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Sex differences in the prescription of anti-hypertensive medications in primary care patients

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Abstract

Background: Pharmacological prescription guidelines for hypertension lack differentiation between the sexes, despite reported sex differences in prevalence, awareness, pathophysiology and pharmacological response.

Aim: We aimed to assess prescription patterns of blood pressure lowering medication among women and men in primary care.

Design and Setting: We analyzed data collected in 2018 during routine primary care practice among those pharmacologically treated for elevated blood pressure, and free from cardiovascular comorbidities or diabetes mellitus.

Methods: We assessed sex differences in the number of prescribed drugs, defined daily dosage, type of antihypertensive medication, and blood pressure control. We adjusted for differences between sexes in age and other covariates.

Results: This observational study included 8596 women and 5788 men. Both women and men were prescribed on average 1.8 antihypertensive agents per person. Women compared to men were prescribed a significantly lower defined daily dosage (1.8 vs 2.1, $p<0.001$), received more often betablockers (35.4% vs 26.3%, $p<0.001$) and diuretics (53.7% vs 50.5%, $p<0.001$), while receiving fewer ACE-inhibitors (35.4% vs 46.3%, $p<0.001$) and calcium channel blockers (28.5% vs 35.6%, $p<0.001$). No sex differences were found for angiotensin receptor blockers (24.3 vs. 24.4%, $p=0.842$). Importantly, women had significantly better controlled hypertension than men (50.2% vs 45.5%, $p<0.001$).

Conclusion: In those pharmacologically treated for elevated blood pressure, differences between women and men exist in defined daily dosage, type of antihypertensive medication, and blood pressure control, with women achieving better hypertension control than men with different type of medication and lower dosage.

Keywords: Hypertension; sex differences; antihypertensive agents; general practice; primary health care.

How this fits in

This study reveals that in primary care, women are prescribed lower doses of antihypertensive medications yet achieve better blood pressure control compared to men. These findings highlight the importance of considering sex-specific factors in hypertension management, suggesting that clinicians may need to tailor treatment strategies more closely to optimize outcomes for both sexes. This research underscores the potential for refining guidelines to better address sex-based differences in hypertension treatment.

Introduction

Cardiovascular disease (CVD) is a major contributor to morbidity and mortality worldwide, and the prevalence and burden continues to escalate globally (1), with hypertension representing a major modifiable risk factor (2). According to the World Health Organization (WHO), approximately 1.28 billion adults aged 30-79 years worldwide suffer from hypertension, with only 42% of them being diagnosed and treated (3). Hypertension management is far from adequate since four out of five hypertensive adults exhibit uncontrolled blood pressure (BP) levels, exceeding the recommended office values of 140/90 mmHg (3). This is of concern as untreated and uncontrolled hypertension considerably increase the risk of future cardiovascular events later in life, independent of other relevant risk factors (4-6).

Sex disparities in hypertension prevalence and response to pharmacological treatment are influenced by variations in the renin-angiotensin system and immune responses (7, 8). Women generally exhibit a more anti-inflammatory immune profile, potentially impacting BP control (7, 8). Pharmacokinetic and pharmacodynamic differences further suggest that lower doses of antihypertensive medications may suffice for women (9, 10).

In the Netherlands, where a significant portion of hypertension management takes place in primary care, general practitioners (GPs) play a central role in patient treatment. Dutch general practice guidelines recommend a stepwise approach to pharmacological treatment of hypertension, with considerations such as comorbidities, side effects, and personal preference guiding medication choice

(11). However, these guidelines also do not address potential sex-based differences in treatment strategies.

We set out to investigate the actual prescription pattern of antihypertensive medications, with a specific focus on sex differences. We seek to assess sex differences in the number, prescribed dose defined as defined daily dosage and type of antihypertensive medication as well as BP control, in hypertensive women and men in Dutch primary care who are prescribed ≥1 type of antihypertensive medication, and free from cardiovascular comorbidities or diabetes.

Methods

Settings and patients

This observational study was conducted using the Julius General Practitioners Network (JGPN) database which encompasses longitudinally routine care of more than 70 general practices serving around 300,000 people in the area of Utrecht, the Netherlands (12). Since nearly every citizen in the Netherlands has a GP, except for the homeless and those in nursing homes, JGPN provides a representative sample of the Dutch population (12). Data is extracted from the electronic health records and each patient-physician consultation is registered according to a systematic format. Reasons for consultation and diagnoses are uniformly coded using the International Classification of Primary Care (ICPC) coding, prescribed medication are coded according to the Anatomical Therapeutic Chemical Classification standard (ATC) and hospital referrals are appropriately categorized.

