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REVIEW

Sex Differences in Bleeding Risk Associated With Antithrombotic Therapy Following Percutaneous Coronary Intervention

Yoshimi Numao, MD; Saeko Takahashi, MD; Yoko M Nakao, MD, PhD, MScEpi; Emi Tajima, MD, PhD; Satsuki Noma, MD, PhD; Ayaka Endo, MD, PhD; Junko Honye, MD, PhD; Yayoi Tsukada, MD, PhD, FJCS

Background: Antithrombotic therapy is crucial for secondary prevention of cardiovascular disease (CVD), but women with CVD may face increased bleeding complications post-percutaneous coronary intervention (PCI) under antithrombotic therapy. However, women are often underrepresented in clinical trials in this field, so evidence for sex-specific recommendations is lacking.

Methods and Results: A search on PubMed was conducted for English-language articles addressing bleeding complications and antithrombotic therapy in women. Despite women potentially showing higher baseline platelet responsiveness than men, the clinical implications remain unclear. Concerning antiplatelet therapy post-PCI, although women have an elevated bleeding risk in the acute phase, no sex differences were observed in the chronic phase. However, women require specific considerations for factors such as age, renal function, and weight when determining the dose and duration of antiplatelet therapy. Regarding anticoagulation post-PCI, direct oral anticoagulants may pose a lower bleeding risk in women compared with warfarin. Concerning triple antithrombotic therapy (TAT) post-PCI for patients with atrial fibrillation, there is a lack of evidence on whether sex differences should be considered in the duration and regimen of TAT.

Conclusions: Recent findings on sex differences in post-PCI bleeding complications did not provide enough evidence to recommend specific therapies for women. Further studies are needed to address this gap and recommend optimal antithrombotic therapy post-PCI for women.

Key Words: Anticoagulants; Antiplatelet therapy; Cardiovascular disease; Percutaneous coronary intervention (PCI); Sex

It is well-established that antithrombotic therapy post-percutaneous coronary intervention (PCI) plays a crucial role in the secondary prevention of cardiovascular disease (CVD).[1–3] However, there is a concern about the potentially higher risk of bleeding among women with CVD under antithrombotic therapy.

Although large randomized controlled trials (RCTs) have investigated the efficacy and safety of various antithrombotic agents in CVD patients, women are underrepresented in those trials, constituting only around a maximum 30%.[4] The factors contributing to this underrepresentation include (1) women's reluctance to participate in clinical trials due to a more serious perception of a greater risk of harm from trial participation and potentially lower socioeconomic status compared with men,[5,6] (2) the presence of specific exclusion criteria, such as older age and childbearing potential,[4] and (3) potential researchers bias, leading to the exclusion of women with CVD in trials due to atypical pathology, comorbidities, and older age.

While numerous studies exploring sex differences in bleeding complications and clinical outcomes after PCI, there is a shortage of comprehensive and consistent data on the impact of antithrombotic agents on women.

Consequently, current guidelines predominantly rely on data derived from men, resulting in a lack of sex-specific recommendations for the use of antithrombotic agents.[1–3] The causes of acute and chronic bleeding after PCI may vary between the sexes,[7,8] and there is limited in-depth

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Department of Cardiology, Itabashi Chuo Medical Center, Tokyo (Y.N.); Department of Cardiology, Shonan Oiso Hospital, Kanagawa (S.T.); Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto (Y.M.N.); Department of Cardiology, Tokyo General Hospital, Tokyo (E.T.); Department of Cardiovascular Medicine (S.N.), Department of General Medicine and Health Science (Y.T.), Nippon Medical School, Tokyo; Department of Cardiology, Tokyo Saiseikai Central Hospital, Tokyo (A.E.); and Cardiovascular Center, Kikuna Memorial Hospital, Kanagawa (J.H.), Japan
Mailing address: Yoshimi Numao, MD, Department of Cardiology, Itabashi Chuo Medical Center, 2-12-7 Azusawa, Itabashi-ku, Tokyo 174-0051, Japan. email: y-numao@umin.ac.jp

