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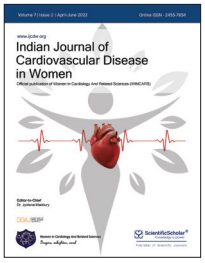

Cardiovascular *Review Article*

Hypertension in Women: The Current Understanding and Future Goals

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ABSTRACT

Hypertension is one of the major contributing risk factor of cardiovascular diseases. Despite enormous advances in the preventive cardiology, hypertension remains the leading cause of death and disability in women. The article aims to focus on the gender specific differences in hypertension, and existing gaps in the current understanding of high blood pressure (BP) in women. Apart from epidemiological differences, hypertension in men and women has distinct pathophysiological mechanisms, impact on cardiovascular system, awareness and control. Prevalence of hypertension is higher in men than women till menopause; following this the prevalence rises steeply in women, and exceeds that of men above 75 years of age. Women with their estrogenic environment are relatively protected from high BP as their hormonal/chromosomal profile govern expression of alternate renin angiotensin axis (RAS) pathway and anti-inflammatory, vasodilatory, anti-proliferative immune cells whereas in males, classical RAS driven inflammatory, pro-hypertensive and proliferative milieu confers higher risk of hypertension. Thus, immunotherapy can have a potential therapeutic role in the treatment of hypertension in future. Cardiovascular consequences of high BP are worse in women than men in majority of trials. Women are now getting more aware of hypertension but the control of BP still remains poorer than men, especially in older age group. There are some noteworthy pharmacokinetic and pharmacogenomics gender differences in response to various antihypertensive drugs, which can be taken into consideration while choosing a particular class of drugs in female population. Standard treatment guidelines recommend same BP targets and management strategies in both the genders, but the trials so far have not been designed in a way to draw women specific conclusions on optimal cut-offs for diagnosis and treatment of BP due to under representation of women in majority of trials. More women centered analysis in future hypertension research projects can provide better scientific insights in various clinical aspects of hypertension.

Keywords: Gender, Cardiovascular, Blood pressure

INTRODUCTION

Cardiovascular (CV) disease is one of the leading causes of death and disability in both males and females. Women in postmenopausal age constitute the highest population burden of sudden cardiac death (13% of all deaths and 50% of all coronary deaths). Of all the modifiable risk factors for all cause death and disability in women, hypertension stands at the foremost position in the list.[1] The average life expectancy of women with hypertension has been reported to be approximately 5 years shorter than women with normal blood pressure (BP) at 50 years of age. Women's Health Initiative in its report also singled out high BP as a prime independent risk factor for sudden cardiac death in post-menopausal women.[2] As there is an exponential relation between high BP and CV mortality, even a smaller attempt to control BP in females can make a huge impact in lowering down the death rate in women.[3] There have been tremendous

advances in the current understanding of gender differences in hypertension but an extensive review of literature calls for more research to explore further the intricacies of hypertension in women.[4] This article aims to present a focused review on various issues related to hypertension in women, highlighting the gender dimorphism in the epidemiology, pathophysiology, CV effects, and pharmacological response to various drugs of hypertension.

SEX VERSUS GENDER: AN OVERLOOKED TRAIT

It is essential to understand the differences between these two synonymously but distinct terms – gender and sex. As defined by the Institute of Medicine Committee on Understanding the Biology of Sex and Gender Differences, sex is a chromosomal driven biological and anatomical identity of an individual assigned at birth as male or female whereas gender is a social and behavioral construct based on individual's self-revelation as man/boy or woman/girl.[5] Gender of a person may or may not match with the sex assigned at birth. Knowing the gender or sex identity of a person is important as our basic conceptual science is based on sexual phenotype whereas much of data collection or research activities to study the impact of a disease process or therapy are based on self-representation of gender at population level. For this reason, the term "sex" is used while referring to basic scientific developments examining male versus female phenotype and the term "gender" refers to clinical studies examining man versus woman identification.

EPIDEMIOLOGICAL DIFFERENCES IN HYPERTENSION: DOES GENDER MATTER?

There has been a remarkable increase in the overall prevalence of hypertension among all age groups in both men and women following the American College of Cardiology/American Heart Association (ACC/AHA) 2017 Hypertension guidelines. Global figures estimate that nearly 1.13 billion people are hypertensive, two-third of which live in low- and middle-income countries.[6] About one out of four men and one out of five women have high BP. In India also, hypertension prevalence is increasing like an epidemic with a recorded 3-fold increase from 2004–2005 to 2011–2012,[7] accounting for 5.1% of total deaths and 15% of CV deaths.[8]

Age-related gender differences

It has now been well established from the global statistics that men are more prone to hypertension than women in premenopausal age group; afterward, the prevalence rises at a much rapid rate in women, and subsequently overshoots in elderly postmenopausal women.[9] National Health and Nutrition Examination Survey BP data from 2011 to 2014 using the Joint National Committee (JNC) 7/8 BP guidelines report comparable prevalence in both the genders between 20–44 and 55–74 years of age, men being more affected in the age group 45–54 and women exceeding men above 75 years of age.[10]

Interestingly, the age-related gender differences in hypertension are found to be exaggerated after application of ACC/AHA 2017 hypertension criteria of BP. Men now have a higher prevalence of hypertension starting from 20 years of age till 65, the prevalence gap then narrows between 65–74 and reverses after 75 years of age. This age-related increase in male prevalence in majority of age groups below 65 years is an indirect evidence that historically there were more men with prehypertension than women as per JNC 7 criteria. A large meta-analysis including 120,605 men and 130,136 women from 13 countries further supported the notion of high-pooled prevalence of prehypertension among men (40%) versus women (33%).[11]

Demographical variables in relation to hypertension in Indian population

The large database from the National Family Health Survey 2015–16 (NFHS-4) provided the following reliable information on sex/gender specific differences in the prevalence of hypertension among the Indian men and women; stratified by socioeconomic status, geographical distribution, cultural, behavioral, and lifestyle characteristics.[12]

- Indian data also mimic the global trends of overall high prevalence in men (16.32%) than women (11.56%).
- Hypertension prevalence rises with increasing age, older adults (40–54 years) having the highest and almost double the prevalence as compared to younger individuals (25–39 years).
- State-wise distribution showed that residents of North, Northeast, and Southern states except Kerala have a relatively higher prevalence of hypertension.
- The prevalence of hypertension is more among men compared to women in majority of states except Delhi where the prevalence among women is higher than men (7.18% vs. 5.22%, respectively).
- Punjab reported the highest prevalence of hypertension among men (25.9%) and Sikkim among women (18.8%).
- The urban residents and people from poor wealth quintile and married adults are more hypertensive than their respective counterparts.
- Daily consumption of alcohol and non-vegetarian diet is strongly associated with high BP.
- Gender dimorphism-
    - Older age women, with low level of education, non-working environment, history of consumption of alcohol, presence of diabetes, and Muslim religion had higher prevalence of hypertension than men.

- Married, non-vegetarians, and highly educated men engaged in professional activities (managerial/sales/administrative) have more odds of having hypertension than women.

HYPERTENSION AND ITS CV IMPACT IN WOMEN

The direct relationship between hypertension and CV disease has been established in various trials since 1960s. Every 20 mm Hg increase in systolic BP or 10 mm Hg increase in diastolic BP almost doubles the risk of CV diseases.[13] In addition, 24-h ambulatory and conventional daytime and nighttime systolic BP recordings are found to be significant predictors of CV events. Ambulatory BP monitoring has also been suggested to be the preferred method of recording BP in high-risk pregnancies for early detection of adverse maternofetal events in a study by Vavilala *et al*.[14]

However, the impact of high BP is different for men and women.[15] Hypertensive women have been found to have more of non-traditional CV risk factors such as central obesity and kidney disease as compared to hypertensive men with more of traditional risk factors such as smoking and dyslipidemia.[16] For a 10 mmHg increase in systolic BP, the CV risk in women rises by 25% compared to only 15% rise in men.[17] Besides this, perimenopausal and menopausal women exhibit more variation in 24-h ambulatory BP measurements[18] and a non-dipping pattern of BP,[19] which may confer poor cardiovascular outcomes and target organ damage in older women.[20] A prospective study by Hermida *et al*. including 3344 participants (48.6% women) demonstrated a stronger relationship between high ambulatory BP and CV risk in women than in men. They also reported optimal BP threshold for CV protection as daytime BP of 135/85 mm Hg in men and 125/80 mmHg in women; and night time BP of 120/70 mm Hg in men and 110/65 mmHg in women.[21]

Hypertension leading to deleterious end organ consequences such as left ventricular hypertrophy, heart failure with preserved ejection fraction, diastolic dysfunction, diabetes, and chronic kidney disease are more common in women than men.[22] A prospective cohort study of participants in Reasons for Geographic and Racial Disparities in Stroke trial found a strong association between increasing hypertension severity and incident ischemic stroke in women compared with men.[23] Another community-based cohort study found an association between cardioankle vascular index (CAVI); a marker of subclinical atherosclerosis and aortic stiffness and BP category in men and women.[24] They found that CAVI increased as the stage of hypertension progressed in males but remained high in all stages of hypertension in females suggesting that optimal management strategy should focus not only on age, comorbidities but also gender. A research paper by Nethi *et al*. reported a rise in carotid-femoral pulse wave velocity in hypertensive women in parallel with the grade of hypertension, confirming the presence of vascular remodeling and increase in arterial stiffness which, in turn, marks the adverse CV consequences in women.[25]

Contrary to all these findings, a meta-analysis (5018 participants) did not find any significant gender differences between conventional home BP measurements and 10-year CV risk.[26]

One of the reasons for this discrepancy in CV outcomes could be difference in the methodology used to measure BP (ambulatory/conventional BP measurement) or the time of day when BP was recorded. Regardless of the reason, there is sufficient evidence that signify a relative higher CV risk in hypertensive females as compared to hypertensive males and makes sense to raise an important fundamental question – "should the optimal outcome based BP target be the same in females as males?"

Possible explanations for the higher CV risk in hypertensive female cohort

- Difference in biologic, behavioral, or hormonal characteristics of women that strongly link hypertension to vascular dysfunction.
- Gender-specific synergism between hypertension and other CV risk factors that contribute to poorer outcomes in women.
- Differences in the pharmacological treatment and poorer therapeutic adherence can be the other possibility of increased CV risk in women.

PATHOPHYSIOLOGY OF HYPERTENSION UNIQUE TO WOMEN

A woman in her life span encounters a varied spectrum of biological transformation; from young adulthood through reproductive age to menopause and old age when each phase has its own implications in onset of hypertension [Figure 1]. Hypertensive disorders of pregnancy, reproductive assisted technologies, and hormonal oral contraceptives/menopausal hormonal replacement therapies have their own pathophysiological mechanisms of hypertension in women population.

Passing over these women specific attributes of hypertension, estrogens in females play an indispensible protective role in maintaining the vascular hemostasis. Estrogens up-regulate nitric oxide (NO) pathway by increasing NO synthetase activity, inhibit endothelin production, and down-regulate the renin angiotensin system (RAS) by decreasing renin and angiotensin converting enzyme activity (ACE) activity and Angiotensin II (Ang II) production.[27-29] Estrogens also reduce the oxidative stress and inflammation through

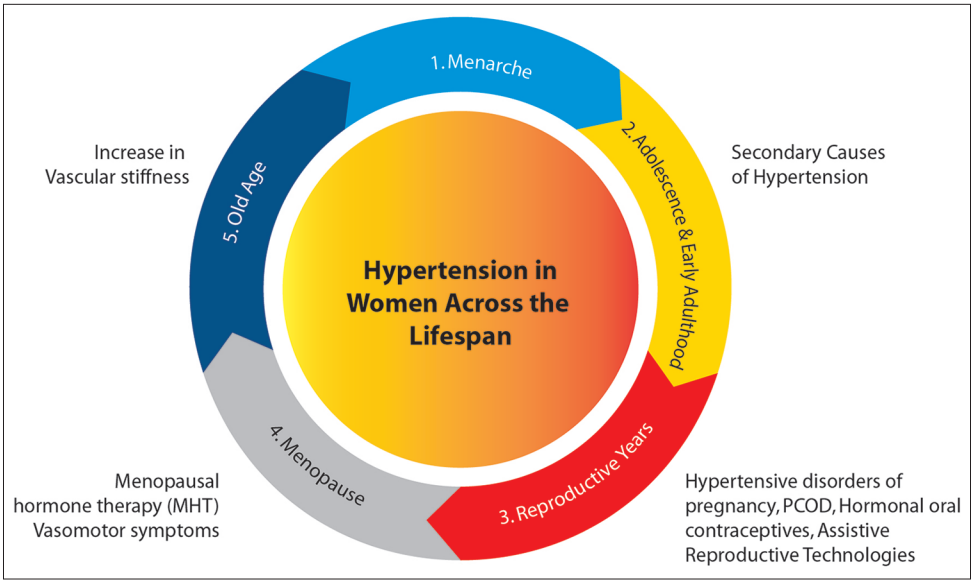

Figure 1: Hypertension in women across different stages of life span.

decreasing the generation of reactive oxygen species, increasing the antioxidant production, and inhibition of pro-fibrotic genes. This explains well the increased risk of hypertension seen in post-menopausal hypoestrogenic women. The hemostatic effects of estrogens are also supported by the fact that younger women with polycystic ovarian disorder or infertility or premature ovarian insufficiency due to any kind of estrogen imbalance have an increased risk of developing hypertension.[30]

The two major systems that contribute to sex differences in pathophysiology of hypertension are:

- RAS
- Immune System

Sex and gender differences in RAS expression

Renin angiotensin axis in our body works in two contrasting pathways – classical and non-classical/alternative. Angiotensinogen from liver is converted into angiotensin I (Ang I) by enzyme renin. ACE 1 further cleaves Ang I to Ang II, which then bind to one of the two angiotensin receptors [ATR].[31] The receptor expression has been found to be primarily under the regulatory control of estrogen and chromosome complement. The basic scientific studies confirm that males have biologically greater expression and physiological responses to activation of the classical RAS pathway (includes Ang II, Ang II type 1 receptor AT1R stimulation, and ACE), whereas females have greater expression and physiological responses to activation of the non-classical RAS pathway (includes Ang 1–7, Ang II Type 2 receptor AT2R, Mas receptor, and ACE2) [Figure 2].

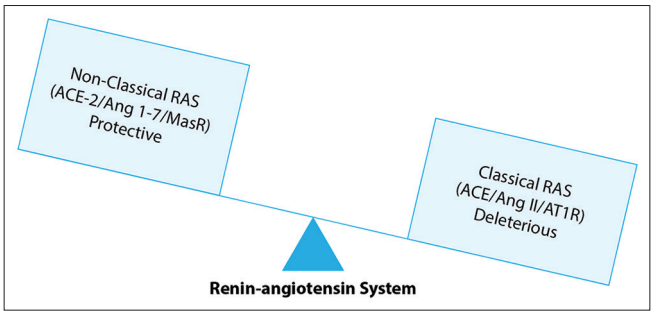

Figure 2: Physiological effects of key peptides of classical versus non-classical RAS.

This means in males, Ang II predominantly binds to AT1R which leads to vasoconstriction, renal tubular sodium reabsorption, and rise in BP through activation of classical RAS pathway. In contrast, in females, Ang II binds to AT2R, which triggers vasodilation and natriuresis through activation of alternate RAS pathway. Another component of non-classical/alternate RAS in females is generation of vasodilatory peptide Angiotensin (1–7) peptide from Ang II by the action of enzyme ACE2. Angiotensin (1–7) binds to the Mas receptor and promotes vasodilation and natriuresis.[32] It also attenuates the hypertensive effects of Ang II [Figure 3].

Apart from these sex divergent effects of angiotensin receptor on hypertension, AT2R stimulation creates an anti-inflammatory milieu in females whereas AT1R stimulation promotes inflammation, proliferation, and angiogenesis in males. This sex specific expression of Ang II receptor in kidneys and vasculature has been validated in spontaneously hypertensive male and female rats models.[33,34]

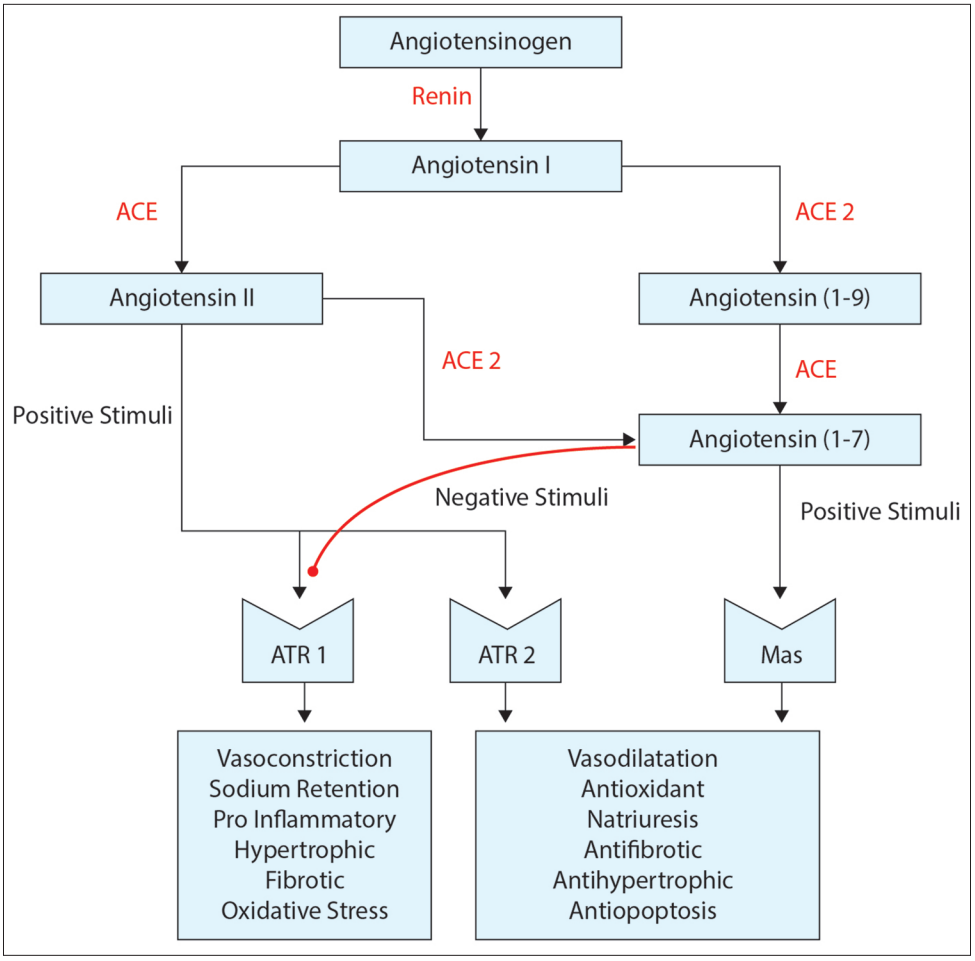

Figure 3: Simplified representation of major angiotensin pathways with their respective peptides, receptors, and effects.

Role of immune cells in sex differences in hypertension

Emerging evidence illustrates the imminent role of T cells in sex specific differences in Ang II mediated hypertension. Different types of T cells (pro-hypertensive and antihypertensive) have been found to exhibit gender specific expression. First report came from animal models by Guzik *et al.* in 2007 who used the male Rag-1−/− mouse model, which lacked mature B and T cells and have a decreased hypertensive response to chronic Ang II infusion and deoxycorticosterone acetate-salt compared to wild type mice.[35] Adoptive transfer of Pan T cells (CD2+CD3+), CD4+, and CD8+ from male donor to male recipient restored the hypertensive response whereas it remained blunted in case of female donor to male recipient or vice versa.[36-38] These findings substantiate the pro-hypertensive role of specific T cells (CD2+CD3+, CD4+, and CD8) in male mice as compared to females.

In addition, there are antihypertensive T cells called as T regulatory cells (Tregs), previously known as T suppressor cells. Renal T cell profile in females has been found to have greater mRNA expression of the anti-inflammatory Tregs (marker FoxP3) and cytokine IL-10 whereas males have greater population of pro-inflammatory Th17+ CD2+, and CD3+ cells, which can account for the gender differences in hypertension.

In short, the above findings provide some basic insights into the contrasting pathophysiological mechanisms of hypertension in both the sexes. It also calls for more research on immune cells functions, especially to explore their therapeutic potential as antihypertensive agents.

GENDER DISPARITIES IN BP AWARENESS AND CONTROL

A longitudinal study during the time period from 2003–2004 to 2011–2012 reported rising awareness of hypertension in both men and women, with the greatest increase in awareness noted in women.[39] However, at the same time, control of BP in women did not match the rising shift in awareness. Overall women are found to have less controlled BP than men in a cross-sectional analysis of >12,000 patients in primary care visits (54.0% vs. 58.7% $P < 0.02$), more so in the age

group 65–80 even after adjustment for multiple covariates. The Framingham Heart Study also reported more striking age-related decline in hypertension control in women than in men. Possible reasons for poor control of BP in women could be inadequate intensification of BP treatment due to underestimation of CV risk in females by primary care providers; treatment non-adherence; societal discrimination in health-care access; or true treatment resistance.

HYPERTENSION TREATMENT TARGETS – IS THERE A NEED OF GENDER SPECIFIC RECOMMENDATIONS?

European society of hypertension and cardiology guidelines (2018) and AHA guidelines (2017)[40,41] recommend the same BP targets in both men and women despite the plentitude of data reporting sex and gender differences in the pathophysiology and control of hypertension. The recommendation came from the scientific grounds of various trials that found no significant gender differences in CV outcomes. A large meta-analysis on antihypertensive agents using similar cutoffs for men and women showed no gender differences in CV outcomes.[42]

However, whether women are represented in adequate, statistical proportions in majority of trials to confirm the current recommendations are still controversial. A large systematic review of 740 CV clinical trials (2010 and 2017) showed that women cohort represented only 38.2% of trial participants despite women constituting more than 50% of total population.[43,44] In addition, the gender specific data were not generated in most of initial publications as they were primarily not designed or powered to analyze the same. Another confounding factor is majority of these trials directly assessing the impact of BP on CV outcomes included women in menopausal and early postmenopausal age groups (average age 53 years), which limits the generalizability of results to all age groups. As this is not the actual age of the highest prevalence of hypertension among women, the women included in most of the study population were not truly at high risk for CV morbidity and mortality. The recent findings of multi-centric systolic BP intervention trial (SPRINT) reported that more intensive BP control resulted in 25% reduction in CV events.[45] However, women enrollment in SPRINT was only 36% so it failed to draw any statistically significant conclusion on CV reduction with intensification of treatment in women. Therefore, it would not be justifiable to draw any definite gender specific inferences on BP targets and impact of BP control on CV health in women, unless a predetermined analysis is being done to eliminate these confounding variables.

SPECIFIC PHARMACOLOGICAL RECOMMENDATIONS FOR HYPERTENSION IN WOMEN

Before going into details of gender dissimilarities in pharmacotherapy of hypertension, it is important to acknowledge some important sex specific differences in pharmacokinetics and pharmacodynamics of drugs in general.

Women have a higher gastric pH, slower gastric emptying, and a longer total gastrointestinal transit time, compared

Table 1: Landmark trials on hypertension with gender specific analysis.

Trial (year)	Study population (age in years)	Total number of patients (women %)	Treatment arms	Results	Gender specific outcomes
LIFE (2002)[49]	Adults with hypertension and LVH (55–89)	9193 (54)	Losartan versus atenolol	Losartan superior to atenolol for CV and stroke outcome	Not tested for CV outcome Stroke outcome: No difference
ALL-HAT (2003)[50]	Adults with hypertension and at least one risk factor for CVD (>55)	33,357 (47)	Chlorthalidone versus amlodipine/lisinopril	No difference in CV outcome between treatment groups	No sex difference in CV outcome Stroke rate was higher with ACEI than chlorthalidone and amlodipine in women
VALUE (2006)[51]	Adults at high risk hypertension (>55)	15,245 (43)	Valsartan versus amlodipine	No difference in CV outcome between treatment groups	CV outcome was superior with amlodipine in women HF outcome was superior with valsartan in men

(Contd...)

