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Sex-Related Bleeding Risk in Acute Coronary Syndrome Patients Receiving Dual Antiplatelet Therapy with Aspirin and a P2Y12 Inhibitor

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Highlights of the Study

- This study found a two-fold higher risk of major bleeding in women, as compared to men, in subjects with acute coronary syndrome undergoing percutaneous coronary intervention and treated with dual antiplatelet therapy.
- This sex difference was caused mainly by an excess femoral access site bleeds in women.
- No differences in the incidence of ischemic events between women and men were found.

Keywords
Acute coronary syndrome/non ST-segment elevation myocardia infarction · Antiplatelet therapy · Bleeding · Vascular access complications · Percutaneous coronary intervention

Abstract
Objective: The aim of this work was to study sex differences in major bleeding risk in relation to dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS). ***Methods and Results:*** The Rijnmond Collective Cardiology Research registry was designed to evaluate the application and outcomes of DAPT after ACS/PCI in the Rijnmond region in the Netherlands. Overall, 1,172 women (median age 67.5 years) and 3,087 men (median age 62.2 years) with ACS/PCI were enrolled between August 2011 and June 2013. Based on a tailored regional DAPT guideline aiming at bleeding risk minimization, 52.6% women and 66.9% men received prasugrel as first-choice P2Y12 inhibitor, in addition to aspirin. Women more frequently had contraindications for the use of prasugrel (and therefore received clopidogrel) than men (47.9 vs. 26.9%, $p < 0.001$).

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Femoral access was more common in women than in men (47.6 vs. 38.1%, $p < 0.001$). Women had higher incidence of major bleeding at 1 year than men (2.6 vs. 1.6%, $p = 0.018$). After adjustment for established bleeding risk factors, female sex was associated with over two-fold higher risk of major bleeding (adjusted hazard ratio 2.33; 95% confidence interval 1.26–4.32). This difference was apparent at discharge and appeared to be caused by access site bleedings (0.9 vs. 0.1%, $p < 0.001$). No sex differences were found in non-access site-related major bleeding up to 1 year. ***Conclusion:*** Women with ACS/PCI receiving DAPT had higher major bleeding risk caused by an excess in access site bleeds, mainly in relation to the femoral approach.

Introduction

The combination of aspirin and a P2Y12 receptor antagonist is the cornerstone of modern treatment of acute coronary syndrome (ACS) [1, 2]. This so-called dual antiplatelet (DAPT) strategy is associated with reduced risk of coronary thrombosis after stent placement, albeit at the cost of increased risk of bleeding [3, 4]. Women presenting with ACS are older and have a worse cardiovascular risk profile than men [5], which predisposes women to an increased risk of thrombotic and bleeding events following invasive therapy.

Current guidelines, mainly based on randomized controlled trials (RCTs), do not provide sex-specific recommendations on the application of antithrombotic treatment [1, 2]. Previous RCTs showed no convincing evidence of sex-related differences in the efficacy and safety of currently available P2Y12 receptor antagonists [6]. Still, it should be realized that RCTs are highly selected and have a lower risk profile than real-world populations, which may limit the external validity of the RCT. Registry studies of daily life settings may provide further evidence, based on representative data with less selected patients and with a more balanced inclusion of both sexes. Against this background, we explored the prospective Rijnmond Collective Cardiology Research (CCR) registry of ACS patients in the Netherlands undergoing percutaneous coronary intervention (PCI) [7]. We studied sex disparities in bleeding complications up to 1 year after the index procedure in patients who received aspirin in combination with prasugrel or clopidogrel according to a tailored region-wide guideline, aiming at bleeding risk minimization.

Subjects and Methods

Study Design and Population

Three high-volume centers with capability for PCI and eight non-PCI hospitals in the Rijnmond region serve a population of 1.5 million. The collaborating cardiologists in the region developed a dedicated guideline for the implementation of modern DAPT in patients with non-ST-segment elevation ACS or ST-segment elevation myocardial infarction undergoing PCI, aimed at bleeding risk minimization. According to the guideline, patients were to receive aspirin and prasugrel (loading dose 60 mg, maintenance dose 10 or 5 mg daily) as first-line option for antiplatelet therapy, unless contraindicated. If any contraindications were present, clopidogrel (loading dose 600 g, maintenance dose 75 mg daily) was advised. Contraindications for prasugrel were based on results of the TIMI-TRITON 38 trial and included a history of stroke or transient ischemic attack (TIA), advanced age (≥75 years), and underweight (<60 kg) [4]. The regional guideline was intended as a working arrangement to standardize local care and practice within the context of the European Society of Cardiology (ESC) practice guideline recommendations but did not dictate treatment [8].

