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REVIEW ARTICLE

Gender Differences in Response to Therapy for Cardiovascular Diseases

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Abstract: In the last decades, aging of population is becoming even more prevalent, with consequent increasing requirement in health assistance and services. Physical and social environments can affect health directly, or through barriers or incentives conditioning opportunities, decisions and behavior. Moreover, the relationship with environment varies according to several personal characteristics including family background, sex and ethnicity. The impact of these factors is often skewed by these characteristics, leading to inequalities in health. In almost all countries, the older population is predominantly female. The prevalence and incidence of Cardiovascular Diseases (CVD) are reported to be lower in women than in men, increasing with age in both genders, but at advanced ages women outnumber men. Gender-differences in the contribution of various pathophysiological processes, combined with suboptimal recognition of female specificities, may explain sex-differences in presentation and outcomes of CVD and also partially explain the differences in cardiovascular drug therapy related to gender, where other behavioral and cultural factors can be involved. Starting by the conflicting data in literature, the aim of this article is to summarize the gender differences available on the use of the main cardiovascular drugs, and the possible explanation for these disparities. Till date, data on gender differences in cardiovascular therapy are still controversial, and overall no established factors have been identified to discriminate the different approach in the choice of cardiovascular drugs by gender. Then further more structured and bigger trials should be performed to target these issues, and to better clarify the underlining involved mechanisms.

Keywords: Digoxin and gender, Beta-blocker and gender, Calcium antagonists and gender, ACE-I and gender, ARBs and gender, Diuretic and gender, Antiplatelet and gender, Anticoagulants and gender.

1. INTRODUCTION

In the last decades, aging of population is becoming even more prevalent, with consequent increasing requirement in health assistance and services. About 13% of the global population was 60 years and older in 2015, and this proportion is expected to almost double by 2050, to 2.1 billion people [1]. The heterogeneity in health and functional status experienced by older people is an intriguing challenge. This is the result of small physiological changes that occur over time, but are only partially correlated to chronological age [2]. In fact, although such a variety in the aging process reflects genetic inheritance [3] or choices made by individuals in the course of their lives, a lot is due to external influences that are not typical of the person and are beyond its control. These environmental and social external factors can affect health directly or through barriers or opportunities or conditioning decisions and behaviors [2]. In addition, the relationship with the environment varies according to personal characteristics, including family background, gender and ethnicity. The impact of these factors is often conditioned by these characteristics, leading to substantial differences in health status [2, 4].

In almost all countries, the older population is predominantly female. Based on the data of Eurostat 2016 circulatory system diseases are one of the main causes of mortality in Europe, with a higher proportion of women (40.5 %) died than men (34.4 %). Women

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show lower incidence and prevalence of Cardiovascular Disease (CVD), while these parameters increase with aging in a similar manner in both genders [5]. In fact older women are more affected by CVD than men, with a total number of CVD higher in females than men [5, 6]. Despite that the incidence and mortality of CVD are declining in man but not in women [7, 8]. The differences between genders in the contribution of different pathophysiological processes, combined with the non-optimal identification of female specificity, as the smallest body size and weight, slower metabolism of drugs and lower renal function, can explain gender-specific differences in CVD presentation and outcomes [7, 9] and also partially justify the differences in cardiovascular drug therapy related to gender, where other behavioral and cultural factors can be involved.

1.1. Gender Differences in Cardiovascular Diseases

The incidence of cardiovascular diseases (CVDs) is typically higher in men, since women up to the menopause enjoy the beneficial effects of estrogens. However, CVDs remain the leading cause of death and disability in both sexes, and because mainly women make up the geriatric age group, is increasing among them the number of deaths from cardiovascular causes [5]. By gender and compared to women of the same age, disability caused by comorbidities is less for under 80 years old men, but increased in over80ies [8].

Regarding gender differences, among the most frequent cardiovascular diseases are coronary artery disease (CAD), one of the major causes of death worldwide in both men and women [10], and acute heart failure for which the women are more hospitalized than men. Although there are differences in the treatment of heart failure in men and women, duration of hospitalization is similar [11]. Women with CAD are generally about 7-10 years older than men, but they carry a greater burden of risk factors and have higher prevalence of symptoms, myocardial ischaemia, and mortality relative to men [5]. Paradoxically, although women have less anatomical obstructive CAD and relatively more preserved left ventricular function, the rates of myocardial infarction and mortality are higher compared with men, even when adjusting for age [12]. Data from Women's Ischemia Syndrome Evaluation (WISE) study [13] implicate adverse coronary reactivity, microvascular coronary dysfunction, and plaque erosion or distal microembolisation, as it is at least, in part, responsible for a female-specific myocardial ischaemia pathophysiology [14]. Women have a similar or even higher prevalence of angina compared with men, but do seem to have fewer typical symptoms; they are more likely to have atypical pain, and symptoms of chest pain rather than a clearly defined event, such as a myocardial infarction [13, 15]. In the WISE study it was shown that young women with endogenous oestrogen deficiency have a more than sevenfold increase in coronary artery risk [16]. However the study failed to demonstrate a role of endogenous oestrogen-related reproductive factors in CAD. Total time of oestrogen exposure was also not related to major adverse cardiovascular events; however, women who used HRT for more than 5 years had a lower prevalence and severity of obstructive CAD. Those results suggest that the paradigm of oestrogen protection from CAD in women may be more complex than oestrogen exposure duration alone.