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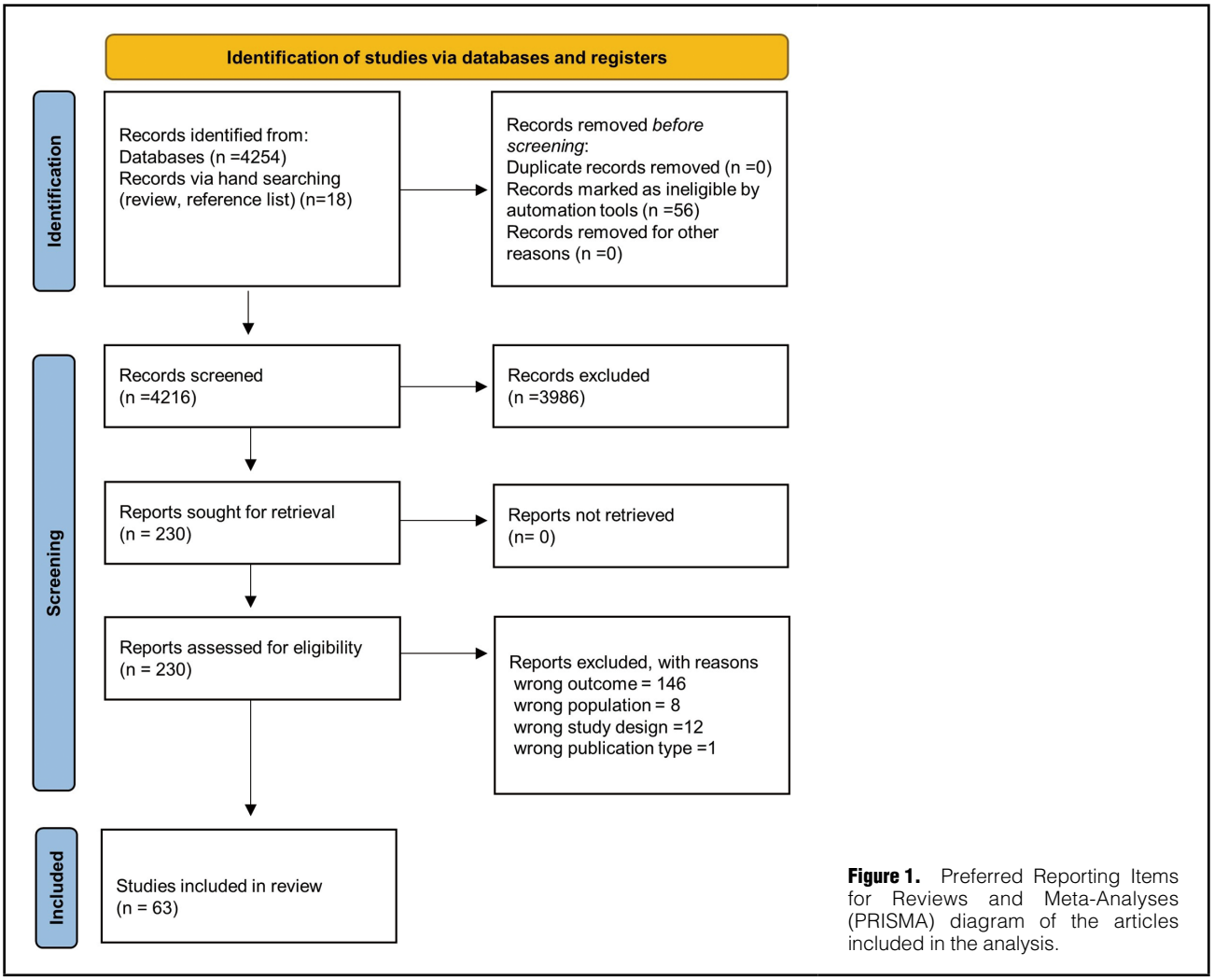

Figure 1. Preferred Reporting Items for Reviews and Meta-Analyses (PRISMA) diagram of the articles included in the analysis.

discussion on whether bleeding complications after PCI are genuinely more prevalent in women.

In this review, our objective was to analyze the clinical evidence concerning potential bleeding risks based on sex, and identify discrepancies in indications for oral antithrombotic therapy.

Methods

This review paper is based on a comprehensive review of available studies and **Figure 1** demonstrates the selection process. We performed English-language searches in PubMed for the period January 1, 2010, to November 3, 2022 using the following keywords: percutaneous coronary intervention, acute coronary syndrome, myocardial infarction, clopidogrel, prasugrel, ticagrelor, dabigatran, edoxaban, apixaban, rivaroxaban, sex, female, bleed and hemorrhage (**Supplementary Appendix 1**, **Supplementary Table**). After identifying all articles, we then reviewed the references from appropriate articles to identify additional references for this review. One investigator (Y.N.) screened titles and abstracts for all articles and identified studies as potentially appropriate for inclusion. We subsequently reviewed the full text of these studies to make a final decision on their appropriateness for inclusion.

Results

Platelet Reactivity

A total of 7 studies identified disparities in platelet reactivity between the sexes.[9–15] Women are considered to have higher baseline platelet counts, increased fibrinogen binding to platelets, and more pronounced activation through interactions with adenosine 5′-diphosphate, collagen, and other mediators.[16–18] Additionally, women exhibit higher levels of inflammatory markers, including C-reactive protein, leukocyte count, and P-selectin expression, together with elevated concentrations of membrane microparticles actively participating in inflammatory processes.[17] These findings suggest women show higher platelet reactivity, given the crucial role of activated platelets in mediating the inflammatory response.[16] However, in a prospective study evaluating sex differences in platelet activity in patients administered 3 platelet inhibitors, women had a higher rate of in-hospital bleeding complications compared with men, but there were no differences in platelet aggregation using the 3 different agonists, reflecting the treatment effects of GPIIb/IIIa inhibitors, clopidogrel, and aspirin.[19] The results were similar in both the acute and chronic phases.

