

Sex Differences in the Use of Cardiovascular Drugs: A Survey of Patients in a Single Center

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Abstract

Objective. Patients and medical professionals have a common misconception that cardiovascular diseases (CVD) predominantly affect men, which can lead to less prescribing of cardiovascular drugs to women. This study examined whether there were sex differences in the administration of cardiovascular (CV) drugs in patients admitted to the intensive care unit of the Internal Medicine Clinic of Foča University Hospital (ICFUH). **Materials and Methods.** The study comprised 332 patients hospitalized at the ICFUH from January 1st to June 30th, 2019. The following data on leading CVD and risks related to CV drug administration were collected: age, hyperlipidemia (HLD), diabetes mellitus (DM), chronic kidney disease (CKD), liver disease (LD), heart failure (HF), hypertension (HTN), myocardial infarction (MI), and stroke (S). The amount of the CV drugs of interest (statins, antiplatelet drugs, calcium channel blockers, ACE inhibitors, beta blockers, diuretics) administered during hospitalization was expressed as the Defined Daily Dose (DDD)/100 bed-days (BD) for patients of both sexes separately. **Results.** During hospitalization in the intensive care unit of ICFUH, female patients were less likely to be treated with statins than male patients (30.1 vs. 57.5 DDD/100 BD, $P < 0.05$). There was no difference between sexes regarding the use of antihypertensive drugs. Women were less likely to be treated by antiplatelet therapy, more precisely by acetylsalicylic acid (30.4 vs. 36.9 DDD/100 BD, $P < 0.05$). **Conclusion.** Our study indicates that there were sex differences in CV drug administration in ICFUH. Presuming that drugs used during hospitalization were at least partially a continuation of the previous therapy prescribed by the family doctor, it is possible that such differences exist in primary care.

Key Words: Sex Differences ■ Cardiovascular Diseases ■ Cardiovascular Drugs ■ Statins.

Introduction

The leading cause of death worldwide, as well as in Bosnia and Herzegovina (B&H), is cardiovascular disease (CVD). Globally, it is estimated that about one third of deaths in both men and women are caused by CVD (1). In 2018, CVD caused 51.5% and 47.2% of overall deaths in the Federation of Bosnia and Herzegovina (FB&H) and the Republika Srpska (RS), respectively (2, 3). In FB&H in 2019, 4 of the 5 leading causes of death in both sexes were forms of CVD. Mortality rates from CVD were similar, but even higher in the female population: 325.3 deaths in women and 319.0 deaths

in men per 100,000 (2). In the same period in the RS, it was found that 12% more women than men died of CVD (3). However, patients and medical professionals have a common misconception that CVD predominantly affects men, which can lead to suboptimal management and treatment of CVD in women (1). There are studies about sex differences in medical treatment of CVD that point out that women with CVD may receive less aggressive care than men (4, 5). Most studies come from high-income countries, most of all from the United Kingdom and the United States of America. Economic status definitely is not the only factor, but together with societal and physiological

factors it can significantly lead to sex differences in the use of cardiovascular (CV) medications. B&H is a middle-income country which indicates possible differences in this field compared to well-developed countries. Greater sex polarization in terms of economic status is expected in countries with lower GDP than in high-income countries. Furthermore, citizens of B&H may have poorer access to medicines compared to countries with a higher GDP (6). We do not have any data on whether sex differences in the administration of CV medications exist in our country. The aim of this study was to examine whether there were sex differences in the administration of the most commonly used groups of cardiovascular medication in patients hospitalized in the intensive care unit of the Internal Medicine Clinic of Foča University Hospital (ICFUH).

Material and Methods

A descriptive cross-sectional drug use study was performed using the administrative health-related databases of the Intensive Care Unit of ICFUH from January 1st to June 30th, 2019. The hospital databases were used to extract data of interest on the medical condition of patients and the drugs administered. All data were taken using a coding system to prevent patient identification during the further process of analysis. Patients with decompensated cirrhosis and patients with stage 5 chronic kidney disease (eGFR <15 mL/min/1.73 m² or dialysis) were previously excluded from the study, as well as patients with acute kidney injury.

Comparison of the Patients' Basic Characteristics between Sexes

The following data on the presence of leading CVD and risks with a strong influence on therapy for CVD were observed for each patient: age, hyperlipidemia (HLD), diabetes mellitus (DM), chronic kidney disease (CKD), liver disease (LD), heart failure (HF), hypertension (HTN), myocardial infarction (MI), and stroke (S). All data were expressed as the percentage of affected patients in

the overall number, for both sexes and for each of the six months analyzed. Patients with HLD, CKD, LD and HF were divided into subgroups on the basis of the stage of their condition, but there were not enough data for statistical analysis. Due to the lack of data in the documentation, it was not possible to calculate the total cardiovascular risk for most patients.

Comparison of Drug Administration to Different Sexes

Data on administration of several classes of CV medication during hospitalization, in terms of drug type, dosage, dosing interval, and duration of administration, were extracted for each patient. The classes of drugs of interest were statins, antiplatelet drugs, calcium channel blockers (CCB), ACE-inhibitors (ACEI), beta blockers (BB) and diuretics. Drug administration (consumption) was expressed as the number of DDD/100 BD (defined daily dose per 100 bed days), and as the percentage of patients treated with each medication group. DDD/100 BD represents the standardized unit for measuring drug consumption for inpatients, allowing comparisons across various time periods and patient groups. DDD is the average maintenance daily dose per its main indication in adults, defined by the World Health Organization. A "bed day" is a day during which a patient stays overnight in a hospital. Patients admitted to the hospital in the morning and released before the night were excluded from the study (7).

Statistical Analysis

All results are given as the mean \pm SD or mean (95% CI). The patient's observed characteristics were compared between men and women by calculating the odds ratio (with female gender used as the reference category). The comparisons between the quantity of drugs administered to women and men were performed using the Wilcoxon rank-sum test. A 2-sided $P < 0.05$ was considered statistically significant. All data analyses were conducted using the SPSS statistical software (version 15 for Windows).

Results

The study included 332 patients hospitalized in the intensive care unit of ICFUH from January 1st to June 30th, 2019. 59.9% of them were men (N=199) and 40.1 were women (N=133). The women were older (67.1±34.3) than the men (63.6±33.1), but the difference was not statistically significant. All patients were stratified into three groups in terms of age as follows: not old (<65), old (65-84) and very old (≥85). We only found sex differences in the group of very old people, where there were more women than men (Figure 1). There was no difference in duration of hospitalization between women and men (5.01±0.85 days for men vs. 4.95±0.74) days for women. Since reliable data on the presence/absence of atherosclerotic cardiovascular disease (ASCVD) were not available for most patients, it was necessary to limit the analysis of ASCVD to MI and S. Both sexes had similar rates of HLD, DM, CKD, LD, HF, HTN, and S, but men were more likely to suffer from MI (Figure 2). Regarding HLD, CKD and LD, the lack of relevant data made it impossible to classify most patients into groups according to the severity of their condition. Regarding HF, it was found that, out of 89 male patients with confirmed HF, 9 of them were in stage C/D. In female patients, we found a very

similar frequency of the most severe stage of HF. Of the 61 female patients who were suffering from HF, there were 7 with stage C/D of the disease.

Comparison of Drug Consumption

The percentage of patients treated was determined for each type of medication studied. 28.6% of men were treated by statins, in relation to 20.3% of women, but the difference was not statistically significant. However, when comparing the consumption of statins expressed as DDD/100 BD, we found that these drugs were administered to men to a higher extent than to women (Table 1). We found no difference between men and women regarding consumption of antihypertensive drugs (diuretics, ACEI, BB and CCB). However, we found that women were less likely to be treated by antiplatelet therapy, more precisely by acetylsalicylic acid (ASA), while there was no difference regarding the frequency and quantity of use of ADP antagonist drugs (Table 1).

We further analyzed statin therapy in order to learn if it was carried out in accordance with the current guidelines for statin prevention of cardiovascular diseases, and therapy (8-10). All male patients with hypercholesterolemia and/or established ASCVD were on high intensity statin therapy. On the other hand, we found 7 women with ACSVD and unregulated blood cholesterol levels who were on medium intensity statin therapy, although we could not find a reason for the lower dose. We also found that 7 women with hyperlipidemia were not treated by statins nor any other type of antilipemic medication. Statins were prescribed for primary prevention of CVD in at least 10 men and only 2 women.

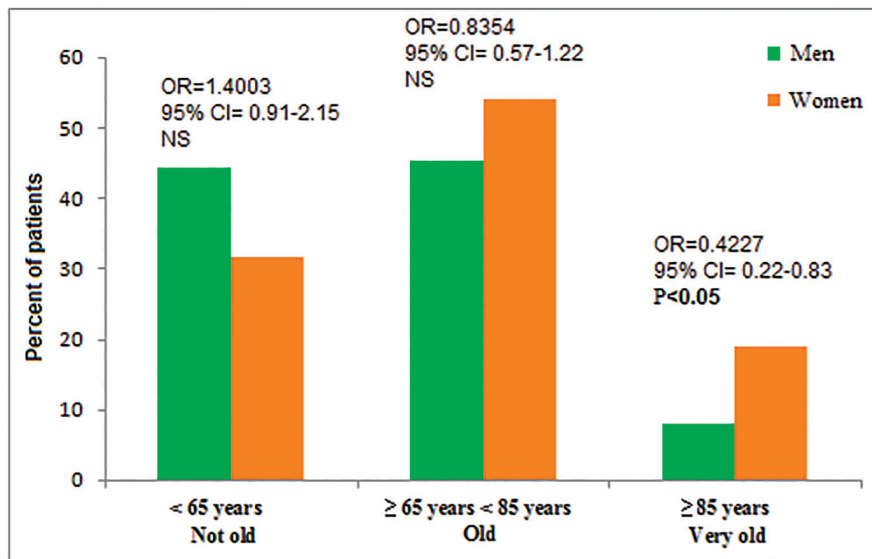


Figure 1. Sex distribution in three age groups of patients.

