

Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC

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Introduction

Cardiovascular (CV) disease is the leading cause of morbidity and mortality in both sexes in developed countries, but gender differences exist in its diagnosis and treatment.

Since the number of women included in CV studies has often been low, most recommendations in women have often been inferred from effects observed in men.¹ This position paper discusses the gaps in knowledge on the effects of gender on pharmacokinetics (PK) and pharmacodynamics (PD) of CV drugs.

Differences in pharmacokinetics/ pharmacodynamics

Gender-related differences in PK may arise from differences in body composition, plasma protein binding, metabolizing enzymes and transporters, excretion activity, and/or physiological hormonal changes (Figure 1).^{2,3} Oral drug absorption is influenced by gastric acid secretion and emptying time, gastrointestinal blood flow and surface area, gut and hepatic metabolism.^{2,3} Although gender differences in these mechanisms exist, they do not significantly affect drug absorption between the two sexes.^{2,3}

Drug distribution depends on body composition, plasma volume, blood flow, and tissue and plasma protein binding. Women have higher per cent of body fat and lower body weight, plasma volume, and organ blood flow. Increased body fat content explains the faster onset and prolonged duration of action and higher volume of distribution (Vd) of lipophilic drugs, while the Vd of hydrophilic

drugs is smaller, producing higher initial plasma levels and greater effects when compared with males.^{3–5}

Plasma and tissue drug concentrations depend on the Vd and clearance (Cl). Exogenous sex hormones increase serum-binding globulins levels.^{2–5} This effect may be relevant for drugs like warfarin whose 97% is bound to plasma proteins. Hepatic drug Cl is a function of cardiac output and liver blood flow, which are lower in women, while hepatic enzyme activity involved in phase I and II reactions, and transporters exhibit sex-specific differences.^{3–5}

Gender differences in renal excretion for most drugs are attributable to body weight and differences disappear after normalisation for body weight.

Despite the effects of oestrogens on PK/PD have been better elucidated than those of testosterone, the influence of sex hormone levels and PK/PD of CV drugs has not been well studied. Phase I studies are often conducted in young healthy volunteers that differ in their hormonal profile to the population of patients that will receive CV treatments.

Gender differences in PD are difficult to quantify as women are often under-represented in trials and the role of sex hormones in the final response is not taken into consideration. Unfortunately, the appropriate dosage and the gender differences in clinical outcomes are still not recognized for many drugs routinely used in clinical practice.

