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EXPERT CONSENSUS

Antithrombotic drugs for acute coronary syndromes in women: sex-adjusted treatment and female representation in randomised clinical trials. A clinical consensus statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the ESC Working Group on Thrombosis

Valeria Paradies[1]* MD (Chair); Giulia Masiero[2], MD; Andrea Rubboli[3], MD, PhD; Heleen M.M. Van Beusekom[4], MD, PhD; Francesco Costa[5,6], MD, PhD; Piera Capranzano[7], MD, PhD; Sophie Degrauwe[8], MD; Diana A. Gorog[9,10], MD, PhD; Claudia Moreira Jorge[11], MD, PhD; Gill Louise Buchanan[12], MD; Mirvat Alasnag[13], MD; Daniela Trabattoni[14], MD; Chiara Fraccaro[2], MD, PhD; Dirk Sibbing[15], MD, PhD; Dariusz Dudek[16], MD, PhD; Gemma Vilahur[17], MD, PhD; Alaide Chieffo[18,19], MD; Roxana Mehran[20], MD; Davide Capodanno[7], MD, PhD; Emanuele Barbato[21], MD, PhD; Jolanta M. Siller-Matula[22], MD, PhD (Co-Chair)

GUEST EDITOR: Franz-Josef Neumann, MD, PhD; *Department of Cardiology and Angiology, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany*

**Corresponding author: Department of Cardiology, Maasstad Hospital, Maasstadweg 21, 3079 DZ, Rotterdam, the Netherlands. E-mail: paradiesvaleria@gmail.com*

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ABSTRACT

Thrombotic and bleeding risks differ between sexes, partly in relation to distinct biology and hormonal status, but also due to differences in age, comorbidities, and body size at presentation. Women experience frequent fluctuations of prothrombotic and bleeding status related to menstrual cycle, use of oral contraceptives, hormone replacement therapy, or menopause. Although clinical studies tend to underrepresent women, available data consistently support sex-specific differences in the baseline thrombotic and haemorrhagic risks. Compared with men, women feature an increased risk of in-hospital bleeding related to invasive procedures, as well as long-term out-of-hospital bleeding events. In addition, the inappropriate dosing of antithrombotic drugs, which is not adapted to body weight or renal function, is more frequently associated with an increased risk of bleeding in women compared to men. While acute coronary syndrome (ACS) studies support similar antithrombotic drug efficacy, irrespective of sex, women may receive delayed treatment due to bias in their referral, diagnosis, and invasive treatment decisions. The current clinical consensus statement highlights the need for an increased awareness of sex-specific risks and biases in ACS management, with a focus on sex-specific bleeding mitigation strategies, antithrombotic management in special conditions (e.g., myocardial infarction with non-obstructive coronary arteries), and barriers to female representation in cardiovascular trials. This manuscript aims to provide expert opinion, based on the best available evidence, and consensus statements on optimising antithrombotic therapy according to sex, which is critical to improve sex-based disparities in outcome.

KEYWORDS: antithrombotic therapies; bleeding; coagulation; gender; haemostasis; platelets; sex; thrombosis

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Sex-based differences in the pathophysiology, epidemiology, clinical presentation, therapy, and outcome of acute coronary syndrome (ACS) are well described[1-4]. Although sex-based disparities in the invasive management of patients with ACS and percutaneous coronary intervention (PCI) have narrowed in recent years, clinical outcomes after ACS remain worse for female compared to male patients[5]. Data consistently show that female patients experience greater delays in the diagnosis and treatment of ACS compared to male patients, these being associated with the consequent late administration of antithrombotic agents during ongoing cardiac ischaemia[6]. Although there is a sex-based bias in referral by both healthcare practitioners and patients[7], differences in coronary anatomy and function, peripheral vascular anatomy and comorbidities, psychosocial factors, and vascular and neural stress responses may contribute to the observed differences in the safety and efficacy of antithrombotic drugs between sexes[8,9]. As women are often underrepresented in randomised controlled trials (RCTs) of antithrombotic treatment, new data and adequately powered trials in women are required to identify independent associations between sex and the efficacy/safety of antithrombotic treatment. Considering these unique challenges to optimising antithrombotic treatment based on sex, the aim of the current consensus statement, led by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the European Society of Cardiology (ESC) Working Group on Thrombosis, is to provide consensus-based guidance, founded on the best available evidence and expert opinion.

Sex and antithrombotic therapies

BASELINE DIFFERENCES BETWEEN SEXES IN THE COAGULATION SYSTEM

The risk of coronary thrombosis differs between females and males. This is especially true before the menopause due to oestrogen and progesterone fluctuations influencing blood platelets and procoagulant factors[10,11]. Oestrogen promotes prostacyclin production, improves nitric oxide availability, and reduces platelet aggregation, which might be protective against the premature onset of coronary artery disease[11]. Fluctuations in hormonal status associated with menstrual cycles, oral contraceptive use, menopause, and hormone replacement therapy all influence thrombotic and bleeding risks[6,12,13] **(Supplementary Appendix 1)**. Of note, lower platelet reactivity in premenopausal women has been related to the presence of oestrogen receptors on the platelet surface[14]. Some reports have also indicated more pronounced platelet adhesion to injured vessels in males[15], but greater agonist-induced platelet activation and aggregation in females[11,16-18] **(Figure 1)**. There are also differences in protease-activated receptor (PAR) signalling pathways between sexes, with platelet PAR1 signalling shown to be reduced in women and increased in men during myocardial infarction (MI)[19]. Increased endothelial shear stress, which is associated with significantly smaller epicardial coronary arteries in females, may influence vascular lipid accumulation, pathological remodelling, and plaque instability. This contributes to distinct coronary atherosclerosis characteristics, including a more diffuse and non-obstructive pattern, reduced overall plaque burden and calcification, and fewer signs of necrosis in the plaque core[20] **(Figure 1)**.

THROMBOTIC/ISCHAEMIC RISK ACCORDING TO SEX IN PATIENTS TREATED WITH ANTITHROMBOTIC AGENTS

The major adverse cardiovascular event (MACE) rate after ACS is higher in female than male patients, which might be due to sex-based disparities in clinical characteristics and treatment[6,21]. Women tend to present with ACS at an older age and with a higher burden of comorbidities such as diabetes, hypertension, and chronic kidney disease, compared to men[1]. The available evidence shows a similar efficacy of antithrombotic agents for ACS/PCI in both sexes. In the Antithrombotic Trialists' (ATT) Collaboration meta-analysis, there was no interaction between sex and the efficacy of aspirin versus placebo for secondary cardiovascular disease (CVD) prevention[22]. As far as dual antiplatelet (DAPT) therapy is concerned, a meta-analysis comparing clopidogrel plus aspirin versus aspirin alone in patients presenting with ACS and/or undergoing PCI showed that the absolute risk of MACE was higher in women than in men, and the relative benefit of clopidogrel therapy appeared attenuated in women versus men (7% vs 16% reduction)[23]. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38 trial), which evaluated prasugrel versus clopidogrel on top of aspirin therapy in

Abbreviations

ACS	acute coronary syndrome
ARC-HBR	Academic Research Consortium for High Bleeding Risk
BARC	Bleeding Academic Research Consortium
CAG	coronary angiography
CCS	chronic coronary syndrome
CMD	coronary microvascular dysfunction
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
FDA	U.S. Food and Drug Administration
GPIIb/IIIa	glycoprotein IIb/IIIa
LMWH	low-molecular-weight heparin
MACE	major adverse cardiovascular events
MI	myocardial infarction
MINOCA	myocardial infarction with non-obstructive coronary arteries
NSTE-ACS	non-ST-segment elevation acute coronary syndrome
PCI	percutaneous coronary intervention
PPR	participation-to-prevalence ratio
RCT	randomised controlled trial
SAPT	single antiplatelet therapy
SCAD	spontaneous coronary artery dissection
TIMI	Thrombolysis in Myocardial Infarction
TTS	Takotsubo syndrome
TXA2	thromboxane A2
UFH	unfractionated heparin

