The numbers are in! Deaths due to cardiovascular disease are declining in the United States. That is the good news. The bad news is that cardiovascular mortality in women exceeds that of men. One factor contributing to this disparity may be low socioeconomic status, which deters some women from seeking medical care. However, this disparity also reflects basic differences in normal physiology and pathophysiology between males and females that are not well understood and remain understudied. The lack of attention to sex differences in etiology of cardiovascular disease has resulted in inadequate methodologies and strategies to prevent, diagnose, and treat cardiovascular diseases in women compared with men. For example, physicians routinely order less stress testing and coronary angiography, and treat with less proven medications, in women they believe to have angina.

This article provides a brief overview of cardiovascular diseases affecting women compared with men, how sex hormones affect vascular function, and illustrative scenarios applicable to reproductive medicine. In this discussion, “sex” is defined by the sex chromosomes and functioning reproductive organs; “gender,” or maleness and female-ness, is defined along a continuum of how an individual functions according to societal attributes or expectations.

Sex disparity in cardiovascular diseases
Cardiovascular diseases fall into 3 general categories with regard to sex disparity: (1)
The genetic variable underlying sex differences in cardiovascular disease is the complement of sex chromosomes (XX or XY).

**Conditions unique to one sex.** This category is particular to reproductive function. Although erectile dysfunction is not a fatal condition, it may be a symptom of more systemic cardiovascular disease/risk, which could be fatal. On the other hand, hypertensive disorders of pregnancy, including pre-eclampsia, can be fatal if not treated. Even when treated successfully, these hypertensive disorders, as well as gestational diabetes, may double the 10-year risk for adverse cardiovascular events in affected women compared with women who do not have a history of pregnancy disorders.

**Conditions occurring in both sexes, with different prevalence.** These conditions are complex and may be due, in part, to sex differences in autonomic control of vascular function and stress. Much remains to be learned about these disorders, reflecting their complexity, perhaps their female predominance, and the lack of animal models. While these conditions reduce quality of life, they do not carry high mortality.

**Conditions that present differently in women than in men.** Myocardial infarction is perhaps the most studied adverse event of atherosclerotic ischemic heart disease. Although women present with chest pain as frequently as their male counterparts, they have greater associated symptoms of neck, jaw, and back pain and nausea. Differential presentation of ischemic heart disease symptoms reflects differences in the underlying etiology and characteristics of the disease. In men, atherosclerotic lesions are more punctuated, while in women they are more diffuse, often involving the microcirculation. Further, increased microvascular disease may contribute to increased rates of angina and have a greater negative impact on quality of life in women, compared with men, after a myocardial infarction.

**Genetic influences on cardiovascular diseases**

The genetic variable underlying sex differences in cardiovascular disease is the complement of sex chromosomes (XX or XY). Genes on the X chromosome affect development of cardiovascular diseases through modulation of mitochondrial function, adiposity, response to hypoxia, apoptosis, and response to androgens. Genetic variance in genes on the X chromosome will have greater influence on the physiologic processes and phenotype in males, who have one copy of the gene, compared with females, in whom mosaic inactivation of either the maternal or paternal X will result in greater heterogeneity of phenotype.

An example of this phenomenon is the CAG repeat polymorphism that encodes the transcriptional domain of the androgen receptor. In males, the length of this repeat is associated with androgen receptor activity and levels of high-density lipoprotein (HDL) cholesterol, abdominal obesity, elevated sympathetic tone, and blood pressure. This repeat polymorphism is, however, seen in women with polycystic ovary syndrome (PCOS) but is not associated with changes in HDL cholesterol, sympathetic tone, or blood pressure.

The SRY of the Y chromosome, while necessary for testicular development, also affects expression of tyrosine hydroxylase, a rate-limiting step in the conversion of tyrosine to dihydroxyphenylalanine (DOPA), required for synthesis of norepinephrine, the adrenergic neurotransmitter. Translocation of this gene from a male hypertensive rat to a normotensive rat or to an autosome of a female animal results in development of spontaneous hypertension in the recipient animal.

**Studies need to analyze data by sex**

Sex as a biological variable is dichotomous. Therefore, results from experimental and clinical studies should be analyzed by sex, as well as using sex as a covariate. This require-
ment for scientific excellence is not yet a reality, since the sex of cultured cells or isolated tissues used to define molecular mechanisms of disease is usually not identified or considered.

