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Sex-specific physiology and cardiovascular disease

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Abstract

Sex differences in cardiovascular diseases can be classified as those which are specific to one sex and those that differ in incidence, prevalence, etiology, symptomatology, response to treatment, morbidity and mortality in one sex compared to the other. All sex differences in cardiovascular conditions have their basis in the combined expression of genetic and hormonal differences between women and men. This chapter addresses how advances in understanding basic mechanisms of hormone responses, imaging diagnostics, integration of genomics and proteomics have advanced diagnosis and improved outcomes for cardiovascular conditions, apart from those related to pregnancy, that are more prevalent in women. These conditions include occlusive and non-occlusive coronary artery disease, microvascular nonocclusive ischemic disease, spontaneous coronary artery dissection, diseases of the cardiac muscle including heart failure and takotsubo cardiomyopathy, and conditions related to neurovascular dysregulation including hot flashes and night sweats associated with menopause and effects of exogenous hormones on vascular function. Improvement in technologies allowing for noninvasive assessment of neuronally mediated vascular reactivity will further improve our understanding of the basic etiology of the neurovascular disorders. Consideration of sex, hormonal status, and pregnancy history in diagnosis and treatment protocols will improve prevention and outcomes of cardiovascular disease in women as they age.

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Keywords

atrial fibrillation; cardiomyopathy; endothelial dysfunction; coronary microvascular dysfunction; 17β-estradiol; heart failure; hot flashes; ischemic nonobstructive coronary artery disease; INOCA; menopause; migraine; SCAD; spontaneous coronary artery dissection; takotsubo; vasomotor symptoms

A. Introduction

The fundamental origin of all sex differences in health and disease results from the presence of the sex chromosomes (XX for female and XY for males). Genes on these chromosomes influence expression of genes on the autosomes, as well as direct the development of the reproductive organs, and ultimately gonadal production of the sex steroids estrogen and testosterone.[1, 2] An important interaction between the sex chromosomes and sex hormones is through the gene for the androgen receptor located on the X chromosome. Variations in this gene will have greater effects in males who carry only one copy of the X chromosome. Females have two copies of the X chromosome but one is inactivated reducing the gene dosage effect, which also results in mosaic distribution of the genetic variants on each X in various tissues of the body. These differences in genes and hormones provide the basis for all sex differences in cardiovascular regulatory mechanisms in health and disease. It is essential when considering expression of various cardiovascular diseases to recall several points: 1) receptors for the sex steroids are present in most tissue of the body, but their relative expression may vary; 2) estrogen is a metabolic product of testosterone, thus both testosterone and estrogen are present in men and women but in different proportions; 3) concentrations of the sex steroids vary across the life span as evidence by increased production at puberty, increases during pregnancy, and decreases in women during the transition to menopause. The dramatic changes in hormone-mediated physiological changes in the cardiovascular (and other) systems of a woman's body with pregnancy demonstrate the activational effects of the sex steroids; that is, reversible phenotypes expressed in the presence of the hormones but diminished in their absence. Specific aspects of cardiovascular physiology associated with pregnancy are discussed in a chapter by Fu. In this section, the focus will be on conditions of the coronary circulation, the heart and a group of conditions that require autonomic neurovascular regulation. A final section will discuss cardiovascular issues related to hormonal treatments in women.

B. The coronary circulation

Obstructive coronary artery disease:

Coronary artery disease (CAD) is the leading cause of death in women in the United States, affecting 6.6 million women a year with higher mortality rates than their male counterparts, from 1985 to 2011.[3] A recent reduction in these rates has been attributed to national and international efforts which focused on fostering understanding, awareness and application of evidence-based therapy to women. Women who present with obstructive CAD are generally older than their male counterparts, have more cardiovascular comorbidities and have a higher incidence of adverse cardiovascular outcomes including mortality following acute

myocardial infarction (MI).[4] Occlusion of the coronary arteries is caused by disruption of plaque resulting from accumulation of infiltrating macrophages and low-density lipoproteins within the vessel wall. Formation of thrombus at the site of the disrupted plaque occludes the artery limiting blood flow to the myocardium resulting in MI. The pathophysiology of CAD and MI is distinctive in women, who are less likely than men to present with plaque rupture. [5] The reasons for this difference remain unclear.

Chest pain is the most prevalent symptom of acute MI in both sexes. However, women are more likely to present with atypical symptoms, including pain in the upper back and neck, fatigue, nausea and vomiting. These differences in symptom presentation, along with the longstanding notion that CAD and acute MI is uncommon in women accounts, in part, for delays in seeking medical advice, poor recognition of symptoms, under-diagnosis, and suboptimal treatment in women.[6–8] Women with MI also are less likely to undergo coronary angiograms when compared to men, despite that this test is the diagnostic and therapeutic gold standard. When obstructive lesions exist, revascularization is most often the treatment of choice in the clinical setting of both ST-elevation MI (STEMI), and high risk non-ST-elevation MI (NSTEMI).[9, 10] However, revascularization of the occluded artery may be more challenging women due to bleeding at the site of access, and small and more tortuous coronary arteries. Future studies should aim at improving the treatment of obstructive CAD in women.

Coronary microvascular dysfunction:

Approximately 30–50% of women who undergo coronary angiography for evaluation of chest pain do not have obstructive CAD.[11, 12] Ischemia in the setting of no obstructive coronary artery disease (INOCA) can be due to coronary microvascular dysfunction (CMD). Clinical suspicion for CMD should be high in patients that present with persistent chest pain, ischemic changes on noninvasive stress testing and no obstructive CAD by invasive or noninvasive diagnostic methods. Once thought to be a benign condition, CMD has been found to have a 2.5% annual rate of major adverse cardiovascular events (MACE) including stroke, heart failure or MI. [13, 14]

Risk factors for CMD are similar to traditional coronary risk factors for obstructive CAD such as smoking, hypertension, hyperlipidemia, and diabetes.[15] In addition, sex-specific risk factors have been identified such as autoimmune diseases [16], treatments for breast cancer with radiation to the chest wall area, as well as certain chemotherapy agents.[17, 18] The gold standard diagnostic test for CMD is an invasive coronary reactivity test (CRT) that uses vasoactive agents to functionally test the coronary microvasculature. During CRT, a Doppler guide wire is positioned in the proximal left anterior descending artery for sequential infusion of the vasoactive drugs adenosine, acetylcholine and nitroglycerin to assess microvascular and macrovascular (epicardial) endothelial and non-endothelial function. Coronary flow reserve (CFR) is the calculated ratio of peak flow velocity to baseline flow after adenosine has been administered. Data from the National Heart Lung and Blood-sponsored Women’s Ischemia Syndrome Evaluation (WISE) study found that women with no obstructive CAD who have a low CFR to adenosine are at higher risk for major adverse cardiac events as compared to those with normal CFR.[14]

Noninvasive imaging of those with nonobstructive coronaries with cardiac magnetic resonance imaging (CMRI) can be used to evaluate the coronary microvascular at both stress (adenosine) and rest. The characteristic finding to diagnoses CMD by CMRI is a decreased perfusion pattern in the subendocardial region of the heart, which can also be seen in the affected coronary distribution of obstructed arteries. CMRI also has prognostic value in women with CMD.[19, 20] Cardiac positron emission tomography, and transthoracic Doppler echocardiography are other noninvasive techniques that measure CFR, but they do not replace diagnosis by intracoronary CRT.

