Sex and Gender Differences in Cardiovascular Drug Therapy

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Contents

Abstract This chapter outlines sex differences in pharmacokinetics and pharmacodynamics of the most frequently used drugs in cardiovascular diseases, e.g., coronary artery disease, hypertension, heart failure. Retrospective analysis of

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previously published drug trials revealed marked sex differences in efficacy and adverse effects in a number of cardiovascular drugs. This includes a higher mortality among women taking digoxin for heart failure, more torsade de pointes arrhythmia in QT prolonging drugs and more cough with ACE inhibitors. Trends towards a greater benefit for women and/or female animals have been observed in some studies for endothelin receptor antagonists, the calcium channel blocker amlodipine, the ACE-inhibitor ramipril and the aldosterone antagonist eplerenone. However, reproduction of these results in independent studies and solid statistical evidence is still lacking. Some drugs require a particularly careful dose adaptation in women: the beta-blocker metoprolol, the calcium channel blocker verapamil, loop-, and thiazide diuretics. In conclusion, sex differences in pharmacokinetics and pharmacodynamics have to be taken into account for cardiovascular drug therapy in women.

Keywords ACE inhibitors • Angiotensin receptor blockers • Beta-blockers • Calcium channel blockers • Endothelin receptor antagonists • Diuretics • Sex differences

Abbreviations

AT1-R	Angiotensin II type 1 receptor
AT2-R	Angiotensin II type 2 receptor
ACE2	Angiotensin converting enzyme-2
Ang II	Angiotensin II

1 Introduction

Gender differences have been observed in the clinical effects of a number of major cardiovascular drugs and drug families. In general, women are at greater risk than men of experiencing an adverse reaction to medication. In an analysis of 48 cohort studies in Great Britain, Martin and colleagues found a 1.5- to 1.7-fold higher risk for adverse events in women compared to age-matched men (Martin et al. 1998). In the cardiovascular area, more adverse effects in women are consistently reported for QT prolonging drugs, for ACE inhibitors and thrombolytics and sex differences in efficacy have been described for others, as digoxin. Parts of the differences may be related to pharmacokinetics. Women and men differ in body composition, weight, mechanisms of absorption and drug distribution, metabolic enzymes and routes of excretion. In addition, true sex differences in pharmacodynamics are also well described. Ion channel composition of different organs, kidney and heart, differs in women and men. Another part of the difference may be due to the fact that drug development is mainly done in young male animals of a well-selected genetic background. Old males are neglected, as well as pre- and postmenopausal

females. Male and female rodents are usually kept on a diet rich in phytoestrogens that may interfere with drug effects and they are kept in a pathogen free environment that may preclude the detection of interactions of drug effects with an activated immune system. These reductionist approaches impair the development of optimal drugs for subgroups, for elderly women and men, and the successful translation of new drugs to the clinics. Phase 1 and 2 studies also include mainly young men, preventing systematic development of adequate doses for women and the elderly [see Raz and Miller (2012)]. These shortcomes in drug development may contribute to the observed sex and gender differences in drug effects, in addition to the biological differences in pharmacokinetics and pharmacodynamics that are reviewed below.

2 Mechanisms of Sex/Gender Differences in Cardiovascular Drug Response

2.1 Role of Genetic Polymorphisms

Genetic polymorphisms may modify drug response. This has been best documented for some anticancer drugs (Deenen et al. 2011). In the cardiovascular field, genetic polymorphisms have been associated with the response to ACE inhibitors, to the metabolism of beta-blockers and calcium-channel blockers ("poor metabolizers"). Some autosomal gene polymorphisms are associated with cardiovascular phenotypes in a sex-specific manner and the resulting sex differences in phenotypes may lead to sex differences in drug responses. Such genes are related to the renin–angiotensin system (see below), lipid metabolism, homocysteine and folate metabolism and to the phenotypes of blood pressure, longevity, ischemic heart disease, cardiovascular mortality and depression (van Suylen et al. 1999; Linnebank et al. 2005; Kokubo et al. 2005).

Genes that are relevant in the cardiovascular system and that are located on the X-chromosome are also candidates for causing sex/gender differences. Mutations in these genes or functionally relevant polymorphisms might be better compensated in women, who have two copies of the gene, than in men. In addition about 15 % of the X-chromosomal genes are assumed to escape X-inactivation, which could result in higher gene doses in women (Carrel and Willard 2005). Genes for angiotensin converting enzyme-2 (ACE2) (Tipnis et al. 2000) and angiotensin II receptor (AT2R) are located on the X-chromosome. The AT2R has been shown to modulate left-ventricular hypertrophy in women with hypertrophic cardiomyopathy independently of the circulating RAS, but not in men. In women left ventricular mass decreased with the number of C alleles of the AT2R gene A/C(3123) polymorphism suggesting an antihypertrophic effect of AT2 in women (Deinum et al. 2001).

In an impressive number of recently reviewed transgenic animal models, a more severe cardiovascular phenotype developed in male than in female animals, and the

progression of heart failure and death from heart failure occurred earlier in the male animals (Leinwand 2003; Du 2004). Reasons for these sex differences are multiple but also dependent on food intake. In particular, phytoestrogens seem to be relevant (Luczak et al. 2011; Bhupathy et al. 2010) and can modify cardiovascular phenotypes and drug responses in a sex-specific manner. Frequently, the more severe cardiovascular phenotype in male animals or in ovariectomized females can be rescued by the administration of estrogens (Xin et al. 2002). Genes involved in these pathways are also candidates for causing sex/gender differences.

2.2 *Role of Sex Hormones*

Estrogens interact with a large number of cardiovascular drugs [see Spoletini et al. (2012)]. Variation of estrogens and other hormones during the menstrual cycle may modify the response to other drugs. Among others, estrogens interfere with angiotensinogen synthesis in the liver and angiotensin I receptor (AT1R) expression in the myocardium. Furthermore, endogenous estrogens may increase the expression of the angiotensin II receptor (AT2R) in the myocardium (Regitz-Zagrosek et al. 2004).

Progesterones expressed in the cardiovascular system, in the myocardium and great vessels, interact partially synergistically/partially antagonistically with estrogens (Edwards 2005). The effect of progesterone on the action of estrogens in the development of atherosclerosis was studied in ovariectomized rabbits treated with estradiol, progesterone or combined sex hormones. Progesterone was dose dependently able to inhibit the beneficial effects of estrogens in experimental atherosclerosis, suggesting that progesterone exerts a direct inhibitory effect on the athero-protective action of estrogens (Hanke et al. 1996). Furthermore, treatment with progesterone significantly ($P < 0.05$) reduced myocardial infarct area, lipid peroxidation level, activity of myeloperoxidase and inhibited serum CK activity and the incidences of ventricular tachycardia in myocardial ischemia/reperfusion (I/R) injured female rats. These cardioprotective effects have not been observed in ischemic male rats. The protective effect could be mediated by the interaction with endogenous estrogens.

Testosterone is a precursor for estrogen biosynthesis. Therefore, its effects can be mediated by testosterone or directly by estrogens. Sometimes these possibilities are difficult to differentiate. Testosterone affects the cardiovascular system through both genomic and non-genomic mechanisms. In human observational studies, men with lower testosterone levels tended to have a higher incidence of cardiovascular diseases. Supplementation of testosterone has been used for improving performance in patients with heart failure and reducing exertional angina threshold. However, results were not convincing. Adverse effects occur mostly with supraphysiological doses, e.g., in athletes abusing androgens (Kaushik et al. 2010).

Sex differences in drug metabolism are due in part to the female-predominant expression of CYP3A4, the most important P450 catalyst of drug metabolism in human liver. The sexually dimorphic expression of P450s and other liver-expressed genes is regulated by the temporal pattern of plasma growth hormone (GH) release by the pituitary gland, which shows significant sex differences. These differences are most pronounced in rats and mice, where plasma GH profiles are highly pulsatile (intermittent) in male animals versus more frequent (nearly continuous) in female animals (Waxman and Holloway 2009).

Little information is available regarding the effects of the human menstrual cycle or the rat estrous cycle on expression and activity of the CYP-dependent enzyme system. Very recently, Lee et al. determined the expression and activity of CYP-dependent drug-metabolizing enzymes in the liver and ovary during the rat estrous cycle. The results indicated that hepatic and ovarian expression and activity of CYP isoforms, cytochrome b5, and NADPH-dependent CYP reductase were not different between diestrus and proestrus, although serum estradiol concentrations were markedly increased in the proestrus phase. This suggests that the CYP 450-dependent system is not sensitive to changes in the estrous cycle (Lee et al. 2012).

3 Sex/Gender Differences in Cardiovascular Drug Families

3.1 *Digoxin*

In 1997, the Digitalis Investigation Group (DIG) reported the positive results of a randomized trial evaluating the efficiency of digoxin therapy for patients with heart failure, however, without running a sex-specific analysis (DIG 1997). Thereafter, guidelines strongly endorsed the use of digoxin for these patients. However, in a post hoc subgroup analysis, digoxin was associated with a significantly higher risk of death among women taking digoxin compared with those taking placebo, an effect that was not observed in men (Rathore et al. 2002). Dose-related effects, as well as an interaction with hormone replacement therapy, were discussed as potential explanations for this unanticipated result. Higher serum digoxin concentrations were associated with increased crude all-cause mortality in men (Rathore et al. 2003). In women, a similar trend was observed, but did not reach significance because the number of women participating in the study was too small. Subsequently, higher drug serum levels due to reduced distribution volume and lower drug elimination due to reduced glomerular filtration rate (GFR) (Yukawa et al. 1997) leading to drug concentrations in the upper normal range were held responsible for the unfavorable survival effects reported in women.

