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# Cardiovascular Alteration and Treatment of Hypertension

## *Do Men and Women Differ?*

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**Cardiovascular disease is one of the most common causes of mortality affecting both men and women in industrialized nations. Sex-related differences have been well established with regard to heart and vascular function as well as cardiovascular disease processes. Nevertheless, the precise mechanisms of action behind these gender-related differences are poorly understood. Premenopausal women have a relatively lower arterial blood pressure compared to age-matched men and postmenopausal women, suggesting a role of ovarian hormones in blood pressure regulation. Sex-related differences in vasculature and neuroendocrine systems are also present that can affect hemostasis, vascular reactivity, and vascular tone. Treatment for cardiovascular disease and hypertension has been challenging and unsatisfactory. Men and women may require different antihypertensive regimens due to differences in the progression and presentation of hypertension. Additionally, hormone replacement therapy in postmenopausal women has been controversial, producing both beneficial and detrimental effects. Therefore, this review will focus on sex-related differences in the heart and vasculature, and treatments for cardiovascular disease, such as hypertension.**

**Key Words:** Gender; blood pressure; heart; vasculature; RAS; hypertrophy; therapy.

### Introduction

Cardiovascular disease is one of the leading causes of death in the United States for both men and women and the elderly in particular *(1–3)*. However, women are less frequently diagnosed and treated for symptoms of cardiovascular disease owing to the perception that women are relatively protected from cardiovascular insult prior to menopause *(4)*. Additionally, a growing number of studies have identified sex-related differences in cardiovascular growth, function, and disease states, but the mechanisms behind these differences have yet to be determined *(5)*. Traditionally, the majority of experimental and clinical studies have been performed on males only, so future research needs to focus on the mechanisms involved for both sexes in cardiovascular function and disease states *(5)*.

Men are generally at greater risk than premenopausal women for cardiovascular disease, however, after menopause women lose their cardioprotection (Fig. 1). Hypertension is a leading cause of cardiovascular disease morbidity and mortality and has been described as a silent killer. Hypertension is a major risk factor for cardiac and cerebrovascular events, and presents itself differently in men and women. Many factors contribute to the development of hypertension, such as body weight, diet, family history, smoking, and alcohol abuse, but one of the key factors influencing hypertension may also be gender or sex. The higher incidence of hypertension in men and postmenopausal women compared to premenopausal women has been associated with sex-related differences and the possible protective effects of the female sex hormones, estrogen and progesterone *(6)*. However, it appears that not all sex-related differences in blood pressure can be explained by differences in sex hormones *(5)*.

Hypertension can result in end organ damage and, although some similarities do exist between genders, essential hypertension usually has a different presentation in men and women *(7)*. Moreover, the precise mechanisms of action leading to the pathogenesis of essential hypertension remain unknown, but some primary causes have been shown to exist only in women, including eclampsia during pregnancy and contraceptive-induced hypertension *(7)*. Additionally, the onset of cardiovascular disease and hypertension is usually delayed in women by about 10 yr compared to men *(7)*. An emphasis needs to be placed on understanding the complex interplay between sex and cardiovascular function in health and disease states.

### The Heart

During development heart growth is closely associated with somatic growth and thus body size is predictive of heart size. Before puberty cardiac growth is comparable for both men and women. However, during puberty male aerobic fitness, which can be an index of cardiac function, may be important in determining heart growth and mature heart

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Top Panel Figure Available at:
American Heart Association
www.americanheart.org

Heart Disease and Stroke Statistics–
2005 Update (All Charts):
Prevalence of cardiovascular diseases in
Americans age 20 and older by age and
sex; NHANES: 1999-2002 (2)

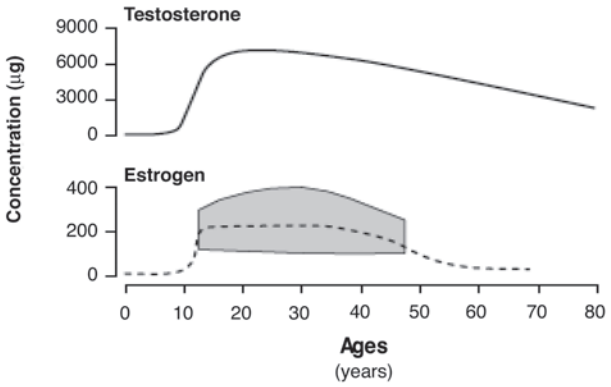


**Fig. 1.** Upper panel: Prevalence of cardiovascular diseases in Americans age 20 and older by age and sex; NHANES: 1999-2002. *Source*: CDC/NCHS and NHLBI. These data include coronary heart disease, congestive heart failure, stroke, and hypertension *(1,2)*. Lower panel: Testosterone and estrogen amounts secreted daily by age. Female reproductive years are shaded *(10)*. Premenopausal women have a decreased prevalence of cardiovascular disease compared to men and postmenopausal women. Female cardioprotection occurs during reproductive years when estrogen levels are highest and declines after menopause as estrogen levels decline, after approx 45–50 yr of age. Figure reproduced with permission from www.americanheart.org © 2005, American Heart Association *(2)* and the *Lancet (10,61)*.

