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SPECIAL ARTICLE
Hypertension

Sex differences in arterial hypertension

A scientific statement from the ESC Council on Hypertension, the European Association of Preventive Cardiology, Association of Cardiovascular Nursing and Allied Professions, the ESC Council for Cardiology Practice, and the ESC Working Group on Cardiovascular Pharmacotherapy

Eva Gerdts [1]*, Isabella Sudano [2], Sofie Brouwers [3,4], Claudio Borghi [5], Rosa Maria Bruno [6,7], Claudio Ceconi [8], Véronique Cornelissen [9], François Diévart [10], Marc Ferrini [11], Thomas Kahan [12], Maja-Lisa Løchen [13], Angela H.E.M. Maas [14], Felix Mahfoud [15], Anastasia S. Mihailidou [16,17], Trine Moholdt [18], Gianfranco Parati [19,20], and Giovanni de Simone [21]

[1]Center for Research on Cardiac Disease in Women, University of Bergen, Bergen, Norway; [2]University Hospital Zurich University Heart Center, Cardiology, University Hospital and University of Zurich, Zurich, Switzerland; [3]Department of Cardiology, Cardiovascular Center Aalst, OLV Clinic Aalst, Aalst, Belgium; [4]Department of Experimental Pharmacology, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium; [5]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [6]Université de Paris Cité, Inserm, PARCC, Paris, France; [7]Service de Pharamcologie, AP-HP, Hôpital Européen Georges Pompidou, Paris, France; [8]University of Cardiologia, ASST Garda, Desenzano del Garda, Italy; [9]Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium; [10]Clinique Villette, Dunkerque, France; [11]Department of Cardiology and Vascular Pathology, CH Saint Joseph and Saint Luc, Lyon, France; [12]Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, Stockholm, Sweden; [13]Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway; [14]Department of Cardiology, Radboudumc, Nijmegen, The Netherlands; [15]Department of Internal Medicine III, Cardiology, Angiology and Intensive Care Medicine, Saarland University Hospital, Homburg/Saar, Germany; [16]Department of Cardiology and Kolling Institute, Royal North Shore Hospital, St Leonards, UK; [17]Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia; [18]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway; [19]Department of Cardiac, Neural and Metabolic Sciences, Instituto Auxologico Italiano, IRCCS, Milan, Italy; [20]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; and [21]Hypertension Research Center and Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy

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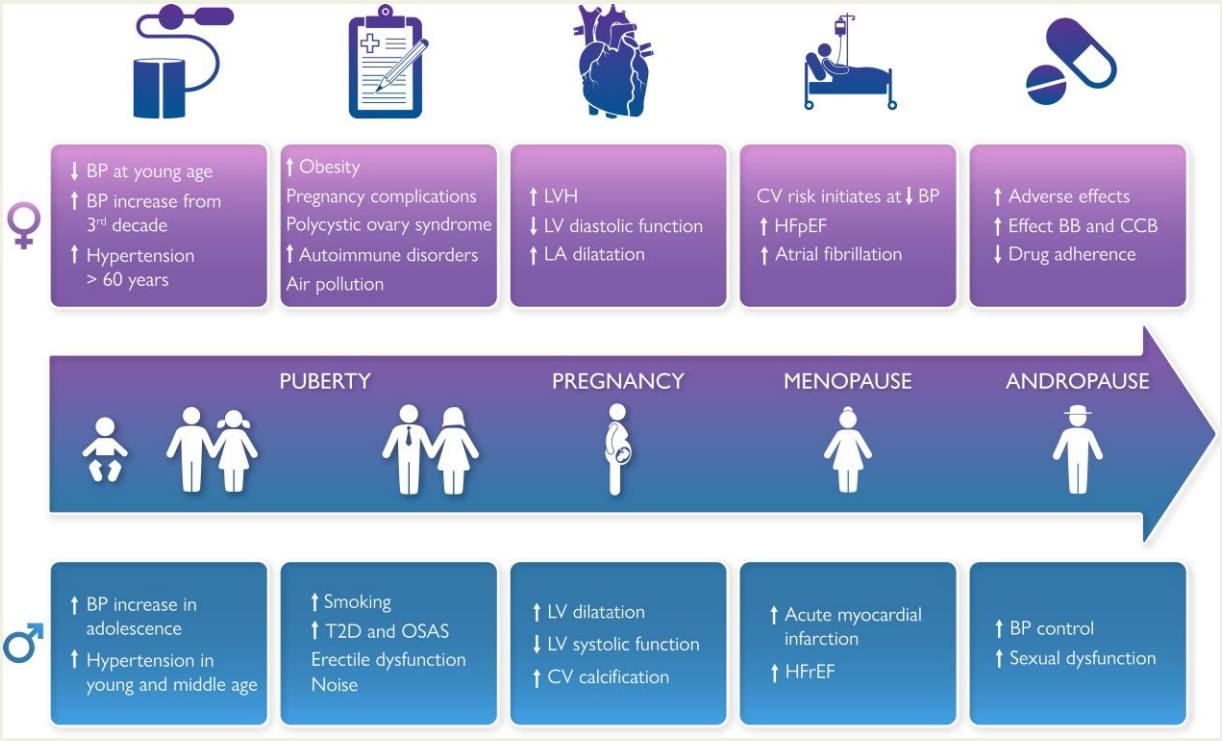
* Corresponding author. Tel: +4792086505, Email: eva.gerdts@uib.no

Graphical Abstract



Sex differences in hypertension. BP, blood pressure; CV, cardiovascular; T2D, type 2 diabetes; OSAS, obstructive sleep apnoea syndrome; LVH, left ventricular hypertrophy; LV, left ventricular; LA left atrial; HFpEF, heart failure with preserved ejection fraction; BB, beta blocker; CCB, calcium channel blocker; HFrEF, heart failure with reduced ejection fraction.

