LEARNING THE ROPES: ASPECTS ON MALE VS. FEMALE SEX IN HYPERTENSION

Sex Differences In Antihypertensive Treatment: Where Are We And Where Do We Go From Here?

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Antihypertensive treatment in hypertension guidelines worldwide do not differentiate the management of hypertension by sex except for pregnancy specific recommendations and avoiding RAAS inhibitors in childbearing potential women. However, there are some compelling reasons that suggest a 'one size fits all' approach may miss important considerations when treating non-pregnant women with hypertension. In this article, we will highlight key sex differences in hypertension treatments including surveillance of hypertension to initiate treatment, sex dimorphism of pharmacological response to drug therapies, and evidence to date on effectiveness of antihypertensive treatments in women and men. We will also discuss potential future strategies to reduce treatment gaps.

Hypertension surveillance policies for initiating and intensifying hypertension treatment generally do not account for the varying development and control of hypertension throughout a woman's life span and among higher risk subgroups of women. Earlier in the series, the regional differences in hypertension epidemiology have been well described. In brief, while younger and middle aged men develop hypertension at a higher prevalence than women, this relationship reverses once women reach menopause. Elderly women with hypertension often outnumber men at this stage and exhibit a greater burden of CVD risk than men. Despite this surge in hypertension diagnosis, CVD risk and therefore the need to initiate drug treatment in women, guidelines do not recommend an intensification of monitoring or treatment during these critical periods. Further, women aged greater than 60 years have worse hypertension

control of than men at any age. These differences can be amplified by ethnicity and socioeconomic status. In the US, African, Latin and Asian American women had worse control of hypertension than other groups ⁽¹⁾. Data from the Bangladesh Demographic and Health Survey (BDHS 2011) of 3870 males and 3955 females, found that non-working women were less likely to be prescribed antihypertensive compared with men (67% vs. non-working males 77%, $p < 0.05$) ⁽²⁾. Women living in poverty had less antihypertensive medication use than men living in poverty ⁽²⁾.

In addition to the sex based differences in physiologic mechanisms underlying hypertension described by Drs. Gerdtz and Midtbo that could affect therapeutic strategies, there is also gender dimorphism in the pharmacological response to antihypertensive medications. The metabolism and bioavailability of antihypertensive drugs depends on sex hormone-regulated absorption for some medications, hepatic cytochrome enzyme metabolism and clearance ^(3,4). Women have on average lower weights but higher proportions of adipose than men that may result in a lower volume of distribution to hydrophilic medications but a higher volume of distribution to lipophilic treatments ^(3,4). Several studies identified sex differences in activity levels of different hepatic cytochrome P450 enzymes that could have various effects on drug metabolism. CYP 3A4 is involved in the metabolism of about 50% of drugs and women frequently have higher clearance of drugs metabolized by this enzyme ⁽⁵⁾. Women's eGFR is also 10-25% lower than men indicating lower clearance of antihypertensive treatments.

While the clinical relevance of these pathophysiologic differences and pharmacologic responses to antihypertensive drugs is still unclear, women experience generally increased adverse effects from antihypertensive therapy compared with men. ACE-inhibitor associated dry cough is three times more common in women than men ⁽⁶⁾. Women have more diuretic-induced hypokalemia and hyponatremia and less gout than men ⁽⁶⁾. Women also report higher rates of peripheral edema with calcium channel blockers than men. Women appear to have more adverse effects with most antihypertensive agents than men except for mineralocorticoid antagonists. Thiazide-type diuretics reduce urinary calcium excretion helping to maintain cortical bone density and lower the risk of osteoporosis in postmenopausal women ⁽⁷⁾. This is associated with a reduced risk of hip and pelvic fractures. There are limited sex specific analyses of other adverse effects such as the cancer risk but a recent network meta-analysis found no differences among the antihypertensive drug classes for risk of breast cancer ⁽⁸⁾.

Antihypertensive treatment significantly reduces cardiovascular disease risk and the ISH Global practice guidelines recommend initiating treatment with ACE inhibitor and calcium channel blocker. However, a meta-analysis of 46 population-based studies from 22 countries, of 123,143 men and 164,858 women aged less than 60 years found that women were more likely prescribed diuretics, while men more often prescribed ACE-inhibitors and calcium-antagonists ⁽⁹⁾. Although these differences have been attributed to the avoidance of RAAS blockers in women of childbearing age, an observational study from Sweden found these sex differences persisted after adjustment for factors influencing the choice of these medications including age ⁽¹⁰⁾. Further, several reports raise concern that adherence to medications being may be worse in women than men. In an observational study of 60 526 patients aged 40–80 years newly treated with antihypertensive drugs in the Italian Lombardy Region, women had a 10% higher discontinuation rate compared with men within the first year of their prescription ⁽¹¹⁾. Although based on self-reported data, which has a higher risk of bias, a recent systematic review of patients aged 65 years or older, found that women had lower self-reported adherence than men ⁽¹²⁾. Whether these cumulative differences in women in prescribing and non-adherence, especially older women, contribute to the worse control of hypertension or higher CVD risk in elderly women is unclear.