size, whereas females are less affected by aerobic conditioning *(8)*. Adult women have also demonstrated better preserved cardiac function with increasing age, with the exception of a higher incidence of diastolic dysfunction in postmenopausal women *(5)*. With increasing age, the ability of body size to predict heart size declines and this may begin sooner in men than in women *(8)*.

In studies of elderly rats, normotensive males were found to have larger, thinner, and more fibrotic hearts with decreased performance indices compared to females *(9)*. Additionally, male rats had a higher prevalence of mitral valve regurgitation *(9)*. In the Framingham study, it was shown that left ventricular hypertrophy increased 15% every decade in men over 60, whereas this increase was 69% in women *(10)*. Women lag behind men before menopause, but there is a sharp increase in left ventricular hypertrophy after menopause and women eventually catch up to men. In hypertensive rats, females have an even greater increase in left ventricular mass compared to males *(9)*. Whether or not these differences are related to sex hormones, however, is still unclear because women are usually far past menopause when cardiovascular problems arise and hormone replacement therapy can actually exacerbate heart disease in postmenopausal women *(5,10)*. Recent studies have tried to establish a link between estrogen and myocardial remodeling and determining the answers to these questions may help to explain the greater longevity of women and why women generally fare better than men during cardiovascular insult, although not always *(4,5,9)*.

## Cardiac Complications: Hypertrophic Cardiomyopathy and Heart Failure

Left ventricular hypertrophy is a compensatory response to chronic pressure overload to the heart and is seen in most individuals with essential hypertension *(11,12)*. It is characterized by an increase in wall thickness relative to chamber radius (concentric hypertrophy) and this remodeling is due to the parallel enlargement of sarcomeres in cardiac myocytes, which causes the cells to increase in width, increasing wall thickness *(13,14)*. This adaptive response is an interaction between hemodynamic load, cardiac remodeling, and ventricular performance and can have serious implications, including sudden cardiac death, myocardial infarction, and congestive heart failure *(11,12)*. It is apparent that both age and sex affect remodeling of the heart, the pattern of hypertrophy, and functional impairment *(11)*.

As stated earlier, postmenopausal women have a greater incidence of left ventricular hypertrophy than both men and premenopausal women; however, women also show greater concentric remodeling and preserved left ventricular function than age-matched men *(4,15)*. Additionally, younger women with mild hypertension have been shown to have better load-dependent and load-independent cardiac functions compared to men of similar age *(4)*.

Recent studies have shown that estrogen may affect cardiomyocytes and cardiac remodeling. Estrogen receptors are found in cardiomyocytes and in female rats with left ventricular hypertrophy, higher levels of sarcoplasmic reticulum $Ca^{2+}$-ATPase mRNA are present compared to males *(4,16)*. In addition, male rats transit to heart failure sooner than females when the heart failure results from chronic hypertension or pressure overload. This is thought to be due to a greater hypertrophic reserve in the female heart and greater preservation of cardiomyocytes in females compared to males *(4)*. In fact, estrogen can block p38 MAP kinase phosphorylation, which is usually activated in the failing human heart. Estrogen has also been implicated in activating the anti-apoptotic protein Akt in the heart *(4)*. Non-genomic estrogenic actions may also confer cardioprotection by increasing nitric oxide production and affecting $Ca^{2+}$ levels within the cell *(17,18)*. Changes in cardiac gene expression and non-transcriptional estrogenic actions may help explain the increased survival rate of females with hypertension and left ventricular hypertrophy.

Electrocardiographic studies have also shown that in older hypertensive patients with left ventricular hypertrophy, women have a higher systolic left ventricular function than men *(19)*. Additionally, male hearts had increased interstitial fibrosis compared to female hearts. Higher interstitial fibrosis is believed to contribute to more severely impaired cardiac function in males *(19)*. Also, in response to systemic hypertension, women had greater left ventricular hypertrophy with smaller left ventricular chamber size consistent with concentric hypertrophy. Men, on the other hand, had decreased wall thickness and higher wall stress, indicative of eccentric hypertrophy *(12)*. Collectively, this pattern indicates that females may have better myocardial remodeling that leads to greater retention of function, although this is debatable.

