

WOMEN'S HEALTH I

SEX-RELATED DIFFERENCES IN DISEASE AND PHARMACOTHERAPY

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Learning Objectives

1. Evaluate historical, environmental, genetic, and physiological differences between men and women that contribute to sex-related differences in diseases.
2. Classify cardiovascular diseases that have distinct characteristics in incidence, presentation, or progression between men and women.
3. Classify the distinct sex-related characteristics in the incidence, presentation, or progression of osteoporosis and systemic lupus erythematosus.
4. Assess the impact of physiologic differences between men and women on the absorption, distribution, and elimination of drugs.
5. Apply current literature to assess potential pharmacodynamic and pharmacological response differences between men and women.

Introduction

History

Historically, women have been underrepresented in clinical trials and overlooked in the development of drugs. In fact, drug regulatory agencies encouraged the exclusion of women of childbearing age from participation in Phase I and early Phase II studies. Early researchers realized that the hormone fluctuations that occur throughout the menstrual cycle in women provided a complex background because of their constantly changing physiology. Because men were believed to have a more consistent concentration of testosterone excretion, they became the accepted model for early drug development.

In the 1980s, the possibility that men and women respond differently to pharmacological agents gained widespread appreciation. Research uncovering physiologic and drug-response differences between men and women contributed to the National Institutes of Health Revitalization Act of 1993 and subsequent amendments. The law now requires that women be included in all human subject research. In addition, the guidelines ensured that Phase III clinical trials include both men and women with a study

design that is appropriate to examine sex/gender-based interactions on the intervention. The common omission of women in clinical trials before 1993 has resulted in a knowledge gap of the pharmacotherapy differences between men and women regarding drugs developed before that time. Currently, most of the available information regarding differences in drug therapy between men and women is for drugs with narrow therapeutic indices or those with life-threatening adverse effects.

Classification

The terms *sex* and *gender* commonly appear in the medical literature when referring to physiological and pharmacological differences between men and women. They have been given distinct definitions to classify the difference between biologic factors and lifestyle. Sex is, therefore, used to solely acknowledge the biologic differences between men and women, such as hormonal influences on physiology, disease, and pharmacotherapy. Gender is used to acknowledge lifestyle differences between men and women. Legitimate arguments have been made to suggest that it is generally too difficult to distinguish between biologic and lifestyle factors contributing to sex-based differences to make such a distinction in the terms. Nonetheless, in this chapter, *sex* will refer to known or suspected biologic differences between men and women, whereas *gender* will be used to describe social or other lifestyle differences. Research into differences in pharmacotherapy between men and women has focused predominantly on sex-based, as opposed to gender-based, disparities. This research will be primarily reviewed. However, societal and nutritional influences on the disposition and response to drugs should not be overlooked.

Sex-Based Differences in Disease

Physiologic Differences

The relatively recent surge in investigations of sex-related differences in pharmacotherapy has led to increased

Abbreviations in This Chapter

CYP	Cytochrome P450
DIG	Digitalis Intervention Group
FDA	U.S. Food and Drug Administration
HIV	Human immunodeficiency virus
I_{Kr}	Rapid component of the delayed rectifier current
P-gp	P-glycoprotein
SLE	Systemic lupus erythematosus
TdP	Torsades de pointes

research into common physiologic differences between men and women. The genetic makeup is clearly different between the sexes, with women having two X chromosomes and men having only one X chromosome with one Y chromosome. The expression of genes encoded in the Y chromosome in men may not have a corresponding gene on the X chromosome. Furthermore, it has been suggested that the expression of certain genes on the X chromosome is higher in women. This finding may not be clinically relevant because only one of the X chromosomes is active in women.

The most obvious anatomic difference that contributes to sex-related physiologic differences is that women are generally smaller than men on a weight basis. Furthermore, men have more muscle mass and a larger intravascular space. Because of women's smaller body size, many of their major organs are smaller than in men. The size of most organs corresponds to the size difference between men and women and contributes to sex-based physiologic differences. For example, women's hearts have a smaller mass than men's hearts. This difference contributes to a smaller heart volume and altered cardiac function, including a smaller stroke volume in women than in men.

In addition to the differences in body size, functional differences exist in certain organs in men and women. There is an obvious difference in the reproductive organs between men and women, but functional differences in other organs important to disease and pharmacotherapy also exist. For example, the difference in kidney function between the sexes is partially because of the differential expression of anion and cation transporters in both the apical and basolateral membranes of the renal tubules. The expression and function of certain active transport proteins in the kidney may be regulated by sex hormones. The specific proteins are not discussed here because the aforementioned differences are largely based on laboratory data without clinically relevant evidence. However, both the abundance and function of active transport proteins in the kidney may be quite different between the sexes, leading to different overall kidney function. The potential disparity in the expression and function of active transport proteins has been suggested to contribute to sex-based differences in the elimination of drugs by the kidneys.

The function and regulation of the heart is also quite different between men and women. Women have greater baseline sympathetic activity than men, which contributes to a higher resting heart rate. In addition, the refractory

time is shorter in the sinoatrial node in women than in men, leading to a quicker recovery to generate an impulse. Differences in cardiac repolarization are also evident between men after puberty and women of childbearing age. These differences appear to be predominantly caused by circulating androgen and estrogen concentrations. Differences in cardiac repolarization are manifested on a surface electrocardiogram by a longer heart rate–corrected QT interval in women than in men. An increased sensitivity to drug-induced ventricular arrhythmias in women is at least partially because of the physiologic difference in cardiac repolarization between the sexes.

Pathophysiologic Differences

Considering the physiologic differences between men and women, it is not hard to imagine that sex-based differences in the pathophysiology and progression of disease also exist. Pathophysiologic differences between the sexes may arise from the underlying sex-based differences in physiologic function. Additional influences on the sex-based difference of disease can be attributed to the environment, genetics, and circulating sex hormones. Commonly, a combination of these factors contributes to sex-based differences in the incidence or progression of disease.

Environment vs. Genetics

The disparity in both environmental and lifestyle factors between men and women may contribute to differences in the pathogenesis of disease. In direct contrast to environmental factors, the influence of genetics on sex-specific disease progression has been a focus of recent research. There has been a large influx of information related to genetic differences between men and women in recent years as technology has advanced and as the sequence of the human genome has been uncovered. A majority of published studies indicating that differences in polymorphisms between men and women contribute to the sex-related development of disease have not been appropriately designed or have not included an adequate sample size to assess sex-based differences.

Hormonal Influence

Circulating sex hormones are protective against certain diseases and can also influence the progression of other pathophysiologic states. The primary sex hormones include the androgenic steroids. The androgens (e.g., testosterone) are responsible for the development of male sex organs and serve as precursors for estrogen production in women. It has been a challenge in biomedical research to directly identify hormones that increase the risk of disease versus hormones that are protective. The underlying challenge is that hormone excretion changes with increasing age, with dramatic changes at both puberty and menopause. Furthermore, the female menstrual cycle adds further challenges to the study of the influence of hormones on pharmacotherapy.

