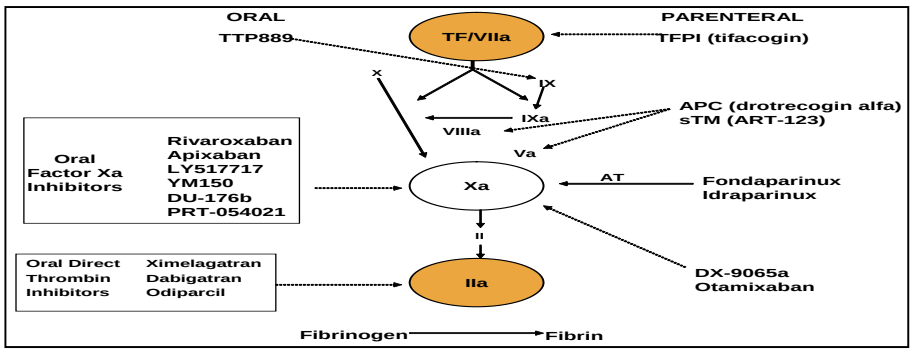
Stroke Prevention in Atrial Fibrillation

Stating that "There is need for alternatives to warfarin," Andrew E. Epstein, MD, Mt. Sinai School of Medicine, New York, NY, reviewed two studies that evaluated other pharmacologic agents. The Stroke Prevention in Atrial Fibrillation (SPAF) Study compared 325 mg/day aspirin or warfarin with placebo in atrial fibrillation (AF) patients. Results showed that aspirin and warfarin reduced primary events of death due to ischemic stroke and systemic embolism by 32% (p=0.02) and 58% (p=0.01), respectively, versus placebo. However, bleeding risk between aspirin and warfarin were the same [SPAF Investigators. Circ 1991].

Dr. Epstein also discussed experimental compounds, including the oral direct thrombin inhibitors ximelagatran (Exanta) and dabigatran (PETRO) [SPORTIF III Investigators. *Lancet* 2003], as well as the factor Xa inhibitors (rivaroxaban and apixaban; Figure 1).

Figure 1. New Anticoagulants.



"In the future, we need to find a drug that beats warfarin's ability to decrease stroke rate to about 1% per year," said Dr. Epstein, adding that the ideal agent would be available in an oral, fixed-dose form and have rapid onset and offset of action, predictable pharmacokinetics, a low propensity for food and drug interactions, a wide therapeutic window, and no need for monitoring.

Oussama M. Wazni, MD, Cleveland Clinic, Cleveland, OH, discussed 3 anticoagulation management strategies that were used during AF ablation in a trial of patients (n=355) who were undergoing pulmonary vein antrum isolation for persistent AF. Patients in one group discontinued warfarin 3 days prior to ablation, and enoxaparin 1 mg/kg^{-1} BID SQ was initiated and continued until a therapeutic INR was achieved postprocedure with warfarin. Transesophageal echocardiography (TEE) was performed in one group just prior to the ablation to rule out left atrial thrombus. In the second group, the same algorithm was followed, except the dose of enoxaparin was 0.5 mg/kg^{-1}. In Group 3, the procedure was performed while patients were therapeutically anticoagulated with warfarin to maintain the INR between 2 and 3.5. No enoxaparin was administered

With careful attention before, during, and after ablation, the use of warfarin without enoxaparin was shown to be safe and efficacious. According to Dr. Wazni, this strategy avoids the necessity to administer low-molecular-weight heparin, which lessens patient inconvenience, expense, and the incidence of bleeding.

Dr. Jonathan L. Halperin, Mt. Sinai School of Medicine, New York, NY, stressed the need to identify the level of stroke risk in AF patients before deciding on an approach to anticoagulation

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therapy, because there is great variability in stroke rate. AF patients at the highest risk are those with mitral stenosis, prosthetic heart valve, left ventricular dysfunction, systolic BP >160 mm Hg, and a history of stroke or TIA. Female gender is an independent risk factor for thromboembolism (and bleeding) and should influence anticoagulant therapy decisions in AF patients.