Male and female rats initially show similar compensatory concentric remodeling due to pressure overload. However, chronic pressure overload is more likely to progress into pathological hypertrophy in males, associated with heart chamber dilation and reduced contractile function typical of eccentric remodeling *(15)*. Eccentric hypertrophy may develop in men from increased blood volume or volume overload due to the hypertensive state. Excess volume and a thinner left ventricular wall can lead to systolic dysfunction in men *(20)*. In women, greater concentric remodeling has been associated with retained ventricular function. However, this adaptation is transient and excessive concentric remodeling may eventually lead to congestive heart failure *(21)*. With concentric hypertrophy, the ventricular wall becomes abnormally thickened with reduced heart chamber size, leading to decreased end diastolic volume and stroke volume. This leads to diastolic dysfunction and the danger of energy depletion, ischemia, and cardiac cell death *(20)*. For both men and women, left ventricular hypertrophy is a major risk factor for adverse cardiac events such as diastolic dysfunction and congestive heart failure (Fig. 2) *(21)*.

Elderly women in particular are at risk for developing diastolic dysfunction leading to diastolic heart failure as a result of chronic hypertension *(12,22)*. With increased age, the prevalence of diastolic dysfunction rises significantly in postmenopausal women *(23)*. Heart failure normally has a later onset in women compared to men, which gives women better survival rates. However, quality of life appears to be lower in women than in men after heart failure *(23)*. The overall prevalence for heart failure is similar between men and women, but the type of heart failure differs *(23)*. This is important because most research related to heart failure is conducted on male subjects. Future research needs to focus on the gender differences in heart failure and appropriate treatments for both *(23)*.

## Perception of Chest Pain

As stated above, men are generally at greater risk than age-matched premenopausal women for hypertension and heart disease; however, women catch up to men after menopause. In fact, since the mid-1980s more women have died every year from cardiovascular disease than men *(4,24)*. Unfortunately, women still do not view heart disease as a serious health threat and diagnosis and treatment for women is not as aggressive as for their male counterparts *(4)*. Difficulties also arise when interpreting atypical symptoms described by women with chest pain *(25)*.

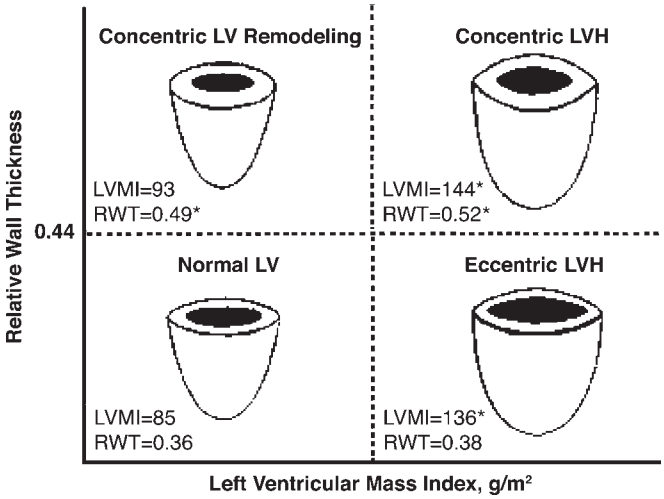


**Fig. 2.** Hypertension leads to left ventricular hypertrophy. Males and females initially show similar concentric remodeling due to pressure overload, but with chronic conditions males usually transition to eccentric hypertrophy and females transition to concentric hypertrophy, both of which increase danger of congestive heart failure. LV = left ventricle; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; RWT = relative wall thickness; $*p = 0.001$ compared with normal persons. Figure presented with permission from *Ann Inter Med (61)*.

The perception and presentation of chest pain can be very different between the sexes *(25–27)*. Women tend to complain about diffuse pain in the stomach, back, chin, upper arm, and neck and are less likely to complain about direct chest pain making a diagnosis more difficult. Women also describe heart-related chest pain as pressure, tightness, heaviness or undefined pain, whereas men generally present with direct chest pain and attribute it to heart disease *(25, 27)*. Women also had more symptoms than men, such as dizziness, nausea, shortness of breath, and irritability, and described more intense pain *(27)*. Treatment options for women are often fewer because women delay seeking treatment, making therapy more difficult and increasing the chance of a fatality *(26)*.

