Stroke Prevention in Atrial Fibrillation: The Roles of Anticoagulants, Devices, and Antidotes

Written by **Wayne Kuznar**

Tools for risk stratification for stroke and bleeding among patients with atrial fibrillation (AF) were reviewed by Gregory Lip, MD, Centre for Cardiovascular Sciences at City Hospital, Birmingham, United Kingdom. The $CHADS_2$ score is frequently used to estimate the risk of stroke in AF patients and to help determine t happropriateness of anticoagulant therapy. However, Prof. Lip noted that one of the limitations of this tool is that in patients with a $CHADS_2$ score of 0, the stroke rate ranges from 0.8% to 3.2% per year [Olesen JB et al. *Thromb Haemost* 2012], and there was significant undertreatment of high-risk patients.

In this regard, the CHA_2DS_2-VASc score is superior to $CHADS_2$. As opposed to $CHADS_2$, which defines age ≥75 years as a major stroke risk factor, the CHA_2DS_2-VASc score assigns 1 point for age 65 to 74 years and assigns extra weight (2 points) for age >75 years [Lip GYH et al. *Chest* 2010]. In addition, the CHA_2DS_2-VASc score adds vascular disease and female sex (if over age 65) as additional risk factors.

Low-risk patients by CHA_2DS_2-VASc are defined by a score of 0 (men) or 1 (women); these patients are uncommon and do not require antithrombotic therapy [Olesen JB et al. *Thromb Haemost* 2012]. All other AF patients with at least one stroke risk factor should be offered oral anticoagulant therapy.

The 2012 European Society of Cardiology guidance also recommends a bleeding risk scoring system, the HAS-BLED score [Camm AJ et al. *Eur Heart J* 2012] which is easy to use and superior to other bleeding risk scores in predicting bleeding events [Lip GYH et al. *Clin Arrhythm Electrophysiol* 2012]. It allows for an informed assessment of bleeding risk and identification of potentially correctable risk factors for bleeding and Prof. Lip emphasized that it should not be used to exclude patients from oral anticoagulant therapy.

The benefit-risk of warfarin and the new oral anticoagulants (OACs) was examined by Elaine M. Hylek, MD, MPH, Boston University Medical Center, Boston, Massachusetts, USA. Warfarin is the most common medication implicated in emergency hospitalizations for adverse drug events in older adults in the United States [Budnitz DS et al. *N Engl J Med* 2011], being responsible for high rates of intracranial hemorrhage (ICH), gastrointestinal hemorrhage, and elevations in the International Normalized Ratio (INR) that require emergency hospitalization. Time spent in the therapeutic range is only 55% in warfarin recipients [Baker WL et al. *J Manag Care Pharm* 2009], confirming the difficulty in dosing and monitoring warfarin.

Alternatives to warfarin are the direct thrombin inhibitors and factor Xa inhibitors. In the RE-LY trial, the oral direct thrombin inhibitor, dabigatran 150 mg BID, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage compared with warfarin [Connolly SJ et al. *N Engl J Med* 2009]. In patients aged ≥75 years, there was a trend toward a higher incidence of major bleeding with dabigatran than with warfarin.

Patients with low INR variability and adequate time in the therapeutic range on warfarin have less to gain from a switch to twice daily dabigatran than patients with high INR variability. In patients with stable INR while on warfarin, the death rate and anticoagulant-related bleeding were significantly lower than in a comparator group (Table 1) [Witt DM et al. *Blood* 2009]. Recent evidence from RE-LY indicates that a polymorphism in the rs2244613 gene, present in about one third of patients, predicts a lower risk of bleeding with dabigatran [Paré G et al. *Circulation* 2013].

In the ROCKET-AF trial there was no difference in the rate of major bleeding with rivaroxaban compared with warfarin though the former was associated with significantly lower rates of critical organ bleeding, death from bleeding, and ICH but comparatively higher rates of transfusion and a decrease in hemoglobin ≥2 g/dL (Table 2) [Patel MR et al. *N Engl J Med* 2011]. In the ARISTOTLE

Official
Peer-Reviewed
Highlights From the
American Heart Association
SCIENTIFIC SESSIONS 2013

trial, the rates of International Society on Thrombosis and Haemostasis major bleeding and ICH were significantly lower with apixaban compared with warfarin [Granger CB et al. *N Engl J Med* 2011].