Osteoporosis

Osteoporosis is a well-known example of a disease with an incidence greatly influenced by sex. About 80% of patients with osteoporosis are women. There is a complexity to the development of osteoporosis that can be attributed to a combination of dietary and genetic components together

with the well-accepted hormonal influence on bone metabolism. Although a genetic component appears to be involved in the development of osteoporosis, this subject is not covered in depth here because there are no overwhelming data to suggest that men or women are more likely to have a polymorphic variant in a candidate gene that is associated with this disease. Therefore, there is a lack of evidence to suggest that the sex-based discrepancies in the development of this disease are caused by a genetic component. However, many genetic studies of osteoporosis have been conducted solely in postmenopausal women because this population is at greatest risk of the disease. Within this population, there may be polymorphic variants in candidate genes that have interactions with the dietary intake of calcium and vitamin D that can contribute to the pathogenesis. Without direct evidence of polymorphic differences between men and women, the current and widely accepted theory of the sex-based difference in the disease is predominantly centered on the sex hormones.

Both testosterone and estrogen have protective effects against the development of osteoporosis by promoting bone metabolism. Advancing age and any accompanying decrease in bone mineral density greatly influence the manifestation of osteoporosis. Specifically, the decline of estrogen production after menopause in women is one of the greatest risks of developing this disease. Hormone replacement therapy with estrogen was used for the treatment and prevention of osteoporosis for more than 50 years. However, more recent concerns about estrogen's adverse effects, together with the results from the Women's Health Initiative and the increased risk of breast cancer, have led to a major reduction in the use of estrogen replacement therapy.

Systemic Lupus Erythematosus

Most autoimmune disorders have a higher incidence in women than in men. In fact, sex is as important a risk factor for developing autoimmune disorders as for developing osteoporosis. About 80% of all autoimmune disorders occur in women. The autoimmune disorder that has a particularly high incidence in women is systemic lupus erythematosus (SLE). The differences in SLE between men and women are discussed in this section.

Systemic lupus erythematosus is an autoimmune disorder that affects multiple organ systems and therefore has several clinical manifestations. It largely affects women of childbearing age, with about a 10 times greater incidence of disease onset than men. In addition, SLE has the highest prevalence in women of African or Asian descent. The reason for the racial difference among women is not clear. However, there appears to be a mixture of genetic and environmental components associated with both the development and exacerbation of the disease. Despite the genetic component, there is a lack of data to suggest that polymorphisms associated with the onset of the disease are on the sex chromosomes. Thus, like osteoporosis, female sex hormones are believed to play a key role in the onset and pathogenesis of SLE.

In addition to environmental influences on SLE (e.g., sun exposure), female sex hormones have the greatest impact on the pathogenesis of the disease. In fact, patients with SLE have altered estrone metabolism, leading to an unbalanced amount of estrogenic compounds. Observational data suggest

that women taking hormone replacement therapy are at an increased risk of contracting the disease. This observation was derived from the Nurses' Health Study, in which women taking hormone replacement had a negligibly increased risk of developing the disease. With this observation was the notion that hormone replacement therapy could lead to an exacerbation of SLE in patients with stable disease. Until recently, most of the data regarding hormone replacement therapy and exacerbations of SLE have been observational. In 2005, the results of the first large randomized trial were published regarding hormone replacement therapy and the risk of disease exacerbation in women. Although there was not a significant increase in major flares of the disease, there was a significant increase in mild to moderate flares in women on hormone replacement versus the placebo group. Despite the increase in mild and moderate flares in this study, the benefits of hormone replacement therapy may still outweigh the risks in certain patients, and the choice of therapy should be individualized. For instance, there may be benefits to short-term administration of hormone replacement therapy in women with severe postmenopausal symptoms who have no symptoms of SLE and who do not have antiphospholipid antibodies in their serum.

Estrogen-containing oral contraceptives are not usually used in patients with SLE, even though most patients are women of childbearing age. Two randomized, placebo-controlled clinical trials recently concluded that neither estrogen-containing nor progesterone-alone oral contraceptives increase the risk of disease flares in patients with stable SLE. Although caution should be taken in the use of oral contraceptives in women with SLE, it does not appear to significantly increase disease flares to the extent that was originally believed.

Cardiovascular Disease

Overview

Osteoporosis and SLE are predominantly diseases of women. Cardiovascular disease is more complex because it afflicts both men and women, and there is strong evidence to support a different pathogenesis between the sexes. There is a clear sex-dependent risk of developing cardiovascular disease, but age, regardless of sex, also plays an important role when assessing cardiovascular risk. Unlike the autoimmune disorders, cardiovascular disease is more predominant in older women than in women of childbearing age. In general, men are more likely to develop cardiovascular disease than matched premenopausal women of the same age. However, a common, but incorrect, perception among health care providers and the general population is that cardiovascular disease is more predominant and fatal in men than in women. To the contrary, cardiovascular disease is a particularly fatal disease in women. Heart disease and stroke are responsible for almost twice as many deaths of women per year than all types of cancer combined. Furthermore, a first myocardial infarction kills more women than men; this is described in the section on ischemic heart disease.

Historically, clinical investigations of cardiovascular disease predominantly included only men; this resulted in a lack of appreciation for the significance of this disease in women. More recent investigations are being designed to incorporate larger numbers of women to increase the study power to determine differences in the incidence, prevalence,

Table 1-1. Prevalence of and Sensitivity to Cardiovascular Risk Factors in Women Compared with Men

Cardiovascular Risk Factor	Prevalence ^a		Sensitivity ^a
	Young	Elderly	Any Age
Cigarette smoking	↔	↔	↑
Diabetes	↔	↑	↑
Hypercholesterolemia	↓	↑	↔
Hypertension	↓	↔	↔
Hypertriglyceridemia	↓	↑	↔
Isolated systolic hypertension	↔	↑	↔
Low-density lipoprotein	↓	↑	↔
Obesity	↓	↑	↔

^aArrows indicate increase (↑), decrease (↓), or no change (↔) for the cardiovascular risk factor in women compared with men.

and pharmacotherapy of cardiovascular diseases between the sexes. This section describes known cardiovascular and hemodynamic differences between men and women that may contribute to sex-related pathogenesis of cardiovascular disease in women.

Hemodynamic Differences

Normotensive men, on average, have a higher blood pressure than women of equal age. The average difference in systolic pressure in men is around 6–10 mm Hg greater than women. However, the mean difference dissipates with increasing age until systolic pressures in men and women eventually coincide around age 70–79 years. Elderly women, therefore, have mean blood pressure recordings similar to elderly men. Despite this convergence of mean blood pressure recordings between the sexes with increasing age, men have a greater risk of uncontrolled hypertension than women. This greater risk of uncontrolled hypertension is likely because of the physiologic difference in blood pressure between the sexes.

The mechanism for the difference in blood pressure regulation between the sexes has not been entirely elucidated. However, like many of the pathophysiologic differences between the sexes, the mechanism appears to be greatly influenced by sex hormones. This influence is evident by changes observed in boys and girls from prepubescence into the onset of puberty. During and immediately after puberty, there is an increased magnitude in the difference of systolic pressure between the sexes. The time of the increasing mean blood pressure in men corresponds to the times when androgens are at the highest concentrations. This indirect evidence, together with the known effects of exogenous testosterone administration and controlled mechanistic studies, suggests that testosterone increases mean arterial pressure. The mechanism by which testosterone increases blood pressure is likely a product of its effects on kidney function and altered natriuresis.

