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Arterial hypertension in the female world: pathophysiology and therapy

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Hypertension is a major risk factor for cardiovascular disease and outcomes in women, and antihypertensive therapy is not always successful in achieving control over the blood pressure (BP). Nonoptimal control of BP remains a crucial risk factor for cardiovascular mortality, and in women, it could be related to sex-specific factors. Historically, women have been under-represented in clinical trials; therefore, the benefits of clinical outcomes and the safety profiles of antihypertensive therapies have been studied less extensively in women. The reasons for the sex differences in BP levels are multifactorial, implying different roles of the sex hormones, the renin–angiotensin system, sympathetic activity, and arterial stiffness. A complete understanding of the pathophysiological features of these differences requires further investigation.

Nevertheless, the prevalence of the use of antihypertensive agents is higher among middle-aged women than among men. Notably, in the United States, hypertensive women use more diuretics and angiotensin receptor blockers than men, whereas hypertensive men more often receive beta-blockers, calcium channel antagonists, or inhibitors of angiotensin-converting enzyme. To date, the explanations for these sex differences in the consumption of antihypertensive drugs remain unknown.

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Introduction

The risk of cardiovascular disease (CVD) in the female sex has been largely underestimated in the past due to the misperception that women were, if not immune, strongly spared against developing these diseases.[1] Although considerable progress has been made in the knowledge, prevention, and treatment of CVD in women over the past decade, a limited consciousness persists regarding the differences in the prevalence, association, and clinical penetrance of various cardiovascular risk factors between the two sexes.[2] In this regard, special attention should be paid to arterial hypertension, one of the main determinants of cardiovascular risk for women, which is able to influence the prognosis, especially when it is present in association with diabetes mellitus or within the cluster of metabolic syndrome.[3] Although arterial hypertension prevalence has increased substantially over the past decade, it often remains undiagnosed for a long time, especially in women.[4,5]

Large observational studies suggest that the associations between age-adjusted SBP and the risk of stroke and coronary heart disease are similar for men and women.[6] However, the most recent scientific evidence seems to suggest that something is changing because hospitalizations for stroke are falling in men and remain unchanged in women.[7] These sexual dissimilarities may be related to biological or pathophysiological factors, as well as to disparities in healthcare or differences in the response to therapy.[8,9]

Pathophysiology

Sexual differences in the pathophysiology of arterial hypertension appear to be multifactorial and are still not entirely understood. The role of sex hormones, differences in sympathetic activation, and arterial stiffness are some of the current hypotheses.

Role of sex hormones

Androgens and estrogens affect cardiovascular function and heart remodeling,[10] together with the regulation of blood pressure (BP), beginning with their effects on the

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renin–angiotensin–aldosterone system (RAAS). Ample evidence demonstrates that androgens increase BP by stimulating RAAS,[11] whereas ovarian hormones have the opposite effect, reducing plasma renin and angiotensin-converting enzyme (ACE) activity.[12] Hypertensive women, apart from individual exceptions, tend to have lower plasma renin activity (PRA) than men with high BP.

Plasma renin activity, intravascular volume, and BP vary during the menstrual cycle in normotensive women. A recent study suggested that BP in hypertensive patients with high PRA can be regulated mainly by RAAS, as opposed to those with low PRA in whom sex steroids appear to play a more important role.[13] PRA increases after menopause,[14] and the up-regulation of angiotensin I receptors, together with the down-regulation of angiotensin II receptors in the postfertile age group, could affect the response to therapy.

The effects of sex hormones on the processing of renal sodium and vascular resistance may also explain the differences in BP control between men and women. Female sex hormones may protect against the salt-induced increase in BP; indeed, Schulman *et al.*[15] found that the prevalence of salt sensitivity increased significantly from 22.5 to 52.5% after ovariectomy.

