



Gender and Sex-related differences in Type 2 Myocardial Infarction: the undervalued side of a neglected disease

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ABSTRACT

Type 2 myocardial infarction (T2MI) occurs due to an imbalance between coronary blood supply and myocardial oxygen demand, leading to ischemia without the rupture of an atherosclerotic plaque, distinguishing it from Type 1 myocardial infarction (T1MI). Although T2MI is frequently diagnosed in clinical practice and associated with a poor prognosis, there is limited understanding of the sex differences in this condition, despite women representing a higher proportion of T2MI cases compared to T1MI. This review explores the definitions, epidemiological aspects, and clinical scenarios that reveal significant differences in T2MI between men and women that contribute to disparities in outcomes. It examines the unique roles that sex and gender play in the development, presentation, and diagnosis of T2MI, emphasizing the need for greater awareness of these factors. Understanding how these differences contribute to this condition is essential for developing patient-tailored approaches to managing this often-undervalued disease and improving outcomes.

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Abbreviations: CAD, Coronary Artery Disease; CCTA, Coronary Computed Tomography Angiography; CMR, Cardiac Magnetic Resonance; SCAD, Spontaneous Coronary Artery Dissection; T1MI, Type 1 Myocardial Infarction; T2MI, Type 2 Myocardial Infarction.

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Introduction

According to the Fourth Universal Definition of Myocardial Infarction (MI), type 2 MI (T2MI) represents a clinical condition identified by ischemia and a concomitant acute myocardial injury determined by a mismatch in myocardial blood demand and supply, in the absence of atherothrombosis or plaque disruption [1,2].

Over the last years, only small observational, single-center studies have explored this condition and expanded the knowledge regarding patients with T2MI [3,4]. In comparison to type 1 MI, T2MI is more common despite being significantly underrecognized, is associated with relevant morbidity and mortality and apparently affects predominantly older patients who are more likely to be

female and affected by other cardiovascular (CV) conditions (diabetes, heart failure and atrial fibrillation) [5].

Supportive treatment targeting the triggering conditions underlying the oxygen supply-demand mismatch and concomitant management of CV risk factors represent the cornerstone approach to patients affected by T2MI [5,6].

Sex- and gender-related differences have been described across a wide spectrum of cardiovascular conditions, both in the setting of ischemic and non-ischemic heart disease [7–9]. Although sex differences in clinical features and outcomes for T1MI patients are well established, little is known regarding the role of sex and gender in T2MI [10–12]. However, women seem to be affected more frequently by T2MI and present with a better long-term prognosis than men with this condition, although findings are inconsistent [4].

In this comprehensive review, we sought to describe the existing knowledge regarding sex and gender-based differences in clinical characteristics, pathophysiology and outcomes of T2MI between female and male patients, and to promote a more sex- and gender-sensitive approach to this clinical condition.

Definition and epidemiology

T2MI is a clinical syndrome characterized by a myocardial injury due to a discrepancy in myocardial blood demand and supply without evidence of plaque disruption or atherothrombosis. After the introduction of MI subtypes in the 2007 update of the universal definition of MI, T2MI was increasingly recognized as an under-rated condition despite being more common and associated with higher morbidity and mortality than T1MI [1].

As demonstrated by McCarthy et al., coronary artery disease (CAD) is frequently observed in T2MI; however, most patients have non-obstructive CAD, highlighting the multifaceted background of ischemia for this population [13].

According to the existing data from the literature, patients with T2MI are older, more likely female, and have a higher prevalence of CV comorbidities, such as heart failure and atrial fibrillation, as compared to individuals with T1MI [6].

The incidence of T2MI differs significantly according to clinical setting, definition, and diagnostic approach: it varies from 12.3 %, as attested in a Scottish emergency department cohort, to 2–37 % when considering patients admitted to hospital [14,15]. In comparison to T1MI, T2MI shows similar incidence in patients older than 75 years [15]; however, it should be taken into account that cardiac troponins are generally assessed in case of high pre-test probability of ischemia or myocardial injury: as a consequence, the real incidence of T2MI may be underestimated, as observed in several prospective cohort studies [16,17].

Regarding the wide spectrum of comorbidities presented by these patients, acute respiratory failure represents the MI trigger associated with the highest risk mortality in comparison to other conditions, while kidney failure is the most prevalent comorbidity among both sexes, with higher mortality in female patients [18].

