Atrial Fibrillation and Its Association With Sudden Cardiac Death

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Evidence is emerging to indicate that atrial fibrillation (AF) is independently associated with an increased risk of sudden cardiac death (SCD). This association has been consistently observed in specific patient subgroups such as patients with myocardial infarction (MI), heart failure, and hypertension, and importantly, in the general population. Data from studies of implantable cardioverter-defibrillator recipients suggest that the rapid and irregular rhythm of AF and the short-long-short cycles that are highly prevalent in AF increase susceptibility to ventricular tachycardia and ventricular fibrillation. An alternative explanation for the association between AF and SCD includes confounding or mediation by shared risk factors such as coronary artery disease and heart failure. Possible risk factors for SCD in patients with AF include black race, left ventricular hypertrophy, history of MI, and diabetes. Additional research is needed to confirm the inherent proarrhythmic nature of AF, identify patients’ characteristics or clinical conditions that potentiate SCD risk, and define effective SCD prevention strategies for patients with AF. (Circ J 2014; 78: 2588–2593)

Key Words: Atrial fibrillation; Risk factors; Sudden cardiac death; Ventricular fibrillation; Ventricular tachycardia

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and with the aging population its prevalence is increasing over time. Additionally, AF is associated with an increased risk of stroke, heart failure (HF), and death. The Framingham Heart Study reported that AF increases the risk of death by 1.5-fold in men and 1.9-fold in women. Similarly, the reported Olmsted County, Minnesota experience showed that new-onset AF doubles the risk of mortality. More recently, the Women’s Health Study revealed that the risk of all-cause death was doubled and cardiovascular death quadrupled by new-onset AF in initially healthy women.

Although the evidence for an independent association of AF with an increased risk of mortality is compelling, there are few data on the causes of death in patients with AF; the most common causes of death in the aforementioned studies were coronary artery disease (CAD) and stroke. There is evidence from post-myocardial infarction (MI) or HF patients that AF is associated with an increased risk of sudden cardiac death (SCD). However, SCD was not specifically reported in previous population-based studies; hence, it is unknown whether AF increases the risk of SCD in the general population. Moreover, because AF and SCD share many common risk factors, such as HF and CAD, it is possible that any possible association between AF and SCD is confounded or mediated by these shared risk factors.

This narrative review aims to summarize the available information that sheds light on a serious sequela of AF that we are only starting to understand – SCD. We will review the evidence for an independent relationship between AF and SCD in different contexts: recipients of implantable cardioverter-defibrillators (ICDs), patients with MI, HF, or hypertension (HT), and finally, in the general population. We will also examine the determinants of SCD in patients with AF and postulate on the mechanisms underlying this novel and intriguing association.

AF and Ventricular Tachyarrhythmias in Recipients of ICDs

One of the earliest lines of evidence to suggest that AF may inherently increase the incidence of ventricular tachycardia (VT) or ventricular fibrillation (VF) comes from patients who have received an ICD. In a study comprising 229 patients who received ICDs between 1995 and 1999 for secondary prevention of SCD, those who had persistent AF (n=38) at the time of ICD implant experienced appropriate device therapy for recurrent ventricular tachyarrhythmias more frequently than patients who were in sinus rhythm at the time of ICD implantation (n=191) (63% vs. 38%, P=0.01). From multivariable analysis, AF was an independent predictor of both appropriate ICD therapy (relative risk 1.8; 95% confidence interval [CI] 1.2–2.9) and inappropriate device therapy (relative risk 2.3; 95% CI 1.2–4.5). Analysis of device-stored electrograms revealed a higher incidence of short-long-short cycles preceding ventricular arrhythmias in AF compared with patients in sinus.
Collectively, the findings of these 3 studies\textsuperscript{19–21} suggest that the presence of persistent or permanent AF may increase susceptibility to VT/VF in patients with (1) history of cardiac arrest from VT/VF, (2) spontaneous or inducible hemodynamically unstable sustained monomorphic VT, or (3) high risk of SCD because of underlying cardiomyopathy.

