

Impact of race and gender on antithrombotic therapy

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Summary

Large randomised trials support the use of a variety of antithrombotic drugs for treatment of atherothrombotic disease processes leading to cardiovascular disease. The heterogeneous case-mix of patients enrolled in these trials, however, hamper the attempt to generalise their findings to subgroups which are not sufficiently represented in the study population, such as women and ethnic minorities. Sex- and race-specific disparities in the clinical presentation, management, and outcomes of coronary artery disease may relate to underlying differences

in thrombotic profiles and response to antithrombotic therapies. The present manuscript provides an overview of the currently available data on the epidemiology of coronary artery disease based on gender and race as well as the biological considerations for their differences in thrombosis and haemostasis and effects of antithrombotic therapy.

Keywords

Antithrombin, platelet pharmacology, antiplatelet agents

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Introduction

Atherothrombosis is the most important underlying mechanism of coronary artery disease (CAD), which is in turn the leading cause of morbidity and mortality worldwide (1). Based on evidence deriving from large randomised studies, a variety of anti-thrombotic drugs are currently used for treatment of cardiovascular disease (2). The heterogeneous case-mix of patients enrolled in these studies, however, is a potential limitation when trying to generalise their findings to subgroups which are not sufficiently represented in the study population. In addition, persistent inequalities have been outlined in cardiovascular health care and outcomes across different patient populations, with women and racial minorities experiencing disproportionately higher mortality and morbidity rates (3, 4).

Sex- and race-specific disparities in the presentation, management, and outcome of CAD may relate to underlying differences in platelet function and response to antithrombotic regimens, which in turn translate into different clinical presentations and survival free from adverse events. Understanding specific differences between genders and races with regard to antithrombotic strategies could lead to the development of gender- and race-optimised therapy for prevention and treatment of ischaemic coronary events. The present manuscript provides an overview of the current available evidence on the use of antithrombotic therapy based on gender and race.

Epidemiology of CAD based on gender and race/ethnic considerations

It is a common misconception that CAD affects mainly men. Men are more affected than women until the age of 39 (15.9% vs 7.8%, respectively), whereas an almost equal prevalence is observed between men and women in the range 40–59 years (37.9% and 38.5%) and in the range 60–79 years (73.3% and 72.6%) (5). Conversely, more women than men have CAD by the age of 80 and more (5). Currently, while during the course of the last decade the advances in the diagnosis and treatment of acute coronary syndromes (ACS) have resulted in a decrease of CAD mortality among men, the mortality rate among women has increased and higher rates of recurrent myocardial infarction (MI) and cardiovascular death are observed annually among women than men (6, 7). Part of this higher risk has been attributed to baseline differences. In particular, given that the onset of clinical manifestations of CAD occurs about 10 years later in women versus men, female subjects are often older and more likely to present with cardiovascular risk factors at the time of presentation (8). Notably, the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative has documented that, despite their higher risk profile compared with men, women with ACS less often receive guideline-recommended antithrombotic therapies (8) (► Fig. 1).

Racial classifications are socially constructed and arbitrary. The United States government requires federal statistical agencies to re-

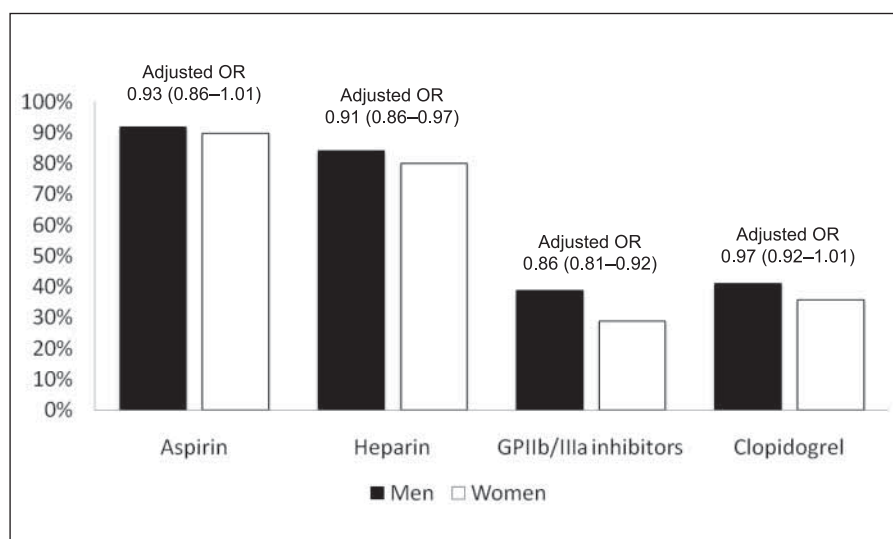


Figure 1: Use of medical treatment by gender with odds ratios for use in women relative to men in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative (8).

cognise four racial/ethnic groups in their reports (White, Hispanic or Latino, African American, Asian). According to the US Census Bureau, the United States total population in 2000 was 281.4 million, of which 75.1% were White, 12.5% were Hispanic, 12.3% were African American, 3.6% were Asian and 2.4% were mixed (9). Several factors, including different combination of cardiac risk factors, lifestyle factors, access to health care and type of medical management may account for differences in the epidemiology of CAD among racial and ethnic groups (10, 11). The mortality from cardiovascular disease in 2003 was 150.5×10^{-5} in the overall US population, with lower rates observed in Hispanics (130.0×10^{-5}) and Asians (92.8×10^{-5}) (5). Conversely, the death rate was higher among African American (men 222.2×10^{-5} , women 148.6×10^{-5}) versus White subjects (men 194.4×10^{-5} , women 115.4×10^{-5}) (12). Importantly, several studies have documented lower compliance with guideline-recommended drug pharmacologic treatments, especially those newer or more expensive, among African Americans (13, 14). This may be the result of lower prescription rate, economic disparities and lack of physician attentiveness for racial and ethnic differences in cardiovascular outcome. Similarly, Hispanics seem to be treated less aggressively during hospitalisation when they present with ACS, although these differences do not seem to be associated with worse clinical outcomes (15).

