International Journal of Cardiology 286 (2019) 198–207

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Thrombotic and hemorrhagic burden in women: Gender-related issues in the response to antithrombotic therapies

Giulia Renda [a,*], Giuseppe Patti [b], Irene Marthe Lang [c], Jolanta M. Siller-Matula [d], Elaine M. Hylek [e], Giuseppe Ambrosio [f], Sylvia Haas [g], Raffaele De Caterina [h], on behalf of Working Group on Thrombosis of the Italian Society of Cardiology

[a] Institute of Cardiology, G. d'Annunzio University, Chieti, Italy
[b] Institute of Cardiology, Campus Bio-Medico University, Rome, Italy
[c] Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Austria
[d] Department of Cardiology, Medical University of Vienna, Austria
[e] Department of Medicine, Boston University School of Medicine, Boston, MA, United States of America
[f] Division of Cardiology, University of Perugia School of Medicine, Italy
[g] Formerly Klinikum rechts der Isar, Technical University Munich, Germany
[h] Division of Cardiovascular Medicine, Cardio-Thoracic and Vascular Department, University of Pisa, Italy

ARTICLE INFO

Article history:
Received 24 August 2018
Received in revised form 9 January 2019
Accepted 4 February 2019
Available online 8 February 2019

Keywords:
Gender medicine
Thrombosis
Coagulation
Antithrombotic therapies
Bleeding

ABSTRACT

Thrombotic and bleeding risks, as well as the incidence and presentation of cardiovascular events and related outcomes, appear to differ between genders, partly in relation to variability in age, comorbidities and body size. Women experience frequent fluctuations of pro-thrombotic activity during their lifetime, related to menstrual cycles, the use of oral contraceptives, pregnancy, menopause, and hormone replacement therapy, all with potential impact on the clinical manifestations of atherosclerotic disease. On the other hand, compared with men, women feature an increased risk of bleeding during hospitalization in the setting of acute coronary syndromes or percutaneous coronary interventions.

At the same time, benefits of antithrombotic therapy may differ in women compared with men in several clinical settings and according to the type of antithrombotic agent used for primary and secondary cardiovascular prevention, for the prevention of thromboembolism in patients with atrial fibrillation, and for the prevention and treatment of venous thromboembolism.

Data from observational and interventional studies do not exclude gender-specific differences in either the thrombotic and hemorrhagic burden, and the effects of antithrombotic drugs on clinical outcomes might also differ between men and women. Pathophysiological mechanisms causing these disparities are not entirely clear. Multiple factors in platelet function and coagulation mechanisms in different vascular beds, partly related to the hormonal status, might contribute to such gender differences.

1. Introduction

Together with the incidence and presentation of cardiovascular events and related outcomes, the risks of thrombosis and bleeding appear to differ between genders, partly in relation to differences in age presentation of cardiovascular disease, comorbidities, and body size. In addition, women experience frequent fluctuations of prothrombotic activity related to menstrual cycles, the use of oral contraceptives, pregnancy, menopause, and hormone replacement therapy, all with potential impact on the clinical manifestations of thromboembolic complications. In parallel, gender-related differences in ex vivo platelet function have been observed, possibly the result of direct effects on platelets of estrogens, progesterone, or androgens. Finally, indirect effect of sex hormones on the vasculature may occur [1].

On the other hand, compared with men, women apparently feature a higher risk of bleeding complications during hospitalization in the setting of acute coronary syndromes (ACS) [2], or percutaneous coronary interventions (PCI) [3]. Benefits of antithrombotic therapy may also differ in women compared with men in various clinical settings, in both primary and secondary cardiovascular disease prevention and according to the type of antithrombotic agent used [4].

Pathophysiological mechanisms causing these gender-related disparities are not entirely clear, and multiple factors, including differences

* Corresponding author at: Department of Neurosciences, Imaging and Clinical Sciences, Experimental Cardiology – CeSI-MeT, G. d'Annunzio University, Chieti-Pescara, via L. Polacchi 11, Institute of Cardiology - SS. Annunziata Hospital, Chieti, Via dei Vestini 31, 66100 Chieti, Italy.
E-mail address: grenda@unich.it (G. Renda).

https://doi.org/10.1016/j.ijcard.2019.02.004
0167-5273/

in platelet biology and/or coagulation activity, may contribute. This narrative review intends to summarise available evidence through a comprehensive analysis of the literature. We searched Medline (via PUBMED), the Cochrane Central Register of Controlled Trials (via Wiley) and Clinicaltrials.gov from inception to December 1, 2018. Studies presented or published in languages different than English were excluded. The studies have to report relevant data on: the epidemiological impact of cardiovascular diseases in women; thrombotic and bleeding risk in women; platelet function and coagulative patterns according to gender; gender-related data on antiplatelet therapies in primary and secondary cardiovascular prevention, and on anticoagulant therapy in various clinical setting; and the use of various antithrombotic drugs in pregnancy. The following terms were searched: 'women', 'gender', 'platelet function', 'coagulation', 'antiplatelet therapy', 'cardiovascular diseases', 'cardiovascular prevention', "myocardial infarction", 'anticoagulant therapy', 'vitamin K antagonists', 'non-vitamin K oral anticoagulants', "direct oral anticoagulants", 'bleeding', 'atrial fibrillation', 'stroke', 'venous thromboembolism' and 'pregnancy'. In addition, we searched the presentations at major cardiovascular scientific sessions, including abstracts form official meetings of the American Heart Association, American College of Cardiology and European Society of Cardiology. Studies were excluded in case of duplicate publication of results. References identified were hand-searched to locate other potentially useful papers. Clinical randomized trials, prospective cohort studies and retrospective analyses were included, as well as meta-analyses. Abstracts were excluded. Discordance regarding inclusion was resolved by consensus.

2. Thrombotic risk in women

Gender-based differences in the epidemiology, pathophysiology, clinical presentation and therapy of atherothrombotic disease have been explored in several studies. Men suffer from coronary artery disease (CAD)-related events more than women until 39 years of age, and almost equally between 40 and 79 years; conversely, the prevalence of CAD in subjects aged ≥80 years is higher in women than men [5]. Studies have indicated that the temporal trend for myocardial infarction (MI) over the last ten years in the mid-life population (age 35–54 years) is characterized by a decreasing prevalence in men and an increasing prevalence in women, mainly due to the increase in smoking, diabetes and hypertension in the latter, in addition to changes associated with the menopause. This impacts on the overall incidence of cardiovascular disease [6,7].

Women have frequent fluctuations of the hemostatic status during their lifetime, due to menstrual cycles, the use of oral contraceptives, pregnancy, the menopause, and hormone replacement therapy, all with potential influence on clinical events related to atherosclerotic disease [1]. It has been postulated that gender differences in ex-vivo platelet function might be the result of a direct action of estrogens, progesterone, or androgens on platelets. At the same time, there could be an indirect effect of sex hormones on the vasculature [8]. Estrogens promote the production of prostacyclin, improve nitric oxide bioavailability, and directly reduce platelet aggregation [9]. Of note, a lower platelet reactivity in premenopausal women has been related to the presence of estrogen receptors on the platelet surface [10]. However, the effects of the endogenous estrogen status in delaying the onset of atherothrombotic events in women are still debated.

2.1. Gender differences in platelet function

Various investigations have shown enhanced platelet reactivity in women [11], both with and without antiplatelet therapy [12], but other studies have not confirmed these findings [13,14]. Some reports have also indicated a more pronounced platelet adhesion to injured vessels in males [15], but greater agonist-induced platelet activation and aggregation in females [9,16]. Several platelet agonists have been shown to activate glycoprotein (GP) IIb/IIIa, the platelet receptor allowing the binding of fibrinogen and platelet aggregation, to a larger extent in women than in men. A higher adenosine diphosphate (ADP)- or collagen-induced aggregability has been described in females vs males [11,16,17]. However, although ex vivo data would indicate a higher platelet function, when bleeding time has been used to evaluate the overall platelet competence, women featured a 20–25% longer in vivo bleeding time compared with men [18].

