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Sex differences in the treatment of arterial hypertension

Diferencias de sexo en el tratamiento de la hipertensión arterial

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INTRODUCTION

Although systemic arterial hypertension (SAH) guidelines do not make specific recommendations by sex (except pregnancy), a substantial body of evidence shows sexual dimorphism in various aspects. This chapter summarizes the main sex-specific differences (SSD) in the treatment of hypertension.

PHARMACOKINETICS

SSD in body composition and organ physiology may influence the pharmacokinetics (PK) (absorption, distribution, metabolism, and excretion) of antihypertensive drugs closely linked to sex hormones.[1-3] These differences are shown in *Figure 1*.

DIFFERENCES IN DRUGS FOR THE TREATMENT OF HYPERTENSION

Diuretics: thiazide and thiazide-type diuretics (TD) are widely indicated in women, and the female sex is a predictor of response to TDs, affecting the reduction of systolic and diastolic blood pressure.[4] In the Women's Health Initiative, a project that recruited 98,705 women between the ages of 50 and 79 with hypertension and no history of cardiovascular disease (CVD), treatment with TD as monotherapy was associated with better blood pressure (BP) control than other drugs used as monotherapy.[5] In middle-aged women, the reduction in systolic blood pressure produced by indapamide was significantly more significant than in men.[6] In another study with SSD analysis including 51% of women, TD presented similar benefits in reducing all cardiovascular events, but a more significant reduction in stroke was observed in women.[7]

There are no gender differences concerning urinary flow rate and excretion rate of sodium and potassium. In older women, although thiazides reduce the risk of bone loss and fractures, becoming an attractive option for this population, the deterioration of glomerular filtration is more pronounced; this fact needs to be considered at the time of its indication since it can lead to more significant adverse drug reactions (ADR).[8] Electrolyte disturbances (hyponatremia and hypokalemia) and arrhythmic events are more common in women. Another possible ADR to consider, is sexual dysfunction, as thiazides decrease vaginal lubrication.[8]

Renin-angiotensin-aldosterone system inhibitors: sex hormones interact with the RAAS at multiple levels; estrogens inhibit it, while androgens increase their activity. However, how sex hormones modulate the efficacy and safety of these drugs remains uncertain.

SSD has not been described in the pharmacokinetics of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), aliskiren, or spironolactone. However, some data on SSD on the efficacy of ACE inhibitors or ARB exists. In a review that included 13 studies with 74,105 patients (39% women), SSD data were reported in

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only nine studies, and in seven of them, both ACE inhibitors and ARB demonstrated slightly greater efficacy in men.[9] Regarding adverse effects, they are also higher in women, having up to three times more incidence of cough with ACE inhibitors. On the other hand, they decrease vaginal lubrication just like TDs (frequent association).[8]

Pharmacokinetic differences	Clinical consequences and specific examples in some drugs
Bioavailability	
• ↓ secretion of gastric acid with slower gastric emptying • Slower intestinal transit • No consistent changes in intestinal metabolism	• ↓ oral availability of drugs that require an acidic environment for their absorption • Delayed/decreased absorption of enteric-coated drugs (captopril, metoprolol, verapamil, aspirin)
Distribution	
Body composition • ↓ body surface area • ↓ body water content and plasma volume • ↑ body fat Binding to plasma proteins • ↓ albumin and α1 acid glycoprotein • ↑ globulins	• ↑ of Vd and longer half-life of lipophilic drugs • ↑ of the Vd of lipophilic drugs reached a higher Cmax with more AED (amlodipine) • Contraceptives ↓ decrease plasmatic albumin and α1-acid glycoprotein and may ↑ free drug levels • Estrogens ↓ α1-acid glycoprotein and ↑ plasmatic binding globulins
Metabolism	
Phase I • ↓ CYP1A2, 2C9, 2D6, 2C19 and 2E1 activity • ↑ CYP2A6, 2B6, 2D6 and 3A4 activity Phase II • ↓ uridine diphosphate glucuronosyltransferase activity (UGTs 1/2) • ↓ N-acetyltransferase and alcohol dehydrogenase activity • ↑ xanthine oxidase activity	• ↑ biotransformation of CYP3A4 substrates (CCB, losartan) • ↓ biotransformation of CYP2D6 substrates (metoprolol, propranolol) - higher exposure in women • CYP1A2 and 2C19 are inhibited by contraceptives and during pregnancy, therefore, their activity is ↓. Contraceptives and estrogens ↑ CYP2A6 and 2B6 activity
Transport • ↓ P-glycoproteins, OCT2, OATP 1B1 and OATP 1B3	• ↑ exposure to substrates of P-glycoproteins (colchicine, dabigatran, digoxin) • Estrogens ↓ the regulation of OCT2 but ↑ the activity of P-glycoproteins
Excretion	
↓ renal blood flow, GFR rate, tubular secretion and/or reabsorption	• ↓ renal chloride with a slower mean elimination time in the excretion of drugs: ACE (atenolol, bisoprolol, nadolol, diuretics) • Differences are reduced when doses are adjusted for weight or creatinine Cl

Vd = volume of distribution. Cmax = maximum concentration. ACE = angiotensin-converting enzyme inhibitors. AED = adverse effects of drugs. CCB = calcium channel blockers. GFR = glomerular filtration rate. OCT2 = organic cation transporter 2. OATP = organic anion transporting polypeptides.

Figure 1: Sex-specific differences in pharmacokinetics (modified from 1-3).