In the absence of definitive evidence, digoxin plasma concentration should be below 0.8 ng per ml (Rathore et al. 2003). These data reinforce the possibilities of gender-related effects and therefore underscore the need to perform gender-specific analysis and to include sufficient numbers of women in trials (Regitz-Zagrosek 2006).

3.2 *Endothelin Receptor Antagonists*

3.2.1 Sex Differences in the Endothelin System

Endothelin is synthesized in the endothelium, the heart, brain, lung, kidney, and some circulating cells. Since 1988 endothelin-1 (ET-1) is known as an endothelial cell-derived contracting factor. ET-1 is one of the most potent vasoconstrictors and became a target for cardiovascular research with the aim to develop a new drug for the treatment of hypertension in humans. Injection of ET-1 in rats (Mortensen and Fink 1990) as well as in the model of human forearm blood flow (Haynes et al. 1995) showed vasoconstrictor effects with increase in blood pressure and total peripheral resistance in healthy volunteers.

Three endothelin isoforms, such as ET-1, ET-2, and ET-3, are expressed in humans. Endothelial ET-1 acts in an autocrine/paracrine manner to produce its physiological effects on vessels (Iglarz and Clozel 2010). Endothelin concentrations acting on the underlying VSMCs may be several orders of magnitude higher than it is in plasma (Benigni and Remuzzi 1999). Signaling pathways activated by ET-1 and sensitizing the contractile proteins of vascular smooth muscle cells to calcium during contraction are under further investigation (Wirth et al. 2008; Rautureau and Schiffrin 2012). ET-1 is cleared from the circulation by endothelial ETB receptors (Kelland et al. 2010). ET is hydrophilic and unable to cross the plasma membrane, therefore it must bind to specific cell surface receptors.

The type A (ETA) receptor has a higher affinity for ET-1 and ET-2 and less for ET-3. Type B (ETB) receptor affinity is not different to the isoforms. ETA receptors are expressed in vascular smooth muscle cells (VSMCs) and coupled to trimeric G proteins (Galpha q/11 or G alpha 12/13) to induce vasoconstriction and cell proliferation. ETB receptors are found on endothelial cells. The ETA receptor is the predominant receptor subtype in the human coronary vasculature (Saetrum Opgaard et al. 1994). The ability to test the specific actions of ETA and ETB is limited because selective agonists are only available for ETB, although antagonists have been developed for both receptors (Pollock 2010).

Sex differences have been shown concerning the function of human ETB receptors. Forearm skin blood flow was measured in male and female volunteers after perfusion of an ETB receptor antagonist and sodium nitroprusside. In men, ETB receptors mediated tonic vasoconstriction but in women tonic vasodilatation. Thus, the contribution of ETB receptors to resting cutaneous vascular tone differs between men and women (Kellogg et al. 2001). Stauffer et al. assessed forearm blood flow in response to intra-arterial infusions of endothelin-1 (ET-1), or a selective ETA or ETB receptor antagonist by venous occlusion plethysmography in 21 women and 25 men. Middle-aged and older men were under greater ETA receptor-mediated vasoconstrictor tone than age-matched women. There was no difference in the vasoconstrictor response to ET-1 between the sexes (Stauffer et al. 2010). Sex difference in vasoconstrictor tone could be a mechanism contributing to the higher prevalence of cardiovascular diseases in middle-aged and older men than

women. Furthermore, the contractile response to ET-1 appears to be modulated by the relative density and distribution of ETA and ETB receptors. Analysis of binding data with endothelium-intact saphenous vein samples obtained from patients undergoing coronary artery bypass graft surgery showed lower endothelin binding capacities of ETA and ETB receptors in women compared to men. In addition, ET-1 induced contractions were twofold higher in men than in women (Ergul et al. 1998). These results indicate sex differences in the ratio and density of ET receptors, which might be an important factor in the regulation of the contractile response of vessels and explain greater vasoconstrictor tone in men.

Further evidence suggests that more differences between the sexes in the endothelin system are modulated by sex hormones: Ovarian hormones reduce ET-1 production and effects. 17ß-estradiol attenuates ET-1 induced coronary artery constriction both in vivo (Lamping and Nuno 1996) and in vitro (Sudhir et al. 1997). Plasma ET-1 levels are higher in men than in age-matched women and testosterone administration in transsexual female patients increases plasma ET-1 levels (Polderman et al. 1993). Estrogen replacement therapy and pregnancy, where estrogens levels are high, decrease ET-1 plasma levels (Best et al. 1998).

Genetic hypertensive animal models treated with ETA- or ETA/ETB receptor antagonists and normalization of blood pressure might suggest that ET participates in the pathophysiology of hypertension. However, blood pressure of ETA knockout mice is high and overexpression of ET-1 or human preproET-1 (transgenic mouse models) is associated with normal blood pressure. In animal models, ET-1 is only responsible for the hypertrophic arterial remodeling when animals are exposed to high salt intake like Dahl salt-sensitive rats and deoxycorticosterone salt-treated rats and mice (Schiffrin 2005). ETB receptor-deficient rats (spotting-lethal rats) are marked by severe salt-sensitive hypertension (Gariepy et al. 2000).

The impact of gene polymorphisms on blood pressure and on the change in blood pressure in humans during antihypertensive treatment has been studied by Hallberg et al. (2004). Preproendothelin-1 mRNA is expressed by human cardiomyocytes and interstitial cells that synthesize and secrete mature ET-1 (Plumpton et al. 1996). ETA and ETB receptors are present in the human myocardium (Molenaar et al. 1993). A G5665T gene polymorphism of preproendothelin-1 has been shown to be associated with higher blood pressure in overweight patients. Patients carrying the T-allele have higher blood pressure than those with the G/G genotype (Iglarz et al. 2002; Tiret et al. 1999). The study of Hallberg et al. suggests a sex-specific relationship between the G5665T preproET-1 polymorphism and the degree of reduction of systolic blood pressure during antihypertensive treatment with the AT1-receptor antagonist irbesartan and the ß1-blocker atenolol. The authors determined the preproET-1 genotype in 102 patients with essential hypertension and LV hypertrophy, randomized to treatment with either irbesartan or atenolol. Carriers of the T-allele responded on average with a more than twofold greater reduction of systolic blood pressure than those with the G/G genotype. This genetic difference was only seen in men. In women no statistically significant differences in blood pressure change have been observed between G/G genotypes and carriers of the T-allele.

3.2.2 Endothelin Receptor (ET) A and ETB Antagonists

The first dual ETA- and ETB receptor antagonist, bosentan, could decrease blood pressure in patients with essential hypertension. However, bosentan as well as other ET receptor antagonists was not successful for the treatment of hypertension or heart failure. The Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1) trial (Lechat et al. 1998) and the Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) study (Coletta et al. 2002) were terminated prematurely because of early worsening of heart failure, an increase in concentrations of liver enzymes and lack of improvement in clinical outcomes. However, endothelin receptor antagonists were useful treatment of portopulmonary hypertension (Kahler et al. 2011). In addition, bosentan, sitaxsentan, atrasentan, and clazosentan are indicated for the management of pulmonary artery hypertension, a condition that predominantly affects women. Clazosentan has been developed initially for treatment of subarachnoid hemorrhage. After infusion of clazosentan plasma levels have been 18 % higher in females compared with males, mainly attributable to a difference in clearance (van Giersbergen et al. 2007).

3.3 *Beta-Blockers*

Beta-blockers are cornerstones in the treatment of heart failure. Women have so far been a minority in clinical trials testing beta-blockers for this indication, representing 20–30 % in the first major trials (Jochmann et al. 2005). Two major trials, the MERIT-HF (metoprolol CR/XL) study and the COPERNICUS trial, failed to find a beneficial effect on mortality in women (MERIT-HF 1999; Packer et al. 1996). In a detailed gender-specific analysis for the CIBIS II study, women profited significantly from treatment with bisoprolol (Simon et al. 2001; CIBIS-II 1999), which had a greater unadjusted effect on all-cause mortality in women than in men. Pooling of mortality results from MERIT-HF, CIBIS II, and COPERNICUS showed survival benefits in both women and men (Ghali et al. 2002). The lack of evidence in some large beta-blocker studies is therefore probably due to the under-representation of women in the trials.

Sex-specific differences in the pharmacokinetics of beta-blockers lead to greater drug exposure in women and frequent reports of drug toxicity in females (Luzier et al. 1999). Drug-metabolizing hepatic enzymes like cytochromes and P-glycoproteins are differently expressed in women and men. 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 (Labbe et al. 2000; Tanaka and Hisawa 1999). In addition, women display lower distribution volumes for metoprolol, leading to increased plasma concentrations in women compared to men. Propranolol reaches plasma levels that are up to 80 % higher in

women compared to men. Moreover, oral contraceptives can interact with metoprolol and further increase its plasma levels (Kendall et al. 1982). Accordingly, women suffer from adverse effects when beta blocker dosage is not adequately adjusted (Walle et al. 1994).

