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Sex-specific Differences in Myocardial Infarction – Literature Review

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Abstract

Background: Acute coronary syndromes in the course of ischemic heart disease remain the dominant cause of death in both female and male populations. In recent years, there has been increasing interest in gender-based differences in disease symptoms and outcomes. Taking the data into consideration and implementing it in a day to day practice might prove beneficial to patients and reduce the sex-specific disparities.

Aim: The aim of this study is to gather recent information on the topic of sex-based differences in myocardial infarction and ischemic heart disease. We wanted to bring awareness to the issue and help clinicians understand what approach is best for patients prognosis.

Material and methods: A review of studies including meta-analyses, clinical trials, cohort studies and systematic reviews was done with the use of various databases. The review focused on studies from last 10 years with individual older papers all mentioning the variations in women and men concerning ischemic heart disease and myocardial infarction.

Results: Larger studies with better female representation seem to highlight the problem of women frequently carrying the burden of different risk profile, pathophysiology behind the disease, delayed presentation and less promising outcomes. However some studies in opposition show less significant differences in men and women regarding symptoms and mortality in myocardial infarction.

Conclusions: The problem of sex differences in acute coronary syndromes should not be disregarded nor treated lightly since it has impact on both female morbidity and mortality. Part of research might still be inconclusive but that should only encourage researchers to delve deeper into it. Women seem to benefit from more personalized approach in both diagnostic procedures as well as treatment options.

Key words: sex differences, sex disparities, sex-based guidelines, gender-based guidelines, myocardial infarction, ischemic heart disease, acute coronary syndrome, sex-specific

1. Introduction

The myocardial infarction (MI) is a disorder of the heart, falling under the spectrum of acute coronary syndromes (ACS). Acute coronary syndromes are a group of conditions resulting from myocardial ischemia which include acute myocardial infarction (AMI) and unstable angina (UA) [1]. AMI diagnosis is based on fourth universal definition of MI – in which AMI term includes a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following: symptoms of myocardial ischaemia, new ischaemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology, identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs) [2]. Depending on ECG findings MI can be divided into non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). AMI is equivalent to cardiomyocyte necrosis with the clinical setting of acute myocardial ischemia while UA being same clinical setting but in absence of heart cells injury. Well characterized risk factors for type 1 MI include among others smoking, raised ApoB/ApoA1 ratio, history of hypertension, diabetes, abdominal obesity and regular alcohol consumption [3].

Cardiovascular disease (CVD) is the most prevalent cause of mortality and morbidity worldwide. ACS is usually the initial clinical onset of CVD. Even though STEMI is mainly diagnosed in developed countries, it is also a significant burden to developing countries. In a study from 2019 the MI prevalence in CAD patients was found 23,3% [4]. Meta-analysis from 2023 indicates discrepancies in published studies concerning gender categorized prevalence of MI. In a large number of entries, a high prevalence of MI was reported in males (>60%) compared to females. While, other literature reported higher MI prevalence in females, probably due to the sedentary lifestyle, metabolic syndrome, and similar risk factors [5]. Additionally according to ESC guidelines from 2023 CVD accounted for just under 2.2 million deaths in females and just over 1.9 million deaths in males in the most recent year of available

data. With ischaemic heart disease being the most common cause of CVD death accounting for 38% of CVD deaths in females and 44% in males [1].

Despite the rapid development of diagnostic methods used in identifying myocardial infarction, approximately 20-60% of all MIs are undiagnosed in the acute phase, depending on the study population and diagnostic technique employed. Sex-related factors often contribute to under-recognition, as evidenced by a higher ratio of unrecognized to recognized MI cases among women compared to men [6]. Therefore, identifying and paying attention to these factors may be crucial to reducing mortality related to MIs. We are also obliged to use the detected variations to reduce differences in treatment outcomes between the sexes.

The purpose of this paper is to highlight crucial variability in clinical presentation and therapeutic outcomes in cases of MI in men and women. Based on scientific publications, we wanted to collect and summarize the proven differences and similarities as well as their significance. Since these nuances are often overlooked by clinicians, we decided to explore the topic from a scientific point of view.

2. Research materials and methods

The primary research for this study was conducted on November 12th, 2025 using databases of PubMed, ScienceDirect, Scopus and Google Scholar. The main keywords of "Gender", "Sex", "Differences", "Myocardial Infarction", "Heart Attack", "Ischemic Heart Disease" were used for comprehensive searching. The selection of studies focused on meta-analyses, clinical trials, cohort studies and systematic reviews that broached the subject of sex based differences in clinical presentation and outcomes of myocardial infarction.

