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ORIGINAL ARTICLE

Gender Differences in Cardiovascular Drugs

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Abstract The different responses of women and men to cardiovascular drugs reflect gender –specific variances in pharmacokinetic profiles and drug sensitivities coupled to inherent differences in the underlying physiology of each sex. Thus, many common cardiovascular drugs exhibit gender -specific therapeutic and adverse effects. For example, the QT interval of the electrocardiogram is longer in women compared to men, and accordingly, drugs that prolong the QT interval are more likely to cause lethal ventricular arrhythmias in female than male patients. As more clinical drug trials include women subjects, our improved knowledge base for assessing the risk/benefit ratio for cardiovascular drugs in women will enable us to consider gender as one factor in prescribing drugs and adjusting drug loading and maintenance dosages. This short review will present evidence for gender- related differences in the responses to common cardiovascular drugs including statins, antiplatelet and antithrombotic agents, β-blockers, digoxin, vasodilator therapies, and drugs associated with the Long QT Syndrome.

Keywords Cardiovascular · Drugs · Therapeutics · Medications · Gender · Side effects · Pharmacokinetics

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Introduction

Women take more medications than men, but these therapies are less likely to follow evidence-based guidelines [1, 2]. For example, the use of aspirin and statins as primary and secondary prevention against cardiovascular events is less common in women compared to men across all races and ethnicities [3]. Women also show lower adherence to medication regimens compared to men [1, 2]. The reasons for disparities between women and men in prescribed medications and adherence to them are poorly understood, but may relate to a complex interplay of many societal, economic and physiological factors. For example, under-representation of women in clinical trials may be a factor contributing to limited recognition of gender-based differences in medication responses, thereby preventing optimization of therapeutics for women of all ages. The 1.5 to 1.7 -fold higher risk of adverse drug events in women may partially relate to less risk recognition in addition to gender-based differences in immune responses [2, 4, 5]. Additionally, men and women show differences in pharmacokinetics and pharmacodynamics of cardiovascular medications [6–8], including altered patterns of absorption, distribution, metabolism and excretion (Table 1).

Pharmacokinetics

Absorption of medications in women may be slower due to reduced gastric acid secretion and gastrointestinal motility [6–11]. Therefore, drugs designed for absorption in the duodenum, including enteric-coated formulations, may exhibit diminished or delayed absorption, especially following a meal [10, 11]. Examples of cardiovascular medications that are reported to show delayed or reduced availability in women due to slowed or attenuated absorption include verapamil,

Table 1 Gender differences in pharmacokinetics

	Women	Men	Refs
Absorption	↓ gastric acid secretion ↑ GI transit time		[6–11]
Distribution	↓ body weight ↓ intravascular volume ↓ organ volume ↓ muscle volume ↑ adipose tissue		[6–8]
Metabolism	↑ CYP2D6 ↑ CYP3A	↑ CYP1A activity ↑ CYP2E1 activity ↑ P-gp activity	[7, 12, 13]
Excretion	↓ GFR		[6–8, 14]

↑, increased ↓, decreased

captopril, felodipine, and enteric-coated aspirin [6–11]. To ensure adequate bioavailability of medications recommended to be taken on an empty stomach, women should take these medications prior to breakfast or wait longer than prescribed after eating a meal if the medication is taken more than once daily [6].

Women also may have a smaller drug volume of distribution due to lower body weight and smaller intravascular, organ, and muscle volumes as compared to men [6–8]. For this reason, special attention should be given when administering loading doses or intravenous boluses of cardiovascular medications with narrow therapeutic indexes to prevent adverse events in women. Weight-based dose adjustments are routinely recommended for class I and class III antiarrhythmic agents, digoxin, heparin and other cardiovascular drugs [6–8]. Another consideration is that despite lower body weight, women generally have a higher percent of body fat, which favors a higher volume of distribution normalized to body weight for lipophilic drugs [6].

Several metabolic enzymes are reported to have higher activity in men compared to women. These enzymes include CYP1A2, CYP2E1, P-glycoprotein (drug efflux pump), and certain isoforms of glucuronyltransferases and sulfotransferases [7]. On the other hand, CYP2D6 and CYP3A are reported to have slightly higher activity in women of childbearing years [7, 12, 13]. No specific gender differences have been reported for CYP2C9 or CYP2C19 [7, 12, 13]. The potential for gender-based metabolic differences to importantly impact the availability and half-lives of cardiovascular drugs in women is poorly understood. In addition, renal clearance or glomerular filtration rate in women is 10 to 25 % slower than in men even after adjusting for body size [6–8]. Thus, cardiovascular medications that undergo primary renal elimination, such as digoxin, will be cleared more slowly [6, 7, 14].

