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Gender differences in antithrombotic therapy

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Summary. Evidence on the management of atherothrombotic diseases derives from clinical trials where women are usually underrepresented; however, it is well known that gender differences in the incidence and clinical presentation of cardiovascular diseases, and in the efficacy and safety of antithrombotic treatment exist. The pathophysiological mechanisms underlying these gender differences are not fully understood, and are likely multifactorial. Among patients with atrial fibrillation, women are at higher risk of stroke than men. The reasons for this elevated risk remain unclear, but may include older age, under-treatment with anticoagulant therapy, and poor anticoagulation control. Few data are available on possible gender differences regarding the efficacy and safety of direct oral anticoagulants. As concerns antiplatelet therapy, the use of aspirin for primary prevention is associated with a higher risk reduction for ischemic stroke in females and for myocardial infarction in males. In the setting of acute coronary syndromes, the female gender is associated with a significantly higher risk of bleeding. These differences could have implications for future sex-specific treatment and prevention strategies for atherothrombotic diseases. However, the inclusion of a larger number of women in randomized trials evaluating cardiovascular outcomes with the use of antithrombotic drugs is needed in order to produce stronger evidence-based recommendations. The aim of this review is to provide an overview of available data on gender differences in antithrombotic therapy, and to analyze the potential reasons accounting for them.

Key words: antithrombotic therapy, gender, atherothrombotic disease, thrombotic risk, bleeding risk, anticoagulant therapy, antiplatelet therapy.

Differenze di genere nella terapia antitrombotica

Riassunto. La gestione delle patologie aterotrombotiche è guidata da evidenze derivanti da studi clinici in cui le donne sono generalmente meno rappresentate rispetto agli uomini; è noto tuttavia che esistono differenze di genere nell'incidenza e nella presentazione clinica delle malattie cardiovascolari, nonché nella risposta alle terapie antitrombotiche in termini di efficacia e sicurezza. I meccanismi fisiopatologici alla base di queste differenze di genere non sono del tutto chiariti e sono verosimilmente multifattoriali. Le donne affette da fibrillazione atriale hanno un rischio di ictus più elevato rispetto agli uomini, che in parte è riconducibile a un'età più avanzata, a un sottotrattamento con farmaci anticoagulanti, oltre che a una peggior qualità di conduzione della terapia anticoagulante orale. I dati disponibili su possibili differenze di genere nell'efficacia e nella sicurezza degli anticoagulanti orali diretti sono al momento più limitati. Per quanto riguarda la terapia antiaggregante piastrinica, nell'ambito della prevenzione primaria, l'aspirina si è dimostrata efficace nel ridurre significativamente gli eventi coronarici maggiori negli uomini, ma non nelle donne. Nella prevenzione secondaria delle sindromi coronariche acute, il sesso femminile è risultato associato invece a un aumentato rischio di sanguinamento in corso di terapia antiaggregante piastrinica. Queste differenze di genere potrebbero avere implicazioni per lo sviluppo di future strategie sesso-specifiche di trattamento e prevenzione delle malattie aterotrombotiche. Tuttavia, sono necessari studi randomizzati che includano un maggior numero di soggetti di sesso femminile, al fine di produrre raccomandazioni basate su solide evidenze.

Parole chiave: terapia antitrombotica, genere, patologie aterotrombotiche, rischio trombotico, rischio di sanguinamento, terapia anticoagulante, terapia antiaggregante piastrinica.

Introduction

It is known that gender differences exist in the incidence and clinical presentation of cardiovascular diseases, and available data show a different response to antithrombotic therapy between males and females in terms of efficacy and safety. Evidence on atherothrombotic disease management derives from clinical trials where women are generally less represented than men, and few studies have focused their attention exclusively on female subjects.

The pathophysiological mechanisms underlying these gender differences are not fully understood, and are likely multifactorial. Available data show that some female biological characteristics might explain, at least in part, the differences in the risk of bleeding and thrombosis related to antithrombotic therapies, making the net clinical benefit of such therapies lower than in men of the same age. In addition, women included in clinical

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trials on antithrombotic drugs are on average older, and have more comorbidities and risk factors than men, being therefore at greater risk of both thrombotic and bleeding adverse events[1].

The aim of this review is to provide an overview of available data on gender differences in antithrombotic therapy, and to analyze the potential reasons accounting for them.

