The Balance Between Stroke Prevention and Bleeding Risk in Atrial Fibrillation

A Delicate Balance Revisited

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See related article, pages 1482–1486.

Although atrial fibrillation (AF) is well recognized to confer a risk of stroke, this risk is not homogeneous. Oral anticoagulation (OAC) with warfarin is highly beneficial, but such therapy is inconvenient and carries a risk of bleeding. Thus, stroke risk stratification schemes have been devised to identify “high risk” AF patients for whom the absolute benefits of OAC exceed its risks.

In general, present treatment guidelines recommend OAC for those classed at high risk of stroke, and aspirin for those at “low risk.” In those at “moderate risk,” either OAC or aspirin is recommended. There are many ways of classifying stroke risk, and in a recent comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular AF, the Stroke Risk in Atrial Fibrillation Working Group identified 7 schemes that were based directly on event-rate analyses (largely been identified from non-OAC arms of clinical trials, and occasionally from cohort studies), whereas 5 resulted from expert panel consensus. The most frequently included features were prior stroke/TIA (in 100% of schemes), patient age, hypertension and diabetes mellitus.

Of the various published schema, the CHADS2 score is probably the most popular, which is well validated and easy to use, where 1 point is given for Congestive heart failure, Hypertension, Age >75 and Diabetes, whereas 2 points are given for Stroke or transient ischemic attack (TIA).2

Based on published test study cohorts, the absolute stroke rates for the different stroke risk schema varied rather widely, and the proportions of patients categorized by the different schemes as low-risk or high risk can differ fairly substantially.1 Indeed, validation studies have shown that no published risk stratification schema is ideal and all can frequently underestimate stroke risk.2,3 The c-statistic (used to assess the predictive accuracy of these risk models) in those patients not receiving OAC ranges from 0.63 to 0.70.2

Limitations of the existing stroke risk stratification schema can perhaps be illustrated by considering those patients classed to be at moderate risk of stroke. In a recent analysis,4 the CHADS2 schema classified the largest cohort of AF subjects as moderate risk (nearly 60%), compared to much lower proportions in other published criteria, with the majority of subjects being classed at high risk by the American College of Chest Physicians (96% to 97%), the van Walraven schema (99.2%) and AF Investigators (85.1%) schemes.

One validation study for the CHADS2 schema classified a score of 0 as low risk, 1 to 2 as moderate risk, and 3 to 6 as high risk.2 This poses a problem because if an AF patient has a stroke or TIA as their only risk factor, they have a CHADS2 score of 2, which categorizes them as moderate risk despite the fact that such patients (which represent a secondary prevention population) have a very high risk group for mortality and recurrent stroke—and need OAC. Given that most guidelines5,6 recommend either aspirin or OAC for moderate risk subjects, having a risk stratification scheme that categorizes more patients into the moderate risk category may confuse clinicians even more on what is the best treatment for an individual patient. Alternatively, the moderate risk category may be used as excuse not to prescribe OAC but to give aspirin instead (since the guidelines ‘allow’ it), sometimes to the detriment of the patient.

What about bleeding risk? A systematic review as part of the evidence-based UK National Institute for Health and Clinical Excellence guidelines on AF management (www.nice.org.uk) identified the following patient characteristics as risk factors for anticoagulation-related bleeding complications: advanced age, uncontrolled hypertension, history of myocardial infarction or ischemic heart disease, cerebrovascular disease, anemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet agents.7 The presence of diabetes mellitus, controlled hypertension, and gender were not identified as significant risk factors. It is increasingly recognized that many risk factors for anticoagulation-related bleeding are also indications for the use of anticoagulants in AF patients, given the increasing bleeding risk with increasing CHADS2 score.8 Various bleeding risk stratification schema have been proposed, but more validation of their value is clearly required, in prospective cohorts of AF patients.