Abstract

There is strong evidence that sex chromosomes and sex hormones influence blood pressure (BP) regulation, distribution of cardiovascular (CV) risk factors and co-morbidities differentially in females and males with essential arterial hypertension. The risk for CV disease increases at a lower BP level in females than in males, suggesting that sex-specific thresholds for diagnosis of hypertension may be reasonable. However, due to paucity of data, in particularly from specifically designed clinical trials, it is not yet known whether hypertension should be differently managed in females and males, including treatment goals and choice and dosages of antihypertensive drugs. Accordingly, this consensus document was conceived to provide a comprehensive overview of current knowledge on sex differences in essential hypertension including BP development over the life course, development of hypertension, pathophysiologic mechanisms regulating BP, interaction of BP with CV risk factors and co-morbidities, hypertension-mediated organ damage in the heart and the arteries, impact on incident CV disease, and differences in the effect of antihypertensive treatment. The consensus document also highlights areas where focused research is needed to advance sex-specific prevention and management of hypertension.

Keywords Hypertension • Sex • Blood Pressure regulators • Hypertension-mediated organ damage • Pharmacological treatment • Adverse events • Cardiovascular disease • Sex hormones

Introduction

Arterial hypertension, in particular elevated systolic blood pressure (BP), remains a major cause of reduced quality of life, cardiovascular (CV) morbidity and mortality and all-cause mortality in the world.[1,2] Both BP development and BP regulation are influenced by biological effects of sex chromosomes, sex hormones and reproductive events.[3] In addition, the sex difference in hypertension prevalence has been related to ethnicity, co-morbidities, socio-economic status, education and environmental pollution in middle-aged and older adults.[4,5] Previous publications have documented important sex differences in hypertension related to main BP regulators, co-morbidities, CV complications and adverse effects of antihypertensive drugs.[6–8] However, there is paucity in reports of sex-specific effects from clinical trials in hypertension. Recent data indicate that risk for CV complications starts at lower BP levels in females than in males, questioning current practice of using the same BP threshold for identification of hypertension in both sexes.[9,10] The scope of this collaborative document is to give a comprehensive overview of current knowledge on sex differences in essential arterial hypertension, associated organ damage and CV disease (CVD)

and hypertension management (*Graphical Abstract*), as well as identifying knowledge gaps hindering the development of sex and gender informed hypertension management.

BP development and hypertension prevalenceover the life course

BP development in the young

Sex differences in BP trajectories are apparent from early life and change across the life course, suggesting that early life factors may play a role in how CVD present differently in females and males.[11] At age seven, both sexes have similar systolic BP, which then increases a little faster in females up to age 12, and thereafter slower in females resulting in a lower systolic BP in females than in males starting from 13 years of age (*Figure 1*).[11] Systolic BP is 10 mmHg higher in males compared with females by the age of 18 years, a difference which slightly increases over time up to 30 years.[11] Diastolic BP is higher in females at age 7, then increases similarly in both sexes up to age 12, thereafter slower in females. From age 16, diastolic BP decreases in both sexes, but faster in males.[11] In the National Health and Nutrition Examination Survey (NHANES), the annual net transition rate from optimal BP (systolic BP <120 mmHg and diastolic BP <80 mmHg) to prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg) was twice as high among males compared with females aged 8–30 years, and highest for young African American males.[14] However, their findings may have been influenced by the lower BP in healthy young females, since the same BP threshold was used in both sexes.

BP in midlife and beyond

The sex-specific BP trajectories from puberty to adulthood continue with different patterns during young and middle-aged adulthood.[12,15] From late adolescence, males have higher levels and steeper slopes of both systolic and diastolic BP than females until early midlife, at which there is a crossover, and females have a steeper rise in BP thereafter throughout their life course (*Figure 1*).[12,16] In subjects older than 40 years, transition from optimal BP to prehypertension was stable or decreased among males, but rapidly increased among females in NHANES.[14] Diversity in the BP development during menopause transition is well demonstrated.[17] An accelerated increase in systolic BP is observed in about 35%, particularly in females with early menopause and vasomotor symptoms,[17] and in women with clustering of CV risk factors.[18] In population-based cohort studies from Italy and the Czech Republic, BP increase during menopause transition was explained by weight gain, obesity and aging.[19,20] In a pooled analysis of longitudinal individual BP measures over 43 years in >32 800 individuals in four population-based cohorts in the USA, a steeper increase in systolic, diastolic and mean BP as well as in pulse pressure was observed in females compared to males already from the third decade onwards (*Figure 1*).[13]

Globally, the age-adjusted prevalence of hypertension in adults (using systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg as definition in both sexes) was 32% in females and 34% in males in 2019, unchanged from 1990, as a result of a comparable decrease in hypertension in high-income countries and increase in low- and middle-income countries.[21] However, due to the aging trend, the absolute number of patients with hypertension almost doubled during this period[21] (*Box 1*).