Given the complexity and challenges associated with T2MI, there is a growing need and demand for more in-depth studies that should focus on the specific pathophysiological mechanisms and sex differences relevant to diagnosis, risk stratification, and short- and long-term management in order to improve outcomes.

Pathogenesis of type 2 myocardial infarction

As mentioned above, the mismatch between oxygen supply and demand identifies the pathophysiological mechanism of T2MI, while T1MI is caused by the rupture of an atherosclerotic plaque, both in obstructive and non-obstructive CAD (Fig. 1) [1,3].

A wide range of clinical conditions contributes to this imbalance (Table 1). These factors, whether cardiac or systemic, can reduce myocardial perfusion, increase myocardial oxygen demand, or involve overlapping mechanisms. Main contributors to the development of T2MI include sepsis, anemia, arrhythmias (both bradyarrhythmias and tachyarrhythmias), and hemodynamic disturbances (hypertension or hypotension). It should be outlined that these factors can individually induce this mismatch or act synergistically to cause myocardial ischemia [6]. Regarding the causes of T2MI, sepsis represents one of the primary triggers: systemic vasodilation and endothelial dysfunction result from the inflammatory response to infection in septic patients, leading to pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and interleukin-1 (IL-1). These molecules disrupt vascular tone regulation and endothelial function with a subsequent reduction of nitric oxide, which is essential for maintaining vascular homeostasis [6].

Anemia represents another important cause of T2MI by reducing myocardial oxygen delivery due to the impairment of blood oxygen-carrying capacity. Conversely, arrhythmias, both tachy- and bradyarrhythmias, might impair coronary perfusion and may induce ischemic episodes by increasing oxygen demand (predominantly tachyarrhythmias). It should be noted that arrhythmias, especially atrial fibrillation, can be triggered by systemic conditions such as sepsis or anemia and worsen the supply-demand mismatch with subsequent myocardial ischemia [6].

The role of sex in the pathogenesis of T2MI

Sex differences play a crucial role in the development and clinical presentation of T2MI.

Although variability exists across studies, women exhibit a significantly higher incidence of T2MI compared to men. This disparity is likely due to anatomical, hormonal, and functional differences [4].

From an anatomical standpoint, women present with smaller coronary arteries compared to men even when adjusted for body surface area (BSA). This anatomical characteristic makes female patients more susceptible to ischemic episodes under systemic stress, as smaller coronary arteries reduce flow reserve and increase the risk of endothelial dysfunction. This results in a diminished capacity to increase blood flow in response to higher demand [19].

In addition, coronary arteries in women, due to the above-mentioned characteristics, are more prone to spontaneous coronary artery dissection (SCAD). SCAD is a well-recognized cause of T2MI: It is characterized by a separation of the layers within the coronary arterial wall, usually due to an intramural hematoma, which may occur with or without an associated intimal tear. The expansion of the false lumen can compress the true lumen leading to reduced coronary blood flow and resulting in myocardial ischemia [20]. Unlike atherosclerotic coronary artery disease, SCAD is not related to plaque rupture. Instead, it is associated with predisposing conditions that compromise the structural integrity of the arterial wall, such as connective tissue disorders (e.g., Marfan or Ehlers-Danlos syndromes), chronic inflammatory diseases (e.g., systemic lupus erythematosus), or acute emotional and physical stressors that may act as triggers [21]. Although SCAD can occur in individuals of any age or sex, it predominantly affects women—accounting for approximately 90 % of cases—most commonly during the perimenopausal period. Importantly, SCAD is the leading cause of myocardial infarction during pregnancy and the postpartum period. Its clinical course is generally favorable with spontaneous healing observed in most cases [20,21].

Furthermore, sex hormones, particularly estrogens and androgens, play a crucial role in cardiovascular physiology and may help explain the observed sex-based differences in T2MI.