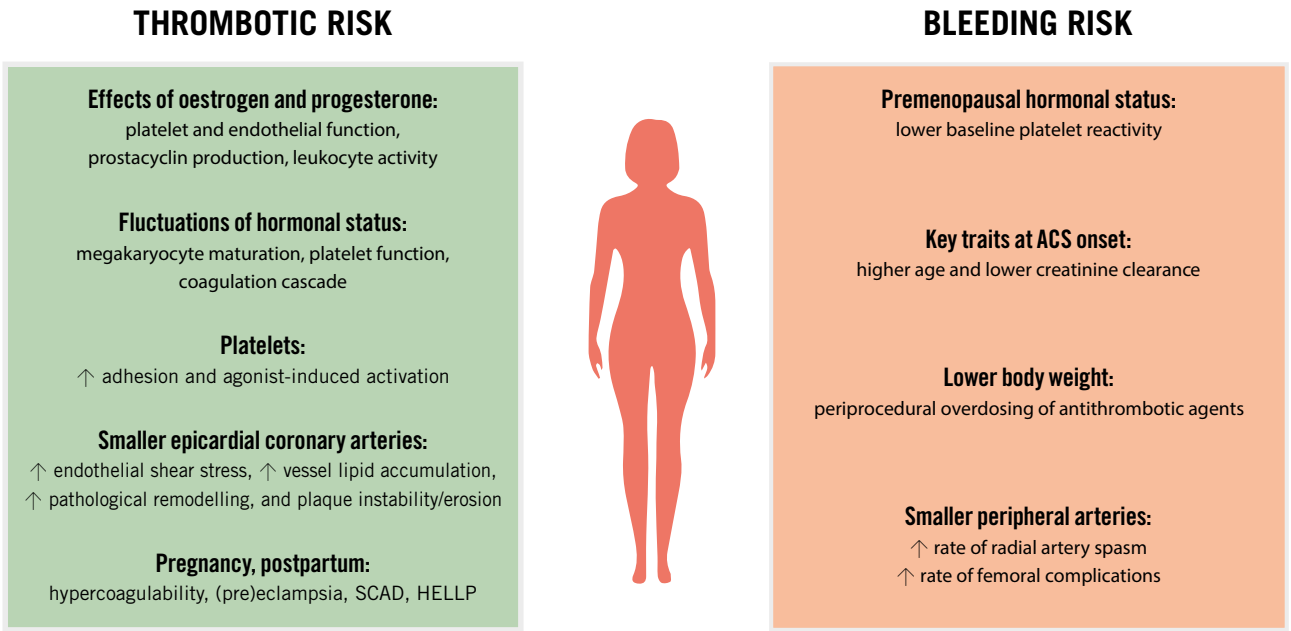


Figure 1. *Factors associated with thrombotic and bleeding risks in women. ACS: acute coronary syndrome; HELLP: haemolysis, elevated liver enzymes and low platelets; SCAD: spontaneous coronary artery dissection*

ACS patients undergoing PCI, there was no significant interaction between the efficacy of prasugrel and sex, but the magnitude of the effect was greater in men at 15-month follow-up[24] **(Supplementary Table 1)**. Similarly, in the PLATelet inhibition and patient Outcomes (PLATO) trial, which compared ticagrelor to clopidogrel in aspirin-treated patients with ACS, no significant sex-related difference was found for MACE reduction at 1 year **(Supplementary Table 2)**[25]. Similar results were observed in the The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5 (ISAR-REACT 5) trial **(Supplementary Table 3)**[26].

Some interest over the combination of antiplatelet therapy and direct oral anticoagulants has emerged. In the Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) trial, rivaroxaban (2.5 mg or 5 mg twice daily) added to aspirin plus clopidogrel reduced the risks of MACE across both sexes[27].

In ACS/PCI patients with an indication for oral anticoagulation and antiplatelet therapy, no significant interaction between sex and major efficacy outcomes was observed **(Supplementary Table 4)**.

CLINICAL CONSENSUS STATEMENTS: ANTITHROMBOTIC AGENTS

There is no significant sex-related difference in the efficacy of antithrombotic drugs for secondary CVD prevention.

Delays in ACS diagnosis and invasive treatment should be addressed to enable timely initiation of treatment with antithrombotic drugs.

BLEEDING RISK ACCORDING TO SEX IN PATIENTS TREATED WITH ANTITHROMBOTIC AGENTS

Although primary analyses of pivotal trials on antithrombotic therapies in ACS do not indicate an interaction between sex and bleeding outcomes **(Supplementary Table 1-Supplementary Table 4)**, there is a wealth of additional data from multivariate analyses of dedicated substudies demonstrating a higher risk of bleeding and vascular complications in females versus males, especially when femoral access for PCI is used[6,10,28,29]. Female ACS patients tend to be older, with more comorbidities when compared to their male counterparts[30]. In this context, it should be noted that female ACS patients may receive higher antithrombotic drug doses than appropriate for their body weight or renal function[31].

The ESC Guidelines for the management of acute coronary syndromes advocate an early invasive approach and use of weight-adjusted unfractionated heparin (UFH) as the first-line anticoagulant agent for most patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS)[32]. In patients undergoing coronary angiography (CAG) outside of the recommended time window, antithrombotic "bridging" with fondaparinux prior to angiography was associated with significantly fewer Bleeding Academic Research Consortium (BARC) 3-5 (adjusted [adj.] hazard ratio [HR] 0.21) and access site-related bleeding events (adj. HR 0.49) compared to enoxaparin in a contemporary patient population[33] and in pivotal fondaparinux trials[34,35]. In the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, fondaparinux substantially reduced the occurrence of major bleeding events and access site-related bleeding in both sexes compared to enoxaparin, but the magnitude of

the effect on bleeding risk reduction was greater in women than in men (HR 0.45 vs 0.60, respectively)[34,35].

The age-dependent risk of bleeding is even more pronounced in premenopausal women, being 4-fold higher for Thrombolysis in Myocardial Infarction (TIMI) major/minor bleeding events in females younger than 50 years of age, compared to males in the same age category[36]. This increased bleeding risk in young females might be partly related to the differential effects of sex hormones on platelet activity, with lower baseline platelet activity in the presence of platelet oestrogen receptors in premenopausal females[1,6,14]. Additionally, young patients, regardless of sex, tend to be treated with excessive doses of anticoagulants in the setting of ACS and PCI; still, this excess dosing is associated with significantly higher bleeding rates in young females than in young males[37]. Importantly, women presenting with cardiogenic shock had a higher risk of major bleeding events compared to men (adj. odds ratio [OR] 1.23; 95% confidence interval [CI]: 1.12-1.34)[38].

Beyond non-modifiable factors such as age, creatinine clearance, and other comorbidities, the modifiable factor of arterial access selection also differs between sexes; femoral access was more frequently used (5-50%) in females than in males in the majority of studies and accounts for almost half of bleeding events[36,39-41]. An effort should be made regarding the proper training and awareness of interventional cardiologists in strategies such as ultrasound-guided access, smaller sheath sizes, and earlier sheath removal in order to mitigate the bleeding events associated with vascular puncture[41,42]. Radial access remains an effective method to reduce access site bleeding complications[43]. Various prevention approaches, including medications like vasodilators and calcium channel blockers, aim to reduce radial artery spasm[44]. Equipment-related prevention includes the use of hydrophilic tools, special 6-in-5 Fr sheaths, minimising catheter exchanges, and avoiding cold intra-arterial injections[45].

CONSENSUS STATEMENTS: MITIGATION OF BLEEDING RISKS

Strategies aiming to mitigate the bleeding risks associated with the femoral access site are advisable **(Figure 2)**:

- Favour radial access over femoral access, with emphasis on spasm prophylaxis and the use of dedicated radial equipment.
- Utilise ultrasound-assisted puncture when femoral artery access is needed.

Avoid excess dosing of periprocedural anticoagulants and antiplatelet agents **(Figure 2)**:

- Body weight and/or renal function-adjusted dosing of periprocedural antiplatelet agents (the $P2Y_{12}$ inhibitor cangrelor or the glycoprotein [GP] IIb/IIIa inhibitors tirofiban or eptifibatide) and anticoagulants (UFH, low-molecular-weight heparins [LMWH], bivalirudin) should be used. When a combination of UFH and GPIIb/IIIa inhibitors is applied, it is advisable to reduce the dose of UFH from 70-100 U/kg to 50-70 U/kg and to monitor its effect using activated clotting time testing.
- For NSTE-ACS patients without an immediate invasive strategy, anticoagulants with a favourable safety profile are preferable. It is advisable to select fondaparinux over enoxaparin.

Long-term selection of antithrombotic treatment type or duration after ACS/PCI should be based on patient