Ischemic Heart Disease

Ischemic heart disease has a sex-related pathogenesis, which is evident from the presentation of the disease to its prognosis and outcome. The death rates in women continue to increase despite the introduction of several effective treatment options in the past few decades. With the increases in evidence and awareness of sex-based differences in the

outcomes of ischemic heart disease, the need for a sex-based approach to diagnose and treat this disease is coming to the forefront of the management of cardiovascular disease.

The fatality of ischemic heart disease in women has partially been attributed to a subdued clinical presentation in combination with a referral bias for women with suspected ischemic heart disease. Historically, women have not received the standard of therapy with appropriate diagnostic tests compared with men given similar risk factors. Based on observational data, this trend appears to be changing with increasing awareness and more women receiving the standard of care. Although the risk factors for developing a coronary event are the same between men and women, there is both a sex and gender difference that contributes to the impact of risk factors on the development of cardiovascular disease. For example, women who smoke cigarettes have almost double the risk of coronary events compared with men who smoke. This risk is intensified because the rate of smoking cessation is lower in women than in men. The relative prevalence of risk factors in women versus men changes with age. The prevalence of risk factors in young and older women relative to age-matched men is presented in Table 1-1. Furthermore, Table 1-1 indicates the risk factors to which women have an increased sensitivity regarding the development of cardiovascular disease.

Women with acute myocardial infarctions may still not be receiving optimal treatment to the same extent as men. Nonoptimized therapy in women may be because of a continued lack of awareness into sex-based differences in the clinical presentation of the disease. In particular, women commonly have less-specific symptoms of the disease (e.g., shortness of breath, nausea). Furthermore, chest pain is generally less predictive of an acute myocardial infarction in women than in men. The misdiagnosis or the failure to refer women for the proper diagnostic testing likely contributes to the sex-based disparity in fatality rates for the disease.

Heart Failure

The incidence and prevalence of heart failure is lower in women than in men, regardless of age. However, women have an age-related risk of developing heart failure that dramatically increases after menopause. The increased risk in postmenopausal women is likely caused by decreased production of estrogen, which may have a protective role in preventing heart failure. Therefore, postmenopausal women

have greater propensity for developing heart failure than premenopausal women.

Certain risk factors for the development of heart failure have a greater influence on the development of the disease in women than in men. Similar to ischemic heart disease, diabetes is a strong risk factor for developing heart failure in women. The incidence of heart failure for women with diabetes and no other risk factors is 3.0% versus 0.4% for women without diabetes. Men and women have distinctive mortality and morbidity rates associated with heart failure, with female sex being a significant independent predictor for survival. The 5-year mortality rate is 14% lower in women than in men based on data from the Framingham Heart Study.

Symptomatic heart failure with preserved left ventricular function appears to be more common in elderly women than in men. The increased likelihood of preserved left ventricular function in women presents a clinical problem, because most of the major heart failure trials included only patients with left ventricular dysfunction. Therefore, most of the trials for which consensus guidelines have been developed exclude one of the most prevalent forms of the disease in women. In addition, diastolic dysfunction may be more common in women than in men. There are conflicting data on the incidence of diastolic dysfunction, but it is currently considered a disease predominantly of elderly women. It is difficult to directly compare studies assessing the sex-based incidence and prevalence of heart failure secondary to diastolic dysfunction because well-defined diagnostic criteria for the disease did not exist when most of these studies were conducted.

Regardless of the difficulty in determining the prevalence of heart failure, there is a sex-dependent pathogenesis of the disease. Physiologic differences in ventricular size and pliability may contribute to differences in the prevalence of diastolic dysfunction. Furthermore, left ventricular remodeling secondary to hypertension and obesity differs between men and women. Women appear to be more susceptible than men to left ventricular hypertrophy associated with combined hypertension and obesity. The skeletal muscle adaptation of changing oxygen supply during the progression of heart failure is reportedly different in men than in women. The underlying mechanisms for the reported differences in the pathogenesis of skeletal muscle adaptation are not known. Therefore, the influence of sex-based differences in heart failure pathogenesis on the response to drugs must be assessed in clinical trials.

Electrophysiologic Differences

Women have a longer period of basal ventricular repolarization than men. The differences in ventricular repolarization are manifested on a surface electrocardiogram by a longer heart rate–corrected QT interval in women than in men. This well-appreciated physiologic difference in women increases their risk of developing torsades de pointes (TdP). Torsades de pointes is a potentially fatal ventricular arrhythmia that can progress to ventricular fibrillation. Female sex is an independent risk factor for developing TdP. Furthermore, in patients with congenital long-QT syndrome, female sex is an independent risk factor for sudden cardiac death. Of interest, the longer basal QT interval in women does not appear until after puberty.

Furthermore, the difference of the postmenopausal QT interval is not as profound as in premenopausal women. These differences suggest a predominant role of the sex hormones on cardiac electrophysiology. The determination of the potential for detrimental electrophysiologic effects of estrogenic compounds and the potential for beneficial effects of testosterone and other androgens is an area of active research.

Regardless of the mechanism, women are at a greater risk of developing TdP than men because of a longer baseline QT interval. However, sex is only one factor that should be considered when assessing the risk of developing this arrhythmia. Other risk factors include electrolyte abnormalities (particularly hypokalemia and hypomagnesemia), underlying coronary artery disease, bradycardia, left ventricular dysfunction, long baseline QT interval, and the use of drugs that prolong the QT interval. This last risk factor is particularly important because many drugs from several therapeutic classes can prolong the QT interval and precipitate TdP. Furthermore, women are at increased risk of developing drug-induced TdP. This topic is discussed in the next section.

Sex-Based Differences in Pharmacotherapy

Overview

The exclusion of women from early Phase I trials before 1993 led to a knowledge gap in sex-based differences that still exists in the pharmacokinetics and pharmacodynamics of drugs marketed before that date. Furthermore, of 163 new drug applications reviewed by the U.S. Food and Drug Administration (FDA) between 1995 and 2000, 11 reported a greater than 40% difference in a pharmacokinetic parameter between men and women. Despite these differences in the pharmacokinetics, there was no recommended sex-based dosing for the drugs approved during this period. Clinical considerations of sex-based pharmacotherapy are predominantly limited to drugs possessing a narrow therapeutic index.

The following sections review the most common sources of pharmacokinetic and pharmacodynamic variability between the sexes while focusing on data from the past 5 years. The discussion is organized into the fundamental pharmacokinetic topics of absorption, distribution, metabolism, kidney excretion, and drug interactions. Reported sex-based differences in the fundamental pharmacokinetic topics discussed in this section are summarized in Table 1-2. Furthermore, examples of potential clinically relevant pharmacodynamic differences between the sexes are reviewed, and implications for pharmacotherapy are discussed. Finally, the clinical impact is discussed in relation to sex-related differences in disease and pharmacotherapy.