Many possible reasons exist to explain the differences in the experience of chest pain. Gender differences in pain perception and neural processing are known *(27)*. In female rats, endogenous opioids are upregulated during pregnancy and parturition, increasing pain thresholds *(27)*. Sex hormone levels can also affect male and female neural pathways differently *(27)*.

Psychologically, women often feel an obligation as a "family caregiver" and avoid acknowledging illnesses. Additionally, society as a whole tends to view cardiovascular disease as a male affliction, causing women to delay seeking treatment or to receive less encouragement to seek treatment. Women may also feel guilty for wasting a doctor's time when reporting an illness *(27)*. Whatever the reasons for differences in the perception and reporting of chest pain, it is clear that better understanding and recognition of symptoms in women need to be identified and both men and women need to be encouraged to seek early treatment for cardiovascular disease *(25–27)*.

## Vasculature

Both the heart and vasculature play a role in the development of high blood pressure. Alterations in vascular responsiveness play a major role in controlling blood pressure and therefore the incidence of hypertension *(6)*. Experimental evidence has revealed sex-related differences in the regulation of hemostasis, vascular reactivity, and vascular tone. Hemostasis is the maintenance of blood flow within the vessels with the ability for rapid clot formation upon injury. This depends on a balance between several factors, such as viscosity, vasoconstriction, platelet activation, and activation of the coagulation cascade *(28)*. Abnormal hemostasis activation can lead to endothelial dysfunction and a more atherogenetic profile, which increases the risk of hypertension and cardiovascular disease *(29)*. Studies have suggested that platelets in males are more reactive than platelets in females, which may in part be mediated by testosterone. It has been demonstrated that testosterone can stimulate and increase thromboxane A2 (TXA2) receptor density and increase platelet response to TXA2 agonists. Platelet-derived TXA2 is a powerful vasoconstrictor and platelet activator and may cause male platelets to be more responsive *(30)*. Male platelets may have a greater ability to aggregate, adhere to, and spread onto the arterial surface *(31)*.

Women may have greater inhibition of platelet aggregation and clot formation. Endothelial cells produce a prostaglandin, prostacyclin, which inhibits platelet adherence and aggregation and acts as a vasodilator (Fig. 3) *(28)*. Estradiol has been shown to stimulate production of prostacyclin in vitro and the effect was prevented by an estrogen antagonist, tamoxifen *(32)*. Less reactive platelets and greater platelet inhibition could provide women with protection from thrombus development, atherosclerosis, and hypertension, at least before menopause. These results suggest that platelets from females are less thrombotic than platelets from males.

Fibrinolytic activity has also been studied in male and female rats. The fibrinolytic pathway occurs after clot formation to dissolve a clot. In this pathway, plasminogen is converted to plasmin, which begins degradation of fibrinogen and the fibrin matrix of a clot *(28)*. In male rats there was a longer clot degradation time, while females had a higher fibrinolytic index and higher plasminogen activator activity than males, which would lead to faster clot lysis in females *(28)*. Again, increased ability to dissolve clots would protect women from narrowing of blood vessels, which can lead to atherosclerosis and hypertension.

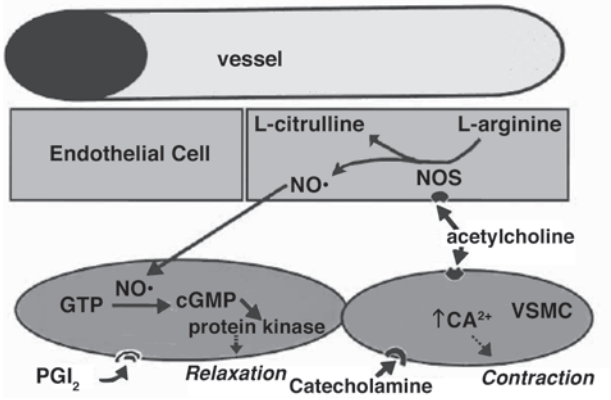


**Fig. 3.** Estrogen can increase relaxation of vascular smooth muscle cells by increasing $PGI_2$ and NO levels. Estrogen decreases vasoconstriction by acting as a $Ca^{2+}$ channel antagonist. Women also appear to be less sensitive to catecholamines. Figure presented with permission from *Heart & Lung (28)*.