Thrombotic and hemorrhagic risk in women: biology of gender differences

The incidence of cardiovascular diseases is higher in men than in women up to 39 years, more or less similar in both sexes between 40 and 79 years, whereas after the age of 80 it becomes greater in females.

The overall rate of coronary artery disease-related mortality is higher for men than for women; however, this difference has diminished over the last decade, with a decrease shown in men, and a simultaneous disproportionate increase in women.

Recent data show that the incidence of myocardial infarction has been increasing in middle age women, due to an increasing prevalence of diabetes and hypertension compared with men. Women with diabetes have a higher risk of developing coronary heart disease or stroke, a worse prognosis after myocardial infarction, and higher cardiovascular mortality than men.

During the course of life women are exposed more frequently than men to prothrombotic changes in the hemostatic balance, in relation to menstrual cycle, oral contraceptives, pregnancy and childbirth, menopause and hormone replacement therapy, with a potential impact on the global incidence of atherothrombotic diseases. In the setting of venous thromboembolism (VTE) the higher incidence reported in females of reproductive age is indeed mainly explained by the use of hormonal contraceptives, pregnancy and puerperium, and it has been shown that, after adjustment for these factors, men have a two-fold increased risk of first VTE compared with women[2].

It has been suggested that hormonal pleiotropic effects, in combination with a prolonged exposure to pro-atherogenic risk factors, a pro-inflammatory state, and gender-specific microvascular dysfunction, are able to induce vascular and metabolic alterations leading to a more accelerated atherosclerotic process and a poorer prognosis in women than in men. In a study of premenopausal women undergoing coronary angiography for suspected myocardial ischemia, a low level of estrogen was significantly associated with the presence of coronary lesions. Similarly, it was shown that a hyperandrogenic state, such in polycystic ovarian syndrome, is associated with a higher incidence of cardiovascular events. Sex hormones play a crucial role in the regulation of the synthesis and metabolism of mediators and receptors acting on the vascular smooth muscle and endothelium-derived vasoactive factors, with subsequent effects on blood flow and peripheral vascular resistance. Moreover, it has been suggested that gender differences in platelet function may be the result of a direct estrogen, progesterone and androgen effect on platelets, or of an indirect effect of sex hormones on the vessels. The increased post-menopausal incidence of cardiovascular diseases could also be an expression of gender differences in lipid metabolism, renin-angiontensin-aldosterone system, and hemostatic system. Finally, the presence of genetically-determined alterations of hemostasis and endothelial function could interact with the hormonal substrate and environmental factors in determining a high risk pro-thrombotic phenotype in women (Figure 1)[1].

As concerns antithrombotic therapies-related hemorrhagic risk, gender differences have also been reported. Available data show that the rate of bleeding complications in the acute phase of coronary events is significantly greater in women than men. This fact can be explained in part by the lower body weight, by a greater incidence of renal failure, as well as by an inappropriate dosing of antithrombotic drugs. The increased risk of bleeding in the acute phase may also affect the lower use of antiplatelet drugs for long-term therapy, with a delay in reintroducing the treatment, and a subsequent higher risk of thrombotic complications[2].

Anticoagulant therapy

Several studies evaluated the possible different anticoagulant effect of warfarin in relation to sex in animal models. In a study of Hara et al., a reduction in warfarin effect was demonstrated by prothrombin time prolongation in female rats. The same authors showed that treatment with 17.3-estradiol inhibited the anticoagulant effect of warfarin without changing warfarin plasma levels[3].

In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) database, consisting of 4,060 patients on oral anticoagulant therapy with vitamin K antagonists for atrial fibrillation (AF), the relationship between sex and the risk of ischemic stroke according to time spent in therapeutic range (TTR) was evaluated: women showed a significantly lower TTR than men (37±0.5% vs 40±0.7, p = 0.0001), and, in particular, a greater percentage of time spent below the therapeutic range. However, a higher TTR was found to be protective against the risk of ischemic stroke in women, but not in men. In addition, women showed a higher estimated thromboembolic risk by Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke ($CHADS_2$) score

