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EDITORIAL COMMENT

Fine Tuning Risk Stratification for Atrial Fibrillation*

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Most clinicians would like to be able to accurately estimate the risk of adverse outcomes, especially if this information could guide management or treatment decisions to lower the risk for an individual. In the case of atrial fibrillation (AF), the most common cardiac arrhythmia, more accurate prediction of its most feared and disabling complication—stroke—remains a major focus (1,2). This issue is pertinent as AF is increasing in prevalence and will affect 1 in 4 men and 1 in 6 women during their lifetime (3–8). Hospitalization for AF is also increasing, with >360,000 admissions annually in the United States for a first AF episode and >2 million admissions for any listing of AF (9–12). AF causes 15% of all strokes and is also associated with a 50% increase in mortality for men and a near doubling of mortality for women compared with matched subjects without AF (12–15).

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Risk scores for predicting stroke in the setting of AF have generally been based on clinical variables that are readily available for most individuals (1,16,17). The $CHADS_2$ score was derived and first validated in 2001 and is based on a history of congestive heart failure, hypertension, age ≥75 years and older, diabetes, and previous stroke (16). It is a simple and widely validated risk score that is endorsed by many guidelines, which more recently have advocated anticoagulation for a $CHADS_2$ score ≥1, based on demonstration of benefit from anticoagulation in this context (16,18,19). As with any simple score, the $CHADS_2$ score has limitations, including that it takes no account of the independent risk of stroke conferred by age older than 65 years and female sex (1,16). The CHA_2DS_2VASc score validated in 2009, includes these additional risk factors for stroke and provides extra weighting for age older than 75 years (17). As a consequence, it appears to discriminate very low risk more accurately than $CHADS_2$ score. Some guidelines have therefore moved toward recommending the CHA_2DS_2VASc score to guide decision making about anticoagulation (20).

Despite their utility and widespread application to define thresholds of stroke risk and to guide anticoagulation for AF, clinical risk scores provide relatively modest overall performance as predictors of stroke (1). When assessed by receiver-operating characteristic analysis, the area under the curve (AUC) for prediction of the risk of stroke by a clinical score is generally 0.6 at best, where an AUC of 1.0 would represent perfect discrimination of events and an AUC of 0.5 is no better than chance for a dichotomous outcome. The strength of clinical risk scores is that low risk values ($CHADS_2$ score of 0, CHA_2DS_2VASc score of 0 to 1) provide very good sensitivity and negative predictive value for stroke, which is helpful for defining thresholds for anticoagulation, but at the cost of poor specificity and overall accuracy (21). As a result, risk scores provide weak discrimination of stroke risk for some individuals, particularly those with intermediate or high scores (1).

Clinical risk scores can potentially be refined by considering additional indices (1). A range of biomarkers that reflect pathophysiological processes relevant to AF and stroke also provide independent risk prediction when added to clinical risk scores (2). These include markers of thrombosis (von Willebrand factor, D-dimer), renal function (creatinine clearance, proteinuria), myocardial necrosis (troponins), and the natriuretic peptides (N-terminal pro–B-type natriuretic peptide [NT-proBNP], BNP) (1,2). The natriuretic peptides, which are powerful markers of risk in the setting of heart failure and acute coronary syndromes, are potentially helpful markers in the setting of AF (22). Secreted from cardiomyocytes, BNP and NT-proBNP levels in plasma reflect left ventricular size, function, and filling pressures, but also renal function, age, and sex, all of which may modify stroke risk in AF (22). Levels of BNP/NT-proBNP are also higher in subjects with AF than in matched subjects in sinus rhythm, and levels fall after cardioversion, presumably reflecting changes in atrial function and pressure (2,23). BNP or NT-proBNP can be easily measured using validated assays that are widely available, which makes them appealing candidates for adjunctive risk markers (22).

In this issue of the *Journal*, Hijazi et al. (24) provide some important insights into the value of NT-proBNP measurements for risk prediction in the setting of AF (24). Their statistically powerful dataset based on a large cohort of 14,892 patients with at least 1 risk factor for stroke and enrolled in the ARISTOTLE trial provides definitive estimates of the incremental value of NT-proBNP levels over clinical risk scores alone for the prediction of adverse events. It is important to note that all participants in the