Thrombosis and haemostasis: Biological considerations and pharmacological issues

There is a large gap in the literature investigating race-specific alterations of haemostasis and differences in platelet function profiles. It is well established that African Americans have increased levels of interleukin-6, fibrinogen, and C-reactive protein which in turn have been associated with a higher likelihood towards the development of atherosclerotic processes and, therefore, may partly account for more clinical events in these patients (16–24). A large

cross-sectional study recently reported that, compared to Whites, Blacks have higher levels of marker of platelet activation assessed by flow cytometry (25). In a study of thromboelastograph parameters, including measures of platelet-fibrin clot properties, African-American race was associated with higher maximum platelet-fibrin clot strength, a shorter time to platelet-fibrin clot formation and higher rates of ischaemic events following percutaneous coronary intervention (PCI) (26). The reasons for these racial/ethnic differences are unknown, but a race-based genetic contribution to platelet receptor density or other cellular markers as well as plas-matic parameters such as coagulation factors cannot be excluded. In the absence of certain data, whether ethnic differences exist with regard to platelet function and antiplatelet responsiveness remains speculative.

On the one hand, it is well established that the propensity to thrombosis may vary between men and women according to biological factors. On the other hand, given what we know about mechanisms of action, there is limited biological plausibility for gender-related differences in the pharmacokinetics/pharmacodynamics of antiplatelet drugs. Studies conducted in animal models and humans have revealed disparities between men and women regarding number of platelets, magnitude of platelet adherence to the vessel wall, platelet activation and platelet aggregation (27, 28). Gender-related differences in platelet aggregation, including higher platelet reactivity in response to aggregation stimuli in male rats and guinea pigs, have been described since 1975 (29). These observations have been somewhat challenged by following reports supporting higher platelet reactivity among women, as showed by stronger spontaneous and adenosine diphosphate- or collagen-induced aggregation (30–31). Importantly, the nature of the agonist used to induce aggregation in the experimental setting and the assay used to detect the effect on platelet may be important on sex differences of platelet function (34–36). Adding to the inconsistencies among studies, which are mostly attributable to different methodologies, mechanisms involved in gender-specific platelet reactivity profiles have not been completely elucidated. Differences

in baseline platelet aggregability among sexes seem independent of platelet count, platelet size and surface expression of $\alpha_{IIb}\beta_2$ and glycoprotein Ib-IX-V (37, 38). Although the number of glycoprotein IIb/IIIa receptors is the same between healthy young men and premenopausal women, these receptors are more prone to be activated following a variety of stimuli in female subjects compared to age-matched men (33). Conversely, different patterns of platelet-subendothelium interactions with enhanced effects in male subjects have been described (39).

A key reason for the observed gender difference in platelet reactivity might be due to sex hormones. A putative protective role of estrogen has been postulated based on the observation that the risk for cardiovascular events in female subjects increase rapidly after menopause and in case of premature cessation of ovarian function (40, 41). Oestradiol has been shown to stimulate the production of prostacyclin, thereby shifting the haemostatic balance toward inhibition of platelet aggregation (42). At physiologic concentrations, oestrogen but not testosterone increases nitric oxide synthesis and release from vascular endothelium, resulting in potent antiplatelet effects (43–45). On the other hand, platelets from men are more responsive to and tend to generate more thromboxane A_2 (TXA₂) than platelets from women, with a mechanism possibly mediated by testosterone (46–48). Overall, the balance of these data suggests that platelets from premenopausal women are less prothrombotic than platelets from men of similar age, possibly as a result of a hormone-regulated greater production of nitric oxide in women and a greater production of prothrombotic TXA₂ and TXA₂ receptors in men. Despite these considerations, it is of note that postmenopausal hormone replacement therapy does not seem to exert a cardioprotective effect (49–51). In addition, the use of oral contraceptives has been clearly associated with an increased risk of thrombotic events, especially in women who smoke (52, 53).

Other factors involved in coagulation and fibrinolysis appear to be influenced by sex hormones. Oestrogen has been associated with decreased levels of fibrinogen, antithrombin III, protein S and plasminogen activator inhibitor 1 (PAI-1) (54). There is a positive correlation between testosterone and coagulation factor VII, α_2 -antiplasmin and plasminogen levels (55, 56), whereas a negative correlation has been advocated with fibrinogen and PAI-1 levels (56–58). These findings appear to suggest that testosterone has profibrinolytic effects. However, due to the complexity of the mechanisms involved in thrombus formation and degradation, a sex difference in one or more components may not lead to an apparent difference in haemostasis. As a matter of fact, investigations focused on the overall functional measures of haemostasis do not support the idea of reduced coagulation or greater fibrinolysis in men compared with women (59, 60). Conversely, women have longer *in vivo* bleeding times than men and the haemostatic activity in male subjects has been found to be enhanced compared with females, as previously discussed (39, 59, 60).

Pharmacokinetic, pharmacodynamics and physiology partly vary among sexes but their contribution to explain differences in haemostasis and coagulation seems minor. In women, aspirin is adsorbed more quickly, distributed in a larger apparent volume and hydrolysed more rapidly (61). While in female subjects a

greater bioavailability may result in diminished clearance (62), this difference disappears in those assuming oral contraception (63).