As with obstructive CAD, treatment of CMD is focused on lifestyle modification and aggressive risk factor control. In addition to its diagnostic utility, CRT allows helps to guide treatment based on which abnormal pathway(s) (i.e. endothelium or smooth muscle) has been found. Medications to treat endothelial dysfunction include statins, angiotensin-converting enzyme inhibitors, and low dose aspirin. Medications to treatment nonendothelial dysfunction include beta-blockers, alpha-beta blockers, and nitrates.[21]

Spontaneous coronary artery dissection:

Spontaneous coronary artery dissection (SCAD) is a cause of acute coronary syndrome that affects women (81–92% of all cases) more than men. Women present with SCAD at an average age of between 42–53 years (range can be 17–71 years or older) and have minimal other cardiovascular risk factors.[22–27]

SCAD is caused by formation of a hematoma within the wall of one or more coronary artery(ies) leading to obstruction of coronary artery blood flow to the myocardium. A tear in the artery is not always observed either because it may be too small to detect or may have occurred before the formation of the hematoma. Associated conditions for SCAD include extracoronary vascular abnormalities (i.e. fibromuscular dysplasia, coronary tortuosity), pregnancy and the postpartum state, extreme emotion/stress/exercise, and connective tissue disease.

SCAD is diagnosed on coronary angiography and previously considered rare with reported prevalence of 0.07–1.1%.[28] However, recent technological advancements in the catheterization laboratory with the ability to visualize intramural hematoma of the coronary wall using intravascular imaging techniques such as intravascular ultrasound or optical coherence tomography has improved both awareness and diagnosis of this condition. Recent studies indicate that SCAD is the etiology of as many as 35% of myocardial infarctions among women <50 years of age, and that SCAD is the most common etiology of pregnancy associated MI.[26, 29]

Accurate diagnosis of SCAD is important as management strategies are different than those for coronary artery disease due to atherosclerosis. While atherosclerotic MI is best managed with revascularization, primarily with stenting, a similar approach for acute SCAD is associated with a high risk of complications.[30] SCAD can self-heal in the majority of conservatively managed patients. Therefore, as long as a patient has normal or near-normal distal coronary blood flow and is clinically stable, acute SCAD can be managed without revascularization.[30]

While patients with history of SCAD fare better survival rates that matched controls with atherosclerosis [23], there is a significant burden of major adverse cardiac events including recurrent SCAD, recurrent myocardial infarction, recurrent chest pain, and heart failure.[22–24] Precipitators of recurrent SCAD and underlying mechanisms of SCAD itself remain poorly understood requiring continued research into the causation, genetic predisposition, diagnostic and prognostic indicators, and treatment options for patients with recurrent SCAD with other comorbidities (e.g. migraine.)[31]

C. The heart

Atrial fibrillation:

Atrial fibrillation (AF) is due to chaotic atrial electrical activity with dysfunctional or nonexistent contraction of the atria; this can be accompanied with irregular and/or rapid ventricular contraction predisposing to heart failure. However, the most serious and immediate risk from AF is the association of stroke; one proposed mechanism is due to formation and dislodgement of thrombus in the poorly contractile and often dilated left atrial appendage.[32] This risk can be reduced with chronic anticoagulation; appropriate patients to treat can be selected using risk stratification techniques including the CHA_2DS_2VASc and HAS-BLED scores to predict risk of stroke and bleeding, respectively.[33] Of note, the female sex is considered an important risk factor for stroke associated with atrial fibrillation, and is accounted for on the CHA_2DS_2VASc tool.[34, 35] Despite many existing hypotheses, the exact pathophysiology as to why the female sex increases stroke risk in the setting of AF is not understood.

The proposed causes of AF are numerous. One hypothesis is that it may involve changes in function of the potassium channels on the atrial muscle leading to prolongation of the electrical refractory period. Variants in genes encoding subunits of the potassium channel, one of which is located on the X chromosome, may account for sex-differences in etiology, prevalence of and mortality from AF.[36, 37] Antiarrhythmic drugs that prolong the QT interval increase risk for torsade-de-pointes in women and was the reason some such drugs were removed from the market.[38] Estrogenic compounds modulate potassium currents in atrial tissue [39, 40], but the relationship between endogenous and exogenous estrogen on incidence of AF in women is not established.

Radiofrequency catheter ablation is effective in reducing AF in women. However, women are often older at the time of presentation, experience more bleeding events during procedures, and higher recurrence rates than men, which may be due to the older age and stage of disease when the procedures are performed.[41–43]

Heart failure:

HF, an important cause of morbidity and mortality [44], is caused by abnormal ventricular diastolic filling, reduced systolic ejection of blood, or a combination of both. It is a clinical diagnosis with a complex range of etiologies and mechanisms. Patients can present with symptoms such as dyspnea, fatigue, exercise intolerance, and fluid retention including edema and ascites.[45] Defining the prevalence of HF is challenging due to varying

definitions and diagnosis methods. Regardless, over one million US hospitalizations in 2010 coded HF as the first discharge diagnosis, and 1 in 8 deaths mention HF on the death certificate.[44]

Left ventricular (LV) HF can be subcategorized into HF with ejection fraction (EF) preserved (HFpEF) and HF where EF is reduced (HFrEF). The severity of HF is stratified based on structural changes to the heart and severity of symptoms and response to treatment, or by severity of symptoms (Table 27.1).[45]

In general, HFrEF refers to a patient whose LVEF is <40%. These patients may also have concurrent diastolic dysfunction with increased LV filling pressures. The diagnosis of HFpEF refers to a patient whose LVEF is >50%. In HFpEF, the diastolic relaxation of the LV is impaired.[45] On clinical evaluation, patients with HFpEF exhibit evidence of arterial and LV stiffness with chronically elevated LV filling pressures. At autopsy, patients with HFpEF have more cardiac hypertrophy, myocardial fibrosis, epicardial coronary atherosclerosis and coronary microvascular rarefaction than matched controls possibly accounting for the observed clinical findings.[46]