Vascular reactivity, described as responsiveness of blood vessels to vasodilation and vasoconstriction, and vascular tone, the sum influence of vasoconstriction and vasodilation, also appear to be affected by sex *(28)*. Sex differences in vascular smooth muscle have been shown to exist. In vascular smooth muscle cells, estrogen may act as a $Ca^{2+}$ channel antagonist, decreasing $Ca^{2+}$ influx and contraction. Estrogen may also have antiproliferative effects on vascular smooth muscle cells *(28,33)* and women have lower levels of certain vasoconstrictor molecules, such as TXA2 and endothelin-1, and appear less sensitive to α-adrenergic stimulated vasoconstriction than males *(34–37)*. Overall, premenopausal women seem to have lower vascular reactivity and greater vasodilation capacity compared to men and postmenopausal women, which may help alleviate problems of high blood pressure (Fig. 3).

## Nitric Oxide

Blood pressure regulation involves many pathways, one of which is endothelial-derived nitric oxide (NO). NO is involved in regulating vascular tone, has vasodilating effects, and prevents platelet activation *(28,38)*. Additionally, inhibitors of endothelial nitric oxide synthase (eNOS), which converts L-arginine to L-citrilline and produces NO, cause increases in blood pressure. Knockout mice deficient in eNOS are also hypertensive compared to wild-type mice *(28,38)*. It is now known that women have higher levels of endothelial-derived NO than men *(39)*. Women also have greater endothelial-dependent vasodilation due to a higher NO release (Fig. 3). However, the NO vasodilation response

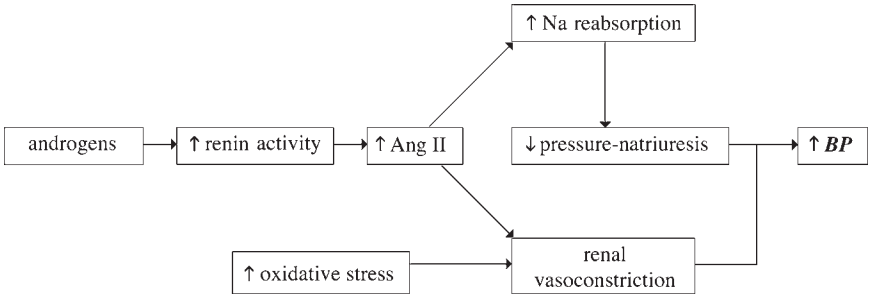


**Fig. 4.** Increased activity of the RAS in men may put males at a greater risk for developing hypertension and cardiovascular disease. Testosterone appears to increase plasma renin and ACE activity, which may increase Ang II. Estrogen appears to suppress ACE activity possibly reducing Ang II. Figure presented with permission from *Hypertension (24)*.

decreases after menopause *(39)*. In premenopausal women, higher estrogen levels may correlate with greater NO production, which may confer an advantage to women in regards to prevention of hypertension *(40)*.

## Renin–Angiotensin System

Development of hypertension is associated with many factors, including the renin–angiotensin system (RAS). There is a sexual dimorphism between male and female rats in the activation of the RAS *(41)*. Male hypertensive rats show increased plasma renin activity and greater serum angiotensin converting enzyme (ACE) activity compared to hypertensive females, suggesting increased angiotensin II (Ang II) levels in males. In fact, testosterone appears to stimulate the RAS and estrogen can suppress ACE activity *(24,41)*. Additionally, both male and female hypertensive rats had altered ACE activity compared to their normotensive counterparts, suggesting that ACE activity is involved in the development of hypertension in both sexes, but to varying degrees *(41)*.

Centrally administered Ang II is also able to induce hypertension in male dogs, but not in females *(42)*. The number of Ang II binding sites has also been shown to decrease with estradiol treatment in the anterior pituitary *(43)* and centrally administered estradiol can decrease pressor responses to Ang II, whereas testosterone can stimulate brain renin release *(44,45)*. Sex differences in the brain RAS system may be involved in the higher incidence of hypertension in men and postmenopausal women compared to premenopausal women.

As discussed, testosterone has been shown to stimulate RAS, which may lead to increased Ang II, a potent vasoconstrictor and stimulator of aldosterone. The biological properties of Ang II appear to be involved in the development of hypertension because Ang II given to normotensive male rats is able to induce hypertension and increase plasma markers of oxidative stress *(24,46)*. Oxidative stress with increased superoxide production could increase blood pressure even further by inactivating NO in males *(24)*. Ang II also stimulates the production of aldosterone, which increases sodium and water reabsorption in the kidney leading to long-term changes in fluid volume. This may be important because in hypertensive men there is a correlation between testosterone, aldosterone, and high blood pressure *(24)*.

Chronic activation of the RAS also contributes to cardiac hypertrophy and Ang II antagonists are able to decrease cardiac hypertrophy *(41)*. It has been postulated that females have delayed development of heart failure due to delayed activation of the RAS *(41)*. In addition, increased generation of Ang II appears to promote ventricular hypertrophy and stiffness *(41)*. Overall, increased RAS activity may put males at greater risk for developing hypertension, cardiac hypertrophy and congestive heart failure compared to women (Fig. 4).

