Mortality and Atrial Fibrillation: Is There a Causal Relationship?

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Almost all studies show that atrial fibrillation (AF) is associated with increased mortality. What is less certain is whether this association is a straightforward cause-and-effect relationship, or if AF is merely a marker of severity of cardiovascular disease(s) or the aging process. AF can lead to the worsening of left ventricular filling, contribute to loss of atrioventricular synchrony, affect cardiac remodeling, and even cause a tachycardia-induced cardiomyopathy. AF could be a marker for underlying atherosclerotic disease that itself determines mortality, or the increased oxygen consumption associated with an increasing ventricular rate may lead to ischemia secondary to increased myocardial consumption and precipitate acute coronary syndromes. Although it is generally accepted that the stasis of atrial blood in AF promotes clot formation, studies have shown increases in specific coagulation factors—all of which have the ability to increase morbidity and/or mortality through their elevations. Another possibility is that AF is not the cause of the hypercoagulable state, but is instead a marker of such a state.

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Atrial fibrillation (AF) is the most common significant arrhythmia, affecting approximately 2.2 million Americans.[1] Several studies have shown an increased mortality in different populations of patients with AF.[2-9] There are at least 3 ways that AF might affect mortality: it may independently contribute to increased mortality, it may act as a marker of associated disease states that cause increased mortality, and it might only increase mortality in the presence of other disease states by acting together with the underlying disease to cause deterioration. It is also possible that, in many cases, mortality is multifactorial, with a mixture of factors contributing to deterioration.

The main question is whether the relationship between AF and mortality is an association or if there is causality. The answer has clear therapeutic implications. This article will review the literature regarding all-cause and cause-specific mortality in patients with AF.

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AF and Overall Mortality

The results of several studies indicate that there is a significant relationship between AF and increased mortality. Krahn and colleagues[3] studied a population of 3983 male US Air Force recruits, examining risk factors for the development of AF, the incidence of AF, and the long-term effects of AF. Over 44 years, 299 (7.5%) of the study population developed AF. After controlling for 9 other covariates, the presence of AF was found to independently increase the all-cause mortality by 1.3-fold ($P < .005$). (Because Air Force recruits are extremely fit as a cohort, these data may not be generalized to other populations.)

Drawing from a large, predetermined study population that included 58,820 patients, Vidaillet and colleagues[2] followed 577 patients with AF and an equal number of controls for an average of 3.6 years. Their results also indicated that AF was independently associated with an increased all-cause mortality (hazard ratio [HR], 2.4; 95% confidence interval [CI], 1.9-3.1; $P < .0001$). Patients treated with warfarin (55% of the group) had decreased mortality compared with those not taking warfarin (HR, 2.0 vs 2.7). The increased mortality observed in patients with AF was statistically significant at all intervals studied (0-6 months, 7-12 months, and >13 months).

Jouven and colleagues[7] evaluated the relationship between lone AF and independent risk of mortality. The study subjects were 25 patients with lone AF and a control group who were followed for longer than 15 years. The results showed that the relative risk (RR) of cardiovascular mortality in patients with AF was 4.22 (95% CI, 2.10-8.47), and the RR of total mortality was 1.97 (95% CI, 1.14-3.40) compared with controls. The authors concluded that lone AF was an independent risk factor for death, although the small sample size should be considered.

The Renfrew/Paisley[4] study was a survey of the cardiovascular health of the residents of 2 neighboring Scottish towns with a combined study population of approximately 12,000 men and women. Between 1972 and 1976, a total of 53 men and 47 women were identified as having AF. Twenty years after the data were gathered, Stewart and colleagues[4] reviewed the country's registry of deaths and compared the mortality of those with AF to those without. Their results showed that AF independently predicted all-cause mortality in men (RR, 1.5; 95% CI, 1.2-2.2) and women (RR, 2.2; 95% CI, 1.5-3.2). However, comparing the baseline characteristics shows that the patients in the AF group were older, were more likely to have chronic obstructive pulmonary disease, and had more frequent cardiovascular disease. Although these differences might have contributed to the group's increased mortality, the hypothesis of whether AF was associated with mortality or whether there was contributing causality was not specifically tested.

Benjamin and colleagues[8] studied the all-cause mortality of the original cohort of patients with AF from the Framingham Heart study. Of the 5209 patients followed, 296 men and 325 women developed AF. After adjusting for age, hypertension, smoking, diabetes, left ventricular hypertrophy, myocardial infarction (MI), valvular heart disease, stroke, and transient ischemic attack, the presence of AF increased the risk of death in men by 1.5 (95% CI, 1.2-1.8) and in women by 1.9 (95% CI, 1.5-2.2). However, most mortality in the AF group occurred within the first 30 days of diagnosis. In fact, eliminating 30-day mortality greatly attenuated the putative increased mortality in both men and women. This confounding observation raises the possibility that AF is a marker of illness rather than a cause of death itself.

Guize and colleagues[9] examined the prevalence, risk factors, and mortality associated with AF in a large French population that included 98,861 men (235 with AF) and 55,109 women (63 with AF). After adjusting for confounding factors (eg, age, cardiomyopathy, left ventricular hypertrophy, hypertension, hypercholesterolemia, diabetes, body mass index, smoking, alcohol consumption, vital capacity), the authors found that AF was associated with a small increased overall mortality (HR, 1.7; 95% CI, 1.1-2.8) and cardiovascular mortality (HR, 2.6; 95% CI, 1.3-5.3) in men with hypertension or cardiomyopathy. There was no increased mortality seen in other groups of men or in any groups of women.

Cause-Specific Mortality in AF

Several trials have looked at cause-specific mortality in patients with AF. The usual causes of death that are examined include MI, heart failure (HF), and stroke.