Previous studies have revealed that among patients with Atrial Fibrillation, women tend to be at higher risk for stroke than men [17], even after adjustment for baseline comorbid conditions and vitamin K antagonist treatment [18-20].

The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry showed that appropriate angiotensin-converting enzyme inhibitor (ACE_I)/angiotensin receptor blocker (ARBs) and beta-blocker use were similar between women and men. However, compared with men, fewer women received hospital discharge instructions ($p < 0.001$) and the length of stay was longer ($p < 0.001$) among the OPTIMIZE-HF hospitals [21]. Also Lenzen *et al.*. [22] demonstrated that, among 8914 patients from the Euro Heart Survey on Heart Failure with confirmed diagnosis of heart failure, women were less often treated with evidence-based drugs, even after adjustment for age and important clinical characteristics suggesting a gender-oriented behavior in cardiovascular drug therapy choice.

Starting by the conflicting data in literature, the aim of this review is to summarize the gender differences available on the use of the main cardiovascular drugs, and the possible explanation for these disparities.

2. DIGOXIN

Digoxin is a cardiac glycoside with positive inotropic and parasympathetic effects, used for the treatment of heart failure and to slow conduction through the atrio-ventricular node [23]. Digoxin displays a reduced volume of distribution and slower renal clearance in women, and this would explain why adverse effects are more frequent in this population [24]. The major adverse effects include cardiac arrhythmias, gastrointestinal symptoms and neurological complaints (visual disturbances, disorientation, and confusion). However, toxicity may also occur with lower digoxin levels, especially if hypokalemia, hypomagnesaemia, or hypothyroidism coexists.

In the DIG study, digoxin therapy was associated with an increased risk of death for any cause and with a

less-evident reduction in the rate of hospitalization for worsening heart failure in women with heart failure than in men [25, 26]. However, afterwards, it emerged from a Dutch study that cardiotonic glycosides are a frequent cause for hospital admissions in women for unwanted drug effect and for poisoning [27]. Recent American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend lower serum concentrations (0.5 to 0.9 ng/mL) to reduce mortality in heart failure patients regardless of gender, but clinicians should adopt the lower serum digoxin concentration range when treating female patients [28]. Moreover, impairment of renal function should be specifically considered in women treated with digoxin.

An additional crucial aspect is hormone replacement therapy in women. There is a significant increased incidence of coronary events in the first year in women under hormone replacement therapy who additionally received digitalis, in secondary prevention for cardiovascular diseases [29]. The authors suggested that because use of digitalis is a marker of congestive heart failure, the association could also reflect a hormone–congestive heart failure interaction [29].

3. BETA-BLOCKERS

The beta-adrenergic receptor blockers (β-blockers) are used to treat a wide range of cardiovascular diseases including hypertension, heart failure, angina, arrhythmias, and post-myocardial infarction. Drug-metabolizing hepatic enzymes like cytochromes and P-glycoproteins (P-gp) are differently expressed in women and men. The cytochrome CYP2D6 is particularly relevant in the metabolism of beta-blockers. Metoprolol and propranolol are primarily metabolized by CYP2D6, which has a lower activity in women [30]. Therefore, it is possible that drugs regulating CYP2D6 could affect metoprolol effect. For example the co-administration of metoprolol with a weak CYP2D6 inhibitor (such as diphenhydramine, a classic antihistamine) could expose women to a greater risk of pronounced and potentially adverse effects compared with men. Approximately 20–30% of clinically used drugs, endogenous neur oregulators and neurotoxins are CYP2D6 substrates [31]. Generally metoprolol dose should be adjusted for body weight, and women should be particularly cautious when taking at the same time diphenhydramine in the higher dose range because it has a greater effect on metoprolol pharmacokinetics and pharmacodynamics.

On the other hand, this higher plasma level of some beta-blocker (especially metoprolol and propranolol) in women involves more benefits than men. In fact women show a greater reduction in heart rate and systolic blood pressure during exercise [32].

