INVESTIGATING SEX DIFFERENCES IN ADVERSE EVENTS OF CARDIOVASCULAR MEDICATIONS

Riikka Holtari

4976010

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With thanks to supervisors:

Professor Dr Olaf Klungel, PhD

Assistant Professor Dr Sophie Bots, PhD

LAYMAN'S SUMMARY

In this literature review, we researched differences in side effects experienced by men and women in response to cardiovascular drugs. First, we conducted a rigorous search for scientific articles, prioritising the most recent ones to ensure the findings were up-to-date. We examined studies investigating sex-based differences in how heart medications impacted patients, particularly concerning Adverse Events (AEs). To achieve this, they explored various proxies, such as effectiveness, actual AEs, and treatment changes, since comprehensive side effect data was often lacking.

The main finding of our study was that women tend to experience side effects more frequently than men. However, it is challenging for researchers to establish this link definitively due to variations in data quality. Nonetheless, the valuable insights from this research will contribute significantly to future investigations focusing on sex differences in medication side effects.

Effectiveness, including factors like mortality and hospitalisation, emerged as valuable proxies to study AEs when comprehensive side effect data is unavailable. This approach allowed researchers to gain valuable information on side effect incidence, even with limited data quality. Additionally, some studies explored predictors for AEs, focusing on medication effectiveness (e.g., reaching target blood pressure measurements). These studies emphasised the importance of considering sex differences when identifying medication side effects, as we found evident sex disparities in AEs related to cardiovascular drugs. The review also investigated spontaneous reporting, different drug classes, physiological predictors, and others, and this method provided essential insights into the incidence of side effects, especially for women and men who may experience different AEs from cardiovascular medications.

In conclusion, this literature review has provided valuable insights into medication side effects related to cardiovascular health. We explored strategies and proxies to uncover crucial information on how AEs may differ between men and women. While data quality remains a challenge, this study's findings contribute significantly to future research efforts to understand and develop personalised treatment plans for both men and women. By acknowledging and addressing sex-based differences in medication side effects, we can take significant steps toward enhancing patient care and safety, ultimately improving health outcomes for all.

Words: 344

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CHAPTER 1

Introduction

Cardiovascular disease remains one of the foremost causes of mortality and morbidity globally (Rosano et al., 2015). The treatment for this disease, or a group of diseases, includes medications such as Angiotensin-converting enzyme (ACE) inhibitors, β blockers, calcium channel blockers, and digoxin. Despite their proven effectiveness, our understanding of their side effects is incomplete, with reported adverse events (AEs) showing variation between the sexes (Tamargo et al., 2017). We believe that this gap in understanding may stem from research on AEs primarily focusing on those reported in men, with less attention given to women's experiences with cardiovascular drugs (Soldin and Mattison, 2020).

Subsequently, understanding these sex-based differences will have significant implications for public health. Despite growing awareness of the disparity, current therapeutic strategies have yet to integrate this knowledge into their approaches fully (Tamargo et al., 2017). This has resulted in a scarcity of pharmacological guidelines that can effectively minimise the incidence of sex-specific side effects and adverse drug reactions (ADRs).

This literature review aims to describe current knowledge on identifying cardiovascular drug side effects using observational data, focusing on sex-based differences. We will conduct a literature review and assess the quality and relevance of the studies we include in our review. We will explore the utilisation of proxies such as effectiveness, actual ADRs and treatment changes in assessing AEs that may not always be reported in traditional data collection methods.

This study will serve as a step towards creating a greater understanding of these sex-based differences, with the ultimate goal of an improved, individualised and effective treatment strategy for cardiovascular disease. A better understanding of sex-based differences in cardiovascular drug side effects can improve patient outcomes and public health.

Methods

Our literature review aims to examine the sex differences in AEs of cardiovascular drugs. We implemented a comprehensive and rigorous search strategy to locate relevant scientific articles to achieve this. We adopted a multi-pronged approach to ensure an exhaustive exploration of the subject matter.

