Review

Impact of Sex and Gender on the Efficacy of Antiplatelet Therapy: The Female Perspective

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Ischemic heart disease is the single leading cause of death and a significant cause of morbidity among women in industrialized countries. Current guidelines recommend antiplatelet therapy as the main cornerstone for the prevention and treatment of cardiovascular disease. Unfortunately, evidence is emerging that the response to antiplatelet drugs differs according to sex, although the biological basis for this gender disparity is unknown. In order to explain the epidemiological data showing a more severe clinical expression of cardiovascular disease in addition to adverse outcomes despite optimal pharmacological and interventional approaches in women compared to men, differences in platelet reactivity related to sex and gender are currently under investigation. In this report, we review available data from clinical trials of antiplatelet drugs administered for primary and secondary prevention, focusing on the underenrollment of female subjects in interventional randomized studies and weak community awareness of the impact of cardiovascular disease on life expectancy in women. Based on our findings, the development of real gender-oriented evidence-based guidelines for antiplatelet use in the setting of cardiovascular disease is urgently required.

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Introduction

In USA, the Institute of Medicine has repeatedly affirmed that sex and gender strongly influence the natural course of diseases from prevention to diagnosis and therapy. This phenomenon may depend on evident biological differences (sex) between men and women that lead to obvious differences in pharmacokinetic parameters (absorption, distribution, metabolism and elimination)[1, 2]. However, gender (considered to be the result of the sex-related sociocultural processes) differences are also considered to be relevant. Heart disease is closely linked with social roles, stress, lifestyle factors and access to health care systems. Although the terms sex and gender are commonly used interchangeably, for the purpose of this review the term sex-gender differences (SGD) will be used to describe differences between men and women. As largely discussed by Marino *et al.*[1, 2], SGD reflect physiological distinctions between the sexes as well as environment influences dictated by differences in lifestyle.

Although cardiovascular disease (CVD) represents the main cause of morbidity and mortality in both sexes worldwide, there are clear disparities between men and women in terms of the clinical presentation, symptoms, response to therapy and outcomes[3, 4]. Throughout the last decade, improvements in the diagnosis and treatment of atherosclerosis have resulted in a marked reduction morbidity and mortality in men, whereas the rates of recurrent atherothrombotic events, including cardiovascular (CV)

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death, in women have increased[5].

In particular, while the number of deaths among men has been steadily declining over the past 15-20 years, the frequency of CV deaths among women remained flat or increased slightly during the 1980's and 1990's. For over 20 years, the number of deaths among women has exceeded that observed in men[5]. Notably, a significant decrease in mortality was observed after the great effort to increase CVD awareness among women in America between 1996 and 2009[4, 5].

However, although CVD remains the leading cause of death for women in western Countries[4] and more women die from CVD than from all cancers combined[6], women remain largely unaware of their risk of developing CVD (**Fig. 1**). Heart disease is commonly considered a "man's disease," and, unfortunately, approximately 36% of women did not perceive themselves as being at risk for CVD[3, 4, 7], thus resulting in an inadequate approach to prevention.

Various SGD in the clinical presentation of CVD have been demonstrated, and some therapeutic options may not be equally effective and safe in men and women[6-9]. Certainly, gender differences in pharmacokinetics and pharmacodynamics may contribute to different responses to CV drugs[1, 8-11]. In addition, different responses have been described with respect to reperfusion techniques. Notably, women with acute myocardial infarction (MI) have a higher mortality rate than men, regardless of the reperfusion technique used[12-16]. In the CADILLAC trial[17], women (n=562, 27% of the entire population) with acute MI undergoing primary angioplasty were found to have higher mortality rates than men.

This phenomenon may be related to the generally smaller body surface area and higher prevalence of comorbidities among women, such as diabetes, hypertension and hyperlipidemia, that predict death, major adverse cardiac events (MACE) and bleeding complications at one year.

This review focuses attention on the relevance of awareness of CV prevention strategies and mortality reduction among women in order to revise the guidelines for antiplatelet therapy, a cornerstone in primary and secondary CVD prevention, in terms of efficacy and safety, with the objective of improving women's health care.

Call for the Action of Women in CVD Management

"Disease awareness," defined as a basic level of knowledge of the existence of a given disease and/or its effects in the community, represents a key step in any public CV health protective intervention.

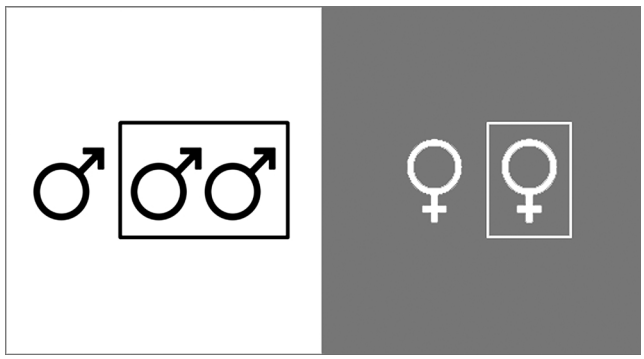

Fig. 1. Remaining lifetime risk for any type of CVD at age 40 in the subjects free from previous CVD[6].

Two-thirds of men are considered at risk, compared to half of women.

Women play an important role in achieving population-based improvements in CVD awareness, as they play a role in health prevention and access in families, select personal and family healthcare providers and engage the family unit in health interventions, as their own health is preserved[7]. However, for decades, clinicians, as well as women, were "unaware" of the impact of coronary artery disease on women's health[18]. Furthermore, the CRUSADE National Quality Improvement Initiative documented that women with CVD less often receive guideline-recommended antithrombotic therapies than men[19].

Only within recent years, has the effects of CVD on the health status of American women gained more recognition and become a focus of public education efforts, such as the "Go Red for Women" campaign, sponsored by the American Heart Association, or the "Red Dress" project sponsored by the Department of Health and Human Services, National Institutes of Health and National Heart Lung and Blood Institute. These programs are, partially, a response to the increasing awareness of CVD as a major source of morbidity and mortality in U.S. women[20].

In addition, there are continuous efforts by federal agencies and scientific societies to increase the enrollment of female subjects in CV trials in order to obtain more evidence-based data regarding CV treatments for women. For example, the FDA's Center for Devices and Radiological Health recently published a Guidance Document "on the study and analysis of sex/gender difference in CV medical device trials," underlining the need for solid data to ensure the safe and effective use of medical therapies and devices in both sexes[21, 22]. Moreover, the European Heart Health Strategy (EuroHeart) project endorsed by the Euro-

pean Society of Cardiology (ESC) and European Heart Network (EHN), co-funded by the European Commission, have addressed the issue of the representation of women in CV clinical research in Europe[23].