The remainder of this chapter will highlight emerging evidence for the unique pharmacology of cardiovascular drugs in women. Pregnancy represents a condition unique to women that not only affects drug choice due to teratogenicity concerns, but also can alter the pharmacokinetics/pharmacodynamics of medications. This topic is reviewed elsewhere [15], and we have chosen to focus more globally on providing a short review of the pharmacokinetics and pharmacodynamics of several important cardiovascular drug categories. These categories of drugs include the statins, antiplatelet and antithrombotic agents, digoxin, β-adrenergic receptor blockers (β-blockers), vasodilator therapies, and drugs that can induce long QT syndrome as they pertain to women. A summary of gender-related therapeutic and toxic effects is provided in Table 2.

Statins

Elevated serum cholesterol levels, specifically low density lipoprotein cholesterol (LDL-C), have long been associated with an increased incidence of cardiovascular events [16, 17]. Statins directly inhibit 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, a key enzyme for cholesterol synthesis in the liver, and thereby reduce circulating LDL-C levels [17]. Statins also exhibit beneficial pleiotropic effects associated with decreased inflammation, improved endothelial function, and enhanced atherosclerotic plaque stability [17–21]. Cardiovascular benefits derived from statin use are attributed to a combination of these effects [17–21].

Several meta-analyses offer conflicting data on the protective effects of statins for primary cardiovascular disease prevention in women [17]. The discrepancies may be related to ill-defined risk stratification or under-utilization of guidelines in women compared to men. Recent guidelines issued by the American College of Cardiology/American Heart Association, while generally more inclusive of women, fail to make a distinction in risk stratification between women and men for initiating and maintaining statin therapy [17]. In addition, some reports suggest that the lower metabolism, reduced muscle mass, and lower body weight of women compared to men predispose to statin-induced myalgias and diabetes [8, 22, 23]. The risk of these adverse events is highest in older women with low body weight [8, 22]. However, health providers are advised to avoid overemphasizing these adverse effects and determine individual risk versus benefit for the use of statins in primary prevention of cardiovascular events in women. Meanwhile, the use of intensive statin therapy for secondary prevention of cardiovascular events in women is routinely recommended, since it has demonstrated significant decreases in myocardial infarction, unstable angina, heart failure and death [16–24].

Table 2 Cardiovascular drugs with gender-specific therapeutic and adverse effects

Drug	Gender-specific effects	Refs
Statins	Increased side effects in older women with low body weight	[8, 22, 23]
Antiplatelet Agents	Ineffective primary prevention of heart attack in women Decreased stroke prevention in men	[8, 25, 27]
Antithrombotic Agents	Increased risk of bleeding	[35–40]
Digoxin	Increased mortality in women	[42, 43]
β-Blockers	Enhanced blood pressure lowering and heart rate reduction in exercising women	[46]
Antiarrhythmic Agents	Increased risk of prolonged QT and TdP in women	[55, 56]
Calcium Channel Blockers	Enhanced blood pressuring lowering in women Increased incidence of edema	[70, 71]
ACE Inhibitors	Increased incidence of cough	[80]
Diuretics	Increased risk of hyponatremia	[81]

TdP, Torsades de Pointes

Antiplatelet Agents: Aspirin

Platelets are crucial to the pathogenesis of atherosclerosis, and their role in the etiology of cardiovascular disease is confirmed indirectly by the clinical benefits of antiplatelet agents, such as aspirin and clopidogrel [25]. Aspirin inhibits platelet function and aggregation by inactivating the enzyme cyclooxygenase (COX)-1, which results in decreased synthesis of prostaglandins and thromboxane A_2 [26]. Studies suggest that aspirin significantly reduces the risk of myocardial infarction in men with little change in risk of stroke [8, 27]. Conversely, aspirin was ineffective as primary prevention of myocardial infarction in women [25, 27], but showed significant protection against stroke [25, 27, 28]. There are several potential reasons for this gender disparity in the benefit conferred by aspirin therapy. First, uncoated aspirin exhibits altered pharmacokinetics in women, displaying faster absorption, a larger volume of distribution and more rapid hydrolysis [29], potentially compromising its beneficial effect. Alternatively, aspirin's differential effects could relate to differing platelet functions and disease pathogenesis between men and women. For example, a recent study identified gender-specific responses to stress in patients with stable ischemic heart disease [30]. These researchers reported that men are more likely to respond to stressors by increasing blood pressure, whereas women exhibit higher platelet aggregation not only after pharmacologic stress with serotonin or epinephrine, but also in response to mental stress [30].