Moreover evidence exists that endogenous estrogens reduce cardiac sympathetic response to catecholamines while a deficiency of these up-regulate myocardial beta1-receptors. So estrogen supplementation can prevent this and it is also seen that oral contraceptives increase drug exposure to metoprolol [32].

Carvedilol is an alfa- and beta-blocker and it is metabolized by CYP2D6 and CYP2C9, and it has been demonstrated that women of fertile age have slightly higher CYP2D6 activity compared with men, while CYP2C9 activity does not seem to be sex-dependent, at least not to a clinically significant extent [33]. This confirms how the female metabolism is strongly dependent on hormonal status, in this way becoming essential to know physiological history before beta-blockers prescription.

Carvedilol can also inhibit P-gp and this might increase the absorption of digoxin (by inhibiting its efflux) and decrease the renal secretion of digoxin (by inhibiting efflux into the urine) in men. So, when the co-administration of these drugs is considered, serum digoxin levels should be monitored especially in man [34].

Generally, women with heart failure enrolled into randomized controlled trials tend to be older than men, and different risk factors (such as higher systolic blood pressure, lower estimated glomerular filtration rate) might often simply reflect this age difference. Data from randomized controlled trials have provided conflicting results about the efficacy of beta-blockers in women. In the MERIT-HF (Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure) [35] and the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) [36] trials the mortality reduction for women was not significant, while in the CIBIS II (Cardiac Insufficiency BIsoprolol Study II) study female sex represent a significant independent predictor of survival in patients with severe heart failure [37].

Recently, a meta-analysis [38] analyzed the efficacy and tolerability of beta-blockers in women and men with reduced ejection fraction heart failure (HFrEF) in sinus rhythm, by pooling patient data from placebo controlled randomized trials, confirming no differences in beta-blocker efficacy according to gender. Cause of death in women and men showed identical proportions and patterns for sudden, heart failure, and non-cardiovascular deaths, which further support the concordance for recommendation of beta-blockers. The conclusion was that treatment with beta-blockers reduced all cause mortality and hospital admissions for heart failure, regardless of age or sex [38].

Although these drugs are often associated with side effects, data from randomized trials consistently show

no true difference compared with placebo [39]. Clinicians should be reassured about the tolerability of beta-blockers in view of the prognostic benefit identified in women and elderly people of both sexes [40], suggesting that sex-related disparities in pharmacokinetics may not always correspond to clinically significant differences in therapeutic response.

4. DRUG-INDUCED LONG QT-SYNDROME

The QT interval of the electrocardiogram accounts for the duration of electrical activity for cardiac muscle cell contraction and ventricular repolarization in the cardiac cycle. Prolongation of the QT interval (Long QT Syndrome) is generally regarded as a pro-arrhythmic state, which can predispose to Torsade de Pointes (TdP), a rare but often fatal polymorphic ventricular arrhythmia. Women present a longer QT intervals at baseline compared to men. At the basis of different ventricular repolarization could play a crucial role the influence of sex hormones [41].

In a meta-analysis of 93 publications involving at least one identified case of TdP associated with the use of Class IA or Class III anti-arrhythmics, women accounted for 64 to 75% of cardiovascular drug-induced TdP [42]. Another meta-analysis, considering patients treated with d,l-sotalol (belonging to Class III anti-arrhythmic), revealed that women had a three-fold higher risk of developing TdP, even after adjusting for additionally identified risk factors [42, 43]. Thus, mechanisms underlying the increased risk of prolonged QT and TdP in women cannot be fully explained by increased serum drug concentrations or differences in autonomic tone, but may depend on menstrual cycle phase [44], because female QT time seems to be longer during ovulation and menstruation [45].

The Multicenter UnSustained Tachycardia Trial (MUSTT) [46] compared prophylactic defibrillator implantation with antiarrhythmic therapy for inducible patients. The study showed no gender-specific differences in respect to the risk of arrhythmogenic death, cardiac arrest, or overall mortality for female (14% included) and male (86% included) patients with coronary heart disease, reduced ejection fraction and spontaneous non-sustained ventricular tachycardia.

