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Sex and gender differences in patients with acute coronary syndromes

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Sex -biological factors- and gender -social and cultural factors-can be considered determinants of health status [1]. Indeed, biological and socio-cultural factors can significantly influence risk profile, clinical manifestations, reactions to pharmacological and non-pharmacological therapies, and prognosis of patients.

However, although the topic is absolutely on trend now, sex and gender are rarely considered crucial factors in the assessment of a patient with Acute Coronary Syndrome (ACS) due to cultural reasons and lack of knowledge and because there is little scientific evidence to date [2].

Ischemic heart disease (IHD) is the leading cause of mortality worldwide in both sexes [2,3]. IHD is more frequent in men up to the age of 65, but after menopause, when the cardiometabolic and hormonal protection decreases in women, there is a reversal in the incidence of cardiac events among men and women.

Both sexes are exposed, even with different impacts [2], to some shared risk factors: smoking, arterial hypertension, diabetes mellitus, dyslipidemia, obesity, sedentary lifestyle, and family history. Moreover, there are female sex-specific risk factors, such as pregnancy complications, early menopause, autoimmune or inflammatory diseases, and gender-specific risk factors, such as partner violence or domestic abuse, habits, or socioeconomic barriers, that contribute to health disparities [2].

Acute coronary syndromes differ significantly in men and women regarding symptoms, pathophysiology, and subsequent treatment implications (Table 1) [4]. Chest pain is the most frequently reported symptom in both sexes, but women more often reported associated symptoms (such as nausea and vomiting, dyspnea, jaw, arms, and shoulder pain) or have asymptomatic presentations [2,4,5]. Among obstructive coronary artery disease, ST-elevation myocardial infarction (STEMI) is more frequently due to atherosclerotic plaque erosion in women and plaque rupture in men [4]. Women with STEMI are older

and with more comorbidities, less and later treated invasively, although growing evidence is demonstrating the effectiveness and safety of primary angioplasty also in women.

Non-ST elevation ACS (NST-ACS) is more frequent in women than in men [5], but women continue to undergo coronary angiogram and revascularization less often, despite many studies demonstrating similar benefits in outcomes between sexes from percutaneous coronary intervention [2,4].

In the past few years, growing evidence has better characterized another clinical entity: Myocardial Infarction with Non-Obstructive Coronary Artery Disease (MINOCA). MINOCA is defined as a myocardial infarction with angiographic evidence of either normal or less than 50% stenosed coronary arteries [4] and is more frequent in women. MINOCA is due to multifactorial pathophysiology, such as spontaneous coronary artery dissection, Takotsubo syndrome, and macrovascular or microvascular impairment. The heterogeneous and poorly studied nature of the diseases included in the MINOCA label explains the difficulty in diagnosis, treatment and prognosis of this entity. Therapeutic options vary based on the etiology of myocardial infarction from lifestyle interventions to pharmacological possibilities, such as calcium channel blockers in coronary vasospasm or anti-ischemic agents in microvascular dysfunction.

Differences in the prognosis of ACS between women and men persist despite greater attention and knowledge of the specific characteristics of both sexes, partly due to the reduced awareness of symptoms, increased comorbidities at the time of presentation, and greater delays in diagnosis and treatment of ACS in women [2,4]. Women have a greater in-hospital mortality [2] and incidence of MACE and mortality than men in the medium term (up to 6 months after the acute event) [3], but not in the long term, when the risk of cardiac death is similar and even lower among women [5]. The worse short-term prognosis is partly ascribable to the different clinical complexity of women with ACS compared to

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Table 1
Main differences in acute coronary syndrome between women and men.