Search Strategy

The search strategy designed to answer the research question is as follows: Do sex differences influence the adverse events associated with cardiovascular drugs? We used the PubMed database for this investigation due to its extensive collection of scientific literature, with a priority on the most recent papers. After analysing frequent MeSH terms and search terms, we finalised a search query which yielded 1,674 results:

(("Cardiovascular Agents" [MeSH]) AND ((Male[tiab] OR man[tiab] OR men[tiab]) OR (Female[tiab] OR wom*n [tiab])) AND ("Adverse Reaction" OR "Adverse Event*" OR "Side effect*"))

Inclusion and Exclusion Criteria

For this literature review, we included articles that examined three crucial elements of our study: sex differences, cardiovascular drugs, and AEs. We sought proxies for ADRs, which we categorised into types: effectiveness (e.g., mortality, hospitalisation), actual ADRs, and treatment changes (e.g., medication switches, dosage changes). We excluded studies on animals, those not in English, and those published before 1 January 2000.

Data Extraction

We extracted data using an Excel spreadsheet, with emphasis on extracting the study design, the source population, the proportion of women included in the study, the medications studied, the comparator group, the proxy type, and any measures of strength reported.

Results

In this study, we began with an initial set of 9 papers found through connectedpapers.com from the starting paper by Hudson, 2007. These papers were used to construct the first version of the search term, which was then improved through several rounds of searching and author review. We then conducted a search query on PubMed, which yielded 1,674 results. We screened the first 300 papers by abstract and title, and after removing two duplicates, this resulted in 65 papers. These papers were then checked for full eligibility criteria, leaving us with a final set of 19 papers for our analysis.