Estrogens, which stimulate the production of nitric oxide, maintain normal endothelial function and induce structural and functional beneficial effects on the arterial wall that reduce vascular stiffness.[12] In addition, they mitigate the activity of the sympathetic nervous system.[16,17] These effects could lead, in premenopausal women with arterial hypertension, to an increase in resting heart rate and greater left ventricular ejection fraction (LVEF), cardiac index, and pulse pressure, which have been reported together with a lower total peripheral resistance and total blood volume, in comparison to men of the same age and with the same level of BP.[13]

The effect of menopause on BP is controversial. Longitudinal studies have not documented a rise in BP with menopause, whereas cross-sectional studies have demonstrated significantly higher values for SBP and DBP in postmenopausal in comparison to premenopausal women. In the NHANES III study, the rate of increase in SBP tended to be accelerated in postmenopausal compared to premenopausal women and until the sixth decade of life, at which time the rate of increase tended to slow down.[18] It has been shown that menopausal women, after adjustment for age and BMI, are twice as likely to have high BP compared to premenopausal women.[19] Surgical menopause may induce hypertension, which occurs shortly after oophorectomy and is correctable with estrogen replacement therapy.[20]

The results of studies investigating the effects of hormone replacement therapy (HRT) on BP have been inconsistent. Mercuro *et al.*[21] found that transdermic estradiol significantly decreases 24-h SBP and DBP and restores the expected reduction in BP during night-time in nondipper women. These data suggest that endogenous estrogen has a role in preserving physiologic circadian fluctuations in BP.[21] Overall, the HRT-related changes in BP are probably modest and should not preclude the use of hormones in normotensive or hypertensive women.[22] All hypertensive women treated with HRT should have their BP monitored closely.

Hormone replacement therapy and selective estrogen receptor modulators must, however, not be used for primary or secondary prevention of CVD, neither should it be ever intended to counteract BP increase after menopause. In younger women in perimenopause, when HRT is prescribed for severe symptoms of estrogen deficiency, the benefits of replacement therapy should be carefully weighed against its potential risks. However, it is unlikely that HRT in postmenopausal hypertensive women could significantly increase BP.[23]

Hemodynamic characteristics

Women younger than 40 years of age have a lower SBP, DBP, and mean BP than their male counterparts. This trend is reversed after 55 years of age.[24] Different anatomical and physiological characteristics may contribute to such differences between men and women. Estrogen has been shown to directly influence remodeling of the arterial wall, increasing the production of elastin and decreasing the deposition of collagen in human arteries.[25]

Sex differences in vascular biology can be related not only to the types and levels of sex hormones but also to tissue and cellular differences that are responsible for sex-specific responses to various stimuli. Receptors for estrogen and progesterone have been identified in the human aorta[26,27]; women have more arterial estrogen receptors than men.

The role of sex hormones in the regulation of arterial elasticity and function is further suggested by studies that measured arterial stiffness during periods of hormonal transition, such as before and after puberty, or during the different phases of the menstrual cycle.[28,29]

An increase in arterial stiffness has been described after menopause.[30] Moreover, several studies have shown that arterial stiffness is improved by HRT[31,32] and deteriorates again after its removal.[33] This finding suggests that female sex hormones (and/or the metabolic environment accompanying them) could play a role in the regulation of large artery compliance.[34] Other studies suggest that women, especially after menopause, have greater arterial pulsatility compared to men.[35,36] Sex differences observed in arterial stiffness and pulsatility may be ascribed to a reduced total length of the arterial tree and the shorter aortic length of women compared to men. This anatomical condition causes accessory reflected

pressure waves that reach the central aorta during the first half of systole, with a faster time of wave travel, increasing the reflection wave and the central pulse pressure and amplifying the systolic peak.[37] Consequently, there is a more rapid rise in brachial and central SBP that can be observed both in postmenopausal women and in men.[38] A recent study has also shown that the carotid–brachial pulse pressure ratio increases with increasing age in both sexes and produces a significant rise in cardiovascular mortality. This impact is greater in women older than 55 years compared to younger women.[39]

Pharmacological control of blood pressure

In most cases, antihypertensive therapy is effective in controlling BP; this is important because nonoptimal control of BP remains the main risk factor for cardiovascular mortality.[40,41]

Historically, women have been under-represented in clinical trials[42]; however, although they are at present well represented in randomized clinical trials in hypertension, the results are not always reported separately for men and women. Therefore, data on the beneficial effects, clinical outcomes, and safety profiles of antihypertensive therapy are not easily obtainable in the female sex. In terms of beneficial effects, an extensive meta-analysis that evaluated the effect of BP-lowering treatment in men and women has shown no difference in the prevention of major cardiovascular events between men and women with all the drug classes.[43]