3. Discussion on results

3.1 Key sex differences in ischemic heart disease

In a review from 2018 the disparities of various aspects of ischemic heart disease (IHD) were brought up. Despite bringing attention to sex- and gender-specific cardiovascular disease (CVD) research and improved understanding of sex-specific pathophysiology for coronary atherosclerosis women with IHD still experience worse outcomes than men, and younger women (<55 years) and subgroups of women defined by race, ethnicity, socioeconomic status, and educational level still show evident inequality in cardiovascular health. The five-year risk

of heart failure after first MI was higher in women in both white and black population in the age range of 45-74 years and higher in white women compared to white men in patients over 75 years. The same five-year risk of death after first MI was also higher in women of both race populations in all age groups over 45 years with highest incidence in black women across all ages. The limited understanding of sex-specific inequities is connected to the lack of female-specific data.

First noticeable difference lies in risk factors. Women possess some cardiac risks that are unique or predominant in their population, such as early menopause or menarche, gestational diabetes mellitus, hypertension, preeclampsia and eclampsia during pregnancy, and systemic inflammatory disorders. At the same time hypertension, smoking and diabetes mellitus seem to be more potent risk factors for MI in women than in men, with an odds ratio (OR) of 1.5, 1.6, and 1.3, respectively. Going further clinical presentation of IHD in women seems to differ from men with less classic symptoms like chest pain (31% compared with 42% men), especially in young patients. IHD in females tends to rather demonstrate as dyspnoea, weakness, arm, back or jaw pain, palpitations, light-headedness, or loss of appetite which can often lead to misdiagnosis and delayed recognition of cardiac origin of the symptoms. The pathophysiology of coronary artery disease also differs by sex, with nearly 60% of symptomatic women having no flow-limiting stenosis. Additionally there are pathophysiologic dissimilarities in MI, with women having a higher prevalence of plaque erosion compared with more plaque rupture in men.

The role of sex-based diagnostic imaging is considered valuable since women more frequently suffer from nonobstructive atherosclerosis that may result in negative stress tests and obscure the diagnosis of IHD. Female population could benefit from additional cardiac imaging techniques that reveal the nonobstructive coronary disease such as coronary computed tomography, and evaluating small vessel disease by use of myocardial perfusion coronary flow reserve (positron emission tomography and stress magnetic resonance imaging).

On top of all these gaps between sexes disparities in outcomes and quality of care exist. Paradoxically, women presenting with ACS have less obstructive disease but exhibit higher in-hospital (OR, 1.85) and 1-year (OR, 1.6) mortality compared with men. At the same time women experience longer median first medical contact-to-device times (80 versus 75 minutes; $P<0.001$) and a lower propensity to achieve the recommended contact-to-device times $\leq$90 minutes target than men (67.5% versus 75.6%; $P<0.001$). This delay was secondary to

differences in both prehospital presentation times and in getting crucial admission procedures, with longest delays in young women (aged 18–55 years). Even with the proven benefits of revascularization, women are less likely than men to be referred for revascularization for ST-segment-elevation MI, non-ST-segment-elevation MI, and stable angina. Furthermore women are less likely to receive guideline-based primary and secondary prevention despite documented efficacy and guideline endorsement. Women are less likely than men to have their cardiac risks evaluated, with the majority not adhering to relevant primary prevention guidelines and instead using nonevidence-based therapies. Discrepancies in medication prescription and adherence might explain the sex differences for suboptimal outcomes post-MI.

Important actions that should be taken in order to ensure equitable healthcare for women include raising awareness of the IHD in women, attention to psychosocial determinants of health, increasing the representation of women in scientific research and expanding the use of sex and gender-specific guidelines [7].

3.2 In search for divergence of presenting symptoms and importance of sex-specific criteria

International guidelines reinforce the view that women are more likely to present with atypical symptoms, such as epigastric pain, dyspepsia, or breathlessness. However a study from 2019 evaluated 1941 patients (39% women) with suspected acute coronary syndrome attending the emergency department and found that typical symptoms are actually more common and have greater predictive value in women than in men with MI, whether diagnosed using sex-specific or uniform criteria. The study relied on prospectively recorded patient-reported symptoms in comparison to others which used clinician-reported symptoms making it susceptible to bias. Chest pain was the most common presenting symptom, reported by 92% (698/756) of women and 91% (1081/1185) of men with suspected ACS (P=0.439). Pain with typical nature descriptors, the presence of radiation, and the presence of additional symptoms were all more common in women with suspected ACS (P<0.04 for all). Women, compared with men, more often reported palpitations as a presenting symptom (11% versus 7%). Women were also more likely to report that their pain radiated to the left arm (36% versus 31%), the back (31% versus 17%), or to the neck or jaw (28% versus 20%) than were men, and were more likely to report associated nausea. Women were also more likely to present additional symptoms other than chest pain (60% versus 55%, P=0,038).

Another important part of the study was identifying myocardial injury by the high-sensitivity cardiac troponin I assay with sex-specific thresholds (>16 ng/L for women and >34 ng/L for men). This approach led to raise in the number of patients diagnosed with type 1 myocardial infarction by 30% (27/90) in women and 4.9% (9/184) in men (P<0.001).

Although this paper disagrees with statements from clinical guidelines that atypical symptom presentations occur more commonly in women it shows the importance of clinical setting and group choice. By enrolling patients with suspected ACS before the diagnosis the risk of selection bias was greatly reduced. The authors emphasize the importance of typical symptoms in female population contrary to previous findings. This distinction may be crucial to minimize the risk of underdiagnosis and treatment of women with myocardial infarction. They also accentuate the utility of sex-specific troponin thresholds which is now endorsed by the fourth universal definition of myocardial infarction and will substantially increase the number of women diagnosed with MI [8].

3.3 Sex differences in symptoms among young patients with MI

Authors of a study from 2018 interviewed 2009 women and 976 men aged 18–55 years hospitalized for AMI at 103 US hospitals using structured forms gathering data on symptom presentation, perception of symptoms, and care-seeking behaviours. The majority of women (87.0%) and men (89.5%) presented with chest pain (defined as pain, pressure, tightness, or discomfort). Women were more likely to present with ≥3 associated symptoms than men (e.g., epigastric symptoms, palpitations, and pain or discomfort in the jaw, neck, arms, or between the shoulder blades; 61.9% for women vs 54.8% for men, p<0.001). In adjusted analyses, women with an ST-elevation AMI were more likely than men to present without chest pain (odds ratio 1.51; 95% confidence interval 1.03–2.22). Compared with men, women were more likely to perceive symptoms as stress/anxiety (20.9% vs 11.8%, p<0.001) but less likely to attribute symptoms to muscle pain (15.4% vs 21.2%, p=0.029). A greater percentage of women sought medical care for similar symptoms prior to being hospitalized for their AMI, as compared with men (29.5% vs 22.1%, p<0.001). However, over half of women (53.4%) reported that their provider did not think these symptoms were heart related, as compared with 36.7% of men (p<0.001). This study also reported that women aged 45–54 years were more likely to present without chest pain compared with men (odds ratio 1.26, 95% CI 1.22–1.30) [9].

Above-mentioned data suggests that in young women the higher prevalence of additional non-chest pain symptoms may change patients perception as well as influence the decision of the physician on initiating a work up for ischemic heart disease, especially if chest discomfort is not the primary or most emphasized symptom at the time of physical examination. Taking these findings into consideration physicians should always listen carefully and consider the diagnosis of heart disease in young patients, specifically those with cardiac risk factors and chest pain or various ways chest pressure is described in their medical history.

3.4 Sex differences in clinical characteristics and outcomes after MI with low EF

In a RCT from 2023 researchers involved a total of 5661 patients (1363 women [24%]) with acute myocardial infarction complicated by reduced left ventricular ejection fraction (≤40%), pulmonary congestion, or both and ≥1 of 8 risk-augmenting factors (age ≥70 years, diabetes, previous MI, estimated glomerular filtration rate [eGFR] <60mL/min per 1.73m2, atrial fibrillation, LVEF <30% associated with index MI, Killip class III or IV, or ST-segment-elevation MI without reperfusion within 24 hours after presentation). The patients were randomized to receive sacubitril/valsartan or ramipril. The primary outcome was cardiovascular death or incident HF. Baseline characteristics, clinical outcomes, and safety events were compared according to sex, a prespecified subgroup. Female participants were older and had more comorbidities. After multivariable adjustment, women and men were at similar risks for cardiovascular death or all-cause death. Women were more likely to have first HF hospitalization (hazard ratio [HR], 1.34 [95% CI, 1.05–1.70]; P=0.02) and total HF hospitalizations (HR, 1.39 [95% CI, 1.05–1.84]; P=0.02). Sex did not significantly modify the treatment effect of sacubitril/valsartan compared with ramipril on the primary outcome (P for interaction=0.11) [10].