2.2. Gender differences in coagulation

Hemostasis in women is influenced by changes in the hormonal status associated with the menstrual cycle, pregnancy, hormone-based contraceptives, and hormone replacement therapy (HRT) preparations [19] (Fig. 1). Hormonal changes affect the levels of coagulation factors, although there does not seem to be any clear evidence of a clinically significant change in the traditional clotting assays during the normal menstrual cycle. An acquired resistance to the actions of activated protein C was observed as a significant factor in changes to hemostasis associated with both pregnancy and combined oral contraceptive use, and it correlates well with clinical findings. Cyclic variations of von Willebrand factor (VWF), fibrinogen, and activated factor VII have been measured in healthy women during the normal menstrual cycle [19]. Pregnancy is a procoagulant state, aimed at preventing bleeding at the time of delivery or miscarriage, with a progressive increase in the levels of factors VII, VIII, IX, X, and XII, fibrinogen, and von Willebrand Factor (VWF), as well as a reduction in the levels or activity of anticoagulant factors (protein S and C) or decreased endogenous fibrinolysis, in particular due to increases in plasminogen activator inhibitor (PAI) type 1 and 2, produced by the placenta, and increased resistance to activated protein C [19]. This prothrombotic status has been described up to 8 weeks after delivery, and may predispose to thrombotic events. During the post-menopausal period, genetic and environmental factors (including diet, smoking habits, reduced physical exercise, a low-grade inflammatory state) "negatively" modulate the expression of proteins involved in the hemostatic process, leading to changes in the hemostatic system at different levels (the vascular endothelium, platelet activity, blood coagulation, fibrinolysis) [20]. This may also contribute to the higher incidence of arterial and venous thrombosis in elderly compared with young women. Moreover, the oral administration of synthetic estrogens has profound effects on liver-derived plasma proteins, coagulation factors, lipoproteins, and triglycerides. It has been demonstrated that estrogens reduce some coagulation regulatory proteins (tissue factor pathway inhibitor, protein S, protein C, and antithrombin) whereas, they increase the levels of procoagulant factors VII, X, XII, and XIII, and prothrombin fragments 1 + 2 [21,22]. This imbalance may result in increased activation of coagulation, whereby the increased levels of factors released by endothelial cells (VWF, factor VIII) might also play a role [23].

3. Bleeding risk in women

Bleeding episodes in patients with a cardiovascular event may impact on later survival, and gender-related differences in the bleeding risk have been observed. Data from the Global Registry of Acute Coronary Events (GRACE) showed that women vs men experience a 43% higher risk of bleeding during the index hospitalization, independently of age [2]. The risk was even higher in patients presenting with ST-segment elevation MI. Compared with men, women receiving a PCI had a significantly higher occurrence of in-hospital major bleeding, also including access-related complications [3]. This higher risk of bleeding is likely in part due to inappropriate dosing of antithrombotic agents [24] because, although there is no difference in dose recommendations according to gender, the lower body weight may increase bleeding risk in women. Importantly, the consequences of a bleeding event extend beyond the acute phase of a coronary event, because patients with bleeding complications are less likely to receive antiplatelet

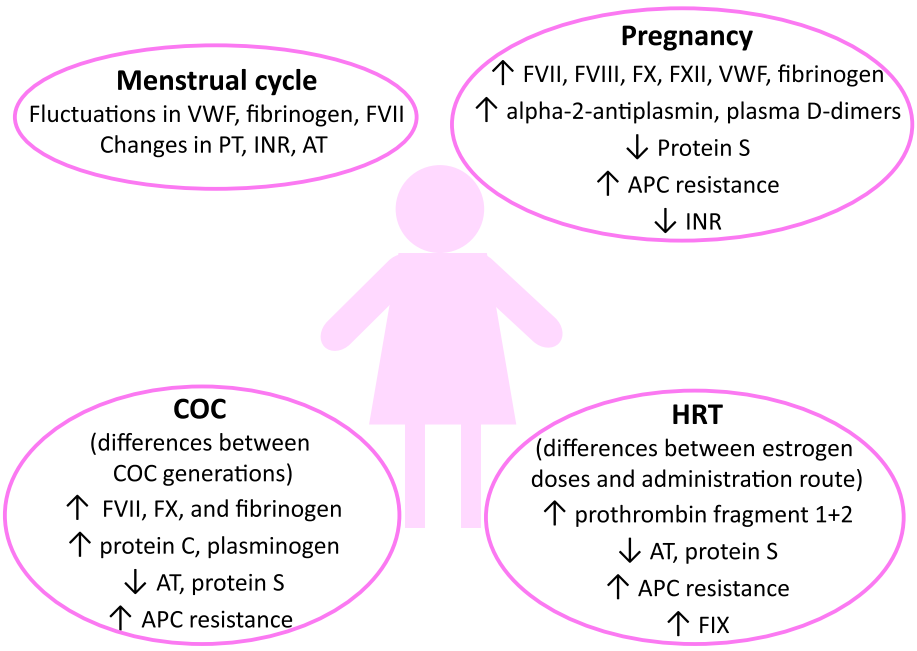

Fig. 1. Hemostasis in women. Changes of coagulation factors and anticoagulant factors according to hormonal status associated with menstrual cycle, pregnancy, hormone-based contraceptives, and hormone replacement therapy are depicted. APC = activated protein C, AT = anti-thrombin, COC = combined oral contraceptives, HRT = hormone replacement therapy, INR = international normalized ratio, PT = prothrombin time, VWF = von Willebrand factor.

treatments during the follow-up, and the re-initiation of therapy is often indefinitely delayed, with a major impact on the risk of future cardiovascular events.

4. Gender implications in response to antiplatelet therapy in various clinical settings

4.1. Primary cardiovascular prevention

The Women's Health Study (WHS) investigated the clinical outcome with aspirin use in 39,876 initially healthy women aged ≥45 years, randomized to receive 100 mg of aspirin on alternate days or placebo, and then followed up to 10 years. Aspirin did not decrease the overall incidence of major cardiovascular events (MACE), but significantly prevented stroke (relative risk 0.83; P = 0.04). The rates of hemorrhagic stroke were similar in the two arms, but a 1.4-fold higher risk of gastrointestinal bleeding requiring transfusion was observed with aspirin use [25]. Pooling data with other trials for a total of 51,342 women, a borderline significant reduction of MACE and ischemic stroke was observed with aspirin use, without benefit on myocardial infarction (MI) or cardiovascular death, and with a higher incidence of overall bleeding [26]. The individual patient-level Antithrombotic Trialists' (ATT) collaboration meta-analysis of 6 randomized trials in primary prevention (of which one performed in women only and 3 in men only, therefore only two allowing within-trial gender comparisons) found a significantly lower rate of MACE with aspirin in men, which was not apparent in women [26].

Various mechanisms might explain this possible gender-related discrepancy in the cardioprotection provided by aspirin: changes in platelet biology and aspirin metabolism, and/or 'aspirin resistance', which, although variably defined, appears to be more prevalent in women than in men [27]. A post-hoc subanalysis of the Women's Health Study (WHS) indicated that a selective treatment achieved a better net clinical benefit than treating none: this was defined as the treatment of women >65 years of age, provided that their 10-year number-willing-to-treat (NWT) to prevent one cardiovascular event, based on their risk profile, was above 50 [28]. Three controlled randomized trials (ASCEND, A Study of Cardiovascular Events in Diabetes [29]; ARRIVE, Aspirin to Reduce Risk of Initial Vascular Events [30]; ASPREE, Aspirin in Reducing Events in the Elderly [31–33]) recently showed no clinical benefit of aspirin in primary cardiovascular prevention, without interaction between treatment effect on outcome and gender.

Thus, although gender differences have been invoked for cardiovascular protection by aspirin, the analysis of the available evidence does not allow to draw firm conclusions. Proposed indications aimed at guiding clinical decision-making of antiplatelet therapy for primary cardiovascular prevention in women are provided in Table 1.

4.1.1. Primary cardiovascular prevention in specific subsets

Some female-related situations require attention in view of possible aspirin use for primary prevention of cardiovascular events, in particular the menopausal status and the occurrence of breast cancer.

The higher incidence of cardiovascular diseases in postmenopausal vs premenopausal women has been correlated with a lowering in estrogen levels, although the findings of studies investigating the effects of hormone replacement therapy on cardiovascular outcome have yielded conflicting results, due to the type of estrogen and/or the timing of hormone replacement therapy. Aspirin might counteract the postulated increased thrombotic risk of postmenopausal women on hormone replacement therapy, but no definite consensus has been reached, and further trials are needed to evaluate the benefit–risk ratio of this approach (Table 1).