Nevertheless, in the United States, the consumption of antihypertensive drugs is higher among middle-aged women compared to men of the same age.[18] In particular, hypertensive females use more diuretics and angiotensin receptor blockers (ARBs) than men,[18,44] whereas hypertensive men more often receive beta-blockers, calcium channel antagonists, and ACE inhibitors (ACEIs).[44] To date, these differences between the two sexes have not received comprehensive explanations.

Although women take more antihypertensive medications than men, they are less likely to achieve the recommended treatment goals.[18,45] Data from a survey showed progressive improvement in BP control in men, but not in women, especially in the elderly population.[18,46] In addition, a more recent Canadian study confirms that arterial hypertension is controlled less in women (30%) than in men (17%), even when age, socioeconomic status, comorbidities, drug classes, anthropometric differences, and other correlates of BP are considered.[47] Currently, the explanations for these sex differences are not well understood, as sex and the role of the physician seem to influence the achievement of therapeutic targets for BP. Moreover, in treated Italian hypertensive patients, a recent survey showed that BP control remains unsatisfactory (33.5% of all patients), although no significant sex differences were evidenced (34.2% in men and 33.4% in women).[48]

The difference in adherence to treatment between sexes is still controversial.[49] A Swedish study involving a large number of men and women showed that only female patients, and not men, treated by female primary healthcare physicians, achieved therapeutic goals for BP more often than women treated by male primary healthcare physicians.[50] Whether and to what extent adherence to therapy is a sex issue is still under discussion. Some studies show that being a woman is a negative predictor for adherence after acute coronary syndrome and myocardial infarction (MI),[5,51,52] as well as in arterial hypertension.[53] This finding could be explained, at least in part, by the increased prevalence of women in the older population.[54] In fact, a recent study in elderly hypertensive patients did not detect significant sex differences with regard to adherence to therapy, but the factors responsible for the low adherence differed between men and women.[54] Specifically, low adherence in men was associated with reduced sexual function and BMI, whereas in women, it was associated with depressive symptoms and dissatisfaction with the communication with their care provider.[54] Awareness is also strictly linked to BP control.[55] Several factors have been associated with low awareness and/or BP control, namely increasing age, low education, non-white race, previous CVD, living alone, decreased physical activity, or depression. Overweight and diabetes have been related to higher BP awareness and adherence to treatment, but not to improved BP control.[56] More recently, in a US female population, hypertension control was improved to 47%, acting mostly on lifestyle interventions.[57]

The present guidelines suggest comparable benefits in the two sexes in terms of cardiovascular morbidity and mortality as a result of the reduction in BP, and also indicate that the majority of patients, including women, require combination therapy.[45,58,59] However, women display a worse safety profile.[60,61]

For brevity, we do not discuss the biological and social factors that explain the observed sex differences in pharmacokinetics. These aspects have been recently and extensively discussed elsewhere.[60–63] However, we should note that pharmacokinetics in women may depend on the phase of the menstrual cycle, pregnancy, lactation, and menopause. We also want to mention the particular importance of sex differences at the level of drug-metabolizing enzymes such as the cytochrome P450 system – a member of the 1, 2, and 3 CYP families, second-phase enzymes, transporters, and the multiple drug-resistance proteins. In recent years, it has been shown that sex also influences pharmacodynamics. In this context, it is important to remember that the sympathetic nervous system, renin–angiotensin–aldosterone axis, and endothelin system are sexually divergent[60–63];

thus, the occurrence of pharmacodynamic sex-dependent differences is plausible.