Table 1. Six-Month Event Rates in Warfarin-Treated Patients With Stable INR

Characteristic	Stable group, n=2504	Comparator group, n=3569	p Value
Received heparin, %*	0.3	3.2	<0.001
Deceased, n (%)	10 (0.4)	58 (1.6)	<0.001
AC-related death, n (%)	1 (0.04)	5 (0.1)	0.411†
AC-related thrombosis, n (%)	10 (0.4)	26 (0.7)	0.100
AC-related bleeding, n (%)	19 (0.8)	101 (2.8)	<0.001
AC-related bleeding or thrombosis, n (%)	28 (1.1)	127 (3.6)	<0.001

AC=anticoagulation.

*Heparin or low-molecular-weight heparin; †Fisher exact test.

Table 2. Safety Outcomes With Rivaroxaban

	Rivaroxaban	Warfarin		
	Event Rate or N (Rate)	Event Rate or N (Rate)	HR	p Value
Major	3.6	3.4	1.04	0.58
>2 g/dL Hg drop	2.8	2.3	1.22	0.02
Transfusion (> 2 units)	1.6	1.3	1.25	0.04
Critical organ bleeding	0.8	1.2	0.69	0.007
Bleeding causing death	0.2	0.5	0.50	0.003
Intracranial hemorrhage	55 (0.5)	84 (0.7)	0.67	0.02

Hg=hemoglobin.

Left atrial appendage (LAA) closure is an option to prevent stroke in patients at high risk of stroke in whom long-term anticoagulation is contraindicated or in whom INR control cannot be achieved, said Amin Al-Ahmad, MD, Texas Cardiac Arrhythmia Institute, Austin, Texas, USA.

Endocardial approaches to close the LAA are the Watchman LAA System and Coherex Medical. The Watchman, not currently approved in the United States, is a self-expanding nitrol frame structure with fixation barbs that engage the LAA wall when the delivery catheter is employed. In a randomized clinical trial of 707 AF patients [Holmes DR. *Lancet* 2009], the Watchman was found to be noninferior to warfarin on the primary efficacy endpoint (a composite of stroke, cardiovascular death, or systemic embolism). Periprocedural complications including cardiac perforation, pericardial effusion with tamponade, and device embolization occurred in 6% to 8% of patients. The Coherex WaveCrest System, also not currently approved in the United States, comes in three sizes to accommodate different ostial diameters, and can be used in a wide variety of LAA anatomies.

Potential issues with endocardial approaches are incomplete closure, thrombus formation at follow-up, and an inability to retrieve the device if deployment is suboptimal.

Measurement and monitoring of the anticoagulant effects of new OACs, although not required routinely because of their predictable pharmacokinetics and a wide therapeutic window, may be useful in some situations, such as in patients with bleeding or at risk of bleeding or thromboembolism, said Graeme J. Hankey, MD, University of Western Australia, Perth, Australia.

Antifactor Xa assays accurately measure the effects of the oral factor Xa inhibitors apixaban and rivaroxaban, depending on the calibrator [Doufils J et al. *Thromb Haemost* 2013; *Thromb Res* 2012]. When interpreting the Hemoclot assay for dabigatran, or the antifactor Xa assay for Xa inhibitors, the timing of the last tablet and the timing of the blood test must be known in order to get an idea of whether the blood concentration should be rising, plateauing, or falling [Mani H et al. *J Thromb Thrombolysis* 2013], said Prof. Hankey.

The other important laboratory test is creatinine clearance. A residual anticoagulant effect is unlikely if renal function is normal and it has been ≥24 hours since the last dose of OAC. A widely and rapidly available assay that correlates with a validated therapeutic window is awaited.

Specific antidotes to the new OACs are still under development. A monoclonal antibody against dabigatran (aDabi-Fab) has shown rapid reversal of the anticoagulant effect in *ex vivo* clotting assays in a rat model [Schiele F et al. *Blood* 2013]. A recombinant protein, r-antidote (PRT064445), to Xa inhibitors reversed the anticoagulant effects of these agents in a rat model [Lu G et al. *Nat Med* 2013]. Another potential antidote to Xa inhibitors is andexanet alfa, which has shown rapid and near complete reversal of apixaban's anticoagulant effect [http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsArticle&ID=1883157&highlight=]. PER 977 is a synthetic small molecule that acts as a universal reversal agent [Laulicht B et al. *Circulation* (abstr 11395)].

In the past 5 years there have been many new developments in the management of AF. Additional information from studies of novel therapeutics will continue to help optimize therapy and reduce the risk of stroke or systemic embolization while minimizing bleeding for patients with AF.