Table 1: *(Continued).*

Trial (year)	Study population (age in years)	Total number of patients (women %)	Treatment arms	Results	Gender specific outcomes
ACCOMPLISH (2008)[52]	Adults with systolic hypertension	11,506 (40)	Hydrochlorothiazide plus benazepril versus amlodipine plus benazepril	ACEI plus CCB is superior than ACEI plus hydrochlorothiazide for CV outcome	No significant gender difference in CV outcomes
HUVET (2008)[53]	Elderly adults (>80)	3645 (64)	Indapamide with or without ACEI	Indapamide with or without ACEI is associated with reduction in stroke outcome	Data not available
SPRINT (2015)[45]	Adults with hypertension and at increased CV risk (>50)	9361 (36)	Intensive (SBP<130) versus standard BP target (SBP<140)	Intensive treatment is superior to standard treatment arm for composite CV outcomes	For women subgroup: Hazard ratio was not significant
HYGIA (2019)[54]	Adults with hypertension (>18)	19,084 (80)	Bedtime drug treatment versus awakening	Bedtime drug treatment is superior to awake drug administration	No significant sex difference

LVH: Left ventricular hypertrophy, CV: Cardiovascular, CVD: CV disease, ACE: Angiotensin converting enzyme, ACEI: ACE inhibitor, CCB: Calcium channel blocker, BP: Blood pressure, SBP: Systolic BP

Table 2: Important sex/gender differences for individual class of antihypertensive drugs.

Antihypertensive drug class	Sex differences
ACEIs[55-57]	• Pharmacokinetics - No sex differences • Pharmacodynamics: Low ACE activity has been observed in women than men • Adverse effects: ACEIs induced cough is 3 times more common in women than men

ARBs[56-58]	• Pharmacokinetics
	  • No sex differences observed for Losartan, candesartan and valsartan
	  • Plasma concentration of Telmisartan has been reported to be more in women than men but without any difference in degree of BP reduction

CCBs[59-61]	• Amlodipine - No pharmacokinetic sex differences but women achieve greater degree of BP reduction and treatment goals than men with amlodipine • Verapamil - Greater clearance rate has been observed in women than men when given by intravenous or oral route • Stroke risk reduction has been reported to be superior with CCBs with greater risk reduction found in women than men • Adverse effects - Women experience more edema with CCBs than men

Beta blockers[62-64]	• Beta blockers are classified into two groups depending on the metabolism
	  • Beta-blockers with CYP 2D6 dependent metabolism: Metoprolol, Carvedilol, Nebivolol and Propranolol
	  • Beta-blockers with CYP 2D6 independent metabolism: Sotalol, atenolol and bisoprolol
	• Women on treatment with beta-blockers having CYP 2D6 dependent metabolism have more adverse effects and drug-drug interactions with other heart rate lowering drugs than men

Thiazide diuretics[65,66]	• Pharmacokinetics: No sex differences
	• Pharmacodynamics
	  • Gender-genotype specific interaction (insertion/deletion polymorphism in ACE gene) has been reported
	  • Women have better BP response to hydrochlorothiazide in response to addition of I alleles whereas addition of D alleles leads to better BP response in males
	  • Thiazides are the preferred agents in postmenopausal women due to their beneficial effects on bone mineral density and reduction of fracture risk
	• Adverse effects: Women experience more frequent hyponatremia and hypokalemia with thiazides than men

ARBs: Angiotensin receptor blockers, CCBs: Calcium channel blockers, ACE: Angiotensin converting enzyme, ACEIs: ACE inhibitors, BP: Blood pressure

Table 3: Hypertension in women: Important learning points.

