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GENDER DIFFERENCES IN CARDIOVASCULAR PROPHYLAXIS: FOCUS ON ANTIPLATELET TREATMENT

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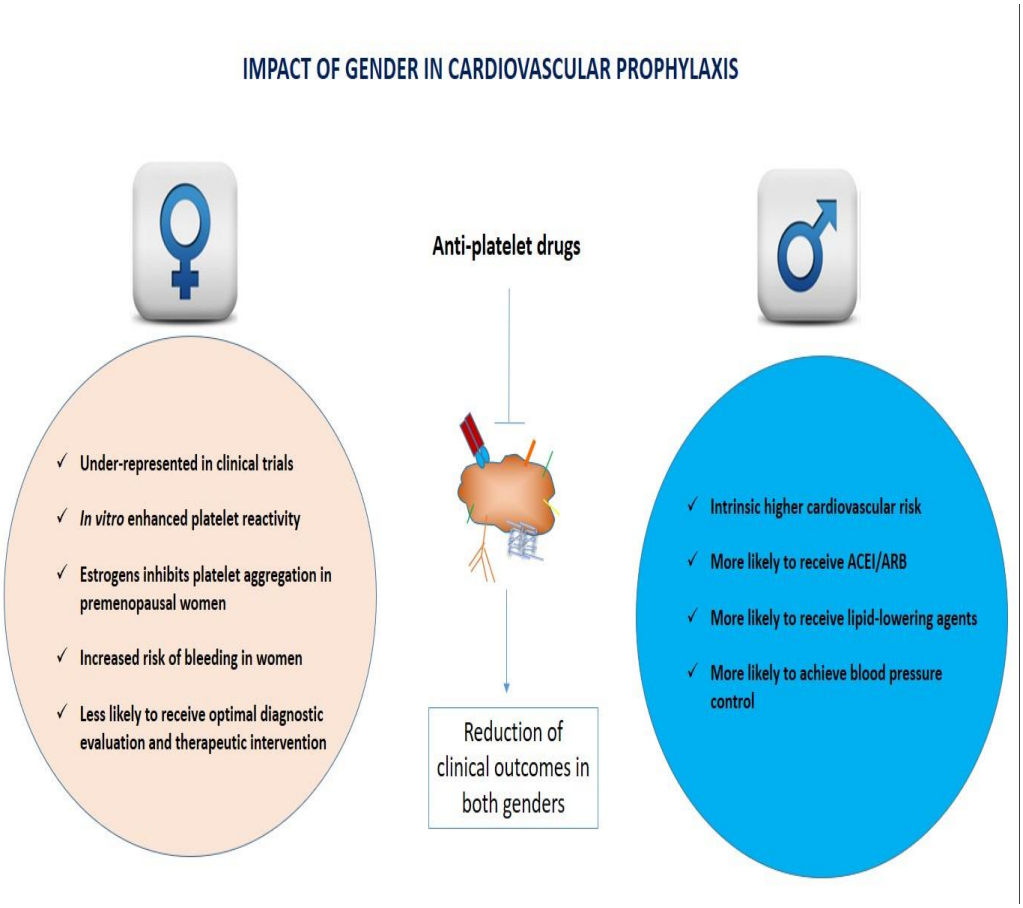
Graphical abstract



Abstract

Cardiovascular disease (CVD) represents the leading cause of death worldwide, and equally affects both sexes although women develop disease at an older age than men. A number of clinical evidence has identified the female sex as an independent factor for poor prognosis, with the rate of mortality and disability following an acute cardiovascular (CV) event being higher in women than men. It has been argued that the different level of platelet reactivity between sexes may account for a different responsiveness to anti-platelet therapy, with consequent important implications on clinical outcomes. However, conclusive evidence supporting the concept of a gender-dependent effectiveness of platelet inhibitors are lacking. On the contrary, sex-related dissimilarities have been evidenced in cardiovascular patients in terms of age of presentation, comorbidities such as obesity, diabetes and renal disease, and a different pharmacological approach to and effectiveness in controlling classical cardiovascular risk factors such as hypertension, glucose profile and lipid dysmetabolism. All these factors could place women at an increased level of cardiovascular risk compared to men, and may concur to an enhanced pro-thrombogenic profile. The purpose of this manuscript is to provide an overview of gender-related differences in cardiovascular treatment, in order to highlight the need to improve the pharmacological prophylaxis adopted in women through a more accurate evaluation of the overall cardiovascular risk profile with consequent establishment of a more effective and targeted anti-thrombotic strategy which is not limited to the use of anti-platelet agents.

Keywords: platelet, antiplatelet treatment, gender, cardiovascular disease

1 Introduction

Cardiovascular disease (CVD), which includes coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease (PAD), is universally recognized as the leading cause of death worldwide [1,2]. The misconception that women are more protected than men against CVD has been largely debunked by the epidemiological data showing equal impact of ischemic heart disease and stroke on mortality rates in both sexes [3], although women manifest disease 10 years later than men. The gender-related difference in the incidence of disease when stratified by age has partly concurred to the disparity in the rate of enrollment of women versus men in cardiovascular trials, which has been generally below 30% of the total participants [3]. This aspect has been considered an important limiting factor in the translatability into clinical practice of experimental data derived from interventional trials on cardiovascular prophylaxis, particularly in light of the clinical observation that prognosis is worse in women than men following an acute thrombotic event. This has raised the concern that the therapeutic approach to CVD should be gender-specific because of the existence of sex-related disparities in cardiovascular physiology that could have important implications on therapy responsiveness and clinical outcomes. The underrepresentation women in large clinical trials can also reflect another important issue related to gender disparity in CVD, which is the underestimation of the cardiac risk and the misconception of symptoms resulting in less referral for cardiac testing and inappropriate diagnosis and treatment in women compared to men [4-6]. These factors, along with the late onset of clinical manifestations and high prevalence of comorbidities could place women at a higher risk of adverse events such as thrombosis and bleeding, than men [7]. Moreover, sex-related differences in arterial coronary size and timing to referral, have been identified as additional determinants to the gender discrepancy observed in early mortality rates post-revascularization, including both percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) [8]. However, gender-related variables remain to be

defined that could account for the increased mortality following myocardial infarction observed also in young women compared to age-matched men [9,10]. Sex-specific differences in platelet function and effectiveness of the antithrombotic therapy have been proposed as a potential explanation, but it remains a controversial topic requiring further investigation in primary and secondary prevention trials. On the other hand, additional differences in the treatment of common cardiovascular risk factors have emerged from observational studies comparing women and men. The choice of distinct classes of anti-hypertensive drugs and lipid lowering strategies could impact on the reduction of the overall cardiovascular risk profile with important implications on the blood pro-thrombotic activity and progression of disease. This manuscript will review the currently available evidence on the gender-specific disparities in cardiovascular pharmacotherapy, in the attempt to highlight those aspects of the clinical management that could influence blood thrombogenicity and responsiveness to anti-thrombotic therapies.