Diuretics

This class of drugs includes the following: thiazides (chlorothiazide, chlorthalidone, indapamide, hydrochlorothiazide bendroflumethiazide, methylclothiazide, and metolazone), which, in most cases, are preferred to other diuretics for the treatment of high BP; potassium-sparing diuretics (amiloride, spironolactone, and triamterene); and loop diuretics (bumetanide, furosemide, ethacrynic acid, and torsemide). Thiazides lower cardiovascular risk, including stroke, and, therefore, should be considered as one of the possible drugs for first-line therapy.[45] The guidelines of the American Heart Association recommend thiazide diuretics should be part of the drug regimen for most patients unless contraindicated or if there are compelling indications for other agents in specific vascular diseases. Initial treatment of high-risk women with acute coronary syndrome or MI should start with beta-blockers and/or ACEIs or ARBs, with the addition of other drugs such as thiazides, as needed to achieve BP control.[5] Notably, after fasting overnight, the diuretic response to oral hydrochlorothiazide is not statistically different between men and women with respect to the urine flow rate and sodium and potassium excretion rates, but because older women have a greater prevalence of reduced glomerular filtration rate, they need to be aware that an inappropriate use of thiazide diuretic might worsen it.

The ALLHAT study has shown that treatment with chlortalidone was associated with an increased relative risk of stroke with respect to lisinopril, whereas amlodipine use tended to reduce the risk of stroke, when compared with chlortalidone. However, the finding of significantly higher stroke mortality for lisinopril versus chlorthalidone evidenced at the first in-trial analysis did not differ significantly by sex during the extension period analysis [hazard ratio 1.20, 95% confidence interval (CI) 1.10–14.1]. Moreover, the risk of stroke reduction evidenced by amlodipine when compared with chlortalidone was not confirmed from the extended-trial analysis.[64]

The IDEAL study (indapamide and perindopril versus placebo) indicates that reduction of SBP is higher in men than in women.[65]

Pharmacovigilance studies indicate that women are at a higher risk for adverse drug reactions (ADRs). The status of being a woman is a risk factor for thiazide-induced hyponatremia.[66] However, a population study[67] showed that age and BMI, but not sex, significantly modified the risk of thiazide-associated hyponatremia. Thiazides also induce hypokalemia, and, again, female sex is considered to be a risk factor.[68] Women have a major risk of hospitalization for this ADR.[69] However, a recent study showed that the risk is more than doubled in men compared to that in women.[70] The reason for this discrepancy is still a matter of discussion; however, previous studies did not consider that more women than men use diuretics.

Thiazides increase the concentration of serum urate, which can lead to glucose intolerance and occasionally may precipitate diabetes mellitus.[71,72] In fact, it remains unclear whether there is a significant effect of sex on these ADRs. However, it is important to remember that women have lower uric acid concentration in the premenopausal state, because of the uricosuric effect of estrogens on tubular reabsorption, which is lost with menopause. The use of a diuretic in women (and especially young women with metabolic abnormalities) is theoretically associated with an increased risk of events, due to an increase of uric acid, because of the deleterious action exerted by uric acid on vessel walls.

Thiazides may be an appropriate option for the female sex. If taken in postmenopausal women, it decreases the risk of hip fracture[45,56,57]; however, ESC guidelines suggest that thiazides can have possible contraindications in pregnancy.[23] Moreover, they should be used with caution in pre-existing reduction of plasma volume[23] and electrolyte concentration should be periodically monitored.

Beta-blockers

The role of beta-blockers in the treatment of hypertension remains a matter of debate, because a recent meta-analysis showed that initiating the treatment of hypertension with beta-blockers (atenolol and propranolol) leads to a modest reduction of CVD and does not have significant effects on cardiovascular mortality.[73] However, it is not known whether newer beta-blockers such as nebivolol and carvedilol are more effective than older drugs in improving cardiovascular prognosis.[74]

In this context, it is important to recall that the pharmacokinetics of some beta-blockers is sex-specific. Some beta-blockers (propranolol, metoprolol) are metabolized mainly by cytochrome P450 (CYP)2D6, which is more highly expressed in men than in women.[62,63] Thus, women experience greater drug exposure than men. No marked differences were observed with carvedilol, nebivolol, and alprenolol, which are substrates of other CYP, or even with atenolol and nadolol, which are eliminated largely unchanged via glomerular filtration.[75] CYP2D6 presents numerous polymorphisms; in particular, 5–10% of the Caucasian population are poor metabolizers.[76] If poor metabolizers use the standard doses of metoprolol, they have an increased plasma concentration of metoprolol, more intense beta-blockade,[77,78] and may be more susceptible to dose-related ADRs such as bradycardia.[76] This could be of particular relevance to women, who have higher plasma concentrations of