From the JGPN database containing information from 2000 to 2019, we first selected all patients aged 18 years and older with hypertension (ICPC code K86 and K87). Next, we selected those who in 2018 were prescribed ≥ 1 antihypertensive agent (as the interest was on patients in whom the GP already had prescribed BP lowering agents). We excluded those with an ICPC code for CVD or diabetes mellitus before 2018, as these patients may be prescribed BP lowering agents for those conditions rather than for the indication hypertension. Antihypertensive medication used in 2018 was classified according to ATC codes and included diuretics, betablockers, calcium channel blockers, renin-

angiotensin system inhibitors, and other antihypertensives. Use of medication was only considered if prescribed for > 30 days, to exclude other, short-term drug indications.

Patients were excluded when they had at least one of the following conditions: ischemic heart disease; percutaneous coronary intervention; coronary artery bypass grafting; heart failure; atrial fibrillation/flutter; transient ischemic attack; stroke; other cerebrovascular disease; peripheral arterial disease; abdominal aortic aneurysm (See **Supplementary Tables 1 and 2** for ATC codes and ICPC codes). This research was conducted in accordance with the European General Data Protection Regulation and within the rules of Dutch legislation.

Outcome

Outcomes of interest were the number of prescribed antihypertensive medications, the defined daily dosage, the type of antihypertensive medication and BP control that were registered between January 1st 2018 and December 31st, 2018. Fixed-dose combination pills were counted as two or three distinct medications (1.6% of the study population used combination pills). The antihypertensive medication was classified according to the ATC codes into: Angiotensin Converting Enzyme (ACE)-inhibitors, Angiotensin Receptor Blockers (ARBs), betablockers, calcium channel blockers, diuretics and other antihypertensives. To assess the dosage of antihypertensive medications prescribed for each individual, we used the defined daily dosage methodology. The defined daily dosage is a statistical measure of drug consumption defined by the WHO Collaborating Centre for Drug Statistics Methodology (13). It is linked to the ATC Code drug classification system for grouping related drugs. The defined daily dosage enables comparison of drug usage between different drugs of the same group, and it was calculated using the following formula for each medication: [dosage * (frequency/day)] / (assumed average maintenance dose per day for the drug given in the literature for each drug). Subsequently, all medication-specific prescribed defined daily dosages were summed to calculate the overall defined daily dosage for each patient.

BP control was assessed using the last recorded office BP measurement from 2018 as documented in the electronic healthcare record. Uncontrolled hypertension was defined as an office systolic BP (SBP) ≥140 mmHg and/or a diastolic BP (DBP) ≥90 mmHg, the average of two measurements, in line with

the Dutch and European guidelines (14, 15). Patients were grouped as either having controlled hypertension (SBP<140 mmHg and DBP<90 mmHg) or uncontrolled hypertension (SBP≥140 mmHg and/or DBP ≥90 mmHg).

Covariates

Covariates considered in our analysis included: cardiovascular risk management (CVRM), history of chronic kidney disease (CKD), dyslipidemia, and current smoking. History of CVRM was based on the presence of the ICPC code for CVRM, indicating that a patient is enrolled in a primary care CVRM program for CVD prevention. CKD encompassed patients with the ICPC code for renal disorder/insufficiency. Dyslipidemia was identified through the ICPC code for lipid disorders or if lipid modifying agents were prescribed. Smoking status was assessed by reviewing the GP's EHR for indications of current smoking. Measurements of height and weight was retrieved from diagnostic files of the HER, and body mass index was calculated as weight (kg) / height $(cm)^2$

Data analysis

Characteristics of the study population were presented as means (standard deviation, SD) for continuous variables and as percentages for categorical variables, for women and men separately. A chi-squared test was performed to assess whether differences between women and men were statistically significant at a two-sided p-value of 0.05. We performed UNIANOVA (Univariate Analysis of Variance) analyses at a 95% confidence interval (CI) and a p-value of 0.05 to account for differences in the distribution between women and men. These analyses were adjusted for age, CVRM history, CKD, dyslipidemia, and smoking status. Analyses were conducted using the Statistical Package for Social Sciences (SPSS), version 26.0 (IBM Corp, Armonk, NY, USA).