2 Gender differences in platelet function and clinical implications

A number of ex vivo functional assays has showed that women possess an increased platelet reactivity compared to their male counterparts, in terms of platelet-to-platelet aggregation [11-14], adhesiveness to fibrinogen [15-20] and interaction with leukocytes to form heterotypic aggregates [21]. In particular, some evidences have shown that platelet aggregation is enhanced in women. Platelets in women seem to express more glycoprotein Ib-IX-V and glycoprotein IIb/IIIa [22]. Moreover, results showed an increase of both activation of the GP IIb/IIIa receptors and platelet reactivity in females in comparison to males by a variety of platelet agonists such as arachidonic acid, adenosine diphosphate, and epinephrine [12,20,22,23,24]. The increase of platelet aggregability in women is proven to be independent of both platelet size and expression of surface adhesion molecules [25]. On the other hand, reduced platelet reactivity in pre-menopausal women has been related to the presence of estrogen receptors on the platelet surface (26). (Figure 1).

Whether or not this platelet hyperactivity, which has been demonstrated in vitro, has clinical implications remains an answered question. Indeed, thrombus formation in vivo is a complex multistep process regulated by multiple factors, including hemodynamic forces, vascular adhesiveness and concentration of pro- and anti-thrombotic humoral substances that, all together, ultimately modulate the function of platelets [23]. Hence, the intrinsic properties of platelets could be a promoting factor but not the only determinant for triggering an acute thrombotic event. This concept is supported by the epidemiologic data reporting the age-stratified prevalence of CVD in women. Indeed, despite their in vitro enhanced platelet reactivity, women are less affected by CVD in the pre-menoupausal age (prevalence in males and females is respectively of 11.9% vs. 10.0% in the range 20-39 years, and 40.5% vs. 35.5% in the range 40-59 years). Post-menopausal women equal the male sex in terms of prevalence of disease (67.9% vs. 69.1% in women and men in the range 60-79 years and 85.9% vs 84.7% by the age of 80 years) [1]. The role of sex hormones has been advocated to explain this age-related shift in the female pro-thrombotic profile, based on the evidence that estrogens inhibit platelet aggregation through stimulation of both prostacyclin [24] and nitric oxide release by the vascular endothelium [25-27]. On the other hand, testosterone is regarded as an inducer of platelet activity and generation of thromboxane A_2 (TXA_2) [19,28,29. However, there is no evidence that postmenopausal hormone replacement therapy may exert a cardioprotective effect [30,31]. Conversely, it has been reported an association between the use of oral contraceptives and increased risk of thrombotic events, especially in female smokers [32-33]. It is likely that other factors play a role and concur to the vascular ageing and pro-atherogenic damage that finally trigger an acute thrombotic event in women. In this setting, enhanced platelet activity could act as a potentiating element that worsens their clinical outcome. The question is of whether a gender-specific anti-thrombotic strategy should be thought and how to achieve a better prophylaxis in women.

2.1 Gender-difference in anti-platelet pharmacodynamics and pharmacokinetic

There is still a lack of data regarding the effects of gender on the levels and efficacy of antiplatelet drugs in patients with or at risk of CV disease, based on differences in pharmacokinetics, pharmacodynamics, and hormonal influences (e.g. menstrual cycle, menopause, pregnancy, and changes in total body water) [34].

Aspirin presents a sex-specific pharmacokinetic profile in both animals and humans. The bioavailability of acetylsalicylic acid is greater in women than in men, as a result of prolonged clearance and, in turn, significant extension of half life [35]. This gender-specific difference is probably due to greater activity of the degradation pathway via conjugation with glycine and glucuronic acid in men. In particular, it has been proven that oral contraceptives can enhance these degradation pathways. For this reason, the bioavailability of acetylsalicylic acid in women under hormonal contraception seems to be similar to men. It has been also highlighted the importance of sex hormone-mediated modulation of the aspirin activity, by the evidence that the rate of aspirin absorption is declined during the menstrual mid-cycle, and the effects of exogenous hormones on the pharmacokinetics of aspirin have confirmed this finding [36]

3. Gender-difference in anti-platelet drug response

The major aspect that has been largely addressed by many Authors, has been the possibility that women present with less responsiveness to anti-platelet therapy. Early clinical trials such as the Second International Study of Infarct Survival (ISIS-2) collaborative group study that tested the benefit of aspirin (either alone or in combination with streptokinase) on 30-day mortality following

myocardial infarction (MI), have reported less effectiveness, albeit not statistically significant, in women compared to men [37]. However, characterization of the cardiovascular risk profile at presentation was not separately analyzed in the two groups. Two additional clinical trials evaluating the protective effect of aspirin on stroke have also raised the hypothesis that platelet inhibition was sex-dependent, since reduction in the rate of cerebrovascular events in response to aspirin was only obtained in the male group [38,39]. However, a revision of the clinical evidence available by 1990 confuted these results, showing that platelet inhibition, irrespective of the anti-platelet agent used, is equally effective in both genders for patients at high risk and for secondary cardiovascular prevention [40]. More recent interventional clinical trials testing contemporary pharmacological approaches, appear to confirm these data, although an overall increased rate of acute events can be generally observed in the female group in all treatment arms, including placebo. In the following paragraphs, we will discuss the main evidence on the impact of gender on the effectiveness of common anti-platelet regimes in the context of secondary cardiovascular prevention. A final section will be dedicated to the analysis of data regarding sex-dependent disparity in the management of total cardiovascular risk, that also could have implications on clinical outcomes. The focus will be on the prophylaxis of coronary disease that has showed the main aspects of controversy.