Sex, race and bleeding complications

Major bleeding are a reason of concern in patients with ACS treated with antithrombotic drugs, as they have shown to be associated with a five-fold increased risk of death at 30 days and a 1.5-fold increased risk of death between 30 days and six months (64–66). Vitamin K antagonists (VKA) are frequently prescribed for different indications including atrial fibrillation, stroke, prosthetic heart valve replacement, MI and venous thrombosis. The determinants which mainly impact the risk of bleeding in patients treated with VKA are patient characteristics, intensity of the anticoagulant effects, length of therapy and interaction with drugs which interfere with haemostasis (67, 68). Among patient characteristics, gender has not been associated with major bleeding, but female sex seems to be an independent risk factor for minor bleeding in patients on oral anticoagulant therapy (69, 70). Conversely, the association of sex and heparin-induced bleeding has not been consistently reported (71).

Important racial/ethnic differences are also deemed to affect the incidence of life-threatening major bleeding. It has been reported that non-Whites with atrial fibrillation on treatment with warfarin are at greater risk for warfarin-related intracranial haemorrhages (72). In White patients, these events account for 15–30% of all strokes, whereas the percentage is approximately two- to four-fold higher among Blacks, Hispanics and Asians (73–76). Death from haemorrhagic stroke is also more frequent among minorities (77). The use of abciximab in Japanese patients with ACS undergoing PCI resulted in no efficacy in reducing major coronary events and a significant increase in the rate of bleeding (78). Due to this reason, GP IIb/IIIa inhibitors are currently not approved by the Ministry of Health, Labour and Welfare for use in Japan.

Pharmacogenetic factors may partially explain race-related differences in the risk of bleeding in patients receiving antithrombotic therapy (79, 80). Variants in the gene for vitamin K epoxide reductase complex 1, the target enzyme which usually catalyses the regeneration of vitamin K from vitamin K epoxide, may account for different response to VKA (81, 82). It has been reported that the frequency of the haplotypes predictive of overdosing is significantly higher among Asian Americans (89%) and lower among African Americans (10–14%) than in the European-American population (37–42%) (83–85). This may also help to explain why, to achieve the same International Normalised Ratio (INR) range, Asians require lower warfarin doses, Caucasians require intermediate doses, and Africans require higher doses (86, 87).

The pharmacological effect of VKA largely depends on hepatic metabolism by the cytochrome P450 (CYP) 2C9 enzyme (88), whose polymorphisms may also contribute to inter-individual variability in VKA response. Thirty CYP2C9 alleles have been described so far in a variety of ethnic populations (79). Bleeding risk appears to be related to overdosing in patients who are slow meta-

Designation	Prevalence in Asians (%)	Prevalence in Whites (%)	Prevalence in Blacks (%)	Effect on warfarin dose
CYP2C9*1	98.2	80.8	94.2	Referent
CYP2C9*2	0	12.7	3.4	-14% to -20%
CYP2C9*3	1.8	7.0	1.5	-21% to -49%

Table 1: Cytochrome P450 2C9 single nucleotide polymorphisms that are known to affect warfarin metabolism (modified from Gage BF et al. *J Thromb Thrombolysis* 2008; 25: 45–51).

bolisers of warfarin or acenocumarol with variants other than the reference sequence and wild-type allele CYP2C9*1 (► Table 1). The CYP2C9*2 and CYP2C9*3 variants are present at allele frequencies of 12.7% and 7% in Caucasians, 0% and 1.8% in Asians and 3.4% and 1.5% in Africans (89–91). Patients with one or two of these alleles have reduced warfarin requirements due to a decreased clearance of VKA which has also been associated with a worse clinical outcome (92). Other less common polymorphisms have been identified in Japanese (CYP2C9*4) and African Americans (CYP2C9*5) (79).

Clopidogrel is a prodrug, and its pharmacologic effect depends on the efficiency of the hepatic CYP system in converting it into the active metabolite. Numerous CYP isoforms are involved in the double oxidation step that is required to generate the active metabolite (80). Importantly, there are considerable racial disparities among the genetic polymorphisms that regulate the functional activity of CYP isoforms (80). The CYP2C19 isoform is involved in both hepatic metabolic oxidation steps of clopidogrel's conversion into its active metabolite. This may explain why pharmacogenetic studies have consistently shown that carriers of the loss-of-function variant allele on the CYP2C19 enzyme are affected by altered pharmacokinetic (reduced generation of clopidogrel's active metabolite) and pharmacodynamic (reduced clopidogrel-induced platelet inhibitory effects) responses (93–96) and are associated with an increased risk of ischaemic events (97–102). Polymorphisms of the CYP2C19 enzyme have been reported in almost 30% of Whites, 40% of Blacks, and more than 55% of Asians (98). The greater prevalence of the CYP2C19*2 among Asians is consistent with the observation that Japanese patients are more prone to sub-optimal response to clopidogrel than Caucasians (103). A recently reported genomic substudy of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial outlined that, among patients treated with clopidogrel, carriers of the homozygotic CYP2C19*2 genotype experience a lower risk of GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) bleeding events than those presenting with the wild type (presented at TCT meeting 2009, San Francisco, CA, USA). This finding outlines that a particularly efficient hepatic biotransformation of clopidogrel may expose to a higher risk of bleeding complications. Similar implications may be drawn by another study assessing the impact of the CYP2C19*17 variant on platelet aggregation and bleeding risk in 1,524 clopidogrel-treated patients undergoing coronary stenting (104). The increased transcriptional activity of the CYP2C19 enzyme deriving from the presence of this genetic variant results in enhanced response to clopidogrel treatment (105). Of note, lower ADP-induced aggrega-

tion compared to wild-type homozygous carriers is observed for both heterozygote and homozygote *17 carriers in a gene-dose fashion, and carriage of the *17 allele is associated with an increased risk of TIMI bleeding (104).

