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Editorial comment

Predicting the development of heart failure in patients with atrial fibrillation

Predicción del desarrollo de insuficiencia cardiaca en pacientes con fibrilación auricular

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Atrial fibrillation (AF) is the most prevalent and clinically significant sustained arrhythmia in adults worldwide.[1] This condition is associated with marked increases in cardiovascular morbidity and mortality,[2] and in the risks of stroke and heart failure (HF) in particular. In addition, patients with AF often have a markedly diminished quality of life.[1]

The prevalence of AF is increasing, similar to that of other chronic diseases This increase is due to population aging, the growing prevalence of predisposing factors such as obesity, and a higher rate of arrhythmia diagnosis.[3] In Europe, 29.5% of the population was older than 55 years in 2010 and this number is expected to increase to 41% by 2060.[4] The estimated prevalence of AF in the general population varies between 2% and 4%,[1] but calculations indicate that it may double in the next 3 decades. The age-adjusted incidence and prevalence of AF are higher in men than in women and in White adults than in Asian, African American, and Hispanic adults.[5] AF has a considerable impact on health care systems in terms of resources and costs due to clinical care.

HF and AF are closely associated, with the presence of either condition predisposing the development of the other, and their coexistence worsens prognosis. Accordingly, up to 50% of patients with HF develop AF at some point in their life, which indicates a risk of arrhythmia development more than twice that of the general population.[6] AF development is common in the entire spectrum of patients with HF but its incidence increases with the left ventricular ejection fraction (LVEF) value and is particularly high in patients with preserved LVEF.[7] Some differences have been found in atrial remodeling among the different phenotypes of patients with HF: the remodeling tends to be more eccentric in patients with reduced LVEF, whereas it is characterized by extensive fibrosis and elevated atrial rigidity in patients with preserved LVEF, which leads to higher atrial pulsatility and wall stress.[8]

Various mechanisms have been proposed to explain how AF development worsens HF. First, loss of the contribution of atrial systole to ventricular filling increases wall stress and decreases ventricular volumes, which, together with the irregular heart beat and the shortened diastolic filling time in patients with a rapid ventricular response, can reduce cardiac output by about 20%.[9] AF onset is associated with greater neurohormonal activation, remodeling of the myocardial exoskeleton, and, if the arrhythmia persists, apoptosis, cell death, and fibrosis.[10] In patients with long-standing AF, the resulting atrial remodeling favors the dilatation of the mitral and tricuspid valve rings, leading to secondary valve regurgitation, which worsens the HF symptoms.

At the same time, HF also constitutes a risk factor for the development of AF. Elevated end-diastolic ventricular pressure is transmitted in a retrograde manner, which increases atrial filling pressures and, consequently, wall stress. This phenomenon activates the neurohormonal system and various inflammatory and profibrotic pathways and alters calcium metabolism in cardiomyocytes. These mechanisms promote the progressive structural and electrical remodeling of the atria, which favors AF development and persistence.[9,11]

Although several biologically consistent pathophysiological mechanisms have been proposed to explain the interrelationship between AF and HF, some knowledge gaps remain, particularly regarding their clinical implications. In a large community-based study conducted in Olmsted County (Minnesota, United States) toward the end of the last century,[12] a 24% cumulative incidence of HF was detected in a cohort of patients with recently diagnosed AF during a mean follow-up of more than 6 years. In addition, HF development was associated with a significantly increased risk of death. Notably, the authors identified AF duration as a factor predicting a higher risk of HF in long-term follow-up, a finding supporting a predisposing role for pathological atrial remodeling in the development of HF in these patients.