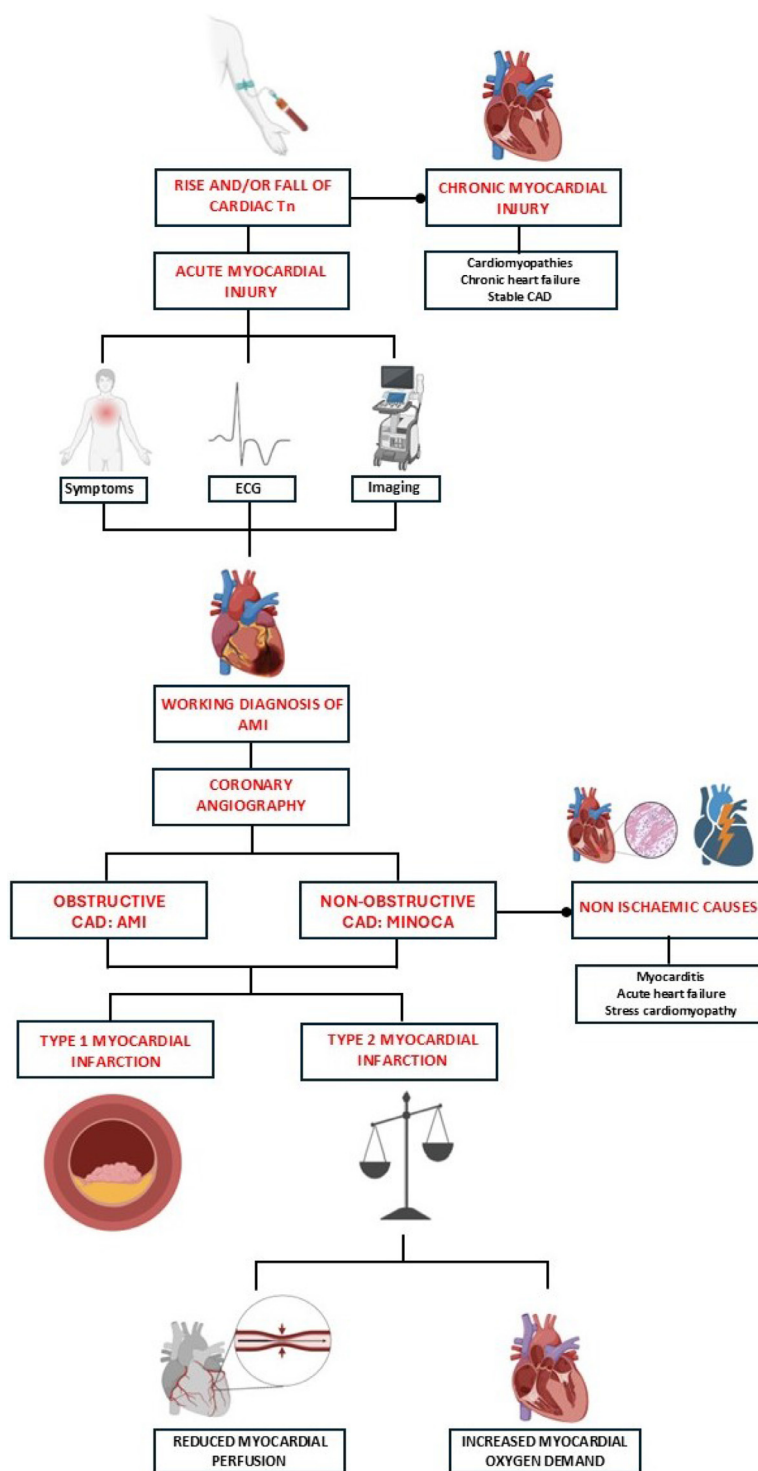


Fig. 1. Diagnostic work up of acute myocardial injury. After excluding non-ischemic causes, acute myocardial infarction (AMI) is further classified into Type 1 AMI due to atherosclerosis complications and Type 2 AMI due to oxygen demand-supply mismatch.

In T2MI, estrogens exert cardioprotective effects by enhancing endothelial function, reducing inflammation, and maintaining vascular tone through nitric oxide-mediated vasodilation [12]. They also inhibit the expression of adhesion molecules and pro-inflammatory cytokines such as $\text{TNF-}\alpha$ and IL-6, thereby attenuating chronic vascular inflammation and preserving endothelial integrity. Following menopause, the decline in estrogen levels leads to a loss of these protective mechanisms, contributing to an in-

creased susceptibility to coronary microvascular dysfunction and vasospasm—key triggers of T2MI [22]. This loss of hormonal protection likely underlies the marked rise in T2MI incidence observed in postmenopausal women [23].

In men, conversely, low testosterone levels have been linked to heightened systemic inflammation and impaired endothelial function, potentially influencing the risk and pathophysiological mechanisms of T2MI [23,24]. Supporting this, Rinaldi et al. demon-

Table 1
The spectrum of different etiologies underlying Type 2 myocardial infarction.

