**Atrial Fibrillation; A Riddle Wrapped in a Mystery Inside an Enigma**

**Fibrilación auricular; un acertijo envuelto en un misterio dentro de un enigma**

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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 one in four 40-year-old individuals of European descent will ultimately develop AF.2 Atrial fibrillation is associated with a 4-fold increased risk of stroke3 and a greater than 2-fold increased risk of heart failure (HF)4 and mortality.5 AF is a common comorbidity of patients hospitalised 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 ischaemic stroke (IS) and mortality. This article responds to an important ongoing debate on whether the presence of AF is associated with differential risk according to the underlying cardiovascular pathology. Whilst AF is consistently shown to increase risk of poor outcomes in other cardiovascular patients, the evidence on its impact in combination with HF has generated controversy that stems two decades. Whether AF adds to risk in HF or is a mere bystander marking more severe HF, is a question that remains unresolved by ongoing conflicting reports.

In their population-based study, Clavel-Ruipérez et al. retrospectively examine 6613 patients (2177 AMI, 2228 IS and 2298 HF) who were consecutively admitted to a district hospital in Spain over a 10-year time period to 2009. They found that the presence of AF (recorded in hospital and remaining at discharge) was higher in those that died than in the 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 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 with more comorbidities than the trial samples and thus better represented the general HF population. The authors recognise 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 forwards.

Six major HF trials have reported opposing effects of AF with SOLVD,7 DIG8 and CHARM,9 finding presence of baseline AF to be associated with increased risk of all-cause and progressive pump-failure death and COMET10 and V-HeFT,11 PRIME-II,12 finding no such association. However sub-analysis in several trials and observational studies indicate that new AF poses higher risk in HF than established AF.8-11,13 The haemodynamic effects of sustained chronic AF in established HF, are intrinsically linked through the shared pathophysiological, neuro-hormonal and electrophysiological mechanisms triggered by both conditions. Prognosis likely relates to the resulting hemodynamic compromise, progressive remodelling over-time or non-cardiac causes such as IS. The resultant impact of AF might be better determined by current HF status and management and 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 resultant compromise as opposed to the arrhythmia itself14 and in PRIME-II and COMET, the unadjusted significant effect of AF disappeared following 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 haemodynamic status at its onset and the compromise incurred overtime 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 longer follow-up, comes the methodological pitfall of using baseline data, which inevitably changes overtime. The authors accept that treatment of patients with AF in HF will have changed over the study time-period with increases in prescribed beta-blockers and anti-coagulants and decreases in prescribed class-1 anti-arrhythmic 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 persisting or permanent AF. However they were unable to account for development of AF in the non-AF baseline group during follow-up. Given the potential higher risk association with new compared to 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 by the temporality of which condition develops first has also been reported, with AF only associated with increased risk where it occurs after HF.15 Where HF is precipitated by AF, the hemodynamic compromise that ensues potentially supersedes the prognostic effect of the AF especially where cardiovascular and HF status is accounted for. When the disease onset is reversed, the development of AF in HF likely indicates mores 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 temporality, aetiology or severity of HF in their analysis. In the DIAMOND trial,16 HF with AF patients with non-ischemic aetiology were found to have favourable outcomes over those with ischaemic aetiology. 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 building evidence is that the question of whether AF directly effects prognosis or is merely a pseudo marker 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 two 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 where AF no longer matters in HF remains to be answered 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 aetiology and duration as well as the severity of both conditions and modifying interventions that change over time.

**CONFLICTS OF INTEREST**

**REFERENCES**

1. Lip G, Fauchier L, Freedman SB, et al. Atrial fibrillation. *Nat Rev Dis Primers*.2016;2:16016.

2. Heeringa J, van der Kuip D, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27:949-953.

3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22983-988.

4. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107:2920-2925.

5. Friberg J, Scharling H, Gadsbøll N, Truelsen T, Jensen GB. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *Am J Cardiol*. 2004;94:889-894.

6. Clavel-Ruipérez FG, Consuegra-Sánchez L, Félix Redondo FJ, et al. Mortality and Atrial Fibrillation in the FIACA Study: Evidence of a Differential Effect According to Admission Diagnosis. *Rev Esp Cardiol*. 2017. [http://dx.doi.org/[10.1016/j.rec.2017.03.026](http://dx.doi.org/10.1016/j.rec.2017.03.026%22%20%5Ct%20%22_blank)](http://dx.doi.org/10.1016/j.rec.2017.03.028).

7. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol*. 1998;32:695-703.

8. Mathew J, Hunsberger S, Fleg J, Mc Sherry F, Williford W, Yusuf S. Incidence, predictive factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. *Chest*. 2000;118:914-922.

9. Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol*. 2006;47:1997-2004.

10. Swedberg K, Olsson LG, Charlesworth A, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J*. 2005;26:1303-1308.

11. Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT Studies. The V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87(6 Suppl):VI102-10.

12. Crijns HJ, Tjeerdsma G, de Kam PJ, et al. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. *Eur Heart J*. 2000;21:1238-1245.

13. Rivero-Ayerza M, Scholte Op Reimer W, et al. New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the EuroHeart Failure Survey. *Eur Heart J*. 2008;29:1618-1624.

14. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667-2677.

15. Wang TJ, Larson MG, Levy D, et al. Temporal Relations of Atrial Fibrillation and Congestive Heart Failure and Their Joint Influence on Mortality. *Circulation*. 2003;107:2920-2925

16. Pedersen OD, Sondergaard P, Nielsen T, et al. Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure. *Eur Heart J*. 2006;27:2866-2870.