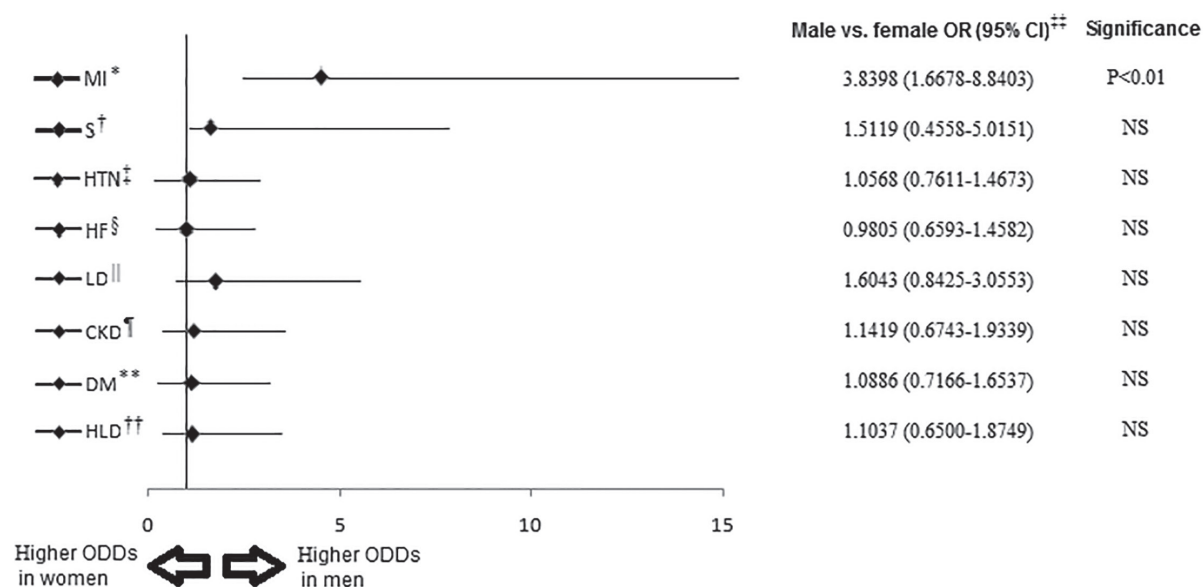


Figure 2. Sex differences in the frequency of medical conditions with a strong influence on the administration of cardiovascular medications. *Myocardial infarction; †Stroke; ‡Hypertension; §Heart failure; ||Liver disease; ¶Chronic kidney disease; **Diabetes mellitus; ††Hyperlipidemia; ‡‡Odds ratio for the prevalence of medical conditions in male and female sex (female sex used as referent category) CI Confidence interval

Table 1. Sex Differences in the Consumption of Cardiovascular Medication

| Drug class | Women DDD/100BD* Mean (95% CI) | Men DDD/100BD* Mean (95% CI) | Significance |
|--------------------|--------------------------------------|------------------------------------|--------------|
| Statins | 30.1 (2.8-80.0) | 57.5 (13.4-85.9) | P<0.05 |
| Diuretics | 85.5 (55.2-118.3) | 89.4 (50.9-136.0) | NS |
| ACE I [†] | 74.3 (38.3-114.4) | 91.5 (61.1-129.1) | NS |
| BB [‡] | 16.2 (8.4-21.7) | 20.0 (11.9-28.3) | NS |
| CCB [§] | 44.6 (19.0-93.4) | 40.5 (8.4-62.9) | NS |
| ASA | 30.4 (21.3-54.5) | 36.9 (35.1-103.9) | P<0.05 |
| CLOP [¶] | 24.6 (15.5-50.2) | 24.4 (19.7-65.2) | NS |

*Defined Daily Doses per 100 Bed Days; †ACE inhibitors; ‡Beta blockers, §Calcium channel blockers, ||Acetylsalicylic acid, ¶Clopidogrel.

Discussion

During hospitalization in the intensive care unit of ICFUH, female patients were less likely to be treated by statins and ASA than male patients. CVD is the leading cause of death of women worldwide. Only in underdeveloped countries is CVD not in first place, because of the large number of deaths from neonatal and infective diseases, such as respiratory infections, diarrhea and malaria (5).

According to the Institute for Public Health of FB&H and the Institute of Statistics of the RS, the

leading cause of death in women in B&H in 2019 were diseases of the circulatory system. In our study, the incidence of leading CVD other than MI was the same for both sexes. Taking into account the average age of our patients, this result is expected and in accordance with data from B&H and other high- and middle-income countries (2, 3, 5). However, patients and medical professional share the common opinion that CVD is mostly found in male patients. This is based on the fact that men generally suffer from CVD at a younger age than women, but it is obvious that women are not im-

immune to CVD, and this problem must be taken seriously. We should be worried because there is evidence that women receive less treatment than men. This may be one of the reasons why women have worse outcomes and higher mortality from CVD than men. On the other hand, the recommendations for prevention and therapy for CVD do not differ for men and women in the latest clinical guidelines (8).

Globally, it is recognized that more medications are given to women than to men, but also the therapy given to women is more often not in accordance with the current therapeutic guidelines than therapy given to men (11, 12). In terms of the adult population of the United States, it has been proven that it is less probable that women will receive guideline-recommended statin therapy (13). It has been found that women more commonly refuse and discontinue statins, but also statins are less often offered to women (14, 15). The situation in Foča University Hospital seems to be similar regarding sex differences in statin use. Beside patients from Foča, patients from the entire eastern part of the RS gravitate to Foča University Hospital. This means that the same pattern can be expected throughout RS or at least its eastern part. The percentage of FB&H patients treated in this hospital is too small to be representative. Although in this study there was no difference in the percentage of patients treated with statins, the DDD/100 BD was higher in men, suggesting that women receive less aggressive statin therapy. In other words, men are more likely to be on intensive statin therapy than women. In the further step, it was shown that all men with conditions indicating high intensity statin were treated in accordance with the recommendations. In contrast, some women with an indication for high-intensity statins were treated by medium intensity statin therapy, and some women with hyperlipidemia were not even treated with statins, nor any other form of antilipemic medication. Statins were prescribed more often in men than in women for primary prevention of CVD, but this finding should be taken with caution, because we were not able to find enough data to evaluate total cardiovascular risk in most of our patients.