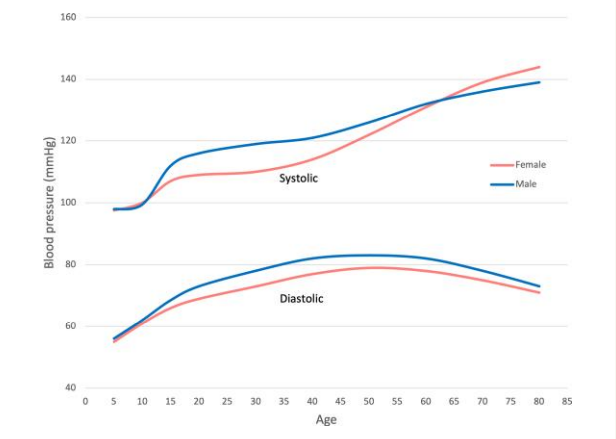


Figure 1 Blood pressure development in females and males during childhood, adolescence, and early adulthood. Based upon O'Keeffe *et al.*,[11] Shen *et al.*,[12] and Ji *et al.*[13].

Box 1 Key messages on sex differences in BP development over the life course

- Healthy young females have lower BP than males at similar age but experience a steeper increase in BP from the third decade of life.
- Better understanding of the underlying mechanisms of BP increase in midlife may provide targets for improved prevention of hypertension in both sexes.

Sex differences in regulators of BP

The regulation of vascular function and BP differs between females and males, in particular due to sex differences related to the autonomic nervous system, the renin-angiotensin-aldosterone system (RAAS), bradykinin, nitric oxide, brain natriuretic peptides and humoral mechanisms related to sex chromosomes, sex hormones and other hormones.[7,22,23]

The autonomic nervous system

The autonomic nervous system plays an important role in BP regulation and contributes to modulate CVD.[24] Although normotensive adult females and males share the same CV autonomic regulation, they exhibit differences in the sympatho-vagal balance and central and reflex neuronal influence on the CV system.[25] Sex-dependent physiological changes related to age, menopause, obesity and physical activity might also influence neuronal hemodynamic regulation. Females have a larger increase in sympathetic nervous activity with age and obesity than males. Compared to healthy males, healthy females are characterized by lower baroreceptor reflex sensitivity and lower heart rate variability.[26,27]

BP effects of sex hormones

Ovarian hormones have a major role in BP regulation, endogenous oestrogen being associated with the lower BP in premenopausal females.[28,29] Oestrogens modulate BP directly through non-genomic effects on vascular, renal and cardiac cells, by reducing calcium pathways and indirectly through genomic actions, controlling expression of potent vasoconstrictors, such as angiotensin II, endothelin 1 and catecholamines, and controlling the RAAS and endothelin pathway.[28,30] On the contrary, testosterone is pro-hypertensive and likely contributes to the

increase in CV risk observed with ageing in males and after menopause in females.[28,29,31] Androgens increase BP by activating the RAAS.[29] Oestrogens reduce plasma renin and angiotensin-converting enzyme (ACE) activity, and up-regulate angiotensinogen expression, leading to increased levels of angiotensin and aldosterone, and sodium retention.[32] Progesterone is a potent aldosterone antagonist, which acts on the mineralocorticoid receptor to prevent sodium retention and counteracts the sodium-retaining effect of oestrogen.[33] When becoming hypertensive, females tend to have lower plasma renin activity than males.[34] The premenopausal cardioprotective effects of oestrogens may in part result from RAAS inhibition.[35] After menopause, increased salt sensitivity is observed in females.[28,36] Thus, lower oestrogen level after menopause is related to both upregulation of hormonal systems such as the RAAS and sympathetic nervous system, and to reduced vascular nitric oxide bioavailability.[23] As a consequence, the synthesis of potent vasoconstrictors such as angiotensin II, endothelin-1, and catecholamines rises after menopause.[37,38] Antihypertensive drug therapy in postmenopausal women may improve endothelial dysfunction caused by decreased vascular nitric oxide bioavailability and thereby reduce CV risk.[39] The roles of relaxin, oxytocin, prolactin and vasopressin in the regulation of BP are less well characterized than for oestrogen, progesterone and testosterone (*Box 2*).

Box 2 Key messages on sex-differences in BP regulators, CV risk factors and co-morbidities

- The activity of autonomic and endocrine BP regulators differs between sexes and may influence drug efficacy and adverse effects.
- The prevalence and influence of traditional risk factors on CVD vary between females and males. Sex-specific CV risk factors are documented in both sexes. Better integration of these differences in risk assessment tools will improve CVD prevention.