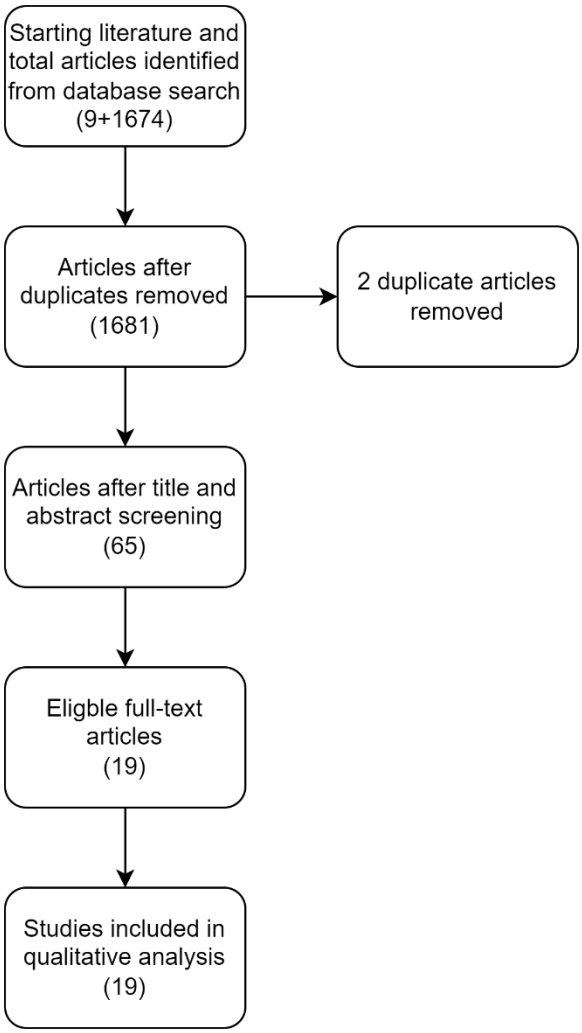

Figure 1: Flowchart to depict data extraction

Authors	Year	Type of Scientific Paper	Outcome
Drici and Clement	2001	Review article	ADRs
Hallberg et al.	2017	Comparative Study	ADRs
Hudson et al.	2007	Cohort Population Study	Effectiveness
Karavitakis et al.	2011	Review article	Treatment Changes
Karny-Rahkovich et al.	2015	Observational Study	Treatment Changes
Lilli et al.	2007	Cohort study	Effectiveness
Ljungman et al.	2015	Cross-sectional study	ADRs
Meyers et al.	2002	Observational Study	ADRs
Mitchell and Philipp	2007	Review Article	Effectiveness
Oertelt-Prigione and Regitz-Zagrosek	2009	Review article	Effectiveness
Park et al.	2021	Observational Study	ADRs
Pedone et al.	2005	Observational Study	ADRs
Rodenburg et al.	2012	Observational Ecological Study	ADRs
Rydberg et al.	2018	Observational Cross-sectional Study	ADRs
Santema et al.	2019	Prospective Observational Cohort Study	Effectiveness
Schwartz	2003	Review Article	Effectiveness
Taira et al.	2010	Review Article	ADRs
Taler	2009	Review Article	Effectiveness
Zucker and Prendergast	2020	Review Article	Effectiveness

Table 1: Table showing the study type of each selected paper.

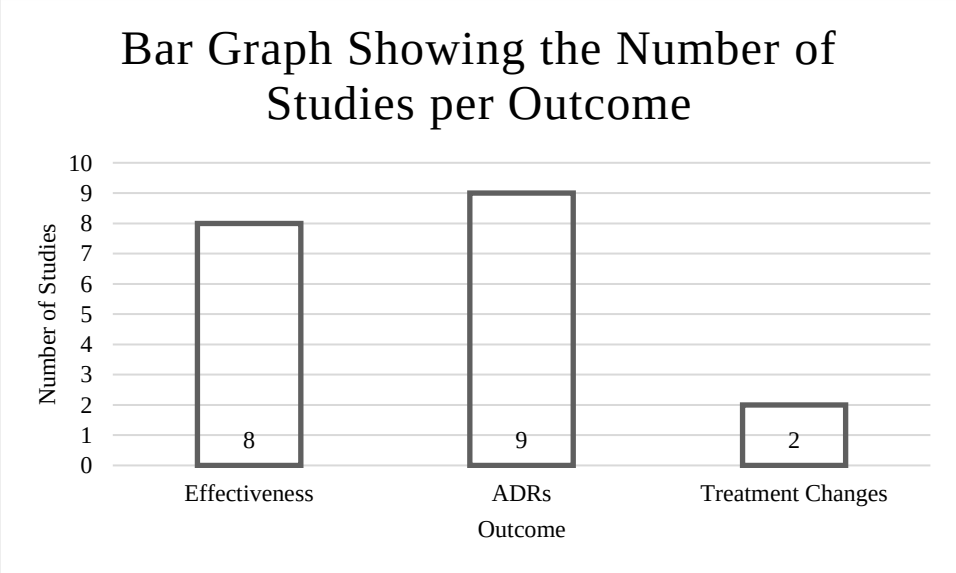

Figure 2: Bar Graph Showing the Number of Studies per Outcome using the following proxies: effectiveness, Actual Adverse Events (ADRs), and Treatment Changes

Pharmacological Differences

Oertelt-Prigione and Regitz-Zagrosek (2009) discussed gender aspects in cardiovascular pharmacology, describing the influence of biological sex on pharmacokinetics and pharmacodynamics. They report that men and women display differences in drug distribution, metabolism, and excretion for several biological reasons. The article also mentions sex differences in the incidence of ADRs and pharmacotoxicity for several classes of drugs. Despite increased knowledge, this has not translated into developing and implementing gender-specific pharmacological guidelines to minimise the incidence of sex-specific side effects and ADRs. The article recommends measures to analyse and possibly improve current therapeutic strategies.

Similarly, Zucker's and Prendergast's paper (2020) discusses sex differences in ADRs specifically. The article mentions that women experience ADRs almost twice as frequently as men, yet the role of sex as a biological predictor in the incidence of ADRs is poorly understood. Most drugs currently used were approved based on clinical trials conducted on predominantly male study populations, suggesting that the effect and efficiency in women are not as well established. The study concludes that sex-specific dosing guidelines, coupled with a broader understanding of sex differences in drug effects among healthcare providers, could potentially reduce the gender disparity in ADRs.

