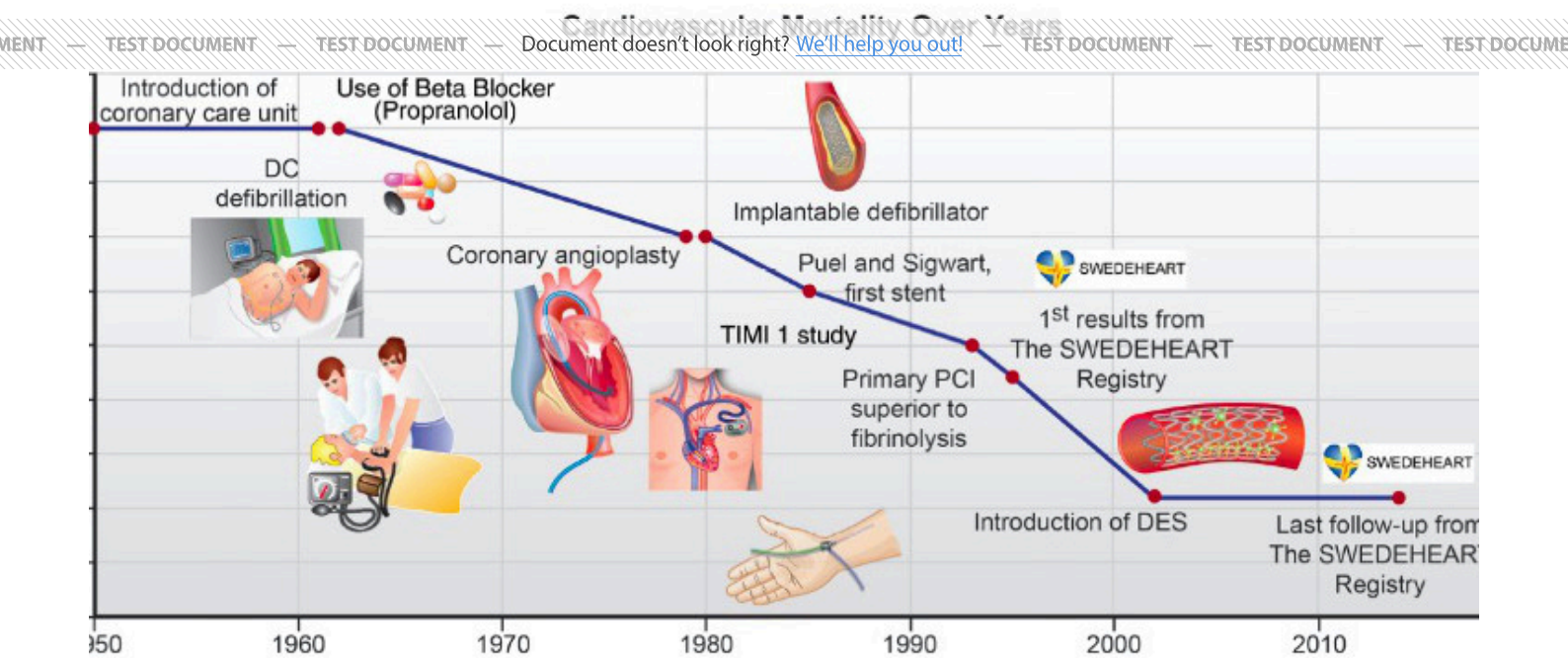




In a Nutshell

Acute Coronary Syndromes in Women and Men

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Introduction

Acute coronary syndrome (ACS) results from an acutely reduced blood flow to the myocardium and is commonly divided into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS

(NSTEMI-ACS) [1]. Despite significant advances in patient care over the past decades, ACS remains a major cause of morbidity and mortality worldwide. Indeed, epidemiologic

data suggest that in the future there is one death per minute due to an ACS [2, 3].

