Atrial fibrillation is associated with increased mortality: causation or association?

Darryl P. Leong1,2*, John W. Eikelboom1, Jeff S. Healey1, and Stuart J. Connolly1

1Population Health Research Institute, McMaster University, Hamilton, ON, Canada; and 2Discipline of Medicine, Flinders University and the University of Adelaide, Adelaide, Australia

This editorial refers to ‘All-cause mortality in 272 186 patients hospitalized with incident atrial fibrillation 1995–2008: a Swedish nationwide long-term case–control study’, by T. Andersson et al., on page 1061

It is important to determine whether the excess mortality observed in patients with atrial fibrillation (AF) is directly due to AF or is just an association. Not only do patients want to know if AF is a cause of premature death, but knowing that there is or is not a causal relationship will influence therapeutic choices. Such knowledge will also certainly impact on the AF research agenda for the future. If AF directly causes excess mortality, then the use of therapies that specifically and successfully eliminate AF—rather than just prevent its symptoms—are preferable. Andersson et al. have now presented their findings from a retrospective observational study of patients with incident AF compared with AF-free controls identified through national databases.1

Strength and consistency of association

Andersson et al. reported an adjusted relative risk for all-cause mortality amongst patients with incident AF of 1.5–2, with higher relative risks in younger individuals and females.1 This represents a moderately strong association.2 To put this relative risk into context, in a 40-year prospective cohort study, smoking exhibited a similar hazard ratio of 1.5 for all-cause mortality.2 In a meta-analysis of the association between cigarette smoking and lung cancer, a relative risk of 5.5 was reported.5 Hence the association between AF and mortality is consistent with a causal one, but not so strong as to constitute strong evidence of causation.

Biological gradient

There is some evidence to suggest a biological gradient for the association between AF burden and all-cause mortality. The Women’s Health Study showed no significant association between incident paroxysmal AF and death, whereas any type of AF (including persistent and permanent) was independently associated with an increased risk of mortality.8 In contrast, data from the Loire Valley AF Project demonstrated no increase in mortality risk in individuals with persistent or permanent AF, compared with paroxysmal AF.12

Biological plausibility

The biologically plausible mechanisms by which AF might cause death include thrombo-embolic events and worsening of heart
failure (induced by tachycardia, or possibly by beat-to-beat ventricular irregularity). However, stroke appears to account for a very small proportion of the deaths in AF patients. In Olmsted County, the most common causes of death in patients with incident AF were coronary artery disease (15%), heart failure (16%), malignancy (14%), and stroke (7%).

Thus it appears that stroke deaths are not the most common modes of death in AF patients. While AF may have caused a proportion of heart failure, it is just as likely that AF resulted from worsening heart failure. In the AF-CHF study, reducing AF in heart failure patients did not prevent worsening heart failure or heart failure deaths. Although stroke mortality explains a part of the increase in death seen with AF, we do not have a clear biological mechanism that explains most of the observed increase in mortality.

Table 1  Studies examining the relationship between atrial fibrillation and all-cause mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Adjusted relative risk of death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersson1</td>
<td>272 186 incident AF vs. 544 344 controls</td>
<td>&lt;65 years: F 2.15 (1.99–2.32)</td>
</tr>
<tr>
<td>Ruigómez6</td>
<td>1035 chronic AF vs. 5000 controls</td>
<td>M 1.76 (1.69–1.84)</td>
</tr>
<tr>
<td>Benjamin7</td>
<td>621 incident AF vs. 1242 controls</td>
<td>F 2.8 (2.2–3.6)</td>
</tr>
<tr>
<td>Conen9</td>
<td>1011 incident AF vs. 33 711 controls</td>
<td>M 1.5 (1.2–1.8)</td>
</tr>
<tr>
<td>Haywood9</td>
<td>334 prevalent AF vs. 30 370 controls</td>
<td>F 2.0 (1.68–2.41)</td>
</tr>
<tr>
<td>Stewart10</td>
<td>100 prevalent AF vs. 15 306 controls</td>
<td>F 2.2 (1.5–3.2)</td>
</tr>
<tr>
<td>Miyasaka11</td>
<td>4618 incident AF vs. general population</td>
<td>2.08 (2.01–2.16)</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CI, confidence interval; F, female; M, male

**Table 2  Modified Hill criteria** for establishing causality

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Evidence to support AF causing excess mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of association</td>
<td>Moderate</td>
</tr>
<tr>
<td>Consistency of association</td>
<td>Strong</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>Weak</td>
</tr>
<tr>
<td>Biological plausibility</td>
<td>Moderate</td>
</tr>
<tr>
<td>Experimental evidence</td>
<td>Against</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation.