Unsurprisingly, these findings have been reported in earlier studies: Schwartz et al. (2003) report that sex should be considered when selecting and dosing cardiovascular medications. Their review revealed growing evidence of clinically significant differences between men and women in the pharmacokinetic processes determining drug concentrations and the pharmacodynamic processes determining physiological responses to drugs.

They also report that women have lower weight and distribution volumes than men and lower renal drug clearance on average. Sex-related differences in hepatic drug clearance are less predictable. In terms of pharmacodynamic responses, women experience increased actual adverse cardiovascular drug effects compared to men, including torsade de pointes arrhythmias, increased risk of haemorrhagic consequences of anticoagulation or thrombolytic therapy, electrolyte abnormalities with diuretics, myopathy with HMG Co-A reductase inhibitors, cough with ACE inhibitors, and increased incidence of thrombosis.

To optimise cardiovascular drug therapy for women, Schwartz et al. recommend individualising drug selection to minimise the number of medications and side effects, adjusting dosage based on age, size, and sex, closely monitoring for side effects, and considering cost and access to medications.

Sex Differences for Optimal Treatment

In a population-based cohort study, Hudson et al. (2007) explored the differences in the effectiveness of ACE inhibitors and Angiotensin receptor blockers (ARBs) between men and women with congestive heart failure (CHF). The results showed that women treated with ARBs had better survival outcomes than those treated with ACE inhibitors, while no significant difference was observed in men. This suggests that there may be sex differences in the optimal treatment of CHF with these medications.

In another study, Lilli et al. (2007) examined the influence of sex on patients treated with cardiac resynchronisation therapy (CRT). The study included 334 consecutive heart failure (HF) patients, 19.7% women. Of these patients, 195 reached clinical and echocardiographic evaluation at 6 and 12 months. The results showed that compared to men, women had more significant changes in left ventricular (LV) volumes at mid and long-term follow-up and a higher LV ejection fraction. Multiple regression analysis revealed that being female was independently associated with a greater reduction in LV end-systolic volume/m(2). At the 12-month follow-up, the majority of responders were women.

Santema et al. (2019) also conducted a post hoc analysis of the BIOSTAT-CHF study to investigate sex differences in the optimal dose of ACE inhibitors, ARBs, and β blockers in heart failure patients with reduced ejection fraction. The study addressed that older women and women with lower body weights and heights than men may respond differently to identical dosages even when their body-mass indexes were not significantly different. Comparable numbers of men and women reached guideline-recommended target doses of ACE inhibitors or ARBs and β blockers: in men, the lowest hazards ratios for hospitalisation and death due to heart failure occurred at 100% of the recommended dosage of ACE inhibitors or ARBs and β blockers. However, women demonstrated an approximately 30% lower risk at only 50% of the recommended dosages.

Age, Sex and Blood Pressure

According to a report in Germany by Mitchell and Philipp (2007), cardiovascular causes account for more deaths among women than men, with women making up more than two-thirds of patients who die directly from high blood pressure. Despite the availability of many drugs for hypertension treatment, less than 30% of hypertensive patients in Germany receive treatment. The report also notes that there is a significant age-dependent difference in blood pressure values between women and men, with younger women having lower blood pressure than men. Hormonal changes associated with menopause are believed to increase cardiovascular risk in postmenopausal women, bringing their risk level in line with that of men in the same age group. Currently, both women and men are treated according to the same guidelines, but the database on potential differences in the effects, side effects, and effectiveness of various antihypertensive drugs based on gender is limited but growing.