Pharmacokinetics

Absorption

Drug absorption after extravascular administration is a potential source of sex-dependent variability in pharmacokinetics. In the assessment of potential

Table 1-2. Sex-Based Differences and Their Potential Effect on the Pharmacokinetics of Certain Drugs

	Men > Women	Men = Women	Women > Men	Comments
Absorption				
Gastric secretion/pH		✓		Differences have been suggested
Gastric emptying time	✓			Clinical significance not assessed
P-gp expression		✓		Conflicting reports; research required
Presystemic clearance	✓			Based on CYP3A probe drug
Distribution				
Lipophilic drugs			✓	
Hydrophilic drugs	✓			
Metabolism				
CYP1A	✓			Minimal research available
CYP2C		✓		Minimal research available
CYP2D6			✓	Clinical significance not assessed
CYP3A		✓		Conflicting reports exist
Kidney elimination				
Glomerular filtration	✓			Clearance formulas may not adequately adjust
Secretion/reabsorption		✓		Differences reported in animal models

CYP = cytochrome P450; P-gp = P-glycoprotein.

differences in drug absorption between men and women, the oral administration route has been studied to the greatest extent. The rate and extent of drug absorption after oral administration is influenced by several factors including surface area for absorption, gastric acid secretion, gastric motility, and expression of hepatic and intestinal enzymes and transporters. Several of the aforementioned components of oral drug absorption have been suggested to be different between the sexes. Overall, there remains a paucity of evidence to suggest that clinically significant differences in drug absorption exist between the sexes after any route of extravascular administration.

Gastric pH and Emptying

Sex-based differences in gastric acid secretion may alter physiologic gastric pH. This difference could potentially alter the absorption of certain drugs between men and women but remains controversial. No differences reportedly exist between the sexes in gastric pH, osmolality, electrolytes, or total concentrations of bile acids. Women have a slower gastric emptying time than men. The disparity in gastric emptying time between the sexes was originally thought to be because of hormonal influences, but this has been disputed. Similar to the case with gastric acid secretion, there are no convincing data to suggest that the underlying physiologic difference in gastric emptying time actually leads to clinically significant differences in the absorption profile for any drug. The sex-based differences in gastric emptying may alter the absorption of aspirin, but the clinical impact has not been assessed.

Active Transport

P-glycoprotein (P-gp) is an active transport protein located on the apical layer of the intestinal cell wall and other locations in the human body, including the bile duct, kidneys, and blood-brain barrier. P-glycoprotein can hinder

drug absorption by actively pumping substrates from the intracellular space back into the intestines. Sex-based discrepancies in P-gp activity in intestinal enterocytes and renal tubules could theoretically lead to differences in bioavailability and kidney clearance of drugs that are P-gp substrates. Furthermore, initial studies suggested that sex-based differences in this efflux drug transporter exist between men and women. However, no differences between men and women in the expression of P-gp in the proximal small intestine were found in a recent investigation. Furthermore, studies using probes for P-gp have concluded that there is no difference between men and women in the function of this transport protein. Therefore, the significance of potential sex-based expression or functional differences in P-gp is likely to have a minimal clinical impact in the absorption or elimination of drugs. More research is required to determine if sex-based differences exist in other intestinal efflux and influx transporters and if there is the potential for clinical significance.

Presystemic Drug Metabolism

Sex-based differences in the presystemic metabolism of drugs that undergo extensive first-pass metabolism may have the biggest influence on absorption differences between men and women. The cytochrome P450 (CYP) 3A isozyme is highly expressed in intestinal enterocytes and contributes to the presystemic clearance of many drugs. Even though no differences between the sexes exist in the intestinal expression of CYP3A, the CYP3A4 probe drug midazolam has traditionally been reported to have less presystemic clearance in women than in men. This result could indicate that functional differences in CYP3A exist between men and women. More data are needed to determine the impact of sex on the presystemic clearance of high extraction ratio drugs metabolized by CYP3A.

Distribution

The distribution of drugs in the human body is reliant on several physiologic factors that differ between men and women. First, women are, on average, smaller than men on a weight basis, with men having an increased muscle mass-to-body fat ratio. Volume of distribution traditionally has been adjusted for body weight in pharmacokinetic studies that have uncovered differences between men and women. The reported difference is commonly attenuated when the volume of distribution is adjusted for weight. However, an adjustment of drug therapy dose based on body weight is not commonly performed in clinical practice. This approach may lead to clinical problems when equivalent doses of certain drugs are administered to men and women. For example, women, in general, have higher plasma concentrations than men at the same fluoroquinolone doses. Standard equivalent dosing between men and women may contribute to observations that women are more susceptible to toxicity associated with the fluoroquinolone antibiotics.

In addition to an increased body weight, men have an increased amount of body water compared with women. Highly lipophilic drugs generally have larger volumes of distribution in women. However, the volumes of distribution are lower for hydrophilic drugs in women than in men. Therefore, drugs that distribute to lean tissue will have a smaller volume of distribution in women and subsequently higher maximal plasma concentrations than in men. In contrast, lipophilic drugs, such as the benzodiazepines, appear to have lower maximal concentrations in women because of a larger volume of distribution compared with men. However, all factors that could alter the pharmacokinetics of drugs must be considered, including the volume of distribution, absorption, and elimination.

Hepatic Clearance

The CYP enzymes are catalysts for most Phase I drug reactions and have been the focus of research to identify potential sex-related differences in the hepatic clearance of drugs. Several *in vitro* studies have shown that this enzymatic system can be altered by hormonal influences. In general, these *in vitro* experiments have not translated into clinical success to identify sex-based differences in drug metabolism caused by hormonal regulation. In fact, the wide variability of systemic clearance of probe drugs observed *in vivo* has led most experts to conclude that there is insufficient evidence to indicate that clinically relevant differences exist in the activity of Phase I or II enzymes between men and women.

Cytochrome P450 3A is the most abundant isoform of the CYP family involved in oxidative drug metabolism and is responsible for the metabolism of around 50% of all drugs. As with other CYP isozymes, hepatic CYP3A activity does not appear to vary between the sexes; however, it may contribute to sex-based differences in presystemic clearance, as discussed previously. There is a large variability observed with CYP3A substrates, but in most cases, sex-related differences in pharmacokinetics are attenuated when factors such as age, hormonal supplementation, race, smoking status, genetics, and other pertinent demographics are taken into consideration. Even though profound differences may not exist in CYP3A metabolism between men and women, the actual differences in metabolic activity of CYP3A may

contribute to clinically significant sex-based interactions when taken into consideration with other physiologic differences.

Kidney Excretion

Sex-based differences in glomerular filtration rate are recognized, and formulas used to predict kidney function have traditionally included a term for sex. For example, the commonly used Cockcroft-Gault formula estimates that women have a 15% lower creatinine clearance rate than men. Furthermore, a more recently validated equation to estimate glomerular filtration rate suggests that women have a 25% lower glomerular filtration rate than men. Regardless of the exact percentage, drugs that are predominantly eliminated through glomerular filtration such as digoxin, vancomycin, and cephalosporins have a lower kidney clearance in women than in men. The decreased clearance by the kidneys of the aforementioned drugs has not translated into consistent clinical dose adjustments based on sex alone. However, evidence is accumulating that the renally filtered glycoprotein IIb/IIIa inhibitors should be closely monitored in women. The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative reported that the incidence of major bleeding events associated with glycoprotein IIb/IIIa inhibitors in women was about double that in men. However, when properly dosed, the risk of bleeding complications in women decreased significantly.

Sex-related differences in the renal tubular secretion of drugs are less clear than with glomerular filtration rate. Sex-related differences in transport proteins located in the kidneys, such as the multi drug-resistant-associated protein or the organic anion transporters, have been reported in animal models. More evidence is needed to determine the influence of active tubular secretion on sex-related differences in drug handling and response.