Type 2 Myocardial Infarction	
Reduced myocardial perfusion	
Cardiac Coronary artery spasm Microvascular dysfunction Spontaneous coronary artery dissection Fixed atherosclerosis Severe aortic stenosis Sustained bradyarrhythmias	Non-cardiac Severe anemia, methemoglobinemia Severe hypotension or shock Respiratory failure, ARDS, severe pneumonia, COPD exacerbation Pulmonary embolism Drug-induced (CO)
Increased myocardial oxygen demand	
Cardiac Sustained tachyarrhythmias Severe hypertension Left ventricular hypertrophy	Non-cardiac Hyperthyroidism High fever Sepsis Pheochromocytoma crisis Prolonged seizures/status epilepticus Drug-induced (cocaine, amphetamines)

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; COPD: Chronic obstructive Pulmonary Disease.

strated that microvascular spasm is more commonly observed in women, whereas epicardial coronary spasm tends to predominate in men—differences that may reflect distinct sex hormone profiles, particularly estrogens [24].

Hormonal influences also appear central to the pathophysiology of SCAD. Elevated estrogen and progesterone levels, especially during pregnancy and the peripartum period, may weaken the arterial wall by promoting smooth muscle relaxation and extracellular matrix remodeling. This hormonal environment increases susceptibility to dissection [22]. Conversely, hormonal withdrawal—such as that occurring postpartum or during perimenopause—may serve as a precipitating factor for SCAD events [20,21].

Sex differences in psychological and physical stress

Stress, both psychological and physical, is widely recognized as a potential trigger for oxygen supply-demand imbalance in the context of myocardial infarction. However, its effects and prevalence vary significantly between sexes [25].

In situations of emotional or physical stress, the adrenal glands release cortisol and adrenaline into the bloodstream in response to the hypothalamic-pituitary-adrenal axis activation. In this setting, females typically exhibit greater hormonal release in response to stressful events compared to men. Prolonged exposure to elevated cortisol and adrenaline levels can raise blood pressure and heart rate, as well as promote endothelial dysfunction. These physiological changes significantly increase the predisposition to an oxygen supply-demand mismatch, thereby increasing the risk of stress-induced myocardial ischemia in women [12,26]. On the other hand, mental health and stress disorders may also be affected by gender differences as a consequence of significant disparities in society roles, representing a gender minority, low self-esteem, gender-based violence [12,27].

Gender-specific considerations also include differences in pain tolerance between sexes. Previous research has suggested that sex differences in pain sensitivity may contribute to variations in MI symptoms between men and women: more precisely, in one study unrecognized MI was associated with a higher pain threshold in females but not in males [12]. Additionally, while pain sensitivity differs between males and females, females exhibit an even lower sensitivity in inflammatory states [28]. However, the role of pain tolerance in explaining differences in MI presentation between men and women has not been properly investigated and remains an area of debate.

Diagnostic work-up of T2MI

Sex-differences in differential diagnosis

The incidence of T2MI is similar between the two sexes and the diagnostic approaches should identify symptoms, the evidence of newly emerged ischemic electrocardiographic changes or development of pathological Q waves, and the imaging evidence of new loss of viable myocardium according to the fourth definition of MI [1]. Concomitantly, biomarkers such as high sensitivity-troponin T (hs-cTnT) must show a rise and/or fall in concentration with at least the 99th percentile combined with at least one of the above-mentioned ischemic pieces of evidence.

The differential diagnosis for T2MI in women encompasses a variety of conditions that share overlapping symptoms, laboratory findings, or pathophysiological mechanisms. Women often present with non-classical or peculiar symptoms, making the diagnosis more challenging [6,12]. The differential diagnosis must consider a wide range of clinical conditions, which imply appropriate therapeutic approaches. Coronary vasospasm and microvascular dysfunction (microvascular angina) as well as Takotsubo Syndrome share similar features and are frequently identified in female patients: acute chest pain and ST elevation mimicking acute MI, regional wall motion abnormalities but no obstructive CAD. Vaso-reactivity and stress-induced catecholamine surge causing transient myocardial stunning [12]. Moreover, myocarditis should be excluded as chest pain, elevated cardiac biomarkers, ECG changes mimicking MI could characterize the clinical presentation [12]. In addition, peripartum cardiomyopathy could mimic MI symptoms, with acute heart failure or chest pain and concomitant elevated cardiac biomarkers during late pregnancy or postpartum. In this setting, chest pain and reduced ejection fraction at the echocardiographic exam are similarly present [9,29]. Moreover, during peripartum period, SCAD also has to be excluded, representing a poorly understood condition with adverse prognosis despite the exponential rise in the volume of focused research and publications within the past decade [20]. In the absence of obstructive CAD, other medical conditions such as anemia-induced ischemia, thyrotoxicosis, or other endocrine disorders, which are traditionally more prevalent in women, must be suspected [1].

