Recent Advances in Stroke Prevention Among Elderly Patients With Atrial Fibrillation

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A common issue in the management of elderly patients with atrial fibrillation (AF) is weighing the relative risks of ischemic stroke and bleeding. The presentations in this session addressed subclinical atrial fibrillation (SCAF), ablation in the elderly, and stroke prevention with new oral anticoagulants (NOACs) as well as left atrial appendage (LAA) closure.

SUBCLINICAL ATRIAL FIBRILLATION DIAGNOSIS AND TREATMENT IMPORTANT FOR STROKE PREVENTION

Much has been learned about atrial tachyarrhythmia (AT) over the last 15 years in studies using pacemakers, which accurately record atrial rhythm changes for prolonged periods. According to presenter Jeff Healey, MD, MSC, McMaster University, Hamilton, Ontario, Canada, pacemakers are the gold standard for detecting atrial high-rate episodes (AHRE).

In a study of 110 patients, recurrent AT was detected in 46% by electrocardiogram (ECG) and in 88% by pacemaker at 19 months follow-up [Israel CW et al. *J Am Coll Cardiol* 2004]. AT duration was >48 hours in 50 patients, 19 (38%) of whom were asymptomatic and in sinus rhythm at follow-up.

Several studies have demonstrated increased stroke rates among patients with SCAF (Table 1). Patients with a high SCAF burden (≥5.5 hours) were more likely to have a stroke than those with a lower burden [Glotzer TV et al. *Circ Arrhythm Electrophysiol* 2009]. The ASSERT trial found that SCAF was associated with a 2.5-fold increased stroke risk but the absolute stroke risk was modest at 1.69%/year [Healey JS et al. *N Engl J Med* 2012]. Only 8% of ASSERT stroke patients had SCAF within 30 days before the event [Brambatti M et al. *Circulation* 2014].

Table 1. Studies of Relationship Between Device-Detected SCAF and Ischemic Stroke

Study	Design	Results
TRENDS [Glotzer TV et al. *Circ Arrhythm Electrophysiol* 2009]	▪ Patients with device-diagnosed AHRE ▪ History prior AF, 20% ▪ Oral anticoagulation, 21% ▪ No AHRE adjudication ▪ Endpoint: stroke/TIA/SE	▪ Low AHRE burden (<5.5 hours), HR, 0.98; 95% CI, 0.34–2.82; p=0.97 ▪ High AHRE burden (≥5.5 hours), HR 2.20; 95% CI, 0.96–5.05; p=0.06
ASSERT [Healey JS et al. *N Engl J Med* 2012]	▪ 2580 patients, history of hypertension, no AF; implanted pacemaker or ICD ▪ Detection of SCAF ▪ Device-detected AT present vs absent ▪ Mean follow-up, 2.5 years ▪ Endpoint: Stroke/SE	▪ Stroke/SE: AT present vs absent, 1.69%/yr vs 0.69%/yr (RR, 2.49; 95% CI, 1.28–4.85; p=0.007) ▪ Clinical AF or flutter: AT present vs absent, 6.29%/yr vs 1.22%/yr (RR, 5.56; 95% CI, 3.78–8.17; p<0.001)
ASSERT [Brambatti M et al. *Circulation* 2014]	▪ 2580 patients, history of hypertension, no AF; implanted pacemaker or ICD ▪ Temporal relationship between SCAF >6 minutes and stroke/SE	▪ 51% with stroke/SE at follow-up had SCAF ▪ 35% had SCAF prior to stroke/SE ▪ 8% had SCAF within 30 days prior to stroke/SE
Copenhagen Holter study [Binici Z et al. *Circulation* 2010]	▪ 678 healthy individuals, aged 55 to 75 years ▪ 48-hr ambulatory ECG monitoring for ESVEA ▪ Primary endpoint, stroke or death ▪ Median follow-up, 6.3 years	▪ ESVEA present in 14.6% ▪ Stroke/death: ESVEA vs no ESVEA, 29 vs 76 events (adjusted HR, 1.64; 95% CI, 1.03–2.60; p=0.036) ▪ Increased rate of AF hospitalization with ESVEA
EMBRACE [Gladstone D et al. ISC 2013 (abstr LB5)]	▪ RCT of 572 patients with cryptogenic stroke without known AF to 30-day ECG monitoring post stroke vs repeat Holter ▪ Endpoint: AF≥30 seconds within 90 days	▪ AF ≥30 seconds: 30-day ECG vs Holter, 16% vs 3% (p<0.001) ▪ 71% with newly detected AF on anticoagulants at 90 days ▪ Anticoagulation at 90 days greater in 30-day vs Holter groups (p=0.01)
CRYSTAL AF [Bernstein RA et al. ISC 2014]	▪ RCT of 441 patients with cryptogenic stroke to ICM vs standard cardiac monitoring ▪ Endpoint: Detection of AF	▪ AF ≥30 seconds: ICM vs control, 30.0% vs 3.0% (HR, 8.78; 95% CI, 3.47–22.19; p<0.0001), at 36 months

AHRE=atrial high-rate episodes; AF=atrial fibrillation; AT=atrial tachyarrhythmia; ECG=electrocardiogram; ESVEA=excessive supraventricular ectopic activity; ICD=implantable cardioverter defibrillator; ICM=insertable cardiac monitor; RCT=randomized control trial; SCAF=subclinical atrial fibrillation; SