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Editorial

Atrial Fibrillation: A Riddle Wrapped in a Mystery Inside an Enigma

Fibrilación auricular: un acertijo envuelto en un misterio dentro de un enigma

Claire Alexandra Lawson[a,b] and Mamas Andreas Mamas[a,*]

[a] Keele Cardiovascular Research Group, Institute of Applied Clinical Science and Centre for Prognosis Research Group, Institute of Primary Care and Health Sciences, Keele University, and Academic Department of Cardiology, Royal Stoke Hospital, Stoke-on-Trent, United Kingdom
[b] Keele School of Nursing and Midwifery, Keele University, Stoke-on-Trent, United Kingdom

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Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice with an estimated 20.9 million men and 12.6 million women living with AF worldwide.[1] With almost 5 million new cases of AF annually, an estimated 1 in 4 individuals aged 40 years old of European descent will ultimately develop AF.[2] Atrial fibrillation is associated with a 4-fold increased risk of stroke[3] and a more than 2-fold increased risk of heart failure (HF)[4] and mortality.[5] AF is a common comorbidity in patients hospitalized with many cardiovascular conditions and is increasingly encountered in the growing elderly population in this arena.[1]

In a recent article published in *Revista Española de Cardiología*, Clavel-Ruipérez et al.[6] explore the relationship between the presence of AF in patients admitted with decompensated HF, acute myocardial infarction (AMI), or ischemic stroke (IS) and mortality. This article responds to an important ongoing debate on whether the presence of AF is associated with a differential risk, according to the underlying cardiovascular pathology. While AF is consistently shown to increase the risk of poor outcomes in other cardiovascular patients, the evidence on its impact in combination with HF has generated controversy for the last 2 decades. Whether AF adds to risk in HF or is a mere bystander that indicates more severe HF is a question that remains unresolved by ongoing conflicting reports.

In their population-based study, Clavel-Ruipérez et al. retrospectively examined 6613 patients (2177 AMI, 2228 IS, and 2298 HF) who were consecutively admitted to a district hospital in Spain over a 10-year period to 2009. They found that the presence of AF (recorded in hospital and remaining at discharge) was higher in those who died than in survivors, for both in-hospital and long-term mortality. This relationship existed in the whole group and in the AMI and IS subgroups but not in the HF subgroup. The association became insignificant for in-hospital mortality after correction for patient age, sex, and comorbidities but remained intact for the whole group, as well as for the AMI and IS subgroups, for longer term mortality. The effect of AF in AMI and IS was consistent with prior evidence but AF was not a predictor of poor prognosis in HF.

From these findings, Clavel-Ruipérez et al. postulate that the differences between their study findings and that of previous HF trials and observational studies was the unselected nature of their HF sample. Indeed, the FIACA sample was older and had more comorbidities than the trial samples and thus better represented the general HF population. The authors recognize some key limitations of their study and acknowledge continued uncertainty about the role of AF in HF prognosis. Indeed core questions on the duration, dynamic nature, and temporality of AF occurrence in HF remain unanswered and require specific consideration in the design of future studies before the debate can move forward.

Six major HF trials have reported opposite effects of AF: SOLVD,[7] DIG,[8] and CHARM[9] found that the presence of baseline AF was associated with increased risk of all-cause and progressive pump-failure death, while COMET[10] and V-HeFT,[11] and PRIME-II[12] found no such association. However, subanalyses in several trials and observational studies indicate that new AF poses a higher risk in HF than established AF.[8–11,13] The hemodynamic effects of sustained chronic AF in established HF are intrinsically linked through the shared pathophysiological, neurohormonal, and electrophysiological mechanisms triggered by both conditions. Prognosis likely relates to the resulting hemodynamic compromise, progressive remodeling over time, or noncardiac causes such as IS. The resulting impact of AF might be better determined by current HF status and management, thus eliminating the effect of AF *per se*. In the landmark AF-CHF trial, rhythm control showed no advantage over rate control, pointing to the importance of the resulting compromise as opposed to the arrhythmia itself,[14] and in PRIME-II and COMET, the unadjusted significant effect of AF disappeared after adjustment for a range of HF factors. Conversely, the prognostic effect associated with new AF is potentially proportional to both the severity of the sudden change in hemodynamic status at its onset and the compromise incurred over time by its persistence, in addition to current HF status. Most studies to date classify AF present on admission as established AF, which ignores the likelihood of heterogeneity of AF duration within the group.

By linking hospital and death data, Clavel-Ruipérez et al. were able to investigate death outcomes over a median of 6.2 years [interquartile range, 3.9-8.8] and provide evidence on the longer-term effects of AF in HF. However, with the clear advantages of

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* Corresponding author: Keele Cardiovascular Research Group, Institute of Applied Clinical Science and Centre for Prognosis Research Group, Institute of Primary Care and Health Sciences, Guy Hilton Research building, Thornburrow Drive, Hartshill, Stoke-on-Trent ST4 7QB, United Kingdom.
E-mail address: mamasmamas1@yahoo.co.uk (M.A. Mamas).

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longer follow-up comes the methodological pitfall of using baseline data, which inevitably change over time. The authors accept that treatment of patients with AF in HF will have changed over the study period, with increases in prescribed beta-blockers and anticoagulants and decreases in prescribed class-1 antiarrhythmic drugs. However, a common omission from studies is accounting for the dynamic nature of AF itself. The authors attempt to counteract misclassification bias by stipulating the requirement for AF to have been present at discharge, assuming this to be persistent or permanent AF. However, they were unable to account for the development of AF in the non-AF baseline group during follow-up. Given the potential higher risk association with new compared with established AF, this is likely to diminish the effect of established AF on outcomes. For example, in PRIME-II, also a negative AF study, 9% of the non-AF group developed new-onset AF during follow-up but remained in the 'non-AF' group in the main analysis.

Finally, a differential prognostic effect of AF has been reported, depending on which condition develops first, with AF being associated with increased risk only when it occurs after HF.[15] When HF is precipitated by AF, the hemodynamic compromise that ensues potentially supersedes the prognostic effect of the AF, especially when cardiovascular and HF status is accounted for. When the disease onset is reversed, the development of AF in HF likely indicates more severe and longer duration of HF, increases the severity of HF at its onset, and is associated with worse outcomes. Clavel-Ruipérez et al. were not able to account for the temporality, etiology or severity of HF in their analysis. In the DIAMOND trial,[16] HF with AF patients with nonischemic etiology were found to have favorable outcomes over those with ischemic etiology. In the former group, AF is more likely to be the precipitator rather than the consequence of HF with different prognostic implications.

What is clear from the growing evidence is that the question of whether AF directly affects prognosis or is merely a pseudomarker of HF severity appears too simplistic. Both conditions are so intrinsically linked that to attempt to assign causation might be somewhat misleading and likely to differ among individuals. The complex interrelationship between the 2 conditions as they develop and the multitude of factors at play makes any attempts to precisely proportion risk to each condition challenging. Whether there is a crossover point at which AF no longer matters in HF remains to be determined, but this does not diminish the potential for AF to be a powerful mediator of HF status. Future studies need to disentangle the influence of factors related to HF and AF etiology and duration, as well as the severity of both conditions and modifying interventions that change over time.

CONFLICTS OF INTEREST

None declared.

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