The CCR study is a prospective, observational registry that is designed to evaluate the management practices and outcomes of ACS/PCI patients after the introduction of the regional DAPT guideline. During August 2011 and June 2013, all patients aged 18 years or older, who were diagnosed with non-ST-segment elevation ACS or ST-segment elevation myocardial infarction, and who underwent PCI with stent placement during the index hospitalization, were enrolled.

Data Collection

Baseline patient and procedural characteristics, concomitant antithrombotic pharmacotherapy, and in-hospital outcomes were extracted from the medical charts and entered into a secure web-based and centralized database by enrolling site personnel. After the index hospitalization, patients were routinely followed up at 1 month and 12 months at the outpatient clinic, where longitudinal information on patient treatment, effectiveness, and safety outcomes was collected and entered into the central database.

Study Endpoints

The main endpoint of the present analysis was the 1-year incidence of thrombolysis in myocardial infarction (TIMI) major bleeding episodes unrelated to coronary artery bypass grafting. This included any intracranial bleeding, clinical overt signs of hemorrhage associated with a decrease in hemoglobin of ≥5 g/dL, and fatal bleeding (bleeding that directly results in death within 7 days) [9, 10]. TIMI major bleeds during the index hospitalization and at 30 days were the key secondary endpoints. We also report on (the composite of) ischemic events, including nonfatal myocardial infarction (MI), stent thrombosis, and ischemic stroke, and on (cardiac) death [9].

When a study endpoint was reached, relevant documents, including hospital discharge summaries, procedural reports, or angiographic films, were obtained. These documents were evaluated by an independent clinical event committee, which had adjudicated the endpoints reported in this study. Clinical follow-up was available for 1,111/1,172 (94.8%) women and (95.7%) men at 1 year. The follow-up of all-cause mortality, assessed using municipal civil registries, was 100% complete.

Statistical Analysis

Continuous variables are presented as both means ± standard deviation and medians with interquartile ranges. Categorical variables are presented as counts and percentages. Differences between women and men were studied by Student *T* tests (normal distribution) or Mann-Whitney tests (skewed distribution). Differences in categorical variables were studied by χ^2 tests or Fisher's exact tests in case any expected value was less than 5. The incidences of the study endpoints are reported as Kaplan-Meier estimates. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were removed from the study. Differences between women and men were evaluated using log-rank tests.

Multivariate Cox proportional hazards regression was applied to obtain an estimate of the relationship between sex and TIMI major bleed, adjusted for factors that have been related with bleeding in previous studies. We considered age, weight, diabetes, history of stroke or TIA, history of peripheral artery disease, access site, and estimated glomerular filtration rate (Cockcroft-Gault) as potential confounders. Further, we considered type of P2Y12 inhibitor as potential effect modifier (by including the sex* P2Y12 inhibitor interaction). A separate multivariable analysis was performed in non-access site-related TIMI major bleeding to control for oral anticoagulation with vitamin K antagonists and elected P2Y12 inhibitors (prasugrel vs. clopidogrel) at discharge. We report adjusted hazard ratios (aHRs) with corresponding 95% confidence intervals (CIs). A two-sided p value <0.05 was considered statistically significant. Analyses were performed using SPSS version 22 (SPSS, Inc., Chicago, IL, USA).

Results

Patient Characteristics

In total, 1,172 consecutive women and 3,087 men were registered. Women were on average 5.3 years older, had a higher prevalence of diabetes mellitus (20.2 vs. 15.7%, $p < 0.001$), hypertension (64.0 vs. 46.9%, $p < 0.001$), and a history of stroke or TIA (8.8 vs. 6.6%, $p = 0.014$), but were less often smokers (29.2 vs. 38.5%, $p < 0.001$) and less often had a history of MI (14.6 vs. 19.7%, $p < 0.001$) than men (Table 1). Fewer women than men had coronary angiography by radial access (47.3 vs. 57.0%, $p < 0.001$).

