comorbidities not requiring antiplatelet therapy, stroke prophylaxis benefit may significantly outweigh the increased bleeding risk.

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REPLY: Limitations of Administrative Data for Examining Secondary Atrial Fibrillation

The clinical benefit of anticoagulation in secondary atrial fibrillation (AF) remains unclear. In our study (1), we did not demonstrate benefit of oral anticoagulation (OAC) therapy in stroke reduction in patients who develop secondary AF associated with acute coronary syndromes, acute pulmonary disease, or sepsis. We agree with Mr. Um and colleagues that one should be cautious in assuming that OAC does not offer benefit in these patients. While awaiting more data on the incidence of recurrent AF in patients with acute medical illnesses and noncardiac surgery and a randomized clinical trial on the benefits of OAC, our study provides much needed information. Dr. Um and colleagues raise issues regarding: 1) ascertainment of AF prevalence; 2) residual confounding; and 3) estimates of benefit of OAC and recurrence of AF.

Dr. Um and colleagues are concerned with ascertainment of AF prevalence because of low sensitivity for detection of secondary AF using administrative databases. Our study was not aimed at measuring prevalence, which we agree would require high sensitivity, but at identifying patients with secondary AF; therefore high specificity rather than high sensitivity was privileged. To ensure true secondary AF (i.e., optimize specificity), our study criteria were designed to exclude both pre-existing primary AF and persistent AF. Unlike the retrospective study cited (2), we included only AF that was coded as a complication of the hospitalization and then additionally excluded patients who had received OAC in the prior year. We also excluded patients who had a previous hospital admission or physician visit with documented AF within the prior year. Thus we believe the patients included in our various cohorts had secondary AF, but we recognize we may not have identified all such patients.

The evidence for benefit of OAC in secondary AF associated with acute medical illness is limited in published reports and is further detailed in our study. Although residual confounding can always be cited to explain results in observational studies, the use of OAC in our study patients was associated with higher bleeding with little evidence of benefit on stroke prevention. The null findings may be more a problem of power than of confounding. The study by Fauchier and colleagues (3), which Dr. Um and colleagues quote, cannot be used as an example of benefit from OAC because this study included patients with primary AF. In fact, 551 of 2,009 (27.4%) of their study patients were reported to have permanent AF. It is unclear how this particular study specifically relates to determining possible benefit of OAC in patients with secondary AF.

Although our study was designed to look at stroke and bleeding risk, we look forward to the results of the ongoing multicenter study (AFOTS [Atrial Fibrillation Occurring Transiently With Stress]; NCT03221777) to determine rates of AF recurrence among patients who experienced transient AF following noncardiac surgery and medical illness. Indeed, little is known about the true risk of recurrence of AF in these patients. We support any further studies that can help define an optimal management strategy for secondary AF.

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Reversible or Provoked Atrial Fibrillation?

The Devil in the Details

In a recent article published in *JACC: Clinical Electrophysiology*, Quon et al. (1) examined patients with "secondary" atrial fibrillation (AF), defined as new-onset AF occurring in the context of acute coronary syndromes, acute pulmonary disease, or sepsis (1). The authors did not find any association between oral anticoagulation (OAC) and ischemic stroke, but a higher risk of bleeding with OAC in acute pulmonary disease (1). Several limitations in using retrospective hospital discharge data were addressed in the accompanying editorial (2). In this letter, we highlight 2 additional problems related to this heterogeneous population.

First, although AF may develop in the context of medical illness (secondary AF), the mechanism and prognostic implications of AF can be further dichotomized into 2 distinct, yet different, populations: reversible AF, which develops solely due to acute illness, with no abnormal substrate and no future risk; and provoked AF, unmasked by acute illness in patients with abnormal substrate and ongoing risk for AF recurrence. In the article by Quon et al. (1), this distinction is most obvious in the pulmonary disease group, whereby 32% of the population had AF in the context of pulmonary infection (acute influenza or pneumonia). Influenza infection alone is associated with an 18% increased risk of developing AF, and among these patients, the benefit of long-term OAC is unclear after return to sinus rhythm (3,4). A similar analogy could be made for patients with hyperthyroidism and AF, where anticoagulation is beneficial in the hyperthyroid state but not necessarily long term (5). By contrast, provoked AF patients may have paroxysmal AF that is unmasked during acute illness. Chronic obstructive pulmonary disease patients with provoked AF may have the underlying cardiac substrate for AF and ongoing risk for AF recurrence, and thus long-term OAC may significantly reduce ischemic stroke in these patients (6). By combining reversible and provoked AF, the authors created a heterogeneous group of patients, and it is of no surprise that the benefit of OAC was unclear.

The second problem is the significant bias among patients receiving OAC in this study. Despite almost all patients meeting OAC indications based on current guidelines (all patients ≥65 years of age, 90% $CHADS_2$ score ≥1) (7–9), Quon et al. (1) reported a variable anticoagulation rate between 27% and 40%. This systematic and gross underutilization of anticoagulation implies unmeasured factors likely influenced the treating physicians. In one circumstance, the treating physician may have considered AF reversible and, thus, long-term anticoagulation not justified. Conversely, others might have felt that competing risks (i.e., bleeding among acute coronary syndromes patients) were not in favor of benefit (i.e., stroke reduction). In this latter case, there would be an expected regression to the mean (high bleeding risk patients and low stroke risk patients left untreated), thus appearing to show no beneficial effect of anticoagulation as well.

Finally, we do not have the absolute event rates in a similar population of patients without AF (or "denominator") to assess the true benefit of anticoagulation. A propensity-matched analysis could delineate 2 populations with similar comorbidities, in which the impact of provoked AF and anticoagulation on ischemic stroke could be evaluated.