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INTEGRATED STUDY MASTER'S THESIS

Gender Consideration in Acute Coronary Syndrome

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1. List of Abbreviations

Abbreviation	Definition
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
AMI	Acute Myocardial Infarction
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
BP	Blood Pressure
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CI	Confidence Interval
CR	Cardiac Rehabilitation
cTn	Cardiac Troponin
CVD	Cardiovascular Disease
DAPT	Dual Antiplatelet Therapy
DTB	Door-to-Balloon
EAPCI	European Association of Percutaneous Cardiovascular Interventions
ECG	Electrocardiogram
ED	Emergency Department
ESC	European Society of Cardiology
GRACE	Global Registry of Acute Coronary Events
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HR	Hazard Ratio
hs-cTn	High-Sensitivity Cardiac Troponin
IHD	Ischaemic Heart Disease
IQR	Interquartile Range
LBBB	Left Bundle Branch Block
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
LMWH	Low Molecular Weight Heparin
LV	Left Ventricular
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
MINOCA	Myocardial Infarction with Non-Obstructive Coronary Arteries

NSTE-ACS	Non-ST-Elevation Acute Coronary Syndrome
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PPCI	Primary Percutaneous Coronary Intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RBBB	Right Bundle Branch Block
RR	Relative Risk
STEMI	ST-Segment Elevation Myocardial Infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TCFA	Thin-Cap Fibroatheroma
TIMI	Thrombolysis in Myocardial Infarction
UA	Unstable Angina
UFH	Unfractionated Heparin
VIRGO	Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients
VO_2 max	Maximal Oxygen Uptake
WISE	Women's Ischemia Syndrome Evaluation

2. Abstract

Acute Coronary Syndrome (ACS) remains a leading cause of global morbidity and mortality, with growing evidence highlighting significant sex- and gender-related disparities in its presentation, diagnosis, management, and outcomes. Although cardiovascular care has improved over the past years, women continue to be under-recognized and undertreated, underscoring the need for gender-sensitive research. This study aims to systematically analyze and synthesize current evidence on gender differences in ACS, focusing on clinical presentation, diagnostic challenges, treatment strategies, and outcomes. The objectives include identifying key sex-based differences, evaluating contributing factors, and assessing their impact on prognosis.

A narrative literature review was conducted using databases such as PubMed, Google Scholar, and the Cochrane Library, alongside international clinical guidelines. Studies published between 1990 and 2026 were included, covering various designs such as randomized controlled trials, observational studies, and meta-analyses. Data were thematically analyzed to address the research questions.

The findings reveal that women with ACS often present with differing symptom patterns, experience diagnostic delays, and are less likely to receive timely and guideline-recommended therapies, including reperfusion and pharmacological treatment. Additionally, women exhibit higher unadjusted mortality rates, largely influenced by older age at presentation, comorbidities, and systemic healthcare disparities. Younger women, in particular, demonstrate worse outcomes compared to men of the same age group.

In conclusion, significant gender disparities persist across all stages of ACS care. Addressing these differences requires improved awareness of sex-specific manifestations, equitable implementation of clinical guidelines, and increased representation of women in clinical research. Targeted interventions are essential to optimize outcomes and ensure more personalized, gender-sensitive cardiovascular care.

Santrauka (lietuvių kalba)

Ūminis koronarinis sindromas (ŪKS) išlieka viena pagrindinių sergamumo ir mirtingumo priežasčių pasaulyje, o vis daugiau tyrimų atskleidžia reikšmingus lyčių skirtumus ligos pasireiškime, diagnostikoje, gydyme ir baigtyse. Nepaisant medicinos pažangos, moterys dažnai lieka nepakankamai atpažįstamos ir gydomos, todėl būtini lyčiai jautrūs tyrimai. Šio darbo tikslas – sistemingai išanalizuoti ir apibendrinti mokslinius duomenis apie lyčių skirtumus ŪKS kontekste, ypatingą dėmesį skiriant klinikiniams simptomams, diagnostikai, gydymo strategijoms ir baigtims. Uždaviniai apima pagrindinių skirtumų nustatymą, juos lemiančių veiksnių įvertinimą bei jų įtakos

prognozei analizę. Tyrimas atliktas kaip naratyvinė literatūros apžvalga, naudojant PubMed, Google Scholar ir Cochrane duomenų bazes bei tarptautines klinikines gaires. Į analizę įtraukti 1990–2026 m. publikuoti tyrimai, įskaitant atsitiktinių imčių, stebėjimo bei metaanalizes. Duomenys sisteminti teminiu principu.
Rezultatai parodė, kad moterys dažniau patiria netipinius simptomus, susiduria su diagnostikos ir gydymo vėlavimais bei rečiau gauna gairėmis pagrįstą gydymą. Nors nepakoreguoti mirtingumo rodikliai moterims yra didesni, tai daugiausia susiję su vyresniu amžiumi, gretutinėmis ligomis ir sisteminiais sveikatos priežiūros skirtumais. Jaunesnės moterys pasižymi blogesnėmis baigtimis nei to paties amžiaus vyrai.
Apibendrinant, lyčių skirtumai ŪKS išlieka reikšmingi visais ligos valdymo etapais. Siekiant pagerinti gydymo rezultatus, būtina didinti informuotumą apie lyčiai būdingus simptomus, užtikrinti vienodą gydymo taikymą ir stiprinti moterų atstovavimą klinikiniuose tyrimuose.

Keywords: Acute Coronary Syndrome; Gender Differences; Cardiovascular Disease; Ischemic Heart Disease, Treatment Disparities;

3. **Introduction**

3.1 Background

Acute Coronary Syndrome (ACS) relates to a range of coronary artery pathologies, including ST-segment elevation myocardial infarction (STEMI) and non-ST-segment myocardial infarction (NSTEMI), as well as unstable angina, which result from acute myocardial ischemia. ACS represents a global burden with high mortality and accounts for millions of hospitalizations each year. Rapid diagnosis and timely intervention to optimize outcomes are crucial (1). Traditionally, men have been thought to be at higher risk, but previous studies have shown that women often experience poorer outcomes following adverse cardiovascular events (2,3).

Global burden and Clinical Relevance

Ischaemic heart disease continues to be the leading cause of mortality worldwide, accounting for nearly 16% of all deaths. Reduced quality of life, long-term disability, and substantial healthcare costs add to this burden. (1) Disparities persist across age, geography, and socioeconomic status and notably between men and women, making gender-specific research essential for improving global cardiovascular outcomes. (2,4)

3.2 Relevance of Gender-Based Analysis

Biological differences and sociocultural influences play vital roles in cardiovascular events, disease manifestation, and treatment outcomes. Compared to men, women frequently present with symptoms considered atypical, such as fatigue, dyspnea, or epigastric pain, contributing to delayed diagnosis and management. (3,5)

Biological factors such as hormonal influences and smaller coronary vessel size may modulate disease pathophysiology, while gender-based factors such as physician bias, healthcare-seeking behavior, and social determinants influence access to care and adherence to therapy. (2,5)

Understanding these multifaceted interactions and implementing gender-based analyses are critical for delivering appropriate and effective cardiovascular care.

3.3 Rationale of the Study

Although sex-specific cardiovascular differences have gained attention in recent years, knowledge gaps persist. Women remain underrepresented in cardiovascular clinical trials, resulting in an evidence base disproportionately focused on men (2,4). Consequently, sex-specific variations are inadequately represented in diagnostic algorithms, risk stratification tools, and therapeutic guidelines (4,5).

Existing data indicate that women with ACS experience delays in hospital presentation, are less likely to receive appropriate reperfusion therapy, and are prescribed guideline-directed medical therapy less often, leading overall to higher mortality (3,5). These disparities point to a systemic under-recognition of sex-specific manifestations and a potential neglect of evidence-based interventions in women.

This literature analysis aims to address these gaps by reviewing current data on gender-based differences in Acute Coronary Syndrome. Better understanding of these disparities is of high importance for the utilization of clinical guidelines, improving early recognition, and optimizing outcomes for both men and women.

3.4 Objectives and Research Questions

To systemically explore and synthesize current evidence regarding gender-related differences in clinical presentation, diagosis, management as well as outcomes of Acute Coronary Syndrome.

1. Key differences in clinical presentation and diagnostic evaluation of ACS between men and women?

2. How do management strategies, including pharmacologic and invasive interventions, differ by gender?
3. What are the differences in short- and long-term outcomes of ACS between male and female patients?
4. Which factors contribute to these gender-related differences in ACS care and prognosis?

This study was conducted as a narrative literature analysis to systematically explore and synthesize current evidence regarding gender-related differences in the clinical presentation, diagnosis, management, and outcomes of acute coronary syndrome (ACS). A comprehensive literature search was performed using the electronic databases PubMed/MEDLINE, Google Scholar, and the Cochrane Library, supplemented by clinical practice guidelines from major cardiovascular societies (European Society of Cardiology, American Heart Association, American College of Cardiology), institutional reports (EuroHeart Reports, World Health Organization), and reference lists of relevant articles. The search was conducted between September 2025-April 2026 using combinations of key terms including "acute coronary syndrome," "myocardial infarction," "STEMI," "NSTEMI," "sex differences," "gender differences," "women," "clinical presentation," "diagnosis," "treatment,", “reperfusion therapy”, “anticoagulation therapry”, "outcomes," "mortality," and "cardiac rehabilitation."

