n = 10752, 9682 (90.0%)	n = 3603, 3216 (89.3%)	0.181

Clopidogrel*	n = 14356, 5378 (37.5%)	n = 10753, 3865 (35.9%)	n = 3603, 1513 (42.0%)	<0.001
Prasugrel*	n = 14356, 2069 (14.4%)	n = 10753, 1705 (15.9%)	n = 3603, 364 (10.1%)	<0.001
Ticagrelor*	n = 14355, 2951 (20.6%)	n = 10752, 2262 (21.0%)	n = 3603, 689 (19.1%)	0.014
Any DAPT*	n = 14355, 9365 (65.2%)	n = 10752, 7059 (65.7%)	n = 3603, 2306 (64.0%)	0.072
Any OAC	n = 14338, 1971 (13.7%)	n = 10743, 1466 (13.6%)	n = 3595, 505 (14.0%)	0.557
Novel oral anticoagulants	n = 11336, 836 (7.4%)	n = 8492, 621 (7.3%)	n = 2844, 215 (7.6%)	0.679
Any DAPT and OAC/NOAC	n = 14339, 250 (1.7%)	n = 10743, 190 (1.8%)	n = 3596, 60 (1.7%)	0.768
Statin	n = 14337, 12042 (84.0%)	n = 10742, 9225 (85.9%)	n = 3595, 2817 (78.4%)	<0.001
PPI	n = 11741, 3993 (34.0%)	n = 8825, 2831 (32.1%)	n = 2916, 1162 (39.8%)	<0.001

\*not stopped before 350 days since index PCI considered compliant.

DAPT= dual antiplatelet therapy; LMWH= low molecular weight heparin; NOAC= new oral anticoagulant; OAC= oral anticoagulant; PPI= proton pump inhibitor

**Table S4. Bleeding events at 1 year according to GUSTO and TIMI classification.**

	Male n=12,514	Female n=4,307	Hazard ratio [95% CI]	p-value
Bleeding BARC (2)	322 (2.8)	95 (2.5)	0.87 (0.69-1.10)	0.237
access site	6 (0.1)	7 (0.2)	3.42 (1.15-10.17)	0.027
non-access site	317 (2.8)	89 (2.3)	0.83 (0.65-1.05)	0.116
Bleeding BARC (3a)	188 (1.6)	95 (2.4)	1.50 (1.17-1.92)	0.001
access site	23 (0.2)	22 (0.5)	2.81 (1.57-5.04)	<0.001
non-access site	168 (1.5)	75 (1.9)	1.32 (1.01-1.74)	0.044
Bleeding BARC (3b)	214 (1.9)	94 (2.4)	1.30 (1.02-1.65)	0.035
access site	24 (0.2)	21 (0.5)	2.57 (1.43-4.62)	0.002
non-access site	192 (1.7)	73 (1.8)	1.12 (0.86-1.47)	0.402
Bleeding BARC (3c)	46 (0.4)	22 (0.6)	1.41 (0.85-2.35)	0.181
Bleeding BARC (5ab)	33 (0.3)	21 (0.5)	1.87 (1.08-3.24)	0.024
access site	0 (0.0)	1 (0.0)	8.72 (0.36-214.01)*	0.256
non-access site	33 (0.3)	20 (0.5)	1.79 (1.02-3.11)	0.041
Bleeding GUSTO (severe or moderate)	419 (3.6)	203 (5.1)	1.44 (1.22-1.71)	<0.001
access site	39 (0.3)	34 (0.8)	2.56 (1.62-4.06)	<0.001
non-access site	385 (3.4)	172 (4.4)	1.33 (1.11-1.59)	0.002
Bleeding GUSTO (severe)	227 (2.0)	118 (3.0)	1.54 (1.23-1.92)	<0.001
access site	14 (0.1)	12 (0.3)	2.51 (1.16-5.43)	0.019
non-access site	215 (1.9)	107 (2.7)	1.47 (1.17-1.86)	0.001
Bleeding GUSTO (moderate)	210 (1.8)	98 (2.5)	1.38 (1.09-1.76)	0.008
access site	25 (0.2)	22 (0.5)	2.59 (1.46-4.59)	0.001
non-access site	186 (1.6)	77 (2.0)	1.23 (0.94-1.60)	0.131
Bleeding GUSTO (mild)	379 (3.3)	116 (3.0)	0.90 (0.73-1.11)	0.337
access site	15 (0.1)	19 (0.5)	3.72 (1.89-7.32)	<0.001
non-access site	366 (3.2)	99 (2.6)	0.80 (0.64-0.99)	0.045
Bleeding TIMI (major or minor)	437 (3.8)	199 (5.0)	1.35 (1.14-1.60)	<0.001
access site	45 (0.4)	42 (1.0)	2.75 (1.80-4.18)	<0.001
non-access site	399 (3.5)	160 (4.1)	1.19 (0.99-1.43)	0.066

Bleeding TIMI (major)	267 (2.3)	114 (2.9)	1.26 (1.01-1.57)	0.037
access site	21 (0.2)	14 (0.3)	1.96 (0.99-3.85)	0.052
non-access site	249 (2.2)	101 (2.6)	1.20 (0.95-1.51)	0.124
Bleeding TIMI (minor)	184 (1.6)	94 (2.4)	1.51 (1.18-1.94)	0.001
access site	24 (0.2)	28 (0.7)	3.43 (1.99-5.92)	<0.001
non-access site	164 (1.4)	67 (1.7)	1.21 (0.91-1.61)	0.191
Bleeding TIMI (minimal)	356 (3.1)	120 (3.1)	1.00 (0.81-1.22)	0.970
access site	8 (0.1)	11 (0.3)	4.03 (1.62-10.03)	0.003
non-access site	348 (3.1)	110 (2.9)	0.93 (0.75-1.16)	0.525

