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Review

Gender differences in cardiovascular prophylaxis: Focus on antiplatelet treatment

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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.

Contents

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

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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 [12,20,22–24]. 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]. (Fig. 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]