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

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

It is both comforting and worrying the fact that much of CVD could be avoided through adequate prevention strategies. Preventing the incidence of these diseases essentially means treating modifiable cardiovascular risk factors. Among these, arterial hypertension (AH) plays a central role [1]. AH represents a major steadily increasing therapeutic challenge to health-care 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 gender 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 translate to women without evidence [5].

Despite the increasing awareness of sex-related differences, latest ESH/ESC [6] guidelines and AHA [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, the treatment of AH associated to some women's comorbidities as thiazide use and risk for osteoporotic fractures among and, finally, the fact that isolated systolic AH is more frequent in elderly women and that its treatment is often associated with orthostatic hypotension, caused or exacerbated by a list of well-known drugs [8].

In this issue of the 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 gender-specific predisposing factors leading to their occurrence. Based on 1000 consecutive patients (560 women and 440 men) diagnosed with AH, a 22 questions structured questionnaire was used to gather demographic and clinical data. Women in the study resulted to be significantly older, had longer hypertensive disease duration and fewer comorbid CVD than men. Women were more likely to report ADRs and the risk increased significantly with age and the coexistence of any respiratory disease. Regarding specific side effects, women complained more frequently than men: hypotension, coughing, oedema, bradycardia and skin lesions. 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 gender 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 could prevent an effective personalization of the antihypertensive therapy.

There are at least three good reasons for reading the paper by Polaczyk et al. [9] in this issue: (1) it is focused on an area of care which is increasingly important in cardiology and public health; the existence of sex-differences in CVD and AH is increasing, but there is still a lack of defined

knowledges; (2) it recalls and underlines an important aspect of AH, namely the conditions of discontinuity 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 clinicals 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 strategy.

There are at least three directly opposing reasons to suggest that the results should be taken as a stimulus for looking ahead, more than as a set of hard 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 sample selected may not be considered satisfactory, been limited to a single center and to a relative short time span, and imposes caution and limitations on the interpretation of the findings and on 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 the fact that the women 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 mandatory 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 gender differences in CVD. The main issue hindering a comprehensive approach seems to be lack of consistent sex-specific data. With the advent of personalized medicine there is a common agreement that gender differences in pharmacotherapy should be studied systematically, and gender should be included in covariate analyses and not only in *post hoc* analysis [10].

Article information

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