## Hemodynamic Factors

Sex-specific hemodynamic factors may help to explain some differences in the development of hypertension between men and women. Women generally display lower systolic, diastolic, and mean blood pressure compared to men at all ages, but the gender difference between systolic and diastolic blood pressure, or pulse pressure, becomes narrower in women as they age, finally surpassing that of men after 55 yr of age *(7)*. Two factors may contribute to higher pulse pressure in older women—shorter stature and higher heart rate. Shorter stature in women means a shorter arterial tree length, which may account for differences in ventriculovascular coupling *(7)*. Higher heart rate is also related to a shorter arterial tree length and may increase with age due to less compliance and increased stiffening of the arterial tree in women *(7)*. After menopause, loss of estrogen leads to elastin fragmentation and collagen accumulation in the arterial tree, resulting in aortic stiffening *(7)*. This results in increased isolated systolic hypertension in women and hypertension with a capacitance component, whereas men are more likely to develop hypertension with a resistive component, due to differences in hemodynamic patterns of aging between the sexes *(7)*. Additionally, higher pulse pressure in older women may explain the greater age-related increase in left ventricular hypertrophy compared to men *(7)*.

**Table 1**

Adverse Cardiac Events Associated with Hypertension by Sex and/or Age

| Premenopausal Women | Postmenopausal Women | Men |
|---|---|---|
| Eclampsia | Left ventricular hypertrophy | Left ventricular hypertrophy |
| Contraceptive-induced hypertension | Concentric hypertrophy | Eccentric hypertrophy |
| | Diastolic dysfunction | Increased fibrosis |
| | Diastolic heart failure | Systolic dysfunction |
| | Aortic stenosis | Systolic heart failure |
| | Isolated systolic hypertension | Mitral regurgitation |
| | Undefined chest pain | Defined chest pain |

## Vascular and Aortic Complications of Hypertension

Large-artery stiffening is one of the main determinants of systolic blood pressure in older patients and often leads to isolated systolic hypertension. Isolated systolic hypertension affects more than 25% of the population over 55 yr of age, and is a major risk factor for stroke and cardiac events *(47)*. Premenopausal women have a less stiffened arterial system than men, but after menopause proximal circulation becomes much more rigid in women compared to men *(47)*. In women, decreased estrogen levels lead to elastin fragmentation and collagen accumulation in large vessels resulting in arterial stiffening *(7)*. These results suggest that postmenopausal women are at greater risk for developing isolated systolic hypertension and stroke due to increased aortic stenosis *(47)*. Table 1 summarizes adverse cardiac events associated with hypertension for premenopausal women, postmenopausal women, and men.

## Treatments for Hypertension and Cardiovascular Disease

### *Physical Exercise and Diet*

While lifestyle changes, including a heart-healthy diet, exercise, and weight reduction are probably the best treatment for cardiovascular disease, these guidelines are often not followed. In fact, women are generally less physically active than men and older populations are generally more sedentary than the young *(48)*. Additionally, the percentage of overweight and obese people in the United States is steadily increasing, with more than 50% of women being overweight or obese *(48)*. However, for perimenopausal women, as little as 30 min of daily exercise and a lower calorie, lower fat diet (1300 kcal diet with 25% dietary fat intake) can reduce both systolic and diastolic blood pressure, total cholesterol, triglyceride levels, waist circumference, and glucose levels *(48)*.

Obesity is also associated with endothelial dysfunction *(49)*. Endothelial dysfunction can affect vascular tone and reduce vasodilation. Additionally, endothelial dysfunction can lead to elevated blood pressure, development of atherosclerosis, inflammation, dyslipidemia, and altered glucose metabolism *(49)*. Weight reduction with a low calorie diet can actually reverse the effects of obesity and improve flow-mediated vasodilation *(49)*. In addition, regular exercise can improve endothelial-dependent vasodilation by enhancing NO production and increasing levels of eNOS *(50)*.

Exercise, healthy diet, and weight loss are very effective, non-pharmacological methods for improving overall cardiovascular health and reducing blood pressure. The benefits of lifestyle modifications, such as increased activity and healthy diet, are very attainable and should be included in clinical prevention and treatment strategies.

