The occurrence of drug-induced side effects in women and men with arterial hypertension and comorbidities

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Related article
by Polaczyk et al.

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Cardiovascular disease (CVD) has been traditionally considered a male disease, and for many years it has been underestimated and underrecognized in women. Nevertheless, CVD remains the leading cause of mortality and morbidity in women in western countries.

It is both comforting and worrying that much of CVD could be avoided through adequate prevention strategies. Preventing the incidence of these diseases essentially means tackling modifiable cardiovascular risk factors. Among these, arterial hypertension (AH) plays a leading role [1]. AH represents a major steadily increasing therapeutic challenge to healthcare systems, affecting almost one billion people worldwide. Although various pharmacological treatment options exist, blood pressure (BP) control is still suboptimal and major efforts are required to improve patients' awareness and compliance, as well as physicians' adherence to treatment guidelines [2].

There is evidence of sex dimorphism in epidemiology, pathophysiology, management, and treatment of AH. Many studies highlight sex differences in the pharmacokinetics and pharmacodynamics of cardiovascular drugs [3]. Disparities may be related to biological factors (body composition) and physiology (hormonal influences during the menstrual cycle, menopause, and pregnancy); furthermore, women are less often treated with evidence-based drugs, experience more relevant adverse drug reactions (ADRs), and remain underrepresented in most clinical trials [4]. Thus, current guidelines are based on trials conducted predominantly in middle-aged men and translated to women without evidence [5].

Despite the increasing awareness of sex-related differences, the latest European Society of Hypertension/European Society of Cardiology [6] and American Heart Association [7] guidelines (2017) recommend the same BP targets and treatments for both sexes. The only certainties we have nowadays regarding AH therapy in women are limited and concern mainly the therapeutic strategy to use (or to avoid) to treat BP pregnancy-related disorders, and the treatment of AH associated with some women's comorbidities such as thiazide use and risk for osteoporotic fractures. Finally, isolated systolic AH is more frequent in elderly women, and its treatment is often associated with orthostatic hypotension, caused or exacerbated by a list of well-known drugs [8].

In this issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Polaczyk et al. [9] present an elegant and detailed analysis of the frequency of ADRs in women and men with AH and comorbidities to assess the sex-specific predisposing factors leading to their occurrence. Based on 1000 consecutive patients (560 women and 440 men) diagnosed with AH, a 22-question structured questionnaire was used to gather demographic and clinical data. Women in the study were significantly older, had longer hypertensive disease duration, and fewer comorbid CVDs than men. Women were more likely to report ADRs, and the risk increased significantly with age and coexistence of any respiratory disease. Regarding specific side effects, women more frequently reported hypotension, coughing,

edema, bradycardia, and skin lesions than men. In male patients, the risk of ADRs increased with the occurrence of hypercholesterolemia and or other metabolic diseases (such as diabetes, gout, obesity, and osteoporosis).

The review of the literature shows that the incidence of ADRs by sex has not always been sufficiently investigated in the controlled clinical trials on which our current treatment guidelines are based and, therefore, useful information on sex differences may have been left out: this omission could prevent an effective personalization of the antihypertensive therapy.

There are at least three good reasons for reading the article by Polaczyk et al. [9] in this issue.

(1) It is focused on an area of care that is increasingly important in cardiology and public health; the awareness of the existence of sex differences in CVD and AH is increasing, but there is still a lack of defined knowledge.

(2) It underlines an important aspect of AH, namely the conditions of discontinuation of the therapeutic strategy. ADRs may significantly affect the quality of life of patients with AH, as well as their disease acceptance and therapy compliance, leading to worse BP control and, thus, poorer prognosis.

(3) It is an attempt to provide a comparative view of possible ARDs in different medical and clinical settings. As AH is a condition linked to aging, it is often associated with multiple other comorbidities that can affect both clinical outcomes and therapeutic strategies.

There are at least three reasons to suggest that the results should be taken as a stimulus for looking ahead, rather than reliable information on which to concentrate technical discussion: (1) despite validation processes, questionnaires remain rather poor instruments for investigating practices; (2) the comparability and representativeness of the selected sample may not be considered satisfactory as it was limited to a single center and a relatively short period, which creates limitations and need for caution while interpreting findings and their generalizability; (3) men are more often prescribed angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists and beta-blockers than women, while more women than men receive diuretics and calcium antagonists. In the present study, women took angiotensin receptor blockers more frequently than men. This could be due to the fact that the female participants were significantly older than their male counterparts and post-menopausal. Moreover, the sample included both hospitalized and outpatient clinic patients; however, it can be assumed that the incidence of ADRs may be higher in patients not requiring hospitalization.

Based on the current analysis by Polaczyk et al. [9], a better understanding of sex-related differences is essential to improve safety (and subsequently efficacy) of AH drugs and to develop proper individualized cardiovascular therapeutic strategies. According to the present study, special attention should be paid to female and elderly patients, as well as people with numerous comorbidities.

Several advances have been made to increase knowledge and awareness of sex differences in CVD. The main issue hindering a comprehensive approach seems to be the lack of consistent sex-specific data. With the advent of personalized medicine, there is consensus that sex differences in pharmacotherapy should be studied systematically, and sex should be included in covariate analyses and not only in *post hoc* analysis [10].

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REFERENCES

1. Lodi E, Stefani O, Reggianini L, et al. Gender differences in cardiovascular risk factors. J Intern Med. 2013; 274(2): 176–191, doi: 10.1111/joim.12073, indexed in Pubmed: 23565931.
2. Thoenes M, Neuberger HR, Volpe M, et al. Antihypertensive drug therapy and blood pressure control in men and women: an international perspective. J Hum Hypertens. 2010; 24(5): 336–344, doi: 10.1038/jhh.2009.76, indexed in Pubmed: 19798089.
3. Cadeddu C, Franconi F, Cassisa L, et al. Arterial hypertension in the female world: pathophysiology and therapy. J Cardiovasc Med (Hagerstown). 2016; 17(4): 229–236, doi: 10.2459/JCM.0000000000000315, indexed in Pubmed: 26910607.
4. Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. Eur Heart J Cardiovasc Pharmacother. 2017; 3(3): 163–182, doi: 10.1093/ehjcvp/pvw042, indexed in Pubmed: 28329228.
5. Strocchi E, Baffoni E, Bragagni A, et al. The attention on gender in studies on the treatment of hypertension: Was it enough? Ital J Gender-Specific Med. 2021; 7(2): 94–101, doi: 10.1723/3600.35813.
6. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39(33): 3021–3104, doi: 10.1093/eurheartj/ehy339, indexed in Pubmed: 30165516.
7. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018; 71(19): e127–e248, doi: 10.1016/j.jacc.2017.11.006, indexed in Pubmed: 29146535.
8. Lodi E, Carollo A, Martinotti V, et al. Hypertension and pharmacological therapy in women. High Blood Press Cardiovasc Prev. 2018; 25(2): 147–150, doi: 10.1007/s40292-018-0257-0, indexed in Pubmed: 29623553.
9. Polaczyk M, Olszanecka M, Wojciechowska W. The occurrence of drug-induced side effects in women and men with arterial hypertension and comorbidities. Kardiol Pol. 2022; 80(11): 1092–1101, doi: 10.33963/KP.a2022.0232.
10. Kalibala J, Pechère-Bertschi A, Desmeules J. Gender differences in cardiovascular pharmacotherapy-the example of hypertension: a mini review. Front Pharmacol. 2020; 11: 564, doi: 10.3389/fphar.2020.00564, indexed in Pubmed: 32435193.