One caveat, however, should be noted. In ICD-based studies, it may often be difficult to distinguish AF with aberrancy from ventricular tachyarrhythmias.\textsuperscript{22} To further investigate the relationship of AF to VT/VF in ICD-based studies, exact diagnosis of wide-complex tachycardia is critical.\textsuperscript{23} In the following sections, we will outline the evidence that atrial arrhythmias would confer the same increased arrhythmia risk in other patients, such as patients with previous MI or HF.

**AF and SCD in Patients With MI**

The TRAndolapril Cardiac Evaluation (TRACE) study consisted of 5,983 consecutive acute MI patients admitted to 27 centers in Denmark from May 1990 to July 1992.\textsuperscript{12} Of these patients, 1,149 (19%) developed AF during the index hospitalization for MI. During follow-up, there were 1,659 (34%) deaths, of which 536 were classified as SCD. In the multivariable analysis of this study, compared with patients who remained in sinus rhythm, the development of AF during MI was associated with a significant 1.3-fold increased risk of SCD.

Similar observations were made in another study of 505 patients with acute MI enrolled from 3 intensive care units in Italy between 1995 and 1998.\textsuperscript{14} Of these patients, 64 (12.7%) developed AF during the first week of hospitalization. After 7
years of follow-up, 217 (43.0%) patients had died. From the multivariable multinomial logistic regression analysis, the presence of AF during the first week of MI was associated with increased odds of SCD (odds ratio, 2.7; 95% CI, 1.2–6.4, P=0.02) but not with HF or other cardiovascular death, and non-cardiovascular death.

AF and SCD in the General Population

Middlekauff et al evaluated the relationship of AF to overall survival and SCD in 390 consecutive patients with New York Heart Association Class III or IV advanced HF. The mean left ventricular ejection fraction was 19±7% and 75 (19%) patients had prevalent AF. After a mean follow-up of 236 days, 98 patients died; 56 (57%) died suddenly, and 36 (37%) died of progressive HF. Overall 1-year survival was 68%, and SCD-free survival was 79%. Overall survival was significantly worse for AF than for sinus rhythm patients (52% vs. 71%, P=0.001). Similarly, SCD-free survival was significantly worse for AF than for sinus rhythm patients (69% vs. 82%, P=0.001). From the multivariable Cox proportional hazards regression analysis, pulmonary capillary wedge pressure on therapy, left ventricular ejection fraction, and AF were found to be independent risk factors for SCD.

In aggregate, the preceding observations suggest that AF is independently associated with increased risk of VT/VF or SCD in specific high-risk patient subgroups: recipients of ICD for primary or secondary prevention of SCD, patients with MI, and patients with advanced HF. The next 2 sections outline the evidence supporting the association of AF with SCD even in lower-risk individuals: patients with HT and community-dwelling individuals.

AF and SCD in Patients With HT

The relationship of new-onset AF to SCD was evaluated in 8,831 hypertensive patients with electrocardiographic (ECG) left ventricular hypertrophy (LVH) in the Losartan Intervention For Endpoint reduction (LIFE) study. The LIFE study was a randomized controlled trial that assigned 9,193 patients with HT and LVH to losartan- or atenolol-based therapy to evaluate the effect of these therapies on cardiovascular outcomes. During 4.7±1.1 years mean follow-up, new-onset AF occurred in 701 (7.9%) patients and SCD in 151 (1.7%) patients. From the univariable Cox analyses, new-onset AF was associated with a 4.1-fold increased risk of SCD (hazard ratio [HR], 4.10; 95% CI, 2.89–5.24; P<0.001). From the multivariable Cox analyses adjusting for statistically significant univariable predictors of SCD, new-onset AF remained associated with a >3-fold increased risk of SCD (HR, 3.13; 95% CI, 2.89–5.24; P<0.001). From the univariable Cox analyses, new-onset AF was associated with a 4.1-fold increased risk of SCD (hazard ratio [HR], 4.10; 95% CI, 2.89–5.24; P<0.001). From the multivariable Cox analyses adjusting for statistically significant univariable predictors of SCD, new-onset AF remained associated with a >3-fold increased risk of SCD (HR, 3.13; 95% CI, 2.89–5.24; P<0.001).