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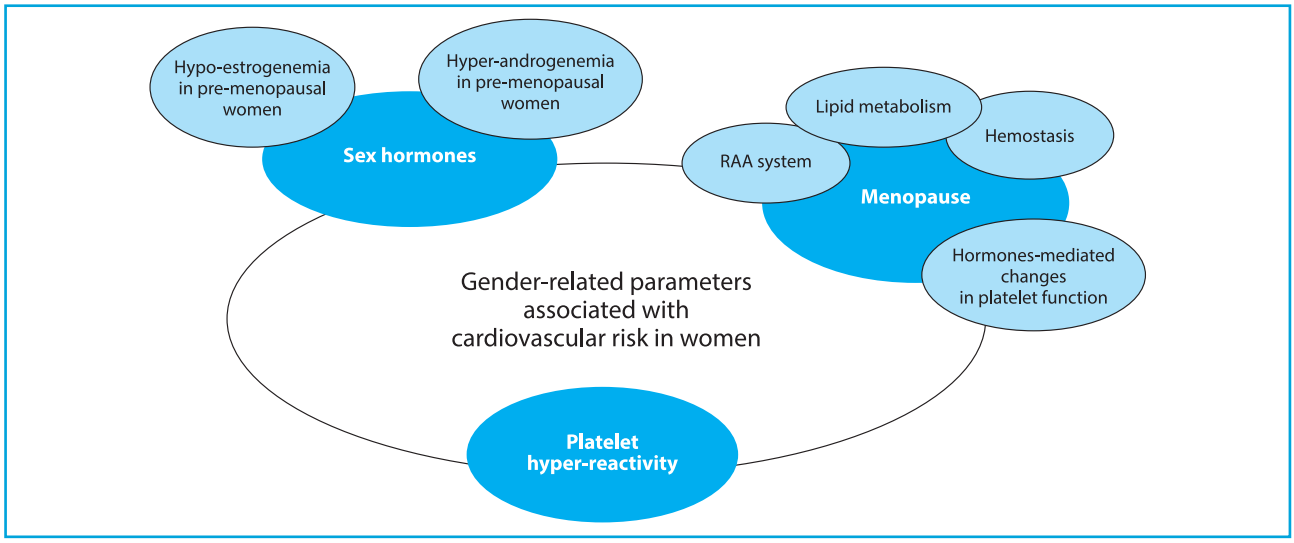

Figure 1. Gender-related parameters associated with cardiovascular risk in women.

(3.7±1.3 vs 2.5±1.3, p <0.0001) and a higher rate of ischemic stroke (5 vs 3%, p = 0.002) compared with men, suggesting that women with AF may benefit from a more aggressive anticoagulation therapy[4]. Data obtained on a large cohort of 13,559 patients with AF showed that women, in the absence of anticoagulation therapy, have a higher annual rate of thromboembolic complications than men (3.5 vs 1.8%; RR 1.6, 95% CI 1.3-1.9), with no significant differences in mortality at 30 days (23% for both sexes). Moreover, warfarin therapy was associated with a significantly lower incidence of thromboembolic complications in both sexes, with a similar annual rate (about 1%) of bleeding complications[5]. A prospective study, involving 780 patients with AF treated with vitamin K antagonists and followed by an anticoagulation clinic, aimed at assessing the role of the female gender as a risk factor for stroke, showed a higher risk in women, despite a similar quality of anticoagulation therapy. No significant difference was found between genders with regard to the quality of anticoagulant therapy and the risk of bleeding complications. However, women showed a higher rate of ischemic stroke than men (2.43 vs 1.2 x100 patient/years, p = 0.042), even after adjustment for age. Furthermore, strokes in women were associated with greater disability, with a relative risk of severe and fatal stroke of 3.1 as compared with men (p = 0.001)[6]. Similarly, a population study conducted in Canada from 1998 to 2007 on 39,398 men and 44,115 women aged ≥65 years with newly diagnosed AF showed that, despite good adherence to warfarin therapy in both sexes, women had a higher risk of stroke than men (2.2 vs 1.61 x100 patient/years; p <0.001), which was confirmed at multivariate analysis adjusted for comorbidities, $CHADS_2$ score risk factors, and treatment with warfarin[7]. On the basis of these results the item "female gender" was added as a risk factor in the most recent thromboembolic risk score Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke/TIA/Thromboembolism, Vascular disease, Age 65-74, Sex category -female- (CHA_2DS_2-VASc). However, female gender does not appear to increase stroke risk in the absence of other stroke risk factors. According to the 2016 European Society of Cardiology Guidelines for the management of AF, oral anticoagulation therapy to prevent thromboembolism is therefore recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more, and should be considered in those with a CHA_2DS_2-VASc score of 2, based on individual characteristics and patient preferences[8].