Breast cancer is the most common cancer in women worldwide, and radiotherapy performed in the early stage reduces recurrence and premature death. However, a linear relationship between radiation doses and future cardiovascular events has also been described [34], particularly for women with preexisting cardiovascular risk factors. Thus, women with breast cancer should optimize their cardiovascular risk factor profile, and the prophylactic use of aspirin might thus be advocated in women undergoing radiotherapy (Table 1). It has to be noted, however, that to date there is no evidence from randomized clinical trials that aspirin use is associated with a net clinical benefit in primary cardiovascular prevention among women undergoing radiotherapy.

Table 1
Suggested antiplatelet strategies for primary and secondary cardiovascular prevention in women. Calculations of risk were done following the SCORE system adopted by the European Society of Cardiology (http://www.escardio.org/communities/EACPR/toolbox/health-professionals/Pages/SCORE-RiskCharts.aspx).

Setting	Suggestions
Primary prevention	
Overall	- Low-dose aspirin (≤100 mg/day) should probably use in women with a risk of >2 major cardiovascular events (death, myocardial infarction and stroke)/100 patients-year (the bleeding risk must be weighted). - Low-dose aspirin may be considered in women with a risk of >1 cardiovascular events/100 patients-year (the bleeding risk - increased by aspirin and the risk of cancer, especially colon cancer, likely reduced by aspirin - along with patients' values and preferences, should be considered). - No convincing data for clopidogrel use
Specific settings	- Low-dose aspirin is indicated in women with type-1 diabetes and target-organ damage (the bleeding risk must be weighted) - Low-dose aspirin may be considered in diabetic women with a risk of >1 cardiovascular events/100 patients-year (the bleeding risk must be weighted) - Low-dose aspirin may be considered in post-menopausal women on hormone replacement therapy (the bleeding risk must be weighed) - Low-dose aspirin may be considered in pregnant women at high risk of early pre-eclampsia - Low-dose aspirin may be considered in women with breast cancer undergoing radiotherapy (the bleeding risk must be weighed)
Secondary prevention	
Women with CAD	- No gender-specific recommendations in patients with stable or unstable CAD
Women with non-cardio-embolic stroke/TIA	- Low-dose aspirin preferred; clopidogrel may be considered

CAD = coronary artery disease; TIA = transient ischemic attack.

4.2. Secondary cardiovascular prevention

In the ATT meta-analysis, there was no conclusive demonstration favoring the interaction between gender and efficacy of aspirin vs placebo for the secondary cardiovascular prevention: in particular, the relative reduction of major coronary events during the follow-up with aspirin was 19% in males and 27% in females (P for interaction = 0.4), and the relative reduction of MACE (cardiovascular death, MI, stroke) was 19% in both genders (P for interaction = 1.0) [26].

A meta-analysis of five placebo-controlled, randomized trials comparing clopidogrel plus aspirin vs aspirin alone in patients with CAD (mainly ACS) or at high risk of cardiovascular disease recurrence [35], showed that the absolute risk of recurrent events during the follow-up is higher in women than in men, and the relative benefit of clopidogrel therapy appears attenuated in women vs men (7% vs 16% reduction). On the other hand, gender differences in the absolute benefit were not striking (0.8% in women vs 1.2% in men). Of note, the use of clopidogrel vs placebo in the background of aspirin therapy led to increased risk of major bleeding in both men and women.

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial, evaluating prasugrel vs clopidogrel on top of aspirin therapy in ACS patients undergoing PCI, there was no interaction between the efficacy of prasugrel and gender, although men again had a higher absolute (2.4% vs 1.6%) and relative (21% vs 12%) decrease of MACE at the 15-month follow-up with prasugrel compared with women [36]. Furthermore, multivariate analysis indicated that female gender was the strongest predictor of non-bypass-related bleeding complications during the follow-up. Similarly, in the PLATelet inhibition and patient Outcomes (PLATO) study, where ticagrelor was compared with clopidogrel in aspirin-treated patients with ACS, no significant gender difference was found in either the absolute or relative MACE reductions at 1 year by ticagrelor [37]. In PLATO, women of age ≥75 years were more represented than men ≥75 years of age. Female gender was, however, associated with enhanced risk of PCI-related bleeding independent of age. This association was not significant for non-PCI-related bleeding.

Suggestions on the use of antiplatelet therapy in women for secondary cardiovascular prevention are summarized in Table 1.

Two recent studies evaluated the safety and efficacy of the factor Xa inhibitor rivaroxaban on top of antiplatelet therapy in patients with CAD. 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) in the background of aspirin plus clopidogrel treatment showed a significant risk reduction of the composite end point (cardiovascular death, myocardial infarction, or stroke) vs dual antiplatelet therapy alone in patients with ACS; this protection was similar in men and women, with a bleeding increase with rivaroxaban use across genders [38].

In the Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) trial, rivaroxaban (2.5 mg twice daily) given on top of aspirin in patients with stable coronary or peripheral atherosclerotic disease reduced the incidence of ischemic events (MACE, all-cause death and cardiovascular death) vs aspirin alone, regardless of gender, and with an increase in bleeding with rivaroxaban across genders [39].

4.3. Primary and secondary prevention of stroke

Prevention of stroke is a relevant and contemporary issue, especially in women. In females aged <75 years, stroke is more prevalent than CAD, and women between 45 and 54 years of age are more than twice as likely as men to suffer from a stroke. Because women have a longer life expectancy than men, their lifetime risk of stroke is higher [40]. Besides a higher tendency to develop systemic hypertension, hormone replacement therapy may further predispose post-menopausal women to future ischemic stroke [41]. Importantly, women have a worse clinical outcome after a stroke compared with men, with lower survival and higher disability, depression, and dementia [40].

4.3.1. Primary prevention

In the WHS, a 17% risk reduction of ischemic stroke was observed with aspirin use, and the most consistent benefit was found in women >65 years old and in those with a >10% cardiovascular risk at 10 years [25]. In that trial, there was only a trend towards a lower incidence of any stroke (ischemic or hemorrhagic) with aspirin, probably due to somewhat higher rates of hemorrhagic stroke.

4.3.2. Secondary prevention

Four antiplatelet agents have been approved for prevention of vascular events in patients with stroke or transient ischemic attacks (TIA): aspirin, ticlopidine, the association of aspirin and dipyridamole, and clopidogrel. These drugs overall decreased the incidence of stroke, MI, or death by 22%, but differences among their effects were demonstrated, with consequences on therapeutic choice.

Among patients with a recent stroke or TIA in randomized studies, aspirin led to 15% relative reduction in the overall risk of a future cerebrovascular event, resulting in a favorable net clinical benefit because the prevention of ischemic stroke was higher than the increase in the risk of hemorrhagic stroke [26]. The recommended doses range from 50 to 325 mg/day, and there are no differential indications for women (Table 1).

Ticlopidine (250 mg twice a day) showed a 25% reduced incidence of cardiovascular events compared with placebo in patients with a recent ischemic stroke, and such benefit was observed, regardless of gender

[42]. When compared with aspirin for the prevention of stroke recurrence in patients with a recent minor stroke or TIA, ticlopidine showed lower 3-year event rates in both genders (1/3 of patients were women), but with a higher incidence of side effects, including neutropenia, skin rash, and diarrhea [43].

In patients with a previous TIA or stroke, the combination of dipyridamole (400 mg daily) and aspirin at low doses (50 mg daily) was evaluated against low-dose aspirin alone (50 mg daily) [44] and higher-dose aspirin alone (50–325 mg daily) [45]. The combination treatment significantly reduced the rates of both stroke and cardiac/cerebral events. No significant interaction was found according to gender, although a trend towards lower benefit with combination therapy was observed in women. However, headache and gastrointestinal symptoms were a main cause of dipyridamole discontinuation, and this represents a major limitation for using this drug in clinical practice.