Sex differences in clinical presentation

Women and men with T2MI share similar presentations and characteristics of CAD. However, women with T2MI are older and

are more likely to display evidence of ischemia on ECG in terms of ST-segment and repolarization abnormalities [5].

Notable differences in ECG findings could be identified during the diagnostic work-up: ischemic ST-segment depression occurs more frequently in women, who are less likely to display T wave inversion in comparison to men [5]. Moreover, initial and peak hs-cTnT values are frequently similar between women and men, despite lower sex-adjusted percentiles in females [17].

Regarding invasive coronary evaluation, women often experience reduced coronary flow reserve (CFR) due to microvascular dysfunction, which limits cardiac capabilities to meet increased oxygen demand during stress (physical or emotional). This condition is particularly common among women with angina and nonobstructive CAD [5]. Intracoronary vasoreactivity testing may be adjunctive in evaluating patients with T2MI to identify underlying mechanisms, like coronary vasospasm or microvascular dysfunction. However, it is generally reserved for stable patients with recurrent symptoms or diagnostic uncertainty [12,30,31].

However, imaging techniques such as angiography may not always align with functional assessments like fractional flow reserve (FFR): more precisely, there is often a discrepancy between the visual findings from angiography and functional assessments using FFR in women. Higher FFR values were observed in female patients for any given stenosis compared with men. This implies that women may experience less functional impairment for a given anatomical narrowing. These findings could be explained by the smaller BSA, left ventricular mass, vessel size or narrower myocardial territory. As a consequence, FFR-guided decision making is especially important in women to prevent unnecessary procedures [32]. FFR could also be derived from computed tomography (FFR-CT), which has the potential to non-invasively identify and quantify these subtle differences between men and women [30,31]. In a post-hoc analysis of the DEFINE TYPE 2 MI trial, Lin et al. evaluated patients with T2MI with FFR-CT: no differences in terms of obstructive and nonobstructive CAD, and total plaque volume according to sex, were found, with women presenting with a lower volume of low-attenuation plaque [5].

In the context of suspected myocardial infarction with nonobstructive coronary arteries (MINOCA), cardiac magnetic resonance (CMR) has emerged as a key test to differentiate between ischemic and nonischemic causes of myocardial injury and identify tissue patterns consistent with myocardial infarction, myocarditis, stress cardiomyopathy, infiltrative disorders and hot-phases of genetic cardiomyopathies (Fig. 2) [33].

These conditions are also known as *acute myocardial infarction mimickers*—acute clinical presentations (mainly chest pain) that resemble myocardial infarction but are not caused by an ischemic mechanism. AMI mimickers may involve alternative forms of myocardial injury, most commonly inflammatory or immune-mediated [12]. However, other potentially life-threatening causes of chest pain such as pulmonary embolism and aortic dissection must be taken into account as AMI mimickers.

AMI mimickers include acute myocarditis with ACS-like symptoms and ECG abnormalities, active phases of non-ischemic cardiomyopathies (particularly arrhythmogenic cardiomyopathy), Takotsubo syndrome and rarer inflammatory cardiac conditions such as rheumatic, autoimmune, or immune-mediated diseases (e.g., cardiac sarcoidosis) [12,34]. Uncommon non-inflammatory causes, such as cardiac contusion or malignant cardiac tumors, may also fall into this category [35].

Importantly, early cardiac magnetic resonance (CMR)—ideally performed within 1–2 weeks of symptom onset—significantly improves diagnostic accuracy. Through advanced tissue characterization using T1 and T2 mapping and late gadolinium enhancement, CMR allows for the detection of non-ischemic myocardial injury [33]. By clarifying the underlying etiology, CMR not only enhances

diagnostic precision but also influences clinical management and therapeutic decision-making, often reclassifying cases initially presumed to be ischemic [33]. Additionally, CMR provides valuable prognostic information in these patients.

As shown by Pizzi and colleagues [36], the presence and extent of LGE and abnormalities in T2 mapping values serve as independent predictors of adverse cardiac events over a 3-year follow-up, underscoring the prognostic utility of timely CMR imaging in MINOCA. Its role is therefore pivotal—not only in guiding diagnosis but also in influencing treatment and long-term outcomes [36]. This nuanced understanding calls for a personalized approach diagnosing and managing CAD in women, focusing on microvascular function and tailored functional assessments.

