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Non ST elevation acute coronary syndrome in women: unstable angina and non ST elevation acute myocardial infarction

Síndrome coronario agudo sin elevación del ST en la mujer: angina inestable e infarto agudo de miocardio sin elevación del segmento ST

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INTRODUCTION

Non-ST-segment elevation acute coronary ischemic syndrome (NSTEACS), in its form of unstable angina or infarction, is a frequent reason for medical care in the emergency room and hospitalization. According to the Global Burden of Disease study in 2019, it was estimated that there were 275.2 million cases of cardiovascular disease (CVD) in women around the world, and even when a reduction in the global prevalence standardized by age in women of 5.8% was seen between 1990 and 2010, the trend seems to increase again after 2010.[1] Hospital admissions for young women with acute myocardial infarction (AMI) increased from 27% in 1995-1999 to 32% in 2010-2014.[1,2]

The immediate and mediate hospital morbidity, and mortality of NSTEACS are lower than in the case of ST-segment elevation acute coronary syndrome (STEACS). However, in the medium-long term, it may be higher. Globally, it was estimated that there were 6.10 million deaths from CVD in women in 1990; while in 2019, they increased to 8.94 million, and the highest mortality rates occurred in low- and middle-income countries.[1,2]

In general, the diagnostic, prognostic, and therapeutic approach to NSTEACS in women should be the same as in men; however, it is crucial to take into account the following gender-specific considerations:

Clinical presentation

In women, it can vary from dyspnea to sudden death or cardiogenic shock, but the most frequent manifestation is pain or pressure/discomfort in the chest or precordium (angina). They are more likely to have accompanying symptoms such as dyspnea, nausea, weakness, and fatigue; the location is different, with less intensity or nonspecific, which generates difficulty and delay in diagnosis. Patients with obstructive coronary artery disease more commonly manifest «typical» angina events, while ischemic heart disease without obstructive coronary lesions (INOCA or MINOCA) and vasomotor disorders present microvascular angina, characterized by a crescendo-decrescendo pattern that changes over time, appearing hours after physical exercise, at rest or associated with stressful situations. They frequently present extreme tiredness that interferes with their daily activities and work capacity.[3-5] Women attend later to receive medical care, compared to men.[4,5]

1. **Electrocardiogram.** They are the same, but women tend to present more frequent

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changes in the T wave and fewer alterations in intraventricular conduction, such as left or right bundle branch block.[3,5]

2. **Biomarkers.** Different studies have reported lower concentrations of ultrasensitive troponins (troponin T or I hs-cTn) in women compared to men. These gender differences could contribute to underdiagnosis and inequality in the treatment of the acute coronary syndrome. The upper level or reference limit for the infarction diagnosis could be twice as high in men. Sex hormones seem to alter the differential expression of hs-cTn. Estrogens appear to exert a protective role on the myocardium; their antioxidant properties and ability to eliminate reactive oxygen species may help to limit cardiomyocyte injury.[6] However, even though the use of sex-specific hs-cTn cut-off points increased the detection of acute infarction in women, it has no impact on short- or long-term prognosis; in contrast, the standard troponin levels criteria misdiagnose one in five heart attacks, and associate with high mortality rate.[7]

   Another biomarker showing gender differences is a brain-type natriuretic peptide (BNP or proBNP). Levels are significantly higher in both healthy and diseased women than in men.[3,4] Women receiving hormone replacement therapy may have higher levels of BNP, suggesting that its production may be sensitive to regulation by estrogens.[8]

3. **Imaging studies.** There is consensus that women tend to receive cardiac catheterization with the intention of revascularization in very high-risk

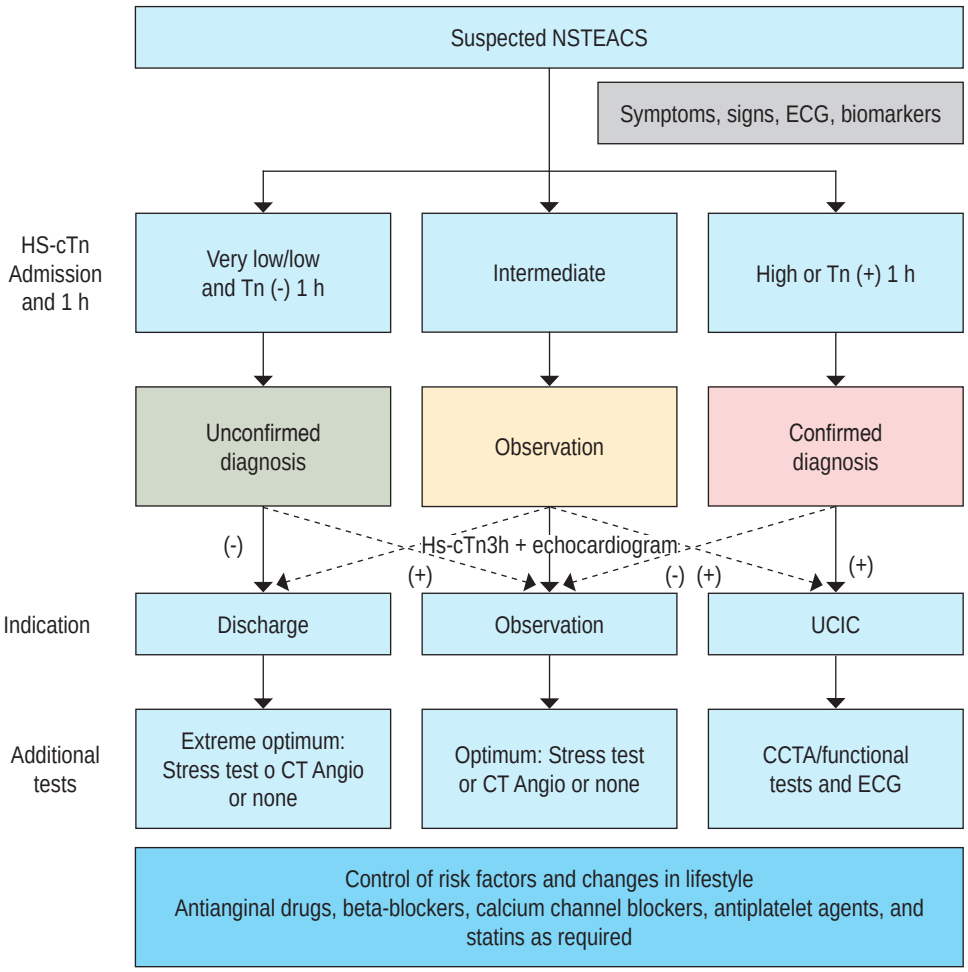

Figure 1:

Algorithm for diagnosis and treatment of patients with SICAsEST.
Adapted from: Collet JP et al.[4]

patients with NSTEACS less frequently. Because they present coronary arteries without significant lesions, microvascular dysfunction, endothelial erosion, non-obstructive lesions, or coronary spasm as the cause of myocardial ischemia more frequently, their evaluation should be completed by intravascular ultrasound with a pharmacological challenge (acetylcholine or adenosine) or coherence tomography optical, to assess coronary vasomotor function.[4,5,9]

Compared to other functional tests, multicenter imaging studies demonstrated the non-inferiority of coronary computed tomography angiography (CCTA). In addition, it allows calculating the functional impact of coronary stenosis by evaluating the fractional flow reserve, non-calcified, non-obstructive plaque characteristics, external remodeling, and coronary dissection or myocardial bridging. Current technology has managed to reduce radiation exposure by up to 80%, which is essential to consider in young women. Its use in the emergency room can accurately identify low-risk patients for safe, cost-effective, and accelerated discharge.[8,9]

4. **Treatment.** In women with NSTEACS, there is less adherence to the guidelines for medical treatment recommendations: aspirin 93.4% vs 94.7%, P2Y12 inhibitors 79.3% vs 86.1% and statins 73.7% vs 77.5%; and revascularization (angiography [adjusted OR 0.71), percutaneous coronary intervention (OR 0.73).[2-4,9] Even when women are underrepresented in clinical trials (less than 39%), no scientific evidence shows that using these recommendations is ineffective. In the case of coronary microvascular dysfunction, it is suggested to include β-blockers, short-acting nitrates, calcium channel blockers, and angiotensin-converting enzyme inhibitors for symptom relief.

It must be recognized that NSTEACS presents differently in women, symptomatically, biochemically, and pathophysiologically, establishing the need to develop clinical studies focused on the identification and better understanding of these differences, as well as the development of guidelines for diagnosis, prognosis, and optimal sex-specific treatment *(Figure 1)*.

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