No specific study has compared clopidogrel and placebo in the setting of secondary stroke prevention. A combination of clopidogrel (75 mg per day) or aspirin (25 mg twice daily) plus extended release dipyridamole (200 mg twice daily) was evaluated in patients with ischemic stroke. A similar incidence of recurrent stroke was observed with the two strategies. The rates of bleeding complications were higher in the aspirin/dipyridamole arm, but the net risk of recurrent stroke or major bleeding was not different [46]. Although the study was not powered to evaluate gender-related differences in outcome, a higher benefit with clopidogrel was observed in women than in men. No significant benefit was demonstrated with the combination of clopidogrel 75 mg/day and aspirin 75 mg/day vs clopidogrel alone in patients with a recent TIA or ischemic stroke, in terms of prevention of a primary composite outcome (MI, ischemic stroke, vascular death, or re-hospitalization for any central or peripheral ischemic event), while the risk of major bleeding was significantly higher [47]. The analysis according to gender achieved similar results.

Cilostazol, a phosphodiesterase inhibitor, was compared to placebo [48] or to aspirin [49] in patients with a history of non-cardioembolic cerebral infarction. Overall, compared with placebo, the use of cilostazol was associated with lower rates of secondary stroke, especially in patients with lacunar infarction, and this suggests a benefit in small vessel disease. Compared with aspirin, cilostazol significantly reduced the risk of vascular events and hemorrhagic stroke, but at the price of a higher incidence of side effects. About one third of the trial population in the comparison with placebo were women.

5. Gender implications in the response to anticoagulant therapy in different clinical settings

Long-term anticoagulant therapy is indicated for the treatment of a variety of disease conditions, mainly including prevention of stroke and systemic embolism in patients with atrial fibrillation, or in patients with mechanical prosthetic heart valve, and the primary and secondary prevention of venous thromboembolism. The clinical effectiveness of oral anticoagulants, such as vitamin K antagonists (VKAs) and the newer non-vitamin K antagonist oral anticoagulants (NOACs) has been established by well-designed clinical trials, but the impact of gender and gender-associated differences in risk factors for thromboembolism and anticoagulant treatment on outcomes in patients with these clinical conditions is not fully understood.

5.1. Atrial fibrillation

Atrial fibrillation (AF) is an independent risk factor for stroke: in general, it confers a five-fold higher risk to affected patients compared with the unaffected population. The risk of stroke is particularly high in patients with so-called "valvular" AF, including patients with mitral stenosis or mechanical prosthetic valves, although patients with all sort of valvular heart disease are on average at higher risk of stroke compared with patients without valvular disease [50], since they are older, have more frequently sustained AF, have a higher prevalence of heart failure and CAD. However, assessing risk factors for stroke over time is crucial to optimize antithrombotic therapy in patients with AF, and current guidelines recommend to estimate the stroke risk in AF patients based on a risk-stratification scheme, currently mostly the CHA_2DS_2-VASc score [51]. According to this, prior stroke or TIA or systemic embolism, and age ≥75 years are considered as "major risk factors" (2 points in the score), heart failure (moderate to severe systolic left ventricular dysfunction, arbitrarily defined as left ventricular ejection fraction ≤40%), hypertension, diabetes, age 65–74 years, vascular disease (MI, peripheral artery disease, and complex aortic plaques), and female gender are defined as "clinically relevant non-major risk factors" (1 point) [52]. Thus, female gender is a recognised risk factor for stroke in the CHA_2DS_2-VASc stroke risk stratification scheme, because it independently increases the risk of stroke in AF, particularly in older women [53–55], although it does not appear to increase stroke risk in the absence of other stroke risk factors [56,57], including patients with <65 years and/or "lone atrial fibrillation". For these reasons, female patients with gender alone as a single risk factor (still a CHA_2DS_2-VASc score of 1) would not need antithrombotic therapy, similar to patients without clinical stroke risk factors, while patients with stroke risk factors (i.e. CHA_2DS_2-VASc score ≥1 or for men, and ≥2 for women) are likely to benefit from oral anticoagulation [51].

Furthermore, the prognosis of women with AF markedly differs from men, and women with AF have a higher risk for adverse events, such as stroke and death [58], even after adjustment for baseline comorbid conditions and treatment with anticoagulants [59], although these data are inconsistently reported in the literature.

In prospective cohort studies, overall the use of anticoagulant therapy for stroke prevention resulted not different in men and women, although women were older than men and had a higher prevalence of comorbid conditions [60]. However, in some reports female AF patients at risk of stroke were less often prescribed OAC and were given aspirin more often than males [61]. Nevertheless, in the recent Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) study, compared with no anticoagulant treatment, anticoagulants lowered the 1-year risk of stroke/systemic embolism to a greater extent in men than women (HR 0.77, 95% CI 0.57 to 1.03 in women; HR 0.45, 95% CI 0.33 to 0.61 in men), and this interaction was significant ($P = 0.01$). The lower impact of anticoagulant treatment on stroke rates in women has been ascribed to a poorer anticoagulation control when treated with vitamin K antagonists [59]. This has been partly explained by a lower adherence to therapy and/or a higher age and/or the use of lower doses and target ranges in women compared to men.

On the other hand, the greater risk of bleeding observed in men in some studies may be explained by more aggressive antithrombotic treatment in men compared with women. Moreover, subtle differences in prescribing patterns by gender, including a more frequent anticoagulant and antiplatelet combination therapy, might be responsible for a higher bleeding rate [59].

A recent meta-analysis collecting almost one million AF patients confirmed a higher risk of stroke in females compared to men; the study did not observe sex differences in either major bleeding events or all cause death, whereas found an increased risk of CV death in female patients with decreasing oral anticoagulant use [62].

However, this gender difference has not been observed in randomized controlled trials (RCT) with the NOACs, although females were largely under-represented in all these RCTs. In the first meta-analysis of the four large phase-III RCT comparing efficacy and safety of NOACs and VKAs in AF patients, no significant interaction for gender was reported for stroke/systemic embolism and for major bleeding [63]. Another meta-analysis indicated that women with AF had a significantly greater residual risk of cerebrovascular accidents and systemic embolization when treated using warfarin compared with men, but the gender difference disappeared when a similar analysis was performed on a pooled population treated with NOACs in published RCT, with significantly less major bleeding in the female cohort compared with male

cohort [55]. A more recent meta-analysis of data from the phase III NOACs trials showed that male patients had a higher risk for stroke/systemic embolism than females, with a greater effect for NOACs in reducing thromboembolic risk, while female patients appeared to be more protected against major bleeding when treated with NOACs [64]. This evidence indicates that NOACs can overrule this risk, achieving the same risk level in females and males. This may be related to pharmacokinetic and pharmacodynamic advantages provided by NOACs, resulting in a more consistent anticoagulant effect, without the disadvantage of subtherapeutic or supratherapeutic anticoagulation [55]. In a recent population-based cohort study, the use of NOACs was associated with a lower risk of ICH and all-cause death compared with warfarin in women but not in men, regardless of the quality of the anticoagulation control in warfarin-treated patients; the risks of stroke/systemic embolism and gastrointestinal bleeding with NOACs versus warfarin were comparable in both sexes [65].

Observational data addressing sex-related differences in NOACs effects suggest that females regardless of age are more likely to receive the lower dose of dabigatran (110 mg), and that male users of dabigatran 150 mg or 110 mg have less major bleeding than females. In first diagnosed AF patients >65 years, rivaroxaban 20 mg was associated with significant stroke reduction in males and more major bleeding in females compared with warfarin [61]. However, data from RCTs did not reveal any clinically relevant difference in NOACs efficacy and safety relative to female sex and a recent consensus document of the European Heart Rhythm Association indicated that, given the lack of significant treatment interactions with sex, the choice of the type of NOAC in females should follow general principles of personalized AF treatment decision-making [61].

The inconsistency of published results is probably due to the different nature of trials, meta-analyses or observational studies, different study designs, patient selection, inclusion criteria, outcomes, and durations of follow-up [66]. However, the role of gender in determining thromboembolic events in AF patients is still not clear, and differential effects of anticoagulants on thromboembolic protection are still not determined. Further data from large observational trials of AF patients treated with NOACs are needed to clarify this issue. To date, there are no differential indication in the prevention of thromboembolism for women with AF.

