Atrial Fibrillation and the Risk of Intracranial Hemorrhage: Predictors and Risk Assessment

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There has been a decreasing trend in stroke rates in patients with atrial fibrillation (AF) over the past few decades, which may be owing to more aggressive treatment of underlying risk factors (eg, hypertension and hyperlipidemia) [Gage BF et al. *Circulation* 2004; Singer DE et al. *Ann Intern Med* 2009; Hart RG et al. *Stroke* 2009]. Though current risk stratification methods are helpful, whether or not a patient is a good candidate for anticoagulation therapy, such as warfarin, is not always obvious. New approaches in stroke prevention in patients with AF and the choice of the appropriate treatment strategy for these patients were topics of a session at the International Stroke Conference in San Antonio, TX.

Daniel E. Singer, MD, Massachusetts General Hospital, Boston, MA, outlined a risk-based approach to the anticoagulation decision in patients with AF. Warfarin reduces the risk of stroke by two-thirds. The general strategy is to recommend warfarin for AF patients whose untreated risk of ischemic stroke is high enough to outweigh the bleeding risk of anticoagulation and the burdens of warfarin management. Stroke risk schemes in AF are not yet highly predictive. Nonetheless, the widely recognized $CHADS_2$ AF stroke risk score provides a straightforward basis for deciding on use of anticoagulant therapy. It applies to patients with persistent or paroxysmal AF. Leading guidelines, including the ACC/AHA/ESC guidelines, generally recommend the approach that is outlined in Table 1 [Gage BF et al. *JAMA* 2001; ACC/AHA/ESC Guidelines. *Europace* 2006]. Studies have shown that the optimal international normalized ratio (INR) with anticoagulation therapy is 2.0 to 3.0; therefore, these anticoagulation intensities are incorporated into the guidelines [SPAF III. *Lancet* 1996; Singer et al. *Circulation Cardiovasc Qual Outcomes* 2009]. To better target the use of anticoagulants in AF, we need better predictors of ischemic stroke and intracranial hemorrhage (ICH).

Table 1. $CHADS_2$ AF Stroke Risk Score-Based Anticoagulation Recommendations for Patients with Paroxysmal or Persistent AF (assuming the patient is not at high bleeding risk and that anticoagulation can achieve the INR 2 to 3 target much of the time).

$CHADS_2$ AF Stroke Risk Score/ Risk Factor Profile	Anticoagulation Treatment Recommendation
$CHADS_2$ Score = 0 0 Risk Factors	Aspirin only
$CHADS_2$ Score = 1 1 Risk Factor with no prior Stroke/TIA	Aspirin or Warfarin
$CHADS_2$ Score ≥2 ≥2 Risk Factors excluding prior Stroke/TIA	Warfarin (INR 2 to 3)
$CHADS_2$ Score ≥2 Prior Stroke/TIA with or without other risk factors	Warfarin (INR 2 to 3)

CHADS: C=CHF; H=Hypertension; A=Age>75 years; D=Diabetes; S=Prior Stroke/TIA

1 point is allotted for each risk factor except in the case of prior stroke/TIA, which is allotted 2 points.

Approximately 30% of major bleeds on warfarin are intracranial [Fang MC et al. *Am J Med* 2007]. Robert G. Hart, MD, University of Texas Health Science Center, San Antonio, TX, pointed out that ICH is the most important complication that is associated with warfarin therapy. In the RE-LY trial, anticoagulation using dabigatran was associated with lower rates of ICH compared with warfarin (.12% vs .38% for warfarin; p<0.001) [Connolly SJ et al. *N Engl J Med* 2009]. These findings could impact the future of anticoagulation therapy. Dr. Hart

suggested ways to minimize ICH during warfarin therapy, such as keeping the INR within therapeutic range during the first 3 months and subsequently under 3.5. After 3 months, if the time in therapeutic range is not at least 50%, alternative treatment options should be considered. Additionally, systolic blood pressure should be kept under 140 mm Hg, and concomitant aspirin should be avoided.

While the use of warfarin has produced significant benefits for the prevention of thromboembolic stroke in patients with AF, warfarin-associated ICH has increased dramatically [Flaherty ML et al. *Neurology* 2007]. The risk and benefit of anticoagulation therapy for those patients in whom stroke and bleeding risk are closely matched can be a source of confusion for clinicians. Furthermore, the decreasing risk of cardioembolic stroke that is attributed to traditional risk factors (as noted in risk prediction tools, such as $CHADS_2$) may have shifted the tipping point in the decision to anticoagulate patients with AF. Although predictors of warfarin-related ICH (ie, prior stroke and age) have been identified, they are not robust enough to serve as consistent predictors, and further screening techniques are required, noted Mark Eckman, MD, University of Cincinnati Medical Center, Cincinnati, OH. However, novel predictors of ICH, such as cerebral amyloid angiopathy, genetic biomarkers, and neuroimaging findings of cerebral microhemorrhage, may be the key to more precise prediction and prevention in the future.

Jonathan Rosand, MD, MSc, Massachusetts General Hospital, Boston, MA, discussed the role that genetics and imaging play in risk of warfarin-related ICH. He noted that the overlap between risk factors for spontaneous ICH overlapped with those for warfarin-related ICH. Furthermore, fully two-thirds of ICH on warfarin occur in patients whose INR is not in the supratherapeutic range. This suggests that identifying the risk factors for vessel rupture within the brain will be crucial to clarifying the risk-benefit calculation for bleeding on warfarin in the future. MRI-detectable microbleeds and leukoaraiosis, both of which increase in prevalence with age, are associated with warfarin-related ICH [Smith EE et al. *Neurology* 2002; Greenberg SM et al. *Lancet Neurol* 2009]. Apolipoprotein E (APOE) polymorphisms have been associated with increased risk for ICH, and variants in other genes, such as VKORC1 and CYP2C9, impact warfarin sensitivity and consequently can alter an individual's warfarin dose requirement and risk of supratherapeutic anticoagulation. The ongoing Genes for Cerebral Hemorrhage on Anticoagulation Study will shed light on the further role of genetics in ICH and warfarin-related hemorrhage. In this multicenter genomewide association study that is being conducted within the International Stroke Genetics Consortium, 2000 ICH cases/controls will be compared with 1800 warfarin-related hemorrhage cases/controls to identify genetic variants that are associated with anticoagulant-related cerebral hemorrhage. There is every reason to expect that genetic risk factors for vessel rupture in patients who are taking warfarin are likely to be predisposed to bleeding on dabigatran as well, concluded Dr. Rosand.

New anticoagulation agents will likely lead to a shift in treatment strategies for AF patients who are at risk for stroke. The decision to anticoagulate has become more dependent upon the ICH risk assessment. Screening for genetic factors or neuroimaging findings in the future could yield superior outcomes, particularly for patients who are at lower risk of ischemic stroke. However, more comprehensive studies are needed to establish the strength and utility of these technologies as predictors of intracerebral hemorrhage and other complications that are associated with anticoagulation therapy.