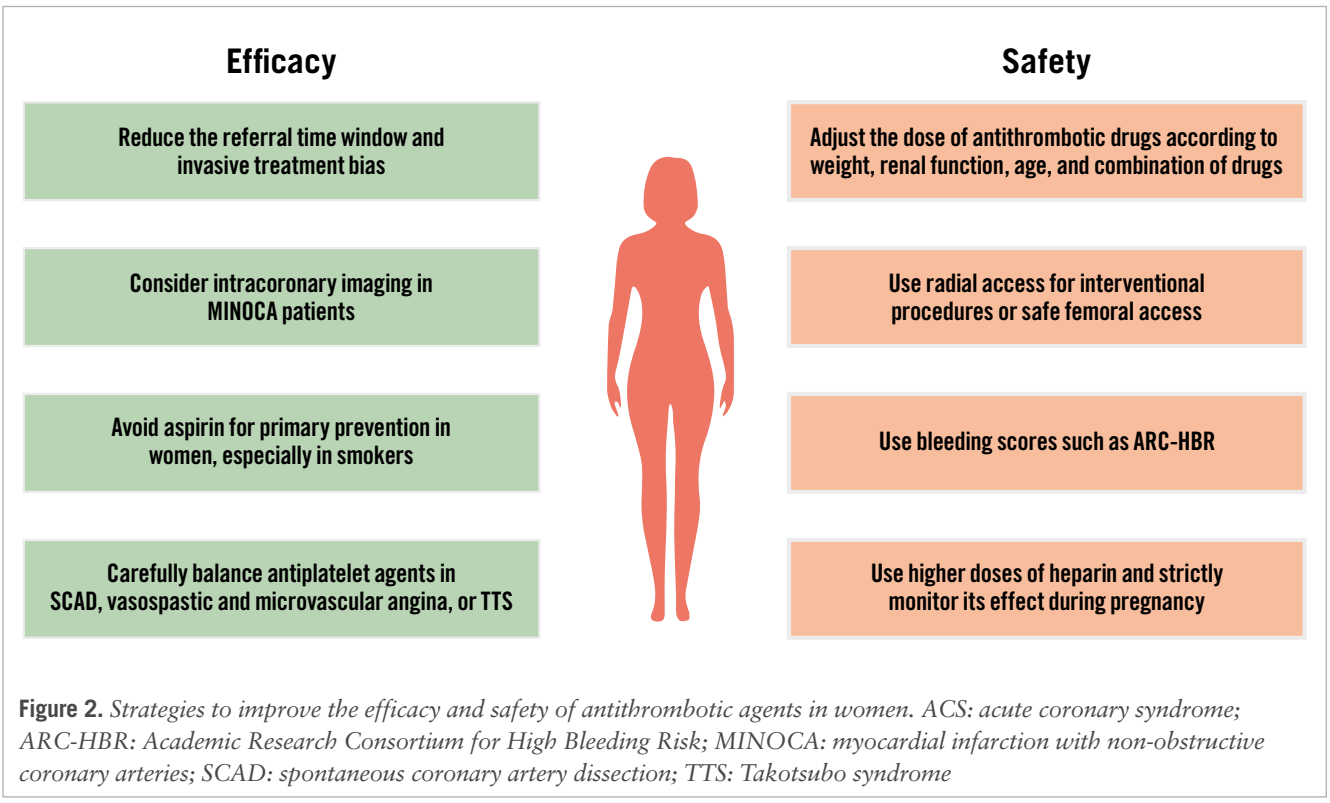


Figure 2. *Strategies to improve the efficacy and safety of antithrombotic agents in women. ACS: acute coronary syndrome; ARC-HBR: Academic Research Consortium for High Bleeding Risk; MINOCA: myocardial infarction with non-obstructive coronary arteries; SCAD: spontaneous coronary artery dissection; TTS: Takotsubo syndrome*

comorbidities rather than sex, recognising the higher comorbidity burden in women compared to men **(Figure 2)**.

Use of guideline-endorsed bleeding scores (such as Academic Research Consortium for High Bleeding Risk [ARC-HBR] and PRECISE-DAPT[46,47]) is advisable **(Table 1)**.

Antithrombotic agents in the settings of MINOCA

Myocardial infarction with non-obstructive coronary arteries (MINOCA)[48] is classified into epicardial and microvascular disease. In the absence of critical coronary stenoses, the main pathological findings are plaque rupture or erosion, epicardial or microvascular spasm, thromboembolism, or spontaneous coronary artery dissection (SCAD)[49]. Data are scarce regarding which antithrombotic drug should be used for the treatment of MINOCA, and underlying pathologies should be addressed.

PLAQUE EROSION

In the small EROSION trial (n=60; <15% women), patients with ACS and plaque erosion were treated with antithrombotic therapies (aspirin, ticagrelor, UFH) without PCI and had favourable 1-year outcomes[50]. In the EROSION III trial in ST-segment elevation MI patients with early infarct artery patency (n=226; 20% women), optical coherence tomography [OCT]-based diagnosis and conservative treatment with antithrombotic therapies (aspirin, ticagrelor, UFH) resulted in comparable MACE rates in both the conservative and PCI-treated arms[51].

SPONTANEOUS CORONARY ARTERY DISSECTION

The majority of SCAD patients are female and undergo conservative management. However, for these patients, there is a lack of consensus regarding the utilisation and duration of either aspirin alone or DAPT. A small study of patients on DAPT who underwent repeat angiography showed dissection healing in nearly all cases of SCAD[52]. Conversely, a small registry of conservatively managed SCAD patients showed that, at 1 year, patients on DAPT had a higher MACE rate than those on single antiplatelet therapy (SAPT)[53].

VASOSPASM

Vasomotor dysfunction (both epicardial and microvascular) is more common in women, with vasoreactivity induced by lower doses of acetylcholine compared to men[54]. Data to support the use of aspirin in patients with vasospasm are lacking. High-dose aspirin (>325 mg daily) inhibits prostacyclin production, and can aggravate vasospasm[55]. Low-dose aspirin (<100 mg) can inhibit thromboxane A2 (TXA2), which is implicated in spasm, but clinical results are conflicting, with some studies showing that low-dose aspirin was also associated with frequent coronary spasm[56].

TAKOTSUBO SYNDROME

Takotsubo syndrome (TTS) is more common in women than in men. Despite aspirin use, women with TTS have been shown to have impaired endothelial function with excess TXA2 formation and enhanced platelet reactivity[57]. In the international Takotsubo registry, aspirin use was not associated with a lower risk of major adverse cardiac or cerebrovascular events at 30 days or 5 years[58]. A subsequent meta-analysis also indicated a higher incidence of cardiovascular events with long-term antiplatelet therapy[59].

CORONARY MICROVASCULAR DYSFUNCTION

The hallmark of coronary microvascular dysfunction (CMD) is enhanced coronary vasoconstriction, and it is much more common in women. TXA2 leads to arterial constriction, platelet aggregation, and vascular injury, while aspirin reduced endothelial platelet adhesion and conferred microvascular protection in mice[60]. Whilst unsupported by evidence, low-dose aspirin could be useful in CMD by reducing platelet-rich microembolism and downstream events, if confirmed in clinical studies.

CONSENSUS STATEMENTS: ANTITHROMBOTICS IN MINOCA PATIENTS

Intravascular imaging is advised to confirm plaque erosion in MINOCA patients who may benefit from a conservative approach consisting of DAPT (potent $P2Y_{12}$ inhibitor and aspirin) for 12 months without undergoing PCI.

In the overall MINOCA population, the choice to treat patients with either DAPT or only aspirin should be based on underlying pathophysiological mechanisms, irrespective of sex.

In patients with conservatively managed SCAD, vasospastic and microvascular angina, or Takotsubo syndrome, the adoption of DAPT is not advisable based on current available data.

Underrepresentation of women in RCTs investigating antithrombotic therapies

PARTICIPATION-TO-PREVALENCE RATIO AND SCREENING FAILURES IN RCTS OF CHRONIC AND ACUTE CORONARY SYNDROMES

Despite the call from regulatory bodies for equal representation, women remain underrepresented in clinical trials, especially in CVD studies, with inclusion rates varying greatly based on disease type[61-65] **(Table 2)**. The participation-to-prevalence ratio (PPR; the percentage of women among trial participants/percentage of women among disease population) has been used to establish female representation in clinical trials relative to their prevalence in the diseased population[66]. After accounting for age and sex-specific disease prevalence, a substantial underrepresentation of women (PPR <0.6) was found for trials in the chronic coronary syndrome (CCS) and ACS domains, and the representation of women was particularly low in studies where the average participants' age was between 61 and 65 years[66,67]. Of note, the PPR strictly depends on disease type and epidemiological data quality, with a potential misalignment between clinical trials and population-based data[66]. Another suggested driver for the unbalanced representation of women was the selection of sex-biased inclusion criteria. A recent analysis of clinical trials supporting U.S. Food and Drug Administration (FDA) approval of cardiovascular drugs, focusing on the percentages of screening failure in both sexes, has shown that only one ACS trial reported a higher percentage of screened-out women as compared to men (32% vs 23%, respectively), hence a lower enrolment of women could not be completely ascribed to this phenomenon[66]. Female patients are better

Table 1. Ischaemic and bleeding risk scores for the secondary prevention of events following ACS and PCI, and the role of sex.