\*Continuity corrected risk ratio with p-value from Fisher's exact test

**Table S5. Univariate analysis for overall, non-access-site and access-site BARC 3 or 5 bleeding at 1 year.**

	OVERALL events/patients 675/16821		NON-ACCESS SITE events/patients: 593/16821		ACCESS-SITE events/patients: 91/16821	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Female sex	1.41 (1.15-1.73)	0.001	1.25 (1.02-1.54)	0.035	2.76 (1.65-4.60)	<0.001
Age (years)	1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.05)	<0.001	1.04 (1.02-1.06)	0.001
BMI	0.95 (0.94-0.97)	<0.001	0.95 (0.93-0.97)	<0.001	0.96 (0.91-1.01)	0.087
Current smoker	0.77 (0.64-0.92)	0.004	0.84 (0.70-1.02)	0.074	0.33 (0.20-0.55)	<0.001
Diabetes mellitus	1.11 (0.86-1.44)	0.431	1.10 (0.85-1.44)	0.463	1.13 (0.70-1.83)	0.609
Hypertension	1.20 (0.96-1.52)	0.116	1.23 (0.97-1.56)	0.094	1.09 (0.60-1.98)	0.777
Hypercholesterolemia	0.83 (0.72-0.94)	0.004	0.81 (0.71-0.93)	0.004	0.81 (0.58-1.13)	0.220
Family history of coronary artery disease	0.77 (0.67-0.89)	<0.001	0.75 (0.62-0.90)	0.003	0.92 (0.66-1.27)	0.594
Previous myocardial infarction	1.11 (0.89-1.38)	0.360	1.13 (0.91-1.40)	0.254	0.84 (0.52-1.36)	0.483
Previous PCIs	0.93 (0.78-1.10)	0.404	0.96 (0.79-1.17)	0.709	0.63 (0.39-1.00)	0.049
Previous CABG	1.00 (0.80-1.24)	0.987	1.10 (0.87-1.40)	0.430	0.30 (0.11-0.86)	0.026
History of Cerebrovascular Accident	1.55 (1.13-2.13)	0.007	1.49 (1.10-2.01)	0.010	1.76 (0.83-3.74)	0.139
Peripheral arterial disease	1.51 (1.20-1.89)	<0.001	1.58 (1.25-2.00)	<0.001	1.17 (0.55-2.48)	0.681
History of malignancy	1.58 (1.22-2.03)	<0.001	1.66 (1.25-2.20)	<0.001	0.92 (0.58-1.45)	0.719
Renal failure [MDRD]	2.57 (2.23-2.98)	<0.001	2.61 (2.17-3.14)	<0.001	2.40 (1.39-4.13)	0.002
History of atrial fibrillation/atrial flutter	2.47 (2.01-3.05)	<0.001	2.48 (2.02-3.05)	<0.001	2.17 (1.44-3.28)	<0.001
Chronic obstructive lung disease	1.64 (1.21-2.21)	0.001	1.71 (1.21-2.42)	0.002	1.36 (0.75-2.47)	0.306
History of spontaneous bleeding	2.49 (1.89-3.28)	<0.001	2.49 (1.89-3.27)	<0.001	2.46 (1.38-4.38)	0.002
Hemoglobin before PCI (g/L)	0.97 (0.97-0.98)	<0.001	0.97 (0.97-0.98)	<0.001	0.97 (0.96-0.98)	<0.001
Left ventricular function (%)	0.97 (0.97-0.98)	<0.001	0.97 (0.97-0.98)	<0.001	0.97 (0.96-0.99)	0.005
Killip II, III or IV	2.92 (2.66-3.19)	<0.001	3.02 (2.75-3.32)	<0.001	2.51 (1.42-4.42)	0.001
Unstable Angina*	0.81 (0.51-1.27)	0.358	0.70 (0.42-1.17)	0.173	1.43 (0.68-3.02)	0.344
NSTEMI*	1.16 (0.97-1.39)	0.103	1.17 (0.99-1.38)	0.069	1.09 (0.71-1.67)	0.700
STEMI*	1.35 (1.10-1.67)	0.004	1.38 (1.07-1.78)	0.012	1.13 (0.63-2.01)	0.684
Femoral access†	1.00 (0.71-1.43)	0.983	0.94 (0.65-1.36)	0.727	1.73 (0.95-3.15)	0.075
IABP	2.92 (1.81-4.72)	<0.001	2.65 (1.44-4.89)	0.002	4.08 (1.50-11.09)	0.006
Percutaneous left ventricular assist device	9.35 (7.31-11.96)	<0.001	8.43 (6.00-11.85)	<0.001	12.34 (5.77-26.41)	<0.001
Number of lesions	1.00 (0.91-1.11)	0.941	0.98 (0.85-1.12)	0.73	1.19 (0.93-1.53)	0.162

Total stent length (mm)‡	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.02)	0.265
Left anterior descending artery	0.85 (0.77-0.93)	<0.001	0.81 (0.70-0.94)	0.005	1.31 (0.75-2.29)	0.345
Restenotic lesion	0.96 (0.72-1.28)	0.799	1.04 (0.76-1.42)	0.822	0.42 (0.13-1.30)	0.131
Evidence of thrombus	1.27 (1.05-1.53)	0.012	1.33 (1.08-1.63)	0.007	0.85 (0.46-1.57)	0.599
Chronic total occlusion	1.13 (0.80-1.61)	0.48	1.18 (0.84-1.66)	0.334	0.96 (0.32-2.87)	0.935
Discharge: Triple therapy DAPT + OAC§	1.84 (1.62-2.10)	<0.001	1.78 (1.49-2.13)	<0.001	2.26 (1.38-3.70)	0.001
Discharge: Any OAC§	1.95 (1.62-2.35)	<0.001	1.89 (1.53-2.35)	<0.001	2.44 (1.55-3.82)	<0.001
Discharge: Any DAPT§	0.65 (0.44-0.96)	0.029	0.67 (0.46-0.97)	0.036	0.52 (0.23-1.18)	0.117
Discharge: Prasugrel or Ticagrelor DAPT§	0.75 (0.57-1.01)	0.056	0.75 (0.56-1.01)	0.061	0.71 (0.50-1.01)	0.057
Discharge: PPI, not at follow-up	2.18 (1.62-2.92)	<0.001	2.23 (1.61-3.08)	<0.001	1.99 (1.28-3.09)	0.002
Follow-up: PPI, not at discharge	1.97 (1.46-2.66)	<0.001	2.16 (1.55-3.01)	<0.001	0.80 (0.44-1.45)	0.465
Discharge and follow-up: PPI	1.33 (1.02-1.74)	0.032	1.32 (1.01-1.72)	0.039	1.38 (0.81-2.35)	0.239
Staged PCI	0.82 (0.64-1.06)	0.126	0.81 (0.59-1.11)	0.186	0.83 (0.51-1.34)	0.437
Staged PCI Femoral access	1.15 (0.81-1.62)	0.432	1.11 (0.76-1.63)	0.580	1.24 (0.62-2.48)	0.548

Cluster robustified estimates by the year of PCI (2009-2018).