Clinical Presentation of Females with ACS

Over many years, ACS was considered a primarily male condition and was initially called

a *man's disease*. While it is indeed true that about two thirds of patients with ACS

are male, data indicate that nowadays the TEST DOCUMENT $\xrightarrow{\text{Prevalence of disease}}$ TEST DOCUMENT $\xrightarrow{\text{social classes}}$ [4], possibly due to differences in lifestyle, particularly in smoking and exercise habits [5].

Among females, incident ACS occurs at relatively low rates until menopause, unless a pronounced risk factor burden such as dyslipidemias, diabetes mellitus, heavy smoking or genetically determined causes are at play. Consequently, females present around 5 to 10 years later with ACS than their male counterparts. Interestingly, females presenting with ACS have a higher comorbidity burden, including obesity, hypertension, and diabetes mellitus – in large part owed to their higher age, but to a lesser degree also to sex-specific differences. As a result, the uncorrected mortality rates in females with ACS are higher than in males [6, 7]. However, when correcting for age at presentation, the mortality rates are similar, and when correcting for comorbidities and cardiovascular risk factors, mortality rates in males and females are almost alike [7].

An important difference of ACS phenotypes in females compared to males is their distinct symptom profile at presentation: while chest pain is the leading symptom in women and men [8], the absence of chest pain or chest discomfort is observed more often in females (40 vs. 30%) [8, 9]. Moreover, the frequency of many other associated symptoms, which are commonly referred to as “atypical”, associated symptoms is higher in women. Generally, female patients with ACS are more likely to present with backpain, neck pain, jaw pain, shortness of breath, nausea or vomiting, weakness or fatigue, dizziness,

or palpitations, and have a higher number of symptoms doesn't look right? [We'll help you out!](#) ^{ESC} These signs are misinterpreted and result in female patients not seeking emergency help. These specifics in clinical presentation may predispose women to longer prehospital delays, delayed diagnosis, and eventually undertreatment of ACS [1, 6, 10]. Hence, awareness of the broad spectrum of ACS symptoms in women and men as well as more comprehensive diagnostic and treatment algorithms that account for sex-specific differences in ACS are required.

Sex-Specific Differences in the Pathobiology across the Spectrum of ACS

In females, ACS is more often caused by single-vessel disease or non-obstructive coronary disease (so-called myocardial infarction with non-obstructive coronary arteries or MINOCA) [11, 12] and more often due to plaque erosion as the primary mechanism underpinning the ACS (fig. 1) [13–15].

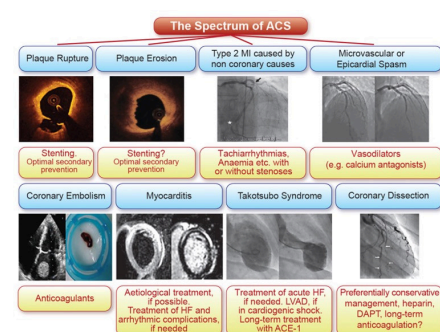


Figure 1: The Spectrum of Acute Coronary Syndrome (ACS). Plaque erosion, takotsubo syndrome and spontaneous coronary artery dissection are particularly common in female patients. Adapted from [43].

MI: Myocardial infarction; HF: Heart failure; LVAD: Left ventricular assist device; ACE-I: Angiotensin converting enzyme inhibitor; DAPT (Dual Antiplatelet Therapy).

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Furthermore, ACS in women is more often caused by rare disease mechanisms such as spontaneous coronary artery dissection (SCAD) [16] and vasculitis [17–19]. SCAD is a rare cause of ACS, commonly occurring in the first month postpartum [16, 20, 21]. The underlying mechanisms of SCAD are not fully understood, though some studies suggest that both hormonal and genetic factors may be involved in its etiology [22].

In addition, takotsubo syndrome (TTS), an acute heart failure syndrome with clinical signs and symptoms comparable to ACS, is particularly common in women, in whom it occurs almost exclusively during menopause [17–19]. Patients with TTS frequently present with similar electrocardiographic and biochemical findings as patients with STEMI or non-ST-elevation myocardial infarction, have similar in-hospital mortality rates (around 4%), and are prone to develop cardiogenic shock with an incidence of roughly 12% [23]. TTS seems to be primarily a brain-mediated disease involving the heart as a target organ. In fact, TTS patients often present with neurological and psychiatric comorbidities [23], alterations in the amygdala, in the hippocampus and in the midbrain with abnormal processing of sympathetic drive (fig. 2) [24]. Whether these changes are mechanistically linked to a postmenopausal decrease in female sex hormones remains to be investigated.

Abstract

Acute coronary syndrome (ACS) remains a major cause of morbidity and mortality worldwide. Emerging data indicates that there are relevant sex-specific differences in the pathobiology, clinical presentation, and management of ACS in women and men. Premenopausal women appear to be largely protected from typical ACS, with women presenting 5 to 10 years later than men. Females tend to experience chest pain or discomfort less frequently and more often present with other associated symptoms, which may contribute to longer prehospital delays and less frequently administered guideline-directed care. Indeed, females are less likely to undergo coronary angiography and percutaneous coronary interventions, and less likely to get a prescription for statins after the acute event. Over the past decades, we made remarkable progress in ACS treatment, reducing short-term mortality from far above 50% to below 10% in both women and men. Novel risk tools for clinical risk assessment such as the machine learning-based GRACE 3.0 risk score may help to further improve the management of female and male non-ST segment elevation ACS patients. In this review, we discuss the role of sex in the diagnosis, management, and outcomes of patients with ACS.

Keywords: Acute coronary syndromes; female patients; GRACE score; mortality; risk stratification

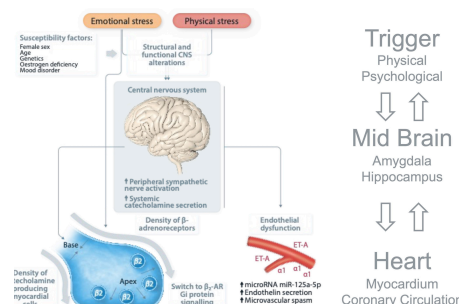


Figure 2: Pathophysiology of takotsubo syndrome. Female patients are particularly susceptible, with nine out of ten patients being female [23]. Adapted from [19].

CNS: Central nervous system.

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Milestones of ACS Management in Female and Male Patients

When the former US president Dwight Eisenhower had an acute myocardial infarction on the golf course of Cherry Hills Coun-

try Club on September 23rd 1955, the treatment of acute coronary syndrome (ACS) was not well understood. In fact, his personal physician, Dr. Howard Snyder, initially misinterpreted the symptoms and dismissed the epigastric discomfort as a gastrointestinal problem. After ten hours, Eisenhower was eventually transferred to a hospital. Upon arrival, electrocardiogram equipment was unavailable and had to be organized from another hospital to make the diagnosis of an anterior STEMI [25]. At this time, the only treatments available were papaverine and amyl nitrite, both having very questionable therapeutic effects. To his luck, Eisenhower did not develop ventricular fibrillation, one of the most frequent and most dreadful early complications following a STEMI. Although at the time, Paul M. Zoll (Harvard Medical School and Beth Israel Hospital, Boston, MA, USA) had described the benefits of electroconversion in ventricular fibrillation in the *New England Journal of Medicine* [28], the required equipment remained unavailable at most institutions.

Ever since Eisenhower's heart attack, management strategies in patients with ACS have made tremendous progress leading to improved cardiovascular outcomes (fig. 3). Indeed, the introduction of resuscitation, defibrillation devices, beta blocker-therapy, thrombolysis, eventually primary percutaneous coronary intervention (PCI) and more recently novel antiplatelet agents and radial access routes, reduced in-hospital mortality rates from historically more than 50% to currently less than 10% [27]. While increasing awareness of sex-specific differences in the outcomes of patients with ACS has led to controversies about the underlying causes, overall, these major advances in ACS management have substantially improved outcomes in both sexes alike over the past decades.