		Epidemiology	Symptoms	Treatment	Prognosis
Obstructive ACS	STEMI	More frequent in men	Typical chest pain in both sexes; more associated symptoms in women (dyspnoea, nausea, vomiting, atypical pain)	Primary percutaneous coronary intervention and optimal medical treatment less proposed to women	Higher in-hospital and worse mid-term mortality in women; similar long-term mortality in both sexes
	NST-ACS	More frequent in older patients, especially women	More frequent atypical (dyspnoea, nausea, vomiting, atypical pain) or no symptoms	Coronary angiogram and revascularization less proposed to women	Higher unadjusted mortality in women; similar mortality between sexes after adjustment for baseline characteristics
MINOCA	STEMI or NSTEMI	More frequent in women	Symptoms depending on the underlying pathogenetic mechanism (i.e., typical chest pain in spontaneous coronary artery dissection, atypical symptoms in Takotsubo syndrome)	Treatments, mainly pharmacological, depending on the underlying pathogenetic mechanism	Lower in-hospital and 12-month mortality than obstructive ACS. Worse prognosis of MINOCA with STEMI than MINOCA with non-ST elevation

Abbreviations: ACS, Acute Coronary Syndrome; STEMI, ST-elevation myocardial infarction; NST-ACS, Non-ST elevation Acute Coronary Syndrome; MINOCA: Myocardial Infarction with Non-Obstructive Coronary Artery Disease; NSTEMI: Non-ST elevation myocardial infarction.

men. Indeed, women at the time of presentation tend to be older, with a greater number of comorbidities and medications, and with greater functional impairment and frailty [5].

After ACS, women less received the recommended secondary prevention medications and are fewer referred to cardiac rehabilitation programs than men [3]. Notably, the knowledge gap related to the inadequate representation of women in the clinical trials that have validated ACS medications was overcome by several studies and meta-analyses that have demonstrated the efficacy and safety of medications in both sexes, such as antiplatelet, anticoagulants, beta-blockers, angiotensin-converting enzyme inhibitors and sartans, and statins [4]. Guidelines recommend the same pharmacological treatments for ACS for women and men, emphasizing the importance of adjusting the dose according to weight and renal function. As regards the newer drugs, whose validation trials have included a greater, sometimes even higher, share of women, the efficacy and safety data are sometimes more favorable in women than in men: this applies to some studies that tested angiotensin receptor neprilysin inhibitors, glyphozines and some of the new lipid-lowering drugs, such as inclisiran or bempedoic acid. Furthermore, health education strategies are needed to prevent therapeutic discontinuation in women, who often underestimate their cardiovascular risk and the consequent need for treatment [2].

Finally, the lower referral to cardiac rehabilitation programs is another gender bias, unfortunately not improved in recent years. This gender discrepancy probably arises from a combination of clinical (misdiagnosis, underestimation of cardiovascular risk), financial, social, and psychological reasons that influence referral and adherence to treatments [2,3].

For example, women often take on caregiving roles within the family and feel guilty about taking personal care time [2].

The prognosis of acute coronary syndrome in women is worse than in men. This gender gap is unacceptable and calls for appropriate consideration and subsequent changes in clinical practice. The most critical points appear to be the misdiagnosis and the subsequent undertreatment of ACS and the inappropriate cardiovascular risk profiling, resulting in lower prescription and adherence to medications and fewer referrals to cardiac rehabilitation programs.

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Declaration of competing interest

The authors declare they have no conflict of interest.

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References

- [1] L. Alcalde-Rubio, I. Hernández-Aguado, L.A. Parker, E. Bueno-Vergara, E. Chilet-Rosell, Gender disparities in clinical practice: are there any solutions? Scoping review of interventions to overcome or reduce gender bias in clinical practice, *Int. J. Equity Health* 19 (2020) 166.
- [2] S. Gauci, S. Cartledge, J. Redfern, R. Gallagher, R. Huxley, C.M.Y. Lee, A. Vassallo, A. O'Neil, Biology, bias, or both? The contribution of sex and gender to the disparity in cardiovascular outcomes between women and men, *Curr. Atherosclerosis Rep.* 24 (2022) 701–708.
- [3] K. Hyun, A. Negrone, J. Redfern, E. Atkins, C. Chow, J. Kilian, R. Rajaratnam, D. Brieger, Gender difference in secondary prevention of cardiovascular disease and outcomes following the survival of acute coronary syndrome, *Heart Lung Circ.* 30 (2021) 121–127.
- [4] J.N. Holtzman, G. Kaur, B. Hansen, N. Bushana, M. Gulati, Sex differences in the management of atherosclerotic cardiovascular disease, *Atherosclerosis* 384 (2023) 117268.
- [5] J. Mehilli, P. Presbitero, Coronary artery disease and acute coronary syndrome in women, *Heart* 106 (2020) 487–492.