Antiplatelet Therapy

The prescription of DAPT was comparable at discharge in women and men and remained similar up to 1 year (Table 2). Women more frequently had contraindications for the use of prasugrel than men (47.9 vs. 26.9%, $p < 0.001$), and, consequently, women less often received prasugrel (52.6 vs. 66.9%, $p < 0.001$). Among the patients without contraindications, fewer women than men received prasugrel (74.0% vs. 79.4%, $p = 0.008$), whereas among those with contraindications, a similar percentage of women and men were nevertheless treated with prasugrel (23.2 vs. 23.8, $p = 0.82$).

TIMI Major Bleeding

A larger percentage of women experienced TIMI major bleeding events than men (2.6 vs. 1.6%, $p = 0.018$) up to 1-year follow-up. This difference was apparent at discharge and was mainly driven by access site bleedings (0.9 vs. 0.1%, $p < 0.001$) (Table 3; Fig. 1). In the period around the intervention, patients with a TIMI major bleeding were more often treated with clopidogrel (43.0 vs. 33.0%, $p = 0.060$) and LMWH (6.3 vs. 2.6%, $p = 0.046$), but less often with prasugrel (40.5 vs. 55.6%, $p = 0.017$). Also, they less often received aspirin (78.5 vs. 92.5%, $p < 0.001$) and any P2Y12 inhibitor (87.3 vs. 96.7%, $p < 0.001$) at discharge but more often vitamin K antagonists (17.7 vs. 8.3%, $p = 0.003$). The use of prasugrel, despite contraindications at discharge, led to a higher absolute number of bleeding events up to 1 year in women (6.2%) than in men (1.2%), although this difference did not reach statistical significance ($p = 0.15$). In patients without contraindications, women treated with prasugrel had more bleedings than men (2.0 vs. 0.8%, $p < 0.001$). We found a significant sex*P2Y12Type interaction (p value for interaction = 0.002) in multivariate analysis. Women treated with prasugrel experienced relatively more often a major bleeding within 1-year follow-up than men treated with prasugrel.

Besides sex, advanced age, current smoking, a previous history of stroke, or peripheral artery disease, a lower estimated glomerular filtration rate and coronary angiography by femoral approach instead of radial approach were associated with TIMI major bleed in our dataset. After adjustment for these potential confounders, women had more than two-fold higher risk of TIMI major bleeding at 1-year follow-up than men (aHR 2.33 and 95% CI: 1.26–4.32, $p = 0.007$). However, an increased risk in women was not observed for non-access site-related TIMI major bleeding (aHR 1.70, 95% CI: 0.83–3.48, $p = 0.139$).

Other Endpoints

We found no differences between women and men in the incidence of ischemic events, neither at discharge (1.5 vs. 1.0%, $p = 0.56$) nor at 1-year follow-up (3.3 vs. 2.9%, $p = 0.52$). All-cause mortality was 2.6 versus 2.8% ($p = 0.47$) in women and men, respectively, and remained similar (5.2 vs. 4.3%, $p = 0.20$) at 1-year follow-up.

Discussion

In this real-world registry of PCI-treated ACS patients who received APT according to a tailored region-wide guideline, and with the aspirin/P2Y12 inhibitor combination as a cornerstone, women experienced more access site