Risk scores#	C-statistic	Predictors	Role of sex and/or strongest (significant) predictor
GRACE (I)*	0.7	Systolic blood pressure, age, Killip class, heart rate, cardiac arrest, serum creatinine levels, ST-segment deviation, cardiac biomarker increase	No interaction between sexes for primary endpoints
CRUSADE (B)#	0.6-0.8	Female sex, diabetes, peripheral arterial disease, heart rate, systolic blood pressure, congestive heart failure, haematocrit level, creatinine clearance	HR female sex 1.31 (95% CI: 1.23-1.39)
GRACE+CRUSADE (I+B)	n.a.	See above	OR cardiac death/bleeding: female: 27.42 (95% CI: 21.64-34.74) male: 34.80 (95% CI: 28.89-41.91)
PARIS CTE (I)	0.7	Diabetes, ACS, smoking, creatinine clearance, prior PCI or CABG	No sex strata
PARIS MB (B)	0.7	Age, BMI, smoking, anaemia, creatinine clearance, triple therapy	No sex strata
DAPT (I+B)*	0.6-0.7	Myocardial infarction, PCI, diabetes, stent diameter <3 mm, smoking, paclitaxel stent, heart failure or low ejection fraction, vein graft intervention, age	No sex strata
CHA_2DS_2-VASc (I)#	0.6	Female sex, age, heart failure, hypertension, CVA, venous embolism, vascular disease, diabetes	OR female sex 2.53 (95% CI: 1.08-5.92)
ACUITY (B)#	0.7	Female sex, age, creatinine, white blood cell count, anaemia, ST-segment elevation	OR female sex 2.32 (95% CI: 1.98-2.72)
HAS-BLED (B)	0.7	Hypertension, abnormal renal and liver function, stroke, prior bleeding, labile INR, alcohol or drug use, predisposition to bleeding (e.g., medication)	No sex strata
PRECISE-DAPT (B)*	0.7	Age, creatinine clearance, haemoglobin levels, white blood cell count, previous spontaneous bleeding	No sex strata

#Taking female sex into account. *Recommended by (ESC) guidelines; C-statistic for risk prediction. ACS: acute coronary syndrome; B: bleeding risk score; BMI: body mass index; CABG: coronary artery bypass grafting; CI: confidence interval; CVA: cerebrovascular accident; ESC: European Society of Cardiology; HR: hazard ratio; I: ischaemic risk score; INR: international normalised ratio; n.a.: not applicable; OR: odds ratio; PCI: percutaneous coronary intervention

represented in the transcatheter treatment of severe aortic stenosis compared to the coronary field, particularly in early landmark trials[5]. Evidence suggests that women may derive greater benefit from transfemoral aortic valve implantation than from surgical treatment. However, the PPR remains consistently around 0.73[68].

PARTICIPATION OF WOMEN IN RCTS ON ANTITHROMBOTIC THERAPY AND SEX REPORTING

We conducted a systematic review of all RCTs on antithrombotic therapies with the goal of determining temporal trends in female enrolment and patterns of sex reporting. There were 29,398 interventional clinical trials on cardiovascular disease registered in the ClinicalTrials.gov database between 1 January 2001 and 31 December 2021 with reported results. Search strategy criteria and details of the trials are displayed in **Supplementary Table 5**-**Supplementary Table 7**. Of those, 1,156 were selected based on the following search criteria: ACS, CCS, PCI, atherosclerosis, antiplatelet, antithrombotic, aspirin, $P2Y_{12}$ inhibitor, prasugrel, ticagrelor, clopidogrel, and cangrelor. After excluding duplicates, phase I and II RCTs, and those with a sample size <500 patients, there remained 64 studies with a publication year between 2001 and 2021, and these were included in the final analysis **(Supplementary Figure 1)**. The overall female representation was 26.6%, with a decreasing enrolment rate per year of publication over the analysed period **(Figure 3)**. Sex-specific analyses of the primary outcome were reported in 42 clinical trials (65.6%). Importantly, only 8 trials (12.5%) reported sex-specific baseline characteristics. In this analysis, women were significantly older than men (mean±standard deviation: 68.79±4.32 years vs 63.77±4.84 years; p=0.03) but had similar body mass index (BMI; 27.15±1.06 kg/m^2 vs 27.53±0.75 kg/m^2; p=0.49). The prevalence of diabetes mellitus was similar in both sexes (26.78±8.68% in women vs 23.71±6.04% in men; p=0.49). The proportion of patients with a history of myocardial infarction was slightly lower in women than in men (16.32±8.07% vs 22.35±10.59%; p=0.22). In line with a previous sex-specific analysis of the most relevant RCTs on antiplatelet therapies, our analysis showed a later onset of clinical manifestations of CCS/ACS in women[69].

CURRENT PITFALLS OF RCTS

SAMPLE SIZE ADJUSTMENTS AND SEX-SPECIFIC SUBANALYSIS

The underenrolment of women in cardiovascular (CV) trials has been increasingly recognised, and various strategies to improve female representation have been proposed[30]. To detect meaningful differences in both main treatment effects and interaction effects between women and men, the sample size of such trials would need to increase significantly[70]. This may be challenging because of increased costs and the lack of infrastructure to enrol so many patients within a reasonable timeframe. In addition, limitations arise from the phase before drug testing enters human clinical research, as animal studies have historically relied on male subjects[71]. Important

Table 2. Sex-specific analysis of the most relevant RCTs on antiplatelet therapies.

	INFUSE-AMI	PLATO	CHAMPION PHOENIX	TROPICAL-ACS	GLOBAL LEADERS	ISAR-REACT 5	MASTER DAPT
Year of publication	2014	2014	2016	2019	2020	2021	2023
NCT number	NCT00976521	NCT00391872	NCT01156571	NCT01959451	NCT01813435	NCT01944800	NCT03023020
Study design	Multicentre, open-label, controlled, single-blind, randomised 2x2 factorial trial	Multicentre, randomised, double-blind trial	Multicentre, randomised, double-blind, double-dummy trial	Multicentre, randomised, parallel-group, open-label, assessor-blinded trial	Multicentre, randomised, open-label trial	Multicentre, randomised, open-label trial	Multicentre, randomised, open-label trial
Population	452 anterior STEMI patients	18,624 ACS patients	11,145 patients undergoing elective or urgent PCI	2,610 ACS patients	15,968 all-comers patients	4,018 ACS patients planned for invasive strategy	4,579 HBR patients randomised at 1 month after PCI to abbreviated or standard DAPT
Female	26%	28%	28%	21%	23%	24%	30.7%
Antiplatelet therapy	Abciximab vs placebo Thrombectomy vs placebo	Loading dose of ticagrelor vs loading dose of clopidogrel within 24 h of the most recent cardiac ischaemic symptoms and before any planned or urgent PCI	Cangrelor (I.V. bolus then infusion) vs clopidogrel before PCI	Guided de-escalation from prasugrel to clopidogrel or standard DAPT therapy	Experimental DAPT (1 month followed by 23 months of ticagrelor monotherapy) vs reference strategy (12 months of DAPT followed by 12 months of aspirin monotherapy)	Loading dose of ticagrelor as soon as possible after randomisation vs prasugrel loading dose once coronary anatomy was known	Abbreviated (immediate DAPT discontinuation, followed by single APT for ≥ 6 months) or standard regimen (DAPT for ≥ 2 additional months, followed by single APT for 11 months)
Results	Higher rate of MACE in women (30 days) No difference in infarct size (30 days) (p for interaction=0.71)	Female sex was not an independent risk factor for adverse clinical outcomes in moderate-to-high risk ACS patients at 1 year (p for interaction=0.78)	Cangrelor reduced the odds of the primary endpoint by 35% in women and by 14% in men compared with clopidogrel at 48 hours (p for interaction=0.23)	The 1-year incidence of the primary endpoint did not differ in guided de-escalation vs control group patients (p for interaction=0.60)	Similar risk of the primary endpoint at 2 years (p for interaction=0.63) Higher risk of BARC 3 or 5 bleeding and haemorrhagic stroke in women at 2 years (p for interaction=0.09)	No significant interaction between sex and study drug effect (p for interaction=0.275) The superior efficacy of prasugrel was more evident in men	Abbreviated DAPT was associated with comparable NACE rates in men and women (p for interaction=0.65) There was evidence of heterogeneity of treatment effect by sex for MACCE, with a trend towards benefit in women (p for interaction=0.04)

ACS: acute coronary syndrome; APT: antiplatelet therapy; BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; HBR: high bleeding risk; I.V.: intravenous; MACCE: major adverse cardiac and cerebrovascular events; MACE: major adverse cardiovascular events; NACE: net adverse clinical events; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

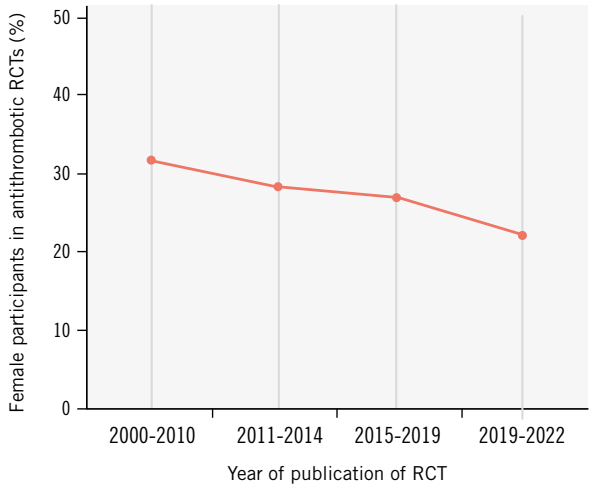


Figure 3. *Mean enrolment rate of female participants in antithrombotic trials by year of publication. RCT: randomised controlled trial*

features of a well-designed trial to provide robust sex-specific evidence include randomisation stratified by sex as well as the avoidance of exclusion criteria that (predominantly) affect women. With regard to the latter, pregnant and lactating women are often excluded based on a protection-by-exclusion strategy, even though this strategy deprives pregnant and lactating women of the benefits of contemporary therapies that would potentially improve their outcomes[72]. Moreover, barriers are routinely placed on women of childbearing potential in participating in clinical trials of antithrombotic therapies owing to concerns about adverse foetal effects of treatment. Nonetheless, anticoagulation poses unique challenges for women of reproductive age, and contraception recommendations in clinical trials may allow equity and access in clinical research[66].

