Editorial

Atrial Fibrillation and Death After Myocardial Infarction
Risk Marker or Causal Mediator?

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A well established association between atrial fibrillation (AF) and increased risk of death exists in the general population.[1,2] Increasingly, it is recognized that AF also is associated with a higher mortality in specific clinical subsets, such as in patients with heart failure,[3] renal failure,[4] stroke,[5] diabetes mellitus,[6] hypertension,[7] and after cardiac surgery.[8] The association between AF and mortality is of little surprise, given the adverse consequences of the arrhythmia, such as stroke and heart failure, which may serve as proximate mediators of death.

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However, a question that remains unsettled is the relation between AF and death among patients with myocardial infarction (MI).[9,10] While investigators have appreciated that AF may predict mortality after MI,[10] some have argued that the arrhythmia is merely a risk marker for death, and not a causal mediator.[11,12] It is possible that AF serves as an indicator of increased activation of neurohormonal or inflammatory pathways, perturbed hemodynamics, comorbidities, or electrical remodeling, all of which are associated with both AF and mortality.

In the current issue of *Circulation*, Jabre et al[13] report a retrospective investigation of the association between AF and death among 3220 individuals who survived a first MI in Olmstead County, Minnesota, between 1983 and 2007. Myocardial infarction was ascertained by use of validated criteria and verified by review of the medical records. Patients with AF antecedent to the MI were identified by use of International Classification of Diseases, 9th Revision (ICD-9) codes, whereas individuals with incident AF occurring concurrent with or after the MI were identified through query of an ECG database. Deaths were analyzed systematically and classified as cardiovascular, cancer, or other in nature.

The investigators found that the cumulative incidence of AF after MI was 19% at 5 years, which corresponds to an incidence rate of 42 per 1000 person-years. This estimate is substantially greater than the age- and sex-adjusted incidence of 3.7 per 1000 person-years previously described in the Olmstead County source population from which this sample was derived.[14] Despite considerable changes in treatments for MI over the last 2 decades, the authors did not detect a difference in the incidence of AF after MI over the study period. The investigators observed that particular MI characteristics were associated with AF, including anterior infarct location, higher Killip class, and lower ejection fraction.

Jabre et al[13] also reported that 30% of AF events occurred within 2 days after an MI. Overall, AF occurring any time after MI was associated with an increased risk of death relative to individuals without post-MI AF, but the magnitude of risk varied according to the timing of AF onset. Atrial fibrillation that was present before or developed within 30 days after MI was associated with a <2-fold estimated increase in the hazard of death relative to those without AF, whereas AF detected beyond 30 days post-MI was associated with an approximately 2.7-fold increased hazard. A number of additional analyses were performed to characterize the associations between AF timing, all-cause mortality, and cardiovascular mortality.

As with all observational studies, the report by Jabre et al[13] has inherent limitations worth considering. First, there is a potential for ascertainment bias. Incident AF was determined by ECG; however, tracings were not collected at standard intervals. As such, subjects with an acute illness or a greater burden of comorbid disease or those who required longer hospitalizations would likely have undergone more ECGs. Such an increase in the number of ECGs might result in a greater probability of capturing AF. Second, as a further consequence of relying on ECGs for case ascertainment, misclassification of early, intermediate, and late AF events after MI easily may have occurred. As an example, asymptomatic AF during the intermediate period of 3 to 30 days post-MI may have only been detected during the late period, beyond 30 days, when individuals sought post-MI care. Indeed, a recent study using implantable monitors after MI demonstrated that more than 90% of AF episodes were asymptomatic.[15] Third, the selected time frames for classifying AF as early, intermediate, or late are somewhat arbitrary, and do not have established biological or clinical relevance. Fourth, residual confounding of the associations between AF and death is another important concern. Residual confounding is particularly relevant given the substantial attenuation in the relative risk estimates that was observed in this

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report after adjustment for potential confounders. Such a weakening of the association between AF and mortality risk after MI following multivariable adjustment has been observed previously.[9]