There is debate regarding the threshold for categorizing mid-range EF, and whether there is a need for sex-specific criterion for phenotyping HF. For example, patients with HF and LVEF of 41–49% are considered borderline HFpEF, because the clinical characteristics, response to treatment, and outcomes are similar to those who have HFpEF.[45] The risk of HFpEF is similar between men and women after adjustment for age and risk factors. [47] However, HFrEF is less frequent among women than men.[47] A recent study suggests women have more reverse remodeling with standard medical therapy than men (≥15% reduction in LV end-systolic volume index in those with HFrEF) resulting in fewer hospitalizations for HF, and fewer cardiovascular and all-cause mortality.[48]

Associated factors and predisposing conditions for HF include coronary artery disease (major etiology of HFrEF), diabetes, cigarette smoking, hypertension, vascular heart disease, hypertension, obesity and age. There are also less common causes of HF such as SCAD, myocarditis, infiltrative disease, substance abuse (e.g., alcohol, methamphetamines), chemotherapy induced (e.g., doxorubicin, trastuzumab), familial cardiomyopathy, which can be challenging to diagnose. Some patients have an unknown etiology of HF.[44, 45]

Current therapy known to benefit those with HFrEF include beta blockers and angiotensin converting enzyme inhibitors (ACEI) and aldosterone antagonists. However, depending on specific patient needs and clinical characteristics, additional therapies such as hydralazine-nitrates, ivabradine, implantable cardiac defibrillators/chronic resynchronization therapy, angiotensin receptor-neprilysin inhibitors, and advanced therapies including mechanical support and cardiac transplantation can be considered for patient management.[45, 47, 49]

Women have historically been underrepresented in clinical trials for the treatment of HFrEF, representing approximately a quarter of patients in studies examining the effects of beta-blockers on this condition.[50]. Women appear to benefit from most recommended goal-directed medical therapies in HFrEF, although the degree of benefit may differ slightly from men. In a meta-analysis of studies reporting the effects of beta-blockers that including 13

833 patients (24% women) from 11 trials, the benefits of beta-blockers remained significant in all ages categories, with no interaction according to sex.[50] In a cohort of 27,837 patients with congestive heart failure (53% women) who filled prescriptions for ACEI, women had improved survival, although to a lesser degree than men [HR 0.80 (0.76–0.85) for women vs. HR 0.71 (0.67–0.75) for men].[51] Although these findings remain to be confirmed in a randomized-controlled trial, a similar population study found that women diagnosed with heart failure appeared to have improved survival when they filled a prescription for angiotensin receptor blockers (ARB) as opposed to an ACEI, whereas men did not [HR 0.69 (0.59–0.80) for women vs. HR 1.10 (0.95 to 1.30) for men].[52]

The first left-ventricular assist devices (LVAD) developed for HF could only be used in patients with a body surface area >1.5m^2, limiting their use in women with advanced HFrEF, who accounted for under a quarter of patients enrolled in early trials.[53–55] Despite current design-related limitations, women who received LVAD therapy while awaiting cardiac transplantation had greater risk of cerebrovascular complications than men but similar mortality rates to men (19% vs. 20%, p=0.89).[56, 57] Newer, smaller LVAD models have recently been developed and may allow more women with advanced HFrEF to benefit from this therapy.

Therapies for patients with HFpEF focus on reducing of volume overload and blood pressure, with a goal systolic blood pressure of less than 130 mmHg. [45, 49] HFpEF patients who have a lower heart rate at hospital dismissal are observed to have lower all-cause mortality.[58]

Takotsubo cardiomyopathy:

Also known as stress cardiomyopathy or broken heart syndrome, takostubo cardiomyopathy is as an acute onset cardiomyopathy first described in 1990.[59] Diagnostic criteria include characteristic wall motion abnormalities on left ventricular angiogram or cardiac echocardiogram extending beyond a single epicardial vascular distribution in the absence of atherosclerotic disease, most often akinesis of the apical and mid myocardial walls with hyperkinesis of the basal segments, resembling its namesake, a Japanese octopus or fish trap. Post-menopausal women account for 90% of diagnosed patients, and takotsubo cardiomyopathy is classically triggered by emotional stress or physical triggers, including anesthesia, infection and respiratory distress.[59] Potential pathophysiologic mechanisms include high catecholamine serum levels, leading to an overstimulation of β_2-adrenoceptors and myocardial stunning, acute multivessel epicardial coronary artery spasm, and acute LV mid-chamber and/or outflow tract obstruction[60–63]

Clinical presentation for takotsubo cardiomyopathy is often indistinguishable from an acute MI, with over 75% of patients presenting with chest pain. Nearly all patients have ischemic ECG changes, and may present as STEMI. Serum troponin levels are elevated in 90% of cases, however peak levels are significantly lower than in patients with STEMI due to vessel occlusion. Brain type natriuretic protein (BNP) is elevated in the acute phase of the disease. Elderly patients and those with hypotension, ventricular arrhythmias, LVOTO, mitral regurgitation, and thrombus formation are at higher risk for complications including

cardiogenic shock, which can occur in up to 25% of cases.[59] Acute ischemic stroke, occurring in up to 14% of patients, can also complicate the clinical course.[64]

Treatment of takotsubo cardiomyopathy includes cardiac monitoring, supportive measures (maintaining blood pressure, perfusion, hemodynamics, airway and fluid volume), as well as the initiation of goal-directed medical treatment for HF. It is important to identify whether there is concurrent left ventricular outflow tract obstruction (LVOTO) versus isolated ventricular systolic failure, which can be assessed by echocardiography, in order to delineate optimal treatment options and anticipated hemodynamic responses to therapies. Current expert consensus suggests 72-hour observation in the intensive cardiac care unit for higher risk patients.[59] In cases of cardiogenic shock specifically if LVOTO is present, the use of inotropic agents is discouraged to avoid adrenergic stimulation.

In conjunction with current HF treatment guidelines, beta-blockers and ACE inhibitors are recommended in the absence of contraindications such as acute cardiogenic shock. Beta-blockers have been considered to prevent detrimental myocardial response to sympathetic nervous system stimulation, however, in the in the largest reported takotsubo cohort which included 1750 patients, there was no association between the use of beta-blocking agents and improved survival.[65] In this same report, ACE inhibitors or angiotensin receptor antagonists were associated with significantly lower rates of death at 12 month follow-up (2% vs. 9%, $p<0.001$).[65] Cases of takotsubo cardiomyopathy demonstrate complete LV systolic function recovery at 3–6 months, and this characteristic is considered a diagnostic criterion by expert groups.[59] ECG changes and elevated BNP can persist up to a year following diagnosis. Takotsubo cardiomyopathy can recur in up to 22% of cases at 5 years, and one study reported that patients diagnosed with takotsubo are at similar 3-year mortality risk as patients who experience acute MI with evidence of occlusive atherosclerosis.[59] However, these findings remain to be confirmed, and future studies are needed to determine optimal medical therapy aimed at preventing complications, recurrence, and adverse cardiovascular events.