Historical data revealed that three-quarters of clinical cardiovascular trials published in leading general medical and cardiology journals did not report sex-specific analyses[73]. Despite federal legislation, national calls, and several author and reviewer guidelines underlining the importance of such analyses, this practice has not changed over the last decade[74,75].

The Lancet was the first journal to adopt a policy of encouraging researchers to enrol women and ethnic groups into clinical trials of all phases and to plan analyses of data by sex and race, including the enrolment of women in clinical trials and separate reporting of data by sex[76]. Clinical research studies published in the New England Journal of Medicine must include a table in the supplementary appendix that provides background information on the disease to ensure that study participants properly represent the patients affected by the condition being studied[77].

DRUG DISCONTINUATION

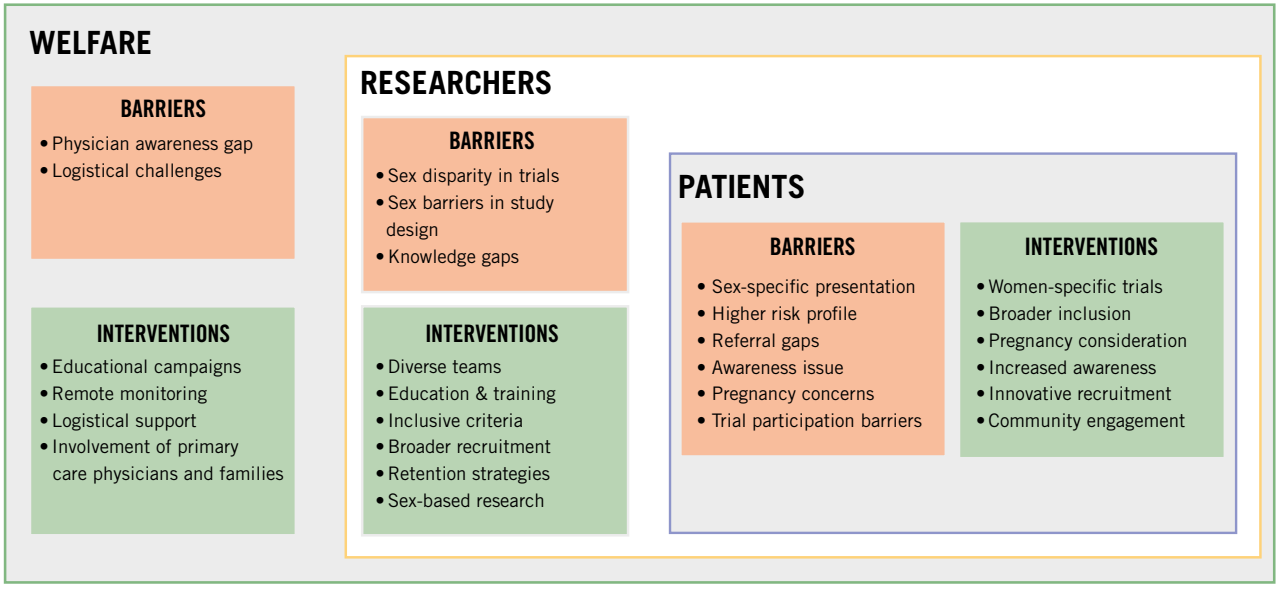
Among the current pitfalls of RCTs on antithrombotic therapies, study drug discontinuation and study retention among women should be listed. Higher odds of premature study drug discontinuation in women versus men may attenuate the observed treatment effect in intention-to-treat analyses and may blunt a potential safety signal. In 135,879 men and 51,812 women enrolled in 11 phase 3 and 4 trials conducted by the TIMI Study Group, and after adjusting for baseline differences, women had a 22% higher odds of premature drug discontinuation (adj. OR 1.22; 95% CI: 1.16-1.28) and were also more likely to withdraw consent compared with men (adj. OR 1.26; 95% CI: 1.17-1.36). The reason behind a higher drug discontinuation rate in women remains incompletely understood. This phenomenon is not explained by differences in age or comorbidities, appears in both active and placebo arms, and has been related and unrelated to bleeding complications[75,76]. Withdrawal of consent and loss to follow-up may compound the interpretation of a possible drug's efficacy or safety.

CURRENT BARRIERS TO WOMEN'S ENROLMENT AND SEX DISPARITIES IN THE RESEARCH SYSTEM

From 1993, the FDA started implementing guidelines encouraging women to participate in clinical trials. The action plan encouraged the completeness, quality, and transparency of demographic subgroup data. However, there is currently no FDA legal requirement for clinical trials to be powered to identify effects for subgroups based on sex, age, or other characteristics. Major barriers to the enrolment of women and minorities are related to cultural, social, and economic constraints. Although poorly investigated, factors such as competing priorities, caregiver roles, or transportation barriers may account for poor female enrolment and premature study discontinuation **(Central illustration)**. Inadequate disease education and poor communication with the research team generate and amplify mistrust in the research system. The leaky pipeline of diversity in the leadership of clinical trials translates into the lack of diversity in enrolled populations. Women currently represent only 1 in 10 lead authors of cardiovascular trials published in high-impact journals, with a minority of first and last authors in cardiovascular research publications[78]. Trials led by female investigators enrol a greater proportion of females (7% higher mean in a recent study) and racial minorities, generating better evidence to assess for sex, race, or ethnicity as effect modifiers of intervention[79,80]. Editorial leadership remains male dominated, and sex bias still affects the peer-reviewing process[81]. Sex disparities in the research system warrant further attention, both to ascertain causes of lower female study enrolment and to target actions that effectively improve female representation in clinical trials contributing to treatment recommendations.

EuroIntervention — Central **Illustration**

Current barriers and potential interventions to improve the recruitment of women in cardiovascular trials.



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CONSENSUS STATEMENT: UNDERREPRESENTATION OF WOMEN IN RCTS

- It is advised to publish sex-specific data, such as the participation-to-prevalence ratio, withdrawal of consent, subanalyses including sex-treatment interaction, reporting adverse events and drug discontinuation by sex, and to provide full access to sex-disaggregated data in RCTs.
- Sample size adjustments and randomisation stratification by sex may be needed to detect relevant differences in treatment effect between women and men, although it may be difficult for economic and logistical reasons.
- All stakeholders from the research system (referring clinicians, investigators and coordinators in research teams, healthcare systems, healthcare administrations, funders, sponsors, professional, and community organisations) should act consistently to ensure the adequate representation of women in RCTs as participants and investigators.
- Action should be taken to increase female patient representation in RCTs such as organising educational campaigns, sharing of experiences by enrolled women, providing logistical support where needed, such as rideshare, childcare, or older adult care, limiting the number of onsite visits, making remote monitoring possible, offering flexible onsite study visitation hours, providing free transportation to study visits, proposing at-home follow-up, evaluating the reasons for study drug discontinuation and withdrawal of consent, expanding inclusion criteria, including pregnant and lactating women after satisfying results in pregnant animals, and involving primary care physicians and family members.
- Institutions, funding agencies and pharmaceutical companies should commit to advancing sex equality in academia at the level of principal investigators and leadership in RCTs. Such actions should have a measurable impact that is assessed through regular and transparent monitoring along the academic seniority pathway and should be incorporated in the rankings of universities and institutions.

Limitations

While transgender-inclusive trials have increased in the past two decades, most have focused on infectious diseases and mental health[82]. There remains a need for greater inclusion of transgender individuals in trials evaluating drugs and biologics for chronic diseases. Consequently, this consensus statement does not address cardiovascular health or provide recommendations on antithrombotic use in transgender women due to the limited quantity and quality of available data.

Conclusions

Despite significant advances in pharmacological and interventional treatments, CVD remains the leading cause of death among women. Differences between sexes in the risks of bleeding and thrombosis should be taken into consideration when using antithrombotic drugs. Importantly, the enrolment and retention of women in RCTs of antithrombotic therapy remain suboptimal and determine important gaps in evidence of drug safety. Barriers to the equal enrolment of women in CV trials have been attributed to several reasons, including patient characteristics, clinical research strategies, and behavioural, socioeconomic, and cultural factors[83,84]. Clinical researchers, sponsors, community organisations, and federal agencies must work together to ensure that representative patient populations are enrolled in future studies.