3.1 Single therapy with aspirin

Several studies have investigated the role of acetylsalicylic acid in primary prevention of CV events. Despite these data, this topic is still debated and continues to be under scrutiny. Notably, primary prevention with aspirin has been proven to reduce the risk for total CV events and nonfatal MI, but to not significantly influence the incidences of stroke, CV mortality, all-cause mortality, and total CHD [41]. Aspirin is the first antiplatelet drug prescribed worldwide. At low doses (75-100 mg per day) it exerts an antithrombotic effect, chiefly due to a selective and irreversible

acetylation of the cyclooxygenase-1 (COX-1), resulting in blocked synthesis of TXA_2 in platelets [42]. It has been evidenced gender differences in the effects of aspirin in clinical trials regarding the primary prevention of CV diseases. The Women's Health Study (WHS) [43] evaluated the efficacy and safety of aspirin by a 10-year follow-up for a first major cardiovascular event (i.e., nonfatal MI or stroke, or death from cardiovascular causes) of 39,876 healthy women aged ≥ 45 years, randomly assigned to receive either 100 mg of aspirin on alternate days or placebo. Aspirin did not reduce the overall risk of major CV events, but the risk of stroke decreased (relative risk, RR: 0.83; 95% CI: 0.69-0.99; $p = 0.04$). Compared with placebo, aspirin had no significant effect on the risk of fatal or non-fatal MI (RR: 1.02; 95% CI: 0.84-1.25; $p = 0.83$) or death from CV causes (RR: 0.95; 95% CI: 0.74-1.22; $p = 0.68$). Moreover, aspirin therapy vs. placebo resulted in a 1.4-fold higher risk of gastrointestinal bleedings requiring transfusion (RR: 1.40; 95% CI: 1.07-1.83; $p = 0.02$). A meta-analysis of six randomized trials performed by Berger et al. [44] with a total enrollment of 95,456 patients (51,342 of whom were women) showed that primary prevention with aspirin provided a significant reduction of CV events, independently of sex. In particular, aspirin therapy was associated with statistically significant reduction in the odds of CV events in both women and men, 12% (OR: 0.88; 95% CI: 0.79-0.99; $p = 0.03$) and 14% (OR: 0.86; 95% CI: 0.78-0.94; $p = 0.01$), respectively. However, the specific benefit varied among sexes, being primarily a reduction of MI in men (OR: 0.68; 95% CI: 0.54-0.86; $p = 0.001$) and ischemic stroke in women (OR: 0.76; 95% CI: 1.35-2.20; $p < 0.001$). A further meta-analysis by the Antithrombotic Trialists' (ATT) collaboration [45] used the same six randomized trials, and demonstrated that aspirin therapy led to a significant reduction of major coronary events in men, but not in women.

In the setting of secondary prevention, the Antithrombotic Trialists' (ATT) collaboration meta-analysis [45] reported pooled results from 16 randomized trials on aspirin use in the secondary prevention setting, stratified by sex. Data did not evidence a significant interaction between gender and the effects of aspirin vs. placebo for the secondary prevention of CVD. Of note, aspirin therapy was associated with a relative risk (RR) reduction of major coronary events of 19% in males and

27% in females (*p* for interaction = 0.4) and decrease in serious CV events (MI, stroke, or vascular death) by 19% in both genders (*p* for interaction = 1.0) [45]. Yerman et al. [46] speculated that gender mix might account for about 25% of the variation in the efficacy of aspirin in reducing the rates of CV events across placebo-controlled trials. In this context, they noted that trials with higher predominance of men demonstrated larger benefits of aspirin in reducing non-fatal MI than those recruiting more women. However, their analysis included both primary and secondary prevention trials. The use of anti-platelet therapy for cardiovascular prophylaxis in asymptomatic subjects, including both genders, merits careful consideration and a critical evaluation of the benefit to risk ratio needs to be conducted on an individual basis. Characterization of the risk profile is a crucial aspect of the treatment-decision making for anti-platelet therapy and this concept applies to both sexes. Indeed, revision of large-population based trials has highlighted that the maximum clinical benefit from platelet inhibitors is achieved in subgroups of patients in whom the high cardiovascular risk largely overcomes the risk of bleeding complications associated to the anti-platelet therapy [47].

3.2 Dual antiplatelet therapy

Dual antiplatelet therapy (DAPT) (aspirin plus ticagrelor, clopidogrel, or prasugrel) is recommended in subjects with acute coronary syndrome (ACS) undergoing PCI with stent placement for the first year after the procedure [48]. Thienopyridines are inhibitors of the platelet ADP $P2Y_{12}$ receptor. Clopidogrel, a second-generation thienopyridine, has largely replaced the first-generation thienopyridine ticlopidine in clinical practice, due to its more favorable safety profile [49]. Clopidogrel is a prodrug, and its conversion into the active form by the hepatic cytochrome P450 (CYP) system provides its pharmacologic effect. CYP isoforms play a pivotal role in the double oxidation step essential to produce the active metabolite [50], Men and women do

not seem to show differences in plasmatic levels of clopidogrel's active metabolite [34], but it has been described some variability in terms of clopidogrel-induced inhibition of platelet aggregation, at least in ex vivo studies [51-53]. Interventional trials specifically focused on the analysis of sex-related differences in the anti-thrombotic activity of clopidogrel indicate that it is similarly beneficial in men and women, although with different degree. The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial [54] compared treatment with clopidogrel vs. placebo in association with aspirin, and enrolled subjects with recent non-STEMI. Compared to men, women showed a smaller absolute (1.2% vs. 2.8%) and RR reduction (12% vs. 25%) in the composite endpoint of CV death, non-fatal MI, or stroke at 1 year with clopidogrel plus aspirin vs aspirin alone. Similar findings were noted in the subgroup of patients undergoing PCI [55]. Effects of long-term therapy with clopidogrel in the secondary prevention setting was evaluated in subjects undergoing elective PCI in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial [56]. The study showed a 26.9% RR reduction in favor of clopidogrel for the composite endpoint of death, MI and stroke at 1 year in the overall population (95% CI: 3.9%-44.4%; $p = 0.02$; absolute reduction: 3%). Notably, and unlikely the CURE trial [54] study demonstrated a greater risk reduction among women for the combined risk of death, MI, or stroke at 1 year (32% vs. 25%). The Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial [57] randomized patients treated with fibrinolysis after the onset of STEMI to DAPT with aspirin plus clopidogrel vs. clopidogrel alone. It was observed a 36% reduction in the risk of the composite ischemic endpoint after clopidogrel treatment in the overall population ($p < 0.001$), without significant differences between men and women (35% vs. 38%, respectively) despite women display a higher event rate in both treatment arms. In the subgroup of patients treated with PCI after 3 days of starting the assigned study medication, the odds of the composite endpoint of CV death, recurrent MI, or stroke at 30 days was 59% in women and 41% in men. The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) [58] compared the effect of treatment with clopidogrel plus aspirin vs. aspirin alone in