Studies were included if they were published in English between 1990 and 2026, with emphasis on literature from the past 10 years, and addressed sex or gender differences in any aspect of ACS including epidemiology, pathophysiology, risk factors, clinical presentation, diagnosis, management, outcomes, or secondary prevention. Eligible study designs included randomized controlled trials, observational cohort studies, cross-sectional studies, systematic reviews, meta-analyses, registry analyses, and clinical practice guidelines involving adult populations (age ≥18 years). Studies were excluded if they were case reports or case series with fewer than 10 patients, focused exclusively on pediatric populations or stable coronary artery disease without reference to ACS, were conference abstracts without full-text availability, had significant methodological limitations, or represented duplicate publications with overlapping patient populations, in which case the most comprehensive or recent publication was retained.
Titles and abstracts were screened for relevance, and full texts of potentially eligible articles were assessed against the inclusion and exclusion criteria. Data extracted from included studies encompassed study design, sample size, patient demographics, geographic location, sex-stratified results, adjusted and unadjusted effect estimates, and key conclusions regarding gender differences.

The quality of included studies was assessed using study design-appropriate criteria, evaluating systematic reviews for comprehensive search strategies and heterogeneity assessment, observational studies for adequate sample size and confounder adjustment, and clinical practice guidelines for the rigor of their development process. Given the heterogeneity of study designs, populations, and outcomes, a narrative synthesis approach was employed rather than formal meta-analysis, with findings organized thematically according to the four primary research questions. As this study involved analysis of previously published literature and did not involve primary data collection from human subjects, ethical approval was not required.

4. Overview of ACS Literature Analysis

4.1 Pathophysiology

The primary pathophysiological mechanism underlying acute coronary syndrome (ACS) involves rupture or erosion of atherosclerotic lesions, resulting in coronary thrombosis and subsequent myocardial ischemia (6,7). Approximately 64% of ACS cases are attributable to rupture of lipid-laden plaques, a process incited by inflammation and followed by platelet-rich thrombosis (6). When thrombosis completely occludes the coronary vessel, ST-segment elevation myocardial infarction (STEMI) occurs, whereas nonocclusive thrombus formation typically results in non-ST-segment elevation myocardial infarction (NSTEMI) (6). ACS most commonly develops as a consequence through one of three main mechanisms: rupture of the fibrous cap, superficial plaque erosion, or, less frequently, disruption of calcified nodules within atherosclerotic coronary plaques. (5–7) Plaque rupture accounts for approximately 76% and 55% of deadly myocardial infarctions in men and women, respectively. Plaque erosion is responsible for 25-40% of ACS cases and occurs more frequently in women than men (37.4% vs 18.5%). (5,8) Calcific nodules represent the least frequent cause of coronary thrombosis, accounting for approximately 2-7% of STEMI cases. (5,9) Major characteristics of vulnerable plaques include thin-capped fibroatheromas (TCFA), spotty calcifications, plaque hemorrhage, adventitial inflammation, neovascularization and angiogenesis, as well as expansive (positive) remodeling of the vessel. (10–12) These plaques are often non-obstructive and clinically silent until they suddenly become obstructive and symptomatic. (13,14) A thin-cap fibroatheroma is defined by a large necrotic core overlain by a thin fibrous cap that is infiltrated by activated macrophages, and it is regarded as the classic form of a plaque that is prone to rupture. (7,15,16).

4.2 Underlying Mechanisms

Atherosclerosis is the primary underlying factor in the pathogenesis of coronary vascular disease, as well as cerebral and peripheral vascular diseases.(17) The following risk factors have been identified as major contributors to atherosclerosis development: dyslipidemia, smoking, and hypertension.(18,19) Moreover, it is evident that both age and gender exert substantial influence on the likelihood of developing atherosclerosis.(18)(20)

The formation of atherosclerotic plaques begins with the development of initial lesions that extend into the vascular lumen.(17,18). Atherosclerosis begins with the deposition of low-density lipoprotein (LDL) cholesterol in the walls of medium- and large-sized arteries (17) This lipid buildup triggers an inflammatory response, promoting the recruitment of immune cells, especially monocytes, macrophages and T lymphocytes. Some of these cells internalize the lipids, transforming into foam cells. (17,19) These lesions are primarily composed of a soft lipid core consisting of cholesterol and cellular debris, surrounded by a fibrous cap composed of collagen-rich matrix and smooth muscle cells covered by endothelial cells. (7,17) The death of foam cells promotes the buildup of cellular debris, apoptotic material, and extracellular cholesterol, contributing to the development of a lipid-rich necrotic core. At the same time, vascular smooth muscle cells migrate from the arterial media into the intima, where they proliferate, take up lipids to become foam-like cells, and synthesize extracellular matrix components such as collagen and elastin. (17) These lesions can result in narrowing of the vessel lumen and, in the event of rupture, obstructive vascular thrombosis.(21) Additionally, changes in the vessel wall can facilitate ischemic damage by increasing the diffusion distance to inner layers. The weakened vessel wall may also promote the formation of aneurysms.

As atherosclerotic plaques evolve, a fibrous cap develops over the lesion, contributing to its structural stability. However, when this cap becomes weakened, thins, or ruptures, it can trigger the formation of an occlusive thrombus within the vessel lumen, often leading to clinical events such as myocardial infarction or stroke. (17) Upon plaque disruption, thrombogenic material within the plaque, such as tissue factor and von Willebrand factor, is exposed to flowing blood, resulting in platelet adhesion and activation of the coagulation cascade.(22) This leads to platelet aggregation and eventual thrombus formation, which can cause acute coronary obstruction.(21,22)

4.3 Diagnostic Criteria

According to the European guidelines for ACS several factors are used for the diagnosis of STEMI or NSTEMI. These are primarily based on a combination of clinical presentation, electrocardiogram (ECG) findings and cardiac biomarkers, specifically high-sensitivity cardiac troponin. (23) STEMI is typically a working diagnosis assigned for patients presenting with acute chest pain and persistent

ST-segment elevation on electrocardiography. ECG criteria suggestive of ongoing acute coronary artery occlusion require new ST-elevation in at least two contiguous leads: in leads V2–V3, the threshold is ≥2.5 mm in men younger than 40 years, ≥2 mm in men aged 40 years or older, or ≥1.5 mm in women regardless of age; in all other leads, the threshold is ≥1 mm in the absence of left ventricular hypertrophy or left bundle branch block. Certain ECG patterns without classic ST-elevation, termed STEMI equivalents, also warrant immediate reperfusion therapy. These include posterior myocardial infarction, characterized by ST-segment depression in leads V1–V3 (especially with a positive terminal T wave) and/or ST-elevation in posterior leads V7–V9; left main or multivessel ischaemia, identified by ST-depression ≥1 mm in six or more surface leads with concomitant ST-elevation in aVR and/or V1; and new or pre-existing left or right bundle branch block in patients with high clinical suspicion of ongoing ischaemia. While triage for STEMI should not be delayed for blood results, the final diagnosis of myocardial infarction is confirmed by a typical rise and/or fall in cardiac troponin levels above the 99th percentile.
Non-ST-segment elevation myocardial infarction (NSTEMI) falls under the broader spectrum of non-ST-elevation acute coronary syndrome, which encompasses patients presenting with ischaemic symptoms but without persistent ST-segment elevation. The ECG in NSTEMI may show persistent or transient ST-segment depression, T-wave abnormalities such as inversions or biphasic T waves, or hyperacute T waves, although in more than one-third of patients the ECG may be non-distinguishable from a normal ECG. The definitive diagnosis of NSTEMI requires evidence of cardiomyocyte necrosis, defined by a typical rise and fall in high-sensitivity cardiac troponin levels with at least one value exceeding the 99th percentile of healthy individuals. If cardiac troponin levels remain below this threshold despite ischaemic symptoms, the patient is diagnosed with unstable angina rather than NSTEMI. To facilitate rapid diagnostic decision-making, the ESC recommends the use of serial high-sensitivity cardiac troponin testing using the 0 h/1 h algorithm (preferred) or the 0 h/2 h algorithm, which enable rule-in or rule-out of NSTEMI based on absolute troponin values and their changes over a short interval. (23)

4.4 Risk factors

Can be classified into two categories: structural and modifiable

4.4.1 Structural Risk Factors

Genetic predisposition is the most noticable structural risk factor for atherosclerosis. (24). The clinical manifestation of disease becomes more common with advancing age, reflecting the gradual progression of artheroscleortic plaque development (25,20) Between 40 to 60 years of age, the incidence of myocardial infarction rises approximately fivefold. (25)

Another important structural risk factor is gender. Atherosclerosis and its complications are more often seen in men compared to premenopausal women of the same age. (26,27) However, when comparing men to postmenopausal women, the incidence for women outweigh men significantly. (28–30) Estrogen has been identified as a protective factor in atherosclerosis, mainly by lowering LDL and increasing HDL. (26,31,32) Interestingly, hormone-replacement therapy for postmenopausal women fails to lower the risk of cardiovascular events. (33–35)

4.4.2 Modifiable risk factors

Hypercholesterolemia is widely regarded as one of the most significant modifiable risk factors, with a substantial impact on the development of atherosclerotic plaques.(36–38) Iindividuals diagnosed with hypertension appear to have a 60% higher risk of developing the condition compared to those with normal blood pressure. (36,39) Smoking has been shown to have a cumulative effect, with the associated cardiovascular risk progressively increasing over time. (37,39) Diabetes mellitus can be regarded as an indirect risk factor for atherosclerosis, given its association with the development of hypercholesterolemia. (37,40) Inflammation has been identified as a significant modifiable risk factor, with its presence being documented at all stages of the formation of atherosclerotic plaques. (41–43) Metabolic syndrome, and central obesity in particular, appears to induce a systemic hypercoagulable and pro-inflammatory state, which in turn serves to further promote the development of atherosclerosis. (44,45) Further modifiable risk factors encompass a sedentary lifestyle, a stressful lifestyle (type A personality) and obesity. (42,45)