Current AF guidelines [Fuster. *JACC* 2006] endorse the use of the $CHADS_2$ risk index (1 point each for CHF, Hypertension, Age > 75 years, Diabetes, and 2 points for Stroke or TIA) to identify patients who are at increased risk for stroke and who should be considered for oral anticoagulation. However, it is not prudent to treat all AF patients with anticoagulants. Low-risk patients ($CHADS_2$ index 0 or 1) can be treated with aspirin, while those with $CHADS_2$ index of 2 or greater might be candidates for warfarin.

Dr. Halperin mentioned the need for better tools to stratify bleeding risk, more precise noninvasive imaging to assess thromboembolism risk, more accurate biomarkers of inflammation and thrombophilia to predict clinical events and guide therapy, and targeted preventive therapy for patients at risk of developing AF as the most important challenges that lay ahead. The goal is "to bring effective therapy to many more patients and prevent thousands of strokes."

Many patients who undergo coronary artery bypass grafting (CABG) eventually develop AF and are at risk for stroke. Over 90% of thrombi are found in the left atrial appendage (LAA) [Blackshear JL & Odell JA. *Ann Thorac Surg* 1996]. Surgical occlusion of the LAA is an attractive method for potentially reducing stroke risk and can be done with little incremental time, cost, and risk.

Shephal Doshi, MD, Pacific Heart Institute, Santa Monica, CA, discussed the WATCHMAN, an implantable device that consists of a coated, self-expanding nitinol cage, which is permanently placed at the opening of the LAA, to prevent blood clots from the LAA from entering the bloodstream and potentially causing a stroke.

Based on a successful 5-year event-free pilot study [Sick PB et al. *J Am Col Cardiol* 2007], the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Atrial Fibrillation) study is currently comparing the WATCHMAN device with long-term warfarin therapy. The primary endpoints are the rates of all stroke, systemic emboli, and cardiovascular death in high-risk patients who are eligible for warfarin therapy with non-valvular AF. Thus far, 757 patients have been enrolled. First analysis of the data is expected in the summer of 2008.

Women with Heart Failure

While discussing heart failure in women, Deborah L. Crabbe, MD, Temple University Hospital, Philadelphia, PA, pointed to a small but intriguing number of studies that suggested that the pathophysiology of heart failure is different in women than it is in men. These include the fact that women often have higher left ventricular ejection fractions (LVEFs) [Bhatia RS et al. *N Engl J Med* 2006; Owan TE et al. *N Engl J Med* 2006] and more hypertrophy [Kostkiewicz M et al. *Int J Cardiol* 1999], and are more likely to have dyspnea and edema [Johnstone D et al. *J Cardiol* 1992]. Women also have a lower risk of death irrespective of the cause of their heart failure [O'Meara E et al. *Circulation* 2007], stated Monica M. Colvin-Adams, MD, University of Minnesota, Minneapolis, MN.

JoAnn Lindenfeld, MD, University of Colorado, Denver, CO, noted that there are several gender differences that impact therapy and adverse events in women, including creatinine clearance, lean body mass, metabolism, thrombogenicity, sex hormones, and QT prolongation. She also pointed out that, although women appear to benefit more from angiotensin receptor blockers than men, the relatively small number of women that has been studied limits the interpretation of these data [Ghali JK & Linderfeld J. *Expert Rev Cardiovasc Ther* 2008].

Cardiac resynchronization and implantable cardioverter defibrillator (ICD) therapy are known to improve survival in patients with heart failure. Jamie B. Conti, MD, Shands Hospital University of Florida, Gainesville, FL, presented data showing that women, however, are significantly less likely than men to receive ICDs and are often underrepresented in device-based efficacy and safety clinical trials. Although the American College of Cardiology/American Heart Association guidelines recommend equal treatment for men and women, women also suffer from bias that results in lower referral rates.

Patricia P. Chang, MD, University of North Carolina, Chapel Hill, NC, spoke about gender disparity in heart transplants. Approximately 25% of recipients are females, while 31% of donors are females. This disparity may be related to women's lower body mass index, which places physical limits on the use of ventricular assist devices (VAD) as a treatment option. Ineligibility for VAD decreases the United Network for Organ Sharing medical urgency status, thus reducing the chance for timely transplantation.

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