Corroborating the need for more evidence from the female "universe," it has been pointed out that the enrollment rate of women in CV clinical trials funded by the National Heart, Lung and Blood Institute through all of 2006 remained unchanged when compared to the estimated rate between 1965 and 1998, corresponding to only 38% of patients, despite several federal mandates calling for an increase in the enrollment of women in clinical studies[24, 25]. The percentage of women is even lower when initial phase (I and II) clinical trials are considered[26].

In our opinion, another field in which awareness should be increased is pharmacological therapy, considering that the guidelines for CV therapy are primarily based on data obtained in men and male animals[27] and because women have been reported to experience more frequent and severe drug reactions[1, 10]. In summary, we include the famous quote from English writer Oscar Wilde, "*The world was made for men and not for women*"[28].

Platelet Function and SGD

Unfortunately, there is a significant gap in basic and clinical knowledge regarding specific cellular mechanisms related to CVD in women. Consequently, the biological basis of SGD in the setting of CVD remains a frontier to explore. As previously mentioned, the paucity of information related to SGD associated with CVD is partly due to the fact that women have been neglected in research studies[6, 25] and because most basic science inquiries into biological factors contributing to CVD are predominately conducted in male animals[27]. Moreover, there is ongoing failure of research tools to include SGD in the study design and analysis.

This fault in study design methodology imbues a perpetual bias in studies in the reporting phase. Consequently, evidence based-guidelines recommended for both sexes are based only on data obtained by predominantly in trials based on male populations. Nevertheless, numerous SGD have been described in platelet biology[29-33]. For example, while it has been reported that oral contraceptives promote platelet aggregation, and controversial data are available regarding the effects of the menstrual cycle on the platelet function[32-35]. Regarding genetic polymorphisms in platelet glycoproteins (Gp), it has been shown that such polymorphisms are linked to the risk of atherothrombotic events[35-38]; however there is little information available about whether these polymorphisms are influenced by sex. Meanwhile, women heterozygous or homozygous for the Gp Ib-alpha5C allele have a higher incidence of composite endpoint (death, MI or unstable angina) compared with those homozygous for the Gp Ib alpha-5T allele[39], and hormonal replacement therapy is associated with a 46% lower adjusted risk of CV in women with the -5C allele versus the -5TT genotype[39]. Consequently, it is not surprising that the response to antiplatelet therapy may be influenced by SGD[40-44].

Platelets play a pivotal role in the pathogenesis of atherosclerosis and occurrence of acute thrombotic events. The importance of platelets in CVD is indirectly confirmed by the benefits of antiplatelet agents (particularly aspirin, clopidogrel and Gp IIb/IIIa inhibitors) in the clinical setting. However, previous clinical trials have suggested that, compared to men, women do not receive equal therapeutic advantages from antiplatelet medications. The physiological mechanisms and clinical implications underlying this sex-gender disparity have yet to be clearly established.

Recently, Wang Y.T. *et al.*[41] reviewed the scarce available data on differences in antithrombotic drug responses.

Although concerns have been raised regarding the differential benefits of antiplatelet drugs in women, the propensity for an increased rate of bleeding among female patients has also been recognized. A better understanding of contributing factors to SGD in terms of platelet biology is warranted. Such factors include: i) differences in the frequency and expression of genetic polymorphisms affecting platelet responsiveness to agonists (with or without antiplatelet therapy), which may be obtained through population-based studies and large controlled clinical trials; ii) the levels of inflammatory markers and their influence on atherothrombotic risks; iii) the effects of hormones on the platelet function and activation.

Antiplatelet Drugs for CVD Prevention in Women

In daily clinical practice, antiplatelet agents are recommended for CVD prevention according to international guidelines. Among all antiplatelet drugs currently available, we will primarily discuss, from a gender-related perspective, the following: i) acetylsalicylic acid (ASA), an irreversible inhibitor of cyclooxygenases; ii) ADP receptors P2Y12 antagonists (clopidogrel, prasugrel, ticagrelor); and iii) Gp IIb/IIIa receptor blockers (abciximab, eptifibatide, tirofiban).

Table 1. Primary prevention studies of aspirin in women

STUDY	YEAR	SUBJECTS (% WOMEN)	AGE eligible range (years)	FOLLOW-UP Mean (years)	TARGET POPULATION	ASPIRIN	RANDOMISED FACTORIAL COMPARISON	PLACEBO CONTROL	CV events No/Tot			
									ASA WOMEN	CTRL WOMEN	ASA MEN	CTRL MEN
HOT [45]	1998	18,790 (47)	50-80	3.8	Men and women with DBP 100-115 mm Hg	75 mg daily	Three blood pressure regimens	Yes	109/4,437	134/4,446	173/4,962	207/4,945
PPP [46]	2001	4,495 (58)	45-94	3.7	Men and women with one or more risk factors for CHD	100 mg daily	Vitamin E open control	No	17/1,277	26/1,306	28/949	38/963
WHS [47]	2005	39,876 (100)	≥45	10.0	Female health professionals	100 mg alternate days	Vitamin E	Yes	477/19,934	522/19,942	–	–
POPADAD [48]	2008	1,276 (56)	≥40	6.7	Men and women with diabetes and ABI ≤0.99	100 mg daily	Antioxidant	Yes	48/352	55/361	68/286	62/267
JPAD [49]	2008	2,539 (45)	30-85	4.3	Men and women with diabetes	81 mg or 100 mg daily	Non aspirin-treatment	Yes	28/556	35/596	40/706	51/681
AAA [50]	2010	3,350 (72)	50-75	8.2	Men and women in general population with ABI ≤0.95	100 mg daily	No	Yes	85/1,194	93/1,202	96/481	83/473

Legend: AAA: Aspirin for Asymptomatic Atherosclerosis trial; ABI: Ankle-Brachial Index; CHD: coronary heart disease; CTRL: controls; CV: cardiovascular; DBP: diastolic blood pressure; HOT: Hypertension Optimal Treatment Trial; JPAD: The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; n.a: not available; PPP: Primary Prevention Project; POPADAD: The Prevention Of Progression of Arterial Disease And Diabetes Trial; WHS: Women's Health Study.