5. Gender Differences in ACS Literature Analysis

5.1 Epidemiology

5.1.1 Overall Incidence and Sex Distribution

The 2025 EuroHeart Report presented aggregated data from 2022-2024, documenting 397,102 total ACS cases, of which 250,144 (63%) were NSTEMI and 146,958 (37%) were STEMI. (46)
More sex-specific data is available from the 2023 EuroHeart Report, which analyzed 40,021 ACS admissions (39,694 across 7 countries including Lithuania) in 2022. Approximately one-third (31.6%) of patients were female and two-thirds (68.4%) were male, a distribution consistent across both STEMI and NSTEMI presentations. (47) This sex distribution is consistent across European countries, with a French nationwide study in 2014 reporting 32.2% women and 67.8% men among 113,407 ACS hospitalizations, and German data (2014-2017) showing 70% of STEMI cases occurring in men. (48,49)

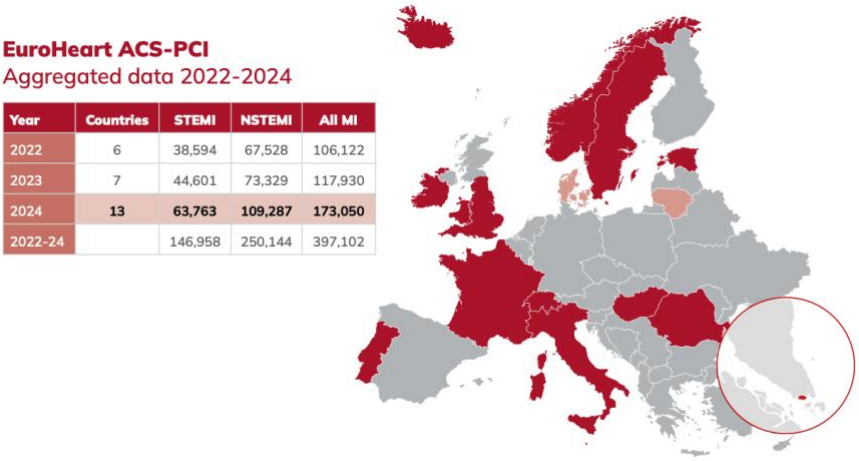

Figure 1.
EuroHeart data on ACS-PCI, 2022-2024 (46)

5.1.2 Trends in ACS Type

European data demonstrate divergent trends between STEMI and NSTEMI incidence over the past two decades. A 25-year population-based study from the Veneto Region in Northeastern Italy (2000-2024) showed that age-standardized AMI hospitalizations declined overall (average annual percentage change -2.30%), driven by marked reductions in STEMI (average annual percentage change -4.72%), whereas NSTEMI increased (+1.05%) and became the predominant phenotype after 2016. (50) In Germany, STEMI cases decreased from 72,894 in 2014 to 68,213 in 2017. (49)

While overall ACS rates have declined in older populations, alarming increases have emerged among younger women in several European countries. A French nationwide study (2004-2014) revealed that age-standardized admission rates for ACS in women under 65 years increased by 6.3%, driven by significant increases in STEMI (+21.7%) and NSTEMI (+53.7%). (48) The largest increase in STEMI was observed among women aged 45-54 years (+3.6% per year). In contrast, women over 65 years experienced significant decreases in all ACS types. (48)

An international study across 6 high-income countries (including England and the Netherlands) found that hospitalization rates for both STEMI and NSTEMI decreased between 2011 and 2018 in all countries, but the hospitalization rate ratio (rate in males/rate in females) increased in virtually all countries, indicating a larger decline in ACS hospitalizations for women than men in older populations.(51)

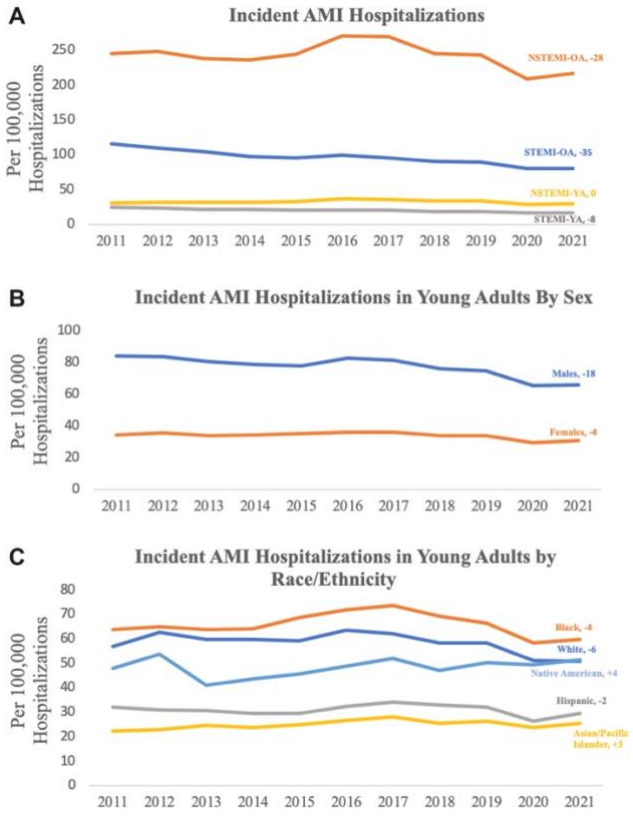

Figure 2.
Trends in Risk Factor Prevalence and Incidence of Acute Myocardial Infarction in Young Adults JACC Adv. 1 September 2025

The figure above illustrates sex-stratified trends in AMI hospitalizations among young adults (18-54 years) from 2011 to 2021. Males consistently show approximately 2-2.5 times higher hospitalization rates than females (approximately 80 per 100,000 for males versus 30-40 per 100,000 for females throughout the study period). (52) Notably, while both sexes experienced declines in AMI hospitalizations, young men experienced more than four times the absolute decline compared to young women over the study period, suggesting that women are not benefiting equally from improvements in primary prevention.

The incidence rate of ACS is consistently lower in women than men across all age groups, though this gap narrows with advancing age. (2,53,54) A large Norwegian population-based study (Tromsø Study) demonstrated that women's MI risk corresponds to that of men 10-15 years younger, with the sex difference persisting throughout life. (55) For age groups 35-54, 55-74, and 75-94 years, adjusted incidence rate ratios for men versus women were 3.64, 2.00, and 1.66, respectively, showing that while the relative risk decreases with age, the absolute difference in risk increases.

5.2 Risk Factor Differences

5.2.1 Distribution

Traditional risk factors for both sexes are widely known, whilst their impact on CVD outcomes among sexes differs. Moreover, gender associated CAD risk factors especially for women are often neglected. According to CVD statistics, hypertension is more common in men (median 41%) than in women across ESC member countries. (47) Obesity prevalence is distributed similarly between sexes in Europe. (47) A large cross-sectional European public health study exposed that men had a greater prevalence of poor cardiovascular health metrics such as smoking, BMI and hypertension compared to women. Women had worse metrics for total cholesterol and physical activity. (56) Additionally, specific risk factors for ACS present in women and are spared in men, these are most likely linked to hormonal exposure. Among others, these include pregnancy, menopause and oral contraceptive therapy. In the peripartum period, women demonstrated a pronounced risk of MI from spontaneous coronary artery dissection. (56) Menopause itself seems to act as an independent contributor for ACS, even after the adjustment for age and other risk factors. A large population-based study found that postmenopausal women had greater estimated 10-year ASCVD risk compared with women before reaching menopause. (28) Pregnancy can introduce multiple medical conditions, which can predict an increase of future cardiovascular events in a woman's life. (57) One being gestational hypertension, which increases the risk of CVD, including heart failure, myocardial injury, stroke, and mortality as well as future diabetes. (57) Women with pregnancy may face critical health complications, including eclampsia, preeclampsia, amniotic fluid embolisms, obstetric shock, and postpartum hemorrhage. Previous research indicates that experiencing such forms of severe maternal morbidity is a significant predictor of elevated cardiovascular disease risk in later years. (58) Preterm birth, defined as delivery occurring before 37 completed weeks of gestation, has been linked to a higher long-term risk of cardiovascular outcomes, including cardiovascular events, coronary heart disease, stroke, and both cardiovascular and all-cause mortality. (58)

Other complications in pregnancy include low birth weight, placental abruption, and stillbirth, which further increase the risk of CVD. (59) On top of that, the absolute risk of ACS is realtively low when it comes to oral contraception. However, the relative risk elevates with higher doses of estrogen. (60) Additionally, the risk of hypertension increases 1.5-1.8-fold in women on oral contraception. (61) Moreover, specific diseases such as polycystic ovary syndrome, endometriosis, and breast cancer can bear additional risk factors for women. (62)