Although data available support the general conclusion that women more frequently develop ventricular arrhythmias than men, the impact on prognosis of this finding is not definitely clear. This situation suggests the necessity of gender-specific analysis, as well as the importance of inclusion of sufficient numbers of women in studies investigating antiarrhythmic drugs. Moreover, especially for female subpopulation, the potential arrhythmogenicity of pharmacological compounds should take this factor into account when establishing the study design

5. CALCIUM-CHANNEL BLOCKERS

Calcium channel blockers are indicated in a variety of cardiovascular diseases including hypertension, angina and supraventricular tachyarrhythmia. Verapamil, non-dihydropyridine-type, is a drug with high first-pass metabolism including the intestinal and hepatic drug metabolizing enzymes cytochrome P450, especially CYP3A4. This cytochrome metabolizes verapamil into norverapamil, the active metabolite. Verapamil is also known as a substrate for the human MDR1 (multidrug-resistance gene 1) gene product P-gp. Women have only one-third to one-half of the hepatic P-gp level of men resulting in increased intra-hepatocellular substrate (verapamil) availability and increased hepatic CYP3A4 metabolism, with consequent increased opportunities for the drug to encounter its metabolizing enzymes.

In surgical liver samples was found 2-fold higher CYP3A4 levels in female compared with male, and higher expression in women was also found for CYP3A4 messenger RNA (mRNA) transcripts, suggesting a pre-translational mechanism [47].

It has been shown after administration of a single 80-mg oral verapamil dose to healthy volunteers the area under the blood concentration–time curve (AUC) for norverapamil to that for verapamil was significantly higher in women than in men [48]. The authors concluded that norverapamil production is a sex-dependent process that is carried out more extensively in women than in men because of a higher activity of CYP3A4 or lower activity of P-gp.

Also the dihydropyridine-types (*e.g.* amlodipine) present lower body weight and higher activity of CYP3A4, but they are not generally considered to be a P-gp substrate, and undergo a faster clearance [40]. Amlodipine reduces diastolic blood pressure more significantly in women than in men, even after adjustment for baseline blood pressure, age, weight and dose in milligrams per kilogram [49]. So the authors concluded that antihypertensive agents, as amlodipine, might be used, as probes, to better understand these sex-differences. Although there is a slight more incidence of edema in females than in men, major hypertension trials with calcium-channel blockers found no gender-specific differences in main outcomes [50, 51].

Recent study results suggest that MDR 1 gene, producer of P-gp, polymorphism and gender are determinant factors of amlodipine pharmacokinetic variability. Lower clearance and higher exposure occurs in female subjects with the MDR1 3435CC o CT genotypes who have greater decreases in blood pressure after treatment with amlodipine. Thus, a higher dosage needs to be administered to males with the MDR1 3435TT genotype to achieve a better antihypertensive effect. These

results may be very important for amlodipine dose optimization and to help in improving efficacy of this drug in patients affected by essential hypertension [52].

6. ANGIOTENSIN CONVERTING ENZYME-INHIBITORS (ACE-I)

The Renin–Angiotensin system (RAS) is influenced by sex hormones, with inter-gender and, for women, intra-gender differences relating to the hormonal cycle. Although it is well known that estrogens inhibit the RAS pathway, by stimulating Angiotensin II receptor type 2 (AT2) plasma levels and consecutively inducing downregulation of Angiotensin-converting enzyme (ACE), renin activity and AT2-t1 receptor expression, in opposite to androgens that upregulate RAS system, apparently no decisive gender-specific differences in ACE-I metabolism have been found. [40, 51, 53-57]. Searching in literature for possible gender-differences in response to treatment with ACE-I some data emerge clearly from the early research, some others remain nebulous and not of univocal interpretation. About differences in prescription, one of the net data is the greater prescriptive of ACE-I in favor of men. This evidence is constant in almost all of the studies analyzed. In a 2015 study, Santalucia *et al*. [58], using the REPOSI registry data of >65 years old patients, described this phenomenon, showing as ACE-I prescription interested 24,7% of women vs 28,7% of men [58]. More recently Dadashova *et al.* [59] confirmed these data in a study in which the ACE-I prescription was 89% in men and 78% in women. Moreover, women show a more discontinuous use and a greater number of therapeutic interruptions than men [60, 61].

The reasons why ACE-Is are less prescribed to women could be cleared by different motivations. First, women show an increased susceptibility to develop Adverse Drug Reactions (ADRs) to cardiovascular drugs, at the beginning of therapy or in the long run, and generally more severe than men [27, 50, 60, 62]. In a Norwegian study, Rodenburg *et al.* [27] analyzed hospital admissions for ADRs differentiating by sex: in 5 years more admissions for ADRs were from women, with a greater overall ADRs risk of 1.5 to 1.7 times in women, confirmed for cardiac drugs too. A second motivation could be the potential ACE-I teratogenicity in fertile women, as demonstrated by some studies that report an increase in age-related administration (from 79,1% to 95,3% in Dadashova analysis) [59, 50, 62]. In contrast other studies show less ACE-I prescription, in particular in older women, [60, 63, 64] as showed by Stafford *et al.* [63] in the over 70 years old population suffering of heart failure.

