Dear Editor,

We have read with interest the article in this issue of *Revista Española de Cardiología*, by Clavel-Ruiperez et al.[1] which explores the relationship between the presence of atrial fibrillation (AF) in patients admitted with decompensated heart failure (HF), acute MI (AMI) or ischaemic stroke (IS) and mortality. This article is important given the increasing prevalence HF and AF in ageing populations which constitute two major public health problems. Both conditions have deleterious effects on patients and health services’ expenditure and often co-occur with up to 50% of HF patients having AF and 20% of AF patients having HF. Yet, whilst AF has been consistently shown to increase risk of poor outcomes in other cardiovascular patients, evidence on its impact in combination with HF has generated controversy that stems two decades. Current debate on whether AF adds additional risk in HF or is a mere bystander marking more severe HF, remains unresolved by ongoing conflicting reports.

In a population-based study, Clavel-Ruiperez et al retrospectively examine 6613 patients (2177 AMI, 2228 IS and 2298 HF) who were consecutively admitted to a district hospital 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 was found for the whole group and in the AMI and IS sub-groups but not in the HF sub-group. 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 sub-groups 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-Ruiperez et al postulate that the differences between their study findings in the HF group and that of previous trials and observational HF 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. 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[2], DIG[3] and CHARM[4], finding presence of baseline AF to be associated with increased risk of all-cause and progressive pump-failure death and COMET[5] and V-HeFT[6], PRIME-II[7], 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 [3-6, 8]. The haemodynamic effects from 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 itself[9] 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-Ruiperez et al are able to investigate death outcomes over a median of 6.2 years (IQR 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 over-time. 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. 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[10]. Where HF is precipitated by AF, the hemodynamic compromise that ensues potentially supersedes the prognostic effect of the AF especially where cardiovascular and heart failure 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 establishes a mutually lethal coupling, determined by the resultant compromise. Clavel-Ruiperez et al were not able to account for temporality, aetiology or severity of HF in their analysis. In the DIAMOND trial[11], 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.
1. “Rev Esp Cardiol. CROSS-REFERENCE