Table 1. Patient baseline characteristics according to sex

	Women (n = 1,172)	Men (n = 3,087)	p value
Risk factors and cardiovascular history			
Age, years	67.5 (12.1), 68.0 (59.0–77.0)	62.2 (12.0), 62.0 (53.0–71.0)	<0.001
Age ≥75 years	384 (32.8)	531 (17.2)	<0.001
Weight, kg[a]	73.9 (13.9), 72.0 (65.0–80.0)	86.2 (15.0), 84.0 (77.0–94.0)	<0.001
Weight <60 kg	100/908 (11.0)	35/2,438 (1.4)	<0.001
Diabetes mellitus	236/1,166 (20.2)	481/3,057 (15.7)	<0.001
Hypertension	743/1,161 (64.0)	1,420/3,029 (46.9)	<0.001
Hypercholesterolemia	431/1,143 (37.7)	1,128/3,006 (37.5)	0.91
Current smoking	332/1,138 (29.2)	1,150/2,984 (38.5)	<0.001
Family history of CAD	462/1,083 (42.7)	1,290/2,870 (44.9)	0.20
Prior MI	170/1,163 (14.6)	604/3,060 (19.7)	<0.001
Prior PCI	179/1,166 (15.4)	584/3,071 (19.0)	0.006
Prior CABG	53/1,167 (4.5)	186/3,075 (6.0)	0.057
Prior CVA or TIA	103/1,164 (8.8)	204/3,070 (6.6)	0.014
PAD	93/1,160 (8.0)	212/3,060 (6.9)	0.22
History of heart failure	38/1,161 (3.3)	124/3,063 (4.0)	0.24
eGFR, mL/min[b]	116.6 (51.6), 107.7 (81.6–142.5)	101.4 (40.1), 97.9 (74.8–123.1)	<0.001
Procedure			
Access site			
Radial access	521/1,102 (47.3)	1,682/2,950 (57.0)	<0.001
Femoral access	525/1,102 (47.6)	1,125/2,950 (38.1)	
Other	56/1,102 (5.1)	143/2,950 (4.8)	
Multivessel PCI	166/1,118 (14.8)	463/2,965 (15.6)	0.55
Hospitalization			
Time admission – PCI, days	1.8 (3.6), 0.0 (0.0–3.0)	1.7 (7.6), 0.0 (0.0–2.0)	0.076
Time admission – discharge, days	5.8 (7.0), 4.0 (3.0–7.0)	5.3 (8.7), 4.0 (3.0–6.0)	0.012
Discharge diagnosis			
STEMI	245/1,172 (20.9)	580/3,087 (18.8)	0.19
NSTEMI	436/1,172 (37.2)	1,134/3,087 (36.7)	
Unstable angina	491/1,172 (41.9)	1,373/3,087 (44.5)	

Continuous variables are presented as both means ± standard deviation (SD) and medians with interquartile ranges (IQR). Categorical variables are presented as counts and percentages. CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; TIA, transient ischemic accident; PAD, peripheral artery disease; mL, milliliter; eGFR, estimated glomerular filtration rate (calculated with Cockcroft-Gault formula); (N)STEMI, (non) ST elevation myocardial infarction. [a]Data available for 908 women and 3,346 men. [b]Data available for 852 women and 2,291 men.

TIMI major bleedings than men. However, no sex differences in bleedings were seen after the procedure until 1-year follow-up, despite differences in bleeding risk factors. Thus, while applying our tailored bleeding risk minimization strategy, the prolonged use of DAPT appears equally safe in women and men. Importantly, no differences were observed in ischemia-related endpoints between women and men, whereas event rates were low overall.

Previous registries and RCTs report incidences of major bleeding across the broad spectrum of ACS, which range from 1.8 to 6.1% [4, 11–15]. Hence, the observed incidence of major bleeding in our region (according to the TIMI definition) was at the lower end of the spectrum. The Rotterdam/Rijnmond APT guideline aimed at intensive platelet inhibition by the P2Y12 inhibitor prasugrel in patients with a supposedly low bleeding risk, and a less intensive inhibition (by clopidogrel) in their counterparts with high-risk features, as revealed by the TIMI-TRITON 38 investigators [4]. Apparently, that strategy of selective prescription, which was also observed in recent registries [16, 17] although not in relation to a specific guideline, has been successful.

Table 2. Medication according to sex

	Women (n = 1,172)	Men (n = 3,087)	*p* value
Medication peri-/postprocedural			
Aspirin	950/1,118 (85.0)	2,619/2,965 (88.3)	0.004
P2Y12 inhibitor	967/1,118 (86.5)	2,647/2,965 (89.3)	0.012
Clopidogrel	439/1,118 (39.3)	915/2,965 (30.9)	<0.001
Prasugrel	528/1,118 (47.2)	1,732/2,965 (58.4)	<0.001
GP IIb/IIIa inhibitor	119/1,118 (10.6)	468/2,965 (15.8)	<0.001
LMWH	39/1,118 (3.5)	72/2,965 (2.4)	0.063
Medication at discharge			
Aspirin	1,072/1,172 (91.5)	2,857/3,087 (92.5)	0.24
P2Y12 inhibitor	1,126/1,172 (96.1)	2,985/3,087 (96.7)	0.32
Clopidogrel	508/1,172 (43.3)	912/3,087 (29.5)	<0.001
Prasugrel	617/1,172 (52.6)	2,065/3,087 (66.9)	<0.001
Prasugrel dose			
5 mg	80/617 (13.0)	102/2,065 (4.9)	<0.001
10 mg	537/617 (87.0)	1,963/2,065 (95.1)	
Ticagrelor	1/1,172 (0.1)	8/3,087 (0.3)	0.27
Vitamin K antagonist	111/1,172 (9.5)	248/3,087 (8.0)	0.13
Triple therapy[a]	59/1,172 (5.0)	134/3,087 (4.3)	0.33
Medication 1-year follow-up			
Aspirin	927/1,057 (87.7)	2,420/2,739 (88.4)	0.58
P2Y12 inhibitor	844/1,057 (79.8)	2,220/2,739 (81.1)	0.40
Clopidogrel	399/1,057 (37.7)	694/2,739 (25.3)	<0.001
Prasugrel	443/1,057 (41.9)	1,514/2,739 (55.3)	<0.001
Prasugrel dose			
5 mg	47/443 (10.6)	59/1,514 (4.0)	<0.001
10 mg	396/443 (89.4)	1,455/1,514 (96.1)	
Ticagrelor	2/1,057 (0.2)	12/2,739 (0.4)	0.26
Vitamin K antagonist	114/1,057 (10.8)	261/2,739 (9.5)	0.25
Triple therapy[a]	32/1,057 (3.0)	63/2,739 (2.3)	0.20