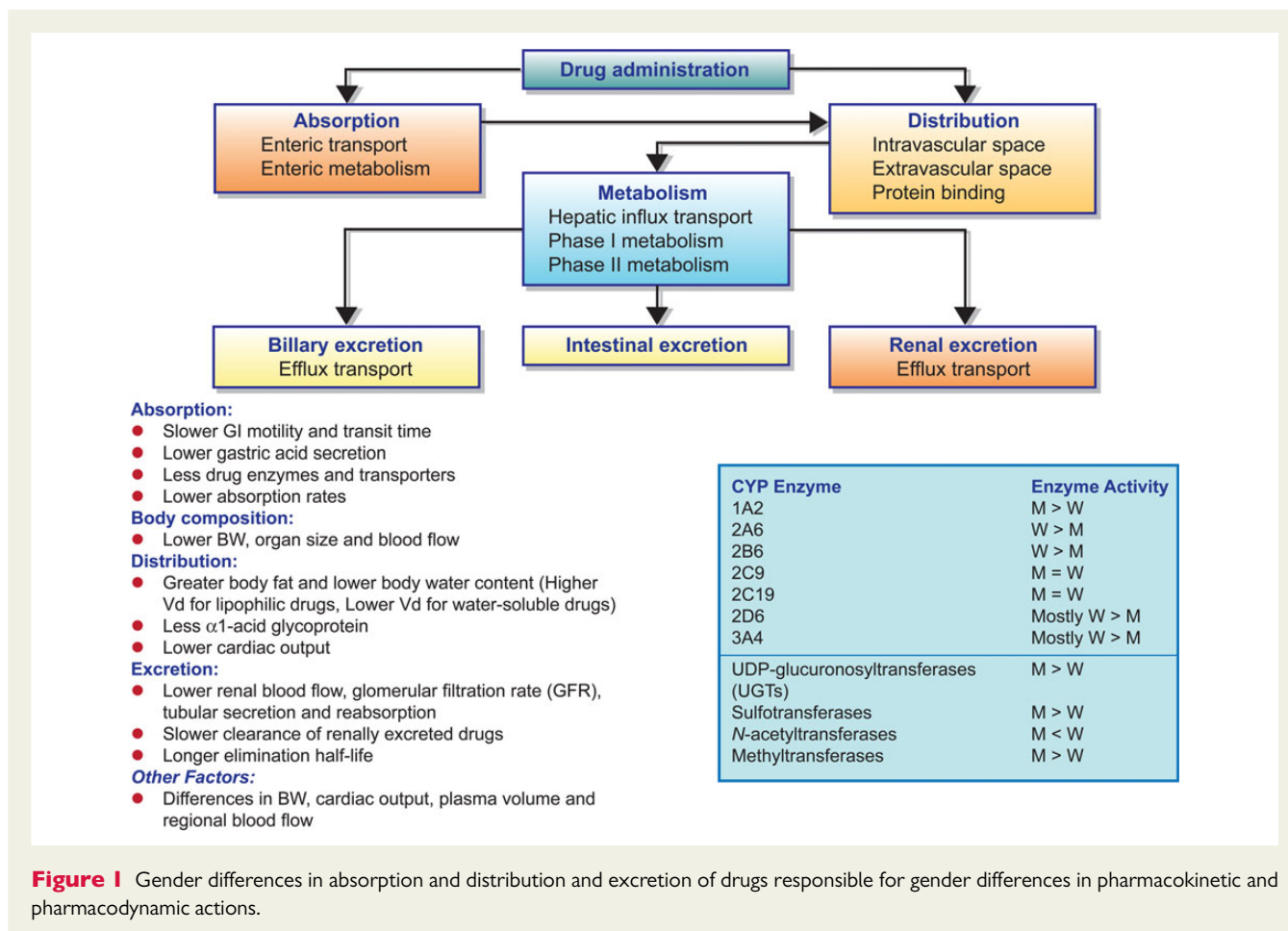
Acetylsalicylic acid

Aspirin has been suggested to be more active in male than in female platelets, although studies have shown that women have a similar decrease in platelet reactivity after low dose aspirin therapy than men.

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The benefits of aspirin in secondary prevention are well documented in both sexes.⁶ Although the effect of aspirin in primary prevention is more controversial, an analysis of primary prevention studies found that aspirin lowered the risk of stroke but not of myocardial infarction (MI) or CV death in females whereas in men aspirin reduced the risk of MI but not the risk of stroke.^{6,7} No gender difference in the risk of bleeding has been reported.

Digoxin

The effects of digoxin on CV mortality and morbidity seem to be sex-dimorphic. 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.⁸ The increased risk of death among women was possibly related to the relatively excessive dosage of digoxin. Although the increased mortality was correlated to the higher serum digoxin concentrations,⁸ sex-based differences in digoxin PK were absent when actual or ideal body weight was used.

Beta-blockers

Although it is known that plasma levels of beta-blockers do not always correlate with therapeutic efficacy, women present higher plasma level of metoprolol and propranolol due to a slower Cl and lower Vd, which results in a greater reduction in exercise heart rate and systolic blood pressure than men. However, metoprolol

might exert a greater therapeutic effect on stress-induced angina pectoris in men than in women in spite of higher plasma levels in females.⁹ Drug exposure to metoprolol is further increased under therapy with oral contraceptives.

Despite some trials suggested that beta-blockers improved survival only in males, but not in females, with hypertension or heart failure several a meta-analysis confirmed that beta-blockers produced a similar survival benefit in heart failure or after MI in both sexes.¹⁰

Inhibitors of the renin-angiotensin-aldosterone system

Because of their potential teratogenic effects drugs acting on the RAAS are not recommended for use in women during childbearing years unless specific contraceptive measures are put in place. This may potential impact the recruitment of young and middle aged women in clinical trials testing drugs acting on the RAAS.

No sex-differences have been described in the PK or in the antihypertensive effects of ACE-inhibitors (ACEI), angiotensin-receptor blockers (ARB) and aliskiren.⁴ Although in early heart failure trials the reduction in mortality and in heart failure requiring hospitalization with ACE-I were observed in men, but not in women, a meta-analysis found comparable effects in males and females.¹¹ As for ARB, relevant gender-specific PK differences have not been observed for most of the AT1 receptor antagonists, although the clinical studies enrolled <30% of women.¹² The ELITE study¹² showed a

similar effects in men and women treated with Losartan, and the CHARM study found similar reduction in CV death or hospitalization associated with the use of candesartan.