Despite the limitations articulated here and by the authors, the relations between AF and mortality after MI are plausible. The increased risk of mortality after MI in individuals who develop AF are generally supported by the previous literature, which Jabre and others have reviewed and summarized elsewhere.[16]

So, is AF a risk marker or a causal mediator of death after MI? Observational reports cannot answer questions of causality. In fact, methodological issues make it challenging to prove that AF is actually a causal mediator of death after an MI, at all. It would have been interesting to examine the causes of death among those with and without AF to look for clues such as the occurrence of cardioembolic stroke as a proximate cause of death. Such a finding would implicate AF as a causal factor. Indeed, ischemic stroke has been observed with an increased frequency among survivors of MI with AF compared with those without AF.[17] Other potential approaches that might suggest causality include more extensive multivariable adjustment or instrumental variable analysis (eg, mendelian randomization). Unfortunately, neither of these approaches is without limitations. Perhaps the most valid approach might be a randomized trial to assess the impact of AF prevention or treatment on survival after MI. However, the identification of appropriate therapies to prevent AF remains an ongoing challenge.[18]

Does it really matter whether AF is a causal factor that contributes to death after an MI? Surely clinicians ought to be cognizant that AF is a marker of a worse prognosis, irrespective of whether AF is a causal mediator. Existing gaps in knowledge (Table) that may inform the clinical management of patients with an MI include determining the optimal method and duration of surveillance for AF, because the incidence of AF after MI may be underestimated.[15] Furthermore, it remains unclear whether identified risk factors effectively discriminate between individuals who do and do not develop AF after an MI, and whether targeting high-risk MI survivors can prevent AF. Because thromboembolism prophylaxis for AF may increase bleeding risk, the optimal regimen in the post-MI period remains unclear, particularly because many individuals treated with stents already require dual-antiplatelet therapy. At this point, the management of AF in the setting of MI is driven by consensus-guided recommendations.[19] Clinical trials are warranted to address these unresolved dilemmas, because specific evidence-based conclusions are lacking.

Other unanswered questions exist beyond the direct clinical implications of AF in patients with MI. One wonders whether AF that occurs after an MI is purely a consequence of the infarction process, or whether patients who develop AF have an underlying predisposition to the arrhythmia. In the case of AF after coronary artery bypass surgery, it is now apparent that many patients have a genetic predisposition to AF at a susceptibility locus present in the general population.[20] Additionally, it is not known whether the sequelae of AF after MI vary by race or ethnicity.

Table. Gaps in Knowledge Regarding AF in the Peri-MI Setting

Epidemiology
- Genetic
  - Do patients with AF after MI have a genetic predisposition to developing AF?
- Risk markers
  - Are there other clinical risk markers or biomarkers for AF after MI?
- Race/ethnicity
  - Is the increased risk of death with AF after MI evident across races/ethnicities?
- Risk prediction
  - How do risk factors for AF after MI perform using contemporary risk prediction metrics?

Management
- Prevention
  - Can AF be prevented after MI by targeting high-risk survivors?
  - If so, with what management strategies (eg, lifestyle, medications, etc)?
- Surveillance
  - What are the optimal methods and duration of surveillance for AF after MI (eg, serial ECGs, event monitor, etc)?
- Treatment
  - In individuals with AF after MI and indications for dual-antiplatelet therapy (eg, after revascularization), what is the optimal therapeutic regimen?
  - Are there other therapies that would diminish risk of post-MI AF complications?

AF indicates atrial fibrillation; MI, myocardial infarction; and ECGs, electrocardiograms.

Despite the aforementioned limitations, Jabre et al[13] should be commended. Their analysis serves as a reminder of the potential adverse consequences of AF in the setting of MI even in the current era of coronary reperfusion. Their work is consistent with other recent analyses that have identified a risk of death associated with AF after MI,[15] and contributes to the growing body of literature tying AF to an increased hazard of death across a variety of disease entities. Moving forward, both clinicians and patients would be well-served by attempts to systematically assess the safety and effectiveness of strategies to prevent and manage AF in specific disease subsets.

Disclosures

None.

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