Results

Out of the 2018 JGPN population comprising 286,624 people, we identified 14,384 patients (8596 women, 59.8%) with hypertension based on the ICPC code (**Table 1**). Women were older compared to men (65.2 vs 62.7 years, p<0.001), with no significant difference in mean SBP (141.0 vs. 141.7

mmHg, p=0.179). Mean DBP was lower in women compared to men (82.4 vs. 83.6 mmHg, p=0.031). Additionally, women had more often a history of CKD (7.4 vs. 6.5%, p=0.05) and obesity (14.8 vs. 9.8%, p<0.001), while they were less likely to have dyslipidemia than men (23.4 vs. 27.8%, p<0.001) (**Table 1**).

The average number of prescribed antihypertensives for both women and men was 1.8 per day. The distribution of patients receiving one, two, three or four or more prescribed drugs was 44.5%, 36.0%, 16.0% and 3.5% in women, and 41.6%, 37.4%, 16.9% and 4.1% in men. After adjustment for potential confounders, we found no difference between women and men in the number of prescribed antihypertensives [1.8 (95% CI: 1.8-1.8) vs 1.8 (1.8-1.9)].

Overall, the defined daily dosage prescribed in women was significantly lower than in men [1.8 (1.8-1.9) vs 2.1 (2.1-2.2), p<0.001]. This difference persisted across strata of number of prescribed medication (**Figure 1** and **Supplementary Table 3**).

Differences in the types of prescribed antihypertensive medication between women and men were observed (**Figure 2** and **Supplementary Table 4**). **Figure 2** provides the differences based on multivariable analyses. Compared to men, women were less frequently prescribed ACE-inhibitors and calcium channel blockers, equally often ARBs, significantly more often betablockers and diuretics and more often other antihypertensives. These findings remained consistent across strata of the number of prescribed antihypertensive medications (**Supplementary Table 4***)*.

BP control was more often achieved in women than in men [54.5% (52.8-56.2%) vs 49.8% (48.5-51.2%), p<0.001] as shown in **Figure 3** and **Supplementary Table 5**. This observation held true for patients receiving up to three prescribed antihypertensives.

Discussion

Summary

Our study identified sex differences in antihypertensive prescription patterns. While both sexes received nearly two antihypertensives on average, women were prescribed lower dosages and different types of medications. Importantly, BP control was more effectively achieved in women than men, with 50.2% of women compared to 45.5% of men achieving office BP below 140/90 mmHg.

Strengths and limitations

The study's strengths include the use of real-life, unselected patient data, reflecting routine primary care (12) and a large sample size enabling meaningful comparisons. Furthermore, we are among the few studies in the domain of BP in which the dosage of prescribed medication was assessed and compared between women and men. Nonetheless, certain limitations may have affected some of our findings. First of all, BP measurements were not available for all patients with an ICPC coded hypertension in the year of our study (**Table 1**). BP measurements take place three to four times a year in those who take part of the primary care CVRM program, but in others BP is only measured non-systematically or on indication. The availability of the measurements depend on the extractability of the information from the electronic medical records. When a GP does not register the measurements in extrable designated areas in the electronic health care records, the information is not available. Missingness here potentially only affects the analyses on controlled hypertension as these are based on measured levels, not the results on the other outcomes. Given that our findings on controlled hypertension align well with the existing evidence, we assume that missingness did not have a major impact. Additionally, we relied on a single BP measurement per patient for our analyses. While this approach aligns with the most widely used practice in routine clinical care, it may not fully capture variability in BP and could lead to some misclassification.

Another important limitation is the lack of data on medication adherence. While adherence is crucial in determining treatment efficacy (16) and could potentially explain some of the observed differences in blood pressure control between men and women, our study was unable to assess adherence due to the nature of the data available. However, previous studies have indicated that women may be less adherent to chronic medications, including antihypertensives, than men (17, 18). This suggests that the better blood pressure control observed in women in our study is unlikely to be entirely attributable to higher adherence. Nevertheless, this aspect warrants further investigation.

Comparison with Existing Literature

Our findings regarding lower rates of uncontrolled hypertension in women compared to men are consistent with several studies conducted in the past (19-23). A recent evidence from a U.S. study analyzing National Health and Nutrition Examination Survey data revealed a concerning decline in BP control among adults with hypertension, particularly among women (22). Data from 1996-2002 reported that 52% of Dutch women and 68% of men aged 30-59 years had uncontrolled hypertension despite treatment (19). A recent U.S. systematic review revealed declining hypertension treatment rates in men, with an increase in uncontrolled hypertension (23). Contrary to some previous findings, our recent data suggest a stabilization in the prevalence of uncontrolled hypertension, with rates remaining alarmingly high but potentially stabilizing for women while showing a positive trend for men.