In patients with acute MI and left ventricular dysfunction, the EPHEsus trial showed a trend towards greater benefit for 30-days all-cause mortality in females treated with eplerenone,¹³ while no differences were observed in the RALES trial with spironolactone.¹⁴

Statins

Plasma concentrations of statins are generally 15–20% higher in women than in men, but dose adjustments are not necessary. Lipophilic statins (i.e. lovastatin, simvastatin, fluvastatin, atorvastatin, and pitavastatin) undergo first-pass metabolism in the liver, through reactions catalyzed by cytochrome P450 3A4 (CYP3A4).⁴ Women, however, have higher concentrations of CYP3A4 and therefore are more capable of metabolizing these statins.⁴

In secondary prevention trials statins reduce the risk of CV events to a similar extent in women and men, the effect of statins in primary prevention is less evident in women.¹ The risk of adverse drug reactions is greater in women.

Calcium-channel blockers

Gender-specific PK differences have been described for verapamil, nifedipine, and amlodipine. Oral clearance of verapamil and amlodipine are faster in females compared with men, probably due to the higher activity of CYP3A4 or lower activity of P-gp in females.¹⁵ Although amlodipine exhibited greater antihypertensive effect and higher incidence of oedema in females than in men, major hypertension trials with calcium-channel blockers found no evidence for gender-specific differences in outcomes.

Thrombolytics, antithrombotics, and anticoagulants

In a meta-analysis of patients with non-ST elevation acute coronary syndromes a treatment benefit for GPIIb/IIIa was observed in men but not in women,¹⁶ because of gender differences in risk profile. Similar benefit from thrombolytic therapy for acute MI is observed in the two sexes, but women show a higher incidence of haemorrhagic stroke.

Warfarin dosage is strongly associated with gender and women required less milligram per week than men, the older women requiring the lowest doses. Exogenous oestrogen and testosterone influence warfarin protein binding and therefore dosing adjustment is required when replacement therapy is initiated.

There are limited data regarding gender differences in the recent trials of novel oral anticoagulants, although ~40% of the patients were women. Dose adjustment was made according to renal function in the Xa inhibitor trials and in certain instances for patient weight, which implies some degree of built-in correction for smaller female patients. There were no significant interactions by gender regarding outcome or safety in these trials.

Gender differences in adverse drug reactions

Sex differences in the incidence of adverse effects (AE) and pharmacotoxicity have been reported for several CV drugs,^{3,4} with women having more AE than men (1.5- to 1.7-fold).⁴ Adverse effect tends to

be more severe in women as they require more often hospital admissions. The higher incidence of AE may be related, at least in part, to a greater use of drugs in women compared with men since increased polypharmacy increases the risk of AE from drug to drug interactions.

Women experience more frequent adverse drug reactions from diuretics (e.g. hyponatremia, hypokalemia, and severe arrhythmias). The peak plasma levels and the area under the curve of plasma levels of torsemide are significantly higher in females than in men, which may explain why in the German Pharmacovigilance Project the majority of hospitalizations due to torsemide occurred in women.¹⁷

Specifically, women have a higher risk of drug-induced torsades de pointes (TdP, 2–2.3-fold greater risk in females) and skin diseases (up to 2-fold), cough with ACE-I (2-fold), haemorrhagic complications with anticoagulants, platelet antiaggregants and thrombolytics, electrolyte abnormalities with diuretics and myopathy with statins.² Females present a longer corrected QT interval (QTc) and two-thirds of drug-induced TdP occur in women, despite equivalent serum concentrations and the men-predominance in usage of antiarrhythmic drugs.¹⁸ Female sex is a primary risk factor for the development of TdP and excess mortality in patients treated with class I and III antiarrhythmic drugs. Sex hormones modulate cardiac K⁺ and Ca²⁺ ion channels involved in ventricular repolarization, oestrogens facilitated bradycardia-induced QT prolongation and the emergence of arrhythmias, whereas androgens shortened the QTc and blunted the QT response to drugs. However, electrophysiological studies have shown that acute estradiol administration stabilises cardiac currents.¹⁹ Several CV and numerous non CV drugs can induce TdP tachycardia and sudden cardiac death. Because of the greater use of drugs in women drug–drug interaction must always be considered since high plasma drug concentrations may represent a predisposing factor to develop AE.

Different gender representation in cardiovascular clinical trials

Women represent only one-third of the study populations. This suggests that the results obtained from most study cannot be fully extrapolated to women especially when different drug dosages are suggested in the different sexes. For future trials, it will be appropriate to size the male and female populations to be studied according to the gender differences, if any, pharmacodynamic effects observed in the earlier phases of drug-development. As a result a deeper understanding of gender differences in CV disease is expected.

Conclusion

Gender differences in PK/PD of CV drugs influence their effectiveness and safety. Future pharmacological studies will need to take into account gender-related differences in PK/PD in order to better size the samples of males and females to be included.

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