In particular, sex specific pharmacokinetic profiles have been described for ASA, while clopidogrel does not show any relevant pharmacokinetic sex differences, although it is metabolized by the hepatic isoenzymes CYP2B6 and CYP3A4[1, 10]. A potential sex and gender clinical difference in the mechanism of action of clopidogrel is suggested by the reduced rate of responsiveness to ADP-mediated aggregation in *ex vivo* experiments among women treated with clopidogrel[1, 10].

CVD Primary Prevention Studies

Currently there is no clear evidence regarding the beneficial effects of antiplatelet drugs in CVD primary prevention studies[45-50], as summarized in **Table 1**. It is well known that ASA, the antecedent to antiplatelet therapy prescribed worldwide, is characterized by a sex-specific pharmacokinetic profile in both animals and human beings For example, it is absorbed and hydrolyzed more rapidly and exhibits a larger distribution in females than in males[51]. Additionally, it has been reported that the rate of ASA absorption slows during the menstrual mid-cycle, suggesting the importance of sexual hormones in modulating the ASA activity. These data are also confirmed by the effects of exogenous hormones on the pharmacokinetics of ASA[51].

As a counterpart to SGD in ASA pharmacokinetics, the response to ASA in CVD primary prevention clinical trials differs between women and men[52].

In a meta-analysis by Berger *et al.*, among 51,342 women, 1,285 episodes of MACE (625 strokes, 469 MIs and 364 CV deaths) were reported, compared to a total of 2,047 MACE among 44,114 men. In women, ASA therapy was found to be associated with a significant reduction in CV events (12%) and stroke (17%), a reflection of a reduced rate (24%) of ischemic stroke, although there were no significant effects on MI or CV mortality. In contrast, although similar protection from CV events was noted, men derived most of the benefits from a reduction in the risk of MI of 32%[52]. However, when adjusted for multiple comparisons[53], the reduction in vascular outcomes did not differ between men and women (**Fig. 2**). It has been suggested that the sex-gender mix accounts for 25% of the variation in the reported efficacy of ASA in reducing the rates of CV events across placebo-controlled trials[45].

Therefore, even in studies not involving sex biases in patient enrollment, differential beneficial effects of ASA have been reported. In the "Prevention of pro-

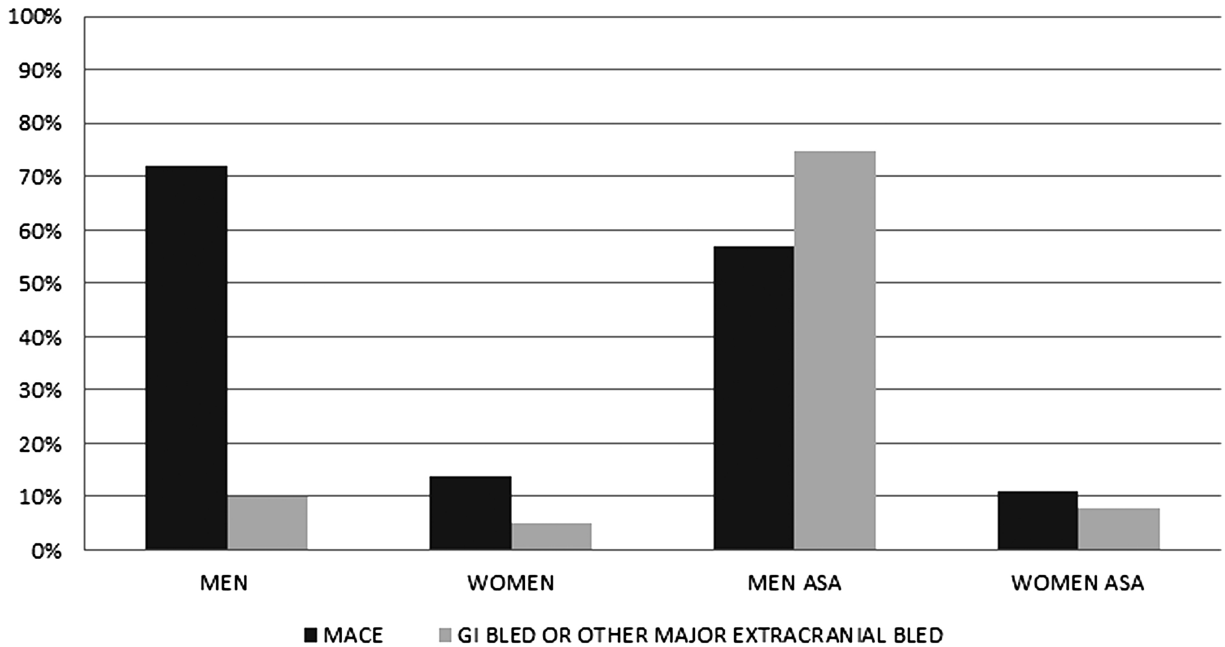

Fig. 2. Rates of cardiovascular and bleeding events per year in the primary prevention studies[53].
GI = gastrointestinal; MACE = Major Adverse Cardiovascular Events

gression of arterial disease and diabetes" (POPADAD) study[48], 1,276 patients (50% females) with diabetes and asymptomatic peripheral artery disease (PAD) (as determined according to a lower-than-normal ankle-brachial pressure index of 0.99 or less, without symptoms) over 40 years of age were randomized to receive either ASA (100 mg) or placebo, an antioxidant or placebo or ASA and an antioxidant or double placebo and followed over eight years. The trial documented no benefits from daily prophylactic ASA use (HR = 0.98; $p = 0.87$). However, it is important to recognize that the POPADAD is smaller than most other ASA trials, with fewer events, and that it is possible that small effects may be demonstrated in larger trials continued for longer periods.

Starting in 2010, the rate of enrollment of women in CVD primary prevention studies increased (more than 50%). Not surprisingly (based on previous evidence), trials have shown no significant benefits to ASA treatment among women, as in the "Aspirin for Asymptomatic Atherosclerosis" (AAA) trial[50]. The AAA trial was an intention-to-treat, double-blind, randomized controlled trial of once daily low-dose ASA (100 mg) vs a placebo that involved 28,980 subjects (72% of the participants were women) 50 to 75 years of age who were free of clinical CVD. All recruited patients underwent an ankle-brachial index (ABI) screening test. Of these subjects, 3,350 with a low ABI (defined as an ABI equal to or less than 0.95) entered the trial. The sample was powered to detect a 25% proportional risk reduction in events. Consequently, ASA was found to be no more effective than the placebo in reducing the primary endpoint (13.7 events per 1,000 person-years in the ASA group vs. 13.3 events per 1,000 person-years in the placebo group; HR, 1.03; 95% CI, 0.84-1.27), and the authors concluded that ASA had no clinical benefits and may actually be harmful in asymptomatic PAD patients.