**Experimental evidence**

According to Bradford Hill, it is through an experiment that ‘the strongest support for the causation hypothesis may be revealed.’ The definitive human experiment to test for causality is the randomized clinical trial, and we have several well designed and executed clinical trials of AF suppression which do not support the hypothesis that AF itself increases mortality. The AFFIRM study was a randomized mortality trial examining the effect of a strategy aimed at restoring and maintaining sinus rhythm in 4060 AF patients. This trial showed no survival benefit in the rhythm control group over the rate control group. As already mentioned, the AF-CHF study showed no mortality benefit from a rhythm control strategy in 1376 patients with both heart failure and AF. One potential reason for the lack of benefit to rhythm control strategies is the deleterious effects of antiarrhythmic drug therapy, which can have both cardiac and extra-cardiac toxicities. Dronedarone, which has a similar electropharmacological profile to amiodarone, has been shown to lower both AF burden and cardiovascular mortality in patients with non-permanent AF. Despite these initial promising results, the PALLAS study demonstrated that dronedarone increased mortality in a higher risk cohort of patients with permanent AF.

Catheter ablation is the most effective strategy to reduce AF, yet at present we do not know if it will reduce mortality because we lack adequately powered studies. Randomized trials of AF ablation that are powered for mortality may help to clarify whether the association is causal, but will require careful interpretation as benefits of AF suppression with ablation may be offset in part by the complications of the procedure.
Could factors associated with atrial fibrillation explain increased mortality?

If it were true that AF does not directly lead to increased mortality, how do we explain the numerous well conducted observational studies which have reported independent increases in mortality with AF?

The answer may be that these studies, despite using sophisticated statistical methods for adjustment of baseline differences, cannot adjust for unmeasured confounders. Examples of potential confounders that were not evaluated in these observational studies include myocardial (left ventricular) fibrosis, concomitant digoxin use and toxicity, obesity, obstructive sleep apnoea, control of hypertension, and patient adherence to heart failure and other therapies. Some or all of these factors can cause AF and may also increase risk of death (Figure 1).

Conclusions and future directions

Consistent evidence indicates that AF is associated with increased mortality, but the extent to which this is a direct effect of AF itself or is related to the numerous serious associated conditions remains a puzzle. It is likely that AF itself directly increases the risk of death in some patients; and it is also a marker of worsening mortality, but the extent to which this is a direct effect of AF itself cannot be determined.

Consistent evidence indicates that AF is associated with increased mortality, but the extent to which this is a direct effect of AF itself cannot be determined. Some or all of these factors can cause AF and may also increase risk of death (Figure 1).

Conflict of interest: none declared.

References

A 52-year-old woman diagnosed with abdominal actinomycosis by exploratory laparotomy was inadvertently injected intravenous Penicillin G potassium 10 million units for 10–15 min period under arterial blood pressure and electrogram (ECG) monitoring on the first postoperative day. Immediately after the injection, the patient suddenly turned pale and then unconscious. The electrocardiogram presented the panoramic view of hyperkalemia. The QRS complex was rapidly widening (*) and sequentially merged with the T wave (8) (Panels A and B). Simultaneously, the blood pressure was declining. Sine wave, a hallmark of hyperkalemia, evolved into ventricular flutter-like pattern (8 Panel C). After cardiac resuscitation and IV injection of calcium chloride, the widened QRS complex (*) recovered gradually (8 Panel D) with elevation of arterial blood pressure. Consequently, normal sinus rhythm with narrow QRS was fully restored 15 min after IV injection of calcium chloride 1200 mg. A sudden rise of potassium level from 3.8 to 6.6 mmol/L was identified by blood sample obtained during cardiac resuscitation. An immediate sequential change of the P-QRS-T morphology following injection of the potassium containing drug Penicillin G potassium and a restoration of sinus rhythm by calcium chloride suggested the arrhythmia was caused by a sudden elevation of circulating potassium in the blood. The electrocardiographic manifestation of hyperkalemia is characterized by peaked T waves, prolongation of the PR interval, widening of the QRS complex, and consequent sine wave. This serial electrocardiogram showed panoramic views of transient, abrupt hyperkalemia from peaked T wave to sine wave within 30 min.