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by excessive production of androgens by the ovaries. (63). It is closely linked to metabolic syndrome and type 2 diabetes

mellitus, conditions that contribute indirectly to an elevated risk of cardiovascular disease in affected individuals. However, it is unclear whether it acts as an independent risk factor. (64)
Endometriosis is a gynecologial disease affecting many women, where tissue similar to the endometrium is growing outside the uterine cavity. (65) A systematic review of six longitudinal studies showed that women suffering from endometriosis had a significantly greater risk of developing ischemic heart disease when compared to healthy women. (66)
Breast cancer history, or more specifically, its treatment might be associated with a greater CVD risk. Medications commonly used, such as anthracycline and trastuzumab, present with cardiotoxic effects, as well as radiotherapy. (67) The increase in risk starts within a few years of exposure and can possibily last for up to twenty years. (68) A large European population-based study of 1.3 million Italian women confirmed that women with breast cancer had an increased risk of myocardial infarction (HR 1.20; 95% CI 1.05–1.38) and stroke (HR 1.58; 95% CI 1.38–1.82), with chemotherapy identified as the major risk factor for MI. (69) Especially patients who have been treated with aromatase inhibitors are linked to higher rates of ischemic heart disease and face and significantely elevated risk of MI when compared to patients who received hormonal therapy. (70)

5.2.2 Risk Factor Awareness

Awareness for risk factors among ACS patients plays a role in secondary prevention and might lead to a decreased risk of recurrent coronary events. (71) The European Journal of Preventive Cardiology investigated this by analyzing 8,261 patients across 27 countries of the ESC EUORP EUROASPIRE V survey. The study included men and women aged 18 to 80 years who were hospitalized for either an initial or recurrent coronary event. Among the risk factors were smoking, physical activity, and obesity as well as target blood pressure, LDL-C levels, and HbA1c levels if the patient had self-reported diabetes. The findings demonstrated that, overall, women had poorer control of cardiovascular risk factors than men. Although women were more often non-smokers, they had higher rates of obesity. At the same time, fewer women achieved target levels for low-density lipoprotein cholesterol and glycated hemoglobin compared with men. (71)

5.3 Pathophysiological Differences

More frequently, women present with nonobstructive CAD, including Myocaridal Infarction with non-obstructive coronary arteries (MINOCA) and microvascular dysfunction, whereas men more often present with large-vessel disease. (72)

According to recent literature, women present with MINOCA significantely more often than men (10.5% of women vs. 3.4% of men; $P < 0.0001$). (72) Data from the VIRGO study of young patients presenting with AMI (age 18-55 years) demonstrated that MINOCA was diagnosed

in 11.1% of women compared to only 2.7% of men. (73) The AHA Scientific Statement confirms that men more often present with obstructive CAD, whereas women with AMI more frequently show MINOCA. (74) Gender disparities have also been analyzed in nonobstructive CAD and Microvascular Dysfunction. The WISE (Women's Ischemia Syndrome Evaluation) study reported that, among approximately 500,000 women in the United States who underwent invasive coronary angiography, around 50% showed no evidence of obstructive coronary lesions. This corresponded to a threefold higher prevalence of non-obstructive coronary artery disease compared with similarly evaluated men. (75) A 2026 European Heart Journal Scientific Statement confirms that women are more likely to experience microvascular disease and endothelial dysfunction. Paradoxically, women seem to be less affected by severe myocardial ischemia at similar levels of coronary stenosis compared to men. (76)

5.4 Clinical Presentation

Sex-related disparities in clinical presentation of acute coronary syndrome (ACS) have been explored and may play a role to delays in diagnosis and treatment, particularly among women. (5) At the time of ACS presentation, women are usually older than men, on average 2 to 10 years older and often carry a larger burden of cardiovascular risk factors. (6,77,78)

Although chest pain persist as the most frequent presenting symptom in both sexes with a pooled prevalence of 79% in men vs. 74% in women, women are more Crucially, the often-used distinction between "typical" and "atypical" symptoms is increasingly recognized as potentially misleading, as symptoms experienced by women with ACS are often named as "atypical" simply because they differ from those experienced by men. A 2020 systematic review and meta-analysis concluded that since these differences have been established for years, symptoms should not be named as "atypical" or "typical." anymore. (78) Data from the GRACE registry and subsequent meta-analyses confirm that while chest pain was the most prominent symptom in both sexes, women with ACS were more likely to present with accompanying symptoms such as vomiting or nausea (OR 1.64; 95% CI 1.48–1.82), pain between the shoulders (OR 2.15; 95% CI 1.95–2.37), as well as shortness of breath (OR 1.34; 95% CI 1.21–1.48) compared to men. (78) Women also had decreased odds of chest pain presentation (OR 0.70; 95% CI 0.63–0.78) and diaphoresis (OR 0.84; 95% CI 0.76–0.94). (78) Despite these differences, chest pain remained the single most frequent presenting symptom, underscoring that so-called "typical" symptoms are still common across sexes. However, ACS continues to be underdiagnosed in women, even when they present with chest pain which results in disadvantages in time to treatment and appropriate care. (79–81) Compared with men, women experiencing STEMI often arrive for care later after symptoms begin. Among those who did seek medical attention before the onset of ACS, women were more frequently told that their

symptoms were unlikely to be of cardiac origin. (53.4% vs. 36.4%; P < 0.001). (79) Age further modifies sex-related differences in presentation. The landmark JAMA study by Canto et al. (2012) of over 1.1 million patients demonstrated that women aged 45 years or younger who experience acute myocardial infarction (AMI) are significantly more likely to present without chest pain than men of the same age group. (adjusted OR 1.30; 95% CI 1.23–1.36), a pattern that attenuates with advancing age. (81) The VIRGO study confirmed that young women with STEMI were 50% more likely than similarly aged men to present without chest pain, with 1 in 5 women perceiving their symptoms as related to anxiety or stress rather than AMI. (73,82) This finding is particularly relevant given that absence of chest pain does not imply lower severity of coronary disease or better prognosis. In fact, younger women presenting without chest pain had higher in-hospital mortality than younger men without chest pain. (81)

The following figure from Canto et al. illustrates how sex differences in MI presentation without chest pain are most pronounced in younger patients and progressively diminish with advancing age.

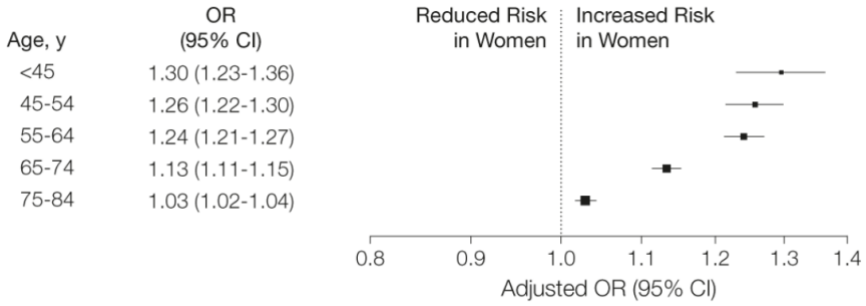

Figure 3.
Sex Differences in Myocardial Infarction Presentation Without Chest Pain/Discomfprt, stratified by Age
Association of Age and Sex With Myocardial Infarction Symptom Presentation and In-Hospital Mortality
JAMA, 2012

5.5 Diagnostic Challenges in Women

Despite improvements in cardiovascular care over the past years, women with acute coronary syndrome continue to face significant diagnostic challenges which contribute to delays, recognition and misdiagnosis as well as suboptimal treatment. (78) Evidence suggest that gender differences exist in recognition and diagnostic pathways which potentially have an adverse affect on outcomes for women.

As noted before, the clinical presentation of women with ACS differs often from those of men, making clinical suspicion more difficult for both patients and clinicians.

These differences are associated with delays at multiple stages of care. Those being longer time to treatment when compared to men, delays in the initiation of care and inconsistencies in the

management of ACS. that ultimately impact outcomes. Current data demonstrates that female sex is significantely associated with more frequent treatment delays in ACS, and women are less prone to undergo invasive management such as coronary angiography and revascularization in appropriate time manners. (3) These finding are supported by the following literature: A pooled analysis on 7 studies from from Vienna inlcuded 4593 patients and reported delays in pain onset to first medical contact in female STEMI patients. Stehli at al. reported comparable findings, noting that women with STEMI experienced longer delays between symptom onset and hospital presentation, even after accounting for age and comorbidities. Many authors attribute these delays to the fact that women more frequently present with atypical or non-cardiac symptoms, which can lead to misinterpretation by both patients and healthcare providers, as discussed previously. (83) Moreover, women suffering from IHD are less likely to be diagnosed in the prehospital setting with myocardial infarction when compared to men. (84) These findings suggest that sex based differences in clinical suspicion and symptom evalutation contribute to diagnostic error, underscoring the need for improved awareness of sex-specific manifestiations of ACS and improved diagnostic approaches in clinical practice.

5.6 Treatment and Management

5.6.1 Reperfusion Therapy according to ESC Guidelines

The 2023 European Society of Cardiology (ESC) guidelines now provide a unified approach to the management of acute coronary syndrome (ACS), treating ST-elevation myocardial infarction (STEMI) and non-ST-elevation ACS (NSTE-ACS) as a single scale of disease, compared to the previous guidelines from 2017. (23) These guidelines prioritize rapid diagnosis, early risk stratification, and the prompt initiation of reperfusion and pharmacological therapy to minimalise myocardial injury and improve clinical outcomes. For patients presenting with a working diagnosis of STEMI, immediate coronary angiography and primary percutaneous coronary intervention (PPCI) remain the first line reperfusion strategy, provided the procedure can be performed within 120 minutes of the ECG-based diagnosis. When primary percutaneous coronary intervention (PCI) cannot be performed in a timely manner, fibrinolytic therapy is advised within 12 hours of symptom onset in patients who have no contraindications. PPCI may still be appropriate for STEMI patients presenting after 12 hours if they exhibit ongoing ischaemic symptoms, haemodynamic instability, or life-treathenting arrhythmias. In contrast, routine PCI of the infarct-related artery is generally not recommended in asymptomatic individuals who present more than 48 hours after symptom onset. Pre-hospital fibrinolysis should be initiated as soon as possible, with a goal of administering the bolus within 10 minutes of diagnosis, followed by an immediate transfer to a PCI-capable centre.