Of note, the 9th ACCP Guidelines for CVD prevention state that, in asymptomatic individuals, low-dose ASA therapy (75-100 mg/d) should be considered in patients >50 years of age, irrespective of gender[54].

CVD Secondary Prevention Studies

Over the years, strategies for secondary prevention of CV events have become progressively more important to counteract the risk of mortality and MACE recurrence, such as after MI[6] (**Fig. 3**).

Single Therapy

Antiplatelet agents are a therapeutic cornerstone in the secondary prevention of CV events in patients with established atherosclerosis. The essential role of antiplatelet therapy has been well established in serial

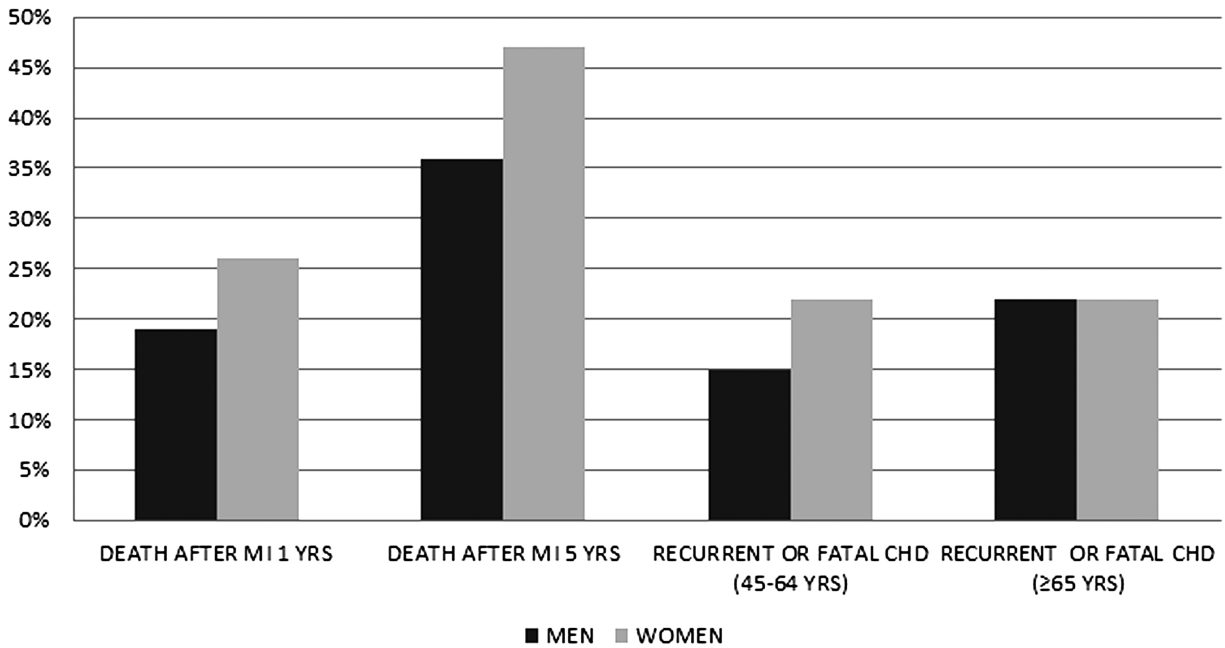

Fig. 3. Rates of cardiovascular events after myocardial infarction[6].

CHD: coronary heart disease; MI: myocardial infarction; YRS: years

publications of the Antithrombotic Trialists' Collaboration (ATC) including over 130,000 patients and 50 trials[55]. This meta-analysis clearly demonstrated a cardioprotective benefit of antiplatelet therapy in a broad population of patients with clinical evidence of atherosclerosis, specifically defined as those with a history of MI, acute coronary syndrome, transient ischemic attack or stroke as well as coronary or carotid revascularization procedures. Notably, antiplatelet therapy resulted in equally beneficial effects in women and men[55] (**Fig. 4**).

Double Therapy: ASA and ADP Receptors/P2Y12 Antagonists

Gender and sex have not been considered, until recently, crucial determinants of antithrombotic therapy in the setting of secondary CVD prevention, as evidenced by the small number of women enrolled in studies designed to test the efficacy of dual antiplatelet therapy[56-69] (**Table 2**) and the lack of drug-response SGD sensitivity analyses.

Interventional studies specifically focused on sex-related differences in the response to clopidogrel support the concept that clopidogrel is similarly beneficial in men and women, although the degree of benefit may vary. In the "Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events" (CURE) trial, which included non-ST elevation myocardial infarction (NSTEMI) patients, a smaller absolute (1.2% vs. 2.8%) and relative (12% vs. 25%) risk reduction in the composite endpoint of CV death, non-fatal MI or stroke after a one-year follow-up was seen in women versus men treated with clopidogrel plus ASA compared to ASA alone at one year[56, 57].

The "Clopidogrel for the Reduction of Events During Observation" (CREDO) trial[58, 59], which enrolled patients undergoing elective percutaneous coronary intervention (PCI), showed a 26.9% relative risk reduction in favor of clopidogrel for the composite endpoint of death, MI and stroke at one year in the overall population. Compared to the results of the CURE trial, the CREDO trial demonstrated a greater risk reduction among women for the combined risk of death, MI and stroke at one year (32% vs. 25%). Moreover, in the "Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28" (CLARITY-TIMI 28) trial, patients receiving fibrinolytic therapy within 12 hours after the onset of ST elevation myocardial infarction (STEMI) symptoms were randomized to receive dual antiplatelet therapy with ASA plus clopidogrel versus clopidogrel alone[60]. Consequently, a 36% reduction in the risk of the composite ischemic endpoint was observed in the subjects treated with clopidogrel among the overall population, with similar reductions for both men and women (35% vs. 38%, respectively), despite a higher