\*Stable CAD patients are the reference category; †Patients with PCI in 2009, 2010, 2011 all femoral access; ‡Stent length zero for ballooning only; §OAC and DAPT at discharge, if deceased in-hospital: as used at procedure; ||No PPI is the reference category

BMI= Body mass Index; CABG= coronary artery bypass graft; DAPT= dual antiplatelet therapy; HR= Hazard Ratio; IABP= intra-aortic balloon pump; NOAC new oral anticoagulant; OAC= oral anticoagulant; PCI= percutaneous coronary intervention; PPI= proton pump inhibitor.

**Table S6. Multivariate analysis for overall, non-access-site and access-site BARC 3 or 5 bleeding at 1 year.**

	Overall events/patients 675/16821		Non-access site events/patients 593/16821		Access site events/patients 91/16821	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Female sex	1.01 (0.81-1.27)	0.918	0.88 (0.72-1.09)	0.244	2.14 (1.22-3.74)	0.008
Age at date of informed consent	1.01 (1.00-1.02)	0.019	1.01 (1.00-1.02)	0.049	-	-
BMI	0.97 (0.95-0.99)	0.001	0.96 (0.94-0.98)	<0.001	-	-
Current smoker	-	-	-	-	0.40 (0.24-0.66)	<0.001
Renal failure [MDRD]	1.38 (1.18-1.62)	<0.001	1.43 (1.18-1.73)	<0.001	-	-
History of atrial fibrillation/atrial flutter	1.64 (1.28-2.09)	<0.001	1.66 (1.32-2.07)	<0.001	-	-
Previous PCls	-	-	-	-	0.58 (0.35-0.93)	0.025
Previous CABG	-	-	0.80 (0.59-1.09)	0.163	-	-
Chronic obstructive lung disease	1.30 (0.98-1.73)	0.074	1.31 (0.94-1.83)	0.113	-	-
History of spontaneous bleeding	1.37 (1.02-1.83)	0.038	1.37 (1.02-1.85)	0.037	1.92 (1.03-3.55)	0.039
Hemoglobin before PCI (g/L)	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.001	0.99 (0.97-1.00)	0.034
Killip II, III or IV	1.68 (1.49-1.90)	<0.001	1.76 (1.54-2.01)	<0.001	1.73 (1.04-2.90)	0.036
Unstable Angina*	1.10 (0.65-1.87)	0.719	0.58 (0.40-0.84)	0.004	-	-
NSTEMI*	1.20 (0.89-1.62)	0.242	0.55 (0.27-1.12)	0.098	-	-
STEMI*	1.81 (1.30-2.53)	<0.001	0.68 (0.51-0.89)	0.006	-	-
Percutaneous left ventricular assist device	5.49 (4.09-7.35)	<0.001	4.77 (3.12-7.31)	<0.001	8.32 (4.11-16.84)	<0.001
IABP (prior or during PCI)	-	-	-	-	2.08 (0.86-5.04)	0.106
Left anterior descending artery	-	-	0.83 (0.72-0.96)	0.010	-	-
Total stent length (mm)***	1.01 (1.00-1.01)	0.002	1.01 (1.00-1.01)	0.002	-	-
Discharge: Any DAPT	0.73 (0.54-0.99)	0.043	-	-	0.50 (0.24-1.07)	0.074
Discharge: potent P2Y12 inhibitor DAPT	0.79 (0.57-1.10)	0.165	0.76 (0.53-1.09)	0.132	-	-
Discharge: Any DAPT and OAC/NOAC	-	-	-	-	2.11 (1.36-3.28)	<0.001
Discharge: PPI, not at follow-up**	2.06 (1.41-3.00)	<0.001	2.16 (1.39-3.35)	<0.001	-	-
Follow-up: PPI, not at discharge**	2.42 (1.71-3.41)	<0.001	2.64 (1.79-3.91)	<0.001	-	-
Discharge and follow-up: PPI**	1.48 (1.10-1.99)	0.010	1.51 (1.07-2.13)	0.020	-	-
Staged PCI	0.65 (0.46-0.91)	0.012	-	-	-	-
Femoral access site at Staged PCI	1.53 (1.09-2.15)	0.014	-	-	-	-

Cluster robustified estimates by the year of PCI (2009-2018).

\*Stable CAD patients are the reference category; †Stent length zero for ballooning only; ‡OAC and DAPT at discharge, if deceased in-hospital: as used at procedure; §No PPI is the reference category.

BMI= Body mass Index; CABG= coronary artery bypass graft; DAPT= dual antiplatelet therapy; HR= Hazard Ratio; IABP= intra-aortic balloon pump; NOAC new oral anticoagulant; OAC= oral anticoagulant; PCI= percutaneous coronary intervention; PPI= proton pump inhibitor.