Basic and preclinical studies conducted on experimental animals in fields of study directly relevant to cardiovascular disease (physiology, pharmacology, and endocrinology) mostly use male animals (Figure 1).14 In clinical trials, women are underrepresented (Table 1).15,16 Further, position papers on diagnostic/treatment modalities or their implementation often do not consider sex.17

Treatment efficacy in women vs men

Despite these shortcomings, many treatment modalities identified from major clinical studies may apply to women, but with some exceptions.3 For example, smoking cessation reduces the risk of myocardial infarction in women and men; however, because sex differences exist in the factors contributing to addictive behaviors and substance abuse, smoking cessation programs are best when tailored to the individual.18

Statins reduce low-density lipoprotein (LDL) cholesterol and global cardiovascular risk in women as in men, but the absolute benefit in women who do not have established coronary disease is small.19 Women with established coronary disease, however, benefit as much from statin therapy as, if not more than, men.20-22

Low-dose aspirin, a standard primary prevention therapy against myocardial infarction in men, is not effective in women and is not recommended in this group until after 65 years of age.23 In both men and women, aspirin is beneficial in patients who have established coronary artery disease.

Reducing blood pressure to target levels (<140/90 mm Hg and <130/80 mm Hg in those with diabetes or chronic kidney disease) decreases cardiovascular risk in women and men.24 The impact of prehypertension on cardiovascular risk may be less in women than men.25 Medications for blood pressure control should be individualized; agents such as angiotensin converting enzyme (ACE) inhibitors may be the treatment of choice if a woman has diabetes or heart failure, but their use should be carefully considered in any woman who may become pregnant because of risk to the fetus.

For detailed treatment strategies based on classifications and levels of evidence for women, the interested reader is referred to the latest Effectiveness-based Guidelines for Prevention of Cardiovascular Disease in Women, published by the American Heart Association.3

Sex hormones and vascular function

Although sex chromosomes provide a genetic basis for sex differences in cardiovascular disease, sex hormones represent modulating factors for genes that have response elements for the steroid receptors on both autosomes and sex chromosomes.

Transcription of these genes is differentially expressed over the life span as the endogenous concentrations of sex steroids change with sexual maturity, reproductive health, pregnancy, and aging to reproductive senescence. Influences of sex steroids on gene expression affect every organ26; however, only some studies of cardiovascular disease examine gene expression accounting...
Estrogen upregulates expression of tyrosine hydroxylase, as well as transporters, for uptake of norepinephrine into the nerve terminal and vascular smooth muscle.

Sex steroid hormones affect all components of the vascular wall and heart: innervation, neurotransmission, extracellular matrix, smooth muscle/myocardium, endothelium/endocardium, as well as blood elements that contact the luminal surfaces (TABLE 2).

**Estrogen regulates adrenergic neurotransmission**

Our earlier discussion on genetics mentioned how adrenergic neurotransmission is affected by the SRY gene on the Y chromosome. However, estrogen upregulates expression of tyrosine hydroxylase, as well as transporters, for uptake of norepinephrine into the nerve terminal and vascular smooth muscle. In addition, estrogen and its metabolites, the catecholestrogens, down-regulate other enzymes, including tyrosinase (required for the synthesis of tyrosine) and catechol-O-methyltransferase (COMT) (required for the degradation of norepinephrine).8

These numerous sites where estrogen could affect adrenergic neurotransmission may in part explain the predominance of vasospastic disorders in women compared with men, the absence of a linear relation-

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**TABLE 1**

Representation of women in randomized clinical trials of therapeutics used to treat cardiovascular disease

<table>
<thead>
<tr>
<th>Class of therapeutic agents</th>
<th>No. of trials</th>
<th>Overall population</th>
<th>% women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker</td>
<td>30</td>
<td>234,028</td>
<td>30.8</td>
</tr>
<tr>
<td>Antiplatelet for secondary prevention of coronary artery disease</td>
<td>21</td>
<td>97,893</td>
<td>27.8</td>
</tr>
<tr>
<td>β blocker</td>
<td>25</td>
<td>84,930</td>
<td>35.6</td>
</tr>
<tr>
<td>Lipid-lowering agents, statins</td>
<td>18</td>
<td>73,693</td>
<td>26.9</td>
</tr>
</tbody>
</table>