Peripartum cardiomyopathy:

Peripartum cardiomyopathy is a form of systolic HF that presents in the last month of pregnancy or in the first five months postpartum in the absence of another underlying etiology (such as acute MI). In some cases, chronic HF persists and may lead to cardiac transplantation. It affects about 1:1000 births worldwide, but the prevalence varies by geographic locations.[29, 66]

Although peripartum cardiomyopathy is the leading cause of maternal peripartum death, little is known regarding origin and underlying mechanisms of its progression. Preeclampsia and gestational diabetes may predispose women to peripartum cardiomyopathy, but the mediators connecting these conditions to the cardiomyopathy are incompletely defined. Some studies suggest that increased cleavage of prolactin by cathepsin D into the proapoptotic and antiangiogenic 16 kDa prolactin fragment may be involved.[67] Alternatively, other studies suggest an upregulation of soluble factors of placental origin (sFlt1, a soluble form of the vascular endothelial growth factor [VEGF] receptor) affects the coronary microcirculation.[67–69] Some women with peripartum cardiomyopathy bear

mutations in titin, also known as connectin, which is a large sarcomeric protein involved in tethering the sarcomere to the cell wall.[70] Titin also binds a number of enzymes involved with maintaining high levels of ATP in regions of high energy demand in the sarcomere.[71] Whether any of these factors can be used as diagnostic, prognostic or treatment targets for the disease remains to be determined.

D. Autonomic neurovascular dysregulation

Vascular conditions associated with decreases in ovarian function:

With decreases or loss of ovarian function about 75% of women experience hot flashes and night sweats. [72] Three contemporary longitudinal studies identified 4 patterns of the vasomotor instability relative to their onset prior to menopause, the intensity of events and their duration relative to menopause (Figure 27.1). [73–75] These patterns are similar among women across the globe, suggesting physiological rather than cultural or environmental causes. Whether or not vasomotor instability places women at risk for various cardiovascular diseases is controversial. Part of the controversy is driven by the absence of reliable and systematic objective measurement of the hot flashes and night sweats. Most studies depend on self-report tools which may under (or over) estimate their number, frequency and severity. However, even with these unsophisticated reporting tools, the emerging data suggest that the severity of the hot flashes and night sweats may associate with reduced endothelium-dependent vasodilatation, hypertension, increased carotid intima-media thickness, coronary artery calcification and CMD.[76–80] The relationships between vasomotor irregularies and soluble markers associated with coagulation requires further study.[81–83] Resolving some of these controversies will require longitudinal studies that are designed to address the specific patterns of the hot flashes and night sweats with specific cardiovascular functions or events.

Hot flashes and night sweats involve the central thermoregulatory system in the hypothalamus, and are mediated through autonomic control of the peripheral vasculature and sweat glands. Therefore, the onset, frequency, intensity and duration of the symptoms may represent differences in underlying dysfunction in central and autonomic mechanisms and may involve other brain regions associated with sleep and mood.[84] Indeed, severe vasomotor symptoms may be related to obstructive sleep apnea [85], which is a risk factor for coronary artery calcification.[86]

The characterization of autonomic function associated with expression of hot flashes and night sweats has not been fully characterized. However, diminished parasympathetic tone may be involved as heart rate variability decreases at menopause [87], and sleep-related decreases in blood pressure are not observed in women who experience hot flashes with insomnia.[88]

Neurons of the hypothalamic-pituitary axis implicated in the development of hot flashes and night sweats are kisspeptin/neurokin B/dinorphin (KNDy) neurons.[89] Although menopausal hormone treatments (MHT) consisting of 17β estradiol, conjugated equine estrogen or progesterone (alone or in combination with the estrogen) reduce both hot flashes

and night sweats in women, antagonists of the KNDy pathway offer a potential alternative option to treat these symptoms.[90]

In addition to menopausal hormone treatments [91], selective serotonin re-uptake inhibitors also are effective in reducing hot flashes in women. Stimulation of serotonergic receptors in the brain alters both sympathetic and parasympathetic nerve activity (see[92] for review). Estrogen modulates gene transcription of serotonin in the neuronal nucleus, augments activity of the serotonin uptake transporter, and increases the sensitivity of 5-HT_{1A} receptors on post-synaptic neurons. Thus, declining levels of estrogen, as would occur at menopause, can decrease the activity of the serotonergic system. An interaction between the serotonergic and adrenergic systems [93] is suggested as both selective serotonin reuptake inhibitors (SSRIs) and clonidine, an $alpha_2$-adrenergic receptor agonist which activates pre-synaptic inhibition in the brain, are effective in relieving vasomotor symptoms in some women.[94]

In addition to central autonomic control pathways mediating vasomotor symptoms, much remains to be learned about how peripheral pathways innervating the vascular smooth muscle (expression of adrenergic or cholinergic receptors), neurotransmitter synthesis, receptor coupling to vasodilatory pathways such as those mediated by cyclic guanylate cyclase [95–97] might differ among women who experience various patterns of hot flashes.

Although hot flashes and night sweats are typically referred to as menopausal symptoms, the fact that they can occur in men with androgen depletion [89] and have different patterns of expression in women suggests that the changes in hormonal milieu may unmask underlying autonomic and vascular dysregulation.

Migraine is another condition that may be unmasked by changes in the hormonal milieu. The hypothesis that changes in sex hormones, in particular estrogen, contribute to the etiology of migraine is supported by the observations that at puberty, migraines occur about 3 times in women than men, and that migraine is associated with estorgen levels during the menstrual cycle, with pregnancy and postpartum, and during perimenopause. While hormonally-related migraine is associated with abrupt declines in estrogen levels, as with menstrual-related migraine, postpartum and in perimenopause, it is unlikely that all migraine variants have a common hormonal etiology.(see [98–100]. Genetic variants considered in the etiology of migraine include those for the estrogen receptor alpha, receptors and neurotransmitters associated with adrenergic, GABAergic and nitrogeneric neurons, and enzymes associated with estrogen metabolism.[98] [101–103]. However, a systematic genomic studies of individuals within the various classifications of migraines may help to better understand comorbid conditions and provide insight into better treatment options. [104] Other emerging concepts for the etiology of migraine suggests an immunological component, mitochondrial dysregulation leading to oxidative stress, and iron deficiency. [105–108].