5.2. Venous thromboembolism

Venous thromboembolism (VTE), consisting of deep-vein thrombosis and pulmonary embolism, is a potentially fatal disorder, with an estimated annual incidence of 0.1% in white populations. Approximately one third of patients with symptomatic VTE manifest pulmonary embolism (PE), whereas two thirds manifest deep vein thrombosis (DVT) alone. Despite anticoagulant therapy, VTE recurs frequently in the first few months after the initial event, with a recurrence rate of about 7% at 6 months. Death occurs in about 6% of DVT cases and 12% of PE cases within 1 month of diagnosis [67].

There are multiple predisposing (risk) factors for VTE, both environmental and genetic. VTE is considered to be 'provoked' in the presence of a temporary or reversible risk factor (such as surgery, trauma, immobilization, pregnancy, oral contraceptive use, or hormone replacement therapy) within the last 6 weeks to 3 months before diagnosis, and 'unprovoked' in the absence thereof [68]. The presence of persistent - as opposed to major, temporary - risk factors may affect the decision on the duration of anticoagulation therapy after a first episode of VTE.

In fertile women, oral contraception is the most frequent predisposing factor for VTE. When occurring during pregnancy, VTE is a major cause of maternal death. The risk is highest in the third trimester of pregnancy and over the 6 weeks of the postpartum period, being up to 60 times higher 3 months after delivery compared with the risk in non-pregnant women [69]. In vitro fertilization further increases the risk of pregnancy-associated VTE [70]. In post-menopausal women who receive hormone replacement therapy, the risk of VTE varies widely depending on the formulation used [71]. However, although women could have these specific risk factors, published data suggest no consistent differences in the incidence of VTE between men and women [72]. A slightly higher incidence rate among younger women, and a modestly higher trend among older men was observed [73]. Among elderly patients, women were observed to have a slightly higher relative risk of DVT and a lower risk of PE [74]. The presence of a malignancy, chemoprevention (with cyclophosphamide, methotrexate, 5-fluorouracil) or adjuvant therapy with selective estrogen receptor modulators (tamoxifen) in patients with a breast carcinoma, appear to increase the risk of VTE in women, mainly if in the presence of other risk factors (age, inherited hypercoagulable states or history of idiopathic VTE) [75]. In particular, selective estrogen receptor modulators seem to confer the same risk of VTE as hormone replacement therapy [75].

Oral anticoagulant treatment is highly effective at preventing recurrent venous thromboembolism, and the duration of treatment is decided on the balance between the increased risk of recurrent VTE if treatment is stopped and the raised risk of bleeding if treatment is continued. Therefore, the identification of risk factors for recurrent VTE can help identify patients who will benefit from long-term anticoagulation. The presence of a temporary risk factor, such as recent surgery, is associated with a lower risk of recurrence than unprovoked thrombosis or a continuing risk factor. Proximal DVT or PE, more than one previous thrombotic episode, and the presence of malignancy or antiphospholipid antibodies increase the risk of recurrence.

Some data suggested that men have a higher risk of recurrent VTE than women after VKA anticoagulant treatment is stopped [76]. In a recent meta-analysis of 6 studies totalling 26,872 patients (15,354 males and 11,518 females) with acute VTE, the use of NOACs was associated with a similar rate of VTE recurrence and VTE-related death compared with VKAs, with a significant reduction of major bleeding [77]. Here NOACs seem to have a similar efficacy in male and female patients with acute VTE, with a nonsignificant heterogeneity between groups. Male and female patients appeared to have a similar risk of VTE recurrence or VTE-related death either in patients treated with VKAs or NOACs. The risk of major bleeding appeared lower in males, both when treated with VKAs or NOACs, but these results should be interpreted with caution since based on studies with a limited sample size. In the evaluation of the extended treatment, the risk of VTE recurrence or VTE-related death was significantly higher in male patients treated with placebo, whereas this risk appeared non-significantly different in male and female patients treated with NOACs. The risk of major bleeding was significantly lower in males treated with placebo, whereas this risk appeared similar in male and female patients treated with NOACs [77]. However, some observational data have suggested that direct oral factor Xa inhibitors might increase menstrual and vaginal bleeding intensity in women of reproductive age [78].

6. Antithrombotic therapies in pregnancy

Pregnancy is a condition at higher risk of thrombotic events, due to a prothrombotic condition, physiologically useful to prevent bleeding at the time of delivery. These hemostatic changes mainly occur in the third trimester, have been attributed to elevated estrogen levels, and involve both platelet function and coagulation [79]. In particular, cardiovascular diseases occur in 0.4–4% of all pregnancies, and ACS is reported in 0.6 to 1.0 cases per 10,000 deliveries, with a maternal mortality comprised between 5 and 37% [80,81].

6.1. Antiplatelet therapies in pregnancy

During pregnancy, platelet count is slightly reduced, with consequent benign gestational thrombocytopenia, due to higher platelet consumption in the utero-placental circulation [82]; this accelerated

platelet turnover and the attendant increased number of immature platelets cause higher platelet aggregability. Pregnancy is also associated with changes in the platelet membrane, with a consequent increase in the activity of calcium adenosine triphosphatase [83]. Finally, a higher production of alpha granule-released proteins, such as beta-thromboglobulin and platelet factor-4, has been documented in the circulation of pregnant women, this indicating stronger platelet activation [83].

Clinical data on antiplatelet agents in pregnancy are scarce, as pregnant women are usually excluded from randomized trials, and in this specific setting the safety profile of drugs is a crucial concern. Regarding the level of risk to the fetus, a risk classification for antiplatelet drugs has been proposed [84], as indicated in Table 2.

Experimental data with aspirin use in the first trimester of pregnancy indicated a higher occurrence of birth defects, including fissure of spine and skull, facial and eye defects, central nervous system malformations and anomalies of visceral and skeletal development [85,86]. However, these findings are not consistent with clinical data on pregnant women treated with aspirin [87]. While the use of high-dose aspirin has been related with a premature closure of the ductus arteriosus and with fetal and maternal hemorrhages, reports have clearly demonstrated the efficacy and safety of low-dose aspirin in pregnant ACS patients [81]. Although aspirin in the third trimester should be avoided (as it may provoke a premature closure of the ductus), low-dose aspirin was associated with a potential benefit in decreasing the rates of pre-eclampsia and the incidence of pre-eclampsia-related preterm delivery [88]. Accordingly, low-dose aspirin may be used in women at higher risk of early preeclampsia [89]. Importantly, no adverse effect was observed with aspirin treatment during breast feeding [81], but aspirin used at high doses may cause rashes, platelet abnormalities, and bleeding in nursing infants. According to the risk to the fetus, aspirin is classified in risk category C for low doses and in risk category D for high doses [84,90] (Table 2).

Reproduction investigations on animal models at clopidogrel doses of up to 300 and 500 mg/kg/day (65 and 78 times the recommended daily human dose, respectively) found no fetal toxicity with clopidogrel. However, as for other antiplatelet drugs, there is no extensive evidence from clinical studies on clopidogrel in pregnant women [85]. Available data mainly derive from isolated case reports [91], where clinical outcome was generally favorable for both the mother and the fetus. According to the risk to the fetus, clopidogrel is classified in risk category B [84,90] (Table 2). No extensive clinical data in pregnancy are available for prasugrel or ticagrelor; thus, these drugs should be prescribed only if the potential advantage to the mother overcomes the potential risk to the fetus. In animal studies, no fetal malformation was described using maternally toxic oral doses of prasugrel, equivalent to 40 times the human exposure [85], while the use of ticagrelor was associated with structural abnormalities of the fetus at maternal doses 5 to 7 times the maximum recommended human doses. According to the risk to the fetus, prasugrel is classified in risk category B and ticagrelor is classified in risk category C [84,90] (Table 2).

Animal studies found that all oral P_2Y12 inhibitors are excreted with the milk, but it is not established whether these agents are excreted in the human milk.

Due to the potential for adverse reactions in nursing infants, P_2Y12 inhibitors should be given during breast feeding only if the potential advantage to the mother overcomes the potential risk to the nursing infant, or - alternatively - the drug can be continued in the mother switching babies to bottle-feeding.

Table 2
Classification of antiplatelet drugs regarding the level of risk to the fetus [84,90].

