Comparing the Imperfect with the Imperfect: The Imprecise Science of Assessing the Risk and Benefits of Anticoagulation in Atrial Fibrillation

Running title: Tan et al.; The Imprecise Science of Assessing Anticoagulation

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Atrial Fibrillation (AF) is the most common arrhythmia in the United States, with approximately 7 million Americans estimated to have AF by 2020.\textsuperscript{1,2} A major cause for morbidity and mortality in AF is stroke. Pharmacologic therapy for the prevention of stroke has undergone a renaissance with the advent of newer oral anticoagulants (NOACs) that are safe and effective alternatives to warfarin. However, the decision to initiate anticoagulation remains a subjective assessment of risks versus benefits. Although guided by well-validated risk scores for stroke and bleeding,\textsuperscript{3,4,5} real world decisions on anticoagulation continue to differ significantly from guidelines, with many patients at high risk not receiving anticoagulation because of a perceived high risk of bleeding, and many low risk patients being anticoagulated due to a perceived low risk of bleeding, the so-called risk-treatment paradox.\textsuperscript{6} This phenomenon is thought to account for the continued underutilization of oral anticoagulation therapy,\textsuperscript{7} however, has yet to be validated in a large outpatient based practice. Therefore, the current study by Steinberg et al in this issue of *Circulation* is a timely effort to better understand and address some of the reasons underlying this risk mismatch in thromboembolic assessment and anticoagulation therapy in a community outpatient based group of patients with stable AF.\textsuperscript{8}

The authors examined 10,094 AF patients enrolled in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) between June 2010 and August 2011.\textsuperscript{9} This is a US prospective registry of incident and prevalent AF formed by a multi-specialty collaboration of healthcare providers including primary care physicians, cardiologist, and electrophysiologists. It is the largest clinical registry of its kind in the US, enrolling approximately 10,000 patients from 200 US outpatient practices. The patients are followed up for at least two years in order to characterize “real world” treatment and outcomes of patients with AF. The empirical stroke and bleeding risks were assessed by CHADS\textsubscript{2} and ATRIA scores.
respectively,\(^5,10\) and were classified as low, intermediate and high risk. They were then compared with physicians’ similarly categorized assessments of stroke and bleeding risks. Multivariable linear regression models were used to determine factors that account for physician-empirical risk mismatch.

This study is elegantly designed and the results thought provoking. The results are startling for the near complete lack of agreement between empirical and physician-assigned risks for both stroke and bleeding. Disagreement between physician-assigned and empirical risks was seen in up to 80% of cases and was particularly marked for patients at high risk for stroke and bleeding, where physicians tended to underestimate risk in both instances. For example, only 16% of patients were assessed to be high risk for stroke compared with 72% who were classified high risk by CHADS\(_2\) score. In addition, only 7% of patients were rated as having a high risk of bleeding on anticoagulation therapy compared with 17% considered high risk by ATRIA score.

In assessing stroke risk, physicians selectively emphasized specific risk factors such as prior stroke or TIA and severe AF symptoms more than diabetes, hypertension, age and congestive heart failure. Therefore, a patient is less likely to be assessed as high risk for stroke if they got to a high CHADS\(_2\) score by a combination of factors than if they had a prior history of stroke. On the contrary, there was less emphasis on anemia and significant renal disease in the assessment of bleeding risk relative to the ATRIA score. Overall, stroke risk had a more significant impact on anticoagulation decisions than bleeding risk. Thus, the results confirm those of prior studies indicating that physicians would accept a higher risk of bleeding for a lower risk of stroke.\(^7\) Where mismatch exists, physicians’ subjective evaluation of risk was the main driver of decision making than objective tools.

Several important questions come to mind. First, how predictive are empirical risk scores
of true event rates? Second, do these differences influence outcomes for anticoagulation? Third, is the discordance a reflection of a lack of complete understanding of the mechanisms for thromboembolism?

In the past 10 years, several different risk stratification schemes have been devised to predict stroke and bleeding risk.\textsuperscript{5,10-12} Amongst them, the CHADS\textsubscript{2} scores have been most widely used for its simplicity and predictive capability.\textsuperscript{5} Since then several improvements to CHADS\textsubscript{2} have been proposed that incorporate age, female sex and renal function.\textsuperscript{13-15} Yet, the predictive capability of objective risk scores for stroke have been shown to be modest at best\textsuperscript{5,16} because our understanding of the mechanisms of thromboembolism remain incomplete, in particular, whether AF is merely an associated condition or mechanistically linked to stroke.

Previously, prolonged AF was thought to predispose to atrial stasis, thrombus formation with subsequent embolism. Therefore, most embolic events were reported to occur if AF was longer than 48 hours duration, which was felt to be the minimum duration required for thrombus formation in the left atrial appendage prior to cardioversion.\textsuperscript{17} However, recent data has cast doubt on this simple construct of AF burden, duration and stroke. In a study of 2580 patients with pacemakers or defibrillators age \textgreater 65 years, although over 50\% of embolic strokes were associated with subclinical AF, only 15\% of all embolic strokes were associated with subclinical AF\textgreater 6 minutes within 1 month of the stroke.\textsuperscript{18} On the other hand, in the ASSERT study of asymptomatic AF detected in patients with a dual-chamber pacemaker, the duration of episodes was more important than the frequency of episodes in determining a patient's thromboembolic risk. Additionally, the location of thrombosis in AF is mostly though not exclusively within the left atrial appendage,\textsuperscript{19} throwing another wrench into the equation. Therefore, the mechanisms of thromboembolism are more complex than previously thought and may be multifactorial.\textsuperscript{20} It may
be related to atrial stasis from an actual prolonged AF episode, with thrombus formation mostly in the LAA, or due to chronic inflammatory, structural and endothelial changes throughout the entire atrium due to multiple prior AF episodes, or merely an epiphenomenon associated with AF. With increasing use of long term continuous monitoring for AF, there is also a shift to the idea of thromboembolic risk as a dynamic property composed of an interaction between AF burden and more traditional risk factors rather than based solely on a fixed set of risk factors per se as embodied by all contemporary risk stratification schemes. Thus, a long shadow is cast on the present and previous efforts that rely on more traditional risk factors. In the light of this, it is not surprising therefore that there is a mismatch between physicians’ assigned and empirical models of risk.

Nevertheless, one interesting aspect of the study is the disconnect between treatment outcome and risk assessment. Though vastly underestimating stroke risk in the high CHADS2 group, physicians chose to anticoagulate at least 70% of patients they consider low risk for stroke, with an overall high rate of anticoagulation use of 76%. This is consistent with previous reports and suggest that (a) physicians view stroke as feared outcome and would accept a higher rate of bleeding for a lower rate of stroke, (b) a general lack of familiarity with bleeding risk guidelines relative to that for stroke, and (c) physicians recognize the limitations of both their own understanding of stroke risks and those of current risk prediction models.

There are several limitations which diminish enthusiasm for this study. First, the study suffers from significant sampling bias as it is derived from a national registry, with over 80% of patients treated by cardiologists and electrophysiologists. The management of atrial fibrillation was quite heterogeneous in this group, with significant inter-specialty differences in the use of rhythm control and anticoagulation between cardiologists and primary care physicians. Thus
the results may not fully reflect “real world” practices in the community where the overall rate of anticoagulation use have been reported to be in the 50-60% range.\textsuperscript{7,24} A global registry aiming to enroll upwards of 50,000 patients in nearly 50 countries is underway and will go some way towards addressing this issue.\textsuperscript{25} Second, the survey was conducted at a time when the NOACs just became available in the United States. Only approximately 12% of patients in this series used dabigatran.\textsuperscript{26} As dabigatran and direct anti-Xa agents become more widely used,\textsuperscript{27} it remains unclear whether the choice of NOACs with their advantages of convenience and in the case of apixaban, lower bleeding risk profile, might affect rates of oral anticoagulant use particularly in the high risk bleeding group.

In summary, the present study by Steinberg et al highlights the discordance between provider assessed risk and empirical risk scores in AF, both of which remain far from precise. Thus, it underscores the importance of further research into the mechanisms of thromboembolism in AF.

**Conflict of Interest Disclosures:** None.

**References:**


11. Roldán V, Marín F, Manzano-Fernández S, Gallego P, Vilchez JA, Valdés M, Vicente V, Lip GY. The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or


22. Conway DS, Pearce LA, Chin BS, Hart RG, Lip GY. Plasma von Willebrand factor and


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