### *Hormone Replacement Therapy: Estrogen and Progesterone*

Strong evidence suggests that estrogen is cardioprotective in younger women. In fact, premenopausal women have been shown to have a decreased risk of cardiovascular disease and hypertension compared to men and postmenopausal women *(51)*. However, the benefits of hormone replacement therapy in postmenopausal women are not clear and are even controversial *(51)*. Additionally, women who have had a hysterectomy are able to take estrogen supplementation alone, whereas women with an intact uterus must take a combination of estrogen and progesterone to decrease risk of endometrial cancer *(51)*.

Studies comparing the effects of estrogen replacement therapy (ERT) and a combined hormone replacement therapy (HRT, CEE plus MPA), with both estrogen and progesterone, have shown that both treatments can increase HDL (high-density lipoprotein) cholesterol and decrease LDL (low-density lipoprotein) cholesterol, although HDL cholesterol was affected to a lesser extent in the estrogen plus progesterone group *(51)*. It was also generally found that both estrogen alone and estrogen in combination with progesterone can reduce atherosclerotic plaques if given early enough after menopausal estrogen deprivation (Fig. 5). However, it can be detrimental given in late menopause *(51)*. Additionally, both ERT and HRT seem to be beneficial in reducing plasma markers of inflammation *(51)*.

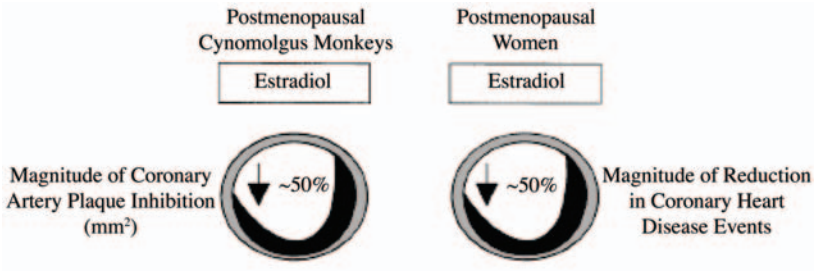


**Fig. 5.** Percentage arterial plaque inhibition in postmenopausal monkeys and women given estradiol treatment. Figure presented with permission from *Steroids (51)* and modified from *Estrogens and Antiestrogens (63)*.

In postmenopausal hypertensive women, both ERT and HRT treatments can reduce left ventricular wall thickness and mass *(52–54)*. This effect may be mediated through an estrogen-induced increase in atrial natriuretic factor (ANF). ANF is normally found in the atria, but may function as a local endocrine antagonist of left ventricular hypertrophy in diseased hearts *(52)*. ERT and HRT have both been shown to decrease serum ACE activity and plasma aldosterone levels in hypertensive women *(41,53)*. Additionally, both ERT and HRT may reduce blood pressure, although conflicting results have been found in this regard *(53,55)*.

There may be reasons for concern, however, when comparing ERT and HRT treatment. Monkeys deficient in estrogen, similar to postmenopausal women, show endothelial dysfunction and increased vasoconstriction. Estrogen treatment improves vasodilation; however, a combination of estrogen and progesterone attenuated estrogen-induced improvements by 50% *(51)*. When examining HRT alone, it appears that administration of HRT in postmenopausal hypertensive patients may increase thromboembolic events *(56)*. Additionally, it has been observed that postmenopausal women given estrogen and progesterone have an increased incidence of breast cancer compared to women receiving estrogen alone *(51)*.

Recently, findings from the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) have created debate between whether or not to prescribe hormone supplementation to women during or after menopause *(57)*. Both studies have suggested that ERT and HRT are risky therapies and as a result patients and doctors have been reluctant to use HRT. However, many researchers disagree with the evidence put forth in these reports *(4,57)*. For example, Wehrmacher and Messmore *(57)* and Schwartzbauer and Robbins *(4)* argue that the patient population involved in the studies consisted of older women already diagnosed with cardiovascular disease. In fact, in the WHI study most participants were 15 yr postmenopausal, a group not normally chosen to start estrogen therapy *(57)*. While caution is advised when prescribing medication, mounting evidence continues to support the beneficial effects of estrogen for menopausal and postmenopausal women, both for cardioprotection and to reduce the adverse symptoms associated with menopause, such as hot flashes and sweating *(57)*.

While the benefits of ERT and HRT in preventing cardiovascular disease and hypertension in postmenopausal women remain controversial, it does appear that both may have positive effects if started during perimenopause or early postmenopause *(57)*. However, both seem to have negative effects when started late in postmenopausal women and HRT may pose an additional risk, with the association between progesterone and breast cancer *(51,57)*.