**Table S7. Univariate analysis for overall, non-access-site and access-site BARC 2, 3 or 5 bleeding at 1 year.**

	OVERALL BLEEDING events/patients 1020/16821		NON-ACCESS SITE events/patients 930/16821		ACCESS-SITE events/patients 104/16821	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Female sex	1.22 (1.03-1.43)	0.020	1.08 (0.91-1.28)	0.368	2.83 (1.83-4.39)	<0.001
Age (years)	1.03 (1.03-1.04)	<0.001	1.03 (1.03-1.04)	<0.001	1.04 (1.02-1.06)	<0.001
BMI	0.97 (0.96-0.98)	<0.001	0.97 (0.95-0.98)	<0.001	0.96 (0.91-1.00)	0.066
Current smoker	0.75 (0.66-0.86)	<0.001	0.80 (0.69-0.92)	0.003	0.39 (0.25-0.60)	<0.001
Diabetes mellitus	1.16 (0.97-1.39)	0.105	1.15 (0.96-1.38)	0.117	1.17 (0.64-2.14)	0.599
Hypertension	1.20 (1.05-1.37)	0.006	1.22 (1.08-1.38)	0.001	1.03 (0.60-1.76)	0.918
Hypercholesterolemia	0.80 (0.71-0.91)	<0.001	0.79 (0.70-0.90)	<0.001	0.79 (0.57-1.08)	0.140
Family history of coronary artery disease	0.69 (0.61-0.79)	<0.001	0.67 (0.58-0.78)	<0.001	0.86 (0.58-1.28)	0.458
Previous myocardial infarction	1.10 (0.88-1.38)	0.414	1.13 (0.91-1.40)	0.283	0.78 (0.43-1.41)	0.412
Previous PCIs	0.94 (0.80-1.10)	0.436	0.94 (0.80-1.11)	0.470	0.76 (0.45-1.28)	0.296
Previous CABG	0.99 (0.84-1.16)	0.890	1.05 (0.90-1.23)	0.537	0.35 (0.14-0.87)	0.023
History of Cerebrovascular Accident	1.47 (1.13-1.90)	0.004	1.43 (1.10-1.87)	0.007	1.52 (0.75-3.05)	0.243
Peripheral arterial disease	1.46 (1.24-1.73)	<0.001	1.54 (1.29-1.84)	<0.001	1.01 (0.45-2.29)	0.981
History of malignancy	1.65 (1.38-1.97)	<0.001	1.71 (1.41-2.08)	<0.001	0.99 (0.65-1.50)	0.966
Renal failure [MDRD]	2.32 (1.98-2.72)	<0.001	2.35 (1.95-2.84)	<0.001	2.32 (1.50-3.58)	<0.001
History of atrial fibrillation/atrial flutter	2.17 (1.81-2.60)	<0.001	2.16 (1.83-2.55)	<0.001	2.15 (1.43-3.22)	<0.001
Chronic obstructive lung disease	1.59 (1.24-2.03)	<0.001	1.63 (1.24-2.14)	<0.001	1.34 (0.80-2.24)	0.263
History of spontaneous bleeding	2.41 (2.05-2.84)	<0.001	2.46 (2.12-2.85)	<0.001	2.12 (1.12-4.01)	0.021
Hemoglobin before PCI (g/L)	0.98 (0.97-0.98)	<0.001	0.98 (0.97-0.98)	<0.001	0.97 (0.97-0.98)	<0.001
Left ventricular function (%)	0.98 (0.97-0.98)	<0.001	0.98 (0.97-0.98)	<0.001	0.98 (0.96-0.99)	0.011
Killip II, III or IV	2.58 (2.34-2.85)	<0.001	2.63 (2.37-2.92)	<0.001	2.38 (1.35-4.19)	0.003
Unstable Angina*	0.97 (0.73-1.29)	0.850	0.93 (0.69-1.25)	0.613	1.47 (0.68-3.14)	0.325
NSTEMI*	1.19 (1.01-1.41)	0.040	1.21 (1.02-1.43)	0.029	1.06 (0.73-1.55)	0.746
STEMI*	1.36 (1.21-1.53)	<0.001	1.36 (1.19-1.56)	<0.001	1.31 (0.74-2.33)	0.357
Femoral access†	0.90 (0.65-1.24)	0.511	0.85 (0.60-1.21)	0.368	1.73 (1.08-2.77)	0.023
IABP	2.43 (1.49-3.96)	<0.001	2.34 (1.31-4.16)	0.004	3.54 (1.26-9.92)	0.016
Percutaneous left ventricular assist device	7.41 (5.42-10.12)	<0.001	6.84 (4.88-9.59)	<0.001	10.64 (4.94-22.89)	<0.001
Number of lesions	0.98 (0.90-1.08)	0.741	0.96 (0.87-1.07)	0.454	1.23 (1.01-1.50)	0.039
Total stent length (mm)‡	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.02)	0.162
Left anterior descending artery	0.86 (0.76-0.99)	0.032	0.84 (0.72-0.99)	0.038	1.28 (0.73-2.25)	0.389
Restenotic lesion	0.95 (0.81-1.13)	0.577	0.99 (0.84-1.18)	0.946	0.48 (0.19-1.24)	0.129
Evidence of thrombus	1.29 (1.13-1.47)	<0.001	1.30 (1.14-1.49)	<0.001	1.05 (0.62-1.77)	0.86
Chronic total occlusion	1.28 (1.05-1.55)	0.013	1.31 (1.08-1.58)	0.005	1.05 (0.44-2.49)	0.912

Discharge: Triple therapy DAPT + OAC <sup>§</sup>	1.88 (1.67-2.12)	<0.001	1.83 (1.59-2.10)	<0.001	2.18 (1.38-3.43)	<0.001
Discharge: Any OAC <sup>§</sup>	1.89 (1.67-2.13)	<0.001	1.84 (1.61-2.09)	<0.001	2.29 (1.47-3.58)	<0.001
Discharge: Any DAPT <sup>§</sup>	0.87 (0.60-1.27)	0.470	0.91 (0.64-1.30)	0.615	0.60 (0.26-1.39)	0.233
Discharge: Prasugrel or Ticagrelor DAPT <sup>§</sup>	0.90 (0.69-1.18)	0.441	0.91 (0.69-1.19)	0.481	0.80 (0.57-1.11)	0.175
Discharge: PPI, not at follow-up <sup>  </sup>	2.24 (1.70-2.94)	<0.001	2.29 (1.69-3.11)	<0.001	1.88 (1.24-2.85)	0.003
Follow-up: PPI, not at discharge <sup>  </sup>	1.79 (1.35-2.38)	<0.001	1.86 (1.36-2.54)	<0.001	1.21 (0.58-2.51)	0.610
Discharge and follow-up: PPI <sup>  </sup>	1.42 (1.06-1.90)	0.019	1.41 (1.04-1.91)	0.026	1.47 (0.98-2.21)	0.062
Staged PCI	1.01 (0.86-1.20)	0.872	1.02 (0.84-1.23)	0.876	0.90 (0.52-1.55)	0.710
Staged PCI Femoral access	1.32 (0.97-1.81)	0.079	1.31 (0.93-1.85)	0.128	1.22 (0.58-2.57)	0.606

Cluster robustified estimates by the year of PCI (2009-2018).

\*Stable CAD patients are the reference category; †Patients with PCI in 2009, 2010, 2011 all femoral access; <sup>‡</sup>Stent length zero for ballooning only; <sup>§</sup>OAC and DAPT at discharge, if deceased in-hospital: as used at procedure; <sup>||</sup>No PPI is the reference category

BMI= Body mass Index; CABG= coronary artery bypass graft; DAPT= dual antiplatelet therapy; HR= Hazard Ratio; IABP= intra-aortic balloon pump; NOAC new oral anticoagulant; OAC= oral anticoagulant; PCI= percutaneous coronary intervention; PPI= proton pump inhibitor.