AF and SCD in the General Population

To evaluate whether or not incident or new-onset AF is independently associated with SCD in community-dwelling individuals, we recently analyzed data from 2 population-based prospective cohort studies: the Atherosclerosis Risk in Communities (ARIC) study and Cardiovascular Health Study (CHS). The ARIC cohort is a bi-racial sample, consisting of 15,792 men and women, 45–64 years of age at baseline (1987–1989), from 4 communities in North Carolina, Mississippi, Mississippi, Mississippi, Mississippi, Mississippi, Mississippi, Mississippi.
After baseline examination, participants had 4 additional examinations, the last in 2011–2013. In addition, ARIC participants have received annual follow-up calls since the first visit (>90% response rate) collecting information on general health and hospitalizations. The analysis in ARIC was based on data obtained from baseline (1987–1989) through December 31, 2001. The CHS is a cohort study of risk factors for CAD and stroke in older people. Between 1989 and 1990, 4 field centers (North Carolina, California, Maryland, Pennsylvania) recruited a total of 5,201 participants aged ≥65 years from Medicare eligibility lists. To enhance minority representation, during 1992–1993, 687 African-American participants were recruited. The analysis in CHS was based on data obtained from baseline (1989–1990 for first cohort and 1992–1993 for second cohort) through December 31, 2006.

For this report on the association of AF and SCD in the general population, we analyzed data from 15,439 (baseline 45–64 years, 55% women, 27% black) ARIC and 5,479 (baseline ≥65 years, 58% women, 15% black) CHS participants. We considered only incident or new-onset AF. SCD was physician-adjudicated, defined as CAD death from a sudden, pulseless condition presumed to be caused by a ventricular tachyarrhythmia and non-SCD was defined as CAD death not meeting SCD criteria. In the ARIC study, 894 AF, 269 SCD, and 233 non-SCD events occurred during follow-up (median, 13.1 years). After adjustment for baseline covariates, the respective multivariable HRs (95% CIs) of incident AF for SCD and non-SCD were 3.26 (1.27–4.91) and 2.43 (1.60–3.71) (Table 1). In the CHS, 1,458 AF, 292 SCD, and 581 non-SCD events occurred during follow-up (median, 13.1 years). The respective multivariable HRs (95% CIs) of incident AF for SCD and non-SCD were 2.14 (1.60–2.87) and 3.10 (2.58–3.72) (Table 1). The respective meta-analyzed HRs (95% CIs) of incident AF for SCD and non-SCD were 2.47 (1.95–3.13) and 2.98 (2.52–3.53) (Table 1).

To account for confounding by change of covariates over time, we adjusted the main analysis for time-dependent covariates by updating the covariates to the time point just before ascertainment of AF, censoring, or SCD incidence, whichever occurred earlier. We found that AF remained significantly associated with an increased risk of SCD (HR, 2.03; 95% CI, 1.30–3.17; P=0.002) (Table 2).

To investigate the determinants of SCD in patients with AF who were randomized to a rate vs. rhythm control strategy, investigators analyzed data from 522 patients in the RAte Control versus Electrical Cardioversion (RACE) study. RACE was a randomized controlled trial that evaluated the cardiovascular outcomes of patients with persistent AF who were randomized to a rate vs. rhythm control strategy. After a mean follow-up of 2.3±0.6 years, SCD occurred in 16 patients. Multivariable Cox proportional hazard regression analysis showed that prevalent MI (HR, 4.9; 95%, 1.8–13.2; P=0.002) and prevalent diabetes (HR, 4.0; 95%, 1.4–11.7; P=0.010) were associated with an increased risk of SCD and the use of β-blockers was protective (HR, 4.0; 95%, 1.4–11.7; P=0.039).

In summary, possible risk factors for SCD in patients with AF include black race, LVH, history of MI and diabetes. However, before extending these findings into the clinical domain, additional work is needed to replicate these observations in other independent prospective studies and to understand the mechanisms underlying this association.
underlying mechanisms.

