Beyond the Guidelines: New Evidence in AF

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Despite the increasing prevalence of atrial fibrillation (AF), no reliable method to detect AF in asymptomatic individuals has been established. This diagnostic uncertainty poses a challenge in implementing important treatment decisions, such as rate versus rhythm control and the need for anticoagulation in asymptomatic patients [Eitel C et al. Europace 2011]. Gerhard Hindricks, MD, PhD, University of Leipzig, Leipzig, Germany, discussed new developments in the diagnosis of AF.

To address limitations of current methods, researchers are pursuing two promising approaches: 1) implantable loop recorders (ILRs) and other monitoring technologies and 2) substrate analysis as a potential basis for individualized therapy.

New ILR Technologies

Advances are being made in implantable cardiac monitors with dedicated AF detection algorithms. They detect AF via R-R variability pattern recognition. In the Xpect Trial, the AF burden that was measured with the implantable cardiac monitor (ICM) was correlated very well with the reference value that was derived from the Holter monitor (Pearson coefficient=0.97). The overall accuracy of the ICM for detecting AF was 98.5% [Hindricks G et al. *Circ Arrhythm Electrophysiol* 2010].

Prof. Hindricks explained that ILR for AF detection is currently limited by a lack of data that support efficacy, including: no direct comparison to external monitoring techniques, no proof that ILRs are superior to existing methods for AF detection, the inability to identify patient populations that may benefit from ILRs, and the absence of scientific evidence that ILRs may improve either quality of life or hard AF-related clinical outcome parameters (reduced stroke risk).

The quest to meet these challenges has led to the development of new technologies for ILRs. These devices automatically detect arrhythmias, store arrhythmia waveforms for visual confirmation, and sense from multiple electrodes. They include patient-triggered ECG storage and are tele-monitoring-enabled (a wireless global system without patient interaction; and transmission of ECG waveforms and detection statistics).

Injectable devices are another new technology. These units constitute less than 10% of current device volume, and provide up to 2 years of full-coverage ILRs. The new single-use external monitors for AF detection provide 14 days of continuous monitoring on one channel versus three channels that are combined into a single output in IRLs.

Technologies to Identify AF Substrate

Magnetic resonance imaging (MRI) is a promising modality for substrate identification. The quality of substrate analysis depends on the ability of MRI to enable detection of left atrial fibrosis, a finding that is associated with AF. This approach may lead to a better understanding of the stage of atrial disease in individual patients. New technologies that are focused on better characterization of atrial fibrosis include delayed-enhancement magnetic resonance imaging (DE-MRI) [Oakes RS et al. *Circulation* 2009; Badger TJ et al. *Circ Arrhythm Electrophysiol* 2010] and late gadolinium enhancement-magnetic resonance imaging (LGE-MRI) [Vergara GR, Marrouche NF. *J Cardiovasc Electrophysiol* 2011].

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Oral Anticoagulant Treatment Innovations

AF is a common cause of ischemic stroke and transient ischemic attack (TIA) [Rizos T et al. *Cerebrovasc Dis* 2011]. Approximately 1% of the population is affected by AF, and its prevalence is growing with the aging population [Font MA et al. *Stroke Res Treat* 2011]. Lars Wallentin, MD, PhD, Uppsala Clinical Research Center, Uppsala, Sweden, discussed new antithrombotic therapies to prevent stroke in AF.

Oral anticoagulants (OACs) are highly effective in reducing stroke in patients with AF, yet continuous OAC is prescribed for less than half of patients with AF who have risk factors for cardioembolism and no contraindications for anticoagulation [Font MA et al. *Stroke Res Treat* 2011].

Warfarin and related oral vitamin K antagonists (VKAs) are the most widely used treatment for thromboembolic prevention in AF. VKA therapy, however, is associated with significant drawbacks, including the need for routine monitoring, numerous drug-drug and food-drug interactions, and risk of intracranial hemorrhage. Newer oral anticoagulants that inhibit factor IIa (eg, dabigatran) and factor Xa (eg, rivaroxaban, apixaban, edoxaban) appear to be safe and efficacious with important benefits, such as reduced risks of dangerous bleeding and no need for routine monitoring. Many novel anticoagulants are being developed that target various factors in the coagulation cascade.