Various risk calculators have been validated for predicting the probability of death and adverse clinical events in patients with HF.[13] However, few tools allow us to reliably estimate the risk of HF development in patients with AF.[14,15] In addition, none of these tools has been specifically validated for use in the Spanish population. In a relevant article recently published in *Revista Española de Cardiología*, Torres-Llergo et al.[16] provide pertinent

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data on this knowledge gap. The authors analyzed a contemporary cohort of 1499 patients with AF included in the prospective observational registry REFLEJA during a 3-year follow-up in the cardiology clinic of the *Hospital Universitario de Jaén* to study the incidence of HF hospitalizations and identify the risk factors for this outcome. The research team should be congratulated for their rigorous execution of the project. Their results show, for example, a low rate of loss to follow-up and exhaustive recording of the clinical events being studied.

One of the most notable findings of Torres-Llergo et al. is the high incidence of hospitalizations for HF in the study population (incidence of 8.51 per 100 person-years). This rate is similar to that of a contemporary cohort of octogenarian patients with AF followed up in another Spanish university hospital.[17] In addition, the study identified 7 clinical factors associated with an increased risk of HF hospitalization during follow-up: older age, diabetes, chronic kidney disease, pulmonary hypertension, significant aortic regurgitation, concomitant use of diuretics, and previous pacemaker implantation. In our opinion, the association of all of the predictors identified in the study with the risk of admission due to HF is understandable and somewhat expected because these factors reflect conditions that also favor the development of HF in patients without AF or even reflect the coexistence of HF symptoms at the start of follow-up, such as the need for diuretic therapy and the presence of pulmonary hypertension. Irrespective of these considerations, the main value of the study lies in the authors' initiative in developing a simple nomogram for predicting HF hospitalization risk in patients with AF and which, when applied to their own cohort, showed strong discrimination capacity, strengthening the internal validity of the study results.

The study included both patients with de novo AF and those with long-term forms, and more than 60% of the patients had persistent or permanent AF. Several of the risk factors identified by Torres-Llergo et al. are conditions affecting the atrial myocardium, which favor the onset and chronification of AF. In a considerable number of patients diagnosed with AF, arrhythmia development reflects changes in atrial structure or function.[18] The atrial myocardium possesses distinct functional characteristics from the ventricular myocardium. The electrophysiological properties of the atria also differ from those of the ventricles, such as those of the action potential and ion channels. These differences mean that the chambers are particularly susceptible to arrhythmia onset, both due to increased automaticity and to re-entrant mechanisms,[19] and, in addition, the cell-to-cell coupling protein distribution differs between atrial and ventricular cardiomyocytes.[20] Moreover, the atria show a particular 3-dimensional structure with complex anatomical relationships. The atrial myocardium can be affected by various conditions, both cardiac and noncardiac (eg, ventricular dysfunction, valvular heart diseases, hypertension, obesity, and drug use), and is more sensitive to these factors than the ventricular myocardium.[21]

In recent years, the concept of atrial cardiomyopathy has attracted particular attention. This condition is defined as a set of structural, architectural, contractile, and electrophysiological changes that affect the atria and may have clinically relevant effects.[22] The presence of AF itself induces progressive functional and structural changes in the atrial myocardium that favor the long-term chronification of the arrhythmia.[23] AF progression comprises a complex pathophysiological process that includes electrical, structural, mechanical, functional, and molecular changes.[24] Atrial cardiomyopathy promotes the development of AF and its persistence fosters the progression of pathological atrial remodeling. The study of this process is limited by diagnostic difficulties but is attracting more and more interest due to its clinical applicability.[25] In the coming years, we will likely see more standardized approaches for evaluating the severity of atrial cardiomyopathy that go beyond merely considering the presence of AF; however, the development of HF in these patients remains unclear and would be an interesting line of research.[26]

Given the relevance of the problem, the predictive tool developed by Torres-Llergo et al. is clinically interestingand has a clear potential for applicability. Nonetheless, before its use can be considered in daily clinical practice, it should be externally validated in other cohorts of patients with AF in Spain. These cohorts should include those managed by cardiology and those managed by other specialties, such as internal medicine and family medicine, who are receiving contemporary treatments. Ideally, this validation would be conducted via prospective multicenter studies.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest in relation to this article.

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