Therapy and outcomes of T2MI

Sex differences in therapy

Despite ongoing progress, the limited understanding of T2MI pathophysiology and the broad spectrum of causes remain the main challenges to its optimal management [6]. As a result, the cornerstone of treatment in this clinical scenario remains the management of the underlying associated conditions and cardiovascular risk factors [1].

Although sex differences in T1MI management are well established with women characterized by higher long-term mortality [15,37], the impact of sex on T2MI is less well understood, although studies addressing this topic are emerging [3,18,31]. Similar to women with T1MI, who are less likely to undergo myocardial revascularization and optimal medical therapy, female patients with T2MI may be treated less aggressively in comparison to men [12,14].

In women, sex influences the therapeutic approach to T2MI, likely due to hormonal differences and a distinct disease profile. Specifically, women are more frequently affected by conditions such as spontaneous coronary artery dissection, which is typically managed conservatively, and myocardial infarction with non-obstructive coronary arteries, for which robust evidence guiding therapy—such as dual antiplatelet therapy, statins, or ACE inhibitors—is lacking [4,7,20].

Kimenai et al. did not find a significant difference in terms of coronary angiography rates between sexes in T2MI, although men presented more frequently with CAD and were therefore more likely to undergo myocardial revascularization and to be prescribed medical therapy at discharge. On the contrary, women were twice as likely to have normal coronary arteries or non-obstructive CAD and therefore more frequently diagnosed with MINOCA. As a consequence, female patients were more likely to receive lower intensity treatment at discharge [3].

However, Ariss et al. reported that chronic heart failure (HF) was an independent predictor of mortality in women with T2MI but not in men [38]: these observations were attributed to gender-related disparities in HF management, with women potentially receiving suboptimal medical therapy [9].

These findings seem to suggest that the decision-making process regarding invasive procedures and pharmacological treatment may be influenced more by disease characteristics than by sex alone. In addition, the lower prevalence of comorbidities in women could influence both treatment decisions and outcomes. However, differences in treatment could also mirror broader, gender-based inequalities in healthcare provision which could contribute to worse outcomes in women with T2MI, as less aggressive treatment strategies may not fully address their clinical needs [11]. More precisely, these differences in management may, at least in part, reflect gender-related factors—understood as the social and cultural constructs associated with sex—including the persistent