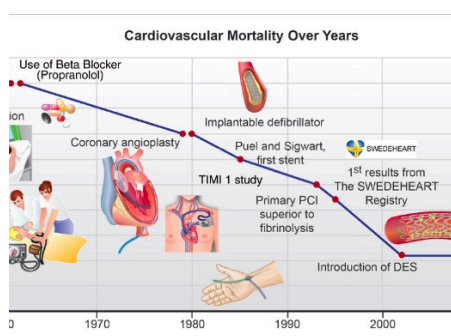


Figure 3: Development of today's management of acute coronary syndromes since Eisenhower's heart attack. Taken from [27].

ACS Management in Women and Men

Document doesn't look right? [We'll help you out!](#) [FOR](#) primarily achieved by PCI and thrombolysis or coronary artery bypass grafting in selected cases, is crucial for reducing morbidity and mortality [28]. Overall, women with STEMI are less likely to receive timely reperfusion which could be partly related to differences in symptom presentation as well as perception by patients and healthcare personnel [6, 29]. As noted before, women often tend to present with unspecific symptoms such as neck pain, fatigue, dyspnea, nausea, and more frequently present with no chest pain at all [6].

In NSTEMI-ACS, early risk stratification is key to identifying patients at high baseline risk to decide on the appropriate treatment strategy [6]. Importantly, women have a different risk factor profile regarding fatal events compared to men [7]. On top of that, female patients with ACS are more prone to bleeding complications [30]. Indeed, while antiplatelet therapy represents a cornerstone of ACS management, women may respond differently to these agents, which can impact their safety and effectiveness [31]. For example, females have a higher risk of early bleeding events when treated with dual antiplatelet therapy [32], however, several studies report similar risk of late bleeding events in both sexes [33–36]. Therefore, there is a need to include sex-related factors into risk-benefit considerations when prescribing antiplatelet drugs and anticoagulants to optimize their clinical use.

Sex-Specific Treatment Rates in the UK and Switzerland

Our observations in contemporary nationwide cohorts in England, Wales, Northern Ireland and Switzerland, totaling more than 420,000 NSTEMI-ACS patients, suggest that women are less likely to receive both invasive and noninvasive treatment [7]. The rates of coronary angiography and PCI treatment at presentation as well as antiplatelet medication, beta blocker therapy and lipid-lowering therapy at discharge were concerning lower in females than males, irrespective of the country studied (fig. 4). Notably, these differences were particularly evident in the UK while being less apparent in Switzerland. Given that the individual factors influencing the medical decision to refrain from applying the above therapies are neither known nor documented, it is important to note that all these unadjusted rates merely document what *has happened* and not what *should have hap-*

Management of NSTEMI-ACS in the UK and Switzerland (2005–2020) stratified

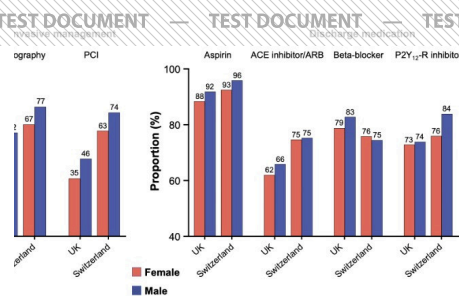


Figure 4: Management of non-ST-elevation acute coronary syndrome (NSTEMI-ACS) patients in women and men in England, Wales, and Northern Ireland (United Kingdom) and Switzerland [7]. PCI: Percutaneous coronary intervention; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker.