Drug Interactions

Gender differences may influence the frequency and extent of drug interactions between men and women. For example, women are more likely to use alternative herbal-based drugs than men. The difference in herbal product use between the genders is greatest in the elderly. Differences in the use of alternative therapy could have a substantial impact on the risk of drug interactions. In addition to gender influences, sex-based differences in pharmacokinetics and drug metabolism may contribute to sex-based differences in the occurrence of drug interactions. Differing expression or function of drug-metabolizing enzymes between the sexes could theoretically alter drug interaction profiles. Like much of the research in this area, there are limited numbers of controlled investigations into the sex-based differences in drug interactions.

Sex-based differences in the induction and inhibition of CYP3A may exist. Rifampin increases the systemic clearance of midazolam to a greater extent in women than in men, but it has a lesser induction effect on the presystemic clearance of CYP3A substrates in women. Because these differences were observed at similar rifampin serum concentrations, CYP3A induction may have differing effects in hepatocytes versus enterocytes between men and women. Furthermore,

clarithromycin, a CYP3A inhibitor, has greater inhibitory effects on presystemic metabolism in women than in men receiving midazolam. The differences in CYP3A induction and inhibition between the sexes are likely substrate-dependent and should not be extrapolated to all CYP3A substrates until more research is conducted. Furthermore, the clinical significance of differences in presystemic drug interactions should be assessed.

The fluctuations in sex hormone concentrations during the female menstrual cycle do not appear to alter CYP3A activity. Furthermore, there is a lack of evidence to indicate that fluctuating endogenous hormone concentrations alter drug metabolism through any enzyme system, and properly designed trials are required. Sex-based differences in endogenous hormones are not the only factor that could influence drug interaction profiles between men and women. Exogenous hormones found in oral contraceptives and hormone replacement therapy may cause pharmacokinetic variability between the sexes. For example, 17 α -ethinyl estradiol, found in many oral contraceptive formulations, has been attributed to a 20-fold decrease in selegiline oral clearance in healthy female volunteers. The altered metabolic ratio of selegiline suggested that the interaction was caused by an inhibition of the CYP2C19 and CYP2B6 enzymes. Currently, data conflict as to precisely which exogenous hormones cause clinically significant drug interactions; this remains an area of active research.

Pharmacodynamics/Clinical Outcomes Overview

Women have about a 1.5-fold increased risk of developing an adverse drug event compared with men. This increased risk could be associated with differences in the occurrence of adverse event reporting, pharmacokinetics, pharmacodynamics, or any combination of the three. Sex-based differences in pharmacological response are difficult to assess given the potential for reporting and fundamental pharmacokinetic differences between men and women. For example, it has been suggested that women have a greater propensity to report adverse drug reactions than men. In general, sex-based differences in drug response are considered pharmacodynamic if men and women have similar plasma concentrations despite a distinctly different drug response. The following section will discuss recent developments in sex-dependent responses or adverse drug reactions.

Cardiovascular Disorders

It is not surprising that sex-dependent characteristics have been observed with the pharmacotherapy of several cardiovascular disorders because the underlying pathophysiology is different between men and women. Differences in cardiovascular drug response between men and women have largely been based on retrospective or observational data. Therefore, when discussing response differences between men and women, the sex bias in managing cardiovascular diseases must be considered. Women are to be less likely than men to receive prompt and optimal treatment of an acute myocardial infarction. Furthermore, women may not receive prompt and optimal heart failure treatment because they are more likely than men to have preserved left ventricular function. This difference may be

partially because women are, on average, older when they develop cardiovascular disease and therefore more likely to have concurrent diseases and treatment contraindications. Nevertheless, the apparent sex-based discrepancy in the aggressiveness of cardiovascular pharmacotherapy should not be overlooked when evaluating reported drug response differences between men and women.

Heart Failure Pharmacotherapy

Large randomized clinical trials assessing heart failure pharmacotherapy have largely been composed of men. Most of the trials have only included patients with left ventricular dysfunction as assessed by a left ventricular ejection fraction less than 40%. This criterion excludes most women with heart failure because they are generally older than men when they develop left ventricular dysfunction despite presenting with symptomatic heart failure. It is therefore difficult to assess the efficacy of angiotensin-converting enzyme inhibitors, β -blockers, digoxin, or spironolactone in women because a large percentage of the study subjects in these landmark trials were men.

Women are less sensitive to β -adrenergic receptor blockade with propranolol compared with men. This result leads to the hypothesis that women may not have the same mortality benefits from β -blockers as men. However, data from the Women's Health Initiative suggest that the combination of a β -blocker with a diuretic has mortality benefits in postmenopausal women similar to those in men with hypertension. Similar to hypertension, β -blockers were originally believed less effective in women than in men for the treatment of heart failure. Pooled data from three large clinical trials demonstrated that β -blockers have similar mortality benefits between men and women in heart failure. Currently available data suggest that women and men have similar responses and mortality benefits from β -blockade therapy in hypertension and heart failure. However, properly designed prospective randomized trials are required to assess sex-based differences in mortality reduction with β -blockers.

A post hoc investigation of the Digitalis Intervention Group (DIG) trial revealed a potential concern regarding digoxin use in women with heart failure. Women randomized to treatment with digoxin had an increased mortality rate from worsening heart failure compared with men on digoxin. Because the original DIG trial was not designed to detect a difference between the sexes, this disparity in death rates between men and women may be attributed to randomization error. However, it is possible that the differences were pharmacokinetic. Women enrolled in the DIG trial received smaller average doses of digoxin but achieved higher serum concentrations than men after 1 month of therapy. It is difficult to assess the clinical significance of the increased plasma digoxin concentrations in women. However, given the increase in mortality, the potential pharmacokinetic and pharmacodynamic differences of digoxin in men versus women may be worthy of further investigation.

Endogenous estrogens inhibit the renin-angiotensin system, but the potential sex-based effects of angiotensin-converting enzyme inhibitors on mortality secondary to hypertension or heart failure have not been assessed. Similarly, the sex-based effects of spironolactone are unknown. In summary, sex differences exist in the effects

of drugs on biologic systems involved in the pathogenesis of heart failure. There are no outcome data from appropriately designed prospective studies assessing the effects of pharmacotherapy on the mortality of the disease.

Antiplatelet Drugs

The benefits of aspirin for the secondary prevention of cardiovascular disease are recognized to be independent of sex. The Physician's Health Study demonstrated that taking 325 mg of aspirin daily reduced the risk of myocardial infarction by 44% in men older than 50 years. Even though sex-specific differences in aspirin pharmacokinetics and platelet response have been recognized for several years, the use of aspirin for the primary prevention of cardiovascular disease in women was not prospectively assessed until the Women's Health Study, published in 2005. This analysis suggests that daily full-dose aspirin therapy should not be used routinely for the primary prevention of cardiovascular disease in women younger than 65. Women in the study had an increased risk of bleeding with aspirin and a risk of hemorrhagic stroke similar to that reported in men. The increased risk of bleeding likely outweighs the benefits from low-dose aspirin.