Sex differences in risk factors and co-morbidities

Sex-specific CV risk factors

Important sex-specific CV risk factors have been identified.[40] In males, erectile dysfunction and androgenic alopecia are associated with increased risk for hypertension as well as for CVD.[41,42] Females undergo important changes in sex hormones throughout their life course that impact CV risk.[18] Pregnancy-related hypertensive disorders increase the risk for chronic hypertension and CVD, even before menopause transition.[43–45] Detailed European recommendations on management of peripartum hypertension were recently published.[46] Women with polycystic ovary syndrome have a higher risk of hypertension, including hypertensive disorders in pregnancy.[47] In transgender populations, insufficient data have been reported on the effects of gender-affirming hormone therapy on the incidence of hypertension.[48]

Inflammatory and autoimmune disorders are associated with increased risk for hypertension and CVD, and both the innate and adaptive immune systems are influenced by sex hormones.[49] While progesterone and androgens are considered immunosuppressive, oestrogens are considered immune-stimulatory, contributing to the observed preponderance of most autoimmune diseases in females.[49]

Traditional CV risk factors in hypertension

Important sex differences in conventional CV risk factors have been reported in hypertension, particularly related to smoking and metabolic risk factors [obesity, type 2 diabetes (T2D) and dyslipidaemia], and to co-morbidities (obstructive sleep apnoea, renal dysfunction, and autoimmune disorders) (*Table 1*). Clustering of more than two metabolic risk factors is often referred to as the metabolic syndrome.[60] Glucose and lipid metabolism are directly modulated by oestrogen and testosterone. Oestrogen deficiency or a relative increase in testosterone promotes insulin resistance and a pro-atherogenic lipid profile.[54] Consequently, the prevalence of the metabolic syndrome is higher in males in a young hypertensive population, but higher in females in older hypertensive population.[54] Dyslipidaemia is highly prevalent in hypertension, particularly among white males.[56] In females, serum levels of total cholesterol, low-density lipoprotein cholesterol and apolipoprotein B increase substantially in the perimenopausal period.[61] In the Women's Health Study, the association of higher serum triglycerides with increased CVD risk attenuated with increasing age of onset.[62]

Obesity is present in at least 50% of individuals with hypertension,[51] and is more common in females.[52] The higher fat mass in females and sex differences in adipose tissue distribution are well documented. Higher abdominal visceral adipose mass has been more strongly associated with risk of hypertension in females, and with risk of metabolic syndrome in males.[53] Obesity and hypertension are both strongly associated with insulin resistance and development of T2D. The prevalence of T2D is age-dependent and higher in males than in females.[55] Presence of T2D in females reduces their innate CV risk advantage, and females with T2D have a comparable risk as males for CVD.[63,64] The relatively worse prognostic impact of T2D in females may be associated with different hormonal modulation of insulin sensitivity,[65] sex disparities in diabetes care and greater risk factor clustering among females with T2D.[66]

Table 1 Sex differences in conventional CV risk factors and co-morbidities in hypertension

Factor	Females	Males	Relevant references
Age	++	+	13,50
Obesity	++	+	8,51,52
Visceral obesity	+	++	8,53
Metabolic syndrome	+ (++ after menopause)	++	8,54
Type 2 diabetes	+	+(+)	55
Dyslipidaemia	+	++	56
Smoking	+	++	57
Obstructive sleep apnoea	+	++	58,59
Autoimmune disorders	+++	+	49
Reduced eGFR	++	+	57
Albuminuria	+	++	57
Gout	+	+++	7,32

+Common; ++more common; +++much more common vs. other sex.

Obstructive sleep apnoea is more prevalent in males.[58] It is an independent risk factor for hypertension in both sexes, but the risk for hypertension is evident at lower sleep apnoea severity in females than in males.[59] Females with hypertension more often have reduced glomerular filtration rate than males. In contrast, males with hypertension more often exhibit albuminuria, possibly due to sex differences in protein handling.[57]

Environmental risk factors

Air pollution contributes to risk for CVD through a number of mechanisms, including oxidative stress, systemic inflammation and vascular dysfunction that all promote hypertension.[67,68] Sex differences in these relations have been little studied, but fine particulate matter (PM2.5) and sulphur dioxide have been suggested as stronger risk factors for hypertension in females and nitric dioxide and carbon monoxide stronger in males in studies from China.[69,70] A post-hoc analysis within the Systolic Blood Pressure Intervention Trial (SPRINT) trial demonstrated that the effect of intensive antihypertensive drug treatment (systolic BP <120 mmHg) was greater in participants exposed to higher PM2.5 levels.[71]

Studies on noise around major European airports have reported aircraft noise to be associated with incident hypertension in males.[72] In the UK Biobank cohort, exposure to road traffic noise above 60 dB was associated with higher systolic and diastolic BP, irrespective of antihypertensive drug treatment[73] (*Box 2*).

Sex differences in hypertensive heart disease

Arterial hypertension causes structural and functional changes in the heart, collectively named hypertensive heart disease.[50] The heart is normally smaller in females than in males from puberty onwards,[74] largely due to differences in body size and composition.[75] Current guidelines therefore recommend sex-specific threshold values for optimal detection of hypertensive heart disease by echocardiography.[50,76]

Left ventricular hypertrophy

Left ventricular (LV) hypertrophy (LVH) is the hallmark of hypertensive heart disease and a powerful prognostic marker in hypertension. Hypertensive LVH is more prevalent and less modifiable by antihypertensive treatment in females than in males.[8,77,78] Persistent LVH is particularly associated with increased arterial stiffness, and higher risk of CV events and mortality during follow-up, independent of achieved BP values.[79]

In the Strong Heart Study, LVH was found in 36% of middle-aged females and in 23% of middle-aged males.[80] During 4 years of follow-up, LVH prevalence increased despite good BP control. The lack of LVH regression was attributed to obesity and a progressive decline in renal function. The prospective Italian Campania Salute Network registry of subjects treated for hypertension demonstrated that presence of LVH off-sets the innate lower CV risk in females, and females and males with hypertension and LVH had comparable risk of CVD.[81] Furthermore, during follow-up, 21% of subjects with hypertension and initial normal LV mass developed LVH, particularly females and those with obesity.[82]

Presence of LVH in hypertension is associated with reduced myocardial function in both sexes, whether assessed by midwall shortening or global longitudinal strain, while LV ejection fraction is usually normal. In hypertension, females exhibit higher LV myocardial function and ejection fraction than males, independent of LV geometry.[83]

Dilated left atrium

A dilated left atrium (LA) is another common sign of hypertensive heart disease. LA dilatation is associated with increased CVD, in particular atrial fibrillation, heart failure (HF) and ischaemic stroke.[84–86] In healthy subjects, the LA is normally larger in males than in females,[87] but in hypertension LA dilatation is more common in females.[88,89] In older subjects with hypertension and LVH, LA dilatation was significantly more prevalent in females.[88] Similarly, also in middle-aged subjects with obesity without known CVD, LA dilatation was significantly more prevalent in females than in males, and particularly associated with co-presence of hypertension and increased arterial stiffness[90] (*Box 3*).

Box 3 Key messages about sex-differences in hypertension mediated organ damage

- Hypertension mediated organ damage like hypertensive heart disease and arterial dysfunction show sex specific incidence, threshold values and treatment success and may develop despite treatment.
- Identification of the underlying mechanisms for such development in females and males may provide targets to reduce high-risk phenotypes and progression to CVD.

Sex differences in arterial dysfunction

Arterial structure and function

Sex differences both in micro- and macrovascular structure and function have been documented.[91] Sex- and age-specific threshold values for diagnosis of arterial dysfunction in large arteries by arterial stiffness and intima-media thickness, and in small arteries by lumen media ratio and flow-mediated vasodilatation have been published.[91–94] Females have smaller aortic root dimensions than males, even after adjusting for body size.[95] Sex differences in ventricular-arterial coupling and higher arterial stiffness in females, particularly in the ascending aorta, have been documented in several studies.[96,97] Augmentation pressure and augmentation index are both higher in females at all ages, while carotid-femoral pulse wave velocity (PWV) does not differ by sex.[94,98] Steeper increases in carotid-femoral PWV and peripheral vascular resistance are observed with aging and hypertension in females compared to males.[97,98]

Arterial stiffness

Arterial stiffness can be estimated from the ratio of pulse pressure to stroke volume index (PP/SVi) or more directly measured by carotid-femoral PWV. In addition to being a predictor of CVD, independent of other hypertension-mediated organ damage like LVH,[99] increased PP/SVi is also an independent predictor of the transition from diastolic to isolated systolic hypertension, with a risk for transition being 30% higher in females than in males.[100] This finding has been confirmed by analyzing sex differences in PWV trajectories over time, demonstrating

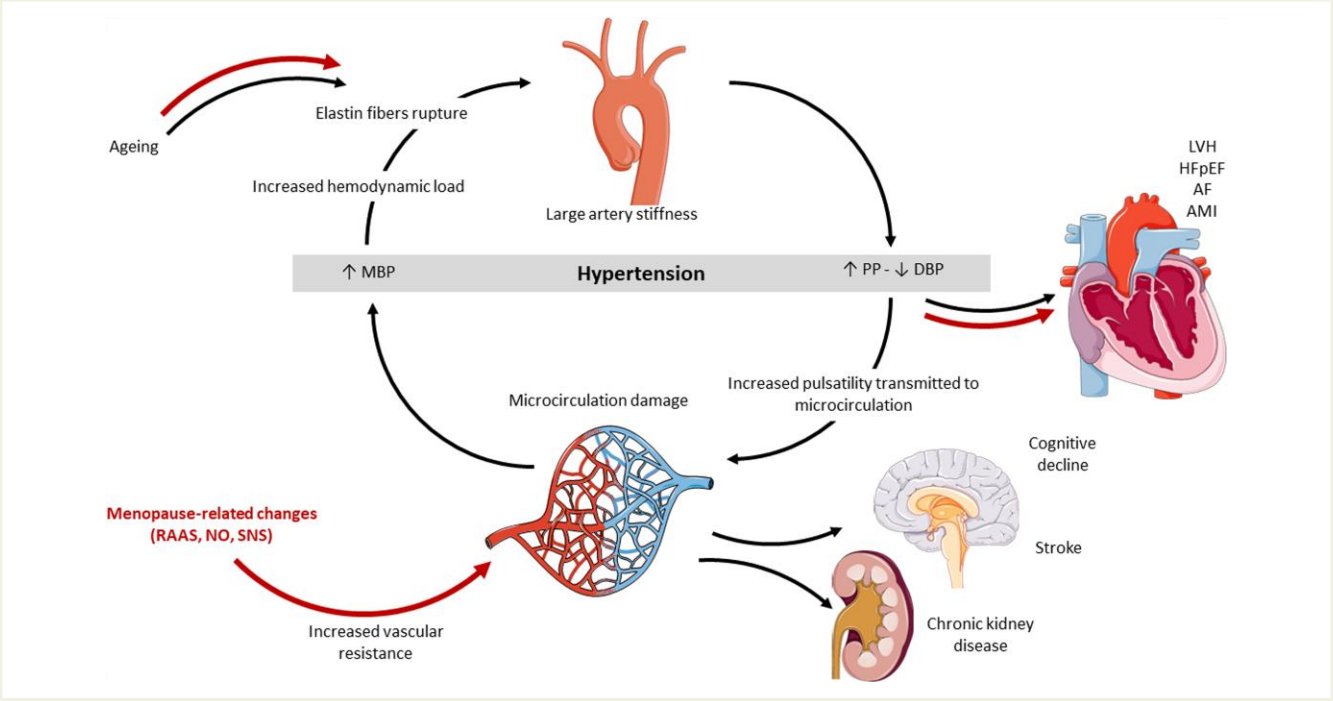


Figure 2 Sex differences in development of arterial dysfunction and related complications. Red arrows indicate mechanisms that are enhanced in females. MBP, mean arterial blood pressure; PP, pulse pressure; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; HFpEF, heart failure with preserved ejection fraction; AMI, acute myocardial infarction; AF, atrial fibrillation; RAAS, renin-angiotensin-aldosterone system; NO, nitric oxide; SNS, sympathetic nervous system.

a more rapid increase in systolic BP and higher prevalence of HF with preserved ejection fraction (HFpEF) in females than in males.[13]

Increased arterial stiffness augments systolic BP and pulse pressure, worsening hypertension through hemodynamic load-induced elastic fibre degradation and collagen deposition in the arterial wall. Higher aortic stiffness and pressure and flow pulsatility increases the pulsatile load on the heart, promoting LVH and reduction in global longitudinal strain in the LV.[101] Excessive stiffness and flow pulsatility have also been associated with microvascular lesions in high-flow organs like the brain and the kidneys, suggesting that pulsatile flow damages small arteries in these organs (*Figure 2*).[101] Arterial stiffness is less modifiable by antihypertensive therapy in females than in males.[99] Greater prognostic significance of arterial stiffness in females than in males was suggested by a study in patients with coronary artery disease,[102] but this finding needs confirmation in patients without coronary artery disease (*Box 3*).

Sex differences in the association of hypertension with CVD

The association of BP with CVD

The 2019 Global Burden of Disease study report confirmed that elevated systolic BP was the most important risk factor for mortality in females worldwide and only second to smoking in males.[2] The majority of these deaths are caused by CVD. Hypertension in midlife seems to be more harmful in females than in similarly aged males, with hypertension being a stronger risk factor for myocardial infarction, cognitive decline and dementia.[9,103–105]

Ambulatory BP recording have documented higher asleep BP in males in population-based studies, but a similar decline in BP from day-time to night-time (dipping) and prevalence of non-dipping in both sexes.[106] Asleep systolic BP is a stronger predictor of all-cause mortality and CVD in females than males.[106] In a study in the Italian Umbria district, non-dipping in hypertension was associated with increased risk of CVD only in females.[107]

Several studies have now documented that the CVD risk increases at a lower BP level in females than in males, including risk for myocardial infarction, HF and stroke.[9,10,103] A case-control study of risk factors associated with myocardial infarction in 52 countries showed that hypertension was associated with greater risk of myocardial infarction in older females than males.[108] Also the community based Tromso Study found higher BP a stronger risk factor for myocardial infarction in females than males.[109]

HF and atrial fibrillation

Females with hypertension develop more vascular and myocardial stiffness than their male counterparts at old age, contributing to their higher risk for atrial fibrillation, HFpEF and stroke.[110–113] Among patients with atrial fibrillation, females have higher prevalence of hypertension than males.[114,115] While some reviews have suggested that hypertension confers similar risk of atrial fibrillation in both sexes,[116,117] the Tromso Study reported a stronger association of elevated systolic BP with incident atrial fibrillation in females than in males.[118] In the same cohort, increased systolic BP was associated with higher risk for both paroxysmal/persistent and permanent atrial fibrillation in females, but only for paroxysmal/persistent atrial fibrillation in males.[119]

Hypertension is associated with high risk for HF in both sexes.[120–122] Hypertension is more prevalent among female than male HF patients (50% vs. 40%) and increases the risk for HF in females by 3-fold, compared to 2-fold in males.[121] Males constitute about 30% of patients with

HFpEF, and females about 40% of patients with HF with reduced ejection fraction (HFrEF) by current definitions.[122] Sex differences in arterial, LA and LV adaptation to pressure overload, and in micro- and macrovascular coronary disease may contribute to the higher prevalence of HFpEF in women.[123] Furthermore, iron deficiency, T2D, obesity, preeclampsia, and autoimmune diseases, all common co-morbidities in females with hypertension, may contribute to higher risk of HFpEF through amplification of cardiac dysfunction and systemic inflammation.[123] Hypertension may contribute to the observed higher risk of stroke in female HFrEF patients.[124] In a post-hoc analysis of data from two large trials in patients with HFrEF, female patients had lower mortality despite suboptimal treatment with diuretics, anticoagulants and device therapy compared to male patients.[124]