Chinese patients with suspected recent MI. As in the CLARITY-TIMI 28, this study observed similar reductions in the primary ischemic endpoint at 28 days with no heterogeneity in effect related to sex, despite a higher rate of events being observed in the female group. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial [59] did not evidence clinical benefit after low-dose aspirin combined with clopidogrel in asymptomatic patients with at least 3 atherothrombotic risk factors and there were no statistically significant differences between men and women. To better understand the impact of gender on the efficacy and safety of clopidogrel in reducing CV events, Berger et al. [60] performed a sex-specific meta-analysis of the CURE, CREDO, CLARITY-TIMI 28, COMMIT, and CHARISMA trials, focusing on differences between men and women on DAPT with clopidogrel in combination with aspirin vs. aspirin alone for the prevention of CVD. The study involved 79,613 patients with CAD (predominantly with ACS) or at a high risk for the recurrence of CVD. The CV event rates over the long term in 23,533 women were 11.0% vs. 11.8% in the clopidogrel group vs. controls, respectively (OR: 0.93; 95% CI: 0.86-1.01); clopidogrel led to a significant decrease in cardiovascular events in men (7.8 vs. 9.0%; OR: 0.84; 95% CI: 0.78–0.91). There was a weak trend for statistical heterogeneity based on gender (p = 0.092), but the authors argued that most of the differences between males and females could be explained by play of chance. Overall, the analysis of the absolute benefit of anti-platelet therapy between genders do not reveal remarkable differences (0.8% in women vs. 1.2% in men). Moreover, the study showed that clopidogrel vs. placebo as add-on therapy to aspirin entailed a similar rate of major bleedings over the long term in both men (OR: 1.22; 95% CI: 1.05-1.42) and women (OR: 1.43; 95% CI: 1.15-1.79). The third generation oral thienopyridine prasugrel inhibits platelet aggregation more rapidly, more consistently, and to a greater extent than clopidogrel. This pharmacokinetic and pharmacodynamic superiority confers to prasugrel improved anti-thrombotic efficacy, at the expense of an increased bleeding rate. [61]. The TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet iNhibition with prasugrel–Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) [62] enrolled aspirin-

treated ACS patients undergoing PCI and compared the effect of prasugrel vs. clopidogrel. Even if, in the prasugrel arm there was higher absolute (2.4 vs 1.6%) and relative (21 vs. 12%) reductions in cardiovascular events among men in comparison to women, there was no significant interaction between treatment and gender. Multivariate analysis indicated that female gender was the strongest predictor of non-bypass-related major bleeding during the follow-up ($p < 0.001$) [63]. On the other hand, the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial has compared clopidogrel versus prasugrel in ACS without ST-segment elevation who do not undergo revascularization. This study reported that there was no statistically significant risk of major bleeding in women or men who took prasugrel as compared to clopidogrel, with an associated hazard ratio (HR) of 1.13 (95% CI: 0.41-3.11) in women and of 1.37 (95% CI:0.80-2.35) in men [64].

The difference in term of beeding risk among women treated with prasugrel could be ascribed to the different dose of prasugrel used in the two studies. In the TRITON-TIMI all patients received a maintanance dose of 10 mg of prasugrel. Conversely, in the TRILOGY trial the dose of prasugrel was adjusted to 5 mg for those who were 75 years of age or older or who weighed less than 60 kg. According to this, women in the TRILOGY study were more likely to receive reduced dose of prasugrel.

Ticagrelor is the first member of a class of non-thienopyridine antiplatelet drugs known as cyclopentyl-triazolo-pyrimidines (CPTP). Unlike thienopyridines, ticagrelor binds reversibly to the ADP $P2Y_{12}$ receptor and exhibits rapid onset and offset of effect [65]. The PLATelet Inhibition and patient Outcomes (PLATO) study [66] compared ticagrelor vs. clopidogrel combined with aspirin in patients with recent ACS. There were no significant differences between the two sexes in both the absolute and relative reductions of adverse events at 1 year by ticagrelor. Female sex was independently related to a greater risk of bleeding in patients undergoing PCI (HR: 2.2), however the association no longer presented statistical significance for non-PCI-related bleeding [67].

In the context of DAPT, it is worth noting that premature discontinuation of DAPT has been associated with an increased risk of stent thrombosis [68]. Two recent studies aimed to study the impact of sex on DAPT regimen after PCI. In a subanalysis of the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) [69] trial it has been investigated whether sex influenced the outcomes in a population undergoing PCI randomly allocated in short (6-month) or prolonged (24-month) DAPT regimen. Gender was not a treatment modifier in terms of DAPT duration and men and women had similar adjusted 2-year ischemic and bleeding outcomes. On the same hand, a pooled analysis of six randomized trials showed that in both sexes short DAPT is associated with similar rates of cardiovascular outcomes but lower risk of bleeding when compared with prolonged DAPT [70].