**Table S8. Multivariate analysis for BARC 2, 3 or 5 bleeding at 1 year.**

	OVERALL BLEEDING events/patients 1020/16821		NON-ACCESS SITE events/patients 930/16821		ACCESS-SITE events/patients 104/16821	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Female sex	0.89 (0.74-1.06)	0.195	0.78 (0.65-0.94)	0.008	2.15 (1.34-3.43)	0.001
Age at date of informed consent	1.02 (1.01-1.02)	<0.001	1.02 (1.01-1.03)	<0.001	-	-
BMI	0.98 (0.97-0.99)	0.004	0.98 (0.97-0.99)	0.007	-	-
Hypercholesterolemia	-	-	0.91 (0.79-1.04)	0.169	-	-
Current smoker	-	-	-	-	0.47 (0.30-0.73)	<0.001
Previous CABG	0.73 (0.61-0.88)	<0.001	0.79 (0.63-0.99)	0.039	0.30 (0.12-0.71)	0.007
History of malignancy	1.24 (1.03-1.49)	0.022	1.28 (1.05-1.55)	0.014	-	-
Renal failure [MDRD]	1.31 (1.13-1.52)	<0.001	1.34 (1.11-1.63)	0.003	-	-
History of atrial fibrillation/atrial flutter	1.55 (1.26-1.90)	<0.001	1.52 (1.27-1.82)	<0.001	-	-
Chronic obstructive lung disease	1.25 (0.99-1.58)	0.058	1.26 (0.97-1.63)	0.084	-	-
History of spontaneous bleeding	1.43 (1.18-1.72)	<0.001	1.43 (1.19-1.73)	<0.001	1.65 (0.84-3.26)	0.149
Hemoglobin before PCI (g/L)	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.001	0.98 (0.97-1.00)	0.007
Left ventricular function (%)	0.99 (0.99-1.00)	0.039	0.99 (0.99-1.00)	0.057	-	-
Killip II, III or IV	1.49 (1.33-1.68)	<0.001	1.52 (1.32-1.75)	<0.001	1.70 (1.03-2.79)	0.036
Unstable Angina*	1.31 (0.91-1.87)	0.144	1.24 (0.84-1.83)	0.289	-	-
NSTEMI*	1.17 (0.97-1.40)	0.094	1.17 (0.96-1.43)	0.112	-	-
STEMI*	1.58 (1.36-1.83)	<0.001	1.54 (1.30-1.82)	<0.001	-	-
Percutaneous left ventricular assist device	4.32 (2.89-6.46)	<0.001	3.79 (2.41-5.97)	<0.001	7.63 (3.59-16.22)	<0.001
Left anterior descending artery	0.86 (0.75-0.98)	0.020	0.86 (0.74-1.01)	0.070	-	-
Chronic total occlusion	1.31 (0.97-1.76)	0.081	1.36 (1.02-1.80)	0.034	-	-
Total stent length (mm) <sup>†</sup>	1.00 (1.00-1.01)	0.012	1.01 (1.00-1.01)	0.003	-	-
Number of lesions	-	-	0.91 (0.83-1.00)	0.062	1.20 (0.98-1.46)	0.070
Discharge: Any OAC <sup>‡</sup>	-	-	-	-	2.09 (1.32-3.28)	0.001
Discharge: PPI, not at follow-up <sup>§</sup>	2.15 (1.57-2.92)	<0.001	2.19 (1.56-3.08)	<0.001	-	-
Follow-up: PPI, not at discharge <sup>§</sup>	2.18 (1.62-2.93)	<0.001	2.27 (1.64-3.14)	<0.001	-	-
Discharge and follow-up: PPI <sup>§</sup>	1.55 (1.16-2.08)	0.003	1.57 (1.15-2.14)	0.005	-	-

Cluster robustified estimates by the year of PCI (2009-2018).

\*Stable CAD patients are the reference category; <sup>†</sup>Stent length zero for ballooning only; <sup>‡</sup>OAC and DAPT at discharge, if deceased in-hospital: as used at procedure; <sup>§</sup>No PPI is the reference category

BMI= Body mass Index; CABG= coronary artery bypass graft; DAPT= dual antiplatelet therapy; HR= Hazard Ratio; IABP= intra-aortic balloon pump; NOAC new oral anticoagulant; OAC= oral anticoagulant; PCI= percutaneous coronary intervention; PPI= proton pump inhibitor.

**Table S9. Contemporary studies reporting a sex-related adjusted risk for bleeding after PCI at a longer follow up (>6 months).**