Categorical variables are presented as counts and percentages. GP, glycoprotein; LMWH, low-molecular-weight heparin; mg, milligram. [a]The combination of aspirin, a P2Y12 inhibitor, and vitamin K antagonist.

Despite the low overall incidence, women experienced more bleeds than men. This observation is in agreement with other studies (registries as well as clinical trials) in patients with ACS [11, 18, 19] and has been explained by their higher age and prevalence of other risk factors for bleeding. However, that explanation is not fully sufficient, as we still revealed sex as a risk determinant after adjustment for these factors. In this respect, it is relevant to note that the excess in bleeding complications in women was driven by access site bleeds. Indeed, higher numbers of access site bleedings in women than in men have been reported repeatedly [20, 21]. A study by Pandie et al. [22] showed that major vascular complications were significantly reduced by the radial approach compared with the femoral approach, regardless of whether PCI was performed. This favorable effect was observed in both genders and was even more prominent in women [22]. However, the radial arteries of females are smaller and more vulnerable to spasm, which adds to operative difficulty and may undermine the efficacy of transradial PCI. As a result, the transradial approach is paradoxically low in women. Also, in our registry, women were more often treated via the femoral approach than men, probably because of failed access or because the operator feared arterial spasm and wanted to avoid access site crossover; the exact reason was not documented [23]. Nevertheless, our findings suggest that radial access must be considered the first option even in women, if technically possible. Recent guidelines also recommend radial access over femoral access for coronary angiography and PCI if performed by an experienced radial operator [1, 2].

Inappropriate dosing of antithrombotic drugs is a risk factor for bleeding. Alexander et al. [24] demonstrated

