Since the report from the Framingham Study in 1991, atrial fibrillation (AF) is said to be associated with 4.5-fold risk of stroke, predominantly ischemic in nature, largely attributable to embolization of a left atrial or left atrial appendage clot. Over the last several decades a large evidence base has been developed, justifying the use of anticoagulant therapy, mostly with warfarin, and recently with oral direct thrombin inhibitors and factor Xa inhibitors. Experience with left atrial appendage occlusion devices is accruing in patients deemed at risk for ischemic stroke, but unable to take an anticoagulant drug. Whether AF per se, in the absence of other predisposing conditions, poses risk of stroke is debatable, and guidelines on AF across the world do not advocate anticoagulation in individuals without risk factors. Thus, the prediction of stroke relies predominantly on risk factors such as previous stroke, old age, and underlying cardiovascular or metabolic disease. A plethora of risk stratification systems have emerged based on combinations of various risk factors that have been derived from the control arms of the anticoagulation trials or from community-based cohorts, based on event-rate analyses. Expert consensus panels have also contributed, but none of the proposed schemes has been capable of entirely satisfying these goals.

The major predicament of all risk stratification schemes is a modest predictive accuracy for stroke and low discriminant ability between different risk strata: when applied to the large AF population that is not on anticoagulation, c-statistic for predicting a thromboembolic event ranged between 0.58 and 0.66. The proportion of patients characterized as low or high risk varied 5- to 7-fold among schemes, resulting in inconsistent recommendations for anticoagulation. The majority of schemes were derived from relatively small cohorts with short follow-up and small numbers of strokes or thromboembolic events. Few included patients with new onset AF. Many used historic cohorts with poor medical therapies for underlying conditions, some of which constitute risk factors for stroke (eg, hypertension), and higher rates of stroke than in contemporary anticoagulation trials. The medical community embraced the CHADS$_2$ (Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke [doubled]) scheme, mainly because of its simplicity. The CHADS$_2$ system is appealing to physicians, and its use has encouraged risk stratification for stroke in large numbers of patients with AF and has led to a greater implementation of anticoagulant therapy.

However, the CHADS$_2$ scheme offers a relatively crude estimation of risk and assigns a non-negligible proportion of patients as low-risk when they are not. Withholding anticoagulation in these individuals may lead to catastrophic consequences. Widely advocated in Europe, the CHA$_2$DS$_2$-VASc (Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category) (female) scheme is a refined version of CHADS$_2$, with an emphasis on the significance of older age, with 2 points assigned to those aged ≥75 years, and inclusion of ages 65 to 74 years (1 point), female sex (1 point), and atherosclerotic disease in coronary, carotid, or peripheral arterial circulation (1 point). The scheme maintains the controversial notion that female gender is a contributor to risk, but only if other components of the stratification system are also present. The CHA$_2$DS$_2$-VASc scheme renders more patients at risk and prompts anticoagulation therapy in larger numbers.

Impaired renal function contributes to increased risk of stroke via procoagulant and inflammatory pathways and changes in arterial compliance/stiffness. In the ATRIA (Anticoagulation and Risk Factors In Atrial Fibrillation) cohort of >10000 participants with AF, proteinuria increased the odds of stroke by 54% and there was a graded, growing risk associated with the reduced estimated glomerular filtration rate, with a 39% greater risk of stroke if estimated glomerular filtration rate fell below 45 mL/min/1.73 m$^2$ compared with normal estimated glomerular filtration rate levels. In the Danish National Patient Registry study, impaired renal function and renal failure conferred increased stroke risks of 49% and 83%, respectively.

Despite the known association between renal dysfunction and thromboembolism in the general population and the emerging reports of its role in AF-related strokes, it has not been included in any of the current stratification schemes. Incidentally, the small c at the end of abbreviation for CHA$_2$DS$_2$-VASc, which stands for [sex]category, was originally intended to stand for creatinine (creatinine clearance [CrCl] < 30 mL/L or proteinuria). However, at the time of...
the development and validation of this score, there had been insufficient evidence for renal dysfunction to become a component of the risk scheme, and renal function was not a part of many of the databases that were used to validate the score.

In this issue of *Circulation*, Piccini et al propose a R\textsubscript{2}CHADS\textsubscript{2} score in which renal impairment defined as creatinine clearance (CrCl) < 60 mL/min/1.73 m\textsuperscript{2} using Cockcroft-Gault formula, has been assigned 2 points—a power equivalent to that of previous stroke or a transient ischemic attack in the CHADS\textsubscript{2} score and of both stroke or transient ischemic attack and age ≥75 years in the CHA\textsubscript{2}DS\textsubscript{2}-VASc scheme. The score was developed based on 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 its performance was further assessed in the ATRIA cohort. In the 14,155-strong ROCKET-AF population with CrCl data, the strength of association between CrCl and stroke or systemic embolism was second to that of previous stroke or transient ischemic attack, but probably not as strong to merit similar weight in the risk stratification scheme. As a continuous measure of renal function, each reduction in CrCl by 10 mL/min increased the odds of stroke or systemic embolism by 9% to 12%.