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ARISTOTLE trial were receiving anticoagulation, either apixaban or warfarin, according to a randomization schedule. In their report, NT-proBNP levels were higher in subjects with persistent or permanent AF compared with paroxysmal AF. There was an increased risk of stroke/systemic embolism (SE) or of cardiac death with increasing quartiles of NT-proBNP, with an increase in hazard ratios of at least 2.3 times for these events for patients in the highest quartile compared with the lowest quartile. Notably, patients in the lowest quartile of NT-proBNP levels had very low stroke/SE rates (≤1%) regardless of CHA_2DS_2VASc score. Clinical risk scores were modest predictors of stroke/SE and of important events including death or other vascular events. NT-proBNP levels significantly improved the prediction of all events compared with risk scores alone. Despite this, overall discrimination remained relatively weak, with AUC improved by NT-proBNP from 0.626 (for the CHA_2DS_2VASc score alone) to 0.646 for prediction of stroke/SE. There was a more impressive increase in AUC from 0.59 to 0.69 with NT-proBNP for the prediction of cardiac deaths. The latter is consistent with NT-proBNP's predictive power for cardiac or all-cause mortality in other settings including heart failure or acute coronary syndromes (22). Consideration of NT-proBNP levels led to more accurate classification of risk. NT-proBNP level more accurately classified patients destined to experience stroke/SE and more accurately excluded patients who later died during follow-up. Importantly, there was no interaction between NT-proBNP level and the treatment effect of apixaban versus warfarin, nor was there any interaction between NT-proBNP and major bleeding risk.

The RE-LY study investigators also recently reported findings from a similar analysis (25). They measured NT-proBNP levels in 6,189 participants in the RE-LY study. Although confidence intervals are wider in the RE-LY study analyses, reflecting the smaller population compared with that of the ARISTOTLE substudy, the findings are remarkably concordant between the 2 studies with respect to NT-proBNP levels, event rates, the hazards ratios for subjects in the highest quartile of NT-proBNP, and the increment in AUC for the prediction of stroke or adverse clinical outcomes when NT-proBNP was added to clinical risk scores (Table 1). Taken together these studies provide a clear picture of the potential value of NT-proBNP in this setting. It is unlikely that further data from this setting will alter the insights that these studies provide due to their size and statistical power.

How do the findings of this study alter our evaluation of risk and management of AF? First, it is important to note some limitations to the data. As the authors point out, all patients were receiving anticoagulation; therefore, it is not possible to translate these findings to guide decision making for patients yet to commence anticoagulation. Although it is possible that NT-proBNP level might provide valuable risk stratification in this context, clear validation of NT-proBNP level as a marker of stroke risk in the setting of no anticoagulation, or before

Table 1 NT-proBNP and Risk Prediction in Atrial Fibrillation: Insights From the ARISTOTLE and RE-LY Trials

	ARISTOTLE	RE-LY
No. of participants	14,892	6,189
$CHADS_2$ score		
≤1	5,057 (34)	2,025 (33)
2	5,367 (36)	2,197 (35)
≥3	4,468 (30)	1,967 (32)
NT-proBNP levels	714 (95% CI: 363–1,250)	801 (95%: 387–1,403)
Event rates		
Stroke/systemic embolism	1.4%/yr	1.3%/yr
Death	3.69%/yr	3.3%/yr
Major bleeding	2.61%/yr	2.45%/yr
Hazards ratio for major events (NT-proBNP, Q4 vs. Q1)		
Stroke	2.35* (1.62–3.40)	2.30* (1.41–4.07)
Death	2.25* (1.80–2.81)	6.73* (3.95–11.49)
Major bleeding	1.07 (0.82–1.40)	1.28 (0.87–1.88)
Added value for stroke/systemic embolism prediction (area under the curve)		
CHA_2DS_2VASc	0.62	0.618
CHA_2DS_2VASc + NT-proBNP	0.646*	0.633
Added value for composite EP† prediction (area under the curve)		
CHA_2DS_2VASc	0.598	0.612
CHA_2DS_2VASc + NT-proBNP	0.66*	0.668*

Values are n (%), unless indicated otherwise. *$p < 0.001$. †Composite EP in the ARISTOTLE trial was ischemic stroke, systemic embolism, myocardial infarction, and cardiac death, and in the RE-LY, it was stroke, systemic embolism, pulmonary embolism, myocardial infarction, and vascular death. Adapted from Hijazi et al. (24,25).

CI = confidence interval; EP = endpoint; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

anticoagulation being commenced, would be required before guidelines could endorse NT-proBNP level for this application. For now, the established clinical risk scores remain the best validated approach to guiding decisions about when to commence anticoagulation. Another limitation of the current data is that findings of the clinical trial setting may not always be replicated in real-world patient populations. Given the large size of the current study, this seems less likely. However, it is important to note that the very elderly, who have a higher AF prevalence and stroke risk, are not represented in the study.

However, the findings from this large substudy of the ARISTOTLE trial and also the smaller substudy of the RE-LY study indicate that among subjects fully anticoagulated for AF, a single measurement of NT-proBNP provides powerful prediction of the residual risk of either stroke/SE or of cardiovascular complications. Subjects who are receiving anticoagulation for AF and who have low NT-proBNP levels (<363 ng/l) are at very low risk of stroke/SE or cardiac death regardless of their CHA_2DS_2VASc score. Conversely, if NT-proBNP levels are high (>1,250 ng/l), the risk of these events is high, even when the CHA_2DS_2VASc score is ≤2. Although guidelines may not endorse routine measurement of NT-proBNP levels, this information may have significant clinical utility, particularly in patients for whom there are concerns about major bleeding or other risks related to anticoagulation (26).

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