Author (year of publication)	PMID	Study name	Type of study	Population	No of patients	Inclusion period	Bleeding definition	Duration follow up	Adjusted bleeding risk increased in females		
									Longest follow-up	Short follow-up	Access-site
Anderson et al. (2012)	22988009	Cath-PCI Registry and Medicare	Obs.	PCI ≥65y	675460	2004 - 2008	Study specific	30 months	N	Y	Y
Berry et al. (2018)	30354781	DAPT	RCT	PCI	25682	2009 - 2011	GUSTO moderate/severe	1 year	Y	-	N
Chandiramani et al. (2020)	32223396	4 post-approval Xience studies	Obs.	HBR patients and PCI with XIENCE V stent	2397	-	TIMI minor/major or GUSTO moderate/severe	4 years	N	N	-
Chandrasekhar et al. (2017)	27152497	Prometheus	Obs.	PCI and ACS <55years	4851	2010 - 2013	Study specific	1 year	N	-	-
Clemmensen et al. (2015)	26386793	TRILOGY ACS	RCT	ACS without PCI	9326	2008 - 2011	GUSTO moderate/severe and TIMI minor/major	30 months	N <sup>*</sup>	-	-
D'Ascenzo et al. (2018)	30228021	RENAMI	Obs.	ACS and PCI	4424	2013 - 2015	BARC 3 or 5	14.1 ± 6.2 months	Y	-	-
Gargiulo et al. (2016)	27544007	PRODIGY	RCT	PCI	1970	2006 - 2008	BARC 2,3 or 5, TIMI minor/major, GUSTO moderate/severe	2 years	N	-	-
Grodecki et al. (2018)	30064688	BleeMACS	Obs.	PCI and ACS	13727	2003 - 2014	Study specific	1 year	N		
Hess et al. (2014)	24510115	TRANSLATE-ACS	RCT	PCI and ACS	6218	2010 - 2012	GUSTO mild/moderate/severe and BARC 1-5	1 year	Y	-	-
Hochholzer et al. (2011)	21606391	TRITON-TIMI 38	RCT	PCI and ACS	13420	2004 - 2007	TIMI minor/major with transfusion	15 months	Y	-	-
Husted et al. (2014)	24682844	PLATO	RCT	PCI and ACS	18624	2006 - 2008	Study specific and TIMI	240 days	N	Y	-
Ko et al. (2010)	20332382	Regional Registry (Ontario, Canada)	Obs.	PCI >65y	22798	2003 - 2007	Study specific	1 year	N <sup>*</sup>	-	-
Mehran et al. (2020)	32432718	LEADERS-FREE	RCT	PCI and HBR	2432	2012 - 2014	BARC 2, 3 or 5	2 years	N	Y	Y
Nakamura et al. (2019)	31748446	PRASFIT-Practice II	Obs.	ACS and PCI treated with prasugrel	4155	2015 - 2018	TIMI minor/major	1 year	N	Y	-
Shin et al. (2014)	24793670	Korean TCI Registry	Obs.	PCI with radial access	1194	2009 - 2009	Study specific	1 year	Y	-	-
Xanthopoulou et al. (2017)	28459500	GRAPE Registry	Obs.	PCI moderate to high risk	2049	2012 - 2013	BARC 1-5	1 year	Y	-	-
Xu et al. (2018)	29490431	Single-centre registry (Beijing, China)	Obs.	PCI patients >60y	10724	2013 - 2013	BARC 1-5	2 years	Y	-	-
Yu J et al. (2015)	25115966	HORIZONS-AMI	RCT	PCI and STEMI	3602	2005 - 2007	Study specific	3 years	Y	-	-
Sawaya et al. (2017)	27426936	IPD Meta-analysis of 6 RCT*			11473		TIMI and BARC		N	-	-
Lau et al. (2017)	28335837	Meta-analysis <sup>†</sup>			87840		TIMI minor/major		N	-	-

Obs.=observational; RCT= randomized controlled trial; IPD=individual patient data

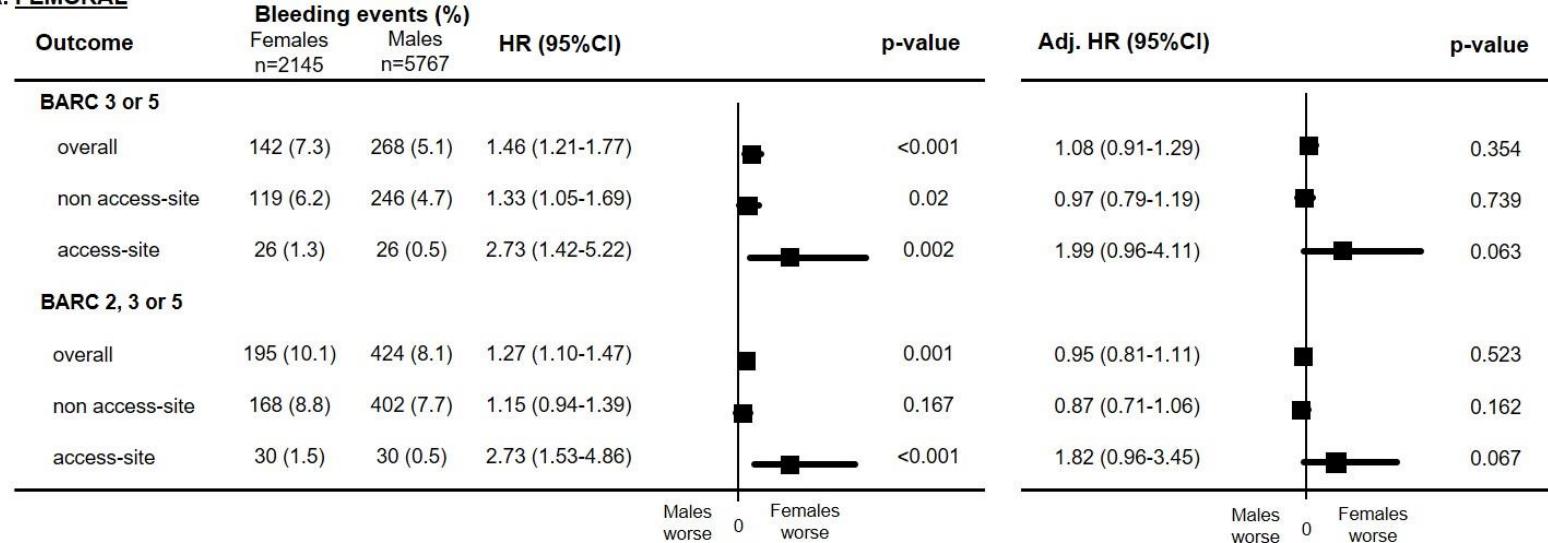
\* RCT included: EXCELLENT, OPTIMIZE, PRODIGY, RESET, SECURITY, ITALIC PLUS

† RCT included: TRITON-TIMI, PLATO, CHAMPION PCI, CHAMPION PLATFORM, TRILOGY-ACS, CHAMPION PHOENIX, PEGASUS-TIMI 54;