Data from Kim AK, et al.15

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**TABLE 2**

Effects of sex steroids on factors regulating vascular tone

<table>
<thead>
<tr>
<th>Adrenergic neurotransmission</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis of NE</td>
<td>Tyrosine hydroxylase</td>
<td>SRY ↑</td>
</tr>
<tr>
<td></td>
<td>Tryosinase</td>
<td></td>
</tr>
<tr>
<td>Uptake of NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degradation of NE by COMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelium-derived NO</td>
<td>Testosterone ↑↓</td>
<td>Estrogen ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testosterone ↓</td>
</tr>
<tr>
<td>Platelet secretome*</td>
<td>Thromboxane</td>
<td>Testosterone ↑</td>
</tr>
<tr>
<td></td>
<td>PDGF</td>
<td>?</td>
</tr>
</tbody>
</table>

*Data obtained from porcine platelets, see Miller VM, et al.35

COMT, catechol-O-methyltransferase; NE, norepinephrine; NO, nitric oxide; PDGF, platelet-derived growth factor; ↑, increase; ↓, decrease; ?, not known.
Endothelial dysfunction and cardiovascular risk increase in women as endogenous estrogen declines due to premature ovarian failure, oophorectomy, or menopause.

Cardiovascular considerations in reproductive medicine

Information presented above supports the hypothesis that changes in concentrations of endogenous sex steroids have vascular consequences. In humans, changes in sex steroids occur throughout life—in puberty, pregnancy, menopause, and gonadal failure—and when exogenous hormonal supplements/treatments are administered.

Decreased estrogen levels raise cardiovascular risk

In the clinical setting, endothelial dysfunction and cardiovascular risk increase in women as endogenous estrogen declines due to premature ovarian failure, oophorectomy, or menopause. Observational and epidemiologic studies provide convincing evidence that administration of estrogen-based therapy reduces both all-cause and cardiovascular mortality associated with these conditions in women.36-38 Randomized controlled clinical trials, however, have not validated the cardiovascular protective effects of estrogenic treatments by reducing such adverse events as myocardial infarction and stroke in postmenopausal women.39

One potential explanation for this discrepancy is the timing at which estrogen treatment is initiated. Occlusive vascular disease occurs on a continuum throughout life. Early intervention with estrogenic treatments in women who have premature ovarian failure, oophorectomy prior to age 50, and menopausal symptoms in the early postmenopause would reduce progression of disease.40 Indeed, carotid intima medial

Hormonal influences on platelets

Blood elements, including platelets, contain receptors for sex steroids. Estrogen and testosterone affect protein content of platelets in the circulation through transcription of genes in bone marrow megakaryocytes, from which the platelets are derived. As platelets turn over (in humans, within about 10 days), changes in circulating hormone levels will affect the characteristics of the pool of circulating platelets.

As might be expected, platelets from reproductively competent male pigs is greater than that in females. Alternatively, aggregability of platelets and their content of the mitogen platelet-derived growth factor (PDGF) increase with ovariectomy in female pigs; these effects are reversed by estrogenic treatments.35

These observations need validation in humans. Since platelets are implicated in vasospasticity and vascular remodeling of atherosclerosis, it is likely that these hormonal effects on platelets and their interaction with the vascular wall contribute to sex differences in expression and development of vascular disease.
thickness (CIMT) and coronary artery calcification are reduced in menopausal women who use estrogenic treatment (including women asymptomatic for menopausal symptoms).41,42

These observations provide the basis for the Kronos Early Estrogen Prevention Study (KEEPS; www.keepstudy.org). KEEPS, which will close in 2012, is evaluating CIMT and coronary artery calcification in women who were less than 3 years past menopause at study entry. Patients were randomized to 4 years of treatment with placebo (oral and transdermal), oral conjugated equine estrogen, or transdermal 17β-estradiol with pulsed micronized progesterone (12 days per month). This study is unique in that it compares oral and transdermal estrogen formulations. Transdermal delivery modalities may carry lower thrombotic risk than oral estrogen products.43