Although migraine was once considered a “essentially benign condition” [109], associations to stroke and SCAD remaining to be comprehensively examined with regard to mirgain with and without aura or relative to hormone levels, hormonal responsiveness and genomics.[31, 110, 111]

E. Exogenous hormones and cardiovascular disease

Exogenous hormones are used by women for contraception, replacement for primary and premature ovarian insufficiency and surgical oophorectomy, and treatment for vasomotor, mood, urogynecological symptoms and osteoporosis following menopause. Metabolism of sex steroid hormones is complex and genetic variants in any one of the numerous enzyme associated with synthesis, uptake and catabolism [112] of the hormones, as well as variation in the hormone receptors [113] will affect responses to exogenous products. The pharmacogenomics estrogen metabolism and response is an emerging area of investigation and greater understanding of genetic variants associated with ovarian function and hormone response will allow for individualizing treatments to maximize benefits and reduce the risk of adverse events with use of these products.

Hormonal Oral contraceptives:

Oral contraceptives to suppress ovulation modify endogenous production of sex steroids from a functioning ovary, and, thus, disrupt the hypothalamic-pituitary-ovary feedback regulatory pathway. Longitudinal randomized control trials evaluating adverse cardiovascular events and cardiovascular risk associated with oral hormone-based contraceptives are confounded by the fact that the composition of the products has changed over the years especially for the type of synthetic progestin allowing for longer cessation of ovulation and decreased frequency of menses (see Table 27.2 and Figure 27.2.) [114, 115] Evaluation of adverse cardiovascular events in older women who may have used various formulations of oral contraceptives is also confounded by their pregnancy history and perhaps use of menopausal hormone treatments. In spite of these limitations, there are some data to support that women who use oral contraceptives have decreased incidence of heart disease and stroke.[116, 117]

Similar to all oral medications, oral hormonal products will enter the entero-hepatic circulation for first pass metabolism in liver. In addition to metabolism of the drugs in the liver, the hormones may stimulate production of proteins involved with coagulation and inflammation, and alter production of triglycerides and lipoproteins. These effects of the hormones on liver metabolism may be important for treating women with polycystic ovarian syndrome.[118] There is an increased risk of venous and pulmonary thrombosis with some products (Table 27.2), therefore, the use of oral contraceptives is not recommended for women with known thrombophilia.[114]

Hormone replacement for ovarian insufficiency and early oophorectomy:

Primary and premature ovarian insufficiencies are defined by loss of ovarian function before the age 40 years, and early oophorectomy is defined as surgical removal of the ovaries prior to 45 years of age. These conditions are characterized by increases in 18 comorbid conditions of premature aging [119–121], including incidence of and mortality from cardiovascular disease and stroke.[122–126] Cardiovascular mortality is reduced by treatment with estrogen at least until the age of natural menopause (Figure 27.3).[120, 122, 127]

Hormone treatment at menopause:

Until 2002, based on evidence from observational and epidemiological studies, it was accepted that use of hormones (in particular, estrogen) during menopause (MHT) reduced mortality due to cardiovascular disease. [128–134] The most frequently used formulation of MHT in those studies was conjugated equine estrogen, and most women initiated use of these products around the time of menopause. Cellular actions of 17β-estratiol encompass regulation of gene transcription, including regulation of nitric oxide synthase and angiotensin converting enzyme, and actions mediated through membrane receptors, ion channels, post-translational modification of enzymes, mitochondrial function and biochemical interactions with oxygen-derived free radicals (see Figure 27.2).[98] Collectively, these mechanistic actions are expected to promote vasodilatation, reduce adhesion of leukocytes to the vascular wall, reduce platelet activation, and thus slow development of atherosclerosis. In addition, oral estrogen products altered the serum lipid profile to reduce low-density lipoproteins and increase high density lipoproteins, an effect that was not observed in women using statins. [134, 135]

However, observational and epidemiological data may be biased as women self-select to use MHT and may represent a healthy subset of women (healthy user bias). Several prospective trials have been conducted to try to address the preventive actions of MHT (Table 27.3). [136]. The first large scale, prospective, randomized trial was the Women's Health Initiative (WHI) that enrolled women between the ages of 50–79 years. The mean age for participants was 63 years, which was as many as 10 years past the age of menopause. Women with a uterus were randomized to placebo or a single dose of oral conjugated equine estrogen plus a continuous combined synthetic progestogen, medroxyprogesterone acetate; women without a uterus were randomized to placebo or oral conjugated equine estrogen alone. Outcomes for the study were adverse cardiovascular events, bone mineral density and breast cancer.[137] The WHI trial was stopped in 2002 because of an excess number of predetermined adverse events, including the cardiovascular outcomes of coronary heart disease, myocardial infarction, stroke and venous thromboembolism.[138] These results drastically altered clinical prescribing practice for MHT for menopausal symptoms and chronic diseases of aging such as osteoporosis, even though MHT was effective in reducing these conditions. However, subsequently over the course of about 15 years, several criticisms of the WHI have emerged that need to be considered. First, women in the WHI were many years past menopause, and, thus, the results cannot be generalized to women who would use MHT around the peri- and immediate time past menopause.[139, 140] Evidence from experimental animals indicates that the timing of initiation of hormonal treatments close to the time of oophorectomy or menopause (the timing hypothesis) is critical to prevent the initiation and progression of cardiovascular disease.[141] Indeed, subsequent sub-analysis of data from the WHI that stratified women by menopausal age at the time of treatment randomization, suggests that women who were within 5 years of menopause had reduced coronary artery calcification, fewer myocardial infarctions and lower all-cause mortality compared to those who were randomized after that time point.[142–144] In addition, the Danish Osteoporosis Prevention Study (DOPS), which began at the same time as the WHI, enrolled women between the ages of 45–58 years. Although these women were treated with different formulations of hormone products (triphasic estradiol and norethisterone acetate, a

type of birth control pill with estrogen dose constant and variable progestin dose, or 2 mg estradiol a day if they had a hysterectomy), after 11 years of follow-up the number of myocardial infarctions, incidence of HF and death were reduced in the treated women compared to controls.[145]

The Early versus Late Intervention Trial (ELITE) directly tested the timing hypothesis. This study enrolled two age groups of women: an early group aged 55 years and a late group aged 65 years. After 5 years of randomization to oral 17β-estradiol, the progression of atherosclerotic plaque measured by intima-medial thickness of the carotid artery was lower in the early aged treated compared to early placebo group. However, the rate of progression of carotid plaque was similar between the treated and placebo in the late aged group.[146]