Only 21% of the subjects enrolled in the ROCKET-AF had moderate renal impairment at enrollment, and none had severe renal impairment. The performance of the R\textsubscript{2}CHADS\textsubscript{2} score expressed using the c-statistic index was modest and was expressed using the c-statistic index was modest and was not substantially better than the performance of CHADS\textsubscript{2} or CHA\textsubscript{2}DS\textsubscript{2}-VASc schema (0.587 versus 0.575 and 0.578, respectively) in the ROCKET-AF or that for CHADS\textsubscript{2} in the ATRIA cohort (0.673 versus 0.672).

The development of the risk score using the ROCKET-AF population is not without limitations. The subjects in ROCKET-AF constitute a large contemporary cohort of AF patients with well-defined risk factors, on optimal medical therapy for underlying cardiovascular and metabolic disease, who were prospectively followed up for nearly 2 years, during which all thromboembolic events were captured. The number of events was significantly higher (n=429) than in the older cohorts used for derivation of risk scores (n=73–130) and included stroke and stroke embolism. Unlike other cohorts, which included patients who were not on anticoagulant therapy and received either no antithrombotic treatment or aspirin, all patients in ROCKET-AF were on anticoagulation. Whether adequate therapy aimed at stroke prevention may alter the impact of risk factors on outcome is not well known, especially for patients treated with rivaroxaban. The present analysis used the ROCKET-AF primary end point that was a composite of stroke and systemic embolism, whereas in the majority of previous schemes analysis was limited to (ischemic) stroke or stroke and transient ischemic attack.

Another concern about the derivation of the R\textsubscript{2}CHADS\textsubscript{2} based on the ROCKET cohort arises from the fact that, by design, patients included in the ROCKET-AF had a CHADS\textsubscript{2} score ≥2 (mean 3.5), and the majority had ≥1 concomitant condition (eg, heart failure in nearly two thirds). The impact of renal dysfunction in individuals with a lower overall risk of stroke could not be established, and this may limit the applicability of R\textsubscript{2}CHADS\textsubscript{2}.

It is impossible to ignore the fact that the Cockcroft-Gault and Modification of Diet in Renal Disease equations contain age, which per se is a powerful predictor of stroke, and its impact in the formula cannot be ignored. Perhaps, to a lesser extent, it is also true for female sex, which, according to some reports, confers on it nearly a 2-fold risk for stroke. The CrCl values overlapped significantly between individuals with and without the primary end point event. The threshold for abnormal CrCl values was selected according to the National Kidney Guideline definition of moderate kidney disease. It is unclear how sensitive the R\textsubscript{2}CHADS\textsubscript{2} score is to the chosen threshold. Of course age alone also reduces creatinine clearance, and it may be that assigning a higher score to age in either the CHADS\textsubscript{2} or CHA\textsubscript{2}DS\textsubscript{2}-VASc schema might have considerably diluted the value of the CrCl as an independent risk factor.

The recognition of renal impairment as a risk factor for stroke is an important contribution to current risk stratification efforts. Unfortunately, thromboembolism and bleeding share many risk factors, and renal disease is one which is included in several bleeding risk assessment schemes (ATRIA, HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly], HEMORR\textsubscript{2}HAGES [Hepatic or renal failure, Ethanol abuse, Malignancy, Older age (over 75), Reduced platelet count or function, Rebleeding risk (doubled), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk (including neurodegenerative and psychiatric disorders) and history of Stroke]). Nevertheless, this report will prevent some physicians from withholding anticoagulation therapy or using a subtherapeutic intensity of anticoagulation in patients with chronic kidney disease. In end-stage renal disease, however, the threshold for anticoagulation therapy to prevent ischemic stroke should probably be higher than in the general population because of the different risk–benefit ratio.

At present, there is little need to discriminate between those at intermediate and high risk of thromboembolism—anticoagulant therapy is increasingly advised for all. However, it is crucially important to identify those at little or no risk of thromboembolism and those with an annual risk that exceeds 1% to 2% per annum. Adding a renal function biomarker will not materially assist this important aspect of risk stratification.

There are other practical implementations of R\textsubscript{2}CHADS\textsubscript{2}, beyond potentially improved risk stratification. New oral anticoagulants all have restrictions in the use in patients with impaired renal function. In general, lower doses are recommended in those with moderate renal impairment. In patients with a severe decrease in renal function and individuals requiring hemodialysis, treatment with vitamin K antagonists remains the better option for balancing risk of stroke and risk of bleeding. R\textsubscript{2}CHADS\textsubscript{2} certainly adds complexity to instant risk stratification as it introduces an extra step in the score calculation. Of course this added complexity may be offset by the widespread availability of electronic devices, but simple scores are generally more simply and more often applied.

**Disclosures**

Dr Camm is an advisor/speaker/investigator for Servier, Novartis, Sanofi, Astra Zeneca, Xention, Bristol-Myers Squibb, Menarini, Sanofi, Astra Zeneca, Xention, Bristol-Myers Squibb, Menarini.
References


Key Words: Editorsials | atrial fibrillation | prevention and control | risk
"R" for "Renal" and for "Risk": Refining Risk Stratification for Stroke in Atrial Fibrillation
A. John Camm and Irene Savelieva

doi: 10.1161/CIRCULATIONAHA.112.147512

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/2/169

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/