Evidence exists that deficiency of sex hormones like estrogens up-regulates myocardial ß1-receptors. Estrogen supplementation can prevent this. Consistently endogenous estrogens reduce cardiac sympathetic response to catecholamines.

Metoprolol is administered as a racemic mixture *S*-metoprolol, that possesses the predominant ß1 blocking actions of this drug. Women have a greater exposure corresponding to a lower clearance of metoprolol enantiomers compared to men. This resulted in a greater reduction in exercise heart rate in women (Luzier et al. 1999). Approximately 85 % of an administered dose of metoprolol is metabolized into three major metabolites: α-hydroxymetoprolol (10 % of the administered dose), *O*-desmethylmetoprolol, and deaminated metoprolol (Lennard 1985). The α-hydroxylation pathway is exclusively mediated by CYP2D6 (Lennard et al. 1983). Administration of diphenhydramine, a prototype classic antihistamine, results in a greater inhibition of clearance of CYP2D6 substrates, like metoprolol, with a resulting higher risk of pronounced pharmacological and adverse effects in women compared to men (Sharma et al. 2010).

Sex differences in the systemic response to adrenoreceptor antagonists during sympathetic activation have been described in a forearm plethysmography study. Enhanced β(2)-adrenergic stimulation in women leads to attenuation of noradrenaline-mediated vasoconstriction. Isometric forearm contraction increased heart rate and mean arterial pressure in both sexes. The ß-blocking agent esmolol attenuated the rise in mean arterial pressure in men but not in women. This study supports findings of sex differences in adrenergic responsiveness and suggests that it is systemically relevant (Coulson and Cockcroft 2011).

Since the pharmacological actions of ß-blockers are also mediated by blocking effects on Ca(2+)-channels, Na(+)-channels and various native cardiac K(+) channels, sex differences in the response to ß-blocking agents could be due to sex differences in ion channel compositions of the myocardium.

3.4 *Calcium-Channel Blockers*

Two main types of calcium-channel blockers are the "non-dihydropyridine-type" like verapamil and the "dihydropyridine-type" like amlodipine and nifedipine. Verapamil is a calcium ion influx inhibitor with antiarrhythmic, antianginal and antihypertensive properties (Gupta et al. 1995). This is a drug with a high first-pass metabolism including the intestinal and hepatic drug metabolizing enzymes cytochrome P450, especially CYP3A4. Verapamil is also known as a substrate for the human MDR1 (multidrug-resistance gene 1) gene product P-glycoprotein (P-gp). Women have only one-third to one-half of the hepatic P-gp level of men resulting in increased intrahepatocellular substrate (verapamil) availability and increased

hepatic CYP3A4 metabolism (Meibohm et al. 2002). The active metabolite is norverapamil. After administration of a single 80-mg oral dose verapamil 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 (Dadashzadeh et al. 2006). The authors conclude 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 (Ueno and Sato 2012). Further pharmacokinetic parameters differed by sex like the significantly shorter verapamil half-life (t1/2) and mean residence time in women than men. These data support the finding of faster elimination of oral verapamil in healthy women. Higher activity of CYP3A4 in women compared with men has been reported for different drugs (Wolbold et al. 2003). Cytochrome P450 isoforms in humans show moderate differences in activity for CYP2E1 and CYP1A2 (higher in men than women) but a female predominant expression and activity of the most clinically relevant human isoform CYP3A. Pharmacokinetic studies investigating the influence of sex steroid hormone levels on CYP3A4 activity are mainly done with rodents or in vitro, e.g., progesterone has been shown to increase CYP3A4 activity (Kharasch et al. 1997). These results could be very interesting for explanation of sex differences in drug metabolism but it should be considered that rodent CYP isoforms are different from human isoforms.

Results of previous studies concerning sex differences of verapamil treatment were inconclusive. This could be explained with the complexity of pharmacokinetics because of individual variations, alternative pathways in the metabolism of CYP3A4 substrates, route of drug administration, and differences in competition for transport mechanisms (Ueno and Sato 2012). One point extensively discussed concerning sex-related differences in verapamil metabolism has been the oral versus intravenous route of drug administration. Krecic-Shepard et al. reported 2000 that verapamil oral clearance was faster in men compared with women administered as either a sustained release or a regular release formulation (Krecic-Shepard et al. 2000a, b). Previously, this group and others reported of faster clearance of intravenously administered racemic verapamil, R-verapamil and S-verapamil, in women (Krecic-Shepard et al. 1999; Dilger et al. 1999). As mentioned earlier, Dadashzadeh et al. (2006) demonstrated a faster elimination rate of verapamil in female than men following single oral dose of 80 mg verapamil. It is possible that the sex differences observed could be due to differences in intestinal P-gp activity, which has not been investigated in human beings. Sex differences in CYP3A or P-gp in the gut counterbalance the sex-related effects in the liver. Sex-related dietary or hormonal differences could also play a role (Rosenberg 1991; Lown et al. 1997). Continued attention should be drawn to the role of intestinal factors determining in vivo pharmacokinetics after oral drug dosing. Cummins et al. (2002) determine that drugs that are substrates for both CYP3A4 and P-gp typically had higher clearance values in women, whereas drugs that were metabolized by CYP3A4 but not transported by P-gp did not exhibit sex-related differences. It is obvious that the data obtained from healthy subjects and the findings of sex-related differences in drug metabolism need to be confirmed in patient groups.

It is not clear whether the pharmacokinetic differences among calcium channel blockers have relevant clinical impact. The major hypertension trials with calcium channel blockers like The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Invention as a Goal in Hypertension Treatment (INSIGHT), Systolic Hypertension in Europe (Syst-Eur) trial, the Swedish Trial in Old Patients with Hypertension-2 (STOP-Hypertension-2) study, and Nordic Diltiazem (NORDIL) study have revealed no evidence for gender differences in outcomes. On the other hand, the data of the Amlodipine Cardiovascular Community Trail (ACCT) trial showed that therapy with amlodipine resulted in more pronounced blood pressure reduction in women than in men. However, this effect depended on whether women used hormone replacement therapy. The Hypertension Optimal Treatment (HOT) study demonstrated a trend toward a decreased rate of myocardial infarction in women with low diastolic blood pressure treated with felodipine.

Amlodipine, a dihydropyridine-type, long-acting calcium channel antagonist, has been extensively assessed in several studies. In contrast to verapamil it has low rates of first-pass metabolism, high bioavailability, is metabolized by several CYP pathways and is not considered to be a P-gp substrate. Kloner et al. (1996) compared amlodipine effects in men and women with mild to moderate hypertension in a prospective study. More women responded with decreased diastolic blood pressure to amlodipine therapy than men. The authors also reported that women had a higher incidence of edema, although this was combined with a greater therapeutic response. Considering the older population, faster clearance of oral administered amlodipine in women compared to men was observed (Kang et al. 2006). These data are similar to that for many other substrates of CYP3A4 due to a greater decrease in CYP3A4 in older men compared with women of the same high age (Greenblatt et al. 2004). The sex differences seem, however, to be small and further evidence is needed to support clinical relevance.

3.5 Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors are part of evidence-based therapy of heart failure and hypertension (BP). In several multicentre studies, e.g., CONSENSUS I, SAVE, and SOLVD, ACE inhibitors led to much smaller mortality reductions in women compared with men. However, these studies were not powered to detect gender differences and only small percentages of women were included (Regitz-Zagrosek 2006). A meta-analysis including 7,105 heart-failure patients claimed that the effects were comparable in women and men, but detailed data by gender were not included (Garg and Yusuf 1995). Later trials, such as AIRE and HOPE, showed a significant benefit of ACE inhibition in women, especially with regard to the secondary prevention of cardiovascular events in high-risk patients (Regitz-Zagrosek 2006). However, the "Second Australian National Blood Pressure Study" (ACE inhibitors versus diuretics) demonstrated a significant

reduction in cardiovascular events in men, but not in women, despite similar reductions in blood pressure in both sexes (Wing et al. 2003). A recently published study has demonstrated that the use of ACE inhibitors is associated with a significant decrease in overall mortality and cardiovascular events in patients with diastolic heart failure (Wu et al. 2010). Despite 32–42 % women have been included in the study groups detailed data by gender are missing. Pharmacokinetics of captopril and lisinopril exhibited no significant sex-specific differences in healthy volunteers (Massana et al. 1997; Saenz-Campos et al. 1996). However, higher plasma levels of ramipril occurred in women than in men, due to women's lower body weight when taking the same dose of 5 mg (Vree et al. 2003).

Adverse effects of ACE inhibitors, especially a typical dry cough are more frequent in women than in men (Mackay et al. 1999; Gibson 1989; Os et al. 1992). Cough occurs within hours of the first dose or weeks or months after the initiation of the treatment. ACE-inhibitor-induced cough has been related not only to the sex of the patient, but also to tobacco habits, ethnicity, and comorbidities and seems to be dose independent. The role of angiotensin-converting enzyme in the metabolism of kinins, mainly bradykinin, has been proposed as a pathogenic mechanism (Kawakami et al. 1998). Bradykinin has been shown to induce the production of proinflammatory metabolites, such as prostaglandins and nitric oxide, which could promote cough (Trifilieff et al. 1993). Very recently, Mas et al. identified genetic polymorphisms in bradykinin receptors (BDKRB2) and ABO genes, related to ACE levels, being associated with ACE-inhibitor-induced cough. The effect of polymorphisms in ABO is sex specific. These results provide ABO as a good candidate gene for pharmacogenetic studies of ACE-inhibitor-related cough (Mas et al. 2011).