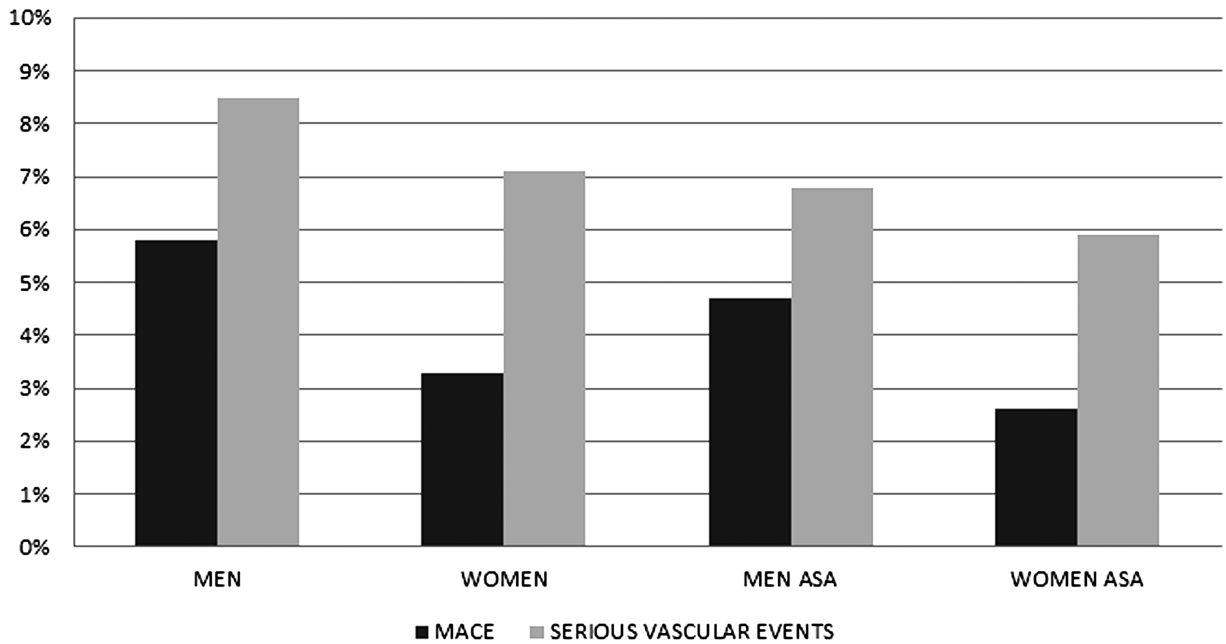

Fig. 4. Rates of major adverse cardiovascular events and serious vascular events in the secondary prevention studies[53].
ASA = acetylsalicylic acid; MACE = Major Adverse Cardiovascular Events

rate of events in women in both treatment arms[60].

Reductions in the primary ischemic endpoint at 28 days with no heterogeneity in the SGD effect, despite higher event rates in women, were also observed in the "ClOpidogrel and Metoprolol in Myocardial Infarction Trial" (COMMIT), which compared the effects of clopidogrel plus ASA versus ASA alone in Chinese patients with suspected MI[61]. In contrast, the "Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance" (CHARISMA) trial failed to demonstrate any clinical benefits associated with the combination of low-dose ASA and clopidogrel in asymptomatic patients with at least three atherothrombotic risk factors, with no statistically significant differences between the sexes[62].

In order to clarify these conflicting data regarding the relative efficacy and safety of clopidogrel in reducing CVD events in both sexes, a meta-analysis of all blinded randomized clinical trials comparing clopidogrel and a placebo was performed[63], which showed no significant SGD in the treatment effect, reducing overall CVD events by 14%. Although a greater number of women experienced bleeding complications, no statistically significant differences in safety were noted between the sexes[63].

Indeed, dual antiplatelet therapy (ticagrelor at 90 mg twice daily plus low-dose ASA at 75-100 mg daily, clopidogrel at 75 mg daily plus low-dose ASA or prasugrel at 10 mg daily plus low-dose ASA over a single course of antiplatelet therapy) is recommended for secondary prevention in acute coronary syndrome (ACS) patients treated with PCI with stent placement for the first year after the procedure[54].

In the "Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel - Thrombolysis in Myocardial Infarction 38" (TRITON-TIMI 38) trial, prasugrel was compared to clopidogrel in addition to ASA in ACS patients (74% NSTEMI). The combined endpoint (death from CV, non-fatal MI or non-fatal stroke) was reduced by prasugrel [9.9% vs. 12.1%], with an HR of 0.81 [95% CI (0.73-0.90)]. However, the rate of major bleeding was significantly higher in the prasugrel-treated patients (2.4% vs. 1.8%, $p = 0.03$)[64]. Similar to the CURE trial findings, a less pronounced and statistically not significant risk reduction in women has been reported. In the "PLATelet Inhibition and Patient Outcomes" (PLATO) trial, the reversible ADP receptor antagonist ticagrelor was also shown to be superior to clopidogrel in ACS patients (38% STEMI), with a lower rate of the primary endpoint, a composite of CV death/MI or stroke (9.8% vs. 11.7%)[65]. A sex-gender related subgroup analysis revealed similar and statistically significant benefits in both men and women.

Table 2. Dual antiplatelet therapy in women and gender-stratified events analyses

STUDY	YEAR	DESIGN	STUDY POPULATION	ACTIVE GROUP (dual antiplatelet therapy)	CONTROL GROUP (other antiplatelet drug or placebo)	PATIENTS ENROLLED (N)	WOMEN (%)	MEN (%)
CURE [56]	2001	RCT	ACS without ST-segment elevation	CLOP (300 mg loading dose followed by 75 mg/d) + ASA (75-325 mg/d)	ASA (75-325 mg/d) + Placebo	12,562	4,836 (39)	7,726 (61)
CREDO [58]	2003	RCT	Planned PCI or coronary angiogram	CLOP (300-mg loading dose followed by 75 mg/d through 12 months) + ASA (81-325 mg/d)	Placebo (loading dose followed by CLOP 75 mg/d until day 28 then placebo) + ASA (81-325 mg/d)	2,116	606 (29)	1,510 (71)
CHARISMA [62]	2006	RCT	Clinically evident cardiovascular disease or multiple risk factors	ASA (75-162 mg/d) + CLOP (75 mg/d)	ASA (75-162 mg/d) + Placebo	15,603	4,644 (30)	10,959 (70)
CURRENT OASIS-7 [68]	2010	RCT	ACS and intended early PCI	Double-dose CLOP (150 mg for 7 days followed by 75mg/d) High-dose ASA (300-325 mg/d)	CLOP-standard dose (75 mg/d) ASA-Low dose (75-100 mg/d)	17,263	4,234 (25)	13,029 (75)
PLATO [65, 66]	2009	RCT	ACS, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours	TIC (180 mg loading dose followed by 90 mg twice/d) + ASA (75-100mg/d)	CLOP (300-mg loading dose followed by a dose of 75mg/d) + ASA (75-100 mg/d)	18,624	5,288 (28)	13,336 (72)
TRITON-TIMI 38 [64]	2007	RCT	ACS with scheduled PCI	PRA (60 mg loading dose followed by 10 mg/d) + ASA (75-162 mg/d)	CLOP (300-mg loading dose followed by a dose of 75mg/d) + ASA (75-162 mg/d)	13,608	3,605 (27)	10,003 (73)
GRAVITAS [69]	2011	RCT	Stable CAD or non-ST-elevation acute coronary syndromes. Patients with high on-treatment reactivity 12 to 24 hours after PCI with drug-eluting stents	CLOP (600 mg followed by 150 mg/d) + ASA (75-162 mg/d)	CLOP (loading dose of placebo followed by 75 mg/d and placebo tablet daily) + ASA (75-162 mg/d)	2,214	773 (35)	1,441 (65)