On the other hand, as concerns bleeding risk, observational studies do not show significant differences in the rate of major bleeding complications between males and females, so that gender is not included as a risk factor in the most commonly used bleeding risk scores, such as the Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol (HAS-BLED) score.

Recently, in the prospective multicenter registry GARFIELD (Global Anticoagulant -The Prospective Registry in the FIELD-Atrial Fibrillation) on 17,184 patients with non-valvular AF, there were no significant differences between the sexes in the use of anticoagulant therapy for the prevention of stroke. However, the use of antithromboembolic prophylaxis was sub-optimal in a significant percentage of men and women, with underuse in the moderate- and high-risk patients, and overuse in those at low risk[9].

Available data on possible gender differences on the efficacy and safety of direct oral anticoagulants (DOACs) are more limited. Sub-group analyses of phase III trials on DOACs showed no significant differences in efficacy

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Table 1. Studies on efficacy and safety of anticoagulant therapy according to gender.

Drug	Study	n (females)	Results
Vitamin K antagonists	Fang, 2005[5]	13,559 (5,795)	Higher risk for AF-related thromboembolism of warfarin in women than in men. Warfarin therapy as effective in women than in men, with similar rates of major hemorrhage.
	Poli, 2009[6]	780 (275)	Higher risk of stroke in anticoagulated AF females than in males, despite a similar quality of anticoagulation.
	AFFIRM, 2012[4]	4,060 (1,594)	Significantly lower time in therapeutic range (TTR) in women than in men. Higher TTR protective against the risk of ischemic stroke in women, but not in men.
	Poli, 2013[13]	3,015 (1,654)	No clear gender differences in the risk of major adverse events. Higher rate of bleeding complications in males, slightly higher rate of stroke in females.
Direct oral anticoagulants	Meta-analysis, Pancholy, 2014[10]	26,260 (9,500)	Equivalent residual thromboembolic risk and less major bleeding risk in women than in men treated for AF.
	Meta-analysis, Dentali, 2015[11]	71,580 AF patients (26,660) 26,872 VTE patients (11,518)	No gender-related difference in efficacy and safety in patients with AF or acute VTE.
	Meta-analysis, Alotaibi, 2013[12]	9,417 VTE patients (4,119)	More bleeding complications in women than in men treated for VTE.

AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management.

and safety according to gender. Pancholy et al., in a meta-analysis evaluating gender differences in residual risk of stroke/systemic embolism and major bleeding in patients with nonvalvular AF treated with either warfarin or DOACs, found that women with AF treated with warfarin have a greater residual risk of thromboembolism and an equivalent risk of major bleeding, whereas those treated with DOACs are at an equivalent residual thromboembolic risk and lower major bleeding risk compared with men[10]. A recent meta-analysis by Dentali et al. on thirteen studies involving over 100,000 patients showed no significant gender-related differences in efficacy and safety between DOACs and vitamin K antagonists in patients treated for non-valvular AF and acute VTE; a trend of an increased bleeding risk with DOACs versus placebo was found in males compared with females in the extended treatment of VTE[11]. In contrast, in the setting of VTE, a meta-analysis of eight randomized controlled trials of 9,417 patients treated with DOACs showed a higher rate of major bleeding in women than in men, with no significant differences between genders in terms of efficacy in the prevention of VTE recurrences and mortality from all causes[12]. Given these conflicting results, further studies are needed to evaluate the clinical impact of potential gender differences in the safety profile of DOACs.

Table 1 summarizes the results of the main clinical studies and meta-analyses on efficacy and safety of anticoagulant therapy according to gender[4-6; 10-13].

Antiplatelet therapy

Several data show a higher platelet reactivity, and a higher prevalence of high platelet reactivity on an aspirin and clopidogrel therapy in females[1,2].