During recent years gender-related differences in medication adherence in the field of secondary prevention, has long been under scrutiny [71]. Indeed, adherence to a medication regimen in postmyocardial infarction patients is one of the most significant challenges of secondary prevention in the field of CVD. It has been showed that women, had worse adherence in cardiovascular medication in the GWTG-CAD (Get with the Guidelines Coronary Artery Disease) registry [72]. On the same hand, in a recent subanalysis of the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimens In Stented Patients: An Observational Single Arm Study) study it has been investigated the incidence and impact of cessation of DAPT in women and men after PCI. DAPT discontinuation was higher in women than men (59.1% vs. 55.9%, $p = 0.007$) mostly due to noncompliance and bleeding. Importantly, non-adherence was associated with higher rates of both ischemic and bleeding events at 2 years. After adjustment for differences in baseline characteristics female sex was an independent predictor of bleeding but not of ischemic events in DAPT interruption [73].

Refer to **Table 1** for more detailed data on the randomized clinical trials mentioned in the above discussion.

3.3 Response to Intravenous GP IIb/IIIa inhibitors

GP IIb/IIIa antagonists inhibit the final common pathway of platelet aggregation by blocking the binding of fibrinogen to the GP IIb/IIIa receptor on the surface of activated platelets, hence stopping platelet aggregation, thrombosis, and thromboembolism. The currently available GP IIb/IIIa antagonists are abciximab, eptifibatide, and tirofiban, which are widely applied during PCI, and their safety and efficacy have been well established in multiple trials and registries [74]. Data derived from 3 large randomized trials on the use of abcximab in patients undergoing PCI demonstrated no gender difference in protection from major adverse outcomes (death, MI, or urgent revascularization) at 30 days, 6 months, and 1 year; however, women had higher rates of both major and minor bleeding events with abciximab than men [75]. On the same hand, treatment with eptifibatide in the Enhanced suppression of the platelet GP IIb/IIIa receptor with Integrilin therapy (ESPRIT) trial [76], was not influenced by gender in terms of death, MI or vessel revascularization at either 48 hours ($p = 0.063$) or 1 year ($p = 0.2$). A meta-analysis conducted by Boersma et al. [77] on six randomized trials designed to investigate the efficacy and safety of GP IIb/IIIa inhibitors in patients with ACS not routinely scheduled for early coronary revascularization, has showed reduction of death and MI, especially in patients at high risk of thrombotic complications. Nevertheless, interaction between sex and the use of GP IIb/IIIa inhibitors with respect to cardiac events resulted highly significant, with men showing a reduction by 19% in the odds of 30-day death or MI compared with placebo or control, whilst an increase by 15% in the risk of death was observed in women. However, the interaction was abolished after adjustment for the levels of troponin at presentation. Other than recurrence of acute thrombotic events, an important factor contributing to early mortality rate post-revascularization, either with or without GP IIb/IIIa inhibitor therapy, is the bleeding rate that the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) Initiative [78] has shown to be more frequent in women than men. Gender-related differences in bleeding risk have been also reported in the Global Registry of Acute

Coronary Events (GRACE) [79], which has evidenced a significantly higher risk of major bleeding in women vs. men (adjusted odds ratio, OR: 1.43; 95% confidence interval, CI: 1.23-1.66; $p <$ 0.0001). Other indicators of increased bleeding risk were age, renal failure and the use of GP IIa/IIIa inhibitors. The most recent Northern New England Percutaneous Coronary Intervention Registry [80] has confirmed that female gender continues to be associated with a > 2-fold risk of bleeding compared with men, although there is a decline in the overall incidence of PCI-related bleeding in both genders. It is known that a proportion of bleeding events in women could be avoided by a more appropriate dosing of antithrombotic drugs, since overdose has been reported in relation to body size, age, and comorbidities [81].

4. Gender difference in response to other cardiovascular pharmacological interventions

Whilst response to anti-platelet therapies appears similar between genders, with even an increased risk of bleeding complications in women, their tendency towards a higher cardiovascular residual profile rises the concern that women present with a higher overall cardiovascular risk score, or that they receive a less effective pharmacoprophylaxis than men. In this setting, it is worth mentioning that female patients who suffered a cardiovascular event often present with a higher prevalence of diabetes, a higher trygliceridaemia and a lower level of high-density lipoproteins (HDL) than their male counterpart [6]. Moreover, it has been registered a higher prevalence of hypertension, diabetes and hypercholesterolemia among women than men in the general population aged more than 60 years [82]. At the same time, an increase in the smoking habit, prevalence of diabetes and hypertension has been noticed also in midlife women (35-54 years) compared with men, with consequent impact on the overall incidence of CVD [10]. Hence, the question is of whether efficacy in the correction of these important cardiovascular risk factors is equally achieved in both genders. Observational studies have reported a different choice of anti-hypertensive drug classes in the treatment of men and women worldwide, with the former more often receiving angiotensin–converting enzyme inhibitor (ACE-I) and the latter more likely to be on diuretics [83,84]. More

importantly, gender disparities have been reported in terms of blood pressure control [85-89]. A recent analysis was conducted by Ljungman et al [90] to ascertain the rationale behind this different pharmacotherapy, using the Swedish Primary Care Cardiovascular Database (SPCCD). Attention was given to the distribution of comorbidities stratified by sex. In agreement with previous finding, the authors found a greater prescription of diuretics and beta-blockers in women, whilst men more often received calcium antagonists and ACE-I. The lower use of both ACE-I and angiotensin receptor blocker (ARB) in women vs men was observed also in the presence of diabetes; gender disparity for the use of ARB was less pronounced within the group of hypertensives with ischemic heart disease. Notably, women had a significantly higher blood pressure level than men, and also presented with impaired renal function, older age and higher LDL cholesterol and trygliceride levels. Further investigations are needed to clarify the sex-related discrepancy in the use of anti-hypertensive drugs that has emerged from these studies. However, these data emphasize an important difference between genders in achieving target blood pressure control. Similarly, glucose level control seems to be more challenging in diabetic women compared with men. A meta-analysis conducted on six randomized clinical trials has demonstrated greater reduction in HbA1c in men than in women on insulin therapy, in spite of an increased incidence of severe hypoglycemic events observed in the female group [91]. Similarly, although pharmacodynamics of metformin does not differ by sex, metformin has more beneficial effects on glucose metabolism in men compared with women [92]. Women treated with metformin seem to have more adverse effects than men and are less adherent to treatment [93]. On the other hand, sex does not appear to affect treatment with other glucose-lowering agents, such as sulphonylureas, thiazolidinediones and incretins [94].