Legend: ACS: acute coronary syndromes; ASA: aspirin; CAD: coronary artery disease; CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance; CLOP: clopidogrel; CREDO: Clopidogrel for the Reduction of Events During Observation; CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events; CURRENT OASIS-7: Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Symptoms; GRAVITAS: Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety; PCI: percutaneous coronary intervention; PLATO: Study of Platelet Inhibition and Patient Outcomes; PRA: prasugrel; TRITON-TIMI 38: Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38; TIC: ticagrelor.

Gp IIb/IIIa Inhibitors

The response to another type of antiplatelet medication, Gp IIb/IIIa inhibitors, has also been shown to have a sex-specific response[1, 10]. More adverse events with Gp IIb/IIIa inhibitors have been reported in women. Indeed, women experience more bleeding than men, independent of the treatment type[1, 10, 67]. Appropriate dosing of antithrombotic agents should improve the care of women with ACS without ST elevation (**Fig. 5**).

Biological Response to Antiplatelet Drugs and Recurrence of MACE

Since platelet reactivity plays a pivotal role in thrombus formation and atherosclerosis, differences in the reactivity of platelets between women and men have been assessed using several methods and in response to varying stimuli[70].

Platelets derived from women without IHD are more reactive than those of men in response to standard concentrations of agonists, such as adenosine diphosphate (ADP) and thrombin receptor agonist protein[71-73]. Activated platelets, by releasing cytokines, mediate an inflammatory response that further amplifies the platelet response and endothelial activation under conditions of plaque rupture[74] Becker D.M. *et al.* in the GeneSTAR (Genetic Study of Aspirin Responsiveness) trial studied healthy men and women[75], demonstrating higher platelet reactivity in women than men after adjusting for age, risk factors, race, menopausal status and hormone therapy[74]. After the administration of ASA therapy, women's platelets remain significantly more reactive than those of men in response to collagen or ADP stimulation which, according to the investigators, likely reflects "platelet activation pathways indirectly related to cyclooxygen-

Table 2. Dual antiplatelet therapy in women and gender-stratified events analyses (continued)

STUDY	PATIENTS ENROLLED (N)	FU (months)	C V EVENTS	WOMEN CTRL FU CV EVENTS/ N. women (%)	MEN CTRL FU CV EVENTS/ N. men (%)	WOMEN TREATED FU CV EVENTS/ N. women (%)	MEN TREATED FU CV EVENTS/ N. men (%)	Clinical Outcomes Subgroups analysis by sex
CURE [56]	12,562	12	MACE	258/2,416 (11)	461/3,887 (12)	231/2,420 (10)	351/3,839 (9)	OR (Active vs Control) 95% CI M: 0.75 (0.65-0.87) W: 0.88 (0.73-1.06)
			ALL CAUSE MORTALITY	140/2,420 (6)	250/3,887 (6)	145/2,420 (6)	214/3,839 (6)	OR ((Active vs Control) 95% CI M: 0.86 (0.71-1.04) W: 1.04 (0.82-1.32)
			MI	148/2,416 (6)	271/3,887 (7)	118/2,420 (5)	206/3,839 (5)	OR (Active vs Control) 95% CI M: 0.76 (0.63-0.91) W: 0.79 (0.61-1.01)
CREDO [58]	2,116	12	MACE	33/297 (11)	81/766 (11)	24/309 (8)	58/744 (8)	OR (Active vs Control) 95% CI M: 0.72 (0.50-1.02) W: 0.67 (0.39-1.17)
			ALL CAUSE MORTALITY	9/297 (3)	15/766 (2)	7/309 (2)	11/744 (1)	OR (Active vs Control) 95% CI M: 0.75 (0.34-1.65) W: 0.74 (0.27-2.02)
			MI	24/297 (8)	66/766 (9)	18/309 (6)	52/744 (7)	OR (Active vs Control) 95% CI M: 0.80 (0.55-1.16) W: 0.70 (0.37-1.33)
CHARISMA [62]	15,603	28-35	MACE	149/2,328 (6)	424/5,473 (8)	150/2,316 (6)	384/5,486 (7)	OR (Active vs Control)95% CI M: 0.90 (0.78-1.03) W: 0.93 (0.86-1.01)
			ALL CAUSE MORTALITY	106/2,328 (5)	268/5,473 (5)	104/2,316 (5)	267/5,486 (5)	OR (Active vs Control)95% CI M: 0.99 (0.84-1.18) W: 0.99 (0.75-1.30)
			MI	45/2,328 (2)	155/5,473 (3)	42/2,316 (2)	144/5,486 (3)	OR (Active vs Control) 95% CI M: 0.92 (0.73-1.16) W: 0.94 (0.61-1.43)
CURRENT OASIS-7 [68]	17,263	1	Composite CV death , MI, Stroke	CLOP SD: 126/2,183 (5.8) ASA SD 110/2,085 (5.3)	CLOP SD: 266/6,520 (4.1) ASA SD 256/6,554 (3.9)	CLOP HD: 93/2,051 (4.5) ASA HD:109/2,149 (5.1)	CLOP HD: 237/6,509 (3.6) ASA HD 247/6,475 (3.8)	HR double vs standard dose (95% CI) CLOP: M: 0.90 (0.76-1.02) W: 0.77 (0.59-1.02) ASA: M: 0.98 (0.83-1.17) W: 0.95 (0.73-1.324)
PLATO [65, 66]	18,624	12	Composite CV death , MI, Stroke	327/2,633 (13.2)	685/6,658 (11.1)	276/2,655 (11.2)	583/6,678 (9.4)	HR M vs W (95% CI) HR 1.02 (0.91-1.16) HR TIC vs CLOP (95% CI) M 0.86 (0.76-0.97); W 0.88 (0.74-1.06)
TRITON-TIMI 38 [64]	13,608	6-15	Composite CV death , MI, Stroke	229/1,820 (12.6)	592/4,975 (11.9)	187/1,703 (11)	485/5,110 (9.5)	RR (Active vs Control) M: RR = 0.79 W: RR = 0.88
GRAVITAS [69]	2,214	6	na	na	na	na	na	na

Legend: ASA: aspirin; CLOP: clopidogrel; CREDO: Clopidogrel for the Reduction of Events During Observation; CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events; CURRENT OASIS-7: Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Symptoms; CV: cardiovascular; GRAVITAS: Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety; HD: high dose; HR hazard ratio MACE: Major Adverse Cardiovascular Events; MI: myocardial infarction; PLATO: Study of Platelet Inhibition and Patient Outcomes; PRA: prasugrel; RR: risk reduction; SD: standard dose; TIC: ticagrelor; TRITON-TIMI 38: Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38.