At the end a third emerging reason of a more-or-less consciously lower prescription in women, could be the evidence of a lower therapeutic efficacy in this population, still clearly to prove, probably also related to an underdiagnostic trend in women. Indeed Santalucia *et al.* [58], in the REPOSI registry, revealed a minor gender-difference in prescription at hospital discharge, compared to hospitalization, perhaps as a result of better diagnostic classification during hospitalization. Another interesting observation in different gender-related prescriptive trend is a correlation also with the physicians' gender [65].

ACE-I are first line drugs in antihypertensive therapy, but It seems not to be clear yet if there is a consistent gender-related difference in blood pressure reduction response. Some issues take for granted the same effect between sexes. Wing *et al.* [66] described a similar beneficial antihypertensive action in both sexes in elderly patient. Saenz-Campos *et al.* [67] demonstrated the same result after 24h from a single dose of drug in young subjects. Other evidences suggest a less efficacy in women as time passes. In a 2008 review, Sullivan reported many studies in humans or in animal models in favour of a reduced antihypertensive response in women compared to men [40, 68-70]. This data could find a partial confirm in the evidence of a demonstrated lower cardiovascular protection in women.

Also in heart failure women seem less protected than men by ACE-I. In particular if women with symptomatic heart failure could even benefit from therapy with ACE-I (but always less than men), no evidences of reduced mortality come from treated women with asymptomatic form [51, 60, 71-75]. In particular Hudson *et al.* [76] have observed that in congestive heart failure, comparing ACE-I vs Angiotensin I Receptor Blockers (ARBs), women showed significantly lower survival with ACE-I, without differences described in survival of men using one or the other class.

ACE-I seem to demonstrate mostly major benefits in men than women in post-Acute Myocardial Infarction patients, with a female higher retained risk of new cardiovascular events, hospitalization, mortality and lower survival [66,71,73]. Women also seem to receive less than man the triple therapy indicated by guideline after acute coronary syndrome diagnosis, that also includes ACE-I (or ARBs) together with beta-blockers and statins [77]. However it's necessary to specify that data also show that in women often a greater amount of time passes between the onset of symptoms of infarction and the intervention time [78]. Moreover often these are individuals who have suffered a delay in diagnosis and who were often undertreated before and, eventually, mostly women who develop an acute cardiovascular event are generally older than men.

Adverse drug reactions from ACE-I are the main reason of interruption and disruption of therapy. The literature mostly shows that women have a greater risk of developing cough, so much so some authors define

the female gender as a significant determinant of risk to develop dry cough ACE-I –related [50, 51, 60, 71, 79-83]. However in Franconi's study [71], men and women showed the same incidence of cough when treated with zofenopril or ramipril, while the treatment with lisinopril was responsible of cough major incidence in women.

Although some authors suggest that female gender could be a risk factor for angioedema too [71, 80, 84], in more recent studies men seem to be more susceptible to angioedema [60, 71, 85]. At the same, men appear more at risk of symptomatic hypotension by using ACE-I [60, 71]. Kidney failure is a cause of therapeutic suspension in both sexes. But the risk of developing or aggravating the disease seems rather determined by pre-existing factors rather than the gender [60, 71]. In a recent work of Liou *et al.*, ACE-i seem a safer category in women than other antihypertensive drugs regarding the risk of developing new-onset diabetes, but in this study were de facto only women enrolled [86].

In conclusion, an important common limitation for almost all the literature consulted, is that women always are the absolute less numerous sample in trials, even in those specifically dedicated to the comparison between genders, and that they often represent the sample with higher average age and with delay in diagnosis and intervention.

7. ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS)

Angiotensin II receptor blockers (ARBs) represent a class of well-tolerated and effective antihypertensive drugs. Their mechanism of action is based on the blockage of angiotensin II molecule- angiotensin II receptor interaction, thereby relaxing smooth muscles, reducing peripheral vascular resistance, reducing plasma volume by the excretion of water and salt, decreasing cellular hypertrophy and reducing myocardial fibrosis. Several studies have reported their beneficial effects on heart failure, hypertrophic cardiomyopathy and diabetic nephropathy. Importantly this class of drugs has demonstrated low incidence of side effects like: dizziness, fatigue, headache, bronchitis and muscle pain [87]. In a study performed on healthy individuals no clinical important difference in the severity or frequency of adverse effects between men and women after irbesartan use was reported. In line with other studies, the side effects described in this study were classified as mild, and it was demonstrated an excellent tolerability with no evidence of dose- related toxicity. A significant reduction of about 56% in irbesartan renal clearance was observed in elderly *vs* young women but not in men. However this information seems not to have a clinical importance, since less than 3% of irbesartan is excreted from kidneys in its unchanged form, suggesting that there is not necessary a dosage adjustment for irbesartan therapy, with respect to gender. Despite some reported differences in plasma concentration for losartan and telmisartan between women and men, there were no recommended dose modifications [88, 89]. Another more recent study Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) [90] reported that after 12 months of losartan therapy women presented a greater reduction in Left Ventricular (LV) mass than men: LV mass was reduced by 8.0 ± 2.8 g more in women than in men (about 6% more). Although the underlying mechanism is not clarified, it has also been suggested a gender-related difference in myocardial fibrosis [90]. Other studies that investigated the effects of valsartan, candesartan and losartan in heart failure or after myocardial infarction did not report important gender related differences [91-94]. It should be underline that in these studies the female participants were about 30-40% [91-93].