Authors' affiliations

1. Cardiology Department, Maasstad Hospital, Rotterdam, the Netherlands; 2. Interventional Cardiology Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy; 3. Department of Emergency, Cardiology and Internal Medicine, Division of Cardiology, S. Maria delle Croci Hospital, Ravenna, Italy; 4. Department of Cardiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands; 5. Área del Corazón, Hospital Universitario Virgen de la Victoria, IBIMA Plataforma BIONAND, Departamento de Medicina UMA, Malaga, Spain and Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Malaga, Spain; 6. Department of Biomedical and Dental Sciences and of Morphological and Functional Images, University of Messina, Messina, Italy; 7. Azienda Ospedaliero Universitaria Policlinico "G. Rodolico-San Marco", University of Catania, Catania, Italy; 8. Cardiology Department, Geneva University Hospitals, Geneva, Switzerland; 9. Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom; 10. Postgraduate Medical School, University of Hertfordshire, Hatfield, United Kingdom; 11. Department of Cardiology, University Hospital Santa Maria, Lisbon, Portugal; 12. Cardiology Department, North Cumbria Integrated Care NHS Foundation Trust, Carlisle, United Kingdom; 13. Cardiac Center, King Fahd Armed Forces Center, Jeddah, Saudi Arabia; 14. Department of Invasive Cardiology, Centro Cardiologico Monzino, IRCCS, Milan, Italy; 15. Department of Cardiology, Ludwig-Maximilians-Universität (LMU) München, Munich, Germany; 16. Department of Cardiology and Cardiovascular Interventions, Jagiellonian University Hospital, Krakow, Poland; 17. Research Institute Sant Pau (IR SANT PAU), CIBERCV, Barcelona, Spain; 18. Vita Salute San Raffaele University, Milan, Italy; 19. Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; 20. Cardiovascular Institute Icahn School of Medicine at Mount Sinai, New York, NY, USA; 21. Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy; 22. Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria

Guest Editor

This paper was guest edited by Franz-Josef Neumann, MD, PhD; *Department of Cardiology and Angiology, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany.*

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Supplementary data

Supplementary Appendix 1. Bleeding and ischaemic risk scores.
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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00876

Supplementary data

Supplementary Appendix 1. Bleeding and ischaemic risk scores.

Bleeding risk scores

While many clinicians recognize sex as a variable considered to weight bleeding risk after stent implantation, the actual impact of sex on the independent risk of bleeding is controversial[1]. Various risk scores for estimating bleeding risk are advisable for guidance of antithrombotic treatment post PCI[2]. The controversy surrounding female sex as a dependent vs. independent risk factor for bleeding is also reflected in those scores as female sex accrues the predicted bleeding hazard among most risk scores. In models predicting in-hospital risk of bleeding events, which are more closely related to the impact of invasive procedures and dose-adjusted parenteral antithrombotic agents, female sex was an independent bleeding predictor in the CRUSADE score (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines)[3], the REPLACE score (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events)[4], the ACTION score (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines)[5], and the ACUITY-HORIZONS-AMI score (Acute Catheterization and Urgent Intervention Triage strategY trial and the Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction trial)[6]. All these scores included common variables as female sex, aneamia, renal function, and age as predictive factors, in addition to others[7 8]. In contrast, sex did not appear to be associated to an increased bleeding risk in the out-of-hospital phase. Sex was not an independent predictor of out-of-hospital bleeding events in a large post-PCI population treated with DAPT in the PRECISE-DAPT, and the predictive ability of the score was consistent irrespective of sex at external validation.[9] The ARC-HBR (Academic Research Consortium High Bleeding Risk), proposed as a consensus of experts collecting the most important long-term bleeding risk features, does not include female sex, but age, renal function and anemia, in addition to other variables[7,10]. Importantly, the ARC-HBR score was significantly higher among women than men (0.82 vs 0.60), 43% of women and 32% of men were qualified as at HBR (defined by the presence of at least 2 minor or 1 major ARC-HBR criterion confirming the role of comorbidities for a different long-term bleeding risk between women and men[11]. In fact, in HBR patients defined according to the ARC-HBR criteria, no interaction for sex and HBR status was observed for the explored ischemic and bleeding endpoints[12]. In contrast, in almost 17000 PCI-treated patients (26% women), female sex was an independent predictor of access-site bleeding irrespective of ARC-HBR criteria[11]. This finding underlines the need for strategies to reduce femoral access‐site bleeding especially among women, irrespective of the bleeding risk status and that overall, 1-year bleeding risk after PCI should not be assessed based on sex but on the other bleeding predictors.

Ischemic risk scores

Importantly, female sex was not independently associated with MACE in ischemic/thrombotic risk scores such as GRACE (Global Registry of Acute Coronary Events) or PARIS-CTE (the Patterns of Nonadherence to Antiplatelet Regimens in Stented Patients registry, for coronary thrombotic events; Table 1). Recently, a GRACE 3.0 score was proposed, which reduces sex inequalities in risk stratification as it better performs in men and women, as the older GRACE 2.0 score underestimated in-hospital mortality in female patients with NSTE-ACS[13].

Recently, sex differences in outcome of the high-risk patients were found when a combination of the GRACE and CRUSADE scores was used: ACS patients with high-risk for both bleeding and ischemia, especially females, were less likely to receive guideline-recommended therapy and experienced significantly worse outcome[14].

Potency and duration of DAPT in women

The ESC Guidelines for the management of acute coronary syndromes underline the importance of using bleeding scores and recommend the ARC-HBR score in the decision-making process about the potency and duration of DAPT[15,16]. In line with the current guidelines, a preferential use of potent P2Y12 inhibitors (prasugrel>ticagrelor) for $\geq$ 12 months is advisable in NSTE-ACS patients at low bleeding risk[15,16]. For patients with high or very high bleeding risk, shorter treatment of DAPT for 1 or 3 months, possibly followed by a P2Y12 inhibitor and the implementation of less potent P2Y12 inhibitor clopidogrel may be appropriate[17,18].[19] This strategy is especially relevant for female patients, as more women (43 in 100) than men (32 in 100) fulfill the criteria to shorten the duration and adapt the potency of DAPT according to the ARC-HBR score (1 major point or 2 minor points in the ARC-HBR score)[11]. Accordingly, the benefits of short DAPT were shown for both sexes. Of importance, recent meta-analyses indicate that short DAPT improves the net-benefit and decreases bleeding risk, irrespectively of PCI complexity[20,21].

Supplementary Table 1. Hazard ratio of ischaemic and bleeding outcomes according to sex with use of potent $P2Y_{12}$ inhibitors versus comparator according to a meta-analysis[22].

	HR (95% CI)		
	Female	Male	p interaction
MACE	0.86 (0.78-0.94)	0.85 (0.80-0.90)	0.93
CV death, MI, stroke	0.89 (0.81-0.97)	0.85 (0.80-0.90)	0.60
CV death	0.87 (0.76-1.01)	0.85 (0.77-0.95)	0.86
MI	0.87 (0.78-0.96)	0.84 (0.76-0.91)	0.65
Definite stent thrombosis	0.49 (0.37-0.65)	0.59 (0.42-0.84)	0.85
Definite/probable stent thrombosis	0.59 (0.28-1.22)	0.61 (0.42-0.899	0.94
TIMI non-CABG major bleeding	1.28 (0.87-1.88)	1.52 (1.12-2.07)	0.62
TIMI non-CABG minor bleeding	2.16 (1.37-3.40)	1.44 (0.89-2.32)	0.55
TIMI non-CABG total bleeding	1.54 (1.16-2.05)	1.45 (1.09-1.93)	0.76
ICH	0.96 (0.46-1.98)	1.47 (1.02-2.11)	0.24
All-cause death	0.89 (0.78-1.01)	0.89 (0.81-0.99)	0.99

MACE= major adverse cardiovascular events; CV= cardiovascular; MI= myocardial infarction; CABG= coronary artery bypass graft; ICH= intra-cranial hemorrhage

Supplementary Table 2. Hazard ratio of ischaemic and bleeding outcomes according to sex in the PLATO trial[23].

CV death, MI, stroke	Male	0.86 (0.76-0.97)	0.78
	Female	0.88 (0.74-1-06)	
All-cause death	Male	0.80 (0.67-0.96)	0.49
	Female	0.90 (0.69-1.16)	
Definite stent thrombosis	Male	0.63 (0.45-0.89)	0.78
	Female	0.71 (0.36-1.38)	
Non-CABG major bleeding	Male	1.37 (1.10-1.72)	0.42
	Female	1.19 (0.90-1.56)	
Major/minor bleeding	Male	1.11 (1.10-1.22)	0.99
	Female	1.11 (0.96-1.30)	
Total bleeding	Male	1.13 (1.03-1.23)	0.60
	Female	1.08 (0.93-1.25)	

CV= cardiovascular; MI= myocardial infarction, CABG= coronary artery bypass graft

Supplementary Table 3. Hazard ratio of ischaemic and bleeding outcomes according to sex with ticagrelor versus prasugrel in the ISAR-REACT 5 trial[24].

	HR (95% CI)		**p interaction**
	Female	**Male**	
Death, MI, stroke	1.10 [0.71-1.70]	1.47 [1.13-1.90]	0,275
BARC 3-5 bleeding	1.04 [0.65-1.67]	1.24 [0.85-1.83	0,571

MI= myocardial infarction

Supplementary Table 4. Hazard ratio of major outcomes by sex in the RCT comparing DAT versus TAT in patients on OAC undergoing PCI and/or with ACS[25].