Of note, a significantly higher body mass index (BMI) was observed in women compared to men, which highlights the potential relevance of pro-inflammatory metabolites derived from the adipose tissue in contributing to glucose metabolism [95] and, in turn, the inflammatory and thrombotic profile of cardiovascular female patients [96]. Finally, but not less important, sex-related difference

have been reported also in the use of statins. Using the Department of Veterans Affairs (VA) administrative data sources, Virani et al have recently reported that a reduced proportion of women with known CVD receive long-term statin treatment compared to male patients in the outpatient setting [97]. The reason behind this different clinical management of lipid dismetabolism in the context of secondary prevention remains to be explained. It could be partly ascribed to the reduced adherence to treatment in women vs men that other authors have previously reported [98]. However, this aspect warrants particular attention in view of the critical beneficial impact of lipid-lowering therapies on cardiovascular clinical outcomes and blood thrombogenicity [99]. All together, these clinical evidence call for the need to further investigate the potential gender discrepancy in the management of cardiovascular patients and reduction of the overall cardiovascular risk profile. Future clinical interventional studies are also required to analyze if poor prognosis in women can be ameliorated by a more aggressive and appropriate pharmacological prophylaxis that includes, but is not limited, to the use of anti-platelet agents.

5 Conclusions

Nowadays, there is an increased attention on the relevance of gender-related dissimilarities in CV health care and outcomes. To date, major attention has been given to the possibility that different anti-platelet agents could produce distinct beneficial effects in women and men. However, careful analysis of the currently available literature suggests that although in vitro data continue to highlight increased platelet reactivity in the female sex, clinical outcomes are equally modulated in women and men by anti-platelet therapy. There is however a tendency, in women, for a higher rate of mortality and morbidity associated to CVD, that needs to be further evaluated in large prospective cohort studies with an equal representation of both sexes. In addition, recent but still limited observational studies point toward an important discrepancy in the pharmacological management of classical cardiovascular risk factors between genders. Paucity of data addressing this important aspect does not allow conclusive remarks. However, the recognition that sex-differences in the

nature and effectiveness of cardiovascular prophylaxis do exist rises the need to promote further clinical research within this field.

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Figure caption.
Figure 1: the figure represents the principal receptors and ligands involved in platelet activation. Receptor and ligands that seem to influence platelet reactivity in females are highlighted in colour. ADP: adenosine diphosphate; vWF: von willebrand factor; ER: estrogen receptor. 5-HT2A: serotonin 2A receptor.

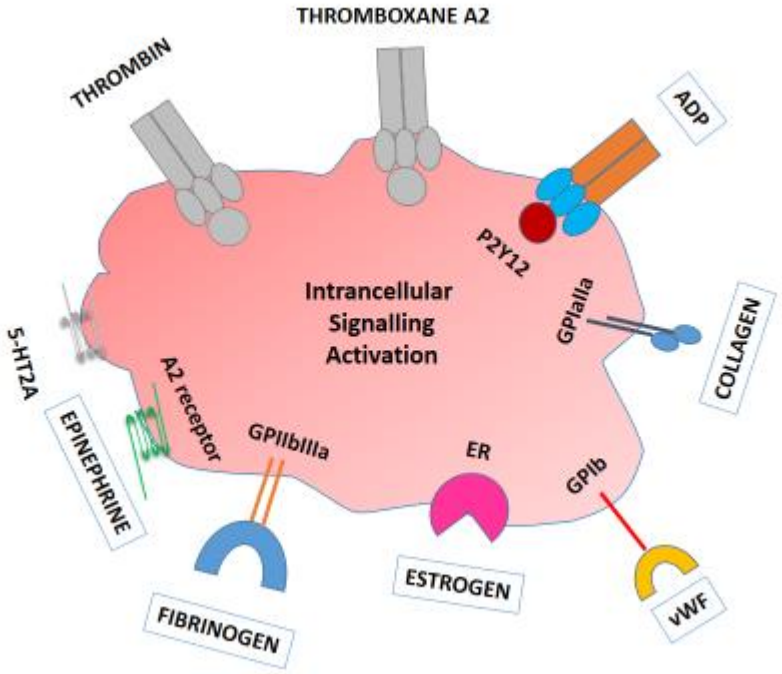

Table caption

Table 1. Secondary prevention of CVD: description of the studies on antiplatelet therapy.

Table 1. Secondary prevention of CV disease: description of the studies on antiplatelet therapy.

STUDY	WOMEN/ TOTAL PATIENTS (%)	AGE eligible range (years)	FOLLOW UP	POPULATION	DRUGS	MAIN ENDPOINTS	CLINICAL OUTCOMES	MAIN SAFETY ENDPOINTS
CURE [54]	4,836/12,562 (38,5%)	> 60	12 months	ACS without ST elevation; onset of symptoms within 24 hours	Clopidogrel (load of 300 mg, then 75 mg/day) plus aspirin (75-325 mg/day) vs. placebo plus aspirin (75-325 mg/day)	Composite CV death, non-fatal MI, stroke	Reduction with clopidogrel (9.3% vs. 11.4%) (RR: 0.80; 95% CI: 0.72-0.90; $p < 0.001$)	Significant raise of major bleeding risk with clopidogrel vs. placebo (3.7% vs. 2.7%) (RR: 1.38; 95% CI: 1.13-1.67; $p = 0.001$)
						First primary outcome or refractory ischemia	Reduction with clopidogrel (16.5% vs. 18.8%) (RR: 0.86; 95% CI: 0.79–0.94; $p <0.001$)	Non-significant raise of life-threatening bleeding with clopidogrel vs. placebo (2.2% vs. 1.8%) (RR: 1.21; 95% CI: 0.95-1.56; $p = 0.13$)
						Death from non-CV causes	Non-significant inter-group differences (0.7% vs. 0.7%) (RR: 0.91; 95% CI: 0.60–1.39)	
CREDO [56]	606/2,116 (28.6%)	≥ 21	12 months	Symptomatic CAD referred for elective PCI, or at high likelihood for requiring PCI	Clopidogrel (load of 300 mg, then 75 mg/day) plus aspirin (81-325 mg/day) through 1 year vs. placebo (load dose, then clopidogrel 75 mg/day until day 28, then placebo) plus aspirin (81-325 mg/day) through 1 year	Composite of death, MI, stroke at 1 year	Reduction with 1-year clopidogrel treatment (RR: 26.9%; 95% CI: 3.9%-44.4%; $p = 0.02$) Non-significant reduction in women vs. men with 1-year clopidogrel treatment (RR: 32.1%; 95% CI -12.1%-58.9% vs. RR: 24.5%; 95% CI: -4.6%-45.5%)	Non-significant greater number of patients with major bleeding event with 1-year clopidogrel vs. placebo (8.8% vs. 6.7%; p = 0.07)
						Composite of death, MI, stroke, urgent target vessel revascularization at 28 days	Non-significant reduction with 28-days clopidogrel treatment (RR: 18.5%; 95% CI: -14.2%-41.8%; $p = 0.23$) Greater reduction by administration of clopidogrel at least 6 hours prior PCI, with borderline significance (RR 38.6%; 95% CI: -1.6%-62.9%; $p = 0.051$)	