For patients with NSTE-ACS, the timing of intervention is determined by risk stratification. An immediate invasive strategy (<2 h) is reserved for patients meeting very high-risk criteria, such as hemodynamic instability or cardiogenic shock. For high-risk patients, including those with a confirmed NSTEMI diagnosis or dynamic ECG changes, an inpatient invasive strategy is recommended, and an early invasive strategy (within 24 h) should be considered. In patients with a low index of suspicion for NSTE-ACS, a selective invasive approach is recommended, where intervention in based on non-invasive testing and clinical assesment.
Core pharmacological principles include the use of antiplatelet therapy, anticoagulation, statins, beta-blockers, and renin-angiotensin system inhibitors, with treatment regimens individualized based on the patient's specific ischemic and bleeding risks. (23)
While the guidelines emphazise that women and men receive uniform benefit from these management strategies and should be treated similarly, they explicitly urge clinicians to be mindful of gender disparities. Healthcare providers should be conscious of potential gender bias, as women are often less likely to receive on-time revascularization and may present with different symptom patterns that require careful assessment.

5.6.2 Gender Disparities in Reperfusion Therapy

Extensive literature has demonstrated persistent sex-based disparities in reperfusion therapy among patients presenting with ACS particularly ST-segment elevation myocardial infarction (STEMI). Women are consistently less likely than men to receive prompt reperfusion treatment, including primary percutaneous coronary intervention (PPCI), and often encounter delays at multiple stages of acute care. (85) A global meta-analysis comprising 56 studies and 705,098 patients, of whom 31% were women, demonstrated that female patients had significantly longer delays to first medical contact, with a mean difference of 42.5 minutes, as well as prolonged door-to-balloon times, averaging 4.9 minutes longer than those observed in men. (79) In a large registry of 13,451 patients undergoing PCI for STEMI or NSTEMI, women accounted for around 22% of the cohort and exhibited significantly longer ischemic times than men. Among STEMI patients, median symptom-to-door time was substantially longer in women (190.1 min) compared with men (148.5 min, $p < 0.001$). After adjusting for age and comorbidities, female sex remained independently associated with an approximately 30-minute longer total ischemic time, indicating that these delays cannot be fully explained by baseline risk differences. (86)
Disparities extend beyond prehospital delay to in-hospital processes, including door-to-balloon (DTB) time. Multiple studies have reported longer DTB times in women with STEMI, even within established PCI networks. In one study, median DTB was overall 8 minutes longer in women, approximately 20 minutes longer in women presenting to the primary Emergency Department, and

12 minutes longer in women presenting as interhospital transfers. (87) A separate analysis of 6,179 consecutive STEMI patients found that women had longer median symptom-to-balloon times (204 vs. 181 minutes; $p < 0.001$) and longer median door-to-balloon times (81 vs. 75 minutes; $p < 0.001$). (5) These delays have been attributed to higher rates of incorrect initial triage, delayed acquisition of the first electrocardiogram, misattribution of symptoms to noncardiac causes by healthcare professionals, implicit gender bias, and underuse of diagnostic tests in women. (88) Importantly, prolonged DTB times in women have been observed even after adjustment for ECG characteristics and clinical confounders, suggesting that female sex might be an independent predictor of delayed reperfusion. (84,86)

Women with ACS are also less probable than men to undergo revascularization therapy overall (adjusted OR for PCI 0.68; 95% CI 0.66–0.70). (5) When PCI is performed, radial access is less frequently used in women, and women faced increased rates of initial radial arterial access failure (11.3% vs. 3.1%; $p < 0.001$). (84,89) Collectively, these findings highlight persistent inequities in both access to and timeliness of reperfusion therapy for women with ACS, with important implications for myocardial salvage and clinical outcomes.

Table 1. Summary of Disparities in Timing

Metric	Women	Men	References
Delay to first medical contact	+42.5 min (mean difference)	—	(79)
Symptom-to-door time (STEMI)	190.1 min (median)	148.5 min (median)	(86)
Door-to-balloon time	+4.9 min (mean difference)	—	(79)
Door-to-balloon (primary ED)	+19 min (median)	—	(87)
Symptom-to-balloon time	204 min (median)	181 min (median)	(5)
Adjusted total ischemic time	+30 min	—	(86)
Likelihood of receiving PCI	aOR 0.68 (95% CI 0.66–0.70)	Reference	(5)
Radial access failure rate	11.3%	3.1%	(84,89)

5.6.3 Overview of Anticoagulation and Antiplatelet Therapy According to ESC Guidelines

Anticoagulation is recommended during the acute phase of ACS, especially in those undergoing an invasive strategy. Initial options include unfractionated heparin and enoxaparin (LMWH), administered at the time of diagnosis or intervention. Management differs between STEMI and NSTE-ACS slightly. (23) In most cases, anticoagulation therapy is discontinued immediately following PCI, with exceptions only in select clinical situations. Routine continuation of anticoagulation after the procedure is generally not required for the majority of patients. (23) Antiplatelet therapy represents a core component in the management of acute coronary syndrome aiming to reduce recurrent ischemic events while balancing bleeding risk. The strategy of choice following an ACS event, according to the European Society of Cardiology, is dual antiplatelet

therapy (DAPT) consisting of aspirin and a $P2Y_{12}$ inhibitor for up to 12 months irrespective of the stent type, unless contraindicated. (23) Ticagrelor or prasugrel is preferred over clopidogrel, given their superior antiplatelet effect, although prasugrel is contraindicated in patients with a previous stroke event. (90)

ESC guidelines emphasize individual risk assessment, particularly in populations at high bleeding risks. However, they do not differentiate antithrombotic treatment recommendations based on sex. Despite these recommendations, real-world data demonstrated notable differences in the initiation, selection, and intensity of antiplatelet and anticoagulation therapy.

5.6.4 Disparities in Antiplatelet and Anticoagulation Therapy

According to the START ANTIPLATELET Registry, which evaluated 840 patients wit ACS there are several key differences in how antiplatelet therapy is administered to men and women. Men were more likely to be treated with DAPT than women (94% vs. 88%, p=0.01) Clopidogrel was significantly more prevalent in women, with 41% of women receiving it compared to 33% of men (p=0.04). Ticagrelor was the most common strategy for both sexes and showed no significant differences in usage. (91,92)

While the efficacy of antithrombotic agents is generally similar between sexes, notable differences in the magnitude of benefit and the risk of adverse events such as bleeding have been found. (92) Evidence from several major clinical trials highlights subtle differences in how men and women respond to antiplatelet regimens. In a meta-analysis of DAPT, the combination of clopidogrel and aspirin appeared to confer a smaller relative benefit in women than in men, with a 7% reduction in major adverse cardiovascular events (MACE) observed in women compared with a 16% reduction in men. (93) The TRITON-TIMI 28 trial demonstrated that, at 15-month follow-up, the treatment effect was greater in men than in women. (94)

A primary distinction in anticoagulation therapy management is the higher bleeding risk faced by women, which influences treatment choices. According to the ESC Workgroup, women were more likely to receive inappropriate doses of anticoagulants such as unfractioned heparin (UFH) because dosing is often not correctly adjusted for their lower body weight or renal function. (92) Additionally, women experience a higher risk of in-hospital bleeding events than men. Aamong patients under the age of 50, the incidence of Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding events was approximately four times higher in women compared with men in the same age group. (95) This increased risk of bleeding in premenopausal women might be partly related to fluctuations in estrogen and progesterone, which influence platelet and procoagulant factors. (94,95) In younger patients, regardless of sex, a tendency toward excessive use of anticoagulants during the management of acute coronary syndromes and percutaneous coronary

intervention has been found. However, this excess dosing is linked to significantly increased bleeding rates exclusively in young women compared with their male counterparts. (92) Gender differences among complications were also presented by Elgendy IY et al. who reported that women presenting with cardiogenic shock are at greater risk of major bleeding events compared with men. (96) Further emphasis on complications is mentioned in the next section.

6. Outcomes and Prognosis Literature Analysis

6.1 Morbidity and Mortality

Mortality outcomes in patients with ACS are typically categorized into short-term and long-term phases to assess the immediate and enduring impact of the cardiac event. (3) Short-term mortality is defined as deaths occurring within the initial hospital stay or within 30 days of the event. Long-term mortality generally refers to all cause deaths, occurring over a more extended follow-up period, specifically at least one year post myocardial infarction. (97)

Evidence from large-scale meta-analyses and national registries indicates significant gender differences in "crude" mortality, meaning raw numbers without taking any covariants into account. These suggest that women face a poorer diagnosis than men.. A worldwide meta-analysis involving 56 studies and 705,098 patients with STEMI reported that women had 91% greater odds of in-hospital mortality compared with men (OR 1.91; 95% CI 1.84–1.99). (98) Similarly, a pooled evaluation of 11 randomized clinical trials in acute coronary syndrome, including 136,247 patients, found that unadjusted 30-day mortality was almost twice as high in women as in men (OR 1.91; 95% CI 1.83–2.00), with mortality rates of 9.6% and 5.3%, respectively. (99) In addition, a meta-analysis of more than 68,000 STEMI patients undergoing primary PCI demonstrated that women had a 93% increased risk of in-hospital mortality (RR 1.93; 95% CI 1.75–2.14) and a 58% higher risk of death at 1 year (RR 1.58; 95% CI 1.36–1.84) in unadjusted analyses. (100)

These crude mortality differences are substantially attenuated and, in some analyses reversed after adjustment for baseline characteristics. In the pooled analysis of TIMI trials (68,730 NSTEACS patients), the crude excess risk of 30-day mortality in women (unadjusted HR 1.24; 95% CI 1.07–1.44) was no longer significant after multivariable adjustment (adjusted HR 0.91; 95% CI 0.76–1.08), and women actually had lower mortality than men from day 30 through follow-up (adjusted HR 0.80; 95% CI 0.74–0.87). (101)

The SWEDEHEART registry similarly found no sex differences in all-cause mortality after adjustment for age, year, and comorbidities. Although women showed greater excess mortality relative to the general population, this disparity was reduced after controlling for the use of guideline-recommended treatments. (102) These findings suggest that the observed crude mortality

disadvantage in women is largely explained by older age at presentation, higher burden of comorbidities, and differences in treatment rather than female sex itself. (103)

The following figure from a recent meta-analysis illustrates the time-dependent sex differences in major adverse cardiovascular events after PCI, showing that women's elevated risk is most pronounced in the short-term period.

