Sex differences in occurrence and reporting of adverse drug reactions in hypertension: What are the clinical implications?

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Related article
By Polaczyk et al.

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DOI: 10.33963/KP.a2022.0247

Received:
November 3, 2022

Accepted:
November 3, 2022

Early publication date:
November 6, 2022

Hypertension is a major cardiovascular and renal risk factor and a leading cause of premature death which affects both men and women [1]. However, blood pressure is a sexually dimorphic trait, and as reported recently [2], there are clear sex differences in the prevalence, pathophysiology, and consequences of hypertension between males and females. For example, one important difference is an interaction between blood pressure and age. Indeed, the rate of hypertension is significantly higher in males compared to age-matched females until the sixth decade, but thereafter, the prevalence of hypertension increases steeply to become higher in females than in males [3]. International recommendations for the management of hypertension in adults do not differ substantially for males and females in terms of diagnosis, investigational procedures, drug therapy, or follow-up [4, 5]. The main exceptions are, of course, pregnancy and the use of some antihypertensive drugs, such as blockers of the renin-angiotensin system, in women with childbearing potential. Yet, one should perhaps be more sensitive to the fact that sexual dimorphism concerns not only the prevalence and pathophysiology of hypertension but also the pharmacology of antihypertensive drugs and risk of developing major blood pressure-related complications [6].

When considering the use of medications for the treatment of hypertension, there is evidence that sex-specificities modulate the pharmacological response to antihypertensive drugs. Indeed, there are well-described pharmacokinetic differences between males and females regarding bioavailability, distribution, and elimination of drugs. Thus, females tend to have a lower ratio of lean-to-fat tissue, lower circulating plasma volume, and lower glomerular filtration rate [7]. Sex variations in the activity of several enzymes of the cytochrome P450 (CYP) system metabolizing antihypertensive drugs are also well documented [8]. Most of the time, these pharmacokinetic aspects are not taken into consideration for therapeutic recommendations because they are thought to have little impact on efficacy and tolerability of antihypertensive medications. Nonetheless, they may result in higher drug exposure in females and hence may increase their susceptibility to dose-dependent adverse drug reactions. Hence, women may respond differently to the prescription of some antihypertensive medications both in terms of efficacy and development of adverse reactions.

In the present issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Polaczyk et al. [9] present the results of a recent survey performed among hypertensive patients hospitalized for arterial hypertension and patients treated in an outpatient clinic for their hypertension. The main objective of the survey was to assess the prevalence of adverse drug reactions in women and men with arterial hypertension and comorbidities and to assess the specific predisposing factors for adverse drug reactions by sex. The study enrolled 1000 consecutive patients (560 women and 440 men; mean age, 62.8 years) starting in 2019. In this population, cardiovascular comorbidities were more frequent among males, whereas endocrine (but not diabetes)

and rheumatoid diseases were more frequent among females. The survey consisted of 22 questions, covering various demographic and clinical factors, which the patients filled in independently or with the help of a research team member. The main observation of the study is that the frequency of reported adverse drug-induced symptoms was significantly higher in female (54%) than in male patients (41%) even though females were taking significantly fewer drugs. Interestingly, this was true also for drug intolerance associated with using antibiotics or analgesics. In both sexes, the reporting of adverse drug reactions increased with age mainly due to an increased number of prescribed drugs. In males, the prescription of other cardiovascular drugs (statins, antiplatelet agents, etc.) contributed significantly to the increased reporting of adverse drug reactions. On the other hand, in females, the risk of developing adverse drug reactions was rather associated with using respiratory drugs and, to a lower degree, with using anti-rheumatoid drugs and antiplatelet agents.

The results of this interesting survey confirm previous observations from various countries suggesting that women are more likely to report adverse drug reactions for most common antihypertensive drugs and are more likely to be admitted to the hospital because of drug-induced adverse reactions [10]. The reasons why women tend to report more adverse drug reactions or drug intolerance are not completely understood. Whether reported events are genuine pharmacological reactions or only perceived events is not always well defined, and the reality is they are probably a mix of both. Thus, it is interesting to note that in placebo-controlled studies, up to 14% of men receiving classical antihypertensive drugs report side effects leading to discontinuation of the drugs, and with statins, this figure may reach 25% [11, 12]. One of the possible reasons for the sex difference may be that women have less confidence in potential benefits of drugs and a different perception of health risks related to their hypertension. One important issue is that the reporting of adverse reactions or multiple drug intolerance, as observed in Polaczyk's study [9], is an important determinant of poor adherence and drug withdrawal. Indeed, the report of several side effects is often an indirect signal for patients to indicate that they are not willing to continue some of their medications. In this respect, it is interesting to mention that observational studies have often reported a lower level of adherence to antihypertensive medications among females than males [13]. However, this observation remains controversial. Actually, a systematic review and meta-analyses of 82 studies (15 517 457 men and 18 537 599 women) did not provide definitive evidence of sex differences in adherence to antihypertensive therapy [14].

Another potential clinical consequence of frequent reporting of drug-related adverse reactions might be poor control of blood pressure mediated by lower adherence to antihypertensive medications. Partial or complete non-adherence is a well-recognized factor associated with a worst control of blood pressure and increased risk of developing cardiovascular outcomes [15]. Unfortunately, Polaczyk et al. [9] did not provide any information on blood pressure values in men and women reporting, or not, adverse drug reactions. This information would have been interesting in evaluating clinical impact of multiple drug intolerance or occurrence of adverse drug reactions.

The data presented by Polaczyk et al. [9] have several clinical implications. As mentioned by the authors, the first is the need to discuss regularly with patients and, in particular, with women how they tolerate their antihypertensive medications and how they feel about them to modify the drug prescription if necessary. In the case of multiple drug intolerance, the possibility of low adherence should be envisaged, and drug adherence should be monitored if blood pressure is poorly controlled. Whenever possible, the pill burden should be reduced using single-pill combinations, and patients should be well informed about the side-effect profile of antihypertensive drugs before they start to take them. At last, the most effective approach is probably to dedicate more time to discuss with patients possible barriers and beliefs that might interfere with their perception of benefits and risks of antihypertensive medications.

Article information

Conflict of interest: None declared.

Funding: None.

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