Similarly, Taler (2009) discusses hypertension in women and reports that systolic blood pressure is higher in African American and Hispanic women over 60 and white women over 70 than in men. Coupled with more prolonged survival, older women have higher hypertension prevalence rates, particularly for isolated systolic hypertension. Hemodynamic characteristics differ by sex for premenopausal women and age-matched men, but these differences lessen after menopause. This transition may result from hormonal or metabolic alterations, including weight gain and tissue adiposity, common after menopause. Clinical trials enrolling many women support the benefits of treatment to minimise cardiovascular events and mortality. However, the trend to enrol subjects with several comorbidities may increase event rates and thus limit the applicability of trial results to healthier women. They conclude that women appear more prone to develop side effects from antihypertensive medications and may metabolise these agents differently.

There is a need for additional studies regarding appropriate drug selection, dosage, and combination therapy for women.

Actual Adverse Events

Angioedema and cough

In a study by Hallberg et al. (2017), risk factors that differ between ACE inhibitor-induced angioedema and cough were identified, including male sex. The study found that male patients were more likely to experience angioedema than cough and that other factors such as smoking, concomitant selective calcium channel blocker treatment, and longer treatment time were also associated with angioedema.

Similarly, a study by Ljungman et al. (2015) examined the influence of various factors, including sex, on prescription patterns and blood pressure control in hypertensive patients. The results showed that men were more likely than women to be treated with calcium channel blockers and ACE inhibitors. Interestingly, in women but not men, having a high educational level and concomitant psychiatric disorders were associated with a higher likelihood of reaching target blood pressure.

Spontaneous Reporting of Adverse Events

Park et al. (2021) explored gender differences in the AEs associated with cardiovascular drugs using a spontaneous reporting system in South Korea. The study used the Korean adverse event reporting system and national health insurance databases. The results showed that compared with men, reporting ratios of women were higher for overall AEs and β blockers and calcium channel blockers. For the AEs, the reporting ratio was higher for musculoskeletal disorders and oedema in women.

Rydberg et al. (2018) conducted a cross-sectional analysis of sex differences in spontaneously reported adverse drug events (ADEs) for antihypertensives in routine care in Sweden. The study found that in women, there was a higher prevalence of ADE reports for ACE, ACE inhibitor combinations, angiotensin receptor blocker combinations, thiazides, diuretics and potassium-sparing agents, and dihydropyridine calcium-channel-blockers, with a potential linkage to dose exposure. For aldosterone antagonists, the study observed a higher prevalence of ADE reports in men but without any sex difference in dose exposure.

Long QT Syndrome

In an article by Drici et al. (2001), they discuss whether gender is a risk factor for ADRs using the example of drug-induced long QT syndrome. The authors report that the condition, also known as drug-induced torsade de pointes, is a rare, life-threatening adverse drug reaction strongly influenced by gender. Drugs that prolong cardiac repolarisation, such as antiarrhythmics, gastrokinetics, antipsychotics, antihistamines, and antibacterials, share the potential to block cardiac voltage-gated potassium channels and therefore lead to arrhythmia. They report that women are perceived to be more prone to these ADRs than men, possibly due to gender-associated differences in drug exposure, the number of drugs

prescribed, drug pharmacology, and possible differences in how the adverse event is perceived. Two-thirds of the cases of drug-induced torsade de pointes occurred in women.

Similarly, Taira also discusses the issue of acquired QT syndrome caused by administering these drugs that prolong ventricular repolarisation. They conclude that the risk of drug-induced torsades de pointes increases with numerous potential predictors, such as genetic susceptibility, female sex, hypokalemia, and cardiac dysfunction. They state that antiarrhythmic agents and other cardiovascular drugs that can prolong the QT interval cause this drug reaction. Out of the 20 of the most commonly reported drugs associated with this condition, 10 were cardiovascular agents.

Adverse Events Related to Digitalis

In an observational study by Pedone (2005), the incidence of AEs related to digitalis-use in men and women in geriatrics and internal medicine acute-care wards in Italy was compared. The study found that women received a higher weight-adjusted dose of Digitalis compared with men and were more likely to suffer from an AE to Digitalis. This finding was confirmed after correction for potential confounding variables. The study concluded that there was a higher incidence of AEs to Digitalis in women than in men in this sample of hospitalised adults in Italy.