Although an association between high platelet reactivity (HTPR) during antiplatelet therapy and increased risk of

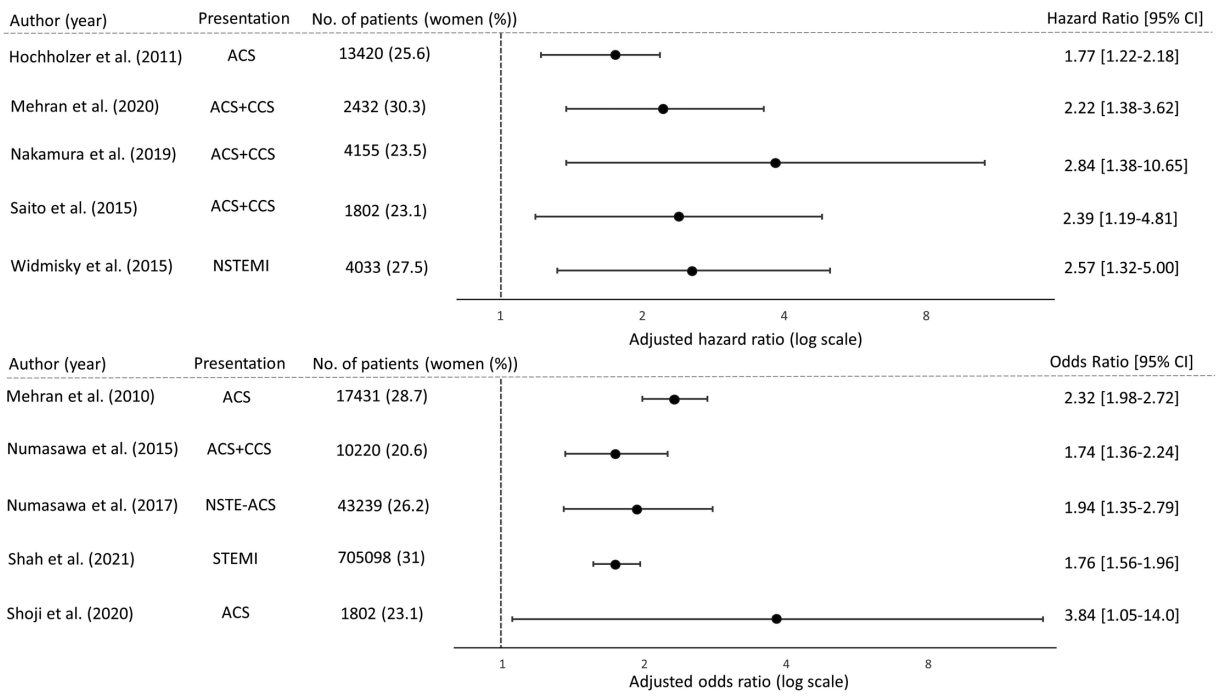

Figure 2. Sex-based differences in acute-phase bleeding post-PCI under antithrombotic therapy. Forest plots show that female sex is an independent risk factor in acute-phase bleeding after PCI under antithrombotic therapy. Horizontal lines represent 95% confidence intervals (CI) and circles represent hazard ratios or odds ratios. ACS, acute coronary syndrome; CCS, chronic coronary syndrome; NSTE-ACS, non-ST-elevation-acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

ischemic events such as cardiovascular death, nonfatal myocardial infarction, stent thrombosis, and ischemic stroke has been observed,[20–22] conflicting reports exist regarding the association between HTPR during antiplatelet therapy and sex. A total of 3 reports showed that HTPR during antiplatelet therapy tended to be more pronounced in women,[11,12,15] but 4 studies showed comparable platelet reactivity to aspirin and P2Y12 inhibitors during dual antiplatelet therapy (DAPT) after PCI.[19,23–25] In addition, a meta-analysis evaluating sex differences in the cardiovascular efficacy of clopidogrel showed no sex differences in either platelet reactivity or therapeutic efficacy.[26,27]

Taken together, the findings suggest platelet reactivity at baseline is higher in women than in men, but conflicting data have been reported regarding platelet reactivity to aspirin and P2Y12 inhibitors, and the clinical effect of sex differences in platelet reactivity is still inconclusive.[9] Additional research is needed to determine whether sex differences in platelet reactivity can be alleviated with novel antiplatelet agents or dosage adjustments, and whether these interventions indeed have an obvious effect on clinically significant outcomes.