The two agents that are in the most advanced stages of development are dabigatran etexilate (approved in the United States, Europe, and Canada) [Connolly SJ et al. *N Engl J Med* 2009] and rivaroxaban [Patel MR et al. *N Engl J Med* 2011]. They inhibit thrombin and factor Xa, respectively. A recent Phase 3 study for the factor Xa inhibitor apixaban, also showed very promising results [Granger CB et al. *N Engl J Med* 2011]. Other agents that are in the early stages of development include several factor Xa inhibitors (betrixaban, darexaban, eribaxaban [PD 0348292], LY 517717, and TAK 442) and one thrombin inhibitor (AZD 0837) [Eriksson BI et al. *Clin Pharmacokinet* 2009].

Three large Phase 3 trials with factor Xa inhibitors have either been reported or are in progress: ROCKET AF (rivaroxaban), ARISTOTLE (apixaban), and ENGAGE-AF (edoxaban). All are double-blind, noninferiority studies, using warfarin as the comparator. The primary outcome is stroke or systemic embolism; the primary safety outcome is bleeding.

In the ROCKET AF trial, the primary endpoint in the per-protocol cohort occurred in 188 patients in the rivaroxaban group (1.7% per year) and 241 patients in the warfarin group (2.2% per year; HR in the drug group, 0.79; 95% CI, 0.66 to 0.96; p<0.001 for noninferiority). However, when all events were included, whether the patients were on or off study drug (intention-to-treat cohort), there was no difference in the primary endpoint between rivaroxaban and warfarin (2.1% per year vs 2.4% per year; p=0.12). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 patients in the warfarin group (14.5% per year; HR, 1.03; 95% CI, 0.96 to 1.11; p=0.44), with significant reductions in intracranial hemorrhage (0.5% vs 0.72%; p=0.02) and fatal bleeding (0.2% vs 0.5%; p=0.003) in the rivaroxaban versus warfarin groups, respectively. The authors concluded that there was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred with less frequency in the rivaroxaban group [Patel MR. et al. *N Engl J Med* 2011].

With apixaban (ARISTOTLE), the rate of the primary outcome was significantly reduced - 1.27% per year versus 1.60% per year in the warfarin group (HR with apixaban, 0.79; 95% CI, 0.66 to 0.95; p<0.001 for noninferiority; p=0.01 for superiority) in the intention-to-treat analysis. The rate of major bleeding was also reduced with apixaban - 2.13% per year versus 3.09% per year in the warfarin group (HR, 0.69; 95% CI, 0.60 to 0.80; p<0.001). Furthermore, apixaban was the first novel anticoagulant to reduce overall mortality in AF (3.52% versus 3.94%, HR, 0.89; 95% CI, 0.80 to 0.99; p=0.047). While the rate of hemorrhagic stroke was substantially reduced with apixaban (0.24% per year versus 0.47% per year in the warfarin group, HR, 0.51; 95% CI, 0.35 to 0.75; p<0.001), there was no difference in the rate of ischemic or uncertain type of stroke (0.97% per year in the apixaban group and 1.05% per year in the warfarin group; HR, 0.92; 95% CI, 0.74 to 1.13; p=0.42) [Granger CB et al. *N Engl J Med* 2011].

Prof. Wallentin ended his presentation by noting that the three new anticoagulants that have completed Phase 3 studies (dabigatran, rivaroxaban, apixaban) show promising efficacy and excellent safety compared with warfarin in patients with AF. Currently, only dabigatran has been approved for use in AF; the other two are being reviewed by regulatory authorities around the world. Future drug choice will depend on the careful weighing of risks versus benefits. Other factors to take into account include drug - specific issues, such as clearance, side effects, survival, patient preferences, and health economics.