Category	Definition
B	Well-controlled studies failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of fetal risk in later trimesters
C	Animal reproduction studies failed to demonstrate a risk to the fetus and there are no well-controlled studies in pregnant women
D	Animal reproduction studies showed an adverse effect on the fetus and there are no adequate studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential fetal risks
E	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential fetal risk
X	Animals or humans studies demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

6.2. Anticoagulant therapies in pregnancy

A 25–56% incidence of miscarriage and a 5–30% incidence of congenital abnormalities have been reported for any VKA when given during the critical period of organogenesis [92]. In particular, warfarin, when used between the 6th and the 12th week after conception, especially at a dose exceeding 5 mg/day, has been associated with fetal neurologic sequelae, congenital heart disease, growth retardation and embryopathy, as well as with a higher risk of fetal bleeding and spontaneous abortion [92]. Of note, more frequent fetal abnormalities and spontaneous abortion have been described also when warfarin was used at a dose ≤5 mg/day in women with mechanical heart valves [93].

Unfractionated heparin (UFH) does not cross the placenta and therefore has no direct risk to the fetus [94]. However, heparin-induced thrombocytopenia and osteopenia with UHF use have been described also in pregnant women, although rarely. Of note, during pregnancy the half-lives of UFH and low-molecular-weight heparins (LMWH) are shorter, and plasma concentrations are lower, due to the physiological increase in maternal blood volume and glomerular filtration [92]. Thus, higher UFH doses are often required and a strict monitoring of the activated partial thromboplastin time (aPTT) (with ≥2 fold prolongation) is needed.

Available evidence indicates that LMWHs are safe drugs during pregnancy. Potential advantages of LMWH versus UFH are less bleeding, a more predictable and stable effect and reduced risk of heparin-induced thrombocytopenia. Given the above-mentioned issue of lower plasma concentrations during pregnancy, also LMWH often requires higher doses, and a strict control of anti-Xa levels (target range 0.8–1.2 U/mL at 4–6 h after subcutaneous administration) is mandatory [92]. For women requiring long-term anticoagulation with a VKA, such as those with mechanical heart valves, international guidelines recommend to monitor pregnancy tests in those attempting pregnancy. They also recommend that, when pregnancy is achieved, the VKA be replaced with heparins (adjusted-dose UFH or LMWH) up to the 12th week of gestation, and then resuming the VKA up to the 36th week, when UFH or LMWHs are given again [95–97]. However, this recommendation should not be generalized as it may differ for various types of VKA; e.g. phenprocoumon is contraindicated during pregnancy. Of note, if a LMWH is chosen as anticoagulant therapy from the 36th week to delivery, it should be replaced with UFH 36 h before the planned delivery. Furthermore, international guidelines also consider the option to use adjusted-dose UFH or LMWH throughout the pregnancy [96,97].

A review of fondaparinux utilization among 65 pregnant women at a higher risk of thrombosis indicated that this drug was well tolerated and the occurrence of pregnancy complications was similar to that documented in the general population. Fondaparinux does not pass through the human placenta in vitro, but a few placental transfers have been observed in the rat model. Thus, the safety of fondaparinux for the human fetus needs to be definitely clarified, and the use of this drug should be limited to patients intolerant to heparins [98].

Regarding NOACs, toxic effects to the fetus have been described with rivaroxaban, dabigatran and edoxaban, but not with apixaban in animal

studies [99]. Pregnant women were excluded from phase III randomized trials evaluating NOACs versus warfarin in patients with AF or venous thromboembolism. Thus, to date NOACs are not recommended in pregnancy and breast feeding. Ten women became pregnant during the edoxaban randomized studies [99], one of whom had a spontaneous abortion and the remaining completed the pregnancy without problems to the fetus. From the real world setting, only two cases of a pregnancy conceived while on rivaroxaban have been reported, both uneventful for the mother and the baby [100,101] No similar reports are available with dabigatran or apixaban.

7. Conclusions

Data from observational and intervention studies may suggest gender-specific differences in thrombotic and hemorrhagic burden, as well as gender-specific effects on clinical outcomes with antithrombotic agents. Multiple factors involved in platelet function and coagulation mechanisms in various vascular beds, partly related to the hormonal status, might contribute to such gender differences. Particularly, in primary cardiovascular prevention the benefit of aspirin seems to be related to a significant decrease of major coronary events with aspirin in men, but not in women. For secondary cardiovascular prevention, although no significant gender-related difference in the efficacy of antiplatelet agents has emerged, special attention should be paid to body weight and dosing strategies when treating women. The lower benefit of anticoagulant treatment with vitamin K antagonists on stroke prevention in women with AF, relative to men, is not fully understood, but suggests that women may be less well anticoagulated. Few evidence points to the existence of gender difference in the response to NOACs, but data are still unclear. In the evaluation of the extended treatment of VTE, the risk of VTE recurrence or VTE-related death in the absence of oral anticoagulation seems significantly higher in male than in female patients, while it appeared non-significantly different in male and female patients treated with NOACs. Some indications are available about the use of antithrombotic drugs in pregnancy, although clinical data are scarce in this setting, as pregnant women are usually excluded from randomized trials, and the safety profile of drugs is here a crucial and largely unresolved concern.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments and disclosures

GR has received speaker and consultancy fees from Boehringer-Ingelheim, Bayer, and Daiichi-Sankyo.

GP has received speaker/consultant/advisory board for Amgen, Sanofi, Bayer, Boehringer-Ingelheim, BMS-Pfizer, Daiichi Sankyo, Astra Zeneca, Sigma-Tau, Malesci, PIAM and MSD.

IML has relationships with drug companies including AOPOrphan Pharmaceuticals, Actelion, Bayer-Schering, Astra-Zeneca, Servier, Cordis, Medtronic, Kaneka, GSK, Ferrer, and Daiichi-Sankyo. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards.

JSM has received speaker and consultancy fees from Bayer, Astra Zeneca, and Daiichi-Sankyo.

EMH has received speaker/consultant/advisory board fees from Bayer, Boehringer-Ingelheim, Bristol Myers Squibb/Pfizer, Janssen, and Portola.

GA has received speakers' bureau fees or consultancy fees from Angelini, Bayer, Behring, Boehringer-Ingelheim, Menarini, Merck, Novartis.

SH has received consultancy and speaker fees from Aspen, Bayer, BMS/Pfizer, Daiichi-Sankyo, Portola, Sanofi.

RDC has received grant support (to his institution) from Boehringer-Ingelheim, Bayer, BMS/Pfizer, and Daiichi-Sankyo; and speaker and consultancy fees from Boehringer-Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Merck, Novartis, Roche, Portola.