Clinical trial cohort of patients with high-risk MI included older women who presented with more comorbidities. Both women and men had similar rates of all-cause mortality and cardiovascular death. Constant improvements in the diagnostics and treatment of acute MI have been made for both men and women which can be seen through decreasing mortality rates in ACS in the last years. Unfortunately some studies show that women are treated less aggressively when presenting with ACS, and they have higher in-hospital, 1-year, and 5-year mortality, with some differences persisting even after adjusting for baseline differences [7]. Physicians should pay close attention to the increased risk of heart failure hospitalization after

high-risk myocardial infarction to mitigate adverse clinical outcomes. It is also important not to disregard women with MI and use guideline-directed medical therapy. Sacubitril/valsartan was shown to be safe and well tolerated treatment option in both sexes and should not be withheld in women when clinically indicated.

3.5 Sex differences and clinical outcomes in patients with MINOCA

Meta-analysis from 2024 investigated whether sex is a risk factor for adverse outcomes in patients with myocardial infarction with nonobstructive coronary arteries (MINOCA). It involved 9 studies, accounting to 30 281 patients with MINOCA (comprising 18 079 women and 12 202 men) included in the review. Women were older and had a higher prevalence of hypertension, diabetes, and stroke compared with men. Even though MINOCA is more common in women analysis revealed no statistically significant difference in the risk of all-cause mortality (OR, 1.03 [95% CI, 0.87–1.22]), major adverse cardiovascular events (OR, 1.18 [95% CI, 0.89–1.58]), heart failure (OR, 1.32 [95% CI, 0.57–3.03]), stroke (OR, 1.13 [95% CI, 0.56–2.26]), and myocardial infarction (OR, 1.04 [95% CI, 0.29–3.76]) between the 2 groups. Regarding short-term outcomes, women had a significantly higher risk of in-hospital major adverse cardiovascular events compared with men (OR, 1.33 [95% CI, 1.16–1.53]) whereas there was no significant difference in the risk of in-hospital mortality (OR, 0.90 [95% CI, 0.64–1.28]) between the 2 patient groups [11].

Patients with MINOCA represent a specific clinical challenge because the underlying cause of MI is often not apparent without additional diagnostic methods. As mentioned above MINOCA is more prevalent among young women. However the evidence of sex-based difference in outcomes of patients with MINOCA is fairly limited and controversial with some studies suggesting that women were at a higher risk of mortality or major adverse cardiovascular events (MACE) compared with men whereas others suggest otherwise. The study cited suggests that sex alone may not be an important long-term risk factor in patients with MINOCA. Nonetheless short-term adverse events seem to be more frequent in women which might warrant greater vigilance and focus on optimizing care in these cases.

3.6 Sex differences in ischemic and bleeding outcomes in patients with non–ST-segment–elevation acute coronary syndrome undergoing percutaneous coronary intervention

In view of the fact that previous works showed poorer outcomes in females with MI but older age and lower use of percutaneous coronary intervention (PCI) in females could be factors that explain the worse outcome, the RCT from 2021 sought to determine whether the female sex is an independent factor of ischemic and bleeding outcomes in non–ST-segment–elevation acute coronary syndrome treated with a systematic invasive approach. In this paper post hoc analysis from the TAO trial was done. The trial randomized patients with non–ST-segment–elevation acute coronary syndrome treated invasively to heparin plus eptifibatide versus otamixaban. The primary ischemic end point (all-cause death, myocardial infarction within 180 days) and the primary safety end point (thrombolysis in myocardial infarction major or minor bleeding within 30 days) were analysed according to sex.

Of 13229 randomized patients, 3980 (30.1%) were females and 9249 (69.9%) were males. Females were older (64.8±11.0 versus 60.7±11.1 years), had more comorbidities, received less peri-procedural antithrombotic therapy, and underwent less frequently revascularization. Overall, females experienced a higher risk of ischemic (10.2% versus 9.1%; odds ratio [OR], 1.15 [1.01–1.30]) and bleeding events (4.2% versus 3.4%; OR, 1.23 [1.02–1.49]) than males. After multivariate analysis, the risk of ischemic outcomes (OR, 1.04 [0.90–1.19]), death (OR, 1.00 [0.75–1.23]), or bleeding (OR, 1.05 [0.85–1.28]), were similar between females and males. Only, noncoronary artery bypass graft related thrombolysis in Myocardial Infarction major bleeding were increased in females (OR, 1.69 [1.11–2.56]) [13].