Estrogens elevate angiotensin II (Ang II) plasma levels and reduce via negative feedback ACE and renin activity (Fig. 1). Expression of the angiotensin II type 1 receptor (AT1-receptor) is decreased (Fischer et al. 2002; Harrison-Bernard et al. 2003). Premenopausal women may benefit from an estrogen-induced inhibition of the renin–angiotensin system (RAS). Whether this contributes to the relative protection of premenopausal women from cardiovascular events remains to be determined.

The RAS is a key regulator of blood pressure. Endogenous RAS activity differs between men and women (Zapater et al. 2004). Animal models are potentially useful to examine the mechanisms leading to differential blood pressure responses in males and females. Male Sprague–Dawley rats (Tatchum-Talom et al. 2005) and also male mice (Xue et al. 2005) have a greater pressure increase after chronic infusion with Ang II when compared to female rodents. After gonadectomy this response was abrogated in mice (Xue et al. 2005).

Treatment of SD rats with the ACE inhibitor enalapril reduced blood pressure to a greater extent in female than in male rats (Sartori-Valinotti et al. 2008). Venegas-Pont et al. tested whether female C57BL/6J mice also exhibit a greater blood pressure response to ACE inhibition during chronic Ang II: Male and female

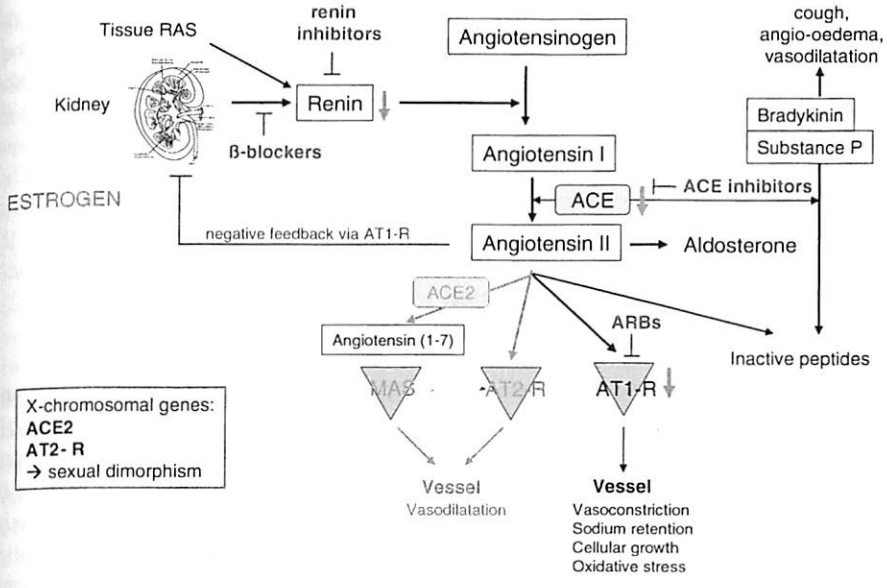

Fig. 1 Estrogens, sex, and RAS—schematic representation of estrogen (E2) effects and sexual dimorphisms (*green*) and effects of interfering drugs (*red*) on the renin–angiotensin system (RAS). Hepatic angiotensinogen synthesis can be regulated by E2. The major peptide angiotensin (Ang) II exerts its main actions by binding to the angiotensin 1-receptor (AT1-R) which is reportedly down-regulated by E2 in some cardiovascular tissues. Some Ang II effects may result from binding to the receptor AT2. Ang II can be further cleaved by angiotensin-converting enzyme 2 (ACE2) into angiotensin-(1–7) which exerts mainly vasodilating effects through its receptor MAS. ACE2- and the AT2-R genes are located at X chromosome and may therefore exhibit higher or more stable expression in women. Polymorphisms of RAS genes are candidates for sexual dimorphic effects of RAS activation. *Dashed lines* refer to experimental data that need further confirmation. *AT1-R* angiotensin II type 1 receptor, *AT2-R* angiotensin II type 2 receptor, *ACE2* angiotensin converting enzyme-2, *ARBs* angiotensin receptor blockers, *MAS* mas receptor

mice, treated with enalapril, were assigned to groups receiving either Ang II or saline for 2 weeks. Blood pressure was higher in male mice than female mice treated with enalapril and Ang II and blood pressure was not different between mice treated with enalapril alone (Venegas-Pont et al. 2010). These experiments show that males exhibit higher blood pressure than females in response to Ang II even during blockade of the endogenous ACE (Venegas-Pont et al. 2010). The mechanisms responsible for the dimorphic blood pressure response are not clear. Another model of Ang II-induced hypertension in rats during ACE inhibition showed that the sex differences were modulated by salt intake. Female rats fed a low-salt diet during ACE inhibition exhibited a greater blood pressure response to Ang II than males. When the same rats were fed a high-salt diet during ACE inhibition, the blood pressure response to Ang II was greater in male rats compared with females (Guo et al. 2008). In contrast to the study in rats, male mice fed a normal-salt diet and treated with enalapril exhibited a greater blood pressure

response to chronic Ang II when compared to female mice (Venegas-Pont et al. 2010). These data suggest that there are sex-specific and species differences in the mechanisms of the blood pressure response to Ang II with or without ACE inhibition. Because endogenous production of Ang II may not be the responsible factor for the dimorphic blood pressure effects in mice, scientists discuss about a differential expression or regulation of Ang II type 1 (AT1) receptors.

3.6 *Angiotensin II Receptor Blockers*

Major studies have investigated the effects of AT1 receptor antagonists. Losartan Intervention for Endpoint Reduction in Hypertension (LIFE), Evaluation of Losartan in the Elderly (ELITE II), and Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) tested losartan for the treatment of hypertension, in the elderly and after myocardial infarction. Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) and Valsartan Heart Failure Trial (Val-HeFT) investigated valsartan for hypertension and heart failure, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) has been conducted with candesartan and patients with heart failure and I-PRESERVE (Irbesartan in heart failure) analyzed irbesartan in heart failure, for example. These studies found no gender-specific differences and showed the same safety profile in both sexes. It should be considered that these studies included fewer women than men with the exception of LIFE (54 % women). In addition, propensity-score matching was preferentially used for statistical analysis in these trials. Propensity-score matching adjusts for differences in all covariates as well as for sex and will only lead to the detection of sex differences if this is specifically the aim of the investigation. To detect sex differences, prespecified subgroup analyses for sex differences in treatment groups would have been more useful. Ofili et al. (2008) published a post hoc analysis of the Irbesartan/Hydrochlorothiazide Blood Pressure Reductions in Diverse Patient Populations (INCLUSIVE) trial. Treatment with irbesartan/hydrochlorothiazide (HCTZ) combination therapy was associated with significant reductions in both systolic and diastolic blood pressure values in women, including "difficult-to-treat" female subgroups, such as the elderly, African Americans, and those with type II diabetes mellitus (Ofili et al. 2008). Systolic and diastolic blood pressure reduction in women was similar to those obtained in the male population of this trial (Saunders et al. 2008) arguing against major sex differences in Irbesartan effects.

Although clinical data do not show any major sex differences concerning the effects of angiotensin receptor blockers, experimental data suggest sex-specific differences in response to renin–angiotensin system activation. It should be noted that results of experimental data could be species dependent and not transferrable to human conditions in all cases. Ang II acts via two main subtypes of receptors, the

angiotensin II type 1 receptor (AT1-R) responsible for vasoconstriction, sodium reabsorption and cell proliferation and the angiotensin II type 2 receptor (AT2-R) characterized by vasodilatation and antiproliferation in humans (Berry et al. 2001; You et al. 2005) (Fig. 1). AT1-R isoforms as well as AT2-R expression differ in rat and human. Sampson et al. hypothesized that chronic administration of Ang II may affect arterial pressure in females differently from males. The group examined the effect of AT2-R blockade on the hemodynamic response to chronic low-dose Ang II treatment in male and female rats (Sampson et al. 2008). The findings suggest an increase in the vasodilatory effects of the RAS in female compared with male rats (Sampson et al. 2008). The hypotensive response to Ang II in female rats agrees with previous data suggesting that the AT2R mediates vasodilatation in both in vitro and in vivo studies (You et al. 2005). Furthermore, basal left ventricular expression and renal AT2R mRNA expression are markedly greater in females as compared with males (Sampson et al. 2008). The AT2R gene is located on the X chromosome. It is speculated that the transcription or expression of this gene would have a greater impact in females compared with males, given that they have two copies of the gene (Lazard et al. 1994). One alternative reason for the shift in balance to vasodilatation in females could be the effects of sex hormones. Sex steroids play an important role in the modulation of ATR function. Estrogens decrease AT1R expression, ovariectomy increases AT1R expression (Nickenig et al. 1998; Zheng et al. 2006) and estrogens upregulate AT2R expression (Armando et al. 2002).

Another finding contributing to the hypothesis that female sex shifts the balance of the RAS toward vasodilatation is the upregulation of the renal ACE2 mRNA. This effect occurs in both sexes but to a greater extent in female rats (Sampson et al. 2008). ACE2 cleaves Ang II into angiotensin-(1–7), which exerts its effects through its Mas receptor. The actions mediated by the Mas receptor and the AT2-R oppose the actions of the AT1-R in vessels. The Mas receptor contributes to vasodilatation and vascular protection, is known for antifibrotic and antiproliferative effects, and reduces proinflammatory cytokines in animal studies (Clarke and Turner 2012).