	Female sex/gender specific distinction
Epidemiology	• Prevalence is higher in men than women till menopause; following this the prevalence rises steeply in women, and exceeds that of men after 75 years of age • Apart from age, gender dimorphism also exists for few socioeconomic, cultural and religious variables
Pathophysiology	• Estrogens in females exhibit favorable effects on vascular physiology via distinct Nitric oxide, sympathetic and endothelin pathways • Estrogen mediated gender differences in RAS and immune cells expression (T cells) confers a relatively vaso-protective effects in females than males
CV impact of hypertension	• Women have more variability in 24 h ambulatory BP and non-dipping pattern of BP with more of non-traditional CV risk factors • Hypertensive women manifest worse CV outcomes than men
Awareness and control	• There is an increase in hypertension awareness in women but BP control remains poor, especially in the older age group
BP treatment targets	• Current guidelines recommend same BP targets in both males and females
Anti-hypertensive drug effects	• Overall benefits of antihypertensive treatment in reducing CV outcomes are similar in hypertensive women and men • No differential treatment recommendations for women • Gender differences exist in pharmacokinetics and pharmacodynamics of different class of antihypertensive drugs • Important gender differences in adverse effect profile can drive treatment choices • Diuretics in postmenopausal age and CCBs for stroke prevention have documented benefits in hypertensive women
Future goals	• To reconfirm whether there should be same or different sex/gender-specific thresholds for the diagnosis and treatment of hypertension in women, especially at different stages of her lifespan by including a predefined gender analysis in future hypertension trials • To explore the potential role of immunotherapy (Tregs) for treatment of hypertension

RAS: Renin angiotensin system, CCBs: Calcium channel blockers, BP: Blood pressure, CV: Cardiovascular

to men, which can affect the drug bioavailability and absorption. Furthermore, women have lesser weight but higher percentage of body fat than men which can affect the distribution of lipophilic and hydrophilic drugs. Drug distribution in women also gets affected due to their lower plasma volume and subsequently lower average organ blood flow,[46-48] in addition to hormonal influence on drug binding proteins. Hepatic drug metabolism has also cytochrome P450 enzyme variability in both the genders. Women also have 10–25% lower GFR than men even after adjusting for body size which can affect the drug excretion.

The majority of randomized controlled trials on hypertension with CV outcomes have made tremendous strides and provided substantial evidence that BP-lowering treatment is beneficial in both women and men. No strong evidence supported that women and men drive different outcome benefits from specific magnitude of BP reduction or with particular class of antihypertensive drug. Important year-wise landmark trials on hypertension with gender specific CV outcomes are summarized in [Table 1], majority of which show no significant differences in outcomes.[49-54]

However, the different groups of anti-hypertensive agents exhibit some important pharmacogenomics differences in both the genders [Table 2] that may influence the choice of one specific class of antihypertensive in women than men.[55-66] Similarly, other factors that may affect the selection of one agent over the other are presence of comorbidities such as heart failure and chronic kidney disease and hypertension in reproductive age group where ACEI and ARBs are avoided. Furthermore, women experience more adverse effects with particular antihypertensive medications than men, which may have its own influence in the choice of drugs and treatment adherence.

Some important practical points to consider are as follows:

- Diuretic therapy may be more beneficial in postmenopausal hypertensive women as it reduces urinary calcium excretion and prevents bone loss.
- Calcium channel blockers (CCBs) have been found to be more effective than ACE inhibitors for stroke prevention in women. Hence, CCBs can be the preferred agents in women at higher stroke risk.
- Avoid thiazides in women at risk of electrolyte imbalance.
- CCBs-induced edema and ACEI-induced cough are more marked in women than men and can be taken into consideration in corresponding clinical scenarios.

To summarize, though no significant gender treatment interaction has been noticed as far as CV outcomes or

drug recommendations are concerned, minor noteworthy differences found in various studies deserve further analysis to draw valid conclusions, especially when existing literature propose gender related incongruities in the various other clinical aspects of hypertension.

Table 3 outlines the key points in relation to hypertension in women discussed so far.

CONCLUSION

In this progressive era of personalized treatment where we are focusing on every other associate of hypertension such as age, ethnicity, and diabetes, gender/sex specific attributes of hypertension have not yet been precisely addressed on scientific grounds. Hypertension in women is a dynamic process and a stimulating area of preventive CV medicine, which needs further in depth research on priority basis so as to curb this global burden of death and disability in women.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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