In addition, according to the percentage of our patients treated by statins, we could assume that statins were not prescribed to the recommended extent according to the current recommendations (8-10, 16). Although most authors studied sex differences in the primary prevention of CVD, there are findings about sex differences in pharmacotherapy in survivors of acute MI, one year after acute MI. It was shown that women under the age of 55 years were less likely to be on optimal therapy by the end of 1 year after discharge (17).

Statins are the most commonly used antilipemic drugs. They can be prescribed for both primary and secondary prevention of CVD. Statin use in inpatients was the continuation of previous therapy in around two-thirds of patients. Less than a third of patients were statin-naïve. In addition, once statin therapy has been initiated in the hospital setting it should be continued after the patient is discharged, if there are no limiting factors. This implies that sex differences in statin use could exist in primary care, and not only in secondary and tertiary care, and that a large number of female patients may be potentially undertreated by statins.

Several studies reviewed differences in prescription of, but also in the pharmacology and pharmacokinetics of the main classes of antihypertensive drugs (18, 19). It was noticed that ACEI, and BB were more often prescribed to men, but in contrast, women were more likely to receive diuretics and CCB (18). The reasons for less prescription of ACEI and ARB in women are found in the fact that young women are at risk of pregnancy (18). Women older than 65 years used 33% more antihypertensive drugs than men of the same age, although women adhered more closely to the prescribed therapy (19). Although our study did not find any differences in the use of antihypertensive drugs, it is not possible to conclude that no differences exist in the entire population. The fact that inpatients are regularly monitored for blood pressure does not leave the possibility of unrecognized hypertension. In addition, the small number of patients may be the reason for not noticing sex differences in the use of antihypertensive drugs.

There are some findings showing that women are less likely to receive ASA and ACE I than men (1, 10). This partly agrees with our findings, because we also noticed less ASA was given to women, but both genders have the same probability of being treated with ACEI. According to our findings, there was no difference in the administration of other antihypertensive drugs between women and men. The sex difference in ASA administration may be based on the fact that ASA is no longer recommended for primary prevention of CVD at all (8), or in people older than 70 years (16). Furthermore, female patients had less chance of being evaluated concerning total CV risk.

In addition to the differences in therapy administered, it is possible that there are some gender differences in adherence to medication regimens (20). Also, the fact that women have a higher risk of experiencing adverse drug reactions than men may contribute to the worse therapeutic management of female patients (21). The reasons for sex differences in CV drug consumption could be at least partly based on the fact that women are more likely to experience some adverse reactions to CV drugs, especially to statins and ASA.

Limitations of the Study

The main limitation of this study is the relatively small number of patients observed. Also, because of the retrospective study design, it was not always possible to determine the reasons for prescribing/not prescribing cardiovascular medication.

Conclusion

Our study indicates that there are sex differences in cardiovascular medication administration in tertiary care. It probably also suggests that such differences persist throughout the primary care of the entire population, because the therapy administered to hospitalized patients to some extent reflects the chronic therapy prescribed by family doctors in primary care. CVD is definitely the most frequent cause of death of women in B&H, but its importance in women is possibly underestimated.

What Is Already Known on This Topic:

Current recommendations for the prevention and therapy of CVD do not recognize sex differences. There is evidence from several countries that women may be treated less well than men, although the prevalence of CVD in both sexes is similar. This problem has not been studied so far in our country or the region.

What This Study Adds:

This study provides insight, for the first time to our knowledge, into the existence of sex differences in the administration of cardiovascular drugs in a hospital in Bosnia and Herzegovina. This study revealed the need to conduct population research on this topic.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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