		DAT vs. TAT HR (95% CI)	p interaction
		Bleeding events (trial definition)	
WOEST	Male	0.40 (0.26-0.62)	0.83
	Female	0.34 (0.17-0.72)	
PIONEER AF-PCI	Male	0.63 (0.47-0.84)	0.45
	Female	0.51 (0.32-0.80)	
RE-DUAL PCI D110 mg	Male	0.46 (0.37-0.59)	84
	Female	0.69 (0.47-1.01)	
RE-DUAL PCI D150 mg	Male	0.71 (0.56-0.90)	0.83
	Female	0.74 (0.48-1.16)	
ENTRUST AF-PCI	Male	0.79-0.594-1.039	0.50
	Female	0.93 (0.598-1.434)	
AUGUSTUS (apixaban vs. warfarin)	Male	0.70 (0.57-0.85)	0.86
	Female	0.66 (0.48-0.90)	
AUGUSTUS (aspirin vs. placebo)	Male	1.98 (1.62-2.43)	0.38
	Female	1.67 (1.22-2.30)	
		Thrombosis/Ischemia (trial definition)	
WOEST	Male	0.64 (0.39-1.05)	0.61
	Female	0.53 (0.17-1.35)	
PIONEER AF-PCI	Male	1.16 (0.66-2.03)	0.65
	Female	0.87 (0.45-1.98)	
RE-DUAL PCI D110 mg	Male	1.16 (0.89-1.52)	0.73

	Female	1.05 (0.65-1.70)	
RE-DUAL PCI D150 MG	Male	0.92 (0.66-1.27)	0.72
	Female	0.82 (0.43-1.50)	
ENTRUST AF-PCI	Male	1.02 (0.641-1.631)	0.76
	Female	1.14 (0.520-2.502)	
AUGUSTUS (apixaban vs. warfarin)	Male	0.95 (0.72-1.23)	0.86
	Female	0.90 (0.61-1.34)	
AUGUSTUS (aspirin vs. placebo)	Male	0.90 (0.69-1.18)	0.80
	Female	0.85 (0.57-1.26)	

Supplementary Table 5. ClinicalTrials.gov search criteria.

N	Conditions	Study type	Study results	Enrolment period	Records
1	Cardiovascular disease AND Acute Coronary syndrome AND Antiplatelet	Intervention	Completed	01/01/2001-31/12/2021	27
2	Cardiovascular disease AND Acute Coronary syndrome AND Antithrombotic	Intervention	Completed	01/01/2001-31/12/2021	2
3	Cardiovascular disease AND Acute Coronary syndrome AND Aspirin	Intervention	Completed	01/01/2001-31/12/2021	19
4	Cardiovascular disease AND Acute Coronary syndrome AND P2Y12 inhibitor	Intervention	Completed	01/01/2001-31/12/2021	1
5	Cardiovascular disease AND Acute Coronary syndrome AND Prasugrel	Intervention	Completed	01/01/2001-31/12/2021	27
6	Cardiovascular disease AND Acute Coronary syndrome AND Ticagrelor	Intervention	Completed	01/01/2001-31/12/2021	39
7	Cardiovascular disease AND Acute Coronary syndrome AND Clopidogrel	Intervention	Completed	01/01/2001-31/12/2021	49
8	Cardiovascular disease AND Acute Coronary syndrome AND Cangrelor	Intervention	Completed	01/01/2001-31/12/2021	4
9	Cardiovascular disease AND Acute Coronary syndrome AND Antiplatelet	Intervention	Completed	01/01/2001-31/12/2021	107
10	Cardiovascular disease AND Coronary artery disease AND Antithrombotic	Intervention	Completed	01/01/2001-31/12/2021	19
11	Cardiovascular disease AND Coronary artery disease AND Aspirin	Intervention	Completed	01/01/2001-31/12/2021	70
12	Cardiovascular disease AND Coronary artery disease AND P2Y12 inhibitor	Intervention	Completed	01/01/2001-31/12/2021	5
13	Cardiovascular disease AND Coronary artery disease AND Prasugrel	Intervention	Completed	01/01/2001-31/12/2021	61
14	Cardiovascular disease AND Coronary artery disease AND Ticagrelor	Intervention	Completed	01/01/2001-31/12/2021	117
15	Cardiovascular disease AND Coronary artery disease AND Clopidogrel	Intervention	Completed	01/01/2001-31/12/2021	162
16	Cardiovascular disease AND Coronary artery disease AND Cangrelor	Intervention	Completed	01/01/2001-31/12/2021	12
17	Cardiovascular disease AND Percutaneous Coronary Intervention AND Antiplatelet	Intervention	Completed	01/01/2001-31/12/2021	27
18	Cardiovascular disease AND Percutaneous Coronary Intervention AND Antithrombotic	Intervention	Completed	01/01/2001-31/12/2021	6
19	Cardiovascular disease AND Percutaneous Coronary Intervention AND Aspirin	Intervention	Completed	01/01/2001-31/12/2021	7
20	Cardiovascular disease AND Percutaneous Coronary Intervention AND P2Y12 inhibitor	Intervention	Completed	01/01/2001-31/12/2021	2
21	Cardiovascular disease AND Percutaneous Coronary Intervention AND Prasugrel	Intervention	Completed	01/01/2001-31/12/2021	17
22	Cardiovascular disease AND Percutaneous Coronary Intervention AND Ticagrelor	Intervention	Completed	01/01/2001-31/12/2021	22

23	Cardiovascular disease AND Percutaneous Coronary Intervention AND Clopidogrel	Intervention	Completed	01/01/2001-31/12/2021	47
24	Cardiovascular disease AND Atherosclerosis AND Cangrelor	Intervention	Completed	01/01/2001-31/12/2021	3
25	Cardiovascular disease AND Atherosclerosis AND Antiplatelet	Intervention	Completed	01/01/2001-31/12/2021	8
26	Cardiovascular disease AND Atherosclerosis AND Antithrombotic	Intervention	Completed	01/01/2001-31/12/2021	2
27	Cardiovascular disease AND Atherosclerosis AND Aspirin	Intervention	Completed	01/01/2001-31/12/2021	18
28	Cardiovascular disease AND Atherosclerosis AND P2Y12 inhibitor	Intervention	Completed	01/01/2001-31/12/2021	0
29	Cardiovascular disease AND Atherosclerosis AND Prasugrel	Intervention	Completed	01/01/2001-31/12/2021	0
30	Cardiovascular disease AND Atherosclerosis AND Ticagrelor	Intervention	Completed	01/01/2001-31/12/2021	3
31	Cardiovascular disease AND Atherosclerosis AND Clopidogrel	Intervention	Completed	01/01/2001-31/12/2021	16
32	Cardiovascular disease AND Coronary artery disease AND Cangrelor	Intervention	Completed	01/01/2001-31/12/2021	1

Supplementary Table 6. PubMed search criteria.

N	Searches	Additional search criteria	Items found
1	Anticoagulant Reversal Agents[Mesh] OR "Fibrinolytic Agents"[Mesh] OR antithombotic* [tiab] OR Anticoagulant Reversal Agents[tiab] OR "Fibrinolytic Agents" [tiab] AND Percutaneous Coronary Intervention[Mesh] OR percutaneous coronary intervention [tiab]	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	3323
2	Anticoagulant Reversal Agents[Mesh] OR "Fibrinolytic Agents"[Mesh] OR antithombotic* [tiab] OR Anticoagulant Reversal Agents[tiab] OR "Fibrinolytic Agents" [tiab] AND Acute Coronary Syndrome[Mesh] OR Acute Coronary Syndrome[tiab]	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	240
3	Acute Coronary Syndrome[Mesh] OR Acute Coronary Syndrome[tiab] AND Platelet Aggregation Inhibitors[Mesh] OR Platelet Aggregation Inhibitors[tiab] OR antiplatelet*[tiab]	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	783
4	Percutaneous Coronary Intervention[Mesh] OR percutaneous coronary intervention [tiab] AND Platelet Aggregation Inhibitors[Mesh] OR Platelet Aggregation Inhibitors[tiab] OR antiplatelet*[tiab]	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	1517
5	Percutaneous Coronary Intervention[Mesh] OR percutaneous coronary intervention [tiab] AND P2Y12inhibitor	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	1536
6	Acute Coronary Syndrome[Mesh] OR Acute Coronary Syndrome[tiab] AND P2Y12inhibitor	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	1541
7	Acute Coronary Syndrome[Mesh] OR Acute Coronary Syndrome[tiab] AND Ticagrelor OR Prasugrel OR Clopidogrel OR Cangrelor	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	2341
8	Percutaneous Coronary Intervention[Mesh] OR percutaneous coronary intervention [tiab] AND Ticagrelor OR Prasugrel OR Clopidogrel OR Cangrelor	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	2345

9	Percutaneous Coronary Intervention[Mesh] OR percutaneous coronary intervention [tiab] AND Aspirin	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	2927
10	Acute Coronary Syndrome[Mesh] OR Acute Coronary Syndrome[tiab] AND Aspirin	Clinical Trial, Phase III, Clinical Trial, Phase IV, Randomized Controlled Trial, English, Adult: 19+ years, from 2001/1/1 - 2021/12/31	2381

Supplementary Table 7. Details and specifications of clinical trials on antithrombotics.