Antithrombotic therapy across sexes and races: General considerations

Women are often less represented in cardiovascular clinical trials, as a result of underestimation of cardiac risk and misconception of symptoms of CAD, which result in less referral for cardiac testing, appropriate treatment and coronary catheterisation during ACS (8, 106, 107). In addition, women present with CAD later than men, and elderly are more likely to be excluded from randomised studies (108, 109). In 1993, the National Institutes of Health (NIH) Revitalization Act established guidelines to reinforce the existing policies for inclusion of women and minorities in clinical research (110). Differently from federally-funded clinical trials, the majority of drug trials are sponsored by pharmaceutical companies and do not have a federal mandate for inclusion of women and minorities. As a result, these trials are frequently found to have an inadequate prevalence of women, which reflects fears related to drug administration in women of childbearing potential. Even when women are included, sex specific analyses were rarely performed in the pivotal safety trials of antithrombotic drugs. More recent regulations put emphasis on protocol design and, because of large single-sex studies such as the Women's Health Study (111) and the Women's Health Initiative (112), more women than men were enrolled in NIH-sponsored phase 3 trials since the NIH Revitalization Act. This important result, however, did not change the general trend towards a substantial under-representation of women in gender-mixed clinical trials. Despite a growing literature slowly accumulating which examines gender-based differences in the presentation, treatment and clinical outcomes of CAD, translation of research evidence into clinical practice is puzzled by several unsolved issues.

Similar considerations may be drawn for racial groups, as previously described. Data on ethnic minorities are even sparser, as subgroup analyses of large trials rarely disclose outcome stratified by race. It has been suggested that racial and ethnic minorities are less willing than non-minority individuals to participate in health research, but data on this matter are not in agreement (113–115). Efforts to address the under-representation of minority groups in health research should focus on ensuring equal access to health research, more than changing attitudes.

Although better than lack of information, subgroup analyses are far from representing the optimal level of ideal evidence to support changes in guidelines. In the absence of large-scale assessment of gender and race disparity at the time of their writing, recommendations of clinical guidelines are typically “gender and race-neutral”.

Antithrombotic therapy

The following section provides an overview on the current knowledge on the impact of race and gender on antithrombotic pharmacology. In particular, antiplatelet, anticoagulant, and fibrinolytic agents will be discussed.

Antiplatelet therapy

Aspirin

Aspirin use has been shown to reduce the risk of thrombotic events across the entire spectrum of CAD (116–118). The antiplatelet effects of aspirin are mainly related to the ability of selectively and irreversibly acetylating cyclooxygenase-1 (COX-1), thereby blocking the formation of TXA₂ synthesis in platelets (116). The magnitude of this effect is similar in both sexes when COX-1 direct pathways are considered, but pathways that are indirectly related to COX-1, such as those stimulated by collagen, ADP and epinephrine, are less inhibited in female subjects (119). These differences persist after adjustment for several potential confounders, including race, and results in higher platelet reactivity in aspirin-treated women with CAD, as demonstrated by several *ex vivo* assays (120–122). Female gender has shown to be a determinant of 11-dehydro thromboxane B2 concentration, a marker of aspirin resistance and thereby of subsequent higher risk of cardiovascular events, in a substudy of the CHARISMA and in the HOPE (Heart Outcomes Prevention Evaluation) trial, reflecting the enhanced *in vivo* platelet activation observed among women (123, 124).

A meta-analysis of six randomised trials enrolling a total of 95,456 patients (51,342 women) demonstrated that primary prevention with aspirin therapy is associated with a significant reduction in the risk of cardiovascular events independently from sex (125). In particular, aspirin therapy was associated with statistically significant 12% and 14% reductions in the odds of cardiovascular events in women and men, respectively. However, the specific type of benefit varied among sexes and was primarily driven by a reduction of MI in men (odds ratio [OR] 0.68, 95% confidence interval [CI] 0.54–0.86, $p = 0.001$) and ischaemic stroke in women (OR 0.76, 95% CI 1.35–2.20, $p < 0.001$). Importantly, aspirin significantly increased the risk of bleeding in both sexes to a similar degree (125). The same six randomised trials were object of a second meta-analysis which had access to individual participant data, thus enabling to more accurately estimate the magnitude of several risk factors, including gender, in affecting selected out-

comes. In addition, the authors reported aggregate data from 16 randomised trials of aspirin use in the secondary prevention setting, with stratification by sex (126). The study results showed that gender does not significantly affect the proportional reduction in serious vascular events either in the primary and secondary prevention trials, suggesting that if the relative risk reduction among men and women is similar, then the absolute risk reduction mainly depends on the individual's absolute risk without treatment. It has been suggested that gender mix can account for ~25% of the variation in the reported efficacy of aspirin in reducing the rates of cardiovascular events across placebo-controlled trials (127). For example, trials that primarily contained male subjects demonstrated larger benefits of aspirin in reducing non-fatal MI rates than those containing mostly female subjects (127).

In a study of 325 aspirin-treated patients with CAD, there were no differences in aspirin sensitivity by race (128). These results are consistent with those observed within a small cohort of patients with diabetes mellitus (129). On the other hand, differential aspirin use may contribute to geographic disparities in cardiovascular outcomes of aspirin-treated patients. In fact, important racial differences still exist in the use of aspirin, with African Americans and Hispanics less likely to take aspirin than Whites (130, 131).

Adenosine diphosphate P2Y₁₂ receptor antagonists

Thienopyridines are irreversible inhibitors of the platelet adenosine diphosphate (ADP) P2Y₁₂ receptor, thereby blocking a key signaling pathway of platelet activation. Due to its more favorable safety profile, clopidogrel, a second generation thienopyridine, has largely replaced the first generation thienopyridine ticlopidine in clinical practice (132).

The plasmatic levels of clopidogrel's active metabolite do not differ in men and women (133). However, some variability has been described in terms of clopidogrel-induced inhibition of platelet aggregation (134–136). Few studies have specifically focused responses of men and women to clopidogrel, but the available evidence support the concept that clopidogrel is similarly beneficial, although the magnitude of the benefit may vary. In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial, which included patients presenting with non-ST elevation myocardial infarction (NSTEMI), a smaller absolute (1.2% vs. 2.8%) and relative (12% vs. 25%) risk reduction in the composite end point of cardiovascular death, non-fatal MI or stroke at one year was seen in women than men with clopidogrel plus aspirin compared to aspirin alone at one year (137). Similar findings were observed in the subgroup of patients undergoing PCI (138). The CREDO (Clopidogrel for the Reduction of Events During Observation) trial enrolled patients undergoing elective PCI, showing a 26.9% relative risk reduction in favour of clopidogrel for the composite of death, MI and stroke at one year in the overall population. Differently from the CURE trial, in the CREDO trial a greater risk reduction was seen among women for the combined risk of death, MI or stroke at one year (32% vs. 25%) (139). In the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Rep-

erfusion Therapy – Thrombolysis in Myocardial Infarction 28), patients undergoing fibrinolytic therapy within 12 hours after the onset of STEMI symptoms were randomised to dual antiplatelet therapy with aspirin plus clopidogrel versus clopidogrel alone. A 36% reduction in the risk of the composite ischaemic endpoint was observed with clopidogrel in the overall population, with similar reduction for men and women (35% vs. 38%, respectively), despite a higher event rate in women in both treatment arms (140). The odds of the composite end point of cardiovascular death, recurrent MI or stroke at 30 days in the subgroup of patients undergoing PCI three days after starting the assigned study medication was 59% in women and 41% in men. Similar reductions in the primary ischaemic endpoint at 28 days with no heterogeneity in effect related to sex, despite higher event rate observed in women, were also observed in the COMMIT (ClopIdogrel and Metoprolol in Myocardial Infarction Trial) trial, which compared the effect of clopidogrel plus aspirin versus aspirin alone in Chinese patients with suspected MI (141). The previously mentioned CHARISMA trial failed to demonstrate any clinical benefit associated to the combination of a low-dose aspirin and clopidogrel in asymptomatic patients with at least three atherothrombotic risk factors and, once again, no statistically significant differences between men and women were reported (142).

A meta-analysis of the above five mentioned randomised trials (CURE, CREDO, CLARITY-TIMI 28, COMMIT, CHARISMA) recently focused on sex-related differences between men and women on dual antiplatelet therapy with aspirin versus clopidogrel versus aspirin alone (143). The study showed that while in men there was a significant 16% relative reduction in the odds of any major cardiovascular events with clopidogrel versus placebo (7.8% vs. 9.0%, OR 0.84; 95% CI 0.78–0.91), the relative reduction among women was 7% but non-significant (11.0% vs. 11.8% OR 0.93; 95% CI 0.86–1.01). However, there was only a trend towards statistical heterogeneity based on gender ($p = 0.092$) and the authors observed that much of the difference between men and women could be explained by chance. In addition, no evidence of statistical heterogeneity between women and men was observed with regards to mortality, MI, stroke and major bleeding. While among men the benefit of clopidogrel were separately significant on MI, stroke and all-cause mortality, the main driver of clinical benefit among women was a reduction in the event rate of MI.

Differently from the other trials on clopidogrel, the CHARISMA study disclosed data on ethnic-specific differences on cardiovascular outcomes (144). Ethnicity was not shown to be an independent predictor of the primary composite endpoint of cardiovascular death, MI, or stroke. However, ethnicity was a significant predictor of cardiovascular and all-cause mortality (African American and Hispanics), and moderate bleeding complications (African American and Asians) (144). It has been demonstrated that the effectiveness of clopidogrel in Asians may not be as strong as for White individuals at the same dose (103, 144, 145). As mentioned above, inter-ethnic variability in the rate of single nucleotide polymorphisms that diminish the activity of CYP2C19, the hepatic enzyme mainly involved in the conversion of clopidogrel to its active metabolite, may contribute to explain these differences

(93, 94, 96, 146). A different prevalence of the loss-of-function variant allele on the CYP2C19 enzyme across races may contribute to explain the increased risk of ischaemic events observed in selected populations (98–103).

Prasugrel is a third generation oral thienopyridine which, due to a more favourable metabolic conversion, produces higher concentrations of its active metabolite compared to clopidogrel and therefore more potent platelet P2Y₁₂ inhibitory effects (147). In the TRITON-TIMI 38 (Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel–Thrombolysis In Myocardial Infarction 38), prasugrel was associated with a significant 19% reduction in ischaemic events compared to clopidogrel in moderate to high-risk ACS patients undergoing PCI (148). The net clinical benefit (defined as death from any cause, non-fatal MI, non-fatal stroke, and TIMI major haemorrhages) was in favour of prasugrel in the overall population, despite an increased risk of bleeding compared with clopidogrel. There were no significant interactions between treatment and sex, despite higher absolute (2.4% vs. 1.6%) and relative (21% vs. 12%) reduction of the primary ischaemic endpoint with prasugrel among men compared to women. With regards to race/ethnic differences in the antiplatelet response to prasugrel, data are limited on pharmacodynamics and support that prasugrel's mean active metabolite exposure following a 60 mg loading dose or during daily 10 mg or 5 mg maintenance dose is higher among Asians than in Caucasians (149). On the other hand, a genetic subanalysis of the TRITON-TIMI 38 showed that functional CYP genetic variants did not affect active metabolite levels, platelet inhibition and cardiovascular outcomes of 1,466 patients allocated to treatment with prasugrel, supporting the knowledge of less pharmacological variability compared with clopidogrel (150).