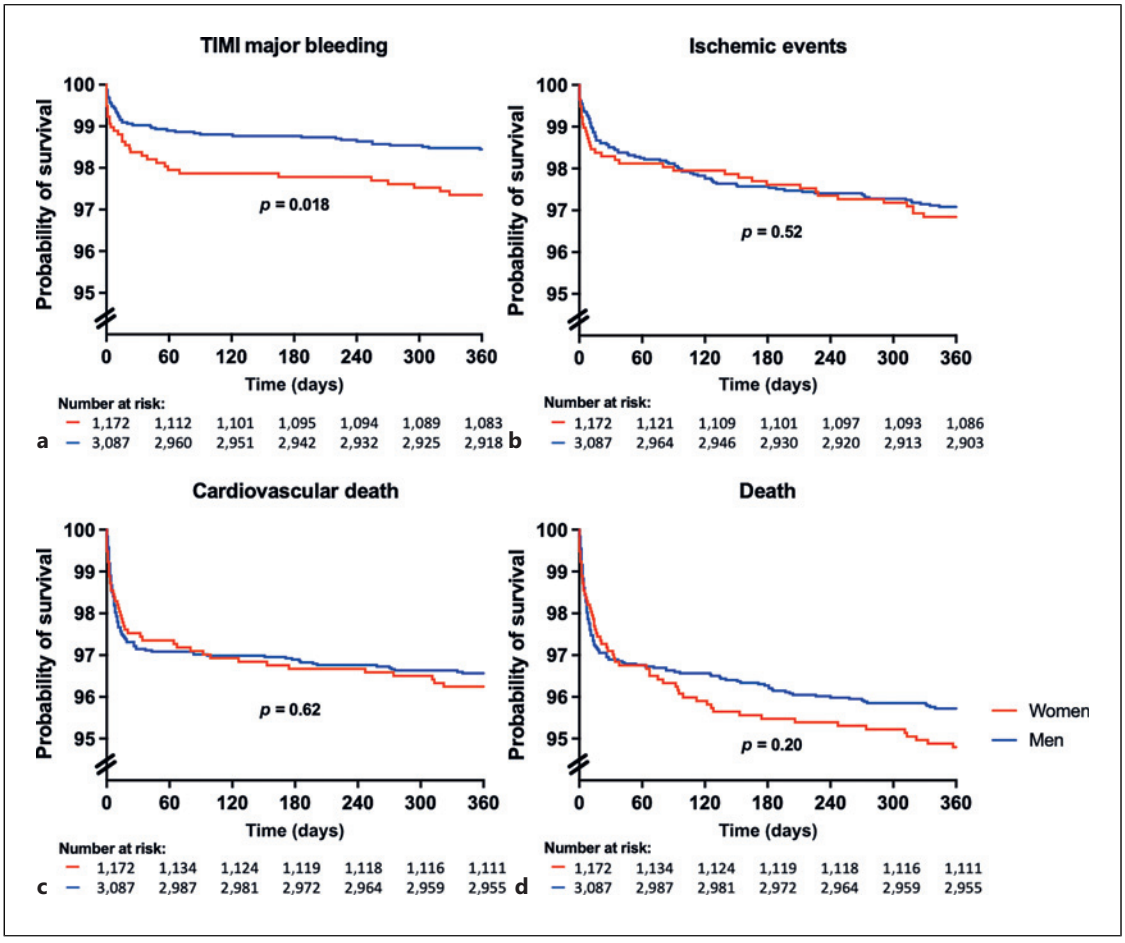
Table 3. TIMI major bleeding and secondary outcomes according to sex

	Women (n = 1,172)	Men (n = 3,087)	*p* value[a]
Outcome at discharge			
TIMI major bleeding	16 (1.4)	21 (0.7)	0.057
Bleeding class			
Access site bleeding	7 (0.6)	3 (0.1)	0.006
GI bleeding	2 (0.2)	5 (0.2)	0.98
Intracranial bleeding	0 (0.0)	3 (0.1)	0.27
Other bleeding	7 (0.6)	10 (0.3)	0.25
Combined ischemic endpoint[b]	17 (1.5)	32 (1.0)	0.56
MI	5 (0.4)	17 (0.6)	0.48
CV death	26 (2.2)	79 (2.6)	0.30
Death	31 (2.6)	87 (2.8)	0.47
Outcome at 30 days			
TIMI major bleeding	19 (1.6)	30 (1.0)	0.075
Bleeding class			
Access site bleeding	8 (0.7)	4 (0.1)	0.002
GI bleeding	3 (0.3)	9 (0.3)	0.85
Intracranial bleeding	1 (0.1)	6 (0.2)	0.43
Other bleeding	7 (0.6)	11 (0.4)	0.28
Combined ischemic endpoint[b]	20 (1.7)	46 (1.5)	0.61
MI	6 (0.5)	23 (0.7)	0.41
CV death	29 (2.5)	88 (2.9)	0.51
Death	35 (3.0)	96 (3.1)	0.84
Outcome at 1 year			
TIMI major bleeding	31 (2.6)	48 (1.6)	0.018
Bleeding class			
Access site bleeding	11 (0.9)	4 (0.1)	<0.001
GI bleeding	5 (0.4)	16 (0.5)	0.70
Intracranial bleeding	3 (0.3)	13 (0.4)	0.43
Other bleeding[c]	12 (1.0)	15 (0.5)	0.048
Combined ischemic endpoint[b]	39 (3.3)	91 (2.9)	0.52
MI	13 (1.1)	55 (1.8)	0.12
CV death	44 (3.8)	106 (3.4)	0.62
Death	61 (5.2)	132 (4.3)	0.20

Categorical variables are presented as counts and percentages. TIMI, thrombolysis in myocardial infarction; GI, gastrointestinal; CV, cardiovascular. [a]Kaplan-Meier estimates, log-rank (Mantel-Cox). [b]Composite of myocardial infarction, stent thrombosis, and ischemic stroke. [c]Other bleedings included pericardial effusion (n = 9), post-traumatic bleeding (including post-resuscitation [n = 3]), postoperative bleeding (n = 2), epistaxis (n = 1), spleen bleeding (n = 1), bleeding due to dislocation of wire (n = 1), or bleedings with unknown origin (n = 10).