Genetic polymorphisms in platelet glycoproteins (Gp) also are linked to increased cardiovascular events. However, the gender distribution of these polymorphisms has not been defined [25]. Some evidence suggests that women who carry at least one Gp Ib-alpha5C allele exhibit a higher risk of cardiovascular events compared to women homozygous for the Gp Ib-alpha5T allele [31]. However, hormone replacement therapy was associated with reduced cardiovascular events in women who carried at least one Gp Ib-alpha5C allele compared to women homozygous for the Gp Ib-alpha5T allele [31]. This finding may align with other reports that estrogen decreases platelet reactivity in women [32, 33]. Future studies are clearly needed to determine gender-specific mechanisms of platelet action and potential differences in antiplatelet therapeutic outcomes. Currently, aspirin is recommended for use in women for the secondary prevention of cardiovascular events [25, 27].

Antithrombotics

Atherothrombosis is the leading cause of unstable angina, myocardial infarction and cardiovascular death [34]. Two pharmacologic strategies are available to decrease thrombosis in patients: anticoagulation and fibrinolytics. Anticoagulants inhibit thrombus or clot formation, while fibrinolytics break up already formed clots [34]. Both strategies have displayed similar reductions in myocardial infarction and cardiovascular death in men and women [35]. However, they were associated with an increased risk of adverse bleeding in women [35]. Specifically, women who received the anticoagulant heparin for acute myocardial infarction were more likely to achieve higher activated partial thromboplastin time (aPTT) than men, a finding associated with increased bleeding risk [36]. Two randomized controlled trials demonstrated that women using thrombolytic therapy for treatment of acute myocardial infarction, which included a combination of heparin with either streptokinase and/or alteplase, have a greater risk for both fatal and nonfatal complications compared to men [37, 38]. In other studies, the female gender was independently associated with higher bleeding rates following fibrinolytic treatment for acute myocardial infarction [39, 40].

Digoxin

Digoxin is a cardiac glycoside with positive inotropic and parasympathetic effects, properties useful for the treatment of heart failure and to slow conduction through the atrioventricular node, respectively [41]. As previously discussed, digoxin has a different pharmacokinetic profile in women compared to men, displaying a reduced volume of distribution and slower renal clearance [6–8]. These pharmacokinetic differences may partially explain the increased mortality risk seen in women taking digoxin for heart failure. A post hoc analysis of the 1997 Digitalis Investigation Group study determined that female heart failure patients using digoxin had a significantly higher mortality risk compared to those taking placebo [42, 43]. These women also exhibited a 5.8 % higher mortality rate compared to men treated with digoxin [42, 43]. Although there was a trend linking higher serum digoxin concentrations to all-cause mortality in women, the small number of women participating in the trial limited the ability to reach statistical significance [8]. Widely accepted therapeutic serum concentrations for digoxin are 0.8 to 2 ng/mL. However, recent American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) guidelines recommend lower serum concentrations (0.5 to 0.9 ng/mL) to reduce mortality in heart failure patients regardless of gender [44]. Although data are limited in women, it is recommended clinicians adopt the lower serum digoxin concentration range of 0.5-0.9 ng/mL, particiularly when treating female patients [44].