Aortic valve stenosis

Both systolic and diastolic hypertension are associated with increased risk for degenerative aortic valve stenosis (AS) among older subjects.[125] In AS, hypertension is particularly common in older females,[126] and associated with impaired LV function and outcome in both sexes.[127] In a Danish population-based study, progression of aortic valve calcification by cardiac computed tomography was particularly associated with hypertension in females, and with dyslipidaemia in males.[128] The ESC recently published a consensus document on how to manage hypertension in AS.[129]

Stroke

Stroke is a major complication in hypertension.[130] Sex differences in stroke incidence, presentation, and outcome are well documented.[131,132] Females with acute stroke often report non-conventional symptoms, which may contribute to delay in diagnosis and treatment, and subsequent increased mortality and disability.[133] Males have higher stroke incidence up to 85 years of age.[134] However, stroke risk increases at a lower BP level in females than in males.[10] A recent meta-analysis demonstrated that young women may be disproportionately at risk for ischaemic stroke.[135] Among patients with ischaemic stroke, females more often present with atrial fibrillation, hypertension, obesity and T2D than males.[136,137]

Peripheral artery disease

Hypertension is a major risk factor for peripheral artery disease in both sexes.[138] Females are usually older and more obese at the time of diagnosis. Claudication is more often reported in males than females during middle age, but this sex difference is not observed at older age.[139] Among patients with critical limb ischaemia, female sex is an independent predictor for pronounced femoral-popliteal involvement and more severe and diffuse atherosclerotic disease.[140] Several studies have noted sex differences in ankle-brachial index with lower values in healthy women[141,142] (*Box 4*).

Box 4 Key messages on sex differences in BP association with CVD

- Females with hypertension more often develop atrial fibrillation and HFpEF, while males more often develop AMI and HFrEF.
- CV risk increases at a lower BP level in females than in males. Future research should explore whether different diagnostic BP threshold values or treatment targets in females and males with hypertension may improve CVD prevention.

Sex differences in the effects of antihypertensive treatment

Adverse effects of antihypertensive drugs

Sex differences in pharmacokinetics and pharmacodynamics are well described and mostly due to differences in either drug transporters affecting absorption (i.e. *P*-glycoprotein) or enzymes affecting metabolism and/or clearance (i.e. cytochrome P450 activity).[35] Interaction of sex hormones with enzymes involved in drug absorption and metabolism influences drug pharmacokinetics and pharmacodynamics, efficacy and adverse effects.[143] Overall, females more often report adverse effects from antihypertensive drugs than males, except for mineralocorticoid receptor antagonists. In particular, females more often experience hyponatremia, hypokalemia and arrhythmia during treatment with diuretics, oedema with dihydropyridine calcium channel blockers (CCBs) and cough with ACE inhibitors (ACEI), while males more often experience gout during treatment with diuretics.[7,144–147] Sexual dysfunction is almost uniquely reported in males, and particularly during beta blocker (BB) treatment.[148]

Efficacy of antihypertensive treatment

In the Dietary Approaches to Stop Hypertension trial, dietary sodium restriction induced a pronounced BP reduction only in females.[149] Structured aerobic exercise therapy reduced BP more in males than in females in a meta-analysis of 93 trials.[150]

Sex differences in drug effects on BP are well described.[35] In particular, females have enhanced BP reduction from treatment with BB and CCB.[35] Studies on prescription of antihypertensive drugs have documented that females are more often prescribed diuretics and males more often ACEI.[151,152] The Stockholm regional database including prescriptions to 292 428 subjects, found that prescription of diuretics and BB increased while prescription of ACEI, angiotensin receptors blockers (ARBs) and CCB decreased with aging in both sexes.[153] In particular, treatment with BB was more common in females than males among subjects without known CVD, while treatment with ACEI or ARB was more common in males than females with HF or diabetes.[153]

Few ancillary analyses in clinical trials of antihypertensive drug treatment have reported sex-specific treatment results. Comparable benefits were demonstrated for females and males in the Nordic Diltiazem Study, the Treatment of Mild Hypertension Study and the Losartan Intervention For Endpoint Reduction in Hypertension Study.,[144,154,155] However, sex differences in antihypertensive drug effects were reported in the Hypertension Optimal Treatment study,[156] the Second Australian National BP Study,[157] and in the Valsartan Antihypertensive Long-term Use Evaluation trial (*Table 2*).[158] In the SPRINT trial, the number of females included was too low to draw conclusions on the benefit of intensive BP control in elderly females,[159] and two subgroup analyses reported contrasting results.[160,161] Still, SPRINT changed the American definition of hypertension and recommendations for BP management in both sexes.[162]

A meta-analysis by the BP Lowering Treatment Trialists' Collaboration including 31 randomized trials published before 2006, and a total of 103 268 men and 87 349 women, found comparable reductions in BP and incidence of CV events in both sexes for treatments based on ACEI, ARB, CCB, diuretics or BB.[163] Similarly, another network meta-analysis based on 40 trials and 152 379 patents documented that no class of medication (ACEI, ARB, CCB or BB) was significantly better than thiazides as first-line therapy for any outcome (all-cause mortality, CV mortality, HF or stroke) in females or males analyzed