According to results from this work in cases on non-ST-segment elevation ACS with PCI, clinical characteristics, antithrombotic, and revascularization treatments largely differ between sexes. Ischemic and bleeding adverse events are higher in females while the adjusted risk is similar for both sexes except for noncoronary artery bypass graft related Thrombolysis in Myocardial Infarction major bleeding risk, which is higher in females. Since bleeding is a powerful determinant of fatal and nonfatal outcomes in ACS it is important to heed these results.

3.7 Sex-specific management in patients with acute MI and cardiogenic shock

One of the most serious complications of AMI is cardiogenic shock (CS). RCT from 2020 researched outcomes of different revascularization strategies in patients with CS complicating AMI: either percutaneous coronary intervention of the culprit-lesion-only or immediate multivessel percutaneous coronary intervention were randomly assigned. In a substudy from this RCT we wanted to focus on researchers investigated sex-specific

distinctions. Authors highlighted the fact that women develop CS more frequently and wanted to explore whether it is connected to a different risk profile and if women with CS complicating AMI should be treated differently than men. The primary end points in the paper were death from any cause or severe renal failure leading to renal replacement therapy within 30 days.

Among all 686 randomized patients included in the analysis, 24% were women. Women were older and more often had diabetes mellitus and renal insufficiency, whereas they less often had history of previous AMI and smoking. After 30 days, the primary clinical end point was not significantly different between groups (56% women versus 49% men; odds ratio, 1.29 [95% CI, 0.91–1.84]; P=0.15). After 1 year of follow-up, clinical end points also showed no significant differences between women and men. There was no interaction between sex and coronary revascularization strategy regarding mortality and renal failure ($P_{interaction}$=0.11). The primary end point occurred in 56% of women treated by the culprit-lesion-only strategy versus 42% men, whereas 55% of women and 55% of men in the multivessel percutaneous coronary intervention group [14].

The main conclusion from this substudy was that women presented with different baseline characteristics, including different ECG patterns (women more often had ST-segment depression, nonanterior ST-segment elevation) and culprit lesions (the culprit lesion was more often found in the right coronary artery). Another crucial point was both sexes having similar outcomes in regards to primary endpoints – death and renal failure. However women suffering from these outcomes had a different risk profile compared to women without. Finally sex did not show to impact the main findings of the trial favouring culprit-lesion-only PCI. Even though women have higher prevalence of infarct-related CS and demonstrated a different initial profile the mortality was comparable to men. Variation in clinical aspects did not influence the advantageous PCI strategy which remained the same for both men and women. Based on these data, women with cardiogenic shock complicating acute myocardial infarction should not be treated differently than men. Nonetheless authors emphasized that women are underrepresented in most studies addressing CS, and data concerning optimal management and treatment of CS among women are controversial thus the topic might need to be explored in detail.

5. Conclusions

Coronary artery disease continues to be the leading cause of death for both men and women despite the drastic improvements in mortality from MI in females. On account of these

statistics sex-based differences in IHD and MI remain an important topic raised fairly often by researchers. Studies show us that women more frequently carry the burden of different risk profile, pathophysiology behind the disease, delayed presentation and less promising outcomes. Scientific associations encourage clinicians to a more sex-specific diagnostic and treatment approach in women using appropriate guidelines and evidence-based methods. However to some extent the topic still remains unresolved with other papers showing that differences between the sexes may not be as significant as we thought. In part of the studies women actually present with similar symptoms to men and suffer from equally morbid outcomes. Nonetheless even in these works that in some way stand in opposition to scientific associations reviews slight disparities are usually present. Additionally the problem of underrepresentation of women in some of these trials is present which may cause the results to be not fully reliable. Despite the interest in the topic in recent years, there is still room for further research to properly explore these issues. In the meantime, the most rational approach seems to be to use a unique clinical methods for women corresponding to sex-specific guidelines for diagnosis and treatment of myocardial infarction. As this approach appears to have yielded significant gains in IHD treatment outcomes in recent years in women without negatively impacting the other sex. Being aware of the sex inequalities in MI research and outcomes is also a crucial step for further bringing attention to the matter. With this work, we would like to make our own contribution to spreading knowledge on this subject and encourage doctors to familiarize themselves with sex- and gender-based guidelines.

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Author Contributions:

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