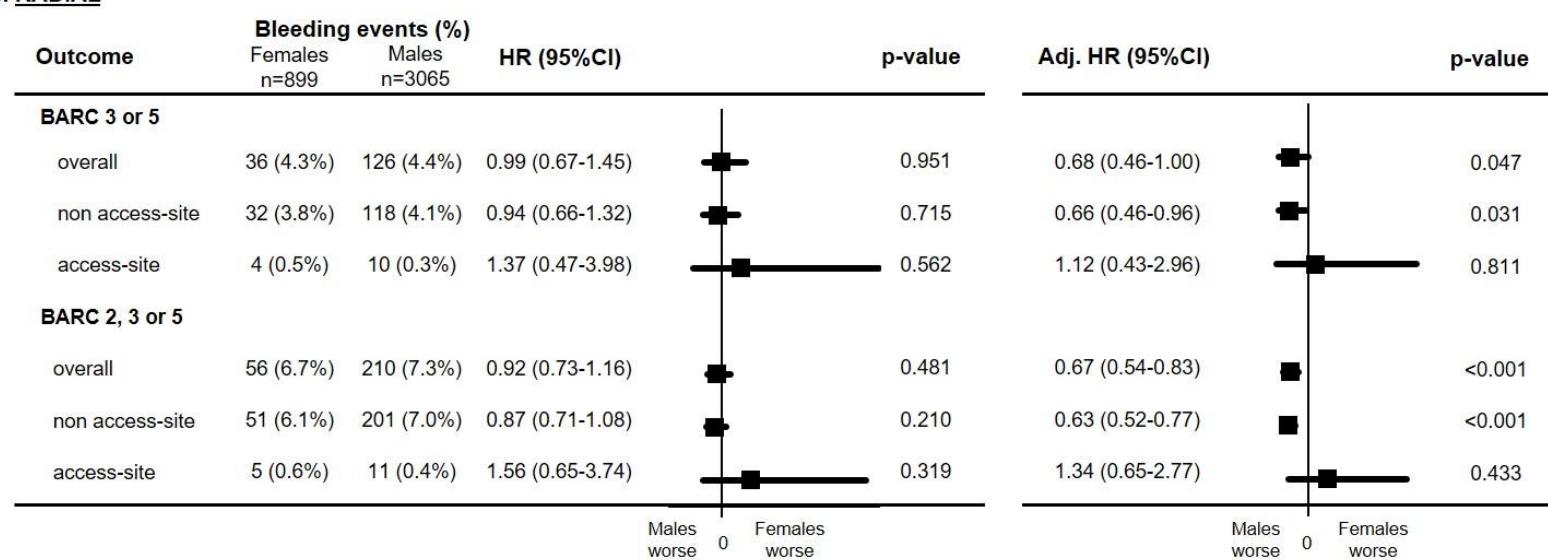
\*increased adjusted risk in male

**Figure S1.** BARC 3 or 5 bleeding at 1 year: crude rates, unadjusted and adjusted Hazard Risks (HR) in males and females in whose a femoral (A) or radial (B) access site was chosen.