8. DIURETICS

Diuretic agents are prescribed frequently in combination with ACE-I, ARBs, or Calcium-antagonists in the treatment of hypertension. They also have a well-established role in HF therapy with potential beneficial effects on hospitalizations reduction.

INCLUSIVE study reported that the decrease in systolic blood pressure after irbesartan/hydrochlorothyazide therapy was significantly greater in women than in men [94]. In another study [95] comparing valsartan monotherapy vs. valsartan/hydroclorothyazide, the mean decrease of blood pressure after 6 weeks of therapy, was greater in women than in men. (3.6 mmHg).

In animal models female rats displayed a lower furosemide systemic clearance and a lower elimination rate from the central compartment, suggesting a difference in the pharmacokinetics of organic anions [96].

Some previous studies have reported that there is a gender difference regarding the thiazide receptor expression and function in a rat model. It was found an increased density of this receptor in female rats, reflected functionally by a greater increase in sodium excretion [97]. Another experimental study reported that diuretic, natriuretic and kaliuretic efficiency of furosemide pharmacodynamics was higher in female rats, explained by the lower abundance of Na-K-2Cl cotransporter in female medullae [98]. Studying the polymorphism of cytochrome CYP2C9 in 24 patients with diastolic or systolic heart failure was observed that the female gender is an independent and significant of the pharmacokinetics of torasemide and that irbesartan significantly increases the plasma concentration and elimination half-life of torasemide [99]. Scwartz and

colleagues [100] studied the interaction of gender and genotype on blood pressure response to hydrochlorothyazyde. In a population of 376 patients they observed that insertion/deletion of ACE-inhibitors polymorphisms and the response to standard dosage of hydrochlorothyazyds was significantly different between women and men and this could be mediated by the enzymatic production of angiotensin II [100].

9. ANTIPLATELETS

Antiplatelets drugs represent one of the most important treatments in patients with cardiovascular disease (CVD), in fact they are recommended for CVD prevention according to international guidelines. Different studies [101, 102] suggest that, compared to men, women may obtain different benefits from antithrombotic therapy. These disparities are not clear and multiple factors may be involved.

Segal *et al.* [103] showed that women had higher platelet counts than men. Already in 1997 Faraday *et al.* [104] showed that the number of GPIIb-IIIa receptors per platelet capable of binding fibrinogen was significantly greater in women than men in response to ADP and thrombin receptor activating peptide (TRAP), while there were not gender difference in the total number of GPIIb-IIIa molecules expressed using specific anti-GPIIb-IIIa monoclonal antibodies. So the authors [104] demonstrated an association of GPIIb-IIIa reactivity with menstrual phase, suggesting that GPIIb-IIIa receptors on platelets from premenopausal women are more "activatable" than those on platelets from young men. Reduced platelet reactivity in premenopausal women has been related to the presence of estrogen receptors on the platelet surface [105]. Therefore platelets in women appear to have a higher surface expression of glycoprotein Ib-IX-V which is responsible for initiating adhesion through von Willebrand factor [106], and higher adenosine diphosphate or collagen-induced reactivity has been observed in female versus male subjects, independently by the expression of surface receptors [107].

9.1. Aspirin

Aspirin was absorbed more rapidly, distributed in larger apparent volume and faster hydrolyzed in women than men [108]. In addition it has been showed a slow ASA absorption during the menstrual mid-cycle, suggesting the role of estrogens in modulating the ASA activity.

All these findings suggest that Aspirin could be more active in male than in female platelets [50], although both sexes have a similar decrease in platelet reactivity after low dose aspirin therapy [109].