Calcium channel blockers: calcium channel blockers (CCB) are a pharmacological group widely used in women. There are PK differences between verapamil and amlodipine *(Figure 1)*. A multicenter study (35% of women) showed that amlodipine was more effective in women older than 65. However, other extensive studies (ASCOT, CONVINCE, INVEST, Nifedipine-GITS, NORDIL, Syst-Eur, STOP-Hypertension) did not find SSD.[10] However, CCB have a more significant effect on reducing stroke than other antihypertensives in women.[11] Peripheral edema is the most common adverse effect and is even more common in older women.[1]

Beta-blockers (BB): propranolol and metoprolol are mainly metabolized by CYP2D6, which is more active in men, so women experience greater exposure with more possibility of adverse effects. There are no differences between carvedilol, atenolol, nebivolol, and nadolol.[8] BBs remain the drug of first choice in women with ischemic heart disease, heart failure with reduced ejection fraction, or atrial fibrillation. In addition, labetalol is the drug of choice in pregnant women with SAH.[11]

DIFFERENCES IN THE TREATMENT, ADHERENCE, AND CONTROL OF SAH

In a recent NCD risk factor collaboration[12] analysis of 1,201 populations analyzed in 2019, with 104 million participants, 59% of women reported a previous diagnosis of SAH vs. 49% of men. Women presented higher rates of treatment and control than men, and a similar behavior was observed in Latin America and the Caribbean, with even more marked differences *(Figure 2)*.

When age groups were analyzed, the behavior was opposite in older women with lower control rates than men and young and middle-aged women. In a Canadian study that examined the rates of treatment and control of SAH in women over ten years, a decline in diagnosis, treatment, and control rates was observed in the period analyzed, a fact that did not occur among men.[13] In the NHANES (2017-2020), the proportion of hypertensive adults with controlled BP is lower in women and only 23% vs. 38% of men older than 80 who presented controlled BP.[14] Whether this is due to biological factors, inappropriate

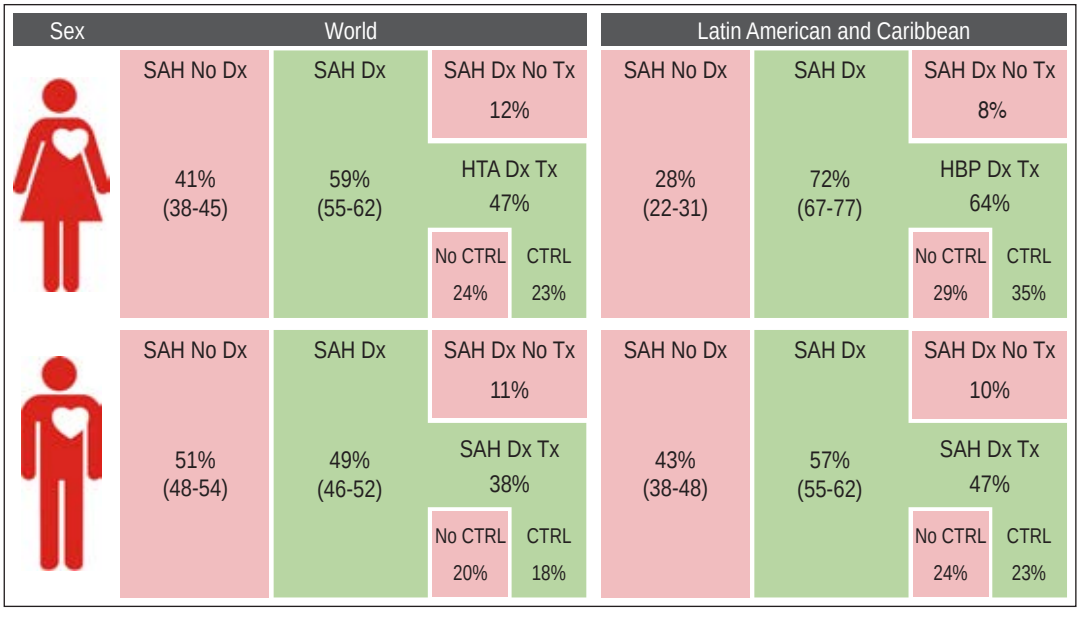

Figure 2: Diagnosis, treatment, and control of hypertension in men and women worldwide and in Latin American and Caribbean regions. Adapted from Zhou B et al.[12]

SAH = systemic arterial hypertension. Dx = diagnosis or diagnosed patient. No Dx = no diagnosis or undiagnosed patient. Tx = treatment or treated patient. No Tx = no treatment or untreated patient. CTRL = control or controlled patient, No CTRL = no control or uncontrol patient.

treatment (medical inertia, wrong choice of drug), lack of adherence, or a higher prevalence of comorbidities is unknown.

Regarding whether one family of antihypertensive drugs is better than another in treating hypertension in women, it is essential to mention that, despite many clinical studies, the specific data for women are limited and sometimes controversial. Until 2000, most studies were conducted mainly in middle-aged people and almost exclusively in men. They were not designed to have the statistical power to assess differences between the sexes. However, the results of these studies greatly influenced the recommendations of the leading clinical practice guidelines. Neverthless, there is a greater enrollment of women in recent studies, and under-representation persists, especially in women over 70, the age group where hypertension is more prevalent.

Furthermore, most SSD information comes from post-hoc analysis, which has limitations. On the other hand, SSD is usually analyzed dichotomously (men vs. women). Still, data on different sub-populations are unavailable, such as women of reproductive age, advanced age, or menopause-treated hormone replacement therapy.

Due to these limitations, more data is necessary to rule out the presence of SSD in the efficacy of antihypertensive agents in controlling SAH. This possibility exists and deserves further investigation.[1] In the guidelines for the primary prevention of CVD in women of the Inter-American Society of Cardiology, taking into account the pathophysiological mechanisms of hypertension in menopause, inhibition of the RAAS with ACE inhibitors or ARA II is suggested, with a grade of recommendation IIa and level of evidence C, since there is still no certainty from studies that more strongly support this recommendation.[15]

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