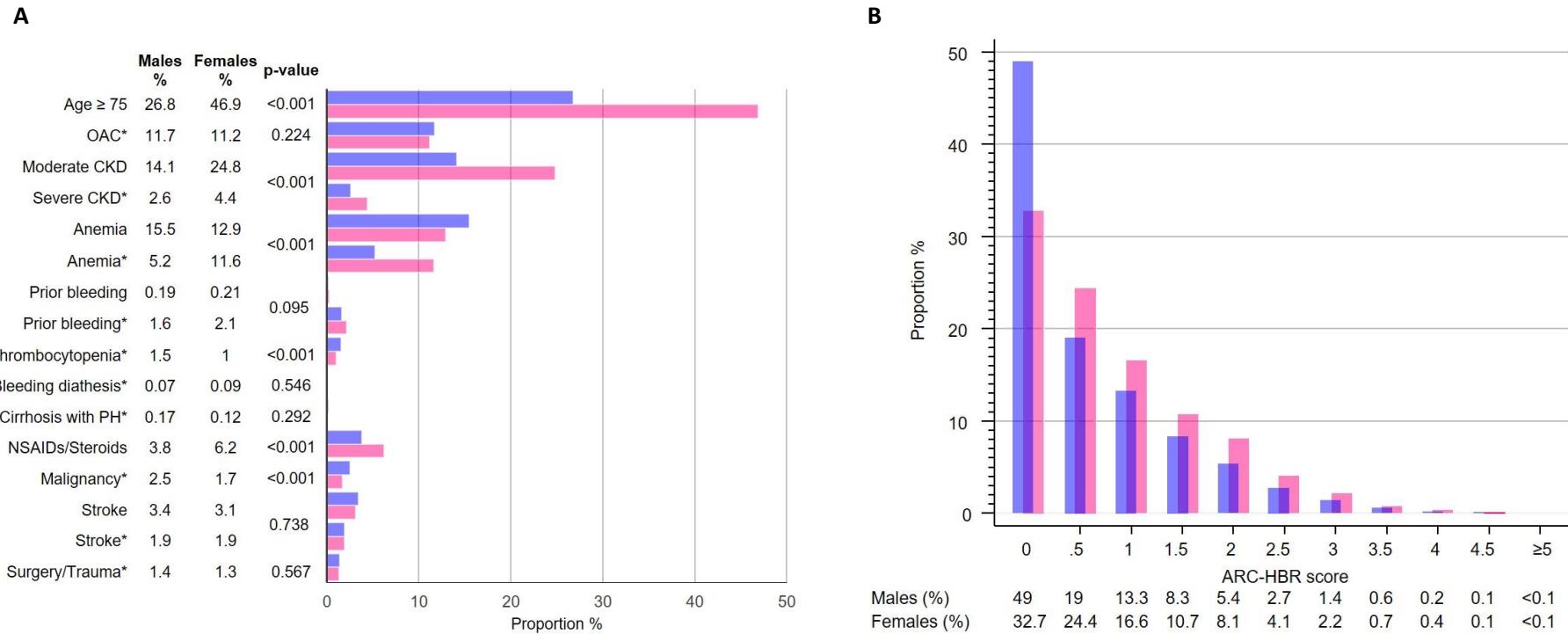
**A. FEMORAL**



**B. RADIAL**

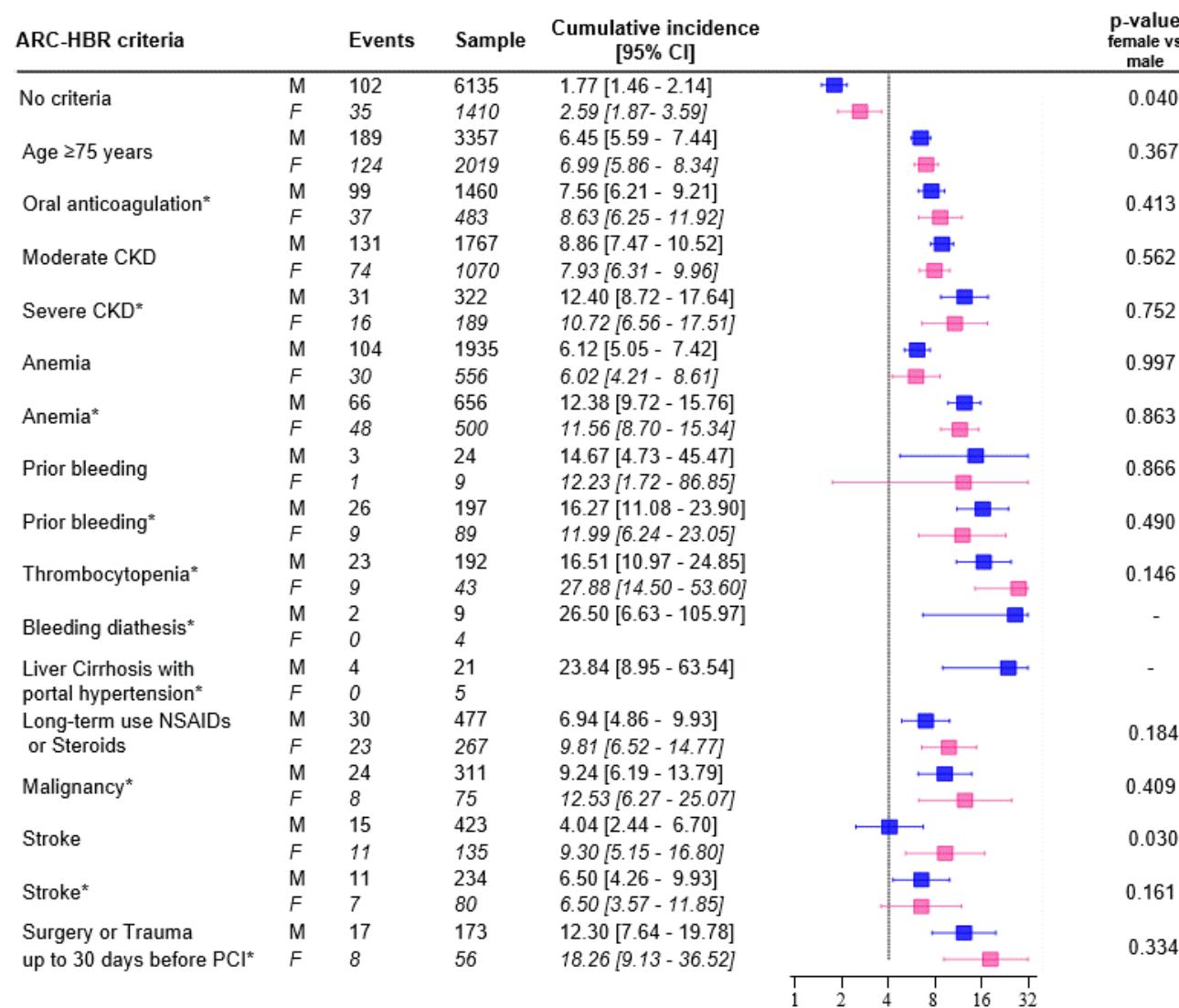


**Figure S2.** Prevalence of minor and \*major ARC-HBR criteria (A) and distribution of ARC-HBR score (B) in males (blue) and females (pink). For definition of each ARC-HBR criterion see table S1.



OAC= oral anticoagulation; CKD=Chronic Kidney Disease; PH= portal hypertension; NSAIDs= non-steroidal anti-inflammatory drugs

**Figure S3.** Unadjusted incidence of BARC 3 or 5 bleedings at 1 year for minor and \*major ARC-HBR criteria in males (blue) and females (pink).

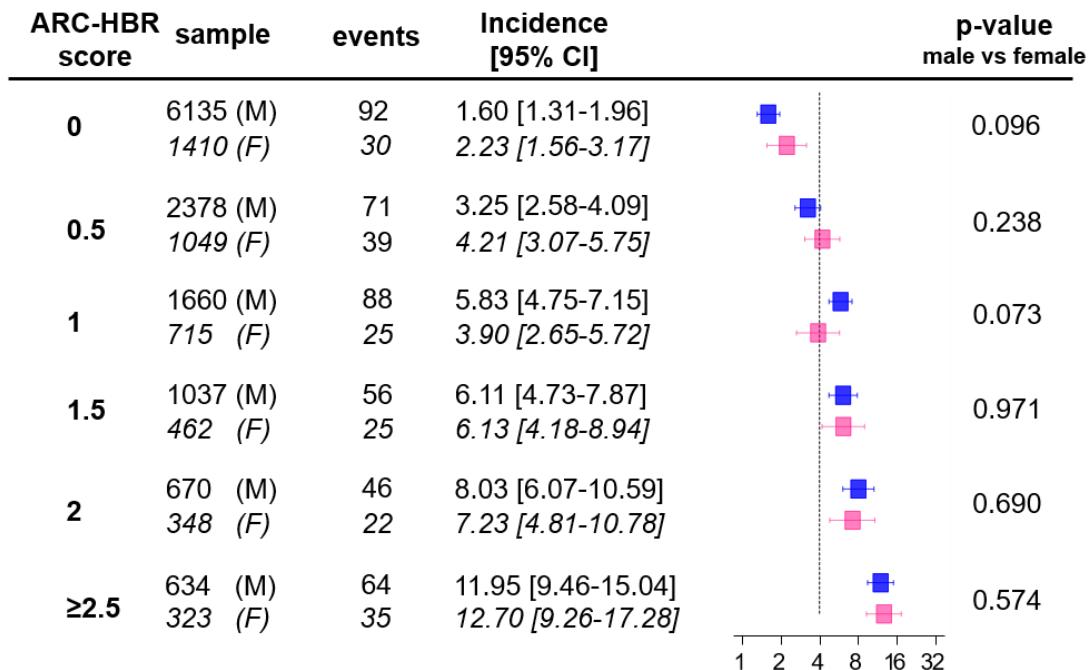


CKD=Chronic Kidney Disease; NSAIDs= non-steroidal anti-inflammatory drugs; PCI= percutaneous coronary intervention

The dotted line indicates a 4% incidence of bleeding, expected in presence of a major ARC-HBR Criterion (definition in Table S1).

**Figure S4.** Non access-site (A) and access-site (B) BARC 3 or 5 bleeding incidence at 1 year for ARC-HBR score values from 0 to  $\geq 2.5$  in males (blue) and females (pink).

**A**



**B**