As concerns primary prevention, the efficacy and safety of aspirin use was evaluated in the Women's Health Study (WHS), on 39,876 healthy women ≥45 years of age, randomized to receive aspirin 100 mg every other day or placebo, and followed up for 10 years. This trial showed that aspirin did not reduce the overall risk of major cardiovascular events, but was associated with a reduced risk of stroke. No significant difference was found in the incidence of hemorrhagic stroke, whereas there was an increased rate (of approximately 1.4 times) of aspirin-related risk of gastrointestinal bleeding[14]. A meta-analysis, analyzing data from this and other studies for a total of 51,342 women, showed a modest protective effect of aspirin on the prevention of cardiovascular events and stroke, a non significant reduction of the risk of myocardial infarction or cardiovascular mortality, and an increased risk of bleeding[15]. The Antithrombotic Trialists' (ATT) collaboration meta-analysis on six randomized primary prevention trials (three conducted only on men, one only on women, and two on both sexes), for a total of 95,000 subjects, showed a significant reduction in major coronary events associated with aspirin use in men, but not in women[16]. Various hypotheses have been sug-

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gested to explain gender differences in the cardioprotective effect of aspirin, including differences in platelet biology, in aspirin metabolism, as well as an increased frequency of platelet hyperreactivity while on aspirin therapy in women versus men. However, literature data are insufficient to draw definitive conclusions.

In the setting of secondary prevention of cardiovascular diseases, in the ATT meta-analysis, no significant interaction between sex and aspirin effect compared with placebo was found: in particular, the relative risk reduction of coronary events during follow-up was 19% in males and 27% females, while the risk reduction of major vascular events (myocardial infarction, stroke, vascular death) was 19% in both sexes[16]. In a meta-analysis of five randomized trials comparing clopidogrel and placebo in addition to aspirin on a total of 79,613 patients with ischemic heart disease (most with acute coronary syndromes -ACS-) or high risk of recurrence of cardiovascular events, the long-term cardiovascular event rate among the 23,533 women analyzed was similar in the two arms of the study (clopidogrel vs placebo, 11% vs 11.8%, respectively), while, among men, clopidogrel was significantly associated with a reduced incidence of cardiovascular events[17]. The authors speculate that most of sex differences may, however, be the effect of chance. In the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet iNhibition with prasugrel – Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trial, comparing prasugrel and clopidogrel in addition to aspirin in patients with ACS undergoing percutaneous revascularization, no significant interaction was found between treatment and gender, although men showed once again a greater reduction of the absolute and relative risk of major cardiovascular events at 15 months with prasugrel compared with women[18]. The PLATelet Inhibition and patient Outcomes (PLATO) trial, comparing ticagrelor and clopidogrel in addition to aspirin in patients with ACS, showed no significant differences between genders in the reduction of the absolute and relative risks of adverse events at one year with ticagrelor[19]. Despite the fact that dual antiplatelet therapy seems to be associated with a reduced risk of ischemic events both in women and men, sex-related differences in bleeding risk are consistently demonstrated in ACS. Women enrolled in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA (CRUSADE) registry who underwent percutaneous revascularization had significantly higher rates of in-hospital major bleeding with respect to men (14.1 vs 5.9 %, p <0.0001), the majority of bleeding being related to the site of access[20]. In the meta-analysis by Berger et al., the use of clopidogrel in addition to aspirin was associated with a higher long-term incidence of major bleeding in both sexes[17]. In the TRITON-TIMI 38, at multivariate analysis, the female gender was found as the strongest predictor of major bleeding not related to coronary-artery bypass grafting during follow-up[18]. In the PLATO study, the female gender was independently associated with a higher risk of procedure-related bleeding, while the association did not remain significant for other types of bleeding complications[19].

Table 2 summarizes the results of the main clinical studies and meta-analyses on efficacy and safety of antiplatelet therapy according to gender[14-15;17-26].

Limitations of available trials on efficacy and safety of antithrombotic therapies according to gender

One of the main limitations of available clinical trials evaluating cardiovascular outcomes with the use of antithrombotic therapies is that women are generally less represented than men. On average, among 801,198 patients enrolled in 156 cardiovascular trials, only 30.6% were women, and only one-third of the trials reported gender-specific results[27]. Potential reasons include an underestimation of cardiac risk and misinterpretation of symptoms in women, with fewer referrals for diagnostic tests, and therefore lower rates of appropriate diagnosis and treatment.

Conclusions

Data from observational and intervention studies suggest that gender-specific differences in clinical manifestations of cardiovascular diseases, and in the efficacy and safety of antithrombotic treatment exist. Different factors affecting vascular, platelet, and coagulation function, partly related to hormonal status, might contribute, although strong evidence is lacking. These differences could have implications for future gender-specific treatment and prevention strategies for atherothrombotic diseases. However, as the female gender is still underrepresented in randomized trials evaluating cardiovascular outcomes with the use of antithrombotic drugs, the inclusion of a larger number of women in such trials is needed, in order to produce stronger evidence-based recommendations.