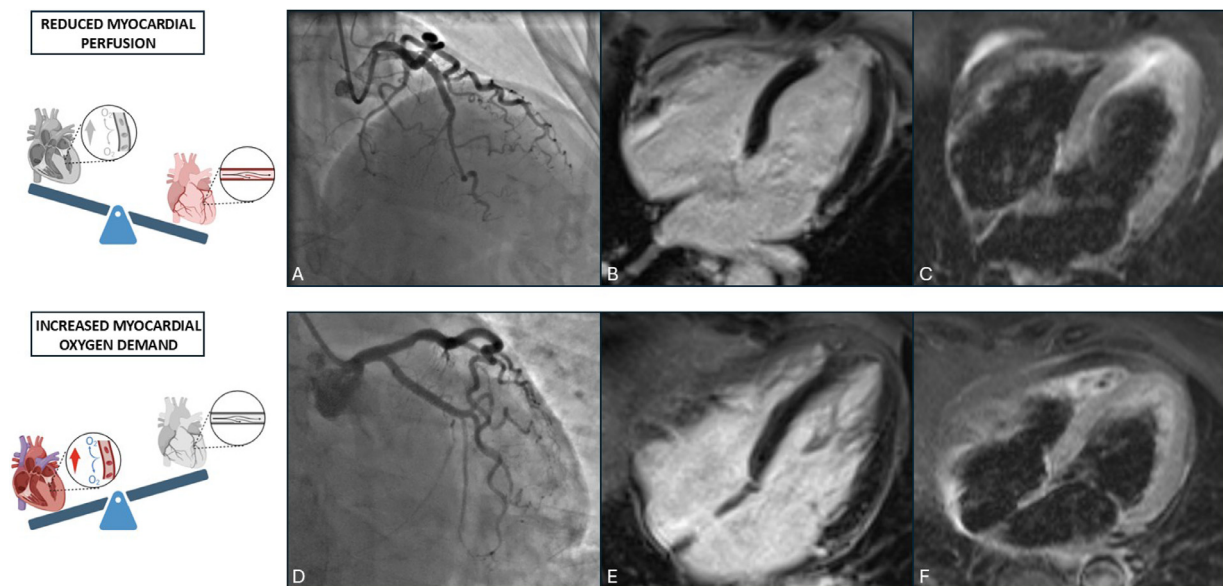


Fig. 2. Examples of Type 2 Myocardial infarction. A) A 54-year-old female patient presented with a spontaneous, obstructive coronary artery dissection involving the distal left anterior descending artery, resulting in Type 2 myocardial infarction (T2MI). B) Late gadolinium enhancement (LGE) sequences demonstrated a transmural apical scar. C) T2-weighted short tau inversion recovery (T2-STIR) imaging revealed diffuse apical myocardial edema. D) No obstructive coronary arteries at coronary angiography in a 75-year-old female patient admitted for T2MI during new-onset atrial fibrillation with a rapid ventricular response. E) LGE sequences showed no evidence of myocardial scarring. F) T2-STIR imaging demonstrated diffuse, mild myocardial edema.

underestimation of cardiovascular risk in women and the under-recognition of rarer causes of myocardial infarction, such as spontaneous coronary artery dissection or coronary vasomotor disorders, which, while rare overall, occur more frequently in women. Nevertheless, clinical studies directly comparing the management and outcomes of men and women with T2MI are still lacking.

Sex differences in outcomes

Patients with T2MI do not experience benign short and long-term prognosis, with only one-third of patients surviving at 5 years after the index event [6,15]. Despite a higher all-cause mortality in T2MI, data from European and US cohorts indicate that the absolute rates of MI and cardiovascular death are comparable between T1MI and T2MI patients when examining cause-specific mortality [14,37,39]. These findings were further confirmed in a cohort of young patients with T2MI: these patients were predominantly women, with a lower prevalence of traditional CV risk factors, but they showed higher long-term all-cause and cardiovascular mortality as compared with matched T1MI patients [40].

Overall, T2MI is associated with a worse prognosis compared to T1MI, with significantly higher mortality rates (20–30 % vs. 7–12 %). It is important to note that these percentages can vary depending on the study cohorts and the specific clinical conditions of the patients, reflecting the heterogeneity in severity of the underlying factors and comorbidities [4]. This highlights the need to enhance risk stratification and secondary prevention measures in this multifaceted scenario.

Emerging evidence is becoming available on sex and gender differences in outcomes associated with T2MI. Kimenai et al. analyzed a cohort from the SWEDEHEART registry and found that men with T2MI had a significantly higher incidence of major adverse cardiovascular events (MACE) and greater long-term mortality compared to women. This was observed despite men being younger and after adjusting for baseline risk factors and comorbidities [3].

Additionally, women exhibited lower intra-hospital mortality in another large-scale observational analysis from an American registry of patients with T2MI, partly explained by their lower preva-

lence of renal and CV comorbidities. In contrast, a smaller, single-center study involving 359 patients with T2MI did not find any significant differences in terms of outcomes, including all-cause mortality, between female and male patients, although other CV comorbidities were more prevalent in men [41].

The importance of pre-existing conditions should be emphasized when analyzing sex-based differences in short- and long-term outcomes: as a matter of fact, the observed disparities between males and females with T2MI in terms of outcomes may be partially explained by the higher prevalence of CV risk factors and comorbidities in men. Nevertheless, other contributors might have a role, as in the SWEDEHEART study sex-based outcome differences persisted after adjustment for known risk factors [3,10].

The difficulty in comparing prognosis and therapeutic management of T2MI highlights the complexity and heterogeneity of this condition. The diverse etiologies and pathophysiological mechanisms of T2MI suggest that patient characteristics, including sex and gender, play a significant role in determining outcomes. The observed sex differences in outcomes and management in T2MI underscore the need for further research into sex-specific factors that influence prognosis and treatment in order to address a tailored management and improve outcomes (Fig. 3).

Knowledge gaps and future directions

T2MI poses unique diagnostic and therapeutic challenges, particularly in women. Women's cardiovascular health has long been understudied, and T2MI in women often overlaps with other conditions like microvascular dysfunction, stress-induced cardiomyopathy, and non-cardiac triggers [5].

Establishing sex-specific biomarkers and imaging strategies to differentiate T2MI from other conditions could ameliorate outcomes. Moreover, expanding participation of women in observational studies and randomized controlled trials focused on T2MI is crucial.

These challenges highlight significant knowledge gaps and potential opportunities for artificial intelligence (AI) to play a transformative role.