metoprolol and propranolol; indeed, the biotransformation of propranolol seems to be stimulated by testosterone in both sexes.[79] In contrast, estradiol has no effect and, consequently, the biotransformation of propranolol remains unchanged during the menstrual cycle.[79] Surprisingly, synthetic ethinyl estradiol, which is present in numerous oral contraceptives, possesses both inhibitory and stimulatory effects.[80] Propranolol is also highly and stereo-selectively bound to plasma proteins.[81] It has been suggested that the stereo-selectivity could be sex-dependent.[82,83] However, these data require confirmation. Moreover, beta-2 receptor sensitivity has been described to be higher in young women compared to that in young men, supporting the importance of estrogen in the regulation of beta-adrenergic activity.[84]

Finally, labetalol at standard doses is generally considered well tolerated for pregnant women.[58] Conversely, atenolol – a pure beta-antagonist with high lipid solubility and beta-1 specificity – has been associated with fetal growth restriction and, therefore, is not recommended.[58]

Drugs that interact with the renin–angiotensin system

Accumulating evidence suggests that RAAS is sexually divergent.[14] For example, the protective RAAS pathways are enhanced in women, including angiotensin type 2 receptor (AT2R). A lower percentage of women compared to men have been included in clinical trials investigating ACEIs and ARBs, and many of these studies were not designed to evaluate sex and sex differences.[60]

There are numerous ARBs in the market: losartan, valsartan, candesartan, irbesartan, olmesartan, eprosartan, and telmisartan, which present relevant differences in pharmacokinetic characteristics. For example, losartan and candesartan are both prodrugs, but losartan requires cytochrome P450-mediated biotransformation to yield the active moiety, EXP-3174; in contrast, candesartan is rapidly converted to the active drug by ester hydrolysis during absorption from the gastrointestinal tract.[85] A Japanese study[86] that included 44% men and 56% women showed that men, but not women, experience major cardiovascular events following treatment with olmesartan[86] versus olmesartan + calcium antagonists. However, at the end of the study, ARB + CCB had a significant effect on the mean systolic pressure compared to the ARB group only for men, but not for women. Furthermore, a study indicated that men may require larger dosages of ARBs than women.[87]

In addition, ACEIs include numerous molecules such as benazepril, enalapril, lisinopril, quinapril, perindopril, ramipril, and zofenopril. One meta-analysis showed that ACEIs are less effective in reducing mortality in women with symptomatic heart failure than in men, whereas these agents do not modify the survival rate in women with asymptomatic heart failure.[88] In women at a high cardiovascular risk, ACEIs reduce cardiovascular events when used for secondary prevention.[89] However, the results of an Australian study demonstrate that ACEIs reduce cardiovascular events in men but not in women.[90] Women seem to develop more angioedema cough in response to treatment with ACEIs.[45,59,60,91]

A pooled analysis evaluated the influence of sex on the pharmacokinetics and pharmacodynamics of the direct renin inhibitor aliskiren in healthy and hypertensive patients and showed that sex affects the plasma concentration–time curve (AUC) and time to maximum plasma concentration (C_{max}), which are lower in men than in women. However, the sex difference disappears after adjusting individual aliskiren AUC and C_{max} values for mean body weight or lean body weight.[92] In hypertensive patients, sex does not significantly influence the antihypertensive effect of aliskiren.

Finally, ACEIs, ARBs, and direct renin inhibitors are contraindicated in women who are or intend to become pregnant because of their potential teratogenic effect.[45,58,59] Moreover, ACEIs and ARBs do not negatively affect menopausal metabolic syndrome.[93]

Calcium channel antagonists

The Blood Pressure Lowering Treatment Trialists Collaboration study showed that calcium channel antagonists confer slightly more protection than ACEIs in women. The BP response to amlodipine is higher in women than in men (91.4 versus 83.0%, respectively), and is greater in individuals aged at least 65 years compared to those aged below 65 years.[61,94] The pharmacokinetic parameters observed for verapamil and amlodipine are sexually different. In particular, men exhibit a faster clearance than women of sustained-release or orally administered verapamil, but not after intravenous injection of the drug.[61] Amlodipine has a slightly higher bioavailability in women than in men, but this difference is likely due to the lower body weight of women because when the data are correct for weight, the bioavailability does not differ between the two sexes.[61]