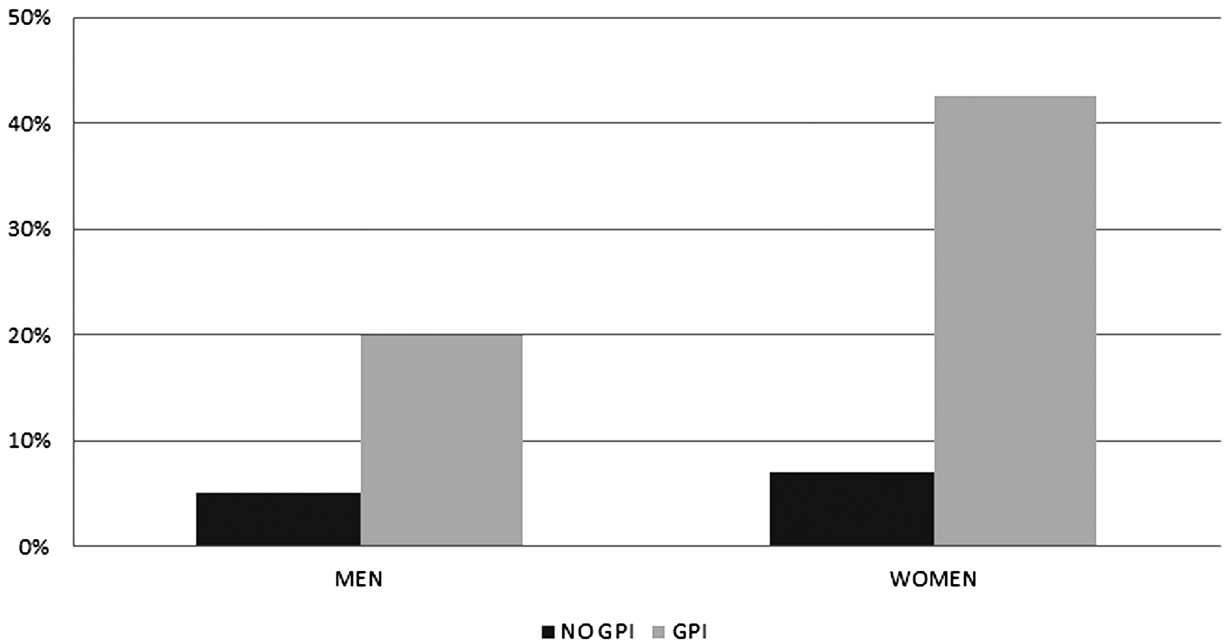

Fig. 5. Rates of major bleeding in men and women following PCI with or without the administration of GP IIb/IIIa inhibitors [adapted from 86].

GPI = GP IIb/IIIa inhibitors

ase-1"[75].

Biological antiplatelet drug responsiveness is highly variable and has been linked to CV outcomes in patients treated with ASA and/or clopidogrel[69, 76, 77]. As summarized in **Table 3**, reported data are conflicting, likely due to the use of different clinical settings (acute versus stable patients) and differences in the timing of platelet function assessments (single vs. repeated) and the definition of high on-treatment platelet reactivity (HPR). HPR is reported to be predictive of ischemic events, with relative risks ranging from 2 to 4 in meta-analyses of studies primarily involving patients with acute vessel injury following ACS or PCI and in the early phase of antiplatelet treatment[78, 79].

Tests used to evaluate antiplatelet drug responsiveness differ according to their specificity for the targets of ASA and clopidogrel. Aggregation-based assays, such as the PFA-100® and agonist-induced platelet aggregation tests, provide assessments of global platelet reactivity.

Prior studies have examined the relationship between platelet reactivity and clinical outcomes using single assessments of the platelet function; however, on-treatment reactivity varies over time. Recently, in the Antiplatelet Drug Resistance and Ischemic Events (ADRIE) trial, a prospective study focusing on the clinical relevance of the platelet response to ASA and/or clopidogrel in 771 stable CV patients, specific and aggregation-based assays were performed twice on two separate occasions in order to assess antiplatelet resistance[80]. The authors observed that neither the specific nor aggregation-based assays of antiplatelet drug responsiveness added any significant predictive values relative to the conventional risk factors for ischemic events recurrence in the stable CV patients, and consequently do not support the use of platelet function testing for MACE risk evaluation in this setting. Currently, data regarding SGD in antiplatelet drug responsiveness, as evaluated based on any type of platelet function tests, are lacking.

Bleeding in Women Undergoing PCI

Historically, women have been reported to have higher rates of bleeding following PCI than men, although the reasons for the large difference are still largely unknown.

SGD have been reported in PCI-secondary bleeding events, the most frequent non-ischemic complication in ACS patients. Data from real-life management in the GRACE registry showed major bleeding rates ranging from 2.7% to 4.7%. In a multivariate analysis, the adjusted OR for bleeding was 1.71 (95% CI, 1.35-2.17) in women compared to men[81], indicating

Table 3. Prospective studies: Data on platelet reactivity

STUDY	YEAR	STUDY POPULATION	ANTIPLATELET DUAL THERAPY	PATIENTS ENROLLED (N)	WOMEN (%)	MEN (%)
POPULAR [70]	2010	Established CAD scheduled for elective stent implantation	ASA (80-100 mg/d) + CLOP (dose loading followed by 75 mg/d)	951	234 (26,4%)	717 (73,6%)
RECLOSE 2-ACS [71]	2011	ACS undergoing an invasive procedure and receiving long-term antithrombotic treatment	ASA (325 mg/d) + CLOP (600 mg loading dose followed by 75 mg/d)	1,789	366 (20%)	1,423 (80%)
ADRIE [74]	2012	Consecutive patients with symptomatic documented ischemic atherothrombotic disease (CAD, ICD, PAD)	ASA and/or CLOP	771	146 (19%)	625 (81%)