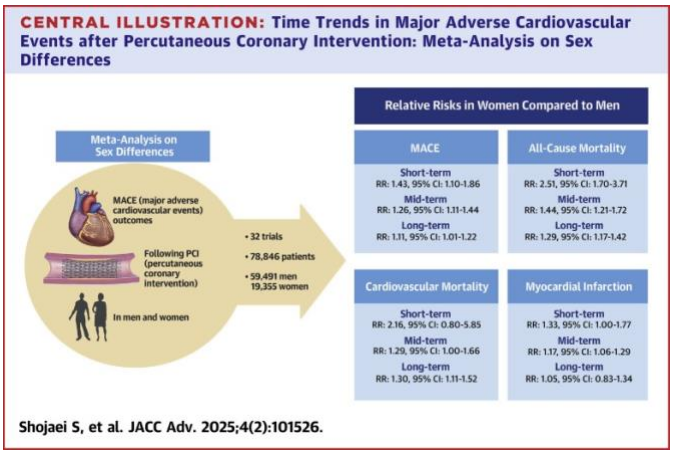

Figure 4.
Time Trends in Major Adverse Cardiovascular Events After Percutaneous Coronary Intervention: Meta-Analysis on Sex Differences, Shojael S, et. Al. JACC Adv. 2025;4(2):101526

Sex disparities have also been found in long term ACS outcomes and prognosis. A systematic review analyzing 39 studies by Bucholz and colleagues found that women experienced higher crude mortality rates at 5 and 10 years following acute myocardial infarction compared to men. However, these observed differences were reduced after accounting for age. (104) A nationwide Dutch investigation conducted by Ten Haaf and colleagues examined around 29,000 patients with acute coronary syndrome. The study showed that women had higher one-year mortality than men overall, especially among those younger than 71 years; in contrast, older women had lower mortality rates compared with men of the same age group. (105) In a separate analysis, Sawano and collaborators used data from the VIRGO study, which enrolled younger patients with acute myocardial infarction across 103 hospitals in the United States. Their results indicated that women aged 18 to 55 were more likely than men to be rehospitalized within one year of discharge for both cardiac and non-cardiac causes, suggesting poorer post-discharge outcomes in younger women relative to men. (106)

6.2 Influence of Age as an Effect Modifier

A critical finding in recent literature is that the risk profile for women is heavily dependent on age. While the overall adjusted mortality might appear similar between genders, especially women under

the age of 65 are at risk of a unfavourable prognosis. (107) Specifically, women younger than 50 face 38% higher odds of death than men of the same age, while those aged 50-65 face 25% higher odds. Interestingly, this trend reverses in older populations; women over 75 are significantly less likely to die in the hospital than men in the same age group. (100) Another meta-analysis supported these findings: Dhah and colleagues conducted an analysis of 56 studies examining hospital outcomes in patients with STEMI. Overall, women experienced higher rates of in-hospital death, recurrent myocardial infarction, stroke, and major bleeding than men. Much of the increased mortality risk in women was attributed to their older age at the time of presentation. (98)

6.3 Systemic Factors Contributing to Female Mortality

Beyond biological differences, several systemic factors that might contribute to higher crude mortality in women have been identified. As mentioned in previous sections, women are significantly more likely to experience delays in seeking and receiving medical care as well as receiving guideline-recommended invasive treatments. (108,109) Additionally, women have a higher likelihood of experiencing healthcare-related complications and are more likely to require longer hospital stays. (100,110) Beyond this, the 2025 ACC/AHA Guidelines not that women are particularly at risk for 30-day readmission following ACS hospitalisation. (86)

6.4 Sex differences in Cardiac Rehabilitaion outcomes

Cardiac rehabilitation forms an important aspect of secondary prevention after ACS and carries a Class I, Level of Evidence A recommendation by major guidelines, based on its function in reducing recurrent events, enhancing survival, improving psychological health, and supporting long-term risk factor control. (86) CR improves mortality after MI in both sexes; however, the risk reduction is more pronounced in women. (88)

Although cardiac rehabilitation (CR) is well established as beneficial, it remains underused, especially among women who are less frequently referred, less likely to enroll, and less likely to complete these programs. This disparity is linked to several factors, including fewer physician referrals, older age at presentation, caregiving responsibilities, financial and transportation challenges, and higher rates of depression and anxiety following acute coronary syndromes. (111) A 2022 review by Smith and colleagues found that women tended to have poorer outcomes in areas such as exercise training and diabetes management, while results for lipid levels, blood pressure, and psychological support were comparable or showed mixed patterns between sexes. (112). More recently, a 2025 meta-analysis by Guo et al. reported that after participation in CR, women had lower peak oxygen uptake, reduced peak metabolic equivalents, and poorer quality of life than men.

However, no significant sex-based differences were observed in all-cause mortality, recurrent myocardial infarction, or rehospitalization during follow-up. (113)

7. Representation in Clinical Trials Literature Analysis

Women continue to be significantly underrepresented in ACS clinical trials despite compromising 32-40 % of real-world ACS patients. (114) ACS trials show the most prominent underrepresentation among all cardiovascular conditions, with only 26% female participants between 2010–2017. (80) A systematic review of 460 ACS trials (2001–2018) found that women's enrollment actually decreased over time, from 27% in 2001–2006 to 24% in 2013–2018. (114) More recent data (2017–2023) show a median female-to-male ratio of only 0.32 in ACS trials, with a participation-to-prevalence ratio of 0.79, indicating women are enrolled at rates below their disease burden. (115)

Barriers to enrollment include: failure to approach women as potential participants, familial responsibilities, sex differences in clinical presentation affecting screening, older age at presentation (often falling outside trial time windows), and lower rates of coronary angiography/PCI which affects eligibility for procedural trials. (114,116) This underrepresentation limits the generalizability of trial findings and the ability to provide sex-specific treatment recommendations (80,117)

8. Methods

This study was conducted as a narrative literature analysis to systematically explore and synthesize current evidence regarding gender-related differences in the clinical presentation, diagnosis, management, and outcomes of acute coronary syndrome (ACS). A comprehensive literature search was performed using the electronic databases PubMed/MEDLINE, Google Scholar, and the Cochrane Library, supplemented by clinical practice guidelines from major cardiovascular societies (European Society of Cardiology, American Heart Association, American College of Cardiology), institutional reports (EuroHeart Reports, World Health Organization), and reference lists of relevant articles. The search was conducted between September 2025-April 2026 using combinations of key terms including "acute coronary syndrome," "myocardial infarction," "STEMI," "NSTEMI," "sex differences," "gender differences," "women," "clinical presentation," "diagnosis," "treatment,", “reperfusion therapy”, “anticoagulation therapry”, "outcomes," "mortality," and "cardiac rehabilitation."

Studies were included if they were published in English between 1990 and 2026, with emphasis on literature from the past 10 years, and addressed sex or gender differences in any aspect of ACS including epidemiology, pathophysiology, risk factors, clinical presentation, diagnosis,

management, outcomes, or secondary prevention. Eligible study designs included randomized controlled trials, observational cohort studies, cross-sectional studies, systematic reviews, meta-analyses, registry analyses, and clinical practice guidelines involving adult populations (age ≥18 years). Studies were excluded if they were case reports or case series with fewer than 10 patients, focused exclusively on pediatric populations or stable coronary artery disease without reference to ACS, were conference abstracts without full-text availability, had significant methodological limitations, or represented duplicate publications with overlapping patient populations, in which case the most comprehensive or recent publication was retained.

Titles and abstracts were screened for relevance, and full texts of potentially eligible articles were assessed against the inclusion and exclusion criteria. Data extracted from included studies encompassed study design, sample size, patient demographics, geographic location, sex-stratified results, adjusted and unadjusted effect estimates, and key conclusions regarding gender differences. The quality of included studies was assessed using study design-appropriate criteria, evaluating systematic reviews for comprehensive search strategies and heterogeneity assessment, observational studies for adequate sample size and confounder adjustment, and clinical practice guidelines for the rigor of their development process. Given the heterogeneity of study designs, populations, and outcomes, a narrative synthesis approach was employed rather than formal meta-analysis, with findings organized thematically according to the four primary research questions. As this study involved analysis of previously published literature and did not involve primary data collection from human subjects, ethical approval was not required.

9. Discussion

This literature analysis examined gender-related differences across the spectrum of acute coronary syndrome, from epidemiology and pathophysiology through clinical presentation, management, and outcomes. The findings reveal persistent and clinically significant disparities that deserve attention from clinicians, researchers, and healthcare systems. Despite decades of research highlighting these differences and repeated calls for action from professional societies, meaningful progress has been slow.