The routine use of glycoprotein IIb/IIIa inhibitors in women with acute coronary syndromes has been questioned secondary to an increased bleeding risk versus men. As discussed previously, differences in kidney function between men and women may contribute to the increased bleeding risk caused by a decreased clearance of the drug. In addition, women have increased bleeding rates associated with the routine treatment of non-ST-segment elevated myocardial infarction. Glycoprotein IIb/IIIa dose adjustments for body size and kidney function decrease bleeding rates in women, but a sex-related difference still exists. The clinical use of glycoprotein IIb/IIIa inhibitors in women is complex because women have a greater mortality rate than men after an acute coronary syndrome together with the increased bleeding risk. Appropriate dosing of glycoprotein IIb/IIIa inhibitors is critical in clinical practice, and their use in women should be based on the individual risk and potential benefits.

QT Interval and TdP

Women have a greater risk of developing drug-induced TdP than men. This difference in risk became well recognized by health care professionals after the withdrawal of several drugs from the U.S. market because of the increased risk of developing this potentially fatal arrhythmia. In addition to the greater baseline QT interval, women are more sensitive to quinidine-induced QT-interval prolongation. This increased sensitivity to quinidine in the absence of pharmacokinetic differences between men and women has been corroborated by two research groups.

The sensitivity to drug-induced QT-interval prolongation with ibutilide may be influenced by the phase of the menstrual cycle. Ibutilide delays ventricular repolarization by inhibiting the rapid component of the delayed rectifier current (I_{Kr}), which is encoded by the *hERG* gene. Inhibiting the *hERG*-related current prolongs ventricular repolarization and is a common mechanism among drugs that precipitate TdP. Several drug classes can inhibit this current and prolong repolarization, including the Vaughn-Williams Class III antiarrhythmics, such as ibutilide. After low-dose ibutilide administration, women appear to be the

most sensitive to QT-interval prolongation during menses and the ovulatory phase. This increased drug-induced QT-interval prolongation does not appear to be caused by pharmacokinetics. The time-dependent changes to the inhibition of I_{Kr} in women could influence studies assessing sex-based differences in the sensitivity to drug-induced QT-interval prolongation when uncontrolled for the menstrual cycle.

Opioid Analgesics

Although several studies have been performed assessing sex-related differences in opioid analgesia, the clinical impact remains unclear. Nonetheless, women are more sensitive to the effects of morphine on pain and to the occurrence of adverse effects including respiratory depression, nausea, and vomiting. The apparent increased therapeutic and toxic effects in women have been studied because men and women have different perceptions of pain. Sex-based opioid sensitivity persists in women, but whether it is a pharmacokinetic or pharmacodynamic difference between the sexes is currently unknown. The difference in opioid response may be because of a smaller body size, or women may have opioid receptor density or sensitivity to analgesics different from men. Furthermore, the hormones estradiol and testosterone have been suggested to modulate the sensitivity to analgesia differently, and this is an area of active investigation. Despite the lack of knowledge of the mechanisms of the observed increased sensitivity in women, sex-based dosing of analgesia has been suggested and may be implemented soon.

Anti-retroviral Pharmacotherapy

An emerging area of interest in sex-based pharmacotherapy is anti-retroviral treatment associated with human immunodeficiency virus (HIV) infection. Areas of particular interest include the characterization of both sex-based pharmacokinetics and pharmacodynamics of these agents. The evolution of clinical trials for HIV therapy has been similar to cardiovascular disease given that only 12% of subjects in a meta-analysis of 49 clinical trials of HIV pharmacotherapy were women. Evidence continues to emerge that women are more sensitive to the adverse effects of nucleoside reverse transcriptase inhibitors than men. Furthermore, early observational evidence suggests that women, compared with men, have a slower rate of disease progression to acquired immune deficiency syndrome and greater virologic suppression when receiving highly active anti-retroviral therapy. Delineating the source of the observed sex-based differences in response to anti-retroviral therapy is particularly important because lifelong therapy is necessary for this chronic disease.

Conclusion and Clinical Impact

Physiologic differences between men and women alter the incidence, pathophysiology, and progression of several diseases. Furthermore, important physiologic differences between men and women alter the pharmacokinetics and pharmacodynamics of several drugs. Table 1-3 presents a summary of important physiologic differences that may

influence disease or pharmacotherapy. In addition to these fundamental differences, several observational and retrospective analyses of pooled clinical trials suggest that, in several diseases, differences in clinical outcomes exist between men and women that are independent of drug concentrations. Sex-specific pharmacotherapy is still in its infancy, and the impact of male and female physiology on real clinical outcomes is still controversial in most diseases.

As the importance of sex on the progression of disease and pharmacotherapy continues to emerge, clinicians are becoming more aware of dissimilarities in the response to treatment between men and women. However, there remains a disconnect between fundamental physiology and the observed outcomes of large clinical trials between men and women. This disconnect has translated into a polarized and often controversial topic of the clinical importance of observed pharmacotherapy differences in men versus women. This topic is even more complicated because of the historic tendency of investigators to include predominantly men in landmark clinical trials in several diseases. The inadequate power to detect sex-based differences in clinical trials has resulted in the use of post hoc observational data to determine an appropriate course of therapy. The FDA and the National Institutes of Health have taken steps to discourage male-based research. Until results of studies that include an adequate number of women are published, sex-based differences in disease and pharmacotherapy will likely remain a controversial topic. Therefore, it is the role of the pharmacist to apply known physiologic, pathophysiologic, pharmacokinetic, and pharmacodynamic differences between the sexes when assessing appropriate pharmacotherapy for men and for women.

Table 1-3. Sex-Based Physiologic Differences That Affect Disease Progression or Pharmacotherapy

Difference	Influence
Physiologic influences	
Muscle-to-fat ratio	May influence drug disposition in men
Organ size, heart	May influence the pathogenesis of cardiovascular disease in men
Cardiac repolarization	Increases risk for acquired QT-interval prolongation in women
Sympathetic activity	Greater resting heart rate in women
Blood pressure	Increases risk for cardiovascular disease in men younger than 70
Hormonal influences	
Bone metabolism	Increases risk for osteoporosis in women after menopause
Estrone metabolism	Altered metabolism increases risk for autoimmune disorders in women
Smoking sensitivity	Increases risk for lung and cardiovascular disease in women
Menstrual cycle	May influence drug pharmacokinetics and/or response in women

Annotated Bibliography

1. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005;353:2550–8.

This double-blind, placebo-controlled, randomized, noninferiority trial was designed to evaluate the effect of oral contraceptives on flares of SLE. This study was of clinical significance because SLE predominantly presents in women of childbearing age. Fluctuations in female sex hormone concentrations contribute to disease flares, although the contribution of exogenous hormone administration is largely unknown. The study subjects were mainly women with inactive disease (n=139 of 186 studied). The remainder of the women had stable disease. About one-half of the women were administered 35 mcg of ethinyl estradiol with a triphasic norethindrone content of 0.5/0.75/1.0 mg every 7 days, followed by 7 days of an inert tablet. The primary end point was the presence of severe flares, which occurred at about the same rate in both groups. Use of oral contraceptives was not associated with an increase in mild-moderate or total flares for the 1-year study period. The authors note that the original planned sample size was not achieved, which may have led to a type II error. This was a novel trial that dispelled the thought that oral contraception should not be used in patients with SLE. It demonstrates that oral contraceptives can be used safely in patients who have had inactive disease for 1 year.

2. Pilote L, Dasgupta K, Guru V, Humphries KH, McGrath J, Norris C, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ* 2007;176:S1–44.