The complex role of the kidney in arterial pressure regulation and the response to Ang II and salt intake deserve further attention. The mechanisms responsible for postmenopausal hypertension in women and the greater salt sensitivity of blood pressure in men than in premenopausal women are not completely understood. In Dahl salt-sensitive rats, high-salt diet increases blood pressure more in males than in females. In this model, the systemic RAS is suppressed in response to high salt in male rats and intrarenal angiotensinogen expression is increased. Testosterone replacement in castrated rats increased blood pressure and renal angiotensinogen. Thus, testosterone may contribute to the development of hypertension in male Dahl salt-sensitive rats on high-salt diet through activation of the intrarenal RAS (Yanes et al. 2009). In addition, the increase of vasodilatory components of the RAS (AT2-R and ACE2) in female rats may also contribute to the sex differences observed in response to RAS activation. The enhancement of the vasodilator pathway of the RAS may be one mechanism for the relative cardiovascular protection in females.

3.7 Renin Inhibitors

Renin inhibitors block the renin–angiotensin system at its origin, by the inhibition of renin. Renin cleaves angiotensinogen to Ang I and ACE converts Ang I into Ang II. ACE inhibitors activate renal renin secretion since they interrupt the normal feedback suppression of renin secretion by circulating Ang II levels. The sequence of renin differs between species. Preclinical studies must be done in primates or in rat models transgenic for human renin and angiotensinogen.

Aliskiren is the first non-peptide active renin inhibitor with a sufficient oral bioavailability, specificity and efficacy. Aliskiren monotherapy (150 and 300 mg) provided equally effective, dose-dependent blood pressure lowering in women and men with mild-to-moderate hypertension. A pooled analysis of eight studies with aliskiren in hypertensive women demonstrated blood pressure lowering also in the elderly, obese or those with metabolic syndrome (Gradman et al. 2010).

A pooled analysis of 17 clinical studies demonstrated small effects of sex on the pharmacokinetics of aliskiren in healthy volunteers. The area under the aliskiren plasma concentration–time curve (AUC) was 22 % and the peak aliskiren plasma concentration (C_{max}) was 24 % lower in men than in women (Jarugula et al. 2010). The authors conclude that gender and differences in body weight are unlikely to have a clinical impact on the efficacy of aliskiren because the higher body weight of men is associated with the reduction in systemic exposure. Furthermore, analysis of clinical studies in patients with hypertension demonstrated no significant differences in the effect of aliskiren to inhibit plasma renin activity and blood pressure effects (Jarugula et al. 2010). The incidence of cough was low (<2 %) in both women and men, although cough was more frequent in women than in men at 300 mg aliskiren. Thus, there is no evidence for significant gender differences in aliskiren effects.

3.8 Aldosterone Receptor Antagonists

Aldosterone receptor antagonists are used as novel therapeutic elements in addition to ß-blockers and ACE inhibitors or angiotensin II receptor blockers (ARBs) for the management of severe systolic heart failure. Eplerenone is similar to the diuretic spironolactone though it is more specific for the mineralocorticoid receptor with minimal effects at other steroid receptors, thereby minimizing many of the hormonal adverse effects. Eplerenone reduces mortality and improves post-myocardial infarction (MI) remodeling in humans (Pitt et al. 2003). Whether these effects are modulated by gender is unclear. The major clinical trial of eplerenone in patients with acute MI and left ventricular dysfunction EPHESUS showed a trend towards a greater benefit for women, treated with eplerenone, at 30 days all-cause mortality analysis compared with men ($p = 0.089$). These results were not verified at 16 months (Pitt et al. 2003). The RALES trial published some years before

investigated the effect of spironolactone on symptomatic heart failure patients without any difference in a treatment benefit between men and women (Pitt et al. 1999). However, just 30 % of the patients enrolled have been women and the trial was not powered to detect gender differences.

Because aldosterone and estrogen signaling pathways interact, mediated through a common pathway involving protein kinase C (PKC-α) (Harvey et al. 2001), the question still remains if aldosterone blockade may depend on sex. Male and female infarcted rats receiving eplerenone or placebo have been investigated for left ventricular remodeling and gene expression. Eplerenone attenuated left ventricular chamber enlargement more effectively in female than in male rats and improved ejection fraction in females. Furthermore, eplerenone also reduced infarct size and cardiac fibrosis in females but not in males (Kanashiro-Takeuchi et al. 2009). Eplerenone preferentially restored altered gene expression to normal in post-MI female rats. Microarrays revealed that in females 19 % of downregulated genes and 44 % of upregulated genes post-MI were restored to normal by eplerenone. In contrast, eplerenone only restored 4 % of overexpressed genes in males. These alterations occurred among others in the renin–angiotensin- and fibrosis-inducing pathways (Kanashiro-Takeuchi et al. 2009).

Eplerenone is primarily metabolized by the cytochrome P450 enzyme CYP3A4. Sex differences in the pharmacokinetics of eplerenone may arise from extensive metabolism in male rats.

3.9 Diuretics

From the database of the German Network of Regional Pharmacovigilance Centres (NRPZ) it is known that women experience more frequently adverse drug reactions associated with diuretics. Data have been collected in urban hospitals between 2000 and 2006. Diuretics caused serious adverse drug reactions in 375 patients, of which 258 occurred in women ($p < 0.001$). The authors considered the fact that physicians prefer to prescribe diuretics to hypertensive women. However, prescription habits in this study could not explain the observed gender difference in the rate of adverse drug reactions (Werner et al. 2008) and additional mechanisms may be involved. Animal studies support the notion that sex-related differences of adverse and therapeutic effects of diuretics may exist. Female rats displayed a significant lower renal clearance of furosemide (loop diuretic), potentially due to the fact that furosemide is a substrate for the renal organic anion transport system (Cerrutti et al. 2002). Furthermore, furosemide as well as torasemide induced diuresis, natriuresis, and kaliuresis more effectively in female rats than in males (Brandoni et al. 2004). Adverse effects like hyponatraemia and hypokalaemia occur more frequently in women than in men taking diuretics, and both of these electrolyte disturbances have the potential to cause severe arrhythmia. This might suggest the possibility that women will experience more arrhythmia than men especially with more long QT-associated rhythm disturbances. However, this suspicion could not be confirmed

in clinical trials. Nevertheless, this fact should be considered when prescribing diuretics for women with a related risk profile.

Werner et al. identified sex as a potential determinant of torasemide pharmacokinetics and examined the impact of genetic polymorphisms of CYP2C9 and of liver-specific organic anion transporting peptide 1B1 (SLCO1B1) in a patient population with hypertension or heart failure. Torasemide, a loop diuretic, is frequently used for the treatment of these patients. Torasemide is cleared from the circulation mainly by hepatic metabolism, partly through the genetically polymorphic cytochrome P450 enzyme CYP2C9, and also by excretion into the urine. The study demonstrated a significant impact of sex and confirms the impact of the SLCO1B1 SNP on the steady-state pharmacokinetics of torasemide. These observations may in part explain the unbalanced distribution of torasemide adverse drug reactions among males and females (Werner et al. 2010).

For thiazide diuretics few sex differences are published. The density of the thiazide receptor was twofold higher in female Sprague–Dawley rats than in males. Ovariectomy decreased thiazide receptor by more than 20 %. In females the excretion of sodium, chloride and ammonium caused by bendroflumethiazide was greater than in male rats. It can be concluded that the renal excretion of electrolytes is, in part, controlled by sex and sex hormones via their regulation of the renal density of the thiazide diuretic receptor (Chen et al. 1994). Single nucleotide polymorphisms in genes encoding or influencing renal sodium transport systems were investigated in patients with hypertension treated with hydrochlorothiazide. However, most polymorphisms investigated were not associated with significant variation in blood pressure response (Turner et al. 2005).

4 Clinical Implications

Women are at greater risk than men of experiencing an adverse reaction to most cardiovascular drugs. Genetic mechanisms like polymorphisms modifying drug response to ACE inhibitors, beta-blockers, and calcium-channel blockers interfere with the effect of sex hormones and menstrual cycle, age, comorbidities, comedication, and self-medication.

Therefore, a complete drug history should be obtained when treating women. Since women often have lower body weight and/or kidney function compared with men, adequate dosing should be discussed when starting novel drug therapy in women. Creatinine clearance should be calculated in all women with borderline kidney function and drug doses should be adapted to kidney function. This may be particular relevant for digoxin, beta-blockers, diuretics and thrombolytics [see Rauch (2012)]. Doctors should be suspicious for adverse effects of beta-blockers or ACE inhibitors (dry cough more frequent in women than in men). In addition, potential interaction of drugs with endogenous hormones or therapeutically supplied hormones should be checked. It should be considered that there are differences in the adequate dose of drugs between pre- and postmenopausal

women, depending on hormonal status, intestinal uptake, hepatic metabolism and renal function. Polypharmacy in women is more frequently associated with arrhythmias than in men because QT time prolongation is known as an adverse effect of multiple drugs like antibiotics, antidepressants and cardiovascular drugs. EKG control should be performed readily if women are treated with such drugs. Administration of the aldosterone receptor antagonist eplerenone might have advantages for women with heart failure and post-myocardial infarction but there is still no firm evidence available. Adverse effects of diuretics may be particularly relevant for women. In summary, drug treatment of cardiovascular syndromes should be done in consideration of gender-related effects.