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Early Risk Stratification in Women and Men with NSTEMI-ACS

Clinical risk stratification represents a cornerstone of contemporary management. To date, there are several tools for early risk stratification available, including the *Global Registry of Acute Coronary Events* (GRACE) score. The GRACE score supports the assessment of future mortality risk to guide treatment decisions recommended by international guidelines (NICE guidelines) [37, 38]. However, many previously suggested risk tools do not account for sex differences in the risk factor profile and may not perform as well in women as in men, leading to inaccurate risk assessment and suboptimal management.

Several studies suggested that women less likely receive invasive management compared to their male counterparts [39]. Recently we assessed the performance of the previously established GRACE 2.0 score, delineated baseline risk profiles in a sex-disaggregated manner and provided a novel machine learning-based risk score, which captures potential non-linear effects of baseline variables in female and male patients alike (GRACE 3.0 score). Our study revealed limited discriminatory properties of the GRACE 2.0 model and risk underestimation in females favoring their incorrect stratification into the low-to-intermediate risk group in which international guidelines do not recommend an early invasive strategy. The updated GRACE 3.0 score was trained, tested and externally validated in prospectively recruited patients with NSTEMI-ACS receiving contemporary ACS management and showed excellent discriminatory properties [7]. GRACE 3.0 provides an updated tool for early risk stratification

and is now available under www.grace-3.com

Sex Differences in Invasive and Medical Management

Primary PCI is recommended for most patients with ACS and several lines of evidence convincingly show its effectiveness to reduce fatal and non-fatal adverse cardiovascular events. Yet, in line with our observations in the UK and in Switzerland, females presenting with NSTEMI-ACS less often received an early invasive strategy than men, with risk-adjusted differences increasing with ascending age [29]. Among NSTEMI-ACS patients with systematic invasive management, females have worse outcomes than men in unadjusted analyses, including higher rates of ischemic and bleeding complications [41]. Multivariable-adjusted analyses suggest that these discrepancies are due to sex-specific differences in the underlying mechanisms, procedural factors such as vessel size and access site as well as comorbidity burden, and thus higher baseline risk in females with NSTEMI-ACS [6]. Beyond deciding on early invasive strategy in high-risk NSTEMI-ACS patients, medical therapy during the initial hospitalization and after hospital discharge represents a hallmark of contemporary ACS management. It is important to note that sex differences in the pharmacokinetics as well as pharmacodynamics of antiplatelet and lipid-lowering agents can impact their efficacy and safety profile. This is exemplified by the observation that women are more likely to stop or switch their statin treatment due to myalgia [42]. Therefore, sex differences in body composition, metabolism, hormonal status, and drug elimination warrant careful consideration in future drug development, study design and clinical testing.

Conclusion

In conclusion, sex-related factors play an important role in the pathobiology, clinical presentation and management of patients across the spectrum of ACS. Importantly, rare, and thus potentially underinvestigated disease mechanisms, such as SCAD or TTS, are particularly common in female patients. These observations highlight the importance of sex-specific diagnostic, prognostic and therapeutic approaches to further improve post-ACS outcomes.

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Conflict of Interest Statement

FAW is supported by the Foundation for Cardiovascular Research – Zurich Heart House and the Lindenhof Foundation. Outside this work, FAW is supported by the European Society of Cardiology, the Swiss Heart Foundation, the Fond zur Förderung des akademischen Nachwuchses of the University of Zurich, the SphingoTec GmbH, 4TEEN4 Pharmaceuticals GmbH and PAM Theragnostics GmbH.

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GGC is coinventor on the International Patent WO/2020/226993 filed in April 2020. The patent relates to the use of antibodies which specifically bind IL-1 α to reduce various sequelae of ischemia reperfusion injury to the central nervous system. GGC is a consultant for Sovida Solutions Limited on a project related to NAD⁺ biology and aging.

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Author Contributions

FAW and TFL wrote the main part of the manuscript. SK and GGC assisted in drafting the manuscript. All authors revised the manuscript critically, agreed to submit the manuscript and to be accountable. All authors have contributed significantly.

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