Another criticism of the WHI was that a conclusion based on single dose and formulation of conjugated equine estrogen was generalized to all hormonal products including those that contain the endogenous form of estrogen 17β-estradiol and to those that might be delivered transdermally.[140] Conjugated equine estrogen is a mixture of steroid metabolites with a ratio of estrone to 17β-estradiol that can range from 6–20:1[147]; sulfonated estrone and estradiol, equilin and other methylated products. The binding affinity of these different ligands for estrogen receptors vary and cannot be compared by dose equivalency with 17β-estradiol. In addition, oral products, which undergo metabolism in the liver before reaching the systemic circulation, will affect production of procoagulant and inflammatory proteins perhaps increasing risk for thrombosis. Indeed, in the Estrogen and Thromboembolism Risk (ESTHER) multicenter case-controlled study, the odd ratio for developing an idiopathic venous thromboembolism was about 4 times higher in women using oral compared to those using transdermal products. In addition, use of micronized progesterone also had a lower odds ratio for developing venous thromboembolism than use of synthetic progestogens.[148, 149] Risk of venous thromboembolism with use of MHT will also be affected by prothrombotic mutations.[150, 151].

The Kronos Early Estrogen Prevention Study (KEEPS) was designed to provide a direct comparison of oral conjugated equine estrogen (0.45 mg/day) and transdermal 17β estradiol (50μg/day) both with pulsed micronized progesterone compared to placebo on slowing progression of atherosclerosis.[152] Unlike women enrolled in the WHI, women in KEEPS were within three years of menopause and were at low risk for cardiovascular disease based on conventional risk factors of body mass index, serum lipid profile, insulin sensitivity, and blood pressure.[153] This phenotypic profile was similar to women in early observational studies and reflects a “healthy user” profile that with subsequent analysis of the WHI was one that demonstrated reduced cardiovascular risk with the treatments.[135, 154, 155] In KEEPS after 4 years of treatment, the rate of change of intima-media thickness in the carotid artery did not differ among groups.[156] However, there were no reports of venous thromboembolisms, and both formulations reduced vasomotor symptoms.[157] However, the products differed in regard to effectiveness in improving mood (oral conjugated equine estrogen being better than the transdermal 17β estradiol) and sexual function (17β estradiol was better than the oral conjugated equine estrogen).[158, 159] Variants in genes associated with innate immunity may have contributed to effects of the products on the cardiovascular outcomes measured in KEEPS.[160, 161]

In summary, evaluation of the effects of sex hormones on cardiovascular function in women need to consider the timing of the initiation of treatment, the type, dose and formulation of the product, the existing cardiovascular risk profile of the woman, and the potential pharmacogenomics effects of the hormones on the outcome of interest.

F. Conclusion

Sex differences in cardiovascular health and disease has origin in the presence of sex chromosomes and the production of sex steroids hormones that varies across the life span, is influenced by pregnancy, and by use of exogenous hormone products. Diagnosis and treatment of some cardiovascular diseases in women have been hampered by the lack of appreciation of symptom presentation in women, poor understanding of cellular mechanisms causing disease, and not treating women according to standard guidelines of care. However, much remains to be learned regarding identification of unique factors which may place women at risk for early development of cardiovascular diseases such as those that might be related to neurovascular autonomic dysregulation. In addition, research is needed to optimize diagnosis and treatment for conditions such as microvascular disease, SCAD and takostubo cardiomyopathies, and to develop prognostic indicators for women who might be at risk for recurrence of these conditions. Longitudinal studies are needed to determine effects of various types of hormonal treatments on cardiovascular function. Large scale clinical trials of new treatment options for cardiovascular conditions need to enroll women, and the results of such studies need to be analyzed by sex in order to inform individualized care that will lead to improved outcomes.

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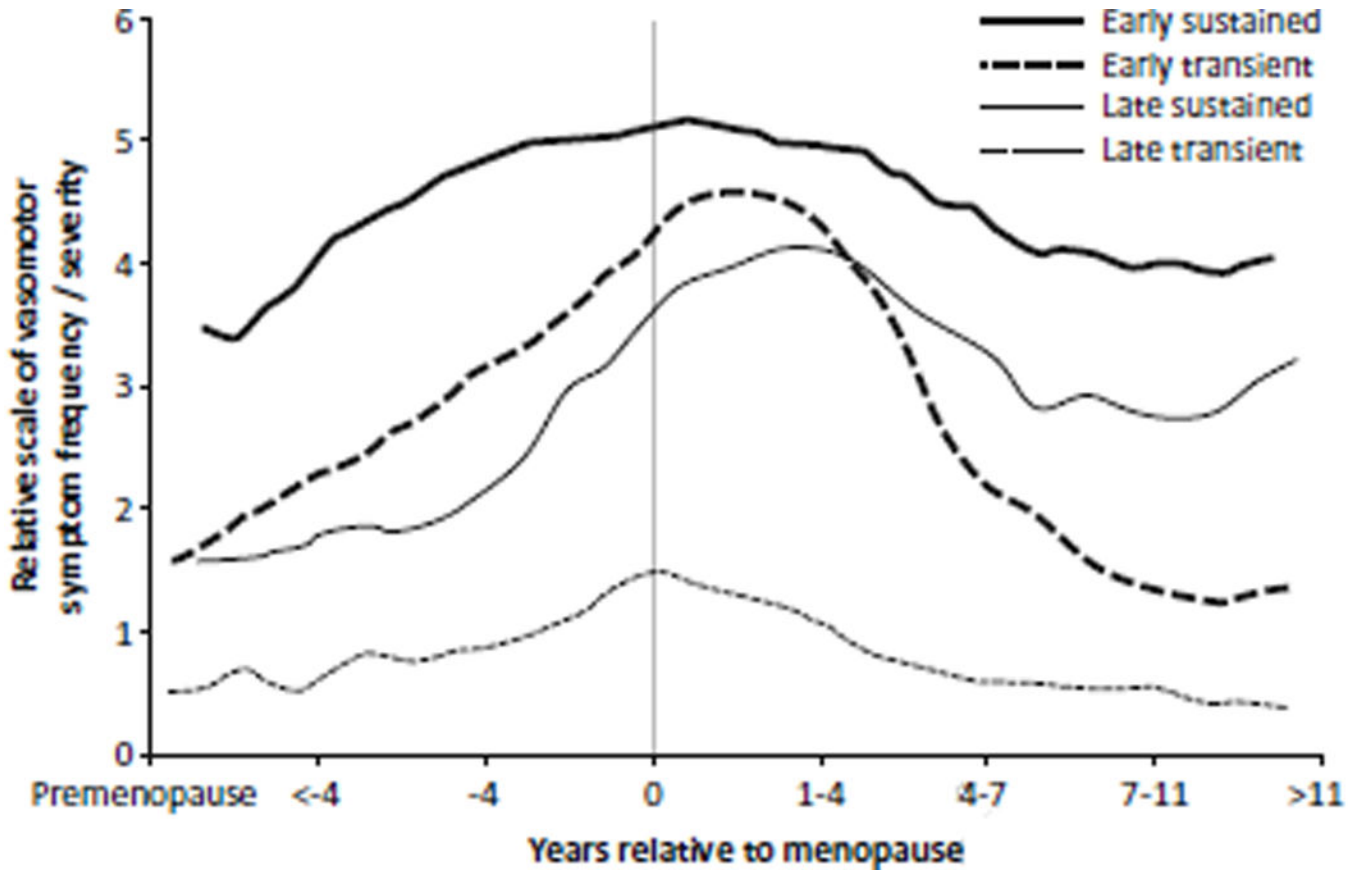