β-Blockers

The beta-adrenergic receptor blockers (β-blockers) are used to treat a wide range of cardiovascular diseases including hypertension, heart failure, angina, arrhythmias, and post-myocardial infarction. These drugs block the ability of endogenous catecholamines (epinephrine and norepinephrine) released from the sympathetic nervous system to bind to β-adrenergic receptors located in the heart, kidney, smooth muscle, and other sites [45]. There are three isoforms (β1, β2, β3) of the β receptor, which exhibit tissue –specific expression and actions, with the β1 receptor the primary target of β-blocker drugs. The β1 receptors in the heart are responsible for enhancing heart rate and force of contraction, and in the kidney, β1 receptors are responsible for renin secretion. Therefore, β1-receptor blockers lower heart rate, decrease force of contraction, attenuate renin secretion, and reduce blood pressure [45]. Evidence suggests β-blockers display gender-specific pharmacokinetics and may confer different survival benefits to men and women. A study of normal healthy volunteers receiving oral metoprolol twice daily revealed no gender-related difference in elimination half-life, but women showed a greater reduction in heart rate and systolic blood pressure during exercise as compared to men [46]. These effects were attributed to increased serum drug concentrations facilitated by enhanced absorption of metoprolol in women [46]. However, despite these presumed higher serum drug concentrations, metoprolol has failed to show increased anti-ischemic effects in women with chronic stable angina compared to men [47]. Moreover, inadequate inclusion of women in large clinical trials has led to conflicting data on the survival benefits of β-blockers in women diagnosed with heart failure after myocardial infarction [8]. Neither the Metoprolol CR/XL study nor the COPERNICUS trial showed decreased mortality associated with the use of β-blockers in women with heart failure [48, 49]. Conversely, a gender-specific analysis of data in the CIBIS II study revealed that treatment with bisoprolol significantly decreased mortality in women compared to men with heart failure [50, 51]. When the mortality data from these three trials were pooled, men and women with heart failure both showed survival benefits associated with β-blocker use [51, 52]. This finding further emphasizes the importance of adequate representation of women in clinical trials.

Drug-Induced Long QT Syndrome

The QT interval of the electrocardiogram accounts for the duration of electrical activity for cardiac muscle cell contraction and ventricular repolarization in the cardiac cycle. Prolongation of the QT interval (Long QT Syndrome) caused by slowed ventricular repolarization is generally regarded as a pro-arrhythmic state, which can predispose to Torsades de Pointes (TdP), a rare but often fatal polymorphic ventricular arrhythmia [53, 54]. The female gender has been identified as an independent risk factor for QT prolongation and TdP [55, 56], which may be partially explained by the fact that women have longer QT intervals at baseline compared to men even after correction for heart rate [57, 58]. This gender-related difference is most pronounced at the onset of puberty and gradually declines with age. By age 50, there appears to be no significant difference in QT intervals between genders [59].

Several studies have sought to determine the influence of sex hormones and the menstrual cycle on QT intervals [59–62]. Findings demonstrate that endogenous testosterone decreases the cardiac action potential, thereby shortening the QT interval [59–62]. This action of testosterone may contribute to the baseline difference in QT interval between men and women [60]. Endogenous progesterone also decreases the duration of the cardiac action potential [60–62]. Progesterone concentrations fluctuate throughout the menstrual cycle, with the highest levels occurring during the luteal phase and much lower levels during the follicular phase. A study utilizing 24-h

electrocardiograms in healthy Japanese women, who pursued normal daily activities during the luteal and follicular phases of their menstrual cycle, found a shorter QT interval during the luteal phase, which correlated with a higher serum concentration of progesterone [61].

In addition to these physiological differences between men and women, which may predispose women to long QT intervals, many common cardiovascular medications can prolong the QT interval and lead to TdP [63]. In a meta-analysis of 93 publications involving at least one identified case of TdP associated with the use of Class IA or Class III anti-arrhythmic or anti-anginal agents (quinidine, procainamide, disopyramide, amiodarone, sotalol, bepridil, or prenylamine), women accounted for 64 to 75 % of cardiovascular drug - induced TdP [55]. A subsequent meta-analysis of 22 clinical trials with a total of 3135 patients treated with d,l-sotalol revealed that women had a three-fold higher risk of developing TdP even after adjusting for additionally identified risk factors (ventricular arrhythmias, congestive heart failure, and d,l-sotalol dose >320 mg/day) [56]. It is possible that the increased risk of drug-induced long QT intervals with the use of anti-arrhythmic and anti-anginal agents in women can be attributed to higher serum drug concentrations due to lower body weight and decreased volume of distribution compared to men. However, considering that there is no defined relationship between serum drug concentration and QT prolongation with certain anti-arrhythmic agents, including quinidine and sotalol, this factor cannot be the only contributing influence [64, 65]. A recent open-label non-randomized trial in healthy young adults demonstrated that women show a higher sensitivity to sotalol-induced prolonged QT interval compared to men even across similar drug serum concentrations [65].