**Possible Mechanisms Underlying the Association of AF With SCD**

Unlike Wolff-Parkinson-White syndrome, in which the mechanism of AF-induced SCD is quite clear, in the general population the mechanisms underlying this association are less clear. The crux of the matter is whether or not AF is inherently proarrhythmic in the ventricle (ie, AF in and of itself, given the appropriate substrate, would induce VT/VF leading to SCD), or if AF is acting via another factor or condition (eg, HF) leading to increased SCD incidence. This is a critical issue because if the former is the dominant mechanism, efforts to maintain sinus rhythm in high-risk AF patients may prevent SCD. On the other hand, if AF is merely acting via another factor, efforts to maintain sinus rhythm may not be as effective in preventing SCD.

Indeed, evidence to suggest that AF may facilitate the induction of ventricular tachyarrhythmias abounds in the literature. A rapid ventricular rate during an atrial tachyarrhythmia will directly reduce ventricular refractoriness,31 promoting ventricular tachyarrhythmias. In addition, the irregular rhythm of AF leads to short-long-short sequences that may be intrinsically proarrhythmic.32 Evidence for AF facilitating induction of ventricular tachyarrhythmias comes from several sources. Somberg et al reported that VT was induced in 25 of 26 dogs by programmed electrical stimulation of the ventricle only during AF, and not in sinus rhythm.33 As discussed earlier, analysis of device-stored electrograms has revealed a higher incidence of short-long-short cycles preceding ventricular arrhythmias in AF compared with patients in sinus rhythm (50% vs. 16%, P=0.002).34 Collectively, these observations suggest that atrial tachyarrhythmias may increase susceptibility to ventricular tachyarrhythmias.

Because AF is also associated with an increased risk of non-SCD, it is possible that the association between AF and SCD is mediated by shared risk factors such as CAD or HF.26,34 The Oregon-Sudden Unexpected Death Study recently reported that in multivariate analysis without considering HF, AF was a significant predictor of SCD. However, in a model that included HF, the AF-SCD association was no longer significant.34 To further assess this issue of confounding or mediation by shared risk factors, we conducted a secondary analysis in the ARIC study by updating covariates to the end of follow-up. Although the association between AF and SCD was attenuated in the analysis, AF remained significantly associated with SCD after adjustment for factors potentially in the causal pathway.26 This observation suggests that the association between AF and SCD is only partially, and not completely, explained by shared risk factors.

**Future Directions**

Many questions remain regarding the relationship between AF and SCD. First, more evidence (laboratory, clinical, and population-based) is needed to confirm the inherent proarrhythmic nature of AF. Second, even if AF is shown beyond doubt to be inherently proarrhythmic, in what patients and under what conditions, is the proarrhythmic risk the highest? The answer to this question is important because of the obvious implication of targeting SCD prevention strategies to high-risk AF patients. Third, is the SCD risk only associated with persistent or permanent AF, and not with paroxysmal AF? An affirmative answer would provide additional support for clinical efforts to prevent paroxysmal AF from progressing to more advanced forms of AF. Fourth, more data on absolute risk estimates for the association between AF and SCD in different contexts are needed to provide insight into whether or not, and in whom, to pursue SCD prevention strategies. Finally, if SCD prevention in AF patients is justifiable, what might it entail? Should it be limited to the use of β-blockers as shown to be beneficial in the RACE study29 or be extended to rhythm control strategy by catheter ablation?19,20 Further, should implantation of ICDs in the highest risk patients also be considered? Answers to the aforementioned questions are critically needed to move this evolving and intriguing field forward.

**Conclusions**

Evidence is emerging to indicate that AF is independently associated with an increased risk of another important public health problem: SCD. The underlying mechanisms are unclear and may include AF being intrinsically proarrhythmic in increasing susceptibility to VT or VF. A comprehensive understanding of the mechanisms and risk factors that increase AF-associated SCD risk is critically needed to reduce the morbidity and mortality of AF.

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**References**