Bleeding Risk in Women With Antiplatelet Therapy

The occurrence of bleeding following PCI under antiplatelet therapy should be evaluated in both the acute and chronic phases. Furthermore, the assessment of risk is refined based on the presence of acute coronary syndrome (ACS) and chronic coronary syndrome (CCS). Research from Europe and the USA has identified women as having a higher risk of in-hospital and short-term bleeding after PCI among patients with ACS (hazard ratio [HR]=1.77–2.57) (**Figure 2**).[28–32] Several studies conducted in Japan, including the PRASFIT-ACS trial,[33] PRASFIT-Practice I and II,[34,35] JCD-KiCS registry,[36] and J-PCI registry,[37] have further supported these findings: women exhibited an increased risk of acute bleeding after PCI for ACS (odds ratio [OR]=1.94–3.84) (**Figure 2**). This sex-related risk extends beyond ACS patients, as observed in a subanalysis of the LEADERS FREE trial,[7] PRASFIT-Practice II[38] and JCD[39] involving CCS patients (HR=2.22 and OR=1.74–3.84) (**Figure 2**). The main factor contributing to the elevated rate of bleeding in women in the acute phase after PCI for both ACS and CCS is bleeding at the vascular puncture site. The rate of bleeding varies according to the puncture site. Transradial intervention (TRI) reduced bleeding events by up to one-third compared with transfemoral intervention (TFI) in both men and women.[7,33,39–41]

In contrast, during the chronic phase following PCI, the majority of the studies conducted outside of Japan[7,29,42–56] did not identify women as a significant risk factor for bleeding complications in either ACS or CCS patients. Despite East Asians being considered to have an elevated tendency for antiplatelet-induced bleeding, women were also not an independent bleeding factor in the chronic phase in the Korean KAMIR-NIH study[52] of both post ACS and CCS patients. Similarly the Japanese PRASFIT-Practice II study revealed that women were not an independent risk factor for bleeding after 31 days within tan observation period of 1 year.[35] The CREDO-Kyoto throm-

Table. Sex Differences During (A) Acute Phase and (B) Chronic Phase in Bleeding Complications Post-PCI

(A) Authors, year, country	Name of study	Total patients	No. of women (%)	Presentation	Topics	Bleeding outcome	Female sex as an independent risk factor of bleeding	OR or HR [95% CI]
Hochholzer et al (2011) Multi-country[29]	TRITON-TIMI 38	13,420	25.6	ACS	Prasugrel (60 mg LD, 10 mg/day maintenance dose) vs. clopidogrel (300 mg LD, 75 mg/day maintenance dose)	TIMI major or minor bleeding (instrumented, traumatic and spontaneous) in hospital period and the follow-up period of the trial (6–15 months)	Yes	HR 1.77 [1.22–2.18]* *Majority (73%) of serious bleeding events occurred within the first 3 days
Hess et al (2014) USA[†1]	TRANSLATE-ACS	6,218	27.5	STEMI or NSTEMI	ADP-receptor inhibitor within the first 12 months after AMI	1-year risk of bleeding according to GUSTO and BARC definitions including patient-reported bleeding not brought to clinical attention	Yes	GUSTO; HR 1.32 [1.06–1.64]* GUSTO moderate or severe; HR 1.63 [1.19–2.24]* *Majority of GUSTO bleeding events observed early after PCI
Mehran et al (2010) Multi-country[30]	ACUITY + HORIZONS-AMI	17,421	28.7	ACS	Development of a practical risk score to predict the major bleeding	Non-CABG related major bleeding within 30 days	Yes	OR 2.32 [1.98–2.72]
Mehran et al (2020) Multi-country[7]	LEADERS FREE	2,432	30.3	ACS+CCS	BMS vs. polymer-free, biolimus A9-eluting drug-coated stent with 1-month DAPT	BARC 3 to 5 major bleeding within 30 days and 60 days	Yes	HR 2.22 [1.38–3.62] within 30 days HR 2.22 [1.42–3.47] within 60 days
						Vascular access site major bleeding	Yes	Unadjusted HR 4.65 [1.99–10.87]
Nakamura et al (2018) Japan[34]	PRASFIT-Practice I	732	23.5	ACS	Low-dose prasugrel (LD/maintenance dose, 20/3.75 mg) vs. standard-dose clopidogrel administration	TIMI major and minor bleeding (64.9±73.8 days)	Yes	NR
Nakamura et al (2019) Japan[35]	PRASFIT-Practice II	4,155	23.5	ACS+CCS	Low-dose prasugrel (LD/maintenance dose, 20/3.75 mg) vs. standard-dose clopidogrel administration	TIMI major or minor bleeding within 30 days	Yes	HR 3.84 [1.38–10.65]
Numasawa et al (2015) Japan[39]	JCD	10,220	20.6	ACS+CCS	Examination of sex differences in in-hospital clinical outcomes after PCI	Those requiring blood transfusion, prolonged hospital stay, or showing a decrease in hemoglobin >3.0 g/dL	Yes	OR 1.74 [1.36–2.24]
Numasawa et al (2017) Japan[37]	Japanese Nationwide Registry	43,239	26.2	NSTE-ACS	Investigation of sex-related differences in patients with NSTE-ACS who underwent PCI	In-hospital bleeding (requiring blood transfusion, including access-site and non-access-site bleeding)	Yes	OR 1.94 [1.35–2.79]
Ohya et al (2018) Japan[59]	Single-center cohort	992	25	ACS	Very low maintenance dose of prasugrel 2.5 mg in HBR patients vs. low dose 3.5 mg	In-hospital BARC 3 and 5 major bleeding	No	NR

(**Table** continued the next page.)