Take Home Messages

- Sex-related disparities in pharmacokinetics are common and some but not all of them will lead to clinically relevant differences in adverse effects and efficacy.
- Treatment with digoxin should lead to plasma levels below 0.8 ng per ml for both sexes. Impairment of renal function should be specifically considered in women treated with digitalis.
- Sex differences in the pharmacokinetics of beta-blockers lead to greater drug exposure and more adverse effects in women. Beta-blockers lead to similar survival benefits in heart failure in women and men.
- Sex differences in pharmacokinetics and effects of calcium channel blockers are small. In the elderly, clearance of oral administered amlodipine was faster in women.
- Adverse effects of ACE inhibitors, especially a typical dry cough are more frequent in women than in men.
- The major clinical trial of eplerenone in patients with acute myocardial infarction and left ventricular dysfunction EPHESUS showed a trend towards a greater benefit for women, for 30 days all-cause mortality. Animal studies support sex differences in eplerenone effects.
- Adverse effects like hyponatraemia and hypokalaemia occur more frequently in women than in men taking diuretics, and both of these electrolyte disturbances have the potential to cause severe arrhythmia.

References

Armando I, Jezova M, Juorio AV, Terron JA, Falcon-Neri A, Semino-Mora C, Imboden H, Saavedra JM (2002) Estrogen upregulates renal angiotensin II AT(2) receptors. Am J Physiol Renal Physiol 283:F934–F943

Benigni A, Remuzzi G (1999) Endothelin antagonists. Lancet 353:133–138

Berry C, Touyz R, Dominiczak AF, Webb RC, Johns DG (2001) Angiotensin receptors: signaling, vascular pathophysiology, and interactions with ceramide. Am J Physiol Heart Circ Physiol 281:H2337–H2365

Best PJ, Berger PB, Miller VM, Lerman A (1998) The effect of estrogen replacement therapy on plasma nitric oxide and endothelin-1 levels in postmenopausal women. Ann Intern Med 128:285–288

Bhupathy P, Haines CD, Leinwand LA (2010) Influence of sex hormones and phytoestrogens on heart disease in men and women. Womens Health (Lond Engl) 6:77–95

Brandoni A, Villar SR, Torres AM (2004) Gender-related differences in the pharmacodynamics of furosemide in rats. Pharmacology 70:107–112

Carrel L, Willard HF (2005) X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 434:400–404

Cerrutti JA, Quaglia NB, Brandoni A, Torres AM (2002) Effects of gender on the pharmacokinetics of drugs secreted by the renal organic anions transport systems in the rat. Pharmacol Res 45:107–112

Chen Z, Vaughn DA, Fanestil DD (1994) Influence of gender on renal thiazide diuretic receptor density and response. J Am Soc Nephrol 5:1112–1119

CIBIS-II (1999) The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 353:9–13

Clarke NE, Turner AJ (2012) Angiotensin-converting enzyme 2: the first decade. Int J Hypertens 2012:307315

Coletta A, Thackray S, Nikitin N, Cleland JG (2002) Clinical trials update: highlights of the scientific sessions of The American College of Cardiology 2002: LIFE, DANAMI 2, MADIT-2, MIRACLE-ICD, OVERTURE, OCTAVE, ENABLE 1 & 2, CHRISTMAS, AFFIRM, RACE, WIZARD, AZACS, REMATCH, BNP trial and HARDBALL. Eur J Heart Fail 4:381–388

Coulson JM, Cockcroft JR (2011) Sex differences in the systemic response to adrenoreceptor antagonists during sympathetic activation. Eur J Clin Invest 41:1129–1132

Cummins CL, Wu CY, Benet LZ (2002) Sex-related differences in the clearance of cytochrome P450 3A4 substrates may be caused by P-glycoprotein. Clin Pharmacol Ther 72:474–489

Dadashzadeh S, Javadian B, Sadeghian S (2006) The effect of gender on the pharmacokinetics of verapamil and norverapamil in human. Biopharm Drug Dispos 27:329–334

Deenen MJ, Cats A, Beijnen JH, Schellens JH (2011) Part 4: pharmacogenetic variability in anticancer pharmacodynamic drug effects. Oncologist 16:1006–1020

Deinum J, van Gool JM, Kofflard MJ, ten Cate FJ, Danser AH (2001) Angiotensin II type 2 receptors and cardiac hypertrophy in women with hypertrophic cardiomyopathy. Hypertension 38:1278–1281

DIG (1997) The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. N Engl J Med 336:525–533

Dilger K, Eckhardt K, Hofmann U, Kucher K, Mikus G, Eichelbaum M (1999) Chronopharmacology of intravenous and oral modified release verapamil. Br J Clin Pharmacol 47:413–419

Du XJ (2004) Gender modulates cardiac phenotype development in genetically modified mice. Cardiovasc Res 63:510–519

Edwards DP (2005) Regulation of signal transduction pathways by estrogen and progesterone. Annu Rev Physiol 67:335–376

Ergul A, Shoemaker K, Puett D, Tackett RL (1998) Gender differences in the expression of endothelin receptors in human saphenous veins in vitro. J Pharmacol Exp Ther 285:511–517

Fischer M, Baessler A, Schunkert H (2002) Renin angiotensin system and gender differences in the cardiovascular system. Cardiovasc Res 53:672–677

Garg R, Yusuf S (1995) Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 273:1450–1456

Gariepy CE, Ohuchi T, Williams SC, Richardson JA, Yanagisawa M (2000) Salt-sensitive hypertension in endothelin-B receptor-deficient rats. J Clin Invest 105:925–933

Ghali JK, Pina IL, Gottlieb SS, Deedwania PC, Wikstrand JC (2002) Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). Circulation 105:1585–1591

Gibson GR (1989) Enalapril-induced cough. Arch Intern Med 149:2701–2703

Gradman AH, Weir MR, Wright M, Bush CA, Keefe DL (2010) Efficacy, safety and tolerability of aliskiren, a direct renin inhibitor, in women with hypertension: a pooled analysis of eight studies. J Hum Hypertens 24:721–729

Greenblatt DJ, Harmatz JS, von Moltke LL, Wright CE, Shader RI (2004) Age and gender effects on the pharmacokinetics and pharmacodynamics of triazolam, a cytochrome P450 3A substrate. Clin Pharmacol Ther 76:467–479

Guo S, Kowalewska J, Wietecha TA, Iyoda M, Wang L, Yi K, Spencer M, Banas M, Alexandrescu S, Hudkins KL et al (2008) Renin-angiotensin system blockade is renoprotective in immune complex-mediated glomerulonephritis. J Am Soc Nephrol 19:1168–1176

Gupta SK, Atkinson L, Tu T, Longstreth JA (1995) Age and gender related changes in stereoselective pharmacokinetics and pharmacodynamics of verapamil and norverapamil. Br J Clin Pharmacol 40:325–331

Hallberg P, Karlsson J, Lind L, Michaelsson K, Kurland L, Kahan T, Malmqvist K, Ohman KP, Nystrom F, Liljedahl U et al (2004) Gender-specific association between preproendothelin-1 genotype and reduction of systolic blood pressure during antihypertensive treatment–results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA). Clin Cardiol 27:287–290

Hanke H, Hanke S, Bruck B, Brehme U, Gugel N, Finking G, Muck AO, Schmahl FW, Hombach V, Haasis R (1996) Inhibition of the protective effect of estrogen by progesterone in experimental atherosclerosis. Atherosclerosis 121:129–138

Harrison-Bernard LM, Schulman IH, Raij L (2003) Postovariectomy hypertension is linked to increased renal AT1 receptor and salt sensitivity. Hypertension 42:1157–1163

Harvey BJ, Condliffe S, Doolan CM (2001) Sex and salt hormones: rapid effects in epithelia. News Physiol Sci 16:174–177

Haynes WG, Strachan FE, Webb DJ (1995) Endothelin ETA and ETB receptors cause vasoconstriction of human resistance and capacitance vessels in vivo. Circulation 92:357–363

Iglarz M, Benessiano J, Philip I, Vuillaumier-Barrot S, Lasocki S, Hvass U, Durand G, Desmonts JM, Levy BI, Henrion D (2002) Preproendothelin-1 gene polymorphism is related to a change in vascular reactivity in the human mammary artery in vitro. Hypertension 39:209–213

Iglarz M, Clozel M (2010) At the heart of tissue: endothelin system and end-organ damage. Clin Sci (Lond) 119:453–463

Jarugula V, Yeh CM, Howard D, Bush C, Keefe DL, Dole WP (2010) Influence of body weight and gender on the pharmacokinetics, pharmacodynamics, and antihypertensive efficacy of aliskiren. J Clin Pharmacol 50:1358–1366

Jochmann N, Stangl K, Garbe E, Baumann G, Stangl V (2005) Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. Eur Heart J 26:1585–1595

Kahler CM, Graziadei I, Vogelsinger H, Desole S, Cima K, Vogel W (2011) Successful treatment of portopulmonary hypertension with the selective endothelin receptor antagonist Sitaxentan. Wien Klin Wochenschr 123:248–252

Kanashiro-Takeuchi RM, Heidecker B, Lamirault G, Dharamsi JW, Hare JM (2009) Sex-specific impact of aldosterone receptor antagonism on ventricular remodeling and gene expression after myocardial infarction. Clin Transl Sci 2:134–142