Secondly, we observed no significant sex differences in the number of prescribed medications, a finding supported by limited evidence from other studies. Two Swedish studies reported that women used fewer antihypertensive medications than men (24, 25). An older study on U.S. adults found that women used three or more antihypertensives less frequently than men (26). However, these studies included patients with CVD and diabetes, complicating direct comparisons due to varying indications for medication prescription.

Thirdly, we showed that women were prescribed lower defined daily dosage compared to men; a difference that increased with an increasing number of prescribed antihypertensive agents. Better controlled hypertension in women compared to men was achieved by the same number of medications at a lower dosage. This observation finding fuels the discussion on whether treatment guidelines should provide different recommendations in the prescription of type of medication for women and men. Sex-related variations in the renin-angiotensin system and the immune system may contribute to variations in medication efficacy and side effects between sexes (10, 27, 28). Moreover, women have a different pharmacokinetic and pharmacodynamic profile, leading to higher plasma drug concentrations and an increase likelihood of adverse effects (11, 12). Consequently, lower dosage might be appropriate for women, as demonstrated in recent research on sex differences in heart failure treatment, suggesting that women may require lower dosages of ACE-inhibitors, ARBs and betablockers compared to men (29). This approach could potentially mitigate side effects and improve

adherence, as lower doses may better align with physiological differences between sexes, resulting in improved treatment efficacy and fewer adverse effects. On the other hand, this also raises questions about whether men are undertreated or exhibit lower medication adherence, as adherence plays a pivotal role in achieving treatment goals (16). A study analyzing pharmacy and medical claims for nearly 30 million adults in the U.S. found that women had lower adherence to chronic medications compared to men, and were also less likely to receive guideline-based drug therapy for conditions like diabetes and CVD (17). Additionally, a systematic review found lower self-reported adherence to antihypertensive therapy in women aged ≥65 years (18). However, definitive evidence of sex differences in adherence to antihypertensive therapy remains inconclusive, emphasizing the urgent need for high-quality studies investigating these issues, particularly among elderly populations.

Fourth, our study revealed sex related variations in the pattern of type of medication, aligning with some aspects of previous research (19-21). For instance, we observed that women were less likely to be prescribed ACE-inhibitors and more likely to receive diuretics, consistent with findings from a recent meta-analysis (30). However, we also observed a higher prescription rate of beta-blockers in women compared to men, whereas the same meta-analysis reported no sex differences in beta-blocker prescriptions (30). This discrepancy may be due to differences in the populations studied; specifically, we excluded patients with a history of coronary artery disease or heart failure, conditions more common in men and often treated with beta-blockers. Differences in healthcare settings and reimbursement policies across countries may also have influenced these results. Such variations in prescribing practices highlight the importance of considering context when interpreting these findings.

Finally, although guidelines suggest that the efficacy of lowering BP is similar among all medication types (11), certain combinations may possess higher efficacy and a more favorable side effect profile. For instance, some studies, reported that ACE-inhibitors showed the best BP control rates in men, whereas diuretics were most effective in lowering BP in women (31). On the other hand, a higher incidence of adverse effects, predominantly dry cough was reported with ACE-inhibitors in women compared to men (24). Unfortunately, our analysis lacked systematically reported information on side effects from JGPN database.

Implications for research and practice

The current study underscores various sex related disparities in the pharmacological treatment of hypertension within Dutch primary care, particularly at the point when the GP has already initiated antihypertensive medication. These aspects are not addressed in the current CVRM including hypertension management. Our findings emphasize the need for greater awareness and further research into aspects such as side effects, adherence, dosage, control frequency in this domain. A major implication is that healthcare providers should recognize that women, on average, may need a lower dose of antihypertensive medication than men. This is important when aiming at achieving a controlled BP while minimazing side effects.

Conclusion

Our study showed disparities in the prescription patterns of antihypertensive medication between women and men. Women and men received, on average the same number of antihypertensives, but differed in the types of drugs prescribed and in the defined daily dosage. Women in our study exhibited better BP control compared to men; however, this observation warrants cautious interpretation given the lack of adherence data and other potential confounders. These findings call for further research and consideration in treatment guidelines to optimize hypertension management while accounting for sex-related differences.