Non-Cardiac Adverse Events

Meyers et al. (2002) conducted a study to assess non-cardiac adverse reactions in nuclear medical outpatients receiving intravenous dipyridamole for pharmacological stress testing. The study included 933 patients referred to 2 cardiac outpatient centres for assessment and could not perform treadmill stress testing. Instead, they underwent pharmacological intravenous dipyridamole stress testing, and their adverse reactions were analysed using a reaction scale.

The results showed that 520 (55.7%) of the 933 patients did not exhibit any adverse reaction to intravenous dipyridamole, while 413 patients (44.3%) experienced some adverse reaction. Some patients had multiple types of reactions, resulting in 604 recorded reactions. The study found that the most common adverse reaction to intravenous dipyridamole was headache, which occurred in 224 patients (37.1%). Chest pain and nausea were the next most common reactions in 73 (12.1%) and 67 (11.1%) patients, respectively. When the results were compared by sex, it was found that 271 out of 454 male patients (59.7%) and 249 out of 479 female patients (52%) did not experience any adverse reactions to the medication. However, when looking specifically at the most common adverse reaction, headache, there was a significant difference between males (37.9%) and females (62.1%).

Hospital Admissions

In a study by Rodenburg et al. (2012), sex differences in cardiovascular drug-induced adverse reactions causing hospital admissions were investigated. The study investigated the differences in hospital admissions for ADRs (ADRs) due to cardiovascular drugs between men and women. Data from the Dutch National Medical Register was used to conduct a nationwide study of all hospital admissions between 2000 and 2005. The risk ratios of hospital admissions due to ADRs for different cardiovascular drug groups were calculated for women compared to men, with risks adjusted for the total quantity of Dutch inhabitants and the total number of prescriptions using an ecological design.

The study found that out of all the hospital admissions, 14,207 (34% of all ADR-related admissions) were attributed to cardiovascular drugs. Of these, 7,690 (54%; 95% confidence interval 53-55%) occurred in women. The majority of ADR-related hospital admissions were due to 'Anticoagulants and salicylates' (n=8,988), 'high- and low-ceiling diuretics' (n=2,242), and 'cardiotonic glycosides' (n=932). When looking at the data by sex, the most significant differences were observed in users of low-ceiling diuretics (relative risk 4.02; 95% confidence interval 3.12-5.19), cardiotonic glycosides (relative risk 2.38; 95% confidence interval 2.06-2.74), high-ceiling diuretics (relative risk 2.10; 95% confidence interval 1.91-2.32), and coronary vasodilators (relative risk 0.77; 95% confidence interval 0.65-0.91).

Treatment Changes

Dietary Impact on Adverse Events

Karny-Rahkovich investigated dietary supplement consumption among cardiac patients admitted to internal and cardiology wards and assessed potential drug-dietary supplement interactions. The study included 149 cardiac patients and 45% dietary supplement consumers. The study found that patients who were admitted to the Internal Medicine Wards were more likely to consume dietary supplements than those admitted to the Cardiology Division. The results also showed that dietary supplement consumption was associated with several factors, including older age, being female, and engaging in routine physical activity. Additionally, having diabetes mellitus or haematological diseases, or taking anti-diabetic medications, were independently associated with dietary supplement intake. They found 16 potential moderate interactions between prescribed medications and dietary supplements.

Sexual Dysfunction

In a paper by Karavitakis (2011), they reviewed current guidelines and recommendations for evaluating sexual function in hypertensive men receiving treatment. The review aimed to evaluate whether hypertension clinical practice guidelines (CPGs) address erectile dysfunction (ED) and other sexual issues as an adverse outcome of chosen therapy or a factor to consider in treatment decisions. The review identified and analysed 12 CPGs, and found that only three emphasised the importance of assessing sexual function before initiation and follow-up of antihypertensive therapy; only five described potential sexual side effects associated with some drugs; and only two provided specific management recommendations on commencing antihypertensive therapy in sexually active men or those with preexisting ED.

