LEARNING THE ROPES: ASPECTS ON SEX AND GENDER

Introduction 2

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Sex differences in hypertension have for a long time been neglected in all areas of hypertension research including basic and clinical science. This general approach has been changing over the past years. Important drivers of this change have been new rules by many funding agencies and by regulatory authorities, which demand the inclusion of subjects or animals of both sexes in preclinical and clinical studies. The change is also owed to the continuous work by individual researchers and societies for raising awareness of the existence and importance of sex differences in pathophysiology, prevalence, diagnosis, awareness, treatment (incl. side effects), and long-term consequences of hypertension.

One of the more recent, important insights from epidemiological studies on sex differences in hypertension is the fact that although prevalence of hypertension is higher in men than women of younger and middle age, this reverses from the 7th decade of life, from when hypertension rates in women exceed those in men ⁽¹⁾. Moreover, higher BP levels in elderly women go hand in hand with a higher risk of stroke than in males of the same age group. Of note, the increase in the risk of stroke with higher BP levels is almost twice as strong in women as it is in men ⁽²⁾.

Obviously, the steep increase in hypertension prevalence in women between menopause and the age of 70 strongly points to a causative role of hormones. It is indeed beyond question that several hormonal systems, which are involved in the regulation of BP, are under the control of sex hormones in men and women ⁽³⁾. These include effects of oestrogen and androgens on the renin-angiotensin-system, the sympathetic nervous system, endothelin, vasopressin, nitric oxide and also the immune system ⁽⁴⁾.

Furthermore, hypertension-induced end-organ-damage has been recognised to be dependent not only on pressure-overload, but also on a series of other contributing factors, many of which are sex dependent as lined out by Eva

Gerdt and Helga Midtbø in their article on “Organ damage and pathophysiology” for this issue of “Learning the Ropes”.

Despite the unquestionable progress of recent years in basic and clinical research on sex differences in hypertension, recommendations in major hypertension guidelines from the leading societies worldwide are still widely sex neutral due to a lack of evidence from clinical trials as pointed out by Nadia Khan in her article on “Sex Differences in Antihypertensive Treatment”. Even the SPRINT study, which compared standard with intensified (systolic BP goal < 120 mmHg) treatment of hypertension, failed in enrolling 50% women as planned, but included only 36%, and was therefore underpowered for this patient group ⁽⁵⁾. Nevertheless, two sub-group analyses were published comparing the outcome in women and men in SPRINT but with contrasting results. This again underlined that SPRINT results are inconclusive for women and that a sex-neutral implementation of SPRINT results into guidelines should be regarded with caution ⁽⁶⁻⁸⁾.

The same limitations in terms of evidence apply to recommendations on the management and treatment of preeclampsia in major guidelines, which refer back to underpowered clinical trials resulting in low-evidence recommendations based on expert opinion as for example pointed out in the WHO guidelines ^(9,10). Furthermore, it was only recognised quite recently that women with a history of gestational hypertension have an increased lifetime risk for CV events ^(11,12), which is another aspect that needs more research, awareness and more consideration in guideline recommendations.

While sex differences are one determinant of the many aspects of hypertension as outlined above, the articles by Lebo Gafane-Matemané and Julia Kagura (Sex Differences in the Epidemiology of Hypertension: The African Perspective), by Patricio Lopez-Jaramillo and Maria Angelica Chacon (The Latin American Perspective), by Ching Siew Mooi, Navin Kumar Devaraj and Lee Kai

Wie (The Asian Perspective) and by Karin Manhem, John – Emil Bager and Charlotta Ljungman (The Western Perspective) document impressively that ethnicity, socioeconomic conditions, education, geography and other life circumstances have an impact on prevalence, awareness and treatment/control of hypertension as well, and that research needs to be intensified in an effort to better understand how all of the confounding factors come together and how we best consider them to provide the best possible care to male and female patients worldwide.

References

1. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, et al. Sex Differences in Blood Pressure Trajectories Over the Life Course. *JAMA Cardiol.* 2020 Mar 1;5(3):19–26.
2. Madsen TE, Howard G, Kleindorfer DO, Furie KL, Oparil S, Manson JE, et al. Sex Differences in Hypertension and Stroke Risk in the REGARDS Study: A Longitudinal Cohort Study. *Hypertension* 2019 Oct;74(4):749–55.
3. Maranon R, Reckelhoff JF. Sex and Gender Differences in Control of Blood Pressure. *Clin Sci* 2013 Oct;125(7):311–8.
4. Colafella KMM, Denton KM. Sex-specific differences in hypertension and associated cardiovascular disease. *Nat Rev Nephrol.* 2018 Mar;14(3):185–201.
5. SPRINT Research Group, Wright JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2015 Nov 26;373(22):2103–16.
6. Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK, et al. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020 May 26;75(20):2602–18.
7. Foy CG, Lovato LC, Vitolins MZ, Bates JT, Campbell R, Cushman WC, et al. Gender, blood pressure, and cardiovascular and renal outcomes in adults with hypertension from the Systolic Blood Pressure Intervention Trial. *J Hypertens.* 2018 Apr;36(4):904–15.
8. Ochoa-Jimenez R, Viquez-Beita K, Daluwatte C, Zusterzeel R. Sex Differences of Patients With Systemic Hypertension (From the Analysis of the Systolic Blood Pressure Intervention Trial [SPRINT]). *Am J Cardiol.* 2018 Sep 15;122(6):985–93.
9. World Health Organization. WHO recommendations: drug treatment for severe hypertension in pregnancy [Internet]. Geneva: World Health Organization; 2018 [cited 2021 Sep 4]. 75 p. Available from: <https://apps.who.int/iris/handle/10665/277234>
10. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database Syst Rev.* 2013 Jul 31;2013(7):CD001449.
11. Garovic VD, Hayman SR. Hypertension in pregnancy: an emerging risk factor for cardiovascular disease. *Nat Clin Pract Nephrol.* 2007 Nov;3(11):613–22.
12. Khosla K, Heimberger S, Nieman KM, Tung A, Shahul S, Staff AC, et al. Long-Term Cardiovascular Disease Risk in Women After Hypertensive Disorders of Pregnancy: Recent Advances in Hypertension. *Hypertension.* 2021 Aug 15; doi: 10.1161/HYPERTENSIONAHA.121.16506

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