References

[1] D.W. Schwertz, S. Penckofer, Sex differences and the effects of sex hormones on hemostasis and vascular reactivity, Heart Lung 30 (2001) 401–426 (quiz 427-8).
[2] M. Moscucci, K.A. Fox, C.P. Cannon, et al., Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE), Eur. Heart J. 24 (2003) 1815–1823.
[3] K.P. Alexander, A.Y. Chen, L.K. Newby, et al., Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (can rapid risk stratification of unstable angina patients suppress ADverse outcomes with early implementation of the ACC/AHA guidelines) initiative, Circulation 114 (2006) 1380–1387.
[4] J.S. Berger, M.C. Roncaglioni, F. Avanzini, et al., Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials, JAMA 295 (2006) 306–313.
[5] W. Rosamond, K. Flegal, G. Friday, et al., Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, Circulation 115 (2007) e69–171.
[6] K. Kotseva, D. Wood, G. De Backer, et al., Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries, Lancet 373 (2009) 929–940.
[7] A. Towfighi, L. Zheng, B. Ovbiagele, Sex-specific trends in midlife coronary heart disease risk and prevalence, Arch. Intern. Med. 169 (2009) 1762–1766.
[8] A.L. Bailey, D.C. Scantlebury, S.S. Smyth, Thrombosis and antithrombotic therapy in women, Arterioscler. Thromb. Vasc. Biol. 29 (2009) 284–288.
[9] T. Caulin-Glaser, G. Garcia-Cardena, P. Sarrel, et al., 17 beta-estradiol regulation of human endothelial cell basal nitric oxide release, independent of cytosolic Ca^{2+} mobilization, Circ. Res. 81 (1997) 885–892.
[10] M.R. Sowers, K.A. Matthews, M. Jannausch, et al., Hemostatic factors and estrogen during the menopausal transition, J. Clin. Endocrinol. Metab. 90 (2005) 5942–5948.
[11] S.F. Haque, H. Matsubayashi, S. Izumi, et al., Sex difference in platelet aggregation detected by new aggregometry using light scattering, Endocr. J. 48 (2001) 33–41.
[12] P. Bobbert, C. Stellbaum, D. Steffens, et al., Postmenopausal women have an increased maximal platelet reactivity compared to men despite dual antiplatelet therapy, Blood Coagul. Fibrinolysis 23 (2012) 723–728.
[13] N.J. Breet, M.A. Sluman, M.A. van Berkel, et al., Effect of gender difference on platelet reactivity, Neth. Hear. J. 19 (2011) 451–457.
[14] A. Singla, K.P. Bliden, Y.H. Jeong, et al., Platelet reactivity and thrombogenicity in postmenopausal women, Menopause 20 (2013) 57–63.
[15] J.B. Lawrence, D.W. Leifer, G.L. Moura, et al., Sex differences in platelet adherence to subendothelium: relationship to platelet function tests and hematologic variables, Am J Med Sci 309 (1995) 201–207.
[16] D.M. Becker, J. Segal, D. Vaidya, et al., Sex differences in platelet reactivity and response to low-dose aspirin therapy, JAMA 295 (2006) 1420–1427.
[17] N. Faraday, P.J. Goldschmidt-Clermont, P.F. Bray, Gender differences in platelet GPIIb-IIIa activation, Thromb. Haemost. 77 (1997) 748–754.
[18] B. Bain, T. Forster, A sex difference in the bleeding time, Thromb. Haemost. 43 (1980) 131–132.
[19] D.E. Trigg, M.G. Wood, P.A. Kouides, et al., Hormonal influences on hemostasis in women, Semin. Thromb. Hemost. 37 (2011) 77–86.
[20] P. Bucciarelli, P.M. Mannucci, The hemostatic system through aging and menopause, Climacteric 12 (Suppl. 1) (2009) 47–51.
[21] M. Canonico, Hormone therapy and hemostasis among postmenopausal women: a review, Menopause 21 (2014) 753–762.
[22] R.E. Peverill, Hormone therapy and venous thromboembolism, Best Pract. Res. Clin. Endocrinol. Metab. 17 (2003) 149–164.
[23] V.M. Miller, M. Jayachandran, W.G. Owen, Ageing, oestrogen, platelets and thrombotic risk, Clin. Exp. Pharmacol. Physiol. 34 (2007) 814–821.
[24] B. Ahmed, W.D. Piper, D. Malenka, et al., Significantly improved vascular complications among women undergoing percutaneous coronary intervention: a report from the Northern New England Percutaneous Coronary Intervention Registry, Circ. Cardiovasc. Interv. 2 (2009) 423–429.
[25] P.M. Ridker, N.R. Cook, I.M. Lee, et al., A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women, N. Engl. J. Med. 352 (2005) 1293–1304.
[26] C. Antithrombotic Trialists, C. Baigent, L. Blackwell, et al., Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials, Lancet 373 (2009) 1849–1860.
[27] T.Y. Wang, D.J. Angiolillo, M. Cushman, et al., Platelet biology and response to antiplatelet therapy in women: implications for the development and use of antiplatelet pharmacotherapies for cardiovascular disease, J. Am. Coll. Cardiol. 59 (2012) 891–900.
[28] J.A. Dorresteijn, F.L. Visseren, P.M. Ridker, et al., Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects, Eur. Heart J. 32 (2011) 2962–2969.
[29] A.S.C. Group, L. Bowman, M. Mafham, et al., Effects of aspirin for primary prevention in persons with diabetes mellitus, N. Engl. J. Med. 379 (2018) 1529–1539.