CHAPTER 4

Discussion

In light of the research question set forth, "Do sex differences influence the adverse events associated with cardiovascular drugs?" this literature review provides a comprehensive understanding of the topic. We conducted a thorough search for scientific articles, with an emphasis on the most recent ones, to ensure the findings were current. Our focus was on studies that investigated sex-based differences in the impact of heart medications on patients, particularly in relation to Adverse Events (AEs). To accomplish this, we examined various indicators, such as effectiveness, actual AEs, and treatment changes, due to the lack of comprehensive side effect data. Combining the knowledge obtained from various studies reveals that, overall, there do seem to be sex differences in adverse events from cardiovascular drugs. Women appear to experience these adverse events more frequently than men.

Our research has revealed the presence of gender-related differences in the pharmacokinetics and pharmacodynamics of drugs. Studies showed that men and women differ in drug distribution, metabolism, and excretion, significantly impacting ADRs and pharmacotoxicity. Many reported notable differences in the pharmacokinetic and pharmacodynamic processes between men and women, which can alter drug concentrations and physiological responses to medications. Additionally, women were found to be more susceptible to adverse cardiovascular drug effects, highlighting the need to optimise drug selection and dosage based on individual attributes such as age, size, and sex.

We analysed eight studies that addressed the impact of gender on treatment effectiveness. Studies by Hudson et al. (2007) and Lilli et al. (2007) provide further insight into the impact of gender on treatment effectiveness. Hudson et al. explored the differences in the effectiveness of ACE inhibitors and ARBs, while Lilli et al. investigated the influence of sex on patients treated with cardiac resynchronisation therapy (CRT). Both studies found gender differences in optimal treatment protocols, suggesting a need for more personalised therapeutic approaches.

Research by Mitchell and Philipp (2007) and Taler (2009) has also examined the impact of age and sex on blood pressure. These studies found significant age-dependent differences in blood pressure values between men and women, as well as a higher prevalence of hypertension among women. Factors such as menopause, weight gain, and tissue adiposity influenced these differences. Both studies highlighted the limited data on gender-based differences in the effects, side effects, and effectiveness of various antihypertensive drugs, reinforcing the need for additional research on appropriate drug selection, dosage, and combination therapy for women.

Gender disparities have been observed in the incidence and nature of ADRs (ADRs) related to cardiovascular medications. A variety of factors, including physiological differences and medication prescription patterns, have been found to contribute to these differences. For example, both Hallberg and Ljungman reported that men were more likely to suffer angioedema, and men were more likely than women to be prescribed calcium channel blockers and ACE inhibitors and that in women, a high educational level and coexisting

psychiatric disorders were associated with an increased likelihood of reaching target blood pressure, suggesting the influence of social determinants of health.

Adverse event reporting also appears to exhibit a gender bias. Park et al. (2021) used a spontaneous reporting system in South Korea to find that reporting ratios for adverse events were higher in women for β blockers and calcium channel blockers, with musculoskeletal disorders and oedema being more commonly reported by women. Similarly, Rydberg et al. (2018) found a higher prevalence of adverse drug event reports in women for multiple types of antihypertensives, suggesting a potential correlation with dose exposure. In contrast, aldosterone antagonists saw higher adverse drug event reports in men.

Sex-based differences also affect the prevalence of specific ADRs, such as drug-induced long QT syndrome, a potentially fatal condition that is predominantly seen in women (Drici et al., 2001; Taira). Pedone (2005) reported a higher incidence of adverse events related to Digitalis in women than in men, which may be attributable to factors such as differential drug exposure, pharmacology, or perception of adverse events. On the other hand, Meyers et al. (2002) noted a significant disparity between male and female patients experiencing headaches as a reaction to intravenous dipyridamole stress testing, with the incidence being higher in women. On a broader scale, Rodenburg et al. (2012) found that women were overrepresented in hospital admissions due to ADRs from cardiovascular drugs, with a higher risk for admission observed in women using low-ceiling diuretics, cardiotonic glycosides, and high-ceiling diuretics.