### *Soy and Phytoestrogens*

The effects of soy-based diets on blood pressure have also been studied in spontaneously hypertensive rats (SHR). Soy products are thought to be beneficial in the diet because they contain plant-derived phytoestrogens, antioxidants, and no animal protein *(58)*. A soy-based diet compared to a diet high in animal protein can decrease hypertension and serum total cholesterol levels in both male and female SHR rats and soy also has vasodilating effects *(58)*. Additionally, populations that consume more soy have decreased cardiovascular-related mortality *(58)*. Phytoestrogens may also have protective effects against breast cancer, delaying tumorigenesis *(59)*. Further studies, however, need to be done on human subjects to determine the effectiveness of soy based diets as treatments for hypertension.

### *Antihypertensive Drugs*

Antihypertensive drugs have often been used in conjunction with ERT and HRT in postmenopausal hypertensive patients. Antihypertensive therapies reduce cardiovascular morbidity and mortality *(60)*. ACE inhibitors, in particular, have been shown to have cardioprotective and vasculoprotective effects *(60)*. ACE inhibitors can decrease left ventricular hypertrophy (Fig. 6), restore balance between myocardial oxygen supply and demand, reduce preload and afterload in the left ventricle, reduce sympathetic input, improve endothelial function, arterial compliance, and vascular tone, decrease platelet stimulation, and prevent migration of smooth muscle cells *(60)*. In addition, ACE inhibitors may reduce athero-

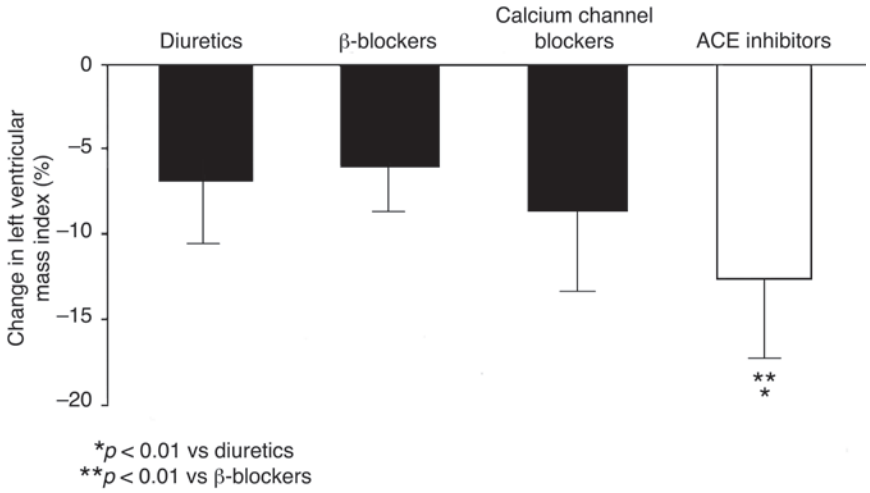


**Fig. 6.** ACE inhibitors are the most effective antihypertensive treatment for regression of left ventricular hypertrophy. Figure presented with permission from *Am J Hypertens (60)*.

**Table 2**

| Common treatments for hypertension and cardiovascular disease |
|---|
| Men and women |
| Physical exercise (30 min daily) |
| Diet (1300 kcal w/ 25% dietary fat) |
| Soy-based diet (phytoestrogens) |
| Antihypertensive drugs (ACE inhibitors*, diuretics, β-blockers, $Ca^{2+}$ channel blockers) |
| Menopausal/postmenopausal women |
| ERT: estrogen replacement therapy (estrogen) |
| HRT: hormone replacement therapy (estrogen plus progesterone) |

*ACE inhibitors are the most effective of the antihypertensive drugs.

genic associated events and enhance fibrinolysis *(60)*. ACE inhibitors may also be more useful in patients with hypertension and renal failure than other antihypertensive drugs, such as diuretics, β-blockers, and $Ca^{2+}$ channel blockers *(60)*. Additionally, new studies are now focusing on sex-related differences in the development and presentation of hypertension in men and women and this may lead to the production of more accurate treatments for hypertension (Table 2).

## Conclusion

Hypertensive men and women differ in development and presentation of the disorder. Men have increased vascular reactivity, platelet activity, and RAS activity that may predispose them to hypertension. Postmenopausal women have increased incidence of left ventricular hypertrophy, diastolic dysfunction, aortic stenosis, and isolated systolic hypertension compared to younger women and men. Estrogen may provide women with cardioprotection and vasoprotection in early years, contributing to increased NO production, decreased RAS and platelet activity, increased vasodilation, and improved cardiac remodeling. Future antihypertensive treatments may utilize different therapies for men, women, and patients of both genders at different stages of life to address these issues.

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