ClinicalTrials.gov	Year of Publication	Population	Phase	Type of Study	Participating sites	Female representation
NCT00250471	2006	18 Years to 80 Years (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	United States	33.0
NCT00133003	2006	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	Europe, Brazil	29.6
NCT00097591	2007	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	United States	26.0
NCT00110448	2008	30 Years to 85 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Investigator, Outcomes Assessor)|Primary Purpose: Prevention	Japan	45.5
NCT00305162	2009	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Treatment	United States	26.9
NCT00391872	2009	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	North and South America, Europe, Asia	28.3
NCT00385138	2009	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Treatment	United States	28.8
NCT00335452	2010	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Factorial Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	North and South America, Europe	24.5
NCT00590174	2010	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	30.0
NCT00714961	2010	18 Years to 75 Years (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	United States, Europe, Africa	20.2

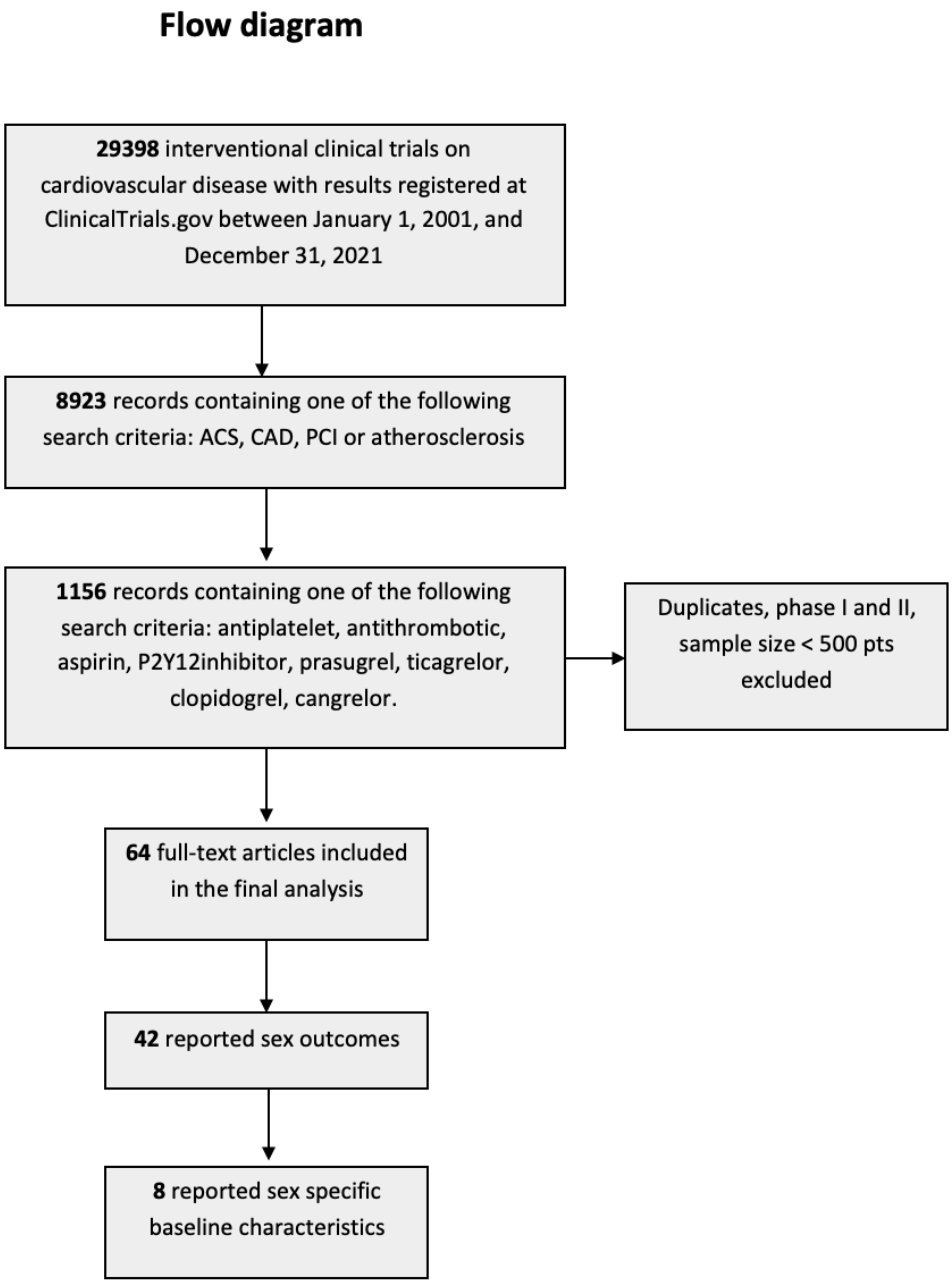
NCT01145079	2012	20 Years to 85 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	63.6
NCT00222261	2012	18 Years to 80 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Norway	22.0
NCT00821834	2012	20 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	Japan	28.0
NCT00611286	2012	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Factorial Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Italy	23.3
NCT00827411	2012	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	France	19.3
NCT00699998	2012	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	North and South America, Europe, Asia	35.9
NCT01156571	2013	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	United States	29.1
NCT00623623	2013	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Europe, South America	21.3
NCT01113372	2013	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Supportive Care	Brazil	36.7
NCT01015287	2013	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	Europe	27.5
NCT01267734	2013	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	31.6
NCT00944333	2014	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Europe	22.8

NCT01192724	2014	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	36.5
NCT01186146	2014	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	31.0
NCT00977938	2014	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Treatment	United States, Europe, New Zealand	25.3
NCT00976092	2014	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Treatment	Germany	22.5
NCT00780156	2014	18 Years and older (Adult, Older Adult)		Time Perspective: Prospective	Europe	19.6
NCT01347580	2015	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	Europe, Canada, Australia	19.8
NCT01225562	2015	50 Years to 130 Years (Adult, Older Adult	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	North and South America, Europe, Asia	23.7
NCT01659034	2015	Child, Adult, Older Adult	Phase 4	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Asia	27.0
NCT01069003	2015	19 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Treatment	United States	30.0
NCT01094457	2015	35 Years to 75 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Treatment	China	33.0
NCT00661206	2015	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	United States, Europe, Asia	19.4
NCT01538446	2016	75 Years and older (Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	France	39.5
NCT02808767	2016	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Treatment	Czech Republic	24.6

NCT00822536	2016	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	France	19.5
NCT01959451	2017	18 Years to 80 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Europe	21.3
NCT01761786	2017	22 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Treatment	Europe	25.0
NCT01514227	2017	20 Years to 80 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Japan	20.9
NCT01459627	2018	18 Years to 85 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Europe	23.0
NCT03056118	2018	20 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Factorial Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Treatment	Korea	31.1
NCT01870921	2018	18 Years to 130 Years (Adult, Older Adult	Phase 4	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	China	21.0
NCT01813435	2018	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Europe, Canada, South America, Australia	23.2
NCT01777503	2018	75 Years and older (Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Treatment	Italy	40.0
NCT02099617	2018	75 Years and older (Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Participant)|Primary Purpose: Treatment	Europe	37.5
NCT02406677	2019	18 Years to 130 Years (Adult, Older Adult	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Health Services Research	United States	31.5
NCT02619760	2019	Child, Adult, Older Adult	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Japan	22.0
NCT02094963	2019	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	25.2

NCT02118870	2019	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Europe and Asia	20.0
NCT02298088	2019	18 Years to 75 Years (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	North and South America, Australia, New Zealand, China, Europe	22.9
NCT01944800	2019	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Treatment	Germany, Italy	23.8
NCT02617290	2020	18 Years and older (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	France	20.5
NCT01742117	2020	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	United States, Canada, Mexico, Korea	25.0
NCT02193971	2020	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	10.7
NCT02317198	2020	70 Years and older (Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Netherlands	36.0
NCT02494895	2020	19 Years to 79 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	20.5
NCT02548611	2020	18 Years to 80 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Treatment	Germany, Hungary	19.0
NCT02605447	2021	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	United States, Europe, Japan	26.0
NCT02018055	2021	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: Non Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	16.8
NCT03381742	2021	18 Years and older (Adult, Older Adult)	Phase 2|Phase 3	Allocation: Non Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Treatment	China	35.1
NCT02044250	2021	20 Years and older (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Korea	4.0

NCT03112707	2022	18 Years and older (Adult, Older Adult)	Phase 4	Allocation: N/A |Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Italy	29.1
NCT03198741	2022	18 Years to 80 Years (Adult, Older Adult)	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (ParticipantCare Provider-InvestigatorOutcomes Assessor)|Primary Purpose: Treatment	China	25.7
NCT03462498	2022	Child, Adult, Older Adult	Phase 4	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	Japan	21.0



Supplementary Figure 1. Flow diagram for the systematic review of the participation of women in RCTs on antithrombotic therapy, and sex reporting.