Clinical trial inclusion of women has been historically poor, and largely focused on Western populations, hindering our ability to understand sex differences of antihypertensive treatments on blood pressure lowering or effectiveness on reducing CV endpoints. A systematic review of 598 CVD trials found that enrollment of women was low at 21% between 1986 and 1990 ⁽¹³⁾. This increased to 33% between 2011 and 2015, yet still remained below the expected prevalence of hypertension in women in the population and below the threshold to detect meaningful differences in CVD endpoints in trials. An overview analyses by Turnbull and colleagues from 2008 of 31 large randomized trials of 103,268 men and 87,349 women, found the degree of BP reductions achieved during these studies was generally similar for each antihypertensive comparison between men and women ⁽¹⁴⁾. Further, there were no significant sex differences in reduction of major CV events from degree of BP lowering or effect of angiotensin-converting-enzyme inhibitors, calcium antagonists, angiotensin receptor blockers, or diuretics/beta blocker based treatments ⁽¹⁵⁾. In more recent clinical trials (see Table 1) including SPRINT that enrolled 36% women, there were no significant differences in the main CVD endpoint in the women and men subgroups ⁽¹⁶⁾. Likewise, the ACCOMPLISH trial published in 2008 enrolled 11506 patients (39.5% women) compared ACE inhibitor and calcium channel blocker with hydrochlorothiazide and beta blocker also reported no interactions by sex on fatal and non-fatal CV endpoints ⁽¹⁷⁾. A pre-specified subgroup analysis of the VALUE trial, comparing valsartan to amlodipine in 15 245 (42% women) showed higher cardiovascular morbidity/mortality with valsartan than amlodipine in women, but not in men ⁽¹⁸⁾. HOPE 3 was a 2-by-2 factorial trial that randomly assigned 12,705 participants (46% women) at intermediate risk who did not have cardiovascular disease to candesartan plus hydrochlorothiazide vs. placebo ⁽¹⁹⁾. There were no significant sex differences in the composite risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke after a median follow-up was 5.6 years (p for interaction 0.32). Taken collectively, these studies suggest that there is no evidence for significant sex based differences in the effect of antihypertensive therapies in those with hypertension. However, our understanding of the effects in important women subgroups such as post menopausal women or women of differing ethnicity remain largely unknown.

There is a paucity of sex specific data to guide hypertension treatment in non-pregnant women despite the fact that almost 800 million women worldwide are

estimated to have hypertension. Where do we go from here? Multipronged strategies are needed to close our knowledge gaps to optimize treatment in diverse women globally.

1. More inclusion of women and reporting sex specific data in CVD treatment trials including women of differing ethnic groups and regions to identify optimal treatments across diverse groups of women.

2. Systematic review of existing studies to evaluate the effects of antihypertensive therapy on CV and other endpoints in subgroups of women by region/ethnicity and age compared with men.

3. Investigate personalized models of care targeting women with more frequent hypertension monitoring, initiation of therapy and tracking adherence during key periods across a woman's life span including the peri- and post-menopausal period.

4. Continue to prescribe antihypertensive therapy as per guidelines as there is no evidence to date that there are clinically relevant sex differences with these treatments.

5. Aggressively monitor for and manage adverse effects from medications in women.

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INVITED PAPER

The ISH Meeting: A new normal born in Kyoto!

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ISH2022 will be held from October 12 to 16 2022 in the City of Kyoto at Kyoto International Conference Center (ICCK) with the theme of "The Wisdom for Conquering Hypertension."

COVID-19 has deprived us of gathering opportunities for quite some time, and we really miss the liberty to meet, chat and have fun with many of our friends and colleagues from all over the world. We believe face-to-face meetings bring us more active debates and create stronger ties than any other formats, and we expect the COVID-19 pandemic will be over by October 2022. However, even if this is not the case, we will take all possible measures to hold a face-to-face meeting ensuring your safety.

Aiming at conquering Hypertension, ISH2022 also aims at creating a new scope of health and longevity by focusing on the three pillars: "Food (food and nutrition)", "Move (movement and fitness)", and "AI (artificial intelligence and digital technology)."

By bringing together multidisciplinary wisdoms regarding hypertension-related diseases, we aspire to explore new directions in diagnostics, prevention and treatment, as well as generate a new paradigm in our shared mission to control the disease.

It is with pride that we invite all of you to participate in the ISH2022. We strongly believe that you will find Japanese hospitality extremely satisfying and will be able to deepen and widen your knowledge and expertise to learn from the best.