[30] J.M. Gaziano, C. Brotons, R. Coppolecchia, et al., Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial, Lancet 392 (2018) 1036–1046.
[31] J.J. McNeil, M.R. Nelson, R.L. Woods, et al., Effect of aspirin on all-cause mortality in the healthy elderly, N. Engl. J. Med. 379 (2018) 1519–1528.
[32] J.J. McNeil, R. Wolfe, R.L. Woods, et al., Effect of aspirin on cardiovascular events and bleeding in the healthy elderly, N. Engl. J. Med. 379 (2018) 1509–1518.
[33] J.J. McNeil, R.L. Woods, M.R. Nelson, et al., Effect of aspirin on disability-free survival in the healthy elderly, N. Engl. J. Med. 379 (2018) 1499–1508.
[34] S.C. Darby, M. Ewertz, P. McGale, et al., Risk of ischemic heart disease in women after radiotherapy for breast cancer, N. Engl. J. Med. 368 (2013) 987–998.
[35] J.S. Berger, D.L. Bhatt, C.P. Cannon, et al., The relative efficacy and safety of clopidogrel in women and men a sex-specific collaborative meta-analysis, J. Am. Coll. Cardiol. 54 (2009) 1935–1945.
[36] S.D. Wiviott, E. Braunwald, C.H. McCabe, et al., Prasugrel versus clopidogrel in patients with acute coronary syndromes, N. Engl. J. Med. 357 (2007) 2001–2015.
[37] L. Wallentin, R.C. Becker, A. Budaj, et al., Ticagrelor versus clopidogrel in patients with acute coronary syndromes, N. Engl. J. Med. 361 (2009) 1045–1057.
[38] J.L. Mega, E. Braunwald, S.D. Wiviott, et al., Rivaroxaban in patients with a recent acute coronary syndrome, N. Engl. J. Med. 366 (2012) 9–19.
[39] J.W. Eikelboom, S.J. Connolly, J. Bosch, et al., Rivaroxaban with or without aspirin in stable cardiovascular disease, N. Engl. J. Med. 377 (2017) 1319–1330.
[40] R.E. Petrea, A.S. Beiser, S. Seshadri, et al., Gender differences in stroke incidence and poststroke disability in the Framingham heart study, Stroke 40 (2009) 1032–1037.
[41] J.E. Rossouw, G.L. Anderson, R.L. Prentice, et al., Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial, JAMA 288 (2002) 321–333.
[42] M. Gent, J.A. Blakely, J.D. Easton, et al., The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke, Lancet 1 (1989) 1215–1220.
[43] W.K. Hass, J.D. Easton, H.P. Adams Jr., et al., A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group, N. Engl. J. Med. 321 (1989) 501–507.
[44] H.C. Diener, L. Cunha, C. Forbes, et al., European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke, J. Neurol. Sci. 143 (1996) 1–13.
[45] E.S. Group, P.H. Halkes, J. van Gijn, et al., Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial, Lancet 367 (2006) 1665–1673.
[46] R.L. Sacco, H.C. Diener, S. Yusuf, et al., Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke, N. Engl. J. Med. 359 (2008) 1238–1251.
[47] H.C. Diener, J. Bogousslavsky, L.M. Brass, et al., Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke (MATCH): study design and baseline data, Cerebrovasc. Dis. 17 (2004) 253–261.
[48] Y. Shinohara, Antiplatelet cilostazol is effective in the prevention of pneumonia in ischemic stroke patients in the chronic stage, Cerebrovasc. Dis. 22 (2006) 57–60.
[49] Y. Shinohara, Y. Katayama, S. Uchiyama, et al., Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial, Lancet Neurol. 9 (2010) 959–968.
[50] G. Renda, F. Ricci, R.P. Giugliano, et al., Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease, J. Am. Coll. Cardiol. 69 (2017) 1363–1371.
[51] P. Kirchhof, S. Benussi, D. Kotecha, et al., 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur. Heart J. 37 (2016) 2893–2962.
[52] G.Y. Lip, R. Nieuwlaat, R. Pisters, et al., Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation, Chest 137 (2010) 263–272.
[53] C.L. Cove, C.M. Albert, F. Andreotti, et al., Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms, Thromb. Haemost. 111 (2014) 385–391.
[54] L. Friberg, M. Rosenqvist, G.Y. Lip, Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study, Eur. Heart J. 33 (2012) 1500–1510.
[55] S.B. Pancholy, P.S. Sharma, D.S. Pancholy, et al., Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants, Am. J. Cardiol. 113 (2014) 485–490.
[56] A.P. Mikkelsen, J. Lindhardsen, G.Y. Lip, et al., Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study, J. Thromb. Haemost. 10 (2012) 1745–1751.
[57] A.J. Wagstaff, T.F. Overvad, G.Y. Lip, et al., Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis, QJM 107 (2014) 955–967.
[58] K.E. Odening, S. Deiss, D. Dilling-Boer, et al., Mechanisms of sex differences in atrial fibrillation: role of hormones and differences in electrophysiology, structure, function, and remodelling, Europace 21 (3) (2018) 366–376.
[59] A.J. Camm, G. Accetta, W. Al Mahmeed, et al., Impact of gender on event rates at 1 year in patients with newly diagnosed non-valvular atrial fibrillation: contemporary perspective from the GARFIELD-AF registry, BMJ Open 7 (2017), e014579.
[60] G.Y. Lip, S.K. Rushton-Smith, S.Z. Goldhaber, et al., Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation, Circ. Cardiovasc. Qual. Outcomes 8 (2015) S12–S20.
[61] C. Linde, M.G. Bongiorni, U. Birgersdotter-Green, et al., Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society, Europace 20 (2018) (1565-1565ao).
[62] I. Marzona, M. Proietti, A. Farcomeni, et al., Sex differences in stroke and major adverse clinical events in patients with atrial fibrillation: a systematic review and meta-analysis of 993,600 patients, Int. J. Cardiol. 269 (2018) 182–191.
[63] C.T. Ruff, R.P. Giugliano, E. Braunwald, et al., Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials, Lancet 383 (2014) 955–962.
[64] M. Proietti, P. Cheli, S. Basili, et al., Balancing thromboembolic and bleeding risk with non-vitamin K antagonist oral anticoagulants (NOACs): a systematic review and meta-analysis on gender differences, Pharmacol. Res. 117 (2017) 274–282.
[65] S.W.Y. Law, W.C.Y. Lau, I.C.K. Wong, et al., Sex-based differences in outcomes of oral anticoagulation in patients with atrial fibrillation, J. Am. Coll. Cardiol. 72 (2018) 271–282.
[66] G. Renda, R. De Caterina, Sex implications in the response to anticoagulant therapy in atrial fibrillation, J. Am. Coll. Cardiol. 72 (2018) 283–286.
[67] R.H. White, The epidemiology of venous thromboembolism, Circulation 107 (2003) I4–I8.
[68] S.V. Konstantinides, A. Torbicki, G. Agnelli, et al., 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 35 (2014) 3033–3069 (3069a-3069k).
[69] E.R. Pomp, A.M. Lenselink, F.R. Rosendaal, et al., Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study, J. Thromb. Haemost. 6 (2008) 632–637.
[70] P. Henriksson, E. Westerlund, H. Wallen, et al., Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: cross sectional study, BMJ 346 (2013), e8632.
[71] S. Sweetland, V. Beral, A. Balkwill, et al., Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study, J. Thromb. Haemost. 10 (2012) 2277–2286.
[72] F.A. Anderson Jr., H.B. Wheeler, R.J. Goldberg, et al., A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study, Arch. Intern. Med. 151 (1991) 933–938.
[73] M.D. Silverstein, J.A. Heit, D.N. Mohr, et al., Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study, Arch. Intern. Med. 158 (1998) 585–593.
[74] W.D. Kniffin Jr., J.A. Baron, J. Barrett, et al., The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly, Arch. Intern. Med. 154 (1994) 861–866.
[75] S.R. Deitcher, M.P. Gomes, The risk of venous thromboembolic disease associated with adjuvant hormone therapy for breast carcinoma: a systematic review, Cancer 101 (2004) 439–449.
[76] S. McRae, H. Tran, S. Schulman, et al., Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis, Lancet 368 (2006) 371–378.
[77] F. Dentali, A.P. Sironi, M. Gianni, et al., Gender difference in efficacy and safety of nonvitamin K antagonist oral anticoagulants in patients with nonvalvular atrial fibrillation or venous thromboembolism: a systematic review and a meta-analysis of the literature, Semin. Thromb. Hemost. 41 (2015) 774–787.
[78] J. Beyer-Westendorf, F. Michalski, L. Tittl, et al., Management and outcomes of vaginal bleeding and heavy menstrual bleeding in women of reproductive age on direct oral anti-factor Xa inhibitor therapy: a case series, Lancet Haematol. 3 (2016) e480–e488.
[79] B. Brenner, Haemostatic changes in pregnancy, Thromb. Res. 114 (2004) 409–414.
[80] A.H. James, M.G. Jamison, M.S. Biswas, et al., Acute myocardial infarction in pregnancy: a United States population-based study, Circulation 113 (2006) 1564–1571.
[81] A. Roth, U. Elkayam, Acute myocardial infarction associated with pregnancy, J. Am. Coll. Cardiol. 52 (2008) 171–180.
[82] P. Juan, G. Stefano, S. Antonella, et al., Platelets in pregnancy, J. Prenat. Med. 5 (2011) 90–92.
[83] R.S. Kazmi, A.J. Cooper, B.A. Lwaleed, Platelet function in pre-eclampsia, Semin. Thromb. Hemost. 37 (2011) 131–136.
[84] G. Patti, R. De Caterina, R. Abbate, et al., Platelet function and long-term antiplatelet therapy in women: is there a gender-specificity? A 'state-of-the-art' paper, Eur. Heart J. 35 (2014) (2213-23b).
[85] W.H. Frishman, U. Elkayam, W.S. Aronow, Cardiovascular drugs in pregnancy, Cardiol. Clin. 30 (2012) 463–491.
[86] C. Kahler, E. Schleussner, A. Moller, et al., Nitric oxide donors: effects on fetoplacental blood flow, Eur. J. Obstet. Gynecol. Reprod. Biol. 115 (2004) 10–14.
[87] E. Kozer, S. Nikfar, A. Costei, et al., Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis, Am. J. Obstet. Gynecol. 187 (2002) 1623–1630.
[88] D.L. Rolnik, D. Wright, L.C. Poon, et al., Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia, N. Engl. J. Med. 377 (2017) 613–622.
[89] CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group, Lancet 343 (1994) 619–629.
[90] G. Briggs, R. Freeman, S. Yaffe, Drugs in Pregnancy and Lactation, P.A. Lippincott Williams & Wilkins, Philadelphia, 2009.
[91] M. De Santis, C. De Luca, I. Mappa, et al., Clopidogrel treatment during pregnancy: a case report and a review of literature, Intern. Med. 50 (2011) 1769–1773.
[92] S. Goland, U. Elkayam, Anticoagulation in pregnancy, Cardiol. Clin. 30 (2012) 395–405.
[93] L. Sadler, L. McCowan, H. White, et al., Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves, BJOG 107 (2000) 245–253.

[94] H.C. Flessa, A.B. Kapstrom, H.I. Glueck, et al., Placental transport of heparin, Am. J. Obstet. Gynecol. 93 (1965) 570–573.
[95] S.M. Bates, I.A. Greer, I. Pabinger, et al., Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition), Chest 133 (2008) 844S–886S.
[96] R.O. Bonow, B.A. Carabello, K. Chatterjee, et al., 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, J. Am. Coll. Cardiol. 52 (2008) (e1-142).
[97] V. Regitz-Zagrosek, C.B. Lundqvist, C. Borghi, et al., ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC), Eur. Heart J. 32 (2011) 3147–3197.
[98] E. Elsaigh, J. Thachil, M.J. Nash, et al., The use of fondaparinux in pregnancy, Br. J. Haematol. 168 (2015) 762–764.
[99] eMC, Summary of product characteristics, Available from: https://www.medicines.org.uk/emc/medicine/30506.
[100] O. Konigsbrugge, M. Langer, M. Hayde, et al., Oral anticoagulation with rivaroxaban during pregnancy: a case report, Thromb. Haemost. 112 (2014) 1323–1324.
[101] B. Myers, R. Neal, O. Myers, et al., Unplanned pregnancy on a direct oral anticoagulant (Rivaroxaban): a warning, Obstet. Med. 9 (2016) 40–42.