(A) Authors, year, country	Name of study	Total patients	No. of women (%)	Presentation	Topics	Bleeding outcome	Female sex as an independent risk factor of bleeding	OR or HR [95% CI]
Saito et al (2015) Japan[33]	PRASFIT Trial	1,802	25.3	ACS+CCS	Low-dose prasugrel (LD/maintenance dose, 20/3.75 mg) vs. standard-dose clopidogrel administration	Periprocedural TIMI major and minor bleeding within 3 days	Yes (ACS)	HR 2.39 [1.19–4.81]
						Periprocedural TIMI major and minor bleeding within 3 days	No (Elective)	NR
Shah et al (2021) Multi-country[31]	Global meta-analysis of 56 studies	705,098	31	STEMI	Evaluation of sex-based discrepancies in clinical outcomes and identifying primary driving factors	Definition varied by study, generally included bleeding requiring transfusion or repeat procedure	Yes	OR 1.74 [1.56–1.96]
Shoji et al (2020) Japan[36]	JCD-KiCS registry	1,802	23.1	ACS	Low-dose prasugrel vs. standard-dose clopidogrel administration	TIMI major or minor bleeding within 72 h after PCI	Yes	OR 3.84 [1.05–14.0]
Simonsson et al (2019) Sweden[32]	SWEDEHEART registry	97,597	35.1	ACS	Development and validation of a new in-hospital bleeding risk score	In-hospital non-CABG major bleeding defined as fatal, intracranial or bleeding requiring blood transfusion or surgery (including endoscopic and vascular intervention)	Yes	NR
Venetsanos et al (2017)[†2] Multi-country	ATLANTIC trial	1,862	20	STEMI	Prehospital vs. in-hospital administration of 180 mg ticagrelor	TIMI or BARC bleeding at 30 days	No	TIMI major; HR 1.28 [0.47–3.48] BARC type 3–5; HR 1.45 [0.72–2.91]
Widimsky et al (2015) Multi-country[28]	ACCOAST	4,033	27.5	NSTEMI	(A) 30 mg prasugrel LD followed by CAG with an additional 30 mg prasugrel at the time of PCI or (B) placebo LD followed by 60 mg prasugrel at the time of PCI	TIMI major bleeding through 7 days	Yes	HR 2.57 [1.32–5.00]

(B) Authors, year, country	Name of study	Total patients	No. of women (%)	Presentation	Topics	Bleeding outcome	Female sex as an independent risk factor of bleeding
Baber et al (2016) USA and Europe[50]	PARIS (External validation of each score was performed in the ADAPT-DES registry)	4,190	25.5	ACS+CCS	Development of risk scores of major bleeding	BARC 2 or 5 bleeding within 2 years	No
Chichareon et al (2020) Multi-country[45]	GLOBAL LEADERS	15,968	23.3	ACS+CCS	1-month DAPT+23-month ticagrelor monotherapy vs. 12-month DAPT+12-month aspirin monotherapy after PCI	BARC 3 or 5 bleeding at 1 year and 2 years	No
Généreux et al (2015) USA and Europe[55]	ADAPT-DES	8,582	25.9	ACS+CCS	Incidence, predictors, and prognostic impact of post-discharge bleeding after PCI with DES	TIMI major or minor bleed; GUSTO severe or moderate bleed; ACUITY major bleed at (<30 days), late (30 days to <1 year), or very late (1–2 years)	No

(**Table** continued the next page.)