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Ethical approval: The JGPN is subject to Dutch privacy law, which states that the use of medical data for scientific research is allowed provided that patients are adequately informed beforehand allowing them an opt out option. As a consequence, all GPs participating in JGPN inform their patients about the anonymous use of their medical records for research purposes. Patients may opt out, and their routine care data will not be used for the JGPN database (opt-out regulation). The law on medical research (WMO) states that medical research on patients requires individual consent if an intervention takes place. Research in JGPN is observational and enlisted patients are not individually approached

for participation. Therefore, the Medical Ethics Committees in the Netherlands do not rank such research as subject to the WMO conditions.

Competing interests: the authors have no competing interests to declare.

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Figure Legends

Figure 1. Sex differences in the defined daily dosage of prescribed antihypertensives, overall and in relation to the number of prescribed antihypertensives, based on multivariable analyses. The range of defined daily dosage indicates the 95% CI, and the asterisk indicates a significant difference between women and men (*=statistically significant at a p-value of 0.05, **=statistically significant at a p-value of <0.001)

Figure 2. Sex differences in the type of prescribed antihypertensives based on multivariable analyses.

Figure 3. Sex differences in blood pressure control overall, and in the number of prescribed antihypertensives, based on multivariable analyses. The range of percentages represents the 95% confidence interval, and the asterisk indicates a significant difference between women and men (*=statistically significant at a p-value of 0.05, **=statistically significant at a p-value of <0.001).

Tables

Table 1*:* Study population characteristics of women and men affected by hypertension, free from CVD and diabetes mellitus

	Women (N=8,596)	Men (N=5,788)	P-value
Age (years)	65.2 (13.0)	62.7 (12.1)	<0.001
BMI (kg/m^2)*	28.7 (6.4)	28.0 (4.3)	<0.001
SBP (mmHg)**	141.0 (16.9)	141.7 (15.8)	0.179
DBP (mmHg)**	82.4 (10.2)	83.6 (10.4)	0.031
History of CKD	633 (7.4%)	377 (6.5%)	0.050
History of dyslipidemia	2012 (23.4%)	1608 (27.8%)	<0.001
History of obesity	1272 (14.8%)	567 (9.8%)	<0.001
History of CVRM	2343 (27.3%)	1621 (28.0%)	0.324
Current smoking	1045 (12.2%)	746 (12.9%)	0.192

ean (SD) or as count (%).

Abbreviations: SD = standard deviation; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; CKD = chronic kidney disease; CVRM = cardiovascular risk management.
* Weight and height measurements, or BMI, were not available for all patients, therefore N total=4,478 patients, N women=2,696, N men=1,782
** Blood pressure measurements were not available for all patients, therefore N total=8,385 patients, N women=5,115, N men=3,270. The SBP and DBP indicate the last available BP measurements from 2018 for each patient.