In the Renfrew/Paisley study,[4] MI was the cause of death in 21% of male patients with AF and in 16% of male patients without AF, translating into a 1.5 RR of death from MI in AF patients (95% CI, 0.8-6.1). There was a similar effect seen in women, with death due to MI increasing from 9% to 11% (RR, 1.8; 95% CI, 0.7-4.3). These data contrast with those from the analysis of Benjamin and colleagues[8] of patients from the Framingham Study, in which AF did not portend any difference in mortality due to MI.

Dries and colleagues[5] performed a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) to determine the effect that AF might have on HF and death. They found that AF was associated with an increase in all-cause mortality (34% vs 23% [$P < .001$]), and, furthermore, that this increase was largely explained by deaths due to pump failure (16.7% vs 9.4% [$P < .001$]). The Renfrew/Paisley follow-up study[4] provided data regarding the risk of death from HF in patients with AF: men with AF had a RR of 5.4 (95% CI, 1.3-2.2) and women with AF had a RR of 4.7 (95% CI, 0.7-34.4) of dying of HF as compared with those without AF.

In Krahn and coworkers' Manitoba follow-up study,[3] the RR of death secondary to stroke in patients with AF was 2.48 (95% CI, 1.35-4.57). Using a population-based registry, Marini and colleagues[10] evaluated the prevalence of AF in patients with a first-ever ischemic stroke. The results showed that the rate of fatal stroke recurrence was higher in those with AF (6.9% vs 4.7%; $P < .0398$) than in those without.

Clinical Implications

Almost all studies show that AF is associated with increased mortality. What is less certain is whether this association is a straightforward cause-and-effect relationship, or if AF is merely a marker of severity of cardiovascular disease(s) or the aging process.

Many patients with AF take a variety of powerful medications, including anticoagulants and antiarrhythmic drugs. Warfarin is used in selected patients to reduce the incidence of embolic stroke.[11] However, warfarin is associated with hemorrhagic stroke, especially in patients at high risk for falls.[12] The increased chance of bleeding secondary to warfarin might contribute to the risk of death in patients with AF, although this risk must be balanced against the benefit derived from reduced embolic stroke.

The risk of death from MI seems to be increased among patients with AF. AF could be a marker for underlying atherosclerotic disease that itself determines mortality, or the increased oxygen consumption associated with increasing ventricular rate may lead to ischemia secondary to increased myocardial consumption and precipitate acute coronary syndromes.

Some have suggested that AF itself may provoke a hypercoagulable state. Although it is generally accepted that the stasis of atrial blood in AF promotes clot formation, studies have shown increases in specific coagulation factors—all of which have the ability to increase morbidity and/or mortality through their elevations. Sohara and colleagues[13] showed that patients in AF had enhanced platelet aggregation and coagulation (demonstrated by increased levels of clotting factors). Chung and coworkers[14] found that patients with AF had elevated levels of tissue factor (TF), an initiator of coagulation, and Choudhury and Lip[15] showed elevated levels of von Willebrand factor and vascular endothelial growth factor in AF, both factors that are involved in coagulation. One questions whether elevations of these factors could contribute to the relationship between AF and mortality.

Another possibility is that AF is not the cause of the hypercoagulable state, but is instead a marker of such a state. This could potentially explain why patients with paroxysmal AF have the same stroke risk as those with persistent AF.[16] This could also explain why the CHADS[11] criteria (congestive HF, hypertension, age > 75 years, diabetes, plus 2 points for previous stroke or transient ischemic attack) prove useful in estimating risk for stroke (if the hypercoagulable milieu itself, not the fibrillating atria, causes thrombosis), and could affect considerations involving duration of anticoagulant therapy for AF patients—even after a "curative ablation."

A similar cause-and-effect conundrum exists when investigating HF deaths in an AF population. As noted earlier, Dries and colleagues[5] examined the SOLVD trials to address this concern and concluded that the presence of AF increased the risk of dying secondary to pump failure. AF can lead to the worsening of left ventricular filling, contribute to loss of atrioventricular synchrony, affect cardiac remodeling, and even cause a tachycardia-induced cardiomyopathy.[17] All these factors could contribute to worsened HF and fatal outcomes. Alternatively, AF can be provoked by high left atrial pressures

and therefore can be a consequence of HF. Is AF causing increased HF mortality, or rather is AF a marker of worse HF?

Conclusion

AF is associated with increased mortality. Whether this increased mortality is directly due to AF or whether AF is a marker for severe cardiac and noncardiac disease is still not definitely proven. More studies must specifically address the mechanism(s) by which AF may increase death rates so that optimal prevention programs can be instituted. ■

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Main Points

- In an evaluation of data from the Framingham study, the presence of atrial fibrillation (AF) increased the risk of death in men by 1.5 and in women by 1.9 (after adjustment for risk factors). However, eliminating 30-day mortality greatly attenuated the putative increased mortality in both men and women.
- There is controversy about the relationship between AF and mortality due to myocardial infarction.
- In one study, the relative risk of death secondary to stroke in patients with AF was 2.48.
- AF could be a marker for underlying atherosclerotic disease that itself determines mortality, or the increased oxygen consumption associated with increasing ventricular rate may lead to ischemia secondary to increased myocardial consumption and precipitate acute coronary syndromes.
- Although it is generally accepted that the stasis of atrial blood in AF promotes clot formation, studies have shown increases in specific coagulation factors—all of which have the ability to increase morbidity and/or mortality through their elevations.
- AF can lead to the worsening of left ventricular filling, contribute to loss of atrioventricular synchrony, affect cardiac remodeling, and even cause a tachycardia-induced cardiomyopathy.