Other studies focused on gender-related differences in autonomic tone demonstrated significant QT prolongation in response to use of β-blockers in healthy women compared to men [66]. Also women with $LQTS_1$, a mutation in the KCNQ1 gene that increases the QT interval, showed significant QT prolongation compared to men with $LQTS_1$ after administration of a β-blocker agent [67]. Thus, mechanisms underlying the increased risk of prolonged QT and TdP in women cannot be fully explained by increased serum drug concentrations or differences in autonomic tone, but may vary depending on menstrual cycle phase. Future studies determining the potential arrhythmogenicity of pharmacological compounds should take this factor into account when establishing the study design.

Calcium Channel Blockers

Calcium channel blockers (CCBs) are indicated in a variety of cardiovascular diseases including hypertension, angina and supraventricular tachyarrhythmias. In arterial smooth muscle cells, the CCBs block voltage-gated "L-type" calcium channels to reduce Ca^{2+} influx and Ca^{2+}-activation of contractile proteins, thereby mediating vasodilation. In the sinoatrial (SA) and atrioventricular (AV) nodes of the heart, CCBs slow the Ca^{2+}-dependent upstroke of the action potential, thereby reducing automaticity of the SA node and slowing impulse conduction through the AV node. Gender-related pharmacokinetic differences for several CCBs, including amlodipine and verapamil, have been described [68, 69]. Women achieve higher plasma concentrations of amlodipine and display faster oral elimination rates for verapamil compared to men. This difference can be partially attributed to the lower body weight, higher activity of CYP3A4 and lower activity of P-gp in women compared to men [68, 69]. An 18 week, open-labeled, prospective study demonstrated that amlodipine exerted a greater antihypertensive effect in women compared to hypertensive men across all age groups [70, 71]. However this enhanced blood pressure lowering effect of amlodipine was accompanied by an increased incidence of peripheral edema in women compared to men [70, 71], potentially resulting in decreased adherence and discontinuation of therapy, thereby negating the beneficial effects of CCBs in women.

Isosorbide Mononitrate

Isosorbide mononitrate is a nitric oxide donor used to dilate blood vessels and relieve anginal pain. In a pharmacokinetic study to determine bioequivalence of a fixed dose of two different extended release formulations of isosorbide dinitrate, women had significantly higher serum plasma concentrations compared to men [72]. This difference was attributed solely to the significantly lower body weights in the female study population, suggesting that doses of extended release isosorbide mononitrate should be based on body weight rather than fixed regimens [72]. However the clinical significance of these findings has yet to be determined.

Other Cardiovascular Agents

Many other medications exist for the treatment of cardiovascular diseases, including diuretics and inhibitors of the renin-angiotensin-aldosterone system (RAAS). The latter family of drugs includes the angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and the renin inhibitor, aliskiren. Although no gender differences in pharmacokinetics or pharmacodynamics have been described for RAAS inhibitors or diuretics [73, 74], prescribing differences in these medications appear to be gender related [75, 76]. Among hypertensive patients, men are more likely to be treated with RAAS inhibitors, while women are more likely to be prescribed a diuretic, even after controlling for age and

comorbidities [75, 76]. One reason for these differences may relate to the potential teratogenic and abortive effects of RAAS inhibitors in women of child bearing years, and the reluctance of health providers to prescribe such RAAS –targeting medications without assurances of adequate birth control [77–80]. It also has been reported that women have an increased risk of adverse events while taking these medications compared to men, including a higher incidence of cough with ACEIs [81], and increased incidence of hyponatremia with diuretics [82]. Thus, women should be monitored carefully for such outcomes after prescribing these drugs.

Summary

Women and men are physiologically different and present with gender-specific clinical manifestations of cardiovascular disease. Therefore, it stands to reason that cardiovascular drugs will exhibit different pharmacological and pharmacokinetic profiles between women and men, and it is insufficient to extrapolate data from drug trials conducted almost exclusively in males to a female patient population. This chapter highlights the importance of adequate inclusion of both genders in drug safety and efficacy trials, and Table 2 summarizes some of the cardiovascular drugs with gender-specific therapeutic and adverse effects. The package inserts for a growing number of cardiovascular drugs, including simvastatin, atorvastatin, lovastatin, heparin, enoxaparin, and sotalol, now recognize gender- related differences in drug profiles, which may guide the adjustment of loading or maintenance doses for female patients. The results of studies reviewed in this chapter suggest that the practice of considering gender as one factor in prescribing drugs will become common, as more studies emerge to improve our knowledge base for weighing risk/benefit of cardiovascular drugs in women and men.

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