Figures

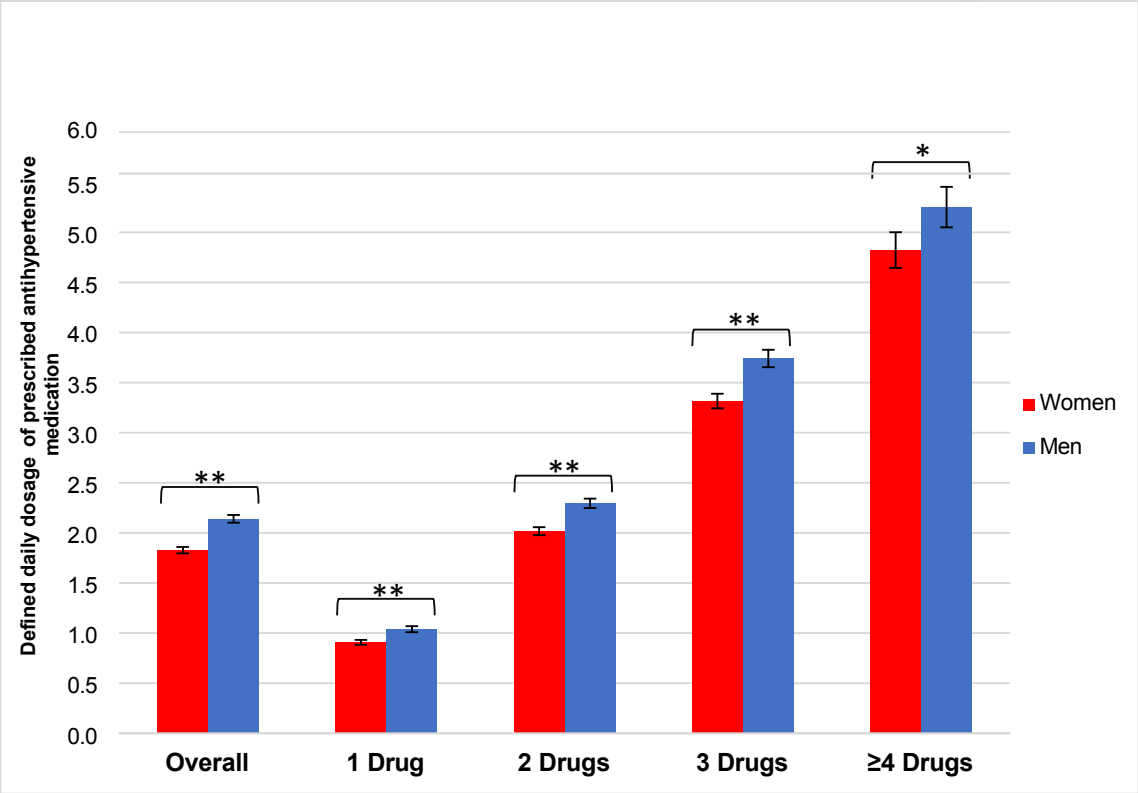

Figure 1*:* Sex differences in the defined daily dosage of prescribed antihypertensives, overall and in relation to the number of prescribed antihypertensives, based on multivariable analyses. The range of defined daily dosage indicates the 95% CI, and the asterisk indicates a significant difference between women and men (*=statistically significant at a p-value of 0.05, **=statistically significant at a p-value of <0.001)