that women – who generally have lower body volume – are more likely to receive excess doses than men. If dosage reduction is possible without nullifying the anti-ischemic effect, bleeding risk complications around the procedure in women might be prevented. Currently, there are no randomized trials that implemented sex-based dosage recommendations. The tailored CCR guideline recommended clopidogrel or low-dose prasugrel (5 mg) in patients with body weight <60 kg. We found no relation between body weight and bleeding risk, neither in men nor in women. Apparently, the weight criterion is appropriate and needs no modification.

Despite the absence of contraindications, women were treated less often with the more potent prasugrel. This is in line with findings of the START ANTIPLATELET registry which also showed that P2Y12 inhibitor choice is influenced by sex [25]. The reason for the lower prescription in our study is unclear. A higher bleeding risk in women in relation



Color version available online

Fig. 1. Outcome at 1-year follow-up according to sex. Kaplan-Meier event-free survival estimates for various endpoints in women (red) and men (blue). *p* values are based on log-rank tests.

to P2Y12 inhibitor treatment has been reported earlier in a meta-analysis by Lau et al. [26], and one might speculate therefore that medical doctors are somewhat reluctant to prescribe DAPT in women. On the other hand, it is equally important to protect women from ischemic complications, and the same meta-analysis described comparable protective effects of P2Y12 inhibitors with regard to ischemic events in women and men. Careful selection of women might lead to lower ischemic risks in women than in men when using more potent P2Y12 inhibitors, without the risk of increased bleeding. This hypothesis cannot be confirmed with currently available studies as many studies have several limitations for a fair comparison. A sex-specific analysis of the ISAR-REACT 5 trial showed a superior efficacy of prasugrel with respect to MI and a composite endpoint of ischemic events in men than in women [27]. However, these differences were explained by the underrepresentation of women in the study and the lower number of women who underwent PCI because of non-obstructive CAD and resulting in a lower prescription of prasugrel at discharge. Other studies also found lower risk reduction percentages for clopidogrel and prasugrel in women compared to men but should be carefully interpreted in te light of limitations in these studies [28, 29].

While the CCR registry was successful in monitoring the application of an APT treatment guideline in a broad range of practices within the Rotterdam/Rijnmond region, in the Netherlands, the registry has some limitations with respect to the current analysis. First, although encouraging from patient's point of view, the low bleeding rates resulted in insufficient statistical power to control the sex-bleeding relation for a broad range of clinicopathological variables. Consequently, residual confounding might be present. Second, cause and timing of bleeding are important components of the TIMI definition but in practice can be rather vague. For example, we found some cases with a decrease in hemoglobin but

without clinically overt signs. Third, we have insufficient data to analyze the effect of inappropriate dosing of antithrombotic drugs in our study. This data might not accurately reflect contemporary practice in other countries, as this registry was conducted in 2011–2013 in only one country, and the practice has likely changed over time (e.g., use of anticoagulants and invasive management) and is different across countries.

Conclusion

The higher TIMI major bleeding risk in women with ACS/PCI receiving aspirin/P2Y12 inhibitor-based DAPT was largely caused by an excess in access site bleeds. Women were more often treated via the femoral artery, and bleeds are thus more common. Hence, our registry confirms that the access site in women with ACS who need PCI under DAPT should be carefully considered. Our registry also showed that, if implemented according to a tailored strategy, prolonged DAPT will result in similarly low rates of ischemic and bleeding events in women and men.

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Statement of Ethics

Patients were not subjected to acts or be imposed to any mode of behavior, other than their regular treatment. Therefore, according to Dutch law, written informed consent was not required. This study was conducted according to the Privacy Policy of the Erasmus MC and according to the Erasmus MC regulations for the appropriate use of data in patient-oriented research and is approved by the Regional Ethics Committee (reference # MEC-2010-417).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Robert-Jan van Geuns, Marc van der Linden, Pieter Smits, Arie de Vries, Tuncay Yetgin, and Eric Boersma designed the original CCR study. Monique ten Haaf analyzed and interpreted the data and drafted the manuscript. Eric Boersma analyzed and interpreted the data. Pieter Doevendans and Yolande Appelman interpreted the data. All authors read, reviewed, and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from E. Boersma in the Erasmus MC.

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