Kang D, Verotta D, Schwartz JB (2006) Population analyses of amlodipine in patients living in the community and patients living in nursing homes. Clin Pharmacol Ther 79:114–124

Kaushik M, Sontineni SP, Hunter C (2010) Cardiovascular disease and androgens: a review. Int J Cardiol 142:8–14

Kawakami Y, Munakata M, Yamaguchi E, Furuya K, Matsuda T (1998) Molecular studies of bronchial asthma, sarcoidosis and angiotensin converting enzyme inhibitor-induced cough. Respirology 3:45–49

Kelland NF, Kuc RE, McLean DL, Azfer A, Bagnall AJ, Gray GA, Gulliver-Sloan FH, Maguire JJ, Davenport AP, Kotelevtsev YV et al (2010) Endothelial cell-specific ETB receptor knockout:

autoradiographic and histological characterisation and crucial role in the clearance of endothelin-1. Can J Physiol Pharmacol 88:644–651
Kellogg DL Jr, Liu Y, Pergola PE (2001) Selected contribution: gender differences in the endothelin-B receptor contribution to basal cutaneous vascular tone in humans. J Appl Physiol 91:2407–2411, discussion 2389–2490
Kendall MJ, Quarterman CP, Jack DB, Beeley L (1982) Metoprolol pharmacokinetics and the oral contraceptive pill. Br J Clin Pharmacol 14:120–122
Kharasch ED, Russell M, Garton K, Lentz G, Bowdle TA, Cox K (1997) Assessment of cytochrome P450 3A4 activity during the menstrual cycle using alfentanil as a noninvasive probe. Anesthesiology 87:26–35
Kloner RA, Sowers JR, DiBona GF, Gaffney M, Wein M (1996) Sex- and age-related antihypertensive effects of amlodipine. The Amlodipine Cardiovascular Community Trial Study Group. Am J Cardiol 77:713–722
Kokubo Y, Iwai N, Tago N, Inamoto N, Okayama A, Yamawaki H, Naraba H, Tomoike H (2005) Association analysis between hypertension and CYBA, CLCNKB, and KCNMB1 functional polymorphisms in the Japanese population–the Suita Study. Circ J 69:138–142
Krecic-Shepard ME, Barnas CR, Slimko J, Gorski JC, Wainer IW, Schwartz JB (1999) In vivo comparison of putative probes of CYP3A4/5 activity: erythromycin, dextromethorphan, and verapamil. Clin Pharmacol Ther 66:40–50
Krecic-Shepard ME, Barnas CR, Slimko J, Jones MP, Schwartz JB (2000a) Gender-specific effects on verapamil pharmacokinetics and pharmacodynamics in humans. J Clin Pharmacol 40:219–230
Krecic-Shepard ME, Barnas CR, Slimko J, Schwartz JB (2000b) Faster clearance of sustained release verapamil in men versus women: continuing observations on sex-specific differences after oral administration of verapamil. Clin Pharmacol Ther 68:286–292
Labbe L, Sirois C, Pilote S, Arseneault M, Robitaille NM, Turgeon J, Hamelin BA (2000) Effect of gender, sex hormones, time variables and physiological urinary pH on apparent CYP2D6 activity as assessed by metabolic ratios of marker substrates. Pharmacogenetics 10:425–438
Lamping KG, Nuno DW (1996) Effects of 17 beta-estradiol on coronary microvascular responses to endothelin-1. Am J Physiol 271:H1117–H1124
Lazard D, Briend-Sutren MM, Villageois P, Mattei MG, Strosberg AD, Nahmias C (1994) Molecular characterization and chromosome localization of a human angiotensin II AT2 receptor gene highly expressed in fetal tissues. Receptors Channels 2:271–280
Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP (1998) Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. Circulation 98:1184–1191
Lee SY, Oh SJ, Yun KU, Kim HM, Kim BH, Lee K, Kim SK (2012) Expression of hepatic and ovarian cytochrome P450 during estrous cycle in rats. Arch Toxicol 86:75–85
Leinwand LA (2003) Sex is a potent modifier of the cardiovascular system. J Clin Invest 112:302–307
Lennard MS (1985) Quantitative analysis of metoprolol and three of its metabolites in urine and liver microsomes by high-performance liquid chromatography. J Chromatogr 342:199–205
Lennard MS, Tucker GT, Silas JH, Freestone S, Ramsay LE, Woods HF (1983) Differential stereoselective metabolism of metoprolol in extensive and poor debrisoquin metabolizers. Clin Pharmacol Ther 34:732–737
Linnebank M, Fliessbach K, Kolsch H, Rietschel M, Wullner U (2005) The methionine synthase polymorphism c.2756Aright curved arrow G (D919G) is relevant for disease-free longevity. Int J Mol Med 16:759–761
Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortlage LA, Brown MB, Guo W, Watkins PB (1997) Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 99:2545–2553
Luczak ED, Barthel KK, Stauffer BL, Konhilas JP, Cheung TH, Leinwand LA (2011) Remodeling the cardiac transcriptional landscape with diet. Physiol Genomics 43:772–780

Luzier AB, Killian A, Wilton JH, Wilson MF, Forrest A, Kazierad DJ (1999) Gender-related effects on metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. Clin Pharmacol Ther 66:594–601
Mackay FJ, Pearce GL, Mann RD (1999) Cough and angiotensin II receptor antagonists: cause or confounding? Br J Clin Pharmacol 47:111–114
Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD (1998) Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. Br J Clin Pharmacol 46:505–511
Mas S, Gasso P, Alvarez S, Ortiz J, Sotoca JM, Francino A, Carne X, Lafuente A (2011) Pharmacogenetic predictors of angiotensin-converting enzyme inhibitor-induced cough: the role of ACE, ABO, and BDKRB2 genes. Pharmacogenet Genomics 21:531–538
Massana E, Barbanoj MJ, Moros C, Morte A, Gich I, Jane F (1997) No sex-related pharmacokinetic and pharmacodynamic differences of captopril. Pharmacol Res 36:41–47
Meibohm B, Beierle I, Derendorf H (2002) How important are gender differences in pharmacokinetics? Clin Pharmacokinet 41:329–342
MERIT-HF (1999) Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 353:2001–2007
Molenaar P, O'Reilly G, Sharkey A, Kuc RE, Harding DP, Plumpton C, Gresham GA, Davenport AP (1993) Characterization and localization of endothelin receptor subtypes in the human atrioventricular conducting system and myocardium. Circ Res 72:526–538
Mortensen LH, Fink GD (1990) Hemodynamic effect of human and rat endothelin administration into conscious rats. Am J Physiol 258:H362–H368
Nickenig G, Baumer AT, Grohe C, Kahlert S, Strehlow K, Rosenkranz S, Stablein A, Beckers F, Smits JF, Daemen MJ et al (1998) Estrogen modulates AT1 receptor gene expression in vitro and in vivo. Circulation 97:2197–2201
Ofili EO, Cable G, Neutel JM, Saunders E (2008) Efficacy and safety of fixed combinations of irbesartan/hydrochlorothiazide in hypertensive women: the inclusive trial. J Womens Health (Larchmt) 17:931–938
Os I, Bratland B, Dahlof B, Gisholt K, Syvertsen JO, Tretli S (1992) Female sex as an important determinant of lisinopril-induced cough. Lancet 339:372
Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH (1996) The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 334:1349–1355
Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M (2003) Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 348:1309–1321
Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 341:709–717
Plumpton C, Ashby MJ, Kuc RE, O'Reilly G, Davenport AP (1996) Expression of endothelin peptides and mRNA in the human heart. Clin Sci (Lond) 90:37–46
Polderman KH, Stehouwer CD, van Kamp GJ, Dekker GA, Verheugt FW, Gooren LJ (1993) Influence of sex hormones on plasma endothelin levels. Ann Intern Med 118:429–432
Pollock DM (2010) Dissecting the complex physiology of endothelin: new lessons from genetic models. Hypertension 56:31–33
Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM (2003) Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 289:871–878
Rauch U (2012) Gender differences in anticoagulation and antithrombotic therapy. In: Regitz-Zagrosek V (ed) Sex and gender differences in pharmacology. Springer, Heidelberg
Raz L, Miller VM (2012) Considerations of sex and gender differences in preclinical and clinical trials. In: Regitz-Zagrosek V (ed) Sex and gender differences in pharmacology. Springer, Heidelberg

Rathore SS, Wang Y, Krumholz HM (2002) Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 347:1403–1411

Rautureau Y, Schiffrin EL (2012) Endothelin in hypertension: an update. Curr Opin Nephrol Hypertens 21:128–136

Regitz-Zagrosek V (2006) Therapeutic implications of the gender-specific aspects of cardiovascular disease. Nat Rev Drug Discov 5:425–438

Regitz-Zagrosek V, Lehmkuhl E, Lehmkuhl HB, Hetzer R (2004) Gender aspects in heart failure. Pathophysiology and medical therapy. Arch Mal Coeur Vaiss 97:899–908

Rosenberg DW (1991) Dietary modulation of cytochrome P450 in the small intestinal epithelium. Pharmacology 43:36–46

Saenz-Campos D, Bayes MC, Masana E, Martin S, Barbanoj M, Jane F (1996) Sex-related pharmacokinetic and pharmacodynamic variations of lisinopril. Methods Find Exp Clin Pharmacol 18:533–538