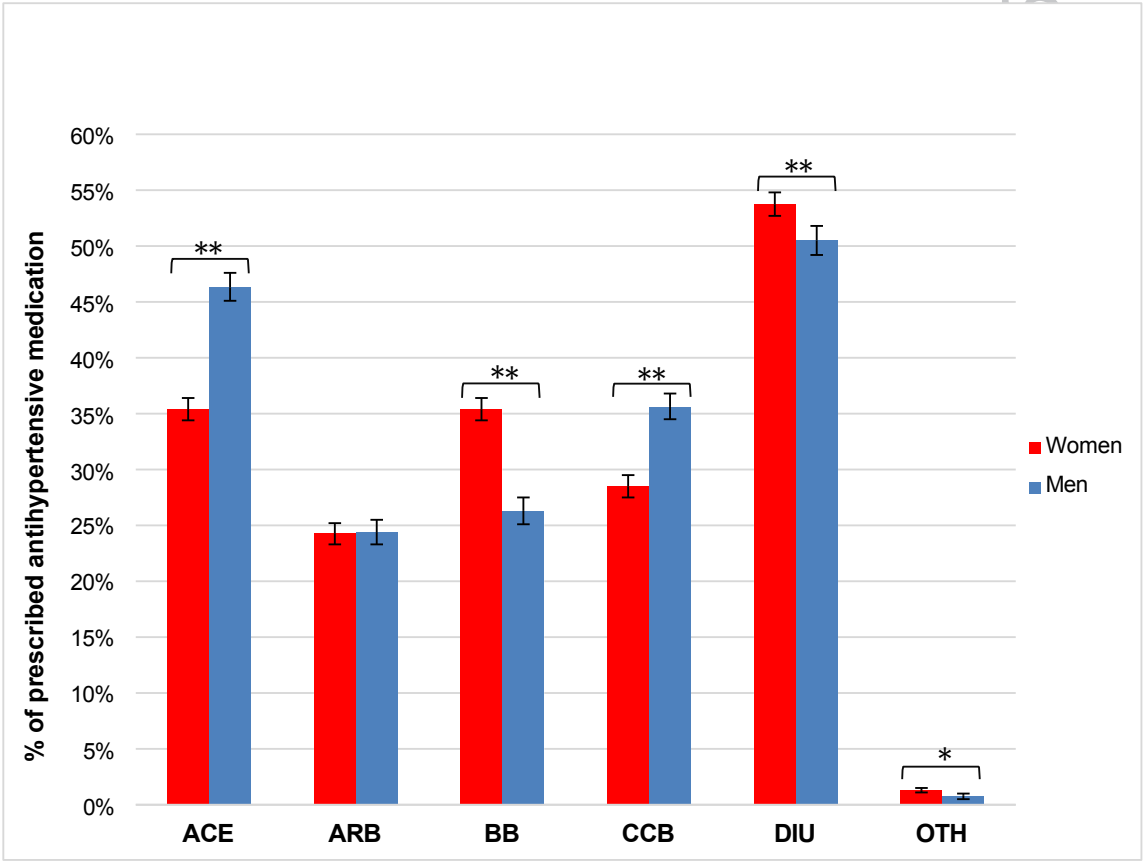

Figure 2: Sex differences in the type of prescribed antihypertensives based on multivariable analyses. Abbreviations: ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = betablocker; CCB = calcium channel blocker; DIU = diuretic; OTH = other antihypertensive. The range of percentages represents the 95% confidence interval, and the asterisk indicates a significant difference between women and men (*=statistically significant at a p-value of 0.05, **=statistically significant at a p-value of <0.001).

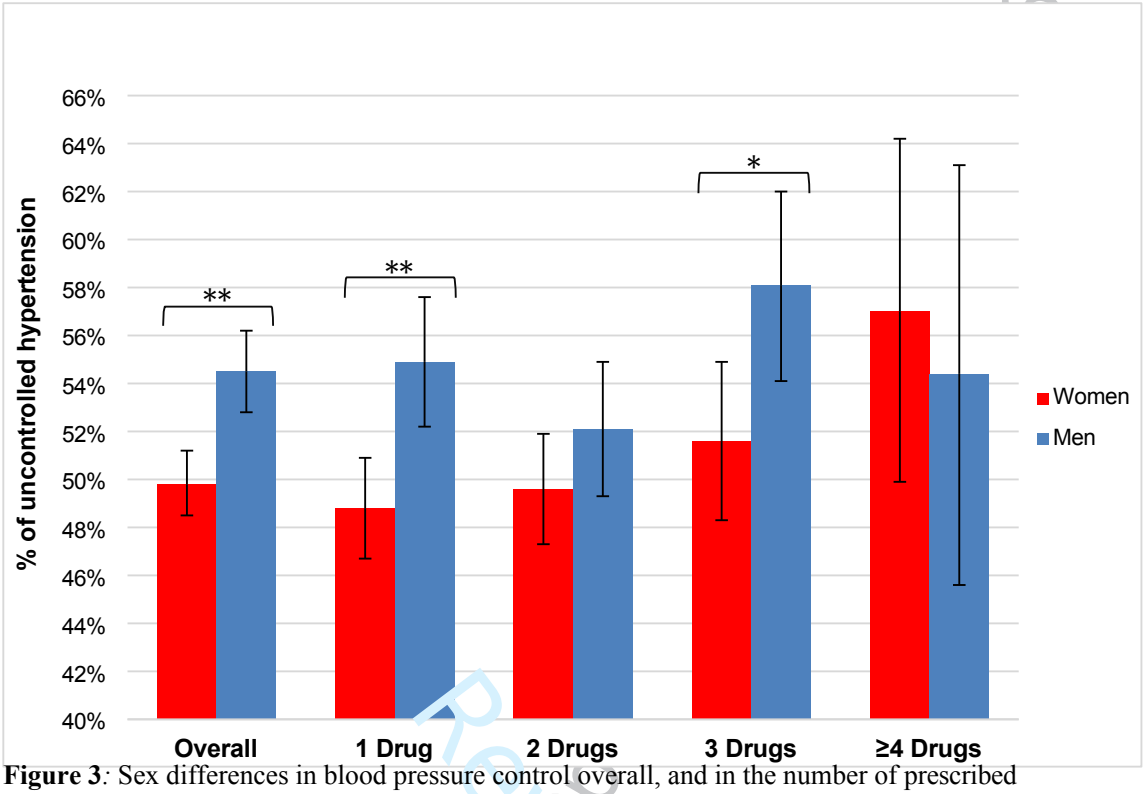

Figure 3: Sex differences in blood pressure control overall, and in the number of prescribed antihypertensives, based on multivariable analyses. The range of percentages represents the 95% confidence interval, and the asterisk indicates a significant difference between women and men (*=statistically significant at a p-value of 0.05, **=statistically significant at a p-value of <0.001).