Figure 27.1.

Composite representation of four patterns of vasomotor instability relative to their onset prior to menopause, the intensity of events and their duration relative to menopause reported in three contemporary studies. [75–77]

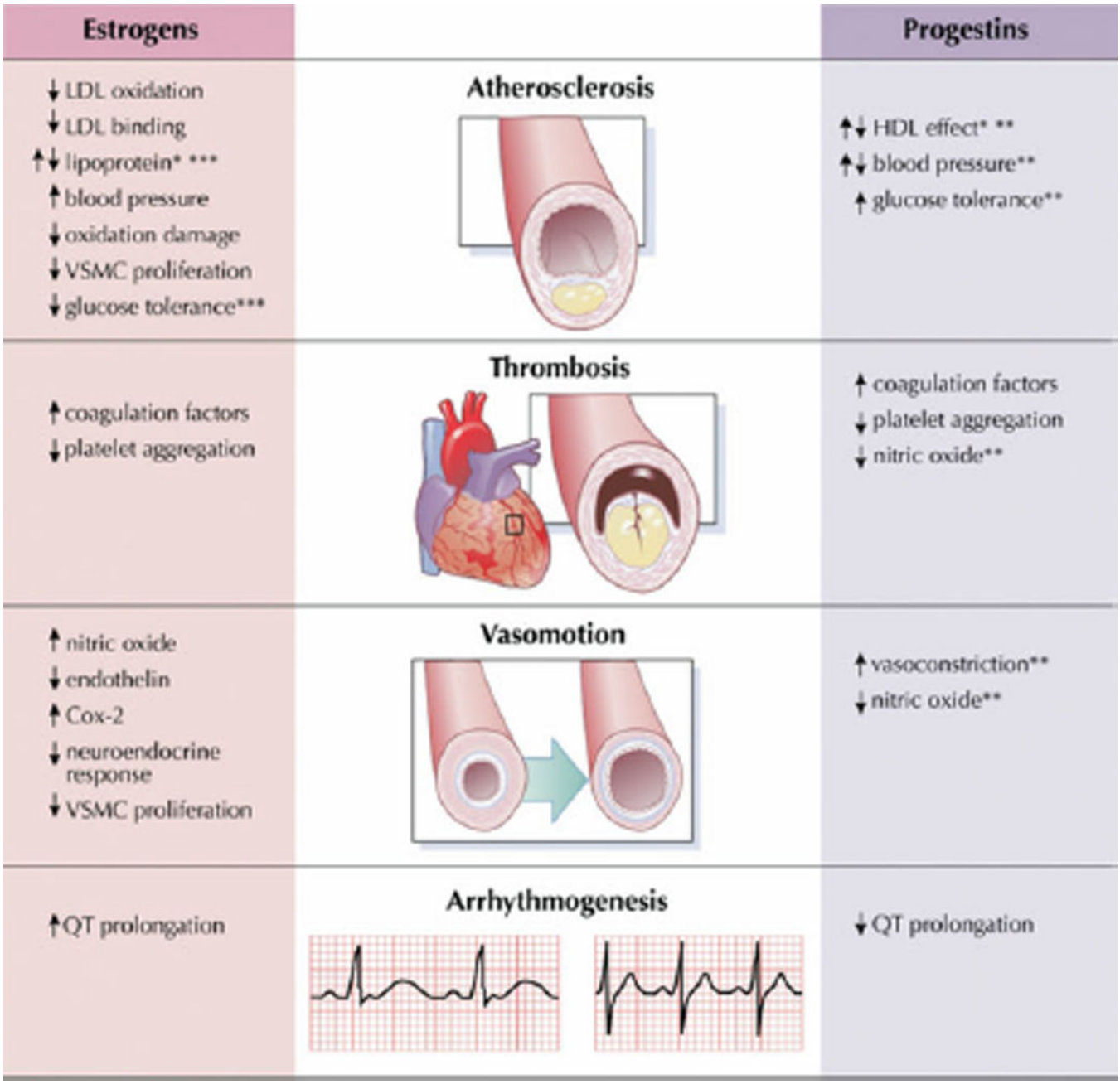

Figure 27.2.

Impact of hormonal contraception on mechanisms of cardiovascular disease.

*Dependent on delivery route of estrogen; **dependent on type of progestin; ***dependent on the dose of estrogen. *Cox-2* = cyclooxygenase-2; *HDL* = high-density lipoprotein; *LDL*= low density lipoprotein; *VSMC* = vascular smooth muscle cell. Reproduced with permission from reference [117].