This comprehensive review covers the major cardiovascular diseases in men and women, including acute coronary syndromes, hypertension, heart failure, atrial fibrillation, and dyslipidemias. It summarizes the disease states in an easy-to-read format, focusing on sex-based differences in prevalence, mortality, and hospital admissions. The remainder of the review also includes specific discussions on research related to the mechanisms of the sex-based differences in the disease. Furthermore, the review examines differences in patient socioeconomic status and in the prescribing habits of physicians to men versus women. It summarizes all of the major headings by clearly indicating the knowledge gaps in the current literature. It is an excellent reference for clinicians because it predominantly presents facts of the diseases with only minor amounts of author interpretation. Finally, it is one of the only sources of review for genetic and sex determinants of disease such as hypertension and coronary vascular disease.

3. Masoudi FA, Havranek EP, Smith G, Fish RH, Steiner JF, Ordin DL, et al. Gender, age, and heart failure with preserved left ventricular systolic function. *J Am Coll Cardiol* 2003;41:217–23.

It has long been suggested that heart failure with preserved left ventricular systolic function is predominantly a disease in women, but this premise was based on data obtained from studies with small sample sizes. Furthermore, the biologic basis was not understood because previous trials did not have an adequate sample size to independently associate sex with the disease. The objective of this trial was to determine the relative contribution of sex, age, and comorbidity on the prevalence of preserved left ventricular systolic function in patients with heart failure. This retrospective trial with

a cross-sectional design used data obtained from 19,710 medical charts of Medicare patients with a diagnosis of heart failure. The number of patients with preserved left ventricular systolic function (ejection fraction more than 50%) was 6754, and 79% were women. The average age of patients with preserved systolic function was older than those with left ventricular dysfunction. After correction for multiple covariates, female sex was a strong predictor of heart failure with preserved left ventricular function. The authors point out that these results should not be extrapolated to all patients with heart failure because these were Medicare beneficiaries who were hospitalized primarily for heart failure. Therefore, younger or ambulatory patients with heart failure were not included in the analysis. This study serves as a reminder that most of the large clinical trials in heart failure were performed in patients with left ventricular systolic dysfunction, which is less common in women. Therefore, women were likely underrepresented in these trials. Furthermore, this trial demonstrated the importance of further research on the sex-based progression and treatment of heart failure.

4. Paine MF, Ludington SS, Chen ML, Stewart PW, Huang SM, Watkins PB. Do men and women differ in proximal small intestinal CYP3A or P-glycoprotein expression? *Drug Metab Dispos* 2005;33:426–33.

The interplay of P-gp with CYP3A substrates has been recognized, and several investigators have described sex-based differences in the expression and function of both of these proteins. P-glycoprotein activity appeared to be greater in men, whereas limited clinical evidence suggested that CYP3A activity was greater in women. This study aimed to characterize the expression of P-gp and CYP3A in the proximal small intestine of healthy men and women. Duodenal tissue was obtained from pinch biopsies after 93 upper intestinal endoscopies, and P-gp, CYP3A4, and CYP3A5 expression was determined by Western blot analysis. There was no sex difference in the expression of any of the proteins. Of interest, CYP3A4 expression was statistically lower in postmenopausal women than in premenopausal women, which may suggest a role for estrogen in protein regulation. This study is limited because it measured protein content from only one location of the intestinal tract and protein expression of drug transporters and CYP enzymes may differ throughout the gastrointestinal tract. Furthermore, the differences in the expression of the proteins may be different in other organs, such as the liver. However, there is inconclusive evidence of sex-based differences in CYP and P-gp substrates from clinical trials, and this study provides a rational explanation for the lack of reported sex differences.

5. Overholser BR, Kays MB, Lagvankar S, Goldman M, Mueller BA, Sowinski KM. Pharmacokinetics of intravenously administered levofloxacin in men and women. *Pharmacotherapy* 2005;25:1310–8.

This clinical pharmacokinetic trial was designed to enroll healthy men and women matched for body mass index. Levofloxacin distributes rapidly and extensively to lean body tissue and was therefore expected to have a larger volume of distribution in men because of the increase in muscle mass compared with women. This was a unique trial because the investigators sought to recruit men and women of similar body weights to characterize the pharmacokinetics of a fluoroquinolone. A total of 11 men and 9 women were enrolled, and pharmacokinetics were assessed after a single intravenous dose of 500 mg of levofloxacin. Despite similar body weights and body mass indexes, the maximal concentrations and overall exposure to levofloxacin were

greater in women than in men. This study supports the notion that physiologic sex-based differences in the muscle-to-fat ratio lead to pharmacokinetic differences of certain drugs between men and women. Furthermore, this study provides insight into a possible pharmacokinetic difference between men and women that may partly explain the apparent sex-related difference in reported adverse events with fluoroquinolone antibiotics.

6. Schwartz JB. The current state of knowledge on age, sex, and their interactions on clinical pharmacology. *Clin Pharmacol Ther* 2007;82:87–96.

This is a recent review of the current knowledge of sex-based differences in clinical pharmacology. This review is unique because it examines the interaction of sex with age as it applies to differences in clinical pharmacology between men and women. It begins by breaking down the basic components of pharmacokinetics and relates bioavailability, volume of distribution, and clearance differences between the sexes in aging populations. This review incorporates other relevant topics such as polypharmacy and other characteristics of an older population when assessing sex-based differences. This article considers both known physiologic and social differences in the elderly and is beneficial for health care professionals who want to assess the differences between men and women in aging populations.

7. Gorski JC, Vannaprasaht S, Hamman MA, Ambrosius WT, Bruce MA, Haehner-Daniels B, et al. The effect of age, sex, and rifampin administration on intestinal and hepatic cytochrome P450 3A activity. *Clin Pharmacol Ther* 2003;74:275–87.

This study was designed to assess sex and age interactions on the extent of CYP3A induction in healthy men and women. Cytochrome P450 3A activity was assessed by both the systemic clearance and hepatic clearance of the probe drug midazolam. Cytochrome P450 activity was induced by 7 days of rifampin administration. Midazolam was orally and systemically administered at baseline and day 7 of CYP induction. There was no difference in the baseline systemic clearance between men and women of any age without induction. This review corroborated the results of several studies to suggest that basal CYP3A activity is not different between the sexes. Of interest, the induction of CYP3A appears to be different between men and women. Furthermore, the location of the enzyme may have a differential extent of induction between men and women. Men displayed a greater extent of CYP3A induction, as assessed by systemic clearance, whereas women had a greater clearance of oral midazolam. This suggests that women have a greater induction of intestinal CYP3A and that men have greater inducible CYP3A in hepatic tissue. Cytochrome P450 3A induction based on midazolam clearance was highly variable, from negligible induction to greater than 300%. The authors suggest that the differential induction profile of CYP3A and the larger variability between the sexes contribute to the conflicting results of basal CYP3A function. This review illustrates the importance of assessing drug interactions in both men and women, even when basal enzymatic activity is the same.

8. Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, et al. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J Med* 2005;353:671–82.