**PCOS: A harbinger of cardiovascular risk**

The most common endocrine disorder affecting women (approximately 4% to 10%) is polycystic ovary syndrome (PCOS). PCOS is associated with one of the earliest forms of coronary artery disease, endothelial dysfunction (**Figure 2**),44 and with a 7-fold increased risk of myocardial infarction.45

Long-term treatment with estrogen and progestogen therapy to restore the estrogenic state has been shown to decrease the progression of hyperinsulinemia, insulin resistance, and abdominal fat deposition associated with PCOS.46 Treatment of PCOS patients with either metformin or thiazolidinediones improved endothelial function.47,48 Women with PCOS often have a cluster of other cardiovascular risk factors, such as central adiposity, hypertension, and diabetes. Thus, cardiovascular prevention in this high-risk population must focus on all risk factors.

**Low testosterone in men**

Although some clinical evidence indicates that low testosterone in men raises cardiovascular risk, it is less clear if treatment to increase testosterone is cardioprotective.49,50 Studies of hormone treatment in men may be confounded by lack of assessment of integrity of the androgen receptors, aromatization of testosterone to estrogen, and assessment of functional estrogen receptors. Similar to studies of estrogenic treatment in women, adverse cardiovascular effects in men may be related to the timing of initiation of testosterone therapy. A study of testosterone treatment in older men (average age, 74 years) found that testosterone therapy increased the hazard ratio for adverse cardiovascular events to 5.4.51

**Where do we go from here?**

Much needs to be learned about the mechanisms by which sex affects development of cardiovascular disease. Effects of sex and treatment outcomes could be clarified by consistent analysis of clinical trial data by sex. Post hoc analysis of published clinical trials may reveal patterns of response and efficacy that will increase our overall knowledge of potential sex differences in various treatments. Accounting for sex as a covariate may not provide the same insight as analysis by sex as a dichotomous variable.

In addition, many questions remain about how hormonal therapies affect cardiovascular health. For example, what is the optimal timing for initiating therapy in conditions of hormonal deficiency, and what treatment duration will maximize benefits while minimizing harm? In women, based on breast cancer outcomes of the Women’s Health Initiative and the Million Women Study, it is recommended that hormone treatment be used for menopausal symp-
toms at the lowest dose for the shortest duration of time.52 This duration, however, may not be long enough to impact progression of cardiovascular disease, which may require from 6 to 8 years for benefit to be seen.53,54 The potential beneficial cardiovascular effects of various formulations of hormonal treatments need to be clarified. Metabolism of sex steroids is complex. Polymorphisms in genes encoding enzymes involved in these pathways have the potential to reduce treatment efficacy. For example, genetic polymorphisms in 17β hydroxysteroid dehydrogenase are associated with menopausal vasomotor symptoms, and those of catechol-O-methyltransferase may affect development of ischemic heart disease.34 Tailoring treatment modalities to genetic profiles is a goal of personalized pharmacogenomics.

Synthetic progestogens have varying degrees of efficacy for binding to glucocorticoid receptors, and some may antagonize estrogen’s effects on the cardiovascular system. Cardiovascular outcome in women using various formulations of contraceptive products, evaluated as cumulative years of exposure, is unclear at this time.30 Alternatively, the impact of fertility treatments on long-term cardiovascular risk remains to be assessed.

Conventional risk assessment tools, such as the Framingham Risk Score and Reynolds’s Score, underestimate cardiovascular risk in women. Hypertensive complications of pregnancy may increase risk for cardiovascular disease in women as they age; the latest guidelines for prevention of cardiovascular disease in women include using a history of preeclampsia, gestational diabetes, or pregnancy-induced hypertension as part of the criteria for risk of cardiovascular disease.3 A validated assessment tool specific for women, which includes information about pregnancy, reproductive history, and hormone exposure, might improve cardiovascular risk stratification for targeting early intervention in women as they age.

Many opportunities exist for reproductive endocrinologists and other women’s and men’s health physicians to partner with basic scientists to address these issues. Gynecologists and reproductive endocrinologists may be the entry point for primary care for many women. Thus, they have the opportunity to initiate cardiovascular risk reduction and preventive strategies with their patients. Physicians can help their patients develop better personal records of hormone use and reproductive history. Some of the disparity in all-cause cardiovascular mortality between women and men will be reduced by increased understanding of how hormonal and reproductive health impact development and risk for cardiovascular disease.

REFERENCES