The epidemiological data consistently demonstrate that women comprise approximately one-third of ACS cases across European registries, with this proportion remaining remarkably stable over time. (1) The 2023 EuroHeart Report documented that approximately 32% of ACS admissions were female across seven European countries, a distribution consistent with French and German national data showing women representing 32% and 30% of ACS hospitalizations, respectively. (2,3) This consistent sex distribution across different healthcare systems and time periods may suggest

fundamental biological and behavioral differences in disease susceptibility rather than artifacts of healthcare access or reporting.

However, concerning trends have emerged when examining age-stratified data. French nationwide data revealed an increase of 21% in STEMI admissions among women under 65 years between 2004 and 2014, while older women experienced significant declines in all ACS types. (48,49) Similarly, international data demonstrated that while overall ACS hospitalization rates declined in both sexes, the rate of decline was smaller in women, resulting in an increasing male-to-female hospitalization ratio over time. (51) These disparieties in trends suggest that younger women are not benefiting equally from improvements in primary prevention and may reflect the rising prevalence of traditional risk factors such as smoking and obesity in this population. The observation that young men experienced more than four times the absolute decline in AMI hospitalizations compared to young women over the past decade is particularly alarming and warrants public health attention. (52)

The age-related patterns in ACS incidence further highlight the importance of sex-specific analysis. Women's MI risk corresponds to that of men 10-15 years younger, with this protective effect persisting throughout life but narrowing with advancing age. The adjusted incidence rate ratios for men versus women decrease progressively from in the 35-54 age group compared to the 75-94 age group, demonstrating that while relative risk decreases with age, the absolute difference in risk actually increases in older populations. (55)

Risk factor profile appears to play a critical role in prevention and risk calculation of ACS. Particulary in women, risk factor profiles include sex-specific conditions, which extend beyond traditional cardiovascular risk factors. (56) These tend to be overlooked in clinical practice. While traditional risk factors such as diabetes, hypertension, smoking and dyslipidemia affect both sexes, their relative impact on cardiovascular outcomes differs. European data indicate that men have higher rates of hypertension and smoking, while women present with worse metrics for total cholesterol and physical activity. (47) The EUROASPIRE V survey revealed that women present with worse overall risk factor control compared to men, being more likely to be obese and less likely to achieve target LDL cholesterol and glycated hemoglobin levels, despite being more likely to be smoking free (71)

Female-specific risk factors represent a critical but underappreciated component of cardiovascular risk assessment in women. Complications during pregnancy have emerged as important predictors of future cardiovascular events, with gestational hypertension elevating the risk of myocardial ischemia, heart failure and mortality. Preeclampsia, preterm delivery, low birth weight, placental abruption, and stillbirth all confer additional cardiovascular risk that may manifest decades after the

index pregnancy. The peripartum period itself carries substantially increased MI risk, particularly from spontaneous coronary artery dissection. (57–59)

Menopause has been identified as an independent contributor to cardiovascular disease risk, even after accounting for age and other conventional cardiovascular risk factors. Postmenopausal women demonstrate significantly higher estimated 10-year ASCVD risk compared with premenopausal women, reflecting the loss of estrogen's protective effects on lipid profiles and vascular function. Paradoxically, hormone replacement therapy has failed to reduce cardiovascular event rates in randomized trials, highlighting the complexity of hormonal influences on cardiovascular risk. (28)

Oral contraceptive use, while associated with low absolute risk of ACS, confers increased relative risk that is dose-dependent with estrogen content and is accompanied by a signifcant increase in hypertension risk. (61) Conditions such as polycystic ovary syndrome, endometriosis, and breast cancer treatment further expand the landscape of female-specific cardiovascular risk factors. Breast cancer treatment is particularly noteworthy, as anthracyclines, trastuzumab, aromatase inhibitors, as well as radiotherapy all confer cardiotoxic effects, that may persist for up to twenty years following exposure. (67–70)

The recognition of these sex-specific risk factors is essential for comprehensive cardiovascular risk assessment in women. Current risk prediction tools were largely developed in male-predominant populations and may inadequately capture the unique risk factor profiles of women, potentially contributing to underestimation of cardiovascular events and delayed implementation of preventive strategies.

A fundamental difference in ACS pathophysiology between sexes lies in the underlying coronary anatomy and mechanisms of ischemia. Women are significantly overrepresented among patients with MINOCA, comprising around 10% of female ACS patients compared to only 3.4% of male patients. (72) The VIRGO study of young AMI patients confirmed this disparity, with MINOCA diagnosed in approximately 11% of women versus 2.7 % of men. Women are more than twice as likely as men to have MINOCA, whereas men more commonly present with AMI associated with obstructive coronary artery disease. (82)

Striking evidence has been provided by the WISE study regarding sex differences in coronary anatomy, demonstrating that among approximately 500,000 women in the United States who underwent invasive coronary angiography, around 50% showed no evidence of obstructive coronary lesions. This corresponds to triple the prevalence of nonobstructive CAD in similarly referred men. (75) Women are more likely to develop coronary microvascular disease and endothelial

dysfunction, yet they often exhibit less severe myocardial ischaemia than men despite having comparable degrees of coronary artery stenosis. (76) These findings may have important implications for diagnosis, as standard coronary angiography may appear near-normal in women despite significant ischemia, potentially leading to false reassurance and inadequate treatment. The mechanisms of plaque disruption also differ between sexes. While plaque rupture accounts for the majority of ACS cases in both sexes, plaque erosion is responsible for a significantly higher proportion of events in women (37.4% vs. 18.5% in men). (5,8) This distinction may have therapeutic implications, as the optimal antithrombotic strategies for erosion-mediated versus rupture-mediated ACS may differ. The greater occurrence of plaque erosion, rather than plaque rupture, in women further highlights the importance of understanding ACS pathophysiology and developing targeted interventions.

The clinical presentation of ACS differs meaningfully between sexes, though the characterization of women's symptoms as "atypical" is increasingly recognized as misleading and potentially harmful. (78) A 2020 systematic review and comprehensive analysis explicitly demonstrated that since sex differences in ACS presentation have been established for a long time, symptoms should no longer be named as "atypical" or "typical." This terminology implies that women's presentations are less common rather than simply different, potentially contributing to diagnostic delays and misinterpretation of symptoms. Chest pain continues to be the most dominant symptom in both sexes, with pooled prevalence of 79% in men versus 74% in women, women present more often with accompanying symptoms. Meta-analyses have shown that women presenting with ACS more frequently report interscapular pain, nausea or vomiting, and dyspnoea, while being less likely than men to present with chest pain or diaphoresis. (79–81) These differences are most pronounced in younger women, the landmark JAMA study by Canto et al. demonstrated that women younger than 45 years with AMI are significantly more likely to present without chest pain compared to similarly aged men, a pattern that attenuates with advancing age. (81). The VIRGO study offered further insight into symptom interpretation among young women with acute myocardial infarction, revealing that approximately one in five attributed their symptoms to anxiety or stress rather than to a cardiac condition. (82) Young women presenting with STEMI had a 50% higher chance to present without chest pain when compated to men. This finding is particularly concerning because the absence of chest pain does not indicate milder coronary disease or more favorable prognosis. In fact, among patients who presented without chest pain, younger women experienced higher in-hospital mortality rates than men of the same age bracket. (81,83)

These presentation difsparities contribute to diagnostic delays and misdiagnosis at multiple levels. Women are less likely to be diagnosed with myocardial infarction in the prehospital setting and are

more often told by healthcare professionals, that their symptoms were not of cardiac orgin before ACS onset. (79,81) Such diagnostic challenges highlight the need for increasexd clinical suspicion and awareness of sex-specific symptom patterns among both patients and doctors.

Despite guideline recommendations emphasizing equal treatment for both sexes, substantial disparities persist in the management of women with ACS. The 2023 ESC guidelines explicitly state that women and men experience equivalent benefit from management strategies and should be treated similarly, while urging clinicians to be mindful of gender disparities and potential gender bias. (23) Nevertheless, real-world data consistently demonstrates that women experience inferior care across multiple domains.

Women experience longer delays at multiple stages of care. A global meta-analysis of 56 studies showed longer waiting times in women until the fist medical contact was reached as well as increased door-to-balloon time, when compared with men. (79) Registry data confirm that among STEMI patients, median symptom-to-door time was substantially longer in women (190.1 minutes vs. 148.5 minutes). After considering age and comorbidities, female sex remained independently associated with approximately 30 minutes longer total ischemic time. The persistence of these delays, suggest that female sex itself might act as an independent risk factor for delayed reperfusion. (86)

Disparities extend beyond prehospital delay to in-hospital processes. Several studies have demonstrated prolonged door-to-balloon times among women with STEMI. Contributing factors include higher rates of incorrect initial triage, delayed ECG aquisition, misattribution of symptoms to noncardiac causes by healthcare professionals, gender bias, and underutilization of diagnostic tools in women. (89,109)

Women tend to undergo revascularization less often overall, with adjusted odds ratios for PCI of 0.68 compared to men. Among patients undergoing PCI, women are less likely than men to receive radial access and have higher rates of initial radial artery access failure. (11% vs. 3%). These procedural differences may reflect both anatomical factors such as smaller vessel size, and implicit bias in clinical decision-making. (84,87,89)

Disparities in pharmacological management mirror those observed in invasive treatment. According to the START ANTIPLATELET Registry, men were more likely to be treated with dual antiplatelet therapy compared to women (94% vs. 88%), and clopidogrel was significantly more prevalent in women (41% vs. 33%), eventhough guidelines recommend ticagrelor and prasugrel, as these are considered as more potent $P2Y_{12}$ inhibitors. (90,91) While the efficacy of antithrombotic agents is

generally similar between sexes, meta-analyses suggest that the relative benefit of clopidogrel plus aspirin could be reduced in women compared to men. (93)

A critical consideration in anticoagulation therapy is the higher bleeding risk faced by women, which influences treatment choices but also reflects inadequate dose adjustment. Women are more likely to receive inappropriate doses of anticoagulants because dosing is often not correctly adjusted for their lower body weight and renal function. This overdosing is linked to substantially higher bleeding rates in young women compared with men, with women under 50 experiencing a fourfold greater risk of TIMI major or minor bleeding events than males of similar age. The elevated bleeding risk observed in premenopausal women may be partially influenced by hormonal fluctuations affecting platelet and procoagulant factors.