Table 1. Secondary prevention of CV disease: description of the studies on antiplatelet therapy (continued).

STUDY	WOMEN/ TOTAL PATIENTS (%)	AGE eligible range (years)	FU	POPULATION	DRUGS	MAIN ENDPOINTS	CLINICAL OUTCOMES	MAIN SAFETY ENDPOINTS
CLARITY-TIMI 28 [57]	Total: 3,491 99.7% referred for fibrinolysis: 685/3,481 (19.7%)	18-75	30 days	Onset of symptoms at rest of ST-elevation MI within 12 hours, scheduled to receive a fibrinolytic agent, an anticoagulant, and aspirin	Clopidogrel (load of 300 mg, then 75 mg/day) plus a fibrinolytic agent plus aspirin (load of 150-325 mg, then 75-162 mg/day) vs. placebo plus a fibrinolytic agent plus aspirin (load of 150-325 mg, then 75-162 mg/day)	Composite of occluded infarct-related artery on angiography (defined by TIMI score), death from any cause or recurrent MI before angiography.	Efficacy of clopidogrel vs. placebo (15.0% vs. 21.7%) (OR: 0.64; 95% CI: 0.53-0.76; $p < 0.001$)	Non-significant raise of major bleeding risk with clopidogrel vs. placebo <u>Through the day after angiography</u> (1.3% vs. 1.1%, $p = 0.64$) <u>At 30 days</u> (1.9 vs. 1.7%, $p = 0.80$)
						Death from CV causes, recurrent MI or ischemia needing urgent revascularization at 30 days	Reduction with 30-day clopidogrel vs. placebo (11.6% vs. 14.1%) (OR: 0.80; 95% CI: 0.65-0.97; $p = 0.03$)	
COMMIT [58]	12,759/45,852 (27.8%)	18-75	Hospital discharge or 28 days	Onset of symptoms of suspected acute MI within 24 hours	Clopidogrel (75 mg/day) plus aspirin (162 mg/day) vs. placebo plus aspirin (162 mg/day)	Composite of death, re-infarction, or stroke	Reduction with clopidogrel vs. placebo (9.2% vs. 10.1%) (OR: 0.91; 95% CI: 0.86-0.97; $p = 0.002$)	Non-significant differences between clopidogrel vs. placebo in bleeding risk: overall (0.58% vs. 0.55%, $p = 0.59$) fatal (0.32% vs. 0.32%, $p = 0.92$) non-fatal (0.27% vs. 0.22%, $p = 0.35$)
						Death from any cause in the treatment period	Reduction with clopidogrel vs. placebo (7.5% vs. 8.1%) (OR: 0.93; 95% CI: 0.87-0.99; $p = 0.03$)	

							Non-significant differences between clopidogrel vs. placebo (6.8% vs. 7.3%) (RR: 0.93; 95% CI: 0.83-1.05; p = 0.22)	
CHARISMA [59]	4,644/15,603 (29.8%)	≥ 45	28-35 months	Multiple CV risk factors, or documented CAD, cerebrovascular disease or symptomatic PAD	Clopidogrel (75 mg/day) plus aspirin (75-162 mg/day) vs. placebo plus aspirin (75-162 mg/day)	First occurrence of MI, stroke of any cause, death from CV causes (including hemorrhage)	<u>Asymptomatic with multiple risk factors</u> 6.6% with clopidogrel vs. 5.5% with placebo (RR: 1.2; 95% CI: 0.91-1.59; p = 0.20) Higher CV death rate with clopidogrel (3.9% vs. 2.2%, p = 0.01) <u>Symptomatic atherothrombosis</u> 6.9% with clopidogrel vs. 7.9% with placebo (RR: 0.88; 95% CI: 0.77-0.998; p = 0.046)	No differences in severe bleeding with clopidogrel vs. placebo (1.7% vs.1.3%) (RR: 1.25; 95% CI: 0.97-1.61; p = 0.09) No differences in fatal bleeding With clopidogrel vs. placebo (0.3% vs. 0.2%) (RR: 1.53; 95% CI: 0.83-2.82; p = 0.17)
						First occurrence of MI, stroke, death from CV causes, hospitalization for unstable angina, TIA or revascularization procedure	Reduction with clopidogrel vs. placebo (16.7% vs. 17.9%) (RR: 0.92; 95% CI: 0.86-0.995; p = 0.04)	No differences in primary IH (clopidogrel 0.3% vs. placebo 0.3%) (RR: 0.96; 95% CI: 0.56-1.65; p = 0.89)

Table 1. Secondary prevention of CV disease: description of the studies on antiplatelet therapy (continued).