Calcium channel antagonists increase the risk of peripheral edema to a greater extent in women than in men.[45,57,59,91]

Finally, for at least 10 years, the use of calcium channel antagonists has been linked to an elevated risk of breast cancer, and this risk is independent of the calcium channel antagonist used.[95]

These results, however, have not been fully accepted, and prospective randomized clinical trials should provide the answer.

Antihypertensive treatment and female and male sexual function

Sexual dysfunction induced by antihypertensive drugs is strongly associated with an impaired quality of life[96–98] and with poor adherence to therapy.[99] In men, sexual

dysfunction induced by antihypertensive medications is characterized by a decrease in libido, difficulty in attaining or maintaining an erection, and ejaculation problems. Among beta-blockers, there are important differences in the effects of different molecules. Metoprolol and carvedilol are, for example, associated with higher rates of sexual dysfunction; atenolol and bisoprolol are associated with intermediate rates; and nebivolol is linked to the lowest rates of erectile dysfunction[100] due to its ability to modulate nitric oxide.[101] Finally, acebutolol is not associated with sexual dysfunction in men.[102]

Thiazide diuretics can negatively affect male sexual function.[103] Indeed, patients treated with beta-blockers and diuretics exhibit a significantly worse sexual function than patients treated with ARBs, ACEIs, and calcium antagonists.[104] The mechanism underlying the increased erection problems observed with thiazide diuretics remains unclear. Among the potassium-sparing diuretics, spironolactone – an antialdosterone agent that can bind progesterone and androgen receptors – can induce breast tenderness, gynecomastia, and erectile dysfunction in men,[105] all of which are ADRs that frequently result in drug discontinuation.[106] Amiloride and triamterene do not seem to affect sexual function.[105]

Not all classes of antihypertensive agents share the same risk of inducing sexual problems. Enalapril does not modify erection;[102] ARB may actually improve erectile function and sexual activity in male hypertensive patients;[107,108] the association of felodipine and irbesartan enhances sexual function, showing improvements in desire, arousal, and orgasm.[109] Poor data are available regarding the relationship between calcium channel antagonists and erectile dysfunction. Amlodipine does not affect erection,[102] whereas impotence,[110] gynecomastia, and ejaculation problem have been reported in association with the use of verapamil.[111,112] Finally, doxazosin and prazosin may reduce sexual dysfunction at a very low rate in men,[102,113] although they may induce retrograde ejaculation.

The effects of antihypertensive drugs on sexual function in women have not been well studied. The available evidence suggests that sexual limitations in the female sex occur at a lower rate than those documented in men.[114] ADRs comprise a loss of vaginal lubrication, decreased libido, and difficulty in achieving orgasm.[99,104,115] Confounding factors in the comparison between the two sexes might include sociocultural effects, limited questions addressed toward women concerning their sexual problems, or the discomfort of women regarding reporting such problems. Finally, women may be less sexually active than men, as described in the TOMHS study, in which 35% of women compared with 15% of men were not married.[102]

In particular, thiazide diuretics may induce a loss of vaginal lubrication,[116] whereas atenolol, enalapril, and isradipine users may experience inadequate vaginal lubrication, diminished libido, and difficulty in achieving orgasm.[117,118] Among the potassium-sparing diuretics, spironolactone may induce menstrual abnormalities in premenopausal women.[105]

In conclusion, the literature clearly suggests that men and women differ in their responses to drugs. Therefore, it is time to include the sex parameter in all stages of scientific research, as well as in medical practice. A sex-dependent knowledge approach could lead to more appropriate therapy, thus reducing the cost of care over time. At present, there is an imbalance that is particularly disproportionate in women, who cost more and often receive suboptimal quality of care.[119] Thus, as recently reported AQ6 in an editorial in *Nature*, it is time to place 'sex on the agenda'.[120]

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