These treatment disparities exist despite evidence that women may experience equal or even larger benefit from guideline-directed therapies. (95–97) The persistence of disparities despite clear guideline recommendations suggests that systemic factors, including implicit bias and inadequate awareness of sex-specific considerations, continue to influence clinical decision-making.

Mortality data reveals a complex picture that is heavily modified by age and requires careful interpretation. Crude mortality rates are consistently higher in women across multiple studies and registries. A global meta-analysis of 56 studies including over 700,000 STEMI patients demonstrated that women had more than 90% higher odds of death within the hospital compared with men. (98) Similarly, a combined analysis of randomized ACS clinical trials demonstrated that unadjusted mortality within 30-days was nearly 2-fold higher in women, with mortality rates of around 10% in women versus 5% in men. Long-term outcomes show similar patterns, with women having approximately 58% higher risk of 1-year mortality in unadjusted analyses. (99,100) However, these crude mortality differences are substantially weakened after adjusting baseline characteristics. In pooled analyses of NSTE-ACS trials, the crude excess risk of womens mortality within 30 days was no longer significant after multivariable adjustment, and women actually had lower rates of death than men from day 30 follow-up. (101) The SWEDEHEART registry similarly found no sex differences in all-cause mortality after adjustment for comorbidities, age and year. (102) These findings may suggest that the observed crude mortality disadvantage in women is largely explained by older age at presentation, greater comorbidity burden, and differences in treatment rather than female sex itself.

Critically, age acts as an important effect modifier that fundamentally alters the relationship between sex and mortality. Women under 50 years face 38% higher adjusted odds of death

compared to similarly aged men, while those aged 50-65 face 25% higher odds. (107) This elevated risk in younger women persists even after considerations for baseline characteristics and treatment differences, suggesting that biological or unmeasured factors may contribute to worse outcomes in this population. (108) Conversely, women over 75 actually have significantly lower mortality than their male counterparts, representing a reversal of the pattern observed in younger patients. (100)This age-dependent relationship has important clinical implications. Younger women represent a particularly vulnerable population that could potentially benefit from tailored interventions to improve recognition, diagnosis, and treatment. The mechanisms underlying the excess mortality in young women remain incompletely understood but may relate to differences in pathophysiology (higher prevalence of MINOCA and microvascular disease), delays in diagnosis and treatment, or unmeasured biological factors. (53,87) Beyond biological differences, several systemic factors contribute to the observed disparities in outcomes. Delays may occur at multiple stages of care, including from symptom onset to first medical contact, from hospital presentation to diagnosis, and from diagnosis to initiation of treatment. (108,109) Women are also less likely to receive guideline-recommended invasive treatments and pharmacological therapies. Additionally, women have increased prevalence of complications related to healthcare and are more likely to require longer hospital stays. (53,101) The 2025 ACC/AHA Guidelines specifically note that women are at particularly elevated risk for 30-day readmission following ACS hospitalization. These systemic factors are potentially modifiable through targeted interventions. Standardized protocols that minimize the influence of implicit bias, educational initiatives to improve awareness of sex-specific presentations, and quality improvement programs focused on reducing treatment delays in women all represent opportunities for intervention. The persistence of disparities despite decades of awareness suggests that more intensive and systematic approaches are needed.

The disparities extend beyond acute management into secondary prevention, where cardiac rehabilitation represents a critical but underutilized tool. Cardiac rehabilitation is strongly recommended as a Class I, Level of Evidence A intervention because of its proven benefits in lowering recurrent cardiovascular events, improving survival, promoting psychological well-being, and facilitating long-term control of cardiovascular risk factors. A key observation is that CR improves mortality after MI in both sexes, with the risk reduction being more pronounced in women. (111–113) Despite the well-established benefits of cardiac rehabilitation, women remain considerably less likely than men to be referred to these programs, participate in them, or complete the full course of rehabilitation. Meta-analyses have shown that women enroll in cardiac rehabilitation at rates approximately 36% lower than those of men. (114) Barriers to participation include lower physician referral rates (a primary predictor of poor attendance), older age at

presentation with greater medical and psychological comorbidities, caregiving duties and family responsibilities, financial and transport barriers, and more elevated levels of depression and anxiety occuring after the ACS event. Depression is almost twice as common in women with MI compared to men, representing both a barrier to CR participation and a target for intervention. (115)
When women do participate in cardiac rehabilitation, outcomes are usually different from those of men. Women demonstrate smaller improvements in functional capacity. However, mortality benefits appear similar between sexes, and there are no significant sex differences in rates of MI or rehospitalization during follow-up. (113,115) These findings suggest that while the magnitude of functional improvement may differ, the clinical benefits of CR are preserved in women, reinforcing the importance of improving referral and completion rates.

A fundamental limitation underlying all sex-specific recommendations is the continued underrepresentation of women in ACS clinical trials. Despite comprising approximately one-third of real-world ACS patients, women account for only 25-27% of trial participants. ACS trials show the most prominent underrepresentation among all cardiovascular conditions, and concerningly, women's enrollment has actually decreased over time, from around 27% in 2001-2006 to 25% in 2013-2018. More recent data show a median female-to-male ratio of only 0.32 in ACS trials, with a participation-to-prevalence ratio of 0.79, indicating that women are enrolled at rates below their disease burden. (114–116)
Barriers to enrollment are multifactorial and include failure to approach women as potential participants, familial responsibilities that limit availability for study visits, sex differences in clinical presentation affecting screening and eligibility, older age at presentation (often falling outside trial age limits or time windows), and lower rates of coronary angiography and PCI which affects eligibility for procedural trials. This underrepresentation limits the generalizability of findings in clinical trials and the ability to develop evidence-based, sex-specific treatment recommendations.
The consequences of underrepresentation extend beyond simple generalizability concerns. When women are inadequately represented in trials, sex-specific adverse effects may go undetected, optimal dosing for women may not be established, and the relative efficacy of interventions in women versus men cannot be reliably assessed. Regulatory agencies and funding bodies have increasingly recognized this problem and implemented requirements for sex-stratified analyses and adequate representation, but progress has been slow. (117)

10. Limitations

Several limitations of this literature analysis should be acknowledged. First, it should be recognized that as a narrative review, selection bias in the inlcuded literaure may have been introduced

compared to systematic review methods. Relevant studies may have been missed despite efforts to conduct a comprehensive search.

The majority of included studies originated from high-income countries in Europe and North America, restricting the generalizability of findings. Low- and middle-income settings where healthcare infrastructure, cultural factors, and disease burden may differ substantially. The included studies varied considerably in their definitions of outcomes, adjustment variables, follow-up periods, and ACS classification criteria, making direct comparisons across studies challenging. In particular, the distinction between unadjusted and adjusted effect estimates was not uniformly reported among chosen studies, complicating the interpretation of sex-based mortality differences. Additionaly, many of the primary studies were observational and therefore subject to residual confounding. While several analyses adjusted for age and comorbidities, unmeasured confounding variables such as socioeconomic status, healthcare access, and psychosocial factors may have influenced the observed disparities.

The terms "sex" and "gender" were often used mutually in the primary literature, despite representing distinct biological and sociocultural constructs. This inconsistency limits the ability to disentangle the relative contributions of biological sex differences from gender-related social and behavioral factors. To add on, publication bias may have influenced the available evidence, as studies reporting significant sex differences may have been more likely to be published than those without relevant findings.

Finally, the restriction to English-language publications may have excluded relevant data from non-English-speaking populations, particularly from regions where gender disparities in cardiovascular care may be most pronounced.

11. Conclusion und Implications for Clinical Practice

The findings of this analysis have several important implications for clinical practice. Clinicians should maintain heightened awareness of sex-specific symptom patterns and avoid dismissing women's symptoms based on presentation differences. The terminology of "typical" versus "atypical" symptoms should be abandoned in favor of recognition that both patterns represent legitimate manifestations of ACS.

Second, healthcare systems should implement strategies to reduce treatment delays in women, including standardized protocols that minimize the influence of implicit bias, mandatory ECG acquisition within specified timeframes regardless of presenting symptoms, and quality metrics that track sex-specific performance indicators. Furthermore, risk assessment in women should incorporate female-specific risk factors including pregnancy complications, menopausal status, hormonal exposures, and conditions such as PCOS, endometriosis, and breast cancer treatment

history. Current risk prediction tools may inadequately capture these factors and should be supplemented with clinical judgment.

Lastly, efforts to improve cardiac rehabilitation referral and completion rates in women are essential for optimizing long-term outcomes. Automatic referral systems, flexible program formats, and attention to psychosocial barriers may offer help.

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