Saetrum Opgaard O, Adner M, Gulbenkian S, Edvinsson L (1994) Localization of endothelin immunoreactivity and demonstration of constrictory endothelin-A receptors in human coronary arteries and veins. J Cardiovasc Pharmacol 23:576–583

Sampson AK, Moritz KM, Jones ES, Flower RL, Widdop RE, Denton KM (2008) Enhanced angiotensin II type 2 receptor mechanisms mediate decreases in arterial pressure attributable to chronic low-dose angiotensin II in female rats. Hypertension 52:666–671

Sartori-Valinotti JC, Iliescu R, Yanes LL, Dorsett-Martin W, Reckelhoff JF (2008) Sex differences in the pressor response to angiotensin II when the endogenous renin-angiotensin system is blocked. Hypertension 51:1170–1176

Saunders E, Cable G, Neutel J (2008) Predictors of blood pressure response to angiotensin receptor blocker/diuretic combination therapy: a secondary analysis of the irbesartan/hydrochlorothiazide blood pressure reductions in diverse patient populations (INCLUSIVE) study. J Clin Hypertens (Greenwich) 10:27–33

Schiffrin EL (2005) Vascular endothelin in hypertension. Vascul Pharmacol 43:19–29

Sharma A, Pibarot P, Pilote S, Dumesnil JG, Arsenault M, Belanger PM, Meibohm B, Hamelin BA (2010) Toward optimal treatment in women: the effect of sex on metoprolol-diphenhydramine interaction. J Clin Pharmacol 50:214–225

Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P (2001) Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). Circulation 103:375–380

Spoletini I, Vitale C, Malorni W, Rosano GMC (2012) Sex differences in drug effects: interaction with sex hormones in adult life. In: Regitz-Zagrosek V (ed) Sex and gender differences in pharmacology. Springer, Heidelberg

Stauffer BL, Westby CM, Greiner JJ, Van Guilder GP, Desouza CA (2010) Sex differences in endothelin-1-mediated vasoconstrictor tone in middle-aged and older adults. Am J Physiol Regul Integr Comp Physiol 298:R261–R265

Sudhir K, Ko E, Zellner C, Wong HE, Hutchison SJ, Chou TM, Chatterjee K (1997) Physiological concentrations of estradiol attenuate endothelin 1-induced coronary vasoconstriction in vivo. Circulation 96:3626–3632

Tanaka E, Hisawa S (1999) Clinically significant pharmacokinetic drug interactions with psychoactive drugs: antidepressants and antipsychotics and the cytochrome P450 system. J Clin Pharm Ther 24:7–16

Tatchum-Talom R, Eyster KM, Martin DS (2005) Sexual dimorphism in angiotensin II-induced hypertension and vascular alterations. Can J Physiol Pharmacol 83:413–422

Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ (2000) A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem 275:33238–33243

Tiret L, Poirier O, Hallet V, McDonagh TA, Morrison C, McMurray JJ, Dargie HJ, Arveiler D, Ruidavets JB, Luc G et al (1999) The Lys198Asn polymorphism in the endothelin-1 gene is associated with blood pressure in overweight people. Hypertension 33:1169–1174

Trifilieff A, Da Silva A, Gies JP (1993) Kinins and respiratory tract diseases. Eur Respir J 6:576–587

Turner ST, Schwartz GL, Chapman AB, Boerwinkle E (2005) WNK1 kinase polymorphism and blood pressure response to a thiazide diuretic. Hypertension 46:758–765

Ueno K, Sato H (2012) Sex-related differences in pharmacokinetics and pharmacodynamics of anti-hypertensive drugs. Hypertens Res 35:245–250

van Giersbergen PL, Gunawardena KA, Dingemanse J (2007) Influence of ethnic origin and sex on the pharmacokinetics of clazosentan. J Clin Pharmacol 47:1374–1380

van Suylen RJ, Wouters EF, Pennings HJ, Cheriex EC, van Pol PE, Ambergen AW, Vermelis AM, Daemen MJ (1999) The DD genotype of the angiotensin converting enzyme gene is negatively associated with right ventricular hypertrophy in male patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:1791–1795

Venegas-Pont M, Sartori-Valinotti JC, Glover PH, Reckelhoff JF, Ryan MJ (2010) Sexual dimorphism in the blood pressure response to angiotensin II in mice after angiotensin-converting enzyme blockade. Am J Hypertens 23:92–96

Vree TB, Dammers E, Ulc I, Horkovics-Kovats S, Ryska M, Merkx I (2003) Differences between lovastatin and simvastatin hydrolysis in healthy male and female volunteers:gut hydrolysis of lovastatin is twice that of simvastatin. ScientificWorldJournal 3:1332–1343

Walle T, Walle K, Mathur RS, Palesch YY, Conradi EC (1994) Propranolol metabolism in normal subjects: association with sex steroid hormones. Clin Pharmacol Ther 56:127–132

Waxman DJ, Holloway MG (2009) Sex differences in the expression of hepatic drug metabolizing enzymes. Mol Pharmacol 76:215–228

Werner D, Werner U, Meybaum A, Schmidt B, Umbreen S, Grosch A, Lestin HG, Graf B, Zolk O, Fromm MF (2008) Determinants of steady-state torasemide pharmacokinetics: impact of pharmacogenetic factors, gender and angiotensin II receptor blockers. Clin Pharmacokinet 47:323–332

Werner U, Werner D, Heinbuchner S, Graf B, Ince H, Kische S, Thurmann P, Konig J, Fromm MF, Zolk O (2010) Gender is an important determinant of the disposition of the loop diuretic torasemide. J Clin Pharmacol 50:160–168

Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE et al (2003) A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 348:583–592

Wirth A, Benyo Z, Lukasova M, Leutgeb B, Wettschureck N, Gorbey S, Orsy P, Horvath B, Maser-Gluth C, Greiner E et al (2008) G12-G13-LARG-mediated signaling in vascular smooth muscle is required for salt-induced hypertension. Nat Med 14:64–68

Wolbold R, Klein K, Burk O, Nussler AK, Neuhaus P, Eichelbaum M, Schwab M, Zanger UM (2003) Sex is a major determinant of CYP3A4 expression in human liver. Hepatology 38:978–988

Wu CK, Luo JL, Tsai CT, Huang YT, Cheng CL, Lee JK, Lin LY, Lin JW, Hwang JJ, Chiang FT (2010) Demonstrating the pharmacogenetic effects of angiotensin-converting enzyme inhibitors on long-term prognosis of diastolic heart failure. Pharmacogenomics J 10:46–53

Xin HB, Senbonmatsu T, Cheng DS, Wang YX, Copello JA, Ji GJ, Collier ML, Deng KY, Jeyakumar LH, Magnuson MA et al (2002) Oestrogen protects FKBP12.6 null mice from cardiac hypertrophy. Nature 416:334–338

Xue B, Pamidimukkala J, Hay M (2005) Sex differences in the development of angiotensin II-induced hypertension in conscious mice. Am J Physiol Heart Circ Physiol 288:H2177–H2184

Yanes LL, Sartori-Valinotti JC, Iliescu R, Romero DG, Racusen LC, Zhang H, Reckelhoff JF (2009) Testosterone-dependent hypertension and upregulation of intrarenal angiotensinogen in Dahl salt-sensitive rats. Am J Physiol Renal Physiol 296:F771–F779

You D, Loufrani L, Baron C, Levy BI, Widdop RE, Henrion D (2005) High blood pressure reduction reverses angiotensin II type 2 receptor-mediated vasoconstriction into vasodilation in spontaneously hypertensive rats. Circulation 111:1006–1011

Yukawa E, Honda T, Ohdo S, Higuchi S, Aoyama T (1997) Population-based investigation of relative clearance of digoxin in Japanese patients by multiple trough screen analysis: an update. J Clin Pharmacol 37:92–100

Zapater P, Novalbos J, Gallego-Sandin S, Hernandez FT, Abad-Santos F (2004) Gender differences in angiotensin-converting enzyme (ACE) activity and inhibition by enalaprilat in healthy volunteers. J Cardiovasc Pharmacol 43:737–744

Zheng W, Shi M, You SE, Ji H, Roesch DM (2006) Estrogens contribute to a sex difference in plasma potassium concentration: a mechanism for regulation of adrenal angiotensin receptors. Gend Med 3:43–53

Sex and Gender Aspects in Antiarrhythmic Therapy

Junko Kurokawa, Masami Kodama, Tetsushi Furukawa, and Colleen E. Clancy

Contents

Abstract Although cardiac arrhythmia had long been considered a predominantly male syndrome, it is now clear that arrhythmia is also a primary cause of mortality in women. Notably, the manifestation of specific arrhythmia syndromes appears to be gender specific. In particular, female sex is an independent risk factor for development of torsade de pointes (TdP) arrhythmias not only in congenital long QT syndromes but also in acquired long QT syndromes which occur as adverse effects of existing drugs. Males, on the other hand, are more likely to develop Brugada syndrome. Recent clinical and experimental studies suggest that these differences may stem from intrinsic sex differences in cardiac tissue. These include fundamental electrical differences resulting from variable ion channel expression and diverse sex hormonal regulation via long-term genomic and acute nongenomic pathways, and sex differences in drug responses and metabolisms. Undoubtedly, determining the effect of gender on cardiac function will be difficult and require

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