(B) Authors, year, country	Name of study	Total patients	No. of women (%)	Presentation	Topics	Bleeding outcome	Female sex as an independent risk factor of bleeding
Grodecki et al (2018) Multi-country[47]	BleeMACS	13,727	23	ACS	Post-discharge bleeding among patients on DAPT after ACS	In-hospital bleeding defined as any TIMI major or minor bleeding, or any GUSTO moderate or severe bleeding, or any BARC 3 bleeding	No
Hess et al (2014)[†1] US	TRANSLATE-ACS	6,218	27.5	STEMI or NSTEMI	ADP-receptor inhibitor within the first 12 months after AMI	1-year risk of bleeding according to GUSTO and BARC definitions including patient-reported bleeding not brought to clinical attention	Yes BARC 1; IRR 1.42 [1.26–1.70] BARC 2; IRR 1.72 [1.36–2.14] No BARC ≥3: IRR 1.14 [0.75–1.75]
Husted et al (2014) Multi-country[51]	PLATO	18,624	28.3	ACS	Ticagrelor vs. clopidogrel	Non-CABG-related study criteria major bleeding at 7 days, 7–240 days, after day 240	No
Kodaira et al (2021) Japan[8]	JCD-KiCS registry	2,494	22	ACS	Investigation of the differences between sexes for long-term bleeding complication requiring readmission in East Asia	Any bleeding event requiring readmission during 2-year follow-up	Yes HR 1.826–1.895 [1.107–3.093]
Lee et al (2018) Multi-country[43]	CURE, COMMIT, CLARITY-TIMI 28, TRITON-TIMI 38, PLATO, CHANCE, TRILOGY ACS, SPS3 and SOCRATES	109,570	30	ACS	Newer P2Y12 inhibitors (ticagrelor and prasugrel) vs. clopidogrel	Defined by the individual studies that used either TIMI or GUSTO, or trial specific criteria	No
Lee et al (2014) Korea[53]	DES LATE	5,045	30.7	ACS+CCS	12-month DAPT after DES implantation followed by aspirin monotherapy vs. further 24-month DAPT	TIMI major bleeding through 48 months	No
Lee et al (2018) Korea[52]	KAMIR-NIH	13,104	24.1	AMI	12-month DAPT after DES implantation with aspirin and clopidogrel (75 mg/day), ticagrelor (90 mg twice daily) or prasugrel (10 mg/day)	TIMI major and minor bleeding at 1 year after PCI	No
Matteau et al (2015) Multi-country[56]	PROTECT+ PROTECT US	9,410	27	ACS+CCS	Predictor of bleeding and ischemic events beyond 1 year	GUSTO moderate/severe bleeding (median follow-up duration was 4.1 years)	No
Mehran et al (2020) Multi-country[7]	LEADERS FREE	2,432	30	ACS+CCS	BMS vs. polymer-free, biolimus A9-eluting drug-coated stent with 1-month DAPT	Major bleeding (BARC 3–5) and major or minor bleeding (BARC 2–5) through 780 days	No
Nakamura et al (2019) Japan[38]	PRASFIT-Practice II	4,155	23.5	ACS+CCS	Low-dose prasugrel (LD/maintenance dose, 20/3.75 mg) vs. standard-dose clopidogrel administration	TIMI major or minor bleeding within 1 year (after 31 days)	No

(**Table** continued the next page.)

(B) Authors, year, country	Name of study	Total patients	No. of women (%)	Presentation	Topics	Bleeding outcome	Female sex as an independent risk factor of bleeding
Natsuaki et al (2018) Japan[40]	CREDO-Kyoto registry cohort 2 vs. RESET and NEXT	9,447	25	ACS+CCS	Development of CREDO-Kyoto thrombotic and bleeding risk scores	GUSTO moderate or severe bleeding through 3 years excluding in-hospital bleeding	No
Sawaya et al (2017) Multi-country[48]	EXCELLENT, OPTIMIZE, PRODIGY, RESET, SECURITY and ITALIC PLUS	11,473	30	ACS+CCS	Short vs. long-term DAPT after DES implantation	TIMI bleeding in 4 trials, the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE) criteria and BARC bleeding at 1 year	No
Schreuder et al (2020) Multi-country[49]	DISPERSE-2, PLATO, PRASFIT-ACS, TRILOGY ACS and TRITON-TIMI 38	43,990	29.6	ACS	DAPT with potent P2Y12 inhibitor vs. clopidogrel after PCI	Major bleeding (TIMI criteria 1, BARC 2, 3, and 5 or GUSTO bleeding criteria 1) and minor bleeding (TIMI criteria 2) with a median follow-up time of 1.06 years	No
Spirito et al (2021) Switzerland[42]	Bern PCI Registry	16,821	26	ACS+CCS	Assessment of the performance of ARC-HBR criteria separately in women and men	1. Composite of BARC 3 or 5, further stratified into non-access-site and access-site related bleeding at 1 year 2. BARC 2, 3 or 5 bleeding, TIMI and GUSTO bleeding	No (overall) Nearly Yes (access site by TFI; HR 1.99 [0.96–4.11] P=0.063) No (access site by TRI)
Yu et al (2016)[†3] USA and Europe	PARIS	5,018	25.5	ACS+CCS	Investigation of the patterns and impact of DAPT cessation in women and men	BARC >3 within 2 years	Yes HR 1.39 [1.02–1.89] P=0.04* *Hb value and renal function data were missing and not adjusted
Vogel et al (2021) Multi-country[54]	TWILIGHT	9,006	23.9	ACS+CCS	Ticagrelor with vs. without aspirin from the 3rd month after PCI	Primary; BARC 2, 3, or 5 bleeding at 1 year Secondary; BARC 3 or 5 bleeding, TIMI major bleeding, GUSTO moderate, severe, or life-threatening bleeding or major bleeding as defined by ISTH at 1 year	No
Xanthopoulou et al (2017)[†4] Greece	GRAPE Registry	2,047	17.6	ACS	1-year DAPT after PCI	Every type of BARC bleeding at 1 year	No (BARC 2–5) Yes (BARC 1; HR 1.58 [1.27–1.96])

Data derived from meta-analyses, randomized clinical trials, and registries with focus on sex differences. Studies are presented in alphabetical order of author.[†1–4] Citation details are provided in **Supplementary Appendix 2**. ACS, acute coronary syndrome; ADP, adenine diphosphate; AMI, acute myocardial infarction; ARC-HBR, The Academic Research Consortium for High Bleeding Risk; BARC, Bleeding Academic Research Consortium; BMS, bare metal stent; CABG, coronary artery bypass graft; CAG, coronary angiography; CCS, chronic coronary syndrome; CI, confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; Hb, hemoglobin; HR, hazard ratio; IRR, incidence rate ratio; ISTH, International Society of Thrombosis or Hemostasis; LD, loading dose; NR, not recorded; NSTE-ACS, non-ST-elevation-acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; REPLACE, Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TRI, transradial intervention.