Our review found that treatment changes, including dietary supplement consumption and managing sexual dysfunction, can impact the incidence of adverse events in patients receiving cardiovascular medications. Dietary supplement consumption was associated with several factors, including older age, being female, and engaging in routine physical activity. The study also identified potential moderate interactions between prescribed medications and dietary supplements. Regarding sexual dysfunction, a review by Karavitakis (2011) evaluated current guidelines and recommendations for assessing sexual function in hypertensive men receiving treatment. The review found that only a few hypertension clinical practice guidelines addressed erectile dysfunction and other sexual issues as an adverse outcome of therapy or a factor to consider in treatment decisions. These findings highlight the need for further research into the impact of treatment changes on adverse events in patients receiving cardiovascular medications.

In conclusion, this literature review presents various ways to identify medication side effects using electronic healthcare data through proxies. By considering effectiveness, treatment changes, and other indicators, researchers can gain valuable insights into side effect incidence, especially in cases where data quality is limited. Additionally, accounting for sex differences is crucial, as women and men may experience different AEs from cardiovascular drugs. These findings will be invaluable in future projects examining sex differences in medication side effects and contribute to enhancing patient care and safety.

We also included review articles, as we consider them a valuable source of information for this literature review. The supplementary review articles provided a comprehensive and critical analysis of the existing literature on this topic, summarising and synthesising the findings of multiple studies. This allowed us to quickly understand the critical issues and debates in the field and identify patterns, inconsistencies, and gaps in the current knowledge. Additionally, the extensive reference lists included in review articles served as a helpful starting point for locating additional primary research articles relevant to our topic. By including review articles in our analysis, we ensured that our literature review was comprehensive, up-to-date, and well-informed by the existing literature.

This literature review offers numerous strengths, including the comprehensive nature of the study selection, the wide variety of cardiovascular drugs explored, and the focus on sex differences, which is a relatively underexplored aspect of pharmacological research. The review extracted studies from a reliable source, PubMed, ensuring a straightforward and extensive source for the analysed literature. Furthermore, it sheds light on important considerations for future research, particularly the need for gender-specific therapeutic strategies. However, several limitations must also be acknowledged.

This review primarily depends on published literature and did not include unpublished studies, potentially introducing publication bias. It also relies on the quality and completeness of the original studies, which varied greatly. Some studies may not have fully adjusted for confounding variables, impacting the reliability of their findings. The review also highlighted the scarcity of studies focusing on female-specific outcomes, indicating a gap. Additionally, there might be inherent biases in the studies due to factors like the predominance of male subjects in clinical trials, which could influence the results and their interpretation. Lastly, this review could not perform a meta-analysis due to the heterogeneity of the included studies, limiting the ability to quantify the effect size of sex differences on the adverse events associated with cardiovascular drugs. Future research should aim to address these limitations by conducting more comprehensive and controlled studies with a balanced representation of both sexes and rigorous methodology.

Overall, the results of this literature review indicate that while some studies have begun to explore sex-based differences in the impact and effectiveness of cardiovascular drugs, there is still much to be uncovered. In particular, the research highlighted an underlying male-centric focus in the current literature, prompting further exploration of how these drugs affect women. This suggests that there is a need for more research to better understand sex differences in medication side effects and to develop more effective and personalised treatment strategies for both men and women.

Conclusion

In conclusion, this literature review aimed to examine sex differences in ADRs associated with cardiovascular drugs. Using a rigorous search strategy and proxies for ADRs, the review found that women tend to experience side effects more frequently. The review explored various proxies for identifying medication side effects such as effectiveness, actual ADRs and treatment changes. The analysis underscored the importance of accounting for sex differences when studying medication side effects, as clear disparities exist in AEs related to cardiovascular drugs. The inclusion of review articles ensured a comprehensive and well-informed analysis. Overall, this review provides valuable insights into sex differences in ADRs associated with cardiovascular drugs and emphasises the need for further research to improve patient outcomes and optimise drug therapy for both sexes.

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