STUDY	FOLLOW UP (Months)	PLATELET TEST EVALUATION	DEFINITION OF HIGH ON-TREATMENT REACTIVITY	CONCLUSIONS
POPULAR [70]	12	-ADP-induced LTA (20 μmol/L) -AA-induced LTA (AA 0.5 mg/mL) -VerifyNow P2Y12-Assay -VerifyNow Aspirin assay	n.a	Incidence of clinical endpoints was similar between women and men despite in women the magnitude of on-clopidogrel platelet reactivity as well as on-aspirin platelet reactivity using LTA, was significantly higher
RECLOSE 2-ACS [71]	24	-ADP induced-LTA (10 μM)	platelet aggregation ≥ 70%	HRPR status was significantly associated with increased risk of ischemic events at short- and long-term follow-up.
ADRIE [74]	36	-TXB2 - VASP-Platelet reactivity index (PRI) - Aggregation based assays: AA 1 mM ADP 5 μM, ADP 20 μM, Collagen 1 μM PFA-100®	-TXB2 ≥ 12 ng/mL -VASP-PRI ≥ 50% -Aggregation based assays AA ≥ 20% ADP 5 μM ≥ 55% ADP 20 μM ≥ 42% Collagen 1 μM ≥ 90th percentile PFA-100® ≥ 190	Biological antiplatelet drug responsiveness, measured with specific or aggregation-based assays, has no incremental predictive value over common CV risk factors for MACE recurrence in stable CV outpatients

Legend: AA: arachidonic acid; ACS: acute coronary syndrome; ADP: adenosine diphosphate; ADRIE: Antiplatelet Drug Resistance and Ischemic Events; ICD: ischemic cerebrovascular disease; ASA: aspirin; CAD: coronary artery disease; CLOP: clopidogrel; LTA: Light Transmission Aggregometry; MACE: Major Adverse Cardiovascular Events; n.a. = not available; PAD = peripheral artery disease; PFA-100: Platelet Function Analyzer-100; POPULAR: Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel Pretreated Patients Undergoing Elective PCI study; RECLOSE 2-ACS: Responsiveness to Clopidogrel and Stent Thrombosis 2-ACS study; TXB2: thromboxane B2.

that a female sex represent an independent predictor of such complications. These findings confirm the data obtained in previous studies, demonstrating that invasively treated (PCI and/or fibrinolysis reperfusion strategies) female patients experience periprocedural vascular and bleeding complications more frequently than male patients, independent of age. Hence, a female sex has been identified to be an independent predictor of bleeding in several ACS trials using different anticoagulation strategies[1, 10, 81].

The risk of bleeding in women under treatment with antiplatelet agents is even more important in specific clinical contexts, such as atrial fibrillation (AF) patients who require stent implantation for ischemic heart disease. In such cases, current international recommendations advocate the use of triple therapy with warfarin (INR 2.0-2.5) and aspirin plus clopidogrel in AF patients with moderate-to-high thromboembolic risks for the shortest possible treatment period (depending on the stent type and individual's bleeding)[82]. Meanwhile, the Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (CHA_2DS_2-VASc) score is, at present, a validated tool for stratify-

ing the risk of thromboembolic stroke in AF patients[83]. A female sex is an independent predictor of thrombosis; therefore, anticoagulants are required in the presence of at least one other thrombosis risk factor[84]. Unfortunately, the benefits of triple therapy in women with AF at risk of both stroke and stent thrombosis may be counterbalanced by a substantial increase in the risk of serious bleeding during the treatment period. However, the availability of new oral anticoagulants (NOACs) that appear to have a more effective and safer profile in terms of bleeding in women should be evaluated carefully in this context in order to ameliorate the effects of antithrombotics. Interestingly, as reported in a recent meta-analysis, NOACs seem to be more effective, with a lower risk of bleeding, in women than in men[85].

Until recently, most results regarding ACS women treated with PCI have been based on sub-study analyses without adequate statistical power, a phenomenon also valid for men.

Bleeding tendencies in women may be partly avoidable by adjusting the dose of antiplatelet agents, considering their smaller distribution volume and reduced renal function[16, 86-88]. In particular, the lack of Gp IIb/IIIa inhibitor dose correction may account for up to 25% of cases of excess bleeding in women[1, 10].

Meanwhile, bleeding avoidance strategies (BAS), including the use of vascular closure devices, bivalirudin and radial access, are being increasingly applied and have been reported to be associated with decreased rates of bleeding following PCI[89-93]. As reported by Daugherty *et al.*[94], in the National Cardiovascular Data Registry's CathPCI Registry, the use of any BAS was associated with a similarly lower risk of bleeding in both genders; however, the absolute risk differences were substantially higher in women. These data underscore the importance of applying effective strategies to limit post-PCI bleeding, especially in women.

A recently published sex-gender-specific analysis, the "Intracoronary Stenting And Antithrombotic Regimen -Rapid Early Action for Coronary Treatment" (ISAR-REACT) trial (1,721 NSTEMI patients, 23% women), confirmed the lack of differences in ischemic events the one-year follow-up among NSTEMI ACS patients randomized to a strategy of bivalirudin or abciximab plus unfractionated heparin according to sex[95].

Conclusions and Perspectives

There is growing recognition of the personal and public health relevance of CVD in women. The CVD burden in women is larger than that observed in men given that women experience more CV events. Since women tend to outlive men, this sex disparity will likely worsen in the years to come as the population continues to age. Bridging this disparity will require a better understanding of sex-gender-specific issues in the setting of CVD, including the differential response to various proven pharmacological interventions in women. Antiplatelet therapy is currently a cornerstone among CVD prevention strategies as well as the early management of ACS; however, there remains a major gap in evidence regarding the actual effects of gender on the efficacy of antiplatelet drugs in patients with or at risk of CVD.

It is important to clarify possible differences between men and women in large prospective cohort studies with equal numbers of male and female patients. Although it is desirable to develop expert consensus guidelines comprising sex-specific recommendations for CVD management, the recently published statement from the Italian Society of Cardiology (SIC) regarding the platelet function and antiplatelet therapy in women strongly underlined the lack of high-level evidence to support more precise and strong recommendations[96]. Therefore, more studies focusing on CVD as the primary endpoint with adequate representation of women and sufficient power to examine SGD are urgently needed. Ultimately, clinicians must be vigilant in ensuring that all women receive antiplatelet medications as part of secondary CVD prevention regimens. However, the selection of optimal antiplatelet agents in women requires further research.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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