For now, those considered at high risk of bleeding are usually prescribed aspirin (rather than OAC) with the perception that this therapy is less risky for bleeding, compared to OAC. In the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study of warfarin versus aspirin 75 mg in elderly AF subjects (age >75) in the primary care setting, OAC was superior to aspirin for stroke prevention, but the rates of major bleeding were no different between OAC and...
aspirin.\textsuperscript{9} Even in low risk AF subjects, aspirin was no different from placebo for vascular events but resulted in more adverse events, especially bleeding.\textsuperscript{10} Indeed, a common scenario is the addition of aspirin to OAC for stable vascular disease associated with AF. Such a strategy does not contribute to stroke prevention but substantially increases bleeding risk.\textsuperscript{11} The situation is quite different in the setting of AF patients presenting with an acute coronary syndrome and/or those who require percutaneous coronary intervention with or without stenting. Such patients very often require a period of triple therapy with OAC, aspirin plus clopidogrel, but such therapy is not based on trial evidence and the management approach again depends on balancing stroke prevention with OAC in the high risk subject against recurrent cardiac ischemia, stent thrombosis and/or bleeding risk.\textsuperscript{12}

Hence the recurrent debate over the delicate balance of stroke risk against bleeding. It has been generally perceived that the stroke risk with 2 or more risk factors would merit OAC rather than aspirin. For those with a CHADS2 score of 1, the margin between benefit and risk with OAC was considered to be small, hence the recommendation for OAC or aspirin in such patients. For some clinicians, as mentioned, this becomes yet another excuse to prescribe aspirin rather than OAC.

In this issue of \textit{Stroke}, an ancillary analysis from the ACTIVE-W trial reports the risks and benefits of OAC compared with aspirin-clopidogrel combination therapy (A+C) in relation to CHADS2 score (CHADS2=1 versus those with a CHADS2>1).\textsuperscript{13} In this analysis, Healey et al\textsuperscript{13} report that the observed stroke rates for those with a CHADS2=1 were 1.25\% per year on A+C and 0.43\% per year on OAC, nearly a 3-fold difference. The risk of major bleeding during OAC was lower among patients with a CHADS2 score of 1 (1.36\% per year) compared with CHADS2>1 (2.75\% per year). Thus, patients with a CHADS2 score of 1 had a low risk of stroke but still derived a modest (but <1\% per year) absolute reduction in stroke with OAC with relatively low rates of major hemorrhage on OAC.

Could antiplatelet therapy be an alternative to OAC for high risk patients with AF? The benefit of OAC over A+C is not too surprising given that thrombogenesis in AF is mainly coagulation factor–related, with red (fibrin-rich) clot predominating in AF,\textsuperscript{14} as illustrated in one study where OAC significantly reduced thrombogenesis whereas A+C did not.\textsuperscript{15} In contrast, thrombus in atherothrombotic vascular disease (eg, coronary artery disease) is mainly platelet rich (white clot).

Finally, is a CHADS2 score of 0 to 1 really “low-moderate” risk among AF populations? In BAFTA, a substantial benefit of OAC over aspirin was seen in these elderly subjects, whether with CHADS2 score of 1 to 2 or >2.\textsuperscript{9} AF also commonly associates with numerous risk factors, many of which also directly enhance the risk of stroke. Many risk stratification schema try to incorporate these in their assessment, but coronary, carotid and peripheral vascular disease have not been routinely assessed in clinical trial cohorts.\textsuperscript{16} Furthermore, echocardiography was not systematically performed in ACTIVE-W (or BAFTA), and moderate-severe left ventricular impairment (which can be asymptomatic) is a major contributor to stroke risk.\textsuperscript{17} On transoesophageal echo-cardiography, the presence of spontaneous echocontrast, low left atrial appendage velocities and complex aortic plaque on the descending aorta are independent risk factors for stroke.\textsuperscript{17} Also, the “hypertension” criterion in CHADS2 may be influenced by the degree of blood pressure control given that stroke and embolism risk substantially increases with poor blood pressure control, rather than “past history of hypertension.”\textsuperscript{18} In addition, a prothrombotic or hypercoagulable state is well-described in AF, and some indices may add to stroke risk and help refine clinical stroke risk stratification schema.\textsuperscript{19} These additional considerations may contribute to stroke and may partly explain the underperformance of some clinical risk stratification schema.

Risk stratification schema can at best be described as “rough guides” to help inform clinicians. Patients never truly obey textbooks or guidelines, and clinicians would often face individual patients where therapeutic decisions are never straightforward. The article by Healey et al\textsuperscript{13} suggests that subjects with CHADS2 scores of 1 and a low bleeding risk would probably benefit from OAC, at least in a clinical trial setting. Notwithstanding the limitations of the latter, we should perhaps proactively think “AF equals warfarin,” unless true compelling indications indicate otherwise.

Disclosures

G.L. was clinical advisor to the National Institute for Health and Clinical Excellence Guidelines on Atrial Fibrillation Management.

References


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