The Women's Health Study (WHS) [110] evaluated the efficacy and safety of aspirin in 39876 initially healthy women ≥45 years of age randomly allocated to receive either 100 mg of aspirin on alternate days or placebo, and then monitored for 10 years. Aspirin did not reduce the overall risk of major cardiovascular events, but decreased the risk of stroke (relative risk [RR] 0.83; p = 0.04), owing to a 24% reduction in the risk of ischemic stroke (RR 0.76; p=0.009) and a no significant increase in the risk of hemorrhagic stroke. Gastrointestinal bleeding requiring transfusion was more frequent in the aspirin group than in the placebo group (relative risk, 1.40; P=0.02) [110]. In subgroup analyses the risk of major cardiovascular events, ischemic stroke, and myocardial infarction was significantly reduced by aspirin among ≥65 years old women [110].

In a metanalysis Berger *et al.* [101] showed that, among more than 50.000 women and 40.000 men enrolled in 6 randomized trials, low-dose aspirin therapy is associated with a significant reduction in cardiovascular events in both women and men. In particular, aspirin had more beneficial effect on the risk of stroke for women and on the risk of MI for men, with a significant risk of major bleeding irrespective of sex (p=0.001) [101].

In the secondary prevention aspirin reduces serious vascular events in both sexes, with a non-significant increase in hemorrhagic stroke, in particular reducing of about a fifth total stroke and coronary events [111].

9.2. Ticlopidine

In the secondary prevention the Canadian American Ticlopidine Study (CATS) [112], a randomized, double blind placebo-controlled trial, showed a beneficial effect of ticlopidine (250 mg twice a day) in both men and women with a recent thromboembolic stroke. Another randomized trial [113] comparing ticlopidine hydrochloride (500 mg daily) with aspirin (1300 mg daily) concluded that ticlopidine was more effective than aspirin in both sexes in preventing stroke in high-risk patients, but the safety profile of ticlopidine was poorer than that of aspirin, with a higher incidence of side effects, including neutropenia (<1% vs 0%), skin rash (14% vs 5.5%), and diarrhea (20% vs 10%).

9.3. Clopidogrel

No significant differences have been observed in plasma levels of the main active metabolite of clopidrogrel between women and men [50]. In 2002 the CURE trial [114] showed that the addition of clopidogrel to ASA therapy provided a smaller (12 % vs 25 %) reduction of the risk of major adverse cardiovascular events in women vs men [114]. Moreover, Hobson *et al.* [115] documented through the use of Short Thrombelastography that women displayed a reduced response to clopidogrel, and greater post-treatment re-

activity while on both aspirin and clopidogrel, mainly in those female patients with a history of stent thrombosis. A meta-analysis [116] of five important blinded randomized clinical trials comparing clopidogrel and placebo involving 79,613 patients, of whom 30% were women showed that clopidogrel was associated with a highly significant reduction in the risk of cardiovascular events in both sexes. Among women enrolled, there were fewer cardiovascular events in the clopidogrel group compared with the placebo group and the risk reduction with clopidogrel seemed to be greatest for MI, with the effects on stroke or total death not statistically significant. While among men enrolled, there were fewer cardiovascular events in those receiving clopidogrel compared with placebo (7.8% *vs* 9.0%), and the risk reduction was significant for MI, stroke, and total death. However clopidogrel increased the risk of major bleeding without gender differences [116].

9.4. Prasugrel

The TRITON-TIMI 38 [106] which compared prasugrel vs. clopidogrel in aspirin-treated acute coronary syndrome (ACS) patients undergoing to percutaneous coronary intervention (PCI) showed there were no significant interaction between treatment and gender, although men again showed higher absolute (2.4% *vs* 1.6%) and relative (21% *vs* 12%) reductions in major cardiovascular events at 15 months with prasugrel than women [117].

A recent retrospective multicenter observational study (PROMETHEUS Study) [118] showed that young women undergoing PCI for ACS have significantly greater prevalence of diabetes (41.0% *vs* 27.9%) and chronic kidney disease (12.7% *vs* 7.2%) than young men; despite a higher risk clinical phenotype in women, prasugrel use was significantly lower in women than men (31.8% in men *vs* 28.1% in women, $p = 0.01$) and women were associated with a significantly higher 1 year risk of death, myocardial infarction, stroke or unplanned revascularization and bleeding than men [118].

9.5. Ticagrelor

In a multicenter, double-blind, randomized trial [119] showing that treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding, there was no significant gender difference in the absolute and relative reductions of adverse events at 1 year by ticagrelor. At this time no study has ever specifically compared platelet aggregation in men and women treated with ticagrelor [119].

Finally a recent study [120] showed that in patients receiving dual antiplatelet therapy gender does not impact on the prevalence of high-on treatment residual platelet reactivity with ASA, clopidogrel or ticagrelor.

