

EDITORIAL COMMENT

Stroke Risk Stratification in Patients With Atrial Fibrillation



Comme Ci, Comme Ça, Plus Ça Change...*

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There has been a huge increase in academic interest in atrial fibrillation (AF) and particularly its major complication: thromboembolism. This sustained flurry of activity is fueled by the development of better thromboprophylaxis with well-controlled vitamin K antagonist (VKA) anticoagulation rather than antiplatelet therapy or poorly controlled management with VKAs. The emergence of new therapies, such as non-VKA oral anticoagulant agents and left atrial appendage occlusion devices with better net clinical benefit (less strokes, fewer intracranial or life-threatening bleeds, and reduced mortality) than with warfarin or aspirin, has also stimulated much academic activity especially by bringing to the field not only new products and ideas but also more research funding.

It has long been established that AF is associated with an increased risk of stroke and systemic embolism and this risk can be substantially reduced by effective anticoagulation, even in largely unselected populations and with less than ideal VKA control (1). However, therapy with an anticoagulant inevitably leads to an increased risk of bleeding, some of which leads to death or disability, consequences arguably worse in many cases than ischemic stroke. Investigators began to develop schemes, such as CHADS₂ (congestive heart failure, hypertension, age ≥ 75 , diabetes, stroke/transient ischemic attack [doubled]),

to identify those most at risk of ischemic stroke and to direct anticoagulant treatment to patients at high risk with most to gain from a therapy with a narrow therapeutic window (2,3). It was clear that patients with a CHADS₂ score of 2 or above warranted anticoagulation. However, even in the lower ranges of the CHADS₂ score are patients who might suffer a thromboembolic event.

An optimum range of international normalized ratio value was established to gain the best reduction of ischemic events while keeping major bleeding events as low as possible. Anticoagulation clinics and other services were introduced to ensure good anticoagulant control, and widespread publicity was given to the drug-drug and food-drug interactions associated with VKAs. Many physicians, however, continued to rely mostly on antiplatelet thromboprophylaxis despite evidence suggesting a therapeutic effect that was no better than marginal for most at-risk patients with AF.

Because unsatisfactory antithrombotic therapy was used too frequently, whereas VKA control had substantially improved and new, safer therapies were under development, the philosophy of patient selection for anticoagulation reversed. The default position became anticoagulation for all patients with AF except those shown to be at little or no risk of thromboembolic events. Risk scores, such as the CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 [doubled], diabetes, stroke/transient ischemic attack [doubled], vascular disease, age 65 to 74, female sex category) scheme, were introduced with this principle in mind (4). A score of zero implied there was virtually no risk of stroke and no need to consider anticoagulation or any other form of antithrombotic therapy. Although there remained some doubt about anticoagulation for the

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intermediate score of 1 (5,6), those with scores of ≥ 2 would be considered for therapeutic anticoagulation. Because CHA₂DS₂-VASc included more risk factors than CHADS₂, more patients would be designated at risk, but this was thought appropriate because the stroke rate in patients with AF remained high despite previous efforts.

The CHA₂DS₂-VASc scheme did not arise from nowhere. Elements of the scheme had been part of thromboembolic AF risk evaluation in the 2006 American Heart Association/American College of Cardiology/European Society of Cardiology (AHA/ACC/ECS) (7) and National Institute for Health and Care Excellence (NICE) guidelines (8) and the scheme had been operating locally in parts of the United Kingdom for some years (9). Several papers validating CHA₂DS₂-VASc and demonstrating advantages over CHADS₂ emerged and the 2010 ESC guidelines recommended extension of the previous CHADS₂ scheme by incorporating the additional CHA₂DS₂-VASc risk factors (10). The 2012 ESC guidelines formally replaced CHADS₂ with CHA₂DS₂-VASc (11) and the American Heart Association/American College of Cardiology/Heart Rhythm Society 2014 and the NICE (2014) guidelines took a similar position (12,13).

However, not all guideline developers agreed. The American College of Chest Physicians (2012) did not forsake the CHADS₂ scheme (14), and neither did the Japanese Cardiovascular Society (15), although it did provide for independent consideration of 3 of the CHA₂DS₂-VASc additional risk factors (omitting female sex and including cardiomyopathy). The Canadian Cardiovascular Society took a somewhat different position, moving to a flow chart based scheme in which an age of 65 years warrants anticoagulation, as do any of the CHADS₂ risk factors. Vascular disease prompts therapy with aspirin and female sex does not attract any consideration (16). It seems therefore that there is far from universal agreement as to how patients with AF should be selected for anticoagulant therapy.

It is no wonder that scientists continue to seek a better method to identify at-risk patients. The current schemes do not include all risk factors and 1 major omission is renal function. This was incorporated in the so-called R₂CHADS₂ (renal impairment [doubled] congestive heart failure, hypertension, age ≥ 75 , diabetes, stroke/transient ischemic attack [doubled]) scheme, which emerged from an analysis of the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) population and was validated in an ATRIA (Anticoagulation and Risk Factors

in Atrial Fibrillation) population (17). This did not catch on, partly because renal function is not always readily available and CHA₂DS₂-VASc already had a head of steam (18).

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Another score was put forward from the ATRIA group that contained elements of R₂CHADS₂ but importantly gave different scores for age ranges that varied according to whether the patient had also suffered a stroke or transient ischemic attack. In this issue of the *Journal* (19) the ATRIA score, which is already validated (20), was directly compared with CHADS₂ and CHA₂DS₂-VASc in a large population of U.K. patients (n = 60,594) with data derived from family practitioners and hospital records. In essence the study showed that ATRIA outperformed CHADS₂ and CHA₂DS₂-VASc largely because its use resulted in an appropriate downward classification (toward no risk). This result withstood sensitivity analyses, such as withdrawing all renal data (that was not always available in the examined data set in any case). The value of the scheme seems to rely specifically in the graduated scoring for age adjusted for previous stroke. The main implication of the study is that if its results were to apply to all similar relatively unselected patients with AF, needless anticoagulation with its attendant bleeding complications of many low-risk patients could be avoided by adopting the ATRIA score.

It is probable that other studies comparing these scoring schemes in large populations of patients will soon follow, and we may then be able to make a well-informed decision about the best score to recommend, although it is increasingly difficult to find large contemporary populations of patients with at-risk AF that have not been exposed to anticoagulant agents. Recently investigators have reported risk factors and scoring schemes derived from data collected during phase III clinical trials or from retrospective analyses of administrative databases not specifically designed to capture the most appropriate data for stroke risk stratification (21,22). There are now large registries of patients in which sizeable proportions of the data relate to patients that remain unanticoagulated, but often for undefined reasons. Interpretation of these data is increasingly difficult and the present investigation that used the General Practice Research Database from the United Kingdom is probably one of the better sources of reliable information, although this may have been compromised by the determined attempts in the U.K. to ensure that vulnerable patients with AF do receive anticoagulant therapy and the database

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