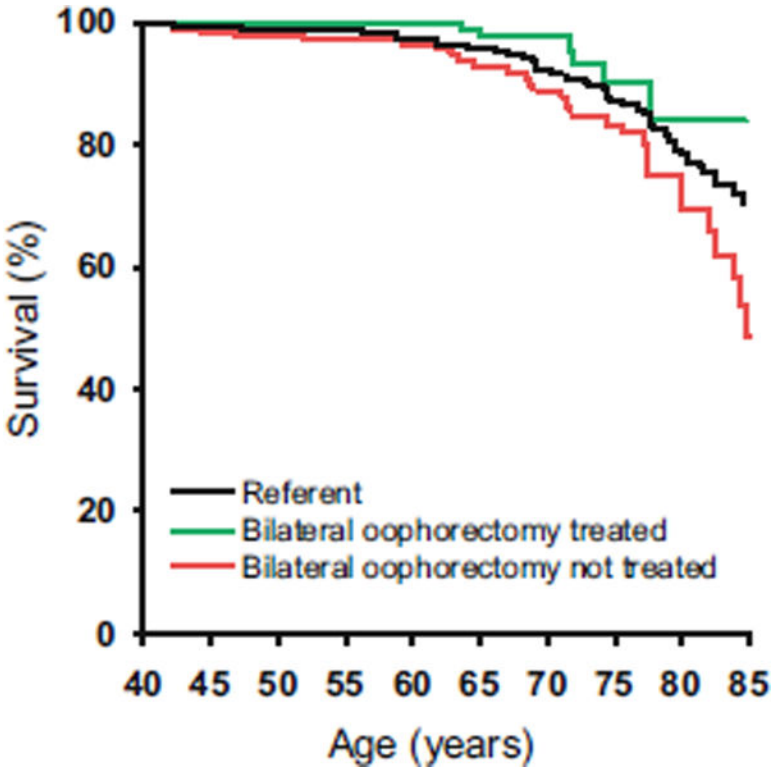

Figure 27.3.

A population study of ccardiovascular mortality in women who underwent bilateral oophorectomy before age 45 years and were or were not treated with estrogen through age 45 years or longer. Reproduced with permission from reference [124].

Table 27.1

Classification of heart failure by structure and function

ACCF AHA stages of heart failure		**NYHA functional classification**		
A	At high risk for heart failure without structural heart disease or symptoms	None		
B	Structural heart disease without heart failure signs or symptoms	I	No limitation of physical activity	Ordinary physical activity does not cause heart failure symptoms
C	Structural heart disease with prior or current heart failure symptoms	I	No limitation of physical activity	Ordinary physical activity does not cause heart failure symptoms
		II	Slight limitation of physical activity	Comfortable at rest, but ordinary activity causes heart failure symptoms
		III	Marked limitation of physical activity	Comfortable at rest, but less than ordinary activity causes heart failure symptoms
		IV	Unable to cany on any physical activity without heart failure symptoms	Heart failure symptoms at rest
D	Refractory heart failure requiring specialized interventions	IV	Unable to cany on any physical activity without heart failure symptoms	Heart failure symptoms at rest

Table adapted from Yancy et al. [49]

ACCF American College of Cardiology Foundation. *AHA* American Heart Association, *NYHA* New York Heart Association

Table 27.2

Progestins in oral contraceptives ranked according to risk for venous thrombosis[a]

Oral contraceptive	Risk of thrombosis
First-generation <50 μg ethinyl estradiol with the progestins norctynodrel, norethisterone. and norcthisterone acetate	6–12/10,000 women
Third-generation <50 μg ethinyl estradiol with the progestins desogcstrel or gestodene or norgestimate	9–12/10.000 women
Fourth-generation <50 μg ethinyl estradiol with the progestins drospirenone. dienogest. or nomegcstrol acetate	9–12/10.000 similar
Second-generation <50 μg ethinyl estradiol with the progestins norgestrel or levonorgestrel	5–7/10.000 women
Progestin-only (norcthisterone. ethynodiol diacetate. levonorgestrel. desogestrel. lynestrenol)	2–3/10.000 women

[a]Derived from Table 27.1 of (iialcraki ct al. [116] reprinted with permission

Table 27.3

Summary of variables for open-label and prospective trials of the use of menopausal hormone treatments and cardiovascular outcomes since the WHI

Trial	Timing of treatment relative to the menopause	Formulation	Participant characterization	Primary cardiovascular outcomcs	Duration
DOPS[a] [146]	3–24 months	Open label - Women with a uterus: triphasic estradiol and norcthisterone acetate (2 mg synthetic 17β-estradiol for 12 days, 2 mg 17β-estradiol plus 1 mg norethisterone acetate for 10 days, and 1 mg 17β-estradiol for 6 days) Women without a uterus: oral 17β-estradiol (2 mgAlay)	Women with and without a uterus 45–52 years of age with FSH >2 standard deviations ova premenopausal values Exclusion: history of bone disease (including non-traumatic vertebral fractures on radiography), uncontrolled chronic disease, previous or current cancer or thromboembolic disease, current or past treatment with glucocorticoids for more than 6 months, current or previous use of hormone replacement therapy within the past 3 months, and alcohol or drug dependency	Death: hospitalisation for myocardial infarctions or heart failure	11 years of intervention; 16 years of follow-up
EPAT [136]	Median 3.5 years	Oral micronized 17β-estradiol (1 mg/day)	Serum estradiol <20 pg/mL 45 years or older No preexisting cardiovascular disease; low-density lipoprotein cholesterol equal to or greater than 3.37 mmol/L (130 mg/ dL)	Rate of change of carotid intima-medial thickness	2 years
KEEPS [153]	6–36 months	Oral CEE <0.45 mg/day) or transdamai 17 |i-estradiol (50 (ig/day) each with oral progesterone <2(X) mg/day for 12 days in a 30-day cyclc)	Women with a uterus between ages of 42 and 58 years Exclusion: history of cardiovascular disease or venous thrombosis: coronary calcification scores >50 Agatston units; body mass index >35 kg/m': triglyceride >400 mg/dL: LDL cholesterol <190 mg/ dL; lipid4owcring medications: untrcatod hypertension (systolic >150 mmHg, diastolic >95 mmHg): diabetes: history of chronic diseases including canca: smoking more than 10 cigarettes/day	Rate of change of carotid intima-medial thickncss: coronary arterial calcification	4 years
ELITE [147]	<6 years or ≥ 10 years	Oral micronized 17β-estradiol (1 mg/day) plus vaginal progesterone (45 mg for 10 days in a 30-day cycle) for women with a uterus	Women with and without a uterus; median ages 55 and 65 years for the two groups, respectively Exclusion: fasting plasma triglyceride level > 500 mg/dL; diabetes mdlitus or fasting serum blood glucose >140 mg/dL: scrum creatinine >2.0 mg/dL: uncontrolled hypertension (systolic/diastolic blood pressure > 16/110 mmHg); untreated thyroid disease; life-threatening disease with prognosis <5 years: history of deep vein thrombosis, pulmonary embolism: breast cancer	Rate of change of carotid intima-medial thickness; coronary arterial calcification	6–7 years (median 5 years)

[a]Reproduced with permission from Miller and Harman [137]

"Abbreviations: *DOPS* Danish Osteoporosis Prevention Study, *EPAT* Estrogen in the Prevention of Atherosclerosis Trial, *KEEPS* Kronos Early Estrogen Prevention Study, *ELITE* Early versus Late Intervention Trial with Estradiol, *CEE* conjugated equine estrogen, *LDL* low-density lipoprotein cholesterol