10. ORAL ANTICOAGULANTS

In 2005 Zhu *et al.* [121] studied gender different pharmacokinetics of warfarin and they showed that, after oral administration of warfarin at a dose of 2 mg/kg, the plasma concentration-time curve from time zero to time infinity (AUC) was significantly greater (345 compared with 180 microg h/ml) in female than in male rats.

Dagres *et al.* [122] analyzed the data of 5,333 patients (42% female) enrolled in the Euro Heart Survey on Atrial Fibrillation (AF) and indicated that compared with men, women were older, had a lower quality of life, more comorbidities, more often had heart failure (HF) with preserved left ventricular systolic function (18% vs 7%, $p<0.001$), and less often had HF with systolic dysfunction (17% vs 26%, $p<0.001$); while they underlined that in patients with atypical or no symptoms (44% of women, 51% of men), women less frequently underwent rhythm control (39% vs 51%, $p<0.001$) than did men, prescription of oral anticoagulants was identical (65%) in both [111]. Furthermore men and women had equal probability to receive thrombolysis and oral anticoagulants when they had stroke and were admitted in stroke unit [123].

In patients with newly diagnosed AF there were race and sex-related differences to receipt oral anticoagulation (female *vs* male: AHR 0.93; $p<0.001$) [124]. There was a higher risk of stroke despite a similar quality of anticoagulation in anticoagulated atrial fibrillation females compared to males [125], but a cross-sectional study [126] conducted in French primary care evidenced that women over 75 were a third less likely to be treated with recommended anticoagulants than men of similar age. Moreover a systematic review [127] confirmed that female atrial fibrillation patients presented an increased risk of stroke, worsened by the lower oral anticoagulant prescription rate related to the concomitant higher hemorrhagic risk profile. Instead a report of 2015 from the Euro Observational Research Program Pilot survey on Atrial Fibrillation Europace [128] showed that women were at higher stroke risk overall and oral anticoagulation was used in a high proportion in them in fact this report evidenced a CHA2DS2-VASc score ≥ 2 in 94.7% of females and 74.6% of males ($p<0.0001$), with oral anticoagulants being used in 95.3 and 76.2%, respectively ($p<0.0001$) and a HAS-BLED score ≥ 3 in 12.2% of females and 14.5% of males. Because female sex is a significant risk factor for AF-related stroke Eckman proposed to incorporate sex female into decision-making about thrombo-prophylaxis in patients with AF [129].

Among patients treated with self-managed oral anticoagulant therapy with vitamin K antagonists, men achieved a significantly better therapeutic INR control than women, but the incidence of major complications is low and similar in both sexes [130]. Moreover hospitalized women receiving an excessive dose of oral anticoagulant have a 4-fold increased risk of bleeding compared with men [131]. A meta-analysis [132] analyzed gender differences between warfarin and novel oral anticoagulant (NOAC) and showed that women with AF taking warfarin were a significantly greater residual risk of cerebrovascular accident and systemic embolism (CVA/SE) compared with men (OR 1.279, p=0.001) and an equivalent major bleeding risk; while no gender difference in residual risk of CVA/SE was noted in patients with AF receiving NOAC agents (OR 1.146, p=0.109) and major bleeding was less frequent in women with AF treated with NOAC. So this meta-analysis suggested an increased clinical benefit of NOAC agents compared with warfarin in treating women with AF [132].

A study conducted by Frost *et al.* [133] showed that there were no clinically age- or sex-related differences in the pharmacokinetics and pharmacodynamics of apixaban. A meta-analysis [134] about novel oral anticoagulants for venous thromboembolism (VTE) showed that there was no gender difference in the primary efficacy outcome of recurrent VTE, men had less major bleeding compared to women [RR 0.79, p=0.03] and women had more bleeding complications than men when receiving novel oral anticoagulants for VTE [134].

A systematic review [135] exhibited that there was no gender-related difference in the efficacy and safety of NOACs compared with vitamin K antagonists in patients treated for non valvular AF and acute VTE and an increased risk of bleeding in male as compared with female patients in the extended treatment of VTE. On the contrary Piovella [136] and later Loffredo [137] suggested that women had a higher risk of bleeding compared to men when treated with NOACs for VTE confirming no differences in treatment efficacy.

CONCLUSION

In conclusion, up to date, data on gender differences in cardiovascular therapy are still controversial, and overall no established factors [138,139] have been identified to discriminate the different approach in the choice of cardiovascular drugs by gender. Then further more structured and bigger trials should be performed to target these issues, and to better clarify the underlining involved mechanisms. These findings could help in a more personalized therapy with reduction in adverse drug reactions [140] and health costs.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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