Table 2 Overview of clinical trials in hypertension reporting results stratified by sex

Paper	Trial name (Reference)	Number of participants	% Females	Results stratified by sex
Studies that documented comparable benefits of study treatment in both sexes				
Kjeldsen *et al.* Influence of age, sex and blood pressure on the principal endpoints of the Nordic Diltiazem Study	The Nordic Diltiazem Study[154]	10 876	51	Similar treatment effect in both sexes.
Lewis *et al.* Efficacy and tolerance of antihypertensive treatment in men and women with stage 1 diastolic hypertension. Results of the Treatment of Mild Hypertension Study	Treatment of Mild Hypertension Study[144]	902	38	Similar treatment effect in both sexes.
Os *et al.* Effects of losartan in women with hypertension and left ventricular hypertrophy: results from the Losartan Intervention for Endpoint Reduction in Hypertension Study	Losartan Intervention For Endpoint reduction in hypertension[155]	9193	54	Similar treatment effect in both sexes. In the losartan group, females had better reduction in the primary endpoint, all-cause mortality and new-onset diabetes.
Studies that documented sex differences in benefits of study treatment				
Kjeldsen *et al.* Influence of gender on prevention of myocardial infarction by antihypertensives and acetylsalicylic acid: the HOT study	Hypertension Optimal Treatment[156]	18 790	47	Achieving target diastolic BP <80 mmHg reduced myocardial infarction in women but not in men. Acetylsalicylic acid reduced incident myocardial infarction in men, but not in women.
Wing *et al.* A comparison of outcomes with angiotensin converting enzyme inhibitors and diuretics for hypertension in the elderly	Second Australian National Blood Pressure Study[157]	6083	51	The benefit of ACEI treatment was only demonstrated in males.
Zanchetti *et al.* Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial	Valsartan Antihypertensive Long-term Use Evaluation trial[158]	15 245	42	Amlodipine lowered BP and reduced the primary endpoint (composite of cardiac mortality and morbidity) better in females than in males. Valsartan reduced the secondary endpoint of hospitalization for heart failure better in males.

BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor.

separately.[164] No interaction analyses between sex and drug class effects were presented.

BP awareness and control

BP control is necessary for optimal CV prevention in hypertension. Awareness of hypertension has traditionally been higher in females than in males.[165–167]

Studies suggest that males treated for hypertension achieve better BP control than females. In the Multi-Ethnic Study of Atherosclerosis these sex disparities increased with age and were largest in participants older than 75 years.[168] Elderly females also have lower BP control rates vs. middle-aged and young females.[7] Whether this is due to biological factors, inadequate treatment (physicians inertia, patient non-adherence, inappropriate drug choice), higher prevalence of CV organ damage or other co-morbidities is unknown.[7] Depression and dis-satisfaction with the health care provider are known factors particularly associated with non-adherence in older females, but not in males.[169] A recent data analysis from the Canadian Health Measures Survey demonstrated a particular decline in hypertension treatment and control rates in females over the period 2007–17.[170] Typically, these females had lower socioeconomic status and used more than three antihypertensive drugs, both factors associated with drug non-adherence in previous research.[171] In the Swedish Primary Care CV Database, BP control was not achieved to the same

Box 5 Key messages on sex-differences in the effect of antihypertensive treatment

- Sex-differences in efficacy and adverse effects of antihypertensive drugs are well described. These differences should be better communicated to health care providers to promote optimal antihypertensive drug treatment.
- In general, males treated for hypertension achieve better BP control than females. Future research should target underlying causes for this difference, including patient related factors, health care related factors, socio-demographic factors and drug related factors to provide sex-specific advice for optimalization of antihypertensive drug therapy.

extent in females as in males with hypertension managed in primary health care, independent of co-morbidities.[152]

In small studies of patients with resistant hypertension, those with drug non-adherence included a higher proportion of females.[172,173] However, sex-specific analyses were not reported (*Box 5*).

Conclusions

Our knowledge about sex differences in hypertension has been substantially advanced over the past decades, but much of this knowledge awaits clinical adoption. Better implementation of sex differences in BP development, regulation, and CV risk factors in prevention tools is likely to improve CVD prevention, in particular in females. Better communication of known sex differences in efficacy and adverse effects of antihypertensive drugs to health care providers may optimize treatment and improve patient adherence.

However, important knowledge gaps remain related to prevention of organ damage and CVD in hypertension. Hypertension-mediated organ damage show sex-specific incidence, threshold value and treatment success. Identification of the underlying mechanisms for CV organ damage development in females and males may provide new strategies for prevention of high-risk phenotypes and progression to CVD. Finally, future clinical studies should explore whether using sex-specific BP threshold values and treatment targets in hypertension may improve CVD prevention.

Authors contribution

E.G. and G.d.S. contributed to conception of this scientific statement; E.G., I.S., S.B., R.M.B., A.S.M., G.P. and G.d.S. drafted individual sections of the manuscript; S.B. drafted the graphical abstract; S.B. and R.M.B. drafted the figures; all authors contributed to revision of the manuscript content and approved the final version.

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Data availability

No new data were generated or analysed in support of this research.

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