The phase III results of the PLATO (Platelet Inhibition and Patient Outcomes) trial recently showed that ticagrelor, the first member of a new class of reversible P2Y₁₂ receptor antagonists called CPTP (CycloPentylTriazolopyrimidine) is associated with a 16% reduction in the composite ischaemic endpoint compared to clopidogrel in patients with ST-elevation ACS intended for primary PCI or with non-ST-elevation ACS intended for an invasive or medical approach (151). In the overall population, no differences were noted in terms of bleedings according to different definitions among ticagrelor and clopidogrel groups. However, ticagrelor was associated with higher rates of major bleeding not related to coronary-artery bypass grafting, including more cases of fatal intracranial bleeding. Compared with men, women showed similar absolute (2.0% vs. 1.9%) and relative reduction (17.0 vs. 15.0%) of the primary endpoint with the use of ticagrelor compared to clopidogrel. Similar effects were also seen in term of major bleeding among different sexes. A predefined subgroup analysis of patients enrolled in the PLATO trial outlined a borderline significant interaction with enrolment geographic area ($p = 0.05$), driven by a trend toward more efficacy of clopidogrel rather than ticagrelor among patients recruited in North America. However, it is unlikely that race had an impact on this outcome. Conversely, ticagrelor was almost equally more effective than clopidogrel among patients recruited in Asia/Australia, Central/South America and Eu-

rope/Middle East/Africa. No differences were observed in terms of major bleeding across geographical areas of recruitment.

Intravenous glycoprotein IIb/IIIa inhibitors

Glycoprotein (GP) IIb/IIIa receptor antagonists (abciximab, tirofiban and eptifibatide) block the final common pathway leading to platelet aggregation by inhibiting the binding of fibrinogen to the GP IIb/IIIa receptor on the surface of activated platelets.

Sex differences in platelet response to GP IIb/IIIa antagonists have not been observed *in vitro* (152, 153). A pooled analysis of data from the three large randomised trials of patients undergoing PCI with adjunctive use of abciximab, demonstrated no gender difference in terms of major adverse outcomes between women and men at 30 days, six months and one year (154). However, women had a higher rate of major and minor bleeding. Similar observations were made with eptifibatide in the ESPRIT (Enhanced suppression of the platelet GP IIb/IIIa receptor with Integrilin therapy) trial, which showed no statistical interaction between sex and treatment in terms of death, MI or urgent target vessel revascularisation either at 48 hours or one year (155). In a meta-analysis of six randomised trials investigating the efficacy and safety of GP IIb/IIIa inhibitors in patients with ACS not routinely scheduled for early coronary revascularisation, GP IIb/IIIa inhibitors were found to reduce the occurrence of death or MI, especially in patients at high risk of thrombotic complications (156). In this study, however, there was a highly significant interaction with respect to cardiac events between sex and the use of GP IIb/IIIa inhibitors. While men showed a 19% reduction in the odds of 30-day death or MI compared with placebo or control, women showed a significant 15% increased risk. Importantly, this interaction remained significant after adjustment for baseline clinical characteristics, including age and co-morbidities. A potential explanation, however, was represented by the higher percentage of men with positive baseline troponins than women (49% vs. 37%). In fact, while a reduction in the 30-day rate of death or MI by GP IIb/IIIa inhibitors was observed in men and women with positive baseline troponins, this effect was not beneficial in both sexes in patients with negative troponins. In this study, no interactions were observed in terms of race. Overall, data on race specific differences with GP IIb/IIIa inhibitors are limited. The contribution of genetic factors specifically affecting the target of GP IIb/IIIa inhibitors has been extensively investigated, but results are controversial (80). Race-related variability in GP IIb/IIIa receptor density or function, as mentioned earlier, have been suggested to justify the enhanced or diminished response to GP IIb/IIIa inhibitors observed among different populations. This may explain the higher rates of bleeding complications associated with the use of GP IIb/IIIa inhibitors in Japanese (78), although this remains to be demonstrated.

Anticoagulant therapy

Indirect thrombin inhibitors

Unfractionated (UFH) and low-molecular-weight (LMWH) heparins bind to antithrombin III and enhance inactivation of factor Xa and, to a less extent, thrombin. LMWH do not usually require laboratory monitoring of activity and have the advantage of a more predictable dose-response. Due to a higher anti-factor Xa:IIa ratio and prolonged duration of anti-factor Xa activity, LMWH also show a kinetic advantage over UFH, as they inhibit the early steps of coagulation cascade and thrombin generation.

In addition to body weight, age, smoking history and diabetes mellitus, sex is considered one of the clinical factors that affect the response to UFH (157, 158). In particular, women are more likely to achieve higher activated partial thromboplastin time (aPTT) in response to the anticoagulant effect of heparin (159). Conversely, a post-hoc analysis of the TIMI 11A (Thrombolysis in Myocardial Infarction 11A) study, a multicenter dose-ranging trial to evaluate the safety of enoxaparin in patients with ACS, showed that the pharmacokinetic and pharmacodynamic profiles after enoxaparin administration are consistent between sexes (160, 161). The only placebo controlled trial of LMWH use reporting data stratified by sex was the FRISC (Fragmin and Fast Revascularization during In-Stability in Coronary artery disease) (162). In this study, dalteparin was associated with a 63% risk reduction in the composite of death and MI during the first six days compared to placebo in patients with ACS. Compared with men, women showed larger absolute (4.5% vs. 2.2%) and relative reduction (13.1% vs. 28.9%) of the primary endpoint. However, minor bleedings associated with the use of dalteparin were more frequent in women compared with men either with the weight adjusted and the fixed dose treatment, and multiple regression analysis confirmed a significant interaction between sex and the anti-Xa activity determined in samples obtained during the acute and the standard dosing phase of treatment (163).