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Table 2. Studies on efficacy (a) and safety (b) of antiplatelet therapy according to gender.

a) Efficacy			
Drug	**Study**	**n (females)**	**Results**
Aspirin	NHS, 1991[21]	n=85,000 Only females	Risk ↓ in death from cardiovascular diseases and stroke (Primary prevention)
	HOT, 2000[22]	n=18,790 (8,883)	Risk ↓ of myocardial infarction in men but not in women (Primary prevention)
	PPP, 2001[23]	n=4,495 (2,583)	Risk ↓ of myocardial infarction in men but not in women Trend of ↓ stroke in women but not in men (Primary prevention)
	Women's Health Study, 2005[14]	n=39,876 Only females	Risk ↓ of stroke but not of myocardial infarction (women >65 years) (Primary prevention)
	ISIS-2, 1988[24]	n=17,187 (3,953)	Risk ↓ in vascular mortality in men and women (22% in men, 16% in women) (Secondary prevention)
	IST, 1997[25]	n=19,435 (9,028)	Risk ↓ of recurrent ischemic strokes both in men and women (Secondary prevention)
Clopidogrel	Meta-analysis, 2009[17]	n=79,613 (23,533)	Risk ↓ of myocardial infarction, but not of all combined endpoints In women,
Prasugrel	TRITON-TIMI 38, 2007[18]	n=13,608 (7,076)	Greater ↓ of risk of major cardiovascular events at 15 months in men compared with women
Ticagrelor	PLATO, 2009[19]	n=18,624 (5,288)	No significant differences between genders in the reduction of risks of adverse events at one year
b) Safety			
Drug	**Study**	**n (females)**	**Results**
Aspirin	WHS, 2005[14]	n=39,876 Only females	↑ risk of gastrointestinal bleeding requiring transfusion (Primary prevention)
	Meta-analysis, 2006[15]	n=51,342 Only females	Significant ↑ risk of bleeding to a similar degree among women and men (Primary prevention)
Clopidogrel	CRUSADE Registry, 2009[26]	n=71,277 (28,369)	Female gender as independent predictor of in-hospital major bleeding in acute coronary syndromes
	CRUSADE Registry: analysis in patients undergoing invasive PCI with Gp IIb/IIIa inhibitors, 2006[20]	n=32,601 (12,152)	↑ rates of bleeding in women than men whether or not they are treated with Gp IIb/IIIa inhibitors
Prasugrel	TRITON-TIMI 38, 2007[18]	n=13,608 (7,076)	Female gender as the strongest predictor of major bleeding not related to coronary-artery bypass grafting
Ticagrelor	PLATO, 2009[19]	n=18,624 (5,288)	Female gender independently associated with higher risk of procedure-related bleeding

NHS, Nurses' Health Study; HOT, Hypertension Optimal Treatment; PPP, Primary Prevention Project; WHS, Women Health Study; ISIS-2, International Study of Infarct Survival 2; IST, International Stroke Trial; TRITON-TIMI 38, TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet iNhibition with prasugrel – Thrombolysis In Myocardial Infarction 38; PLATO, PLATelet Inhibition and patient Outcomes; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation.

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Key messages

- Gender differences exist in the incidence and clinical presentation of cardiovascular diseases, and in the efficacy and safety of antithrombotic treatment.
- Multifactorial pathophysiological mechanisms, including genetically-determined alterations of homeostasis and endothelial function, hormonal effects, and environmental factors, may be responsible for these gender differences.
- Among patients with atrial fibrillation, women are at higher risk of stroke than men, probably, at least in part, due to older age, under-treatment with anticoagulant therapy, and poor anticoagulation control.
- The use of aspirin for primary prevention of cardiovascular diseases is associated with a greater risk reduction for ischemic stroke in females and for myocardial infarction in males, whereas in the setting of acute coronary syndromes, the female gender is associated with a significantly higher risk of bleeding if on antiplatelet therapy.
- These differences could have implications for future sex-specific treatment and prevention strategies for atherothrombotic diseases. However, the inclusion of a larger number of women in randomized trials evaluating cardiovascular outcomes with the use of antithrombotic drugs is needed in order to produce strong evidence-based recommendations.

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