Several studies between 1980 and the early 1990s suggested that women did not receive optimal management

of myocardial infarctions and that a sex-based difference in treatment existed. The goal of this study was to assess the potential differences in the management of acute myocardial infarctions based on sex and race. This study used the National Registry of Myocardial Infarction database to obtain a sample of 598,911 patients who were deemed appropriate to receive optimal treatment after hospital admission for a myocardial infarction. Optimal treatment was based on the 1990 ACC/AHA consensus guidelines. Optimal treatment included reperfusion therapy (ST-segment elevation) and both aspirin and β -blocker administration within 24 hours of admission. An additional primary end point was a coronary angiography during hospitalization at facilities that had the appropriate capabilities. Differences in the treatment of and mortality rate from an acute myocardial infarction were similar for white women and white men. The largest differences were between white men and African American men compared with African American women. Furthermore, African American women had the highest mortality associated with myocardial infarction. The use of aspirin and β -blockers was not dependent on sex or race. Although sex-based differences in the management of myocardial infarction still exist, this study illustrates that disparities according to race may be more profound. This study also corroborated results of previous trials that suggested African American women have the highest mortality rate associated with myocardial infarction, which may be because they are the most likely to receive less than optimal management. The sex-based gap in the optimal treatment of acute coronary events appears to be narrowing. However, this study illustrates that more research is required to eliminate both sex and racial differences in the optimal management of cardiovascular disease.

9. Wassertheil-Smoller S, Psaty B, Greenland P, Oberman A, Kotchen T, Mouton C, et al. Association between cardiovascular outcomes and antihypertensive drug treatment in older women. *JAMA* 2004;292:2849–59.

The objective of this study was to assess cardiovascular mortality associated with the use of various antihypertensive regimens in postmenopausal women. The results of this study contributed to the literature after the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) concluded that diuretics should be used in most patients with hypertension as monotherapy or in combination with other agents. The subjects were women with hypertension from the Women's Health Initiative Observational Study, which was a cohort study of 93,676 women age 50–79 at enrollment. In the hypertensive arm of this study, 11,294 women were treated with monotherapy consisting of an angiotensin-converting enzyme inhibitor, β -blocker, diuretic, or calcium channel blocker; and 4493 were on some combination of these classes. The prospective observation period was, on average, 5.9 years. Calcium channel blockers plus diuretics were associated with twice the risk of cardiovascular death compared with diuretics plus β -blockers. As monotherapy, calcium channel blockers were associated with increased morbidity and mortality from cardiovascular disease compared with diuretics alone. After adjusting for covariates, diuretics were the best at controlling blood pressure in the women enrolled in this study. The authors conclude that the increased likelihood of reaching target blood pressure in the diuretic groups may explain some of the results of the study. Despite the large sample size used in this trial, the assessed outcomes were in a small number of patients, specifically the groups not receiving diuretics, and some of the results of this trial may have been observed because of sampling error. The use of

calcium channel blockers for treating hypertension without other cardiovascular disease increased in the years leading up to the ALLHAT trial. This study should raise caution for the routine use of calcium channel blockers in postmenopausal women who have only hypertension.

10. Ghali JK, Pina IL, Gottlieb SS, Deedwania PC, Wikstrand JC. 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* 2002;105:1585–91.

Women have been underrepresented in clinical trials for the treatment of heart failure with left ventricular systolic dysfunction. The objective of this study was to assess the response of women with heart failure and impaired left ventricular function to β -blockade. Pooled data from three large clinical trials of carvedilol, controlled-release metoprolol, and bisoprolol were used to address the two primary outcomes of total mortality or the combined end point of all-cause mortality or all-cause hospitalizations. None of the three studies had an adequate number of women to properly assess mortality benefits between the sexes in the individual trials. A significant reduction in both primary end points in women was reported in the pooled trials. This retrospective study concluded that β -blockers have similar mortality benefits in heart failure between men and women. Although this study was retrospective, it helped dispel the belief that women respond to β -blockers in ways different from men in heart failure with left ventricular systolic dysfunction. However, prospective trials are needed to properly assess potential sex-based differences in mortality associated with heart failure treatment.

11. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002;347:1403–11.

This study was a post hoc subgroup analysis of the DIG trial to determine if there was a sex-based difference in the response to digoxin. The original DIG trial reported that digoxin did not decrease the risk of mortality in patients with heart failure. Similar to other large clinical trials for the treatment of heart failure, the original DIG trial enrolled patients with left ventricular systolic dysfunction only and did not assess sex-based differences. This retrospective analysis revealed that mortality rates because of worsening heart failure and cardiovascular disease were significantly higher in women receiving digoxin than in women receiving placebo. In contrast, digoxin significantly reduced mortality associated with heart failure in men compared with placebo. Furthermore, women randomized to digoxin had an increased mortality rate from worsening heart failure compared with men on digoxin. The observed differences in mortality may have been a pharmacokinetic interaction because women had significantly higher serum digoxin concentrations despite receiving a lower average dose. However, the DIG trial had about 4 times as many men as women and was not designed to detect a difference between the sexes. The disparity in death rates between men and women may therefore be attributed to randomization error. However, this study raised several questions regarding the safety of digoxin use in women with heart failure. This study, together with other retrospective analyses of the DIG trial, has increased the awareness of maintaining serum digoxin concentrations in the lower end of the therapeutic range.

12. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in

the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293–304.

This is the first study to prospectively assess the use of aspirin for the primary prevention of cardiovascular disease in women. The Women's Health Study was a randomized, placebo-controlled trial in 39,876 healthy women 45 years or older without a history of a previous cardiovascular event. Women were randomized to receive placebo or aspirin 100 mg every other day and monitored for 10 years for a cardiovascular event. This study did not find a significant risk reduction of myocardial infarction in the women randomized to aspirin, as previously reported in men. However, the women had a significant decrease in the risk of ischemic stroke, which was not observed in men in other trials. A subgroup analysis reported in this study suggested that aspirin is beneficial for the primary prevention of major cardiovascular events in women older than 65. The authors also conducted a meta-analysis of aspirin to further validate the results of this trial. Indeed, the results of the meta-analysis agreed with this trial. It therefore appears that the benefits of aspirin for the primary prevention of cardiovascular disease are inversely related in women compared with men. This study suggests that the routine use of aspirin to reduce cardiovascular disease should not be recommended for women younger than 65 because the risks outweigh the benefits.

13. Alexander KP, Chen AY, Newby LK, Schwartz JB, Redberg RF, Hochman JS, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. *Circulation* 2006;114:1380–7.

Women have an increased risk of bleeding associated with the routine treatment of non–ST-segment elevated myocardial infarction compared with men. The objective of this study was to assess the safety of glycoprotein IIb/IIIa inhibitors in women and assess the proper dosing of these agents. This study used a large database of patients with a high risk of a non–ST-segment elevated acute coronary syndrome. Patient information was entered in the database through retrospective chart review, and there was multicenter involvement in the United States. This analysis included 32,601 men and women who were eligible for treatment with a glycoprotein IIb/IIIa inhibitor, and 56.6% of these patients were administered a glycoprotein IIb/IIIa inhibitor. The primary outcome assessed was the occurrence of a major bleeding event. A majority of the patients in this analysis were men, with 37.3% of the entire sample being women. The incidence of major bleeding associated with glycoprotein IIb/IIIa inhibitors was about double in women compared with men. Adjustments for both body size and kidney function decreased the observed bleeding rates in women, but a sex-related difference remained. The results of this study suggest that appropriate dosing of glycoprotein IIb/IIIa inhibitors is critical in clinical practice. Furthermore, use of these agents in women should be based on the individual risk and potential benefits to the patient.

