Letters to the Editor

Factors Impacting Prognosis Among Patients with Tako-tsubo Syndrome

Factores que afectan al pronóstico de pacientes con síndrome de tako-tsubo

To the Editor,

Pérez-Castellanos et al. published an excellent analysis of the prospective RETAKO registry describing important gender disparities among patients with tako-tsubo syndrome (TTS).[1] They observed worse prognosis with higher in-hospital mortality, longer intensive care unit length of stay, and a higher prevalence of heart failure in men whereas women exhibited higher rates of functional mitral regurgitation. Dynamic left-ventricular outflow tract obstruction occurred exclusively in women.

The higher mortality rates among men with TTS could be explained by the following considerations. Men generally have a higher incidence of acute critical conditions with increased serum catecholamine concentrations, which may result in higher in-hospital mortality.[2] Furthermore, the lack of the direct protective effects of estrogen on the sympathetic nervous system and coronary vasoreactivity may also predispose men to the development of TTS. Estrogen improves coronary blood flow by exerting its beneficial effects on the coronary microcirculation through endothelium-dependent and independent pathways. It has been shown that the lack of estrogen replacement in postmenopausal women may be a risk factor for the development of TTS.[3] Furthermore, experimental murine models have demonstrated greater left ventricular dysfunction in ovariectomized female rats than in ovariectomized rats receiving estradiol supplementation exposed to stress.[4] Since estrogen plays a major role in the pathophysiology of TTS, most affected patients are postmenopausal women. Moreover, since estrogen has an essentially negligible role in men developing TTS, they may potentially develop at any age, mostly due to an overwhelming surge of plasma catecholamines (much higher than in women), which may potentially result in more serious short-term and long-term direct cardiotoxic effects. This may be one of the possible reasons for the higher mortality in men. In the present study, men exhibited a mortality rate of 4.4%, which is comparable to the mortality of ST-segment elevation myocardial infarction in the primary percutaneous coronary intervention era, thus making this entity particularly relevant even among men.

Traditionally thought to be a benign condition, recent studies have demonstrated that patients with TTS have higher short- and long-term mortality than previously recognized. Apart from the impact of sex on mortality, another important factor, prognostication of TTS, also depends on the underlying trigger for TTS and thus it may be important to clinically subdivide patients into those with primary and secondary TTS forms, as we have discussed elsewhere.[5]

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Factors Impacting Prognosis Among Patients with Tako-tsubo Syndrome. Response

Factores que afectan al pronóstico de pacientes con síndrome de tako-tsubo. *Respuesta*

To the Editor,

We appreciate the interest and comments of Khalid et al. regarding our article.[1] The results of the successive registries and experimental studies add evidence to support that estrogens play an important role in the modulation of catecholaminergic discharge on the heart, thus affecting the development and outcome of tako-tsubo syndrome (TTS). It is interesting to think that this could lead in the future to design strategies for targeted treatment in patients with TTS. However, other sex-related factors probably influence this different prognosis. For instance, the number of previous pregnancies has recently been shown to be associated with a better prognosis in women with heart failure.[2] Also, important sex-related differences have been described in patients with acute myocardial

infarction.[3] Irrespective of these considerations, we agree that, with respect to the prognosis of patients with TTS, the underlying trigger is also an important factor. In fact, in a previous work by our group,[4] we reported that the clinical course during hospitalization (length of stay and complications) and follow-up (recurrences) was worse in secondary than in primary TTS. This is why we proposed to extend this simple nomenclature. Primary TTS has no identifiable trigger, or is triggered by major psychological stress, while secondary TTS is triggered by physical factors (such as respiratory exacerbation, surgery, and trauma).[5]

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Definition of Myocardial Infarction Type 4a: Can We Define Its Diagnosis and Systematize Clinical Practice?

Definición de infarto tipo 4a: ¿podemos definir mejor su diagnóstico y sistematizar la práctica clínica?

To the Editor,

After reading the article "Comments on the 2018 ESC Fourth Universal Definition of Myocardial Infarction",[1] we are prompted to comment on the diagnosis of type 4 a acute myocardial infarction (AMI), which describes AMI occurring after percutaneous coronary intervention (PCI). We note a major discrepancy between the definition put forward by the European Society of Cardiology (ESC)[2] and the concept of "clinically relevant myocardial infarction" proposed in 2014 by the Society for Cardiovascular Angiography and Interventions (SCAI)[3]; we furthermore believe that this discrepancy generates conspicuous and undesirable variability in clinical practice. Guideline documents should examine this issue in greater depth, in order to establish a consensus definition and thereby eliminate this variability.

In the previous and current ESC guidelines, the key diagnostic criterion for type 4 a AMI is a post-PCI elevation $\geq$ 5 times the 99th percentile upper reference limit for myocardial injury markers. A confirmed diagnosis requires this to be concurrent with one of the following factors: new ischemic electrocardiogram changes, new Q waves, imaging evidence of the loss of viable myocardium, or angiographic evidence of a vascular complication explaining the marker elevation.

The SCAI uses distinct criteria, defining "clinically relevant myocardial infarction" as a biomarker elevation $\geq$ 70 times the local laboratory upper limit of normal or $\geq$ 35 times that limit if accompanied by new pathological Q waves in 2 contiguous leads or new persistent left bundle branch block.[3] The SCAI authors argue that the AMI definition adopted by the ESC is not clearly linked to subsequent events such as death or heart failure; widespread adoption of this biomarker threshold may therefore have serious consequences for the appropriate assessment of devices and treatments, potentially affecting clinical care pathways and leading to misinterpretation of physician competence. Thus, in place of an AMI definition sensitive to mild myonecrosis, the SCAI consensus document recommends the use of a higher biomarker elevation threshold that has shown strong links to subsequent adverse events in clinical studies.[3]

Likely as a consequence of this lack of consensus, current clinical practice shows an alarming variability. Moreover, in health care settings where cost concerns are more pressing, the lack of consensus and the resulting uncertain applicability of recommended thresholds to decision-making have resulted in low rates of biomarker measurement. This is evident from the US National Cardiovascular Data Registry, which shows that post-PCI biomarkers were measured in only 26% of 157 825 Medicare patients undergoing elective PCI at 711 hospitals between 2004 and 2008; the registry furthermore shows that the likelihood of postprocedure biomarker surveillance was significantly dependent on the treating hospital.[4]

In light of these observations, further efforts should be directed at improving the diagnosis of type 4 a AMI and systematizing clinical practice. A more precise knowledge base would provide needed clarity, helping to identify those patients truly in need of biomarker analysis and providing health care savings by avoiding unnecessary biomarker determinations. Such savings are especially advisable in the current climate of escalating costs, which places a priority on dispensing with measures that do not provide value.[5]

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