botic and hemorrhagic risk score, developed to predict long-term thrombotic and bleeding events in Japan, does not include women as a specific risk factor.[40] In contrast to these findings, 2-year follow-up of the Japanese JCD-KiCS registry found that women remained an independent bleeding risk factor even after 2 years.[8] However, that study did not provide details of DAPT duration after PCI, and the implantation of drug-eluting stents (DES) was notably more prevalent in women (58.4% vs. 53.1%) compared with bare metal stents.

Attention should be directed towards age-related considerations in CVD among East Asians. A study of patients aged £55 years in an overseas trial revealed that younger women (24%) had a significantly higher risk of 1-year major adverse cardiovascular events and bleeding than men, although female sex was not an independent factor.[57] Conversely, in a Japanese study,[58] the percentage of female ischemic heart disease (IHD) patients under 55 years of age was exceedingly small (7.8%) compared with overseas cohorts. However, the prevalence of background factors such as anemia, hemodialysis, and cancer were significantly higher in women than men, all of which are thrombotic and bleeding risks to be considered. There is limited data on long-term bleeding risk related to young women in Japan, and future evidence needs to be accumulated.

Although discrepancies exist in the definition of bleeding complications and the duration of DAPT across various trials, studies have consistently indicated that factors such as advanced age, chronic kidney disease (CKD), and low body weight can account for chronic-phase bleeding in women under antithrombotic therapy after PCI. Consequently, those studies do not consider female sex as an independent factor for chronic-phase bleeding.[7,29,35,42–52,55] However, in the future there remains a need for long-term data to integrate P2Y12 inhibitors with the recommended duration of DAPT outlined in recent guidelines.

Data derived from meta-analyses, RCTs, and registries investigating sex differences during the acute and chronic phases of bleeding complications post-PCI are summarized in the **Table**.

DAPT Regimens

The type and duration of DAPT following PCI should be determined by a balance between ischemic and bleeding risks tailored to each patient.

Type of DAPT Regarding the type of DAPT, meta-analyses have demonstrated equivalent safety and efficacy between the sexes[43,44] for both clopidogrel and novel P2Y12 inhibitors (ticagrelor, prasugrel, and cangrelor). These findings were observed in trials involving ACS patients.

In the GLOBAL LEADERS trial, female patients with CCS treated with ticagrelor monotherapy showed an elevated bleeding rate up to 1 year compared with the patients under clopidogrel + aspirin 1-year DAPT, and this result suggests cautious use of potent P2Y12 inhibitors such as ticagrelor in female CCS patients.[45] However, in Japan, the indication of ticagrelor is limited to ACS, old myocardial infarction and patients who cannot tolerate other P2Y12 inhibitors.

Prasugrel has been approved with a reduced dose (loading and maintenance, 20/3.75 mg) in Japan, because there is an acknowledged bleeding risk among East Asians. The prasugrel post-marketing surveillance in Japan indicated that women did not have a bleeding risk factor from day 31 to 12 months post-PCI, even for CCS patients and the elderly.[35] Therefore, sex may not be a significant consideration when using prasugrel, even in CCS patients. Furthermore, a study on the safety and efficacy of a 2.5-mg maintenance dose of prasugrel in Japanese ACS patients at elevated risk of bleeding demonstrated comparable outcomes to the 3.75-mg dose of prasugrel.[59] Within that study, women were not identified as independent risk factor for in-hospital major bleeding. Therefore, sex may not be a significant consideration when using prasugrel, possibly with dose reduction criteria, even in CCS patients.

Duration of DAPT Assessing bleeding risk to determine the duration of DAPT, the 2016 ACC/AHA guideline emphasized qualitative bleeding risk factors, and women were identified as a risk factor.[2] In contrast, the 2017 ESC guideline and the 2020 JCS Focused Update Guidelines recommend that evaluating high bleeding risk (HBR) should be conducted primarily for the duration of DAPT.[1,3] To assess HBR, the 2020 ESC guidelines utilized the PRESICE-DAPT score[60] and the ARC-HBR criteria as references.[61] The ARC-HBR criteria represent a consensus on a series of clinical and biochemical standards and do not include sex.[62] However, it is important to realize that women are more likely to meet the ARC-HBR criteria and consequently have higher ARC-HBR scores than men due to their higher prevalence of factors such as older age, CKD, and anemia.[7,42,62] The 2020 JCS Focus Update Guidelines established their own J-HBR criteria. Heart failure, low body weight, peripheral arterial disease, and frailty were included as Japanese-specific factors in addition to the ARC-HBR criteria.[3] The J-HBR criteria have been validated as more sensitive but less specific than the original ARC-HBR criteria.[63]

The 2017 ESC guidelines[1] stated that there was no compelling evidence to advocate a regimen for women based on sex-specific differences in both efficacy and safety. In this review, we do not recommend that the type, dosage, and duration of antithrombotic agents should be altered based solely on sex. However, it is crucial to acknowledge that female patients with IHD, particularly Japanese women, often fall into the HBR category due to specific risk factors such as advanced age, low body weight, renal dysfunction, and anemia.[3] Therefore, individualized antiplatelet therapies should be considered, tailoring the duration and dosage according to the patient's specific risk profile.

