Atrial Fibrillation and Sudden Cardiac Death

Is Heart Failure the Middleman?*

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Atrial fibrillation (AF) is a world-wide epidemic, affecting more than 33 million individuals across the globe (1). Beyond its impact on quality of life, AF is associated with increased risks of stroke, heart failure, cognitive impairment, and death (2,3). Emerging evidence suggests that AF may be associated with an increased risk of sudden cardiac death (SCD) as well (4,5).

Several recent observational studies have shown an association between AF and SCD. In the Cardiovascular Health Study, the unadjusted incidence of SCD was 12 per 1,000 person-years in those with AF versus 3.8 per 1,000 person years in those without AF. Following adjustment, AF remained associated with an increased hazard of SCD (hazard ratio [HR]: 2.14 [95% confidence interval (CI): 1.60 to 2.87]) (4). Findings in a validation cohort of individuals ages 45 to 64 were similar (4). In the LIFE (Losartan Intervention for Endpoint) study, hypertensive patients with left ventricular hypertrophy and new-onset AF were observed to have a more than 4-fold increased risk of SCD after adjustment for multiple factors, including heart failure (HF) (HR: 4.69 [95% CI: 2.96 to 7.45]) (5).

Finally, new-onset AF has also been associated with an increased risk of malignant arrhythmias following myocardial infarction (6).

It is plausible that AF independently contributes to the risk of SCD, and potential mechanistic explanations include: 1) genetic or other propensity favoring fibrillation in the ventricles in those with fibrillating atria; 2) AF-related adverse myocardial remodeling; 3) tachycardia-induced tachycardia; 4) proarrhythmic long–short sequences during AF; 5) impaired calcium handling; or 6) repolarization abnormalities (7–10).

Alternatively, AF may be a marker for occult or more advanced cardiovascular disease, including hypertrophy or HF, either with reduced or preserved ejection fraction (EF). The AF–SCD relationship may thus be a confounded one. In the 18,000-patient RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial, 20% of deaths were due to SCD, and these events were best predicted by the presence of HF (HR: 2.24 [95% CI: 1.75 to 2.87], p < 0.0001) (11). This raises the question, “Is HF the middleman responsible for the observed increased risk of SCD in patients with AF?”

In this issue of JACC: Heart Failure, Reinier et al. (12) analyzed the association between AF and SCD with case-control methodology. The investigators compared 652 SCDs in the Oregon Sudden Unexpected Death Study with age- and sex-matched controls. AF was much more common in SCD cases than matched controls (27% vs. 18%, p = 0.0001). However, after adjustment using logistic regression and propensity score matching, the AF–SCD association was no longer significant. Patients with SCD more frequently had HF (45% vs. 19%, p < 0.0001) and low EF (30% vs. 14%, p < 0.001) than controls. When the prevalence of AF stratified by HF status was compared in cases and controls, there was no difference (p = 0.13). Reinier et al. (12) conducted a host of sensitivity analyses using alternative definitions of HF based upon left ventricular function and brain natriuretic peptide levels, all of which failed to demonstrate an independent association of AF and SCD.

Another interesting, but subtle, finding in Reinier et al. (12) was the more frequent use of digoxin in SCD cases versus controls with HF. Despite some efficacy for rate control in AF, and symptom control in HF, digoxin is known to have proarrhythmic effects. Digoxin has been associated with an increased risk of SCD and all-cause mortality in patients with AF (with and without HF) (13–15). Furthermore, digoxin is also associated with increased risks of implantable cardioverter-defibrillator shocks, even after adjustment for AF (16). This finding represents yet another association that requires further investigation, particularly given the known safety concerns surrounding digoxin pharmacotherapy.

There are several limitations that need to be considered when interpreting the findings from this case-control analysis. Most importantly, all of the controls in the study had coronary artery disease, and therefore, the results may not be generalizable to patients without coronary artery disease. Although multiple methods of adjustment were employed, the propensity matching was performed on different sources of patients, using a relatively limited set of covariates (n = 5), and the potential for unmeasured confounding was significant. Finally, all case-control studies suffer from selection bias, and the cases described in the Oregon-SUDS

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(Oregon Sudden Unexpected Death Study) may not entirely be representative of other cohorts.

The findings from Reiner et al. (12) have important implications for both cardiovascular investigators and clinicians. The relationship between AF, HF, and SCD in this analysis serves as an important reminder of the clear and present danger of confounding in all observational studies. Further investigation is required to clarify whether AF contributes to the risk of SCD. However, these data also highlight the risks of SCD in patients with concomitant AF and HF. Perhaps the best method for preventing SCD in patients with AF is the prevention of HF.

Although we have many effective therapies for stroke prevention, we have little randomized evidence for the prevention of HF in patients with AF, despite the fact that the incidence of HF is approximately 2-fold greater than the incidence of stroke in patients with AF (17). Moreover, the incidence of HF in AF patients has not decreased over the last few decades (18). Pharmacological rhythm control has so far been relatively ineffective in preventing morbidity and mortality in AF patients with low EF (19). Limited data suggest AF ablation can ameliorate HF in AF patients (20,21), but larger more definitive trials are underway. More research and effective therapies are needed for the primary prevention of HF in patients with AF. Although the causal nature of AF in SCD remains uncertain, it is clear that HF and AF is a bad combination that is best avoided.

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