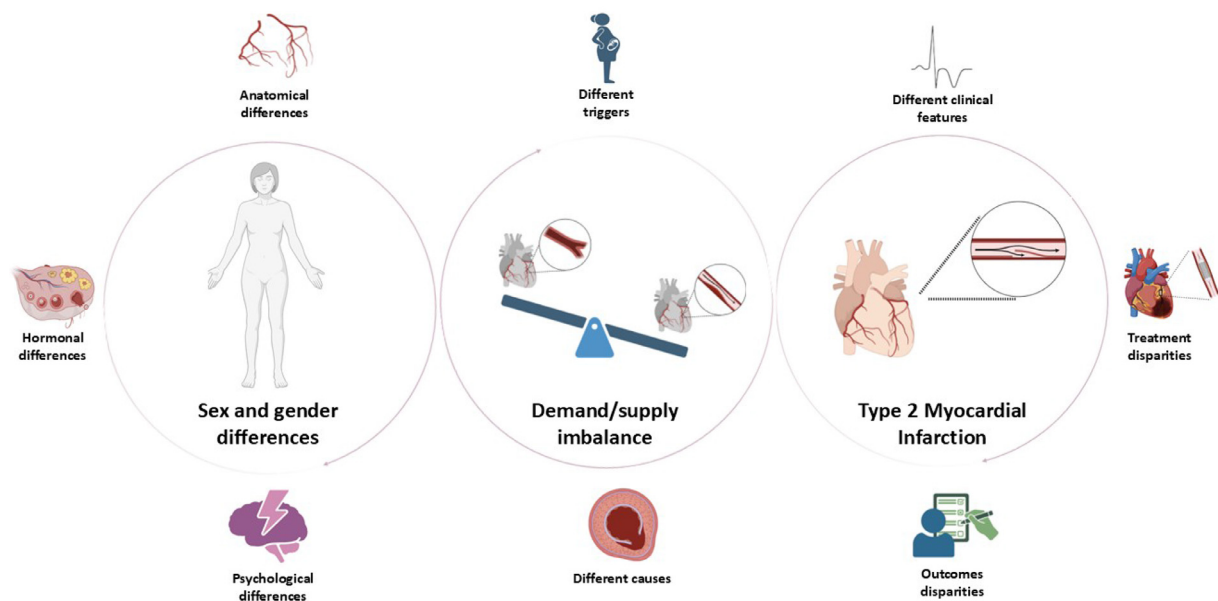


Fig. 3. Specific sex and gender background contributing to different clinical spectrum, management and outcomes of Type 2 Myocardial infarction in women.

AI offers promising tools to address sex- and gender-specific challenges in the diagnosis and management of T2MI. AI can process vast amounts of clinical data—including ECGs, cardiac imaging, and biomarker profiles—to identify under-recognized sex-specific disease phenotypes [42]. For instance, women with T2MI are more likely to present with coronary microvascular spasm or spontaneous coronary artery dissection, both of which are frequently missed by standard diagnostic approaches. AI algorithms can be trained to detect these subtle, sex-related variations in presentation by recognizing patterns that may otherwise be underestimated [42].

An emerging example is the development of the "sex-discordance score" based on ECG findings, which help to reveal atypical or non-classic presentations more common in women and improve risk stratification [43]. In SCAD, AI-enhanced imaging interpretation may assist in differentiating true luminal narrowing from intramural hematoma and identifying features predictive of spontaneous healing versus recurrence. Additionally, AI models incorporating sex, hormonal status, comorbidities, and psychosocial factors can support more personalized decision-making and improve prognostic predictions. Moreover, AI could support clinical decision-making by highlighting drug-drug interactions and comorbidity considerations more common in women. Ultimately, these technologies could reduce diagnostic bias, optimize therapy, and contribute to more equitable cardiovascular care across sexes [42]. Nevertheless, AI models trained on predominantly male datasets may not perform well in identifying sex-specific differences: new sex-based data need to be collected to bridge this significant gap.

Conclusions

T2MI represents a multifaceted condition with a poorer prognosis in comparison to atherothrombotic myocardial infarction. Sex and gender differences have been described for T2MI, but they remain to be appropriately investigated. An improved knowledge of biological and gender differences between men and women with T2MI, particularly regarding clinical and CAD characteristics, is therefore pivotal to an optimal treatment and to future research targeting potential evidence-based solutions to close definitively this gender gap.

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Data availability

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