STUDY	WOMEN/ TOTAL PATIENTS (%)	AGE eligible range (years)	FU	POPULATION	DRUGS	MAIN ENDPOINTS	CLINICAL OUTCOMES	MAIN SAFETY ENDPOINTS
TRITON-TIMI 38 [62,63]	3,605/13,608 (26.5%)	≥ 18	6-15 months	Moderate-to-high-risk ACS with scheduled PCI	Prasugrel (load of 60 mg, then 10 mg/day) plus aspirin (75-162 mg/day) vs. clopidogrel (load of 300 mg, then 75 mg/day) plus aspirin (75-162 mg/day)	Composite of CV death, non-fatal MI or stroke	<u>Prasugrel vs. clopidogrel</u> Reduction of composite endpoints (9.9% vs. 12.1%) (HR: 0.81; 95% CI: 0.73-0.90; p < 0.001) Reduced rate of non-fatal MI (7.4% vs. 9.7%) (HR: 0.76; 95% CI: 0.67-0.85; p < 0.001)	Greater rate of major bleeding with prasugrel vs. clopidogrel (2.4% vs. 1.8%) (HR: 1.32; 95% CI: 1.03-1.68; p = 0.03) Greater rate of life-threatening bleeding with prasugrel vs. clopidogrel (1.4% vs. 0.9%) (HR: 1.52; 95% CI: 1.08-2.13; p = 0.01)
						Urgent target-vessel revascularization	Reduction with prasugrel vs. clopidogrel (2.5% vs. 3.7%) HR: 0.66; 95% CI: 0.54-0.81; p < 0.001)	Greater rate of fatal bleeding with prasugrel vs. clopidogrel (0.4% vs. 0.1%) (HR: 4.19; 95% CI: 1.58-11.11; p = 0.002) Greater rate of non-CABG-related

						Stent thrombosis	Reduction with prasugrel vs. clopidogrel (1.1% vs. 2.4%) (HR: 0.48; 95% CI: 0.36–0.64; $p < 0.001$)	bleeding with prasugrel in women vs. men (HR: 1.77; 95% CI: 1.44-2.18; $p < 0.001$)
TRILOGY [64]	9326 (39.1)	≥ 18	Up to 30 months of treatment (median FU 17 months).	Patients with an acute coronary syndrome without revascularisation and treated with aspirin.	Prasugrel (load of 30 mg, then 10 mg/day or 5 mg/d for patients ≥75 years and/or 60 kg) plus aspirin (75-162 mg/day) Clopidogrel (load of 300 mg, then 75 mg/day) plus aspirin (75-162 mg/day)	Composite of CV death, MI, stroke	No differences between prasugrel vs. clopidogrel:13.9% of the prasugrel group and 16.0% of the clopidogrel group (HR in the prasugrel group, 0.91; 95% CI, 0.79-1.05; $p = 0.21$)	At 30 months, the key bleeding end points of non–CABG-related severe or life-threatening events (according to GUSTO criteria) (HR: 0.94; 95% CI: 0.44–1.99; p = 0.87) and major bleeding (according to TIMI criteria) (HR: 1.31; 95% CI: 0.81–2.11; $p = 0.27$) occurred with similar frequency among patients under the age of 75 years in the two study groups
						CV death	No differences between prasugrel vs. clopidogrel: HR for the comparison between prasugrel and clopidogrel for the overall results through 30 months of 0.93 (95% CI, 0.75-1.15, $p = 0.48$)	
						MI	No differences between prasugrel vs. clopidogrel: HR for the comparison between prasugrel and clopidogrel for the overall results through 30 months of 0.89 (95% CI, 0.74-1.07; p=0.21)	
						Stroke	HR for the comparison between prasugrel and clopidogrel for the overall results through 30 months of 0.67 (95% CI, 0.42-1.06; $p = 0.22$)	Non-significant higher non-PCI-related major bleeding risk in women vs. men with an associated hazard ratio (HR) of 1.13 (95% CI: 0.41-3.11) in women and of 1.37 (95% CI:0.80-2.35) in men
						Death from any cause	No differences between prasugrel vs. clopidogrel. HR for the comparison between prasugrel and clopidogrel for the overall results through 30 months of 0.96 (95% CI 0.79–1.16, p=0.63)	

Table 1. Secondary prevention of CV disease: description of the studies on antiplatelet therapy (continued).

STUDY	WOMEN/ TOTAL PATIENTS (%)	AGE eligible range (years)	FU	POPULATION	DRUGS	MAIN ENDPOINTS	CLINICAL OUTCOMES	MAIN SAFETY ENDPOINTS
PLATO [66,67]	5,288/18,624 (28.4%)	≥ 18	12 months	ACS with or without ST-elevation, onset of symptoms within 24 hours	Ticagrelor (load of 180 mg, then 90 mg twice/day) plus aspirin (75-100 mg/day) vs. clopidogrel (load of 300 mg/day, then 75 mg/day	Composite of CV death, MI, stroke	Reduction with ticagrelor vs. clopidogrel (9.8% vs. 11.7%) (HR: 0.84; 95% CI: 0.77-0.92; $p < 0.001$)	No differences in major bleeding risk with ticagrelor vs. clopidogrel (11.6% vs. 11.2%) (HR: 1.04; 95% CI: 0.95-1.13; $p = 0.43$)
						CV death	Reduction with ticagrelor vs. clopidogrel (4.0% vs. 5.1%) HR: 0.79; 95% CI: 0.69-0.91; $p = 0.001$)	Higher rate of non-CABG-related major bleeding with ticagrelor vs. clopidogrel (4.5% vs. 3.8%) (HR: 1.19; 95% CI: 1.02-1.38; $p = 0.03$)

	MI	Reduction with ticagrelor vs. clopidogrel (5.8% vs. 6.9%) (HR: 0.84; 95% CI: 0.75-0.95; $p = 0.005$)	Higher PCI-related major bleeding risk in women vs. men (HR: 2.245; 95% CI: 1.416–3.559)
	Stroke	Non-significant reduction with ticagrelor vs. clopidogrel (1.5% vs. 1.3%) (HR: 1.17; 95% CI: 0.91-1.52; $p = 0.22$)	Non-significant higher non-PCI-related major bleeding risk in women vs. men (HR: 0.765; 95% CI: 0.587–0.996)
	Death from any cause	Reduction with ticagrelor vs. clopidogrel (4.5% vs.5.9%) (HR: 0.78; 95% CI: 0.69-0.89; $p < 0.001$)	

ACS: acute coronary syndrome; CABG: coronary artery by-pass graft; CAD: coronary artery disease; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; IH: intracranial hemorrhage; MI: myocardial infarction; OR: odds ratio; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; RR: relative risk; TIA: transient ischemic attack; TIMI: Thrombolysis In Myocardial Infarction