Anticoagulation Following PCI

Direct Oral Anticoagulants (DOACs) vs. Warfarin Sex differences in the efficacy and safety of DOACs compared with warfarin for patients with atrial fibrillation (AF) have been reported. The 2 meta-analyses of major anticoagulation trials of 4 DOACs[64,65] showed no sex-specific differences in the efficacy of stroke prevention between DOACs and warfarin. One of these meta-analyses showed that women treated with DOACs had lower rates of major bleeding compared with men (OR=0.84).[64] Similarly, women receiving rivaroxaban in the ROCKET AF trial[66] and apixaban in the ARISTOTLE trial[67] had a reduced risk of major bleeding complications compared with men after multivariable adjustment (HR=0.82 and 0.74).

Consequently, DOACs may be the preferred anticoagulant for women.

Regarding specific types of DOACs, a meta-analysis of major anticoagulation trials, with warfarin as an indirect comparator, suggested that the safety profile in female patients with AF did not significantly differ for any of the DOACs concerning safety and efficacy.[68]

Triple Antithrombotic Therapy Approximately 10–15% of patients undergoing PCI for IHD are diagnosed with AF.[69] According to the 2020 ESC Guidelines, AF patients with relevant CVD have a CHA2DS2-VASc score of at least 1 (often higher due to the presence of other cardiovascular risk factors) and thus have an indication for DOACs.[61,69] Current clinical guidelines recommend triple antithrombotic therapy (TAT), which involves the use of 3 distinct antithrombotic agents for a specified duration as anticoagulation therapy after PCI in patients with AF.[1–3] In a recent study, the triple-drug combination therapy (comprising an anticoagulant, clopidogrel, and aspirin) and dual-drug combination therapy (comprising an anticoagulant and clopidogrel) were compared in 69% of patients with AF and undergoing PCI.[70] The dual-drug combination therapy treatment significantly reduced the incidence of bleeding complications at 1 year (HR=0.36), and this effect was consistent regardless of sex. On the other hand, an analysis of patients discharged on TAT from the SWEDEHEART registry found that women had a significantly higher rate of early TAT discontinuation due to bleeding compared with men. However, there was no sex difference in the incidence of coronary events, because the study was underpowered to assess potential sex differences in the association between TAT discontinuation and ischemic events due to its relatively small size.[71]

Study Limitations

Our review has several limitations. We had an emphasis on investigating bleeding complications in women under antithrombotic therapy, rather than post-PCI bleeding complications. Moreover, most analyses focusing on sex differences in RCTs involving DAPT and TAT after PCI have not been conducted to influence treatment strategies, potentially limiting the statistical power of RCT data and leading to false-negative findings. In addition, we presented sex-specific differences in bleeding complications after PCI under antithrombotic therapy using results mostly derived from sub-group and post-hoc analyses of RCTs, which might yield false-positive results compared with prespecified analyses.[72] Furthermore, the low representation of women in CVD trials limits the ability to derive sex-specific recommendations. A deeper comprehension of sex-specific variations in clinical outcomes related to antithrombotic therapy post-PCI is essential for developing sex-specific treatment approaches. Future clinical trials should actively incorporate a substantial number of female participants, especially in bleeding-prone populations such as Asians, aiming to establish robust, evidence-based recommendations in this field.

Conclusions

Women appear to have heightened baseline platelet reactivity compared with men, but the clinical significance of this discrepancy on the selection and dosage of antiplatelet agents remains uncertain. Notably, women face an elevated risk of bleeding in the acute phase post-PCI under antiplatelet therapy, but there is no apparent sex disparity in the chronic-phase bleeding risk. To optimize the efficacy of antiplatelet agent and minimize bleeding complications in women, special attention to factors such as age, renal function, weight, and dosing strategy is necessary. Although DOACs may have a lower bleeding risk in women compared with warfarin, there is a lack of evidence to support recommendations for sex differences in TAT regimens.

Our review has identified recent evidence highlighting sex differences in platelet responsiveness and bleeding complications in antithrombotic therapy after PCI. However, recent findings on sex differences in post-PCI bleeding complications did not provide enough evidence to recommend specific therapies for women. Further studies will be needed to formulate sex-sensitive recommendations for post-PCI antithrombotic therapy in future guidelines.

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Authors' Contributions

Y.N. screened the records, extracted the data and wrote the manuscript draft. S.T. and Y.M.N. supervised and edited the manuscript. All authors reviewed the final manuscript and approved its contents.

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Supplementary Files

Please find supplementary file(s);
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