Few trials which directly compared LMWH with UFH disclosed data based on sex. A pooled data meta-analysis of two large trials showing that enoxaparin is more effective than UFH in reducing the risk of death and severe cardiac events in patients with ACS showed that these results are applicable to a vast array of subgroups (164). However, while a significant relative risk reduction was seen independently from sex with regards to the composite triple endpoint of death, MI or recurrent angina prompting urgent revascularisation, a significant benefit of enoxaparin over UFH with regards to the double composite endpoint of death or MI was significantly observed in women, but not in man (164). In the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) study, enoxaparin was not superior but also non-inferior to UFH with a modest increase in the risk of major bleeding (165). This lack of differences was observed across multiple subgroups, including those stratified by sex and study site (165). The ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction) study randomised

STEMI patients with planned fibrinolysis to a regimen of enoxaparin or UFH as adjunctive antithrombin therapy. Women, who were older and more likely to have hypertension and diabetes compared to men, derived a similar relative benefit (16% vs. 19%) and a greater absolute benefit (2.9% vs. 1.9%) than men when treated with enoxaparin, despite increased rates of short term mortality (166).

There is a paucity of data on heparin use based on ethnicity. In a study of 1,287 patients undergoing PCI, the recommended weight-adjusted heparin-dosing regimen derived from the Western population seemed equally applicable to the Asian patients (167).

Direct thrombin inhibitors

Direct thrombin inhibitors (hirudin, bivalirudin, melagatran, argatroban, dabigatran, lepirudin and desirudin) block directly the interaction of thrombin with its substrates. Features of this class of antithrombotic drugs include their ability to reduce the thrombin-mediated activation of platelets, thus exerting some degree of antiplatelet effects. Bivalirudin is currently recommended in class Ib in the guidelines for the management of non ST elevation ACS and for primary PCI in patients with STEMI, whether or not the patient received pretreatment with heparin (168, 169). These recommendations are based on data from randomised trials and registries, which emphasise the safety and efficacy of bivalirudin across the broad spectrum of CAD.

The use of bivalirudin seems to provide similar benefits independently from sex, while the higher risk of bleeding observed among women may partly reflect the impact of their worse baseline co-morbidities. In the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events-2) trial, treatment with bivalirudin plus provisional GP IIb/IIIa inhibitors resulted in similar ischaemic outcomes at 30 days, similar mortality at one year, and a significant decrease of bleeding complications compared with heparin plus GP IIb/IIIa inhibitors in patients with stable or unstable angina undergoing PCI, with no differences based on sex (170, 171). In a post-hoc multivariate analysis, female gender was shown to be significantly associated with a 1.5-fold increased risk of major bleeding (172). In the ACUTY (Acute Catheterization and Urgent Intervention Triage strategY) trial, bivalirudin plus provisional GP IIb/IIIa inhibitors resulted in similar ischaemic event rates at 30 days, less bleedings, and superior net clinical outcomes compared with heparin plus GP IIb/IIIa inhibitors in patients with ACS undergoing an early invasive strategy. Subgroup analysis revealed no significant interactions in terms of net clinical outcomes, composite ischaemia and major bleeding between the use of bivalirudin and numerous variables, including gender (173, 174). On the other hand, female gender was found to be independently associated with an almost two-fold increased risk of major bleeding (175). These observations were further corroborated by a study specifically focused on sex-related difference among patients enrolled in the ACUTY trial (176). This study showed that, despite differences in risk factors, women with ACS do not experience an increased risk of one- and 12-month is-

chaemic complications or mortality compared with men but, due to a higher risk of bleeding, they have higher rates of net clinical adverse events. However, in women with ACS, treatment with bivalirudin monotherapy is associated with similar short- and long-term protection from ischaemic events and significantly less bleeding compared with a regimen of UFH plus GP IIb/IIIa inhibitors, irrespective of the treatment strategy selected. In the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, bivalirudin monotherapy significantly reduced net adverse cardiac events, cardiac death and major bleedings at 30 days and one year compared with heparin plus a GP IIb/IIIa inhibitor in patients with acute MI (177, 178). The early efficacy of bivalirudin in reducing net adverse cardiac events and major bleeding was observed independently from gender (179).

In a large European registry of 3,799 patients undergoing PCI, in-hospital bleeding with the use of bivalirudin occurred in 1.7% of patients and female gender was significantly associated with an increase in bleeding events (180). Similarly, women showed a trend towards higher risk of bleeding events at 30 days in the APPROVE (The Angiomax Peripheral Procedure Registry of Vascular Events Trial) Registry, a multi-center trial that assessed the feasibility of bivalirudin in renal, iliac and femoral interventions (181). A further small study on patients undergoing PCI found a significant univariate association between female gender and a composite of early ischaemic events and bleeding events with bivalirudin (182). However, the multivariate analysis failed to demonstrate a significant interaction between female sex and major bleeding.

The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) investigators reported the results of a randomised comparison between two fixed doses of dabigatran, an oral direct competitive thrombin inhibitor which is administered twice daily and does not require regular monitoring (183), versus warfarin in reducing the risk of stroke or systemic embolism in 18,113 patients with atrial fibrillation. Both dabigatran doses (110 mg twice daily and 150 mg twice daily) were not inferior to warfarin with respect to the primary endpoint and no interaction was observed with sex (184).

Argatroban has shown to significantly improve outcomes in patients with heparin-induced thrombocytopenia, an immune-mediated disease caused by heparin-platelet factor 4 antibodies (185, 186). Even if the clearance of argatroban is greater in women than men, there are no differences in the anticoagulant response depending on sex (187, 188). It has been reported that despite the use of argatroban anticoagulation, African Americans and Hispanics may have worse outcomes in case of heparin-induced thrombocytopenia (189). The reason for this difference is unknown.

Factor Xa inhibitors

Fondaparinux, a selective inhibitor of the coagulation factor Xa, binds antithrombin III leading to a conformational change which results in increased affinity for factor Xa and potentiates its natural inhibitory effect (190). Advantages of fondaparinux are represented by a long half-life and a predictable and sustained anti-

coagulation which requires only a single daily subcutaneous administration.

In the OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial, fondaparinux and enoxaparin showed similar efficacy in reducing the risk of ischaemic events at nine days in patients with ACS, but fondaparinux was associated with diminished rates of major bleeding and long-term mortality and morbidity (191). The reduction in the composite endpoint of death, MI, refractory ischaemia or major bleeding with fondaparinux as compared with enoxaparin was observed in both sexes. However, compared with men, women showed a higher absolute reduction of major bleeding (3.0% vs. 1.3%) with the use of fondaparinux, resulting in a trend for statistical interaction (p for interaction = 0.07) (191). In the OASIS-6 (Sixth Organization to Assess Strategies in Acute Ischemic Syndromes) trial, fondaparinux reduced the primary endpoint – a composite of death or reinfarction at 30 days – compared to usual care (placebo in those in whom UFH was not indicated or UFH for up to 48 hours followed by placebo for up to eight days) in patients with STEMI (192). Similar trends for a reduction by fondaparinux treatment in the primary endpoint were found in women and men in the overall population and in a pre-specified subgroup of patients not receiving reperfusion treatment (192, 193).

Vitamin K antagonists (VKA)

The oral anticoagulants are a class of drugs that antagonise the effects of vitamin K and therefore impair γ -carboxylation of the coagulation factors II, VII, IX, and X in the liver, resulting in reduced coagulant activity.

Warfarin is at least equally effective in reducing the risk of thromboembolism in both sexes, but some studies highlighted a potential higher benefit in women (194, 195). There is growing evidence that the major bleeding risk associated with warfarin use is similar between men and women (194, 196, 197). However, gender may influence the required dose to maintain a therapeutic INR (198). Sex and race-specific bleeding issues with the use of VKA have been previously discussed in this manuscript.

Fibrinolytic therapy

A review of the larger placebo-controlled trials of fibrinolytic therapy showed that the relative benefit of fibrinolytic treatment among patients presenting with ST elevation or bundle-branch block is irrespective of sex (199). It is well established that women enrolled in clinical trials of fibrinolytic therapy are generally older and more frequently have co-morbidities, conditions which may partly explain the observed higher rates of mortality compared to men (199–206). After adjustment for worse baseline characteristics, however, data are contradictory regarding the risk of morbidity and mortality compared to men in the setting of thrombolysis (207–210). In the International Tissue Plasminogen Activator/Streptokinase Mortality Study, women showed similar adjusted

risk of morbidity and mortality compared to men but suffered from a higher incidence of haemorrhagic stroke (207). Other studies reported that women who receive thrombolytic therapy for treatment of acute MI are at greater risk for both fatal and non-fatal complications than men (208, 209). Female gender has been independently associated with higher rates of bleeding complicating fibrinolysis for acute MI (211, 212). The GUSTO V trial enrolled a large contemporary cohort of women and men with STEMI undergoing fibrinolytic therapy (213). Patients were randomised to reteplase alone versus half-dose of reteplase plus abciximab. This second strategy resulted in a 0.3% absolute and 5% relative reduction in the rate of 30-day mortality, fulfilling the criteria for non-inferiority. A post-hoc analysis of the GUSTO V study corroborated the understanding that female sex is independently associated with death and bleeding complications among fibrinolysis-treated patients with MI (214).

Lower rates of thrombolysis have been reported in Black patients compared with White patients with acute MI (215–218). The reason for this disparity is unknown but has been associated with a longer delay to presentation and institution of thrombolysis (219). In the TIMI II trial, changes in haemostatic factors five hours after infusion of recombinant tissue plasminogen activator showed a significant decrease of fibrinogen levels in Black patients compared with those observed in Hispanic or White patients (220). These findings, however, did not translate into different infarct-related artery patency, haemorrhagic complications or mortality.

Conclusions

While mortality rates for CAD in men have decreased over the past two decades, clinical outcomes seem to improve more slowly among women and minorities. Understanding the reason for these differences with regard to platelet function profiles and response to antithrombotic medications could lead to the development of gender- and race-optimised therapy for prevention and treatment of ischaemic coronary events. However, although the literature focusing on disparities among sexes and races is slightly growing, data are still sparse and sometimes contradictory. There are evidences supporting a role of sex hormones in altering the haemostatic balance and platelet function, thereby translating into sex-specific differences in the likelihood of thrombosis and response to antiplatelet therapy. Part of these disparities is likely to reflect a different presentation of CAD between women and men. Numerous factors lead to the challenge of defining optimal antithrombotic drug regimens across different races. Adding to the substantial under-representation of minorities into clinical trials other issues, including lower prescription rate of antithrombotic medications due to economic disparities and lack of physician consideration for racial and ethnic differences in cardiovascular outcome, make data interpretation particularly troublesome. Given these assumptions, the absence of specific recommendations on the optimal antithrombotic treatment for women and minorities do not probably entirely reflect the complexity of the topic and data from large scale

clinical trials or even dedicated studies assessing the safety and efficacy of antithrombotic treatment strategies in specific populations are warranted.

Conflict of interest

Dominick J Angiolillo: a) *Honoraria/Lectures*: Bristol Myers Squibb; Sanofi-aventis; Eli Lilly and Company; Daiichi Sankyo, Inc. b) *Honoraria/Advisory board*: Bristol Myers Squibb; Sanofi-aventis; Eli Lilly and Company; Daiichi Sankyo, Inc.; Astra Zeneca; The Medicines Company; Portola Pharmaceuticals; Novartis; Arena Pharmaceuticals; Evolva Pharmaceuticals. c) *Research Grants*: GlaxoSmithKline; Otsuka; Accumetrics; Eli Lilly and Company; Daiichi Sankyo, Inc.; The Medicines Company; Astra-Zeneca; Eisai; Portola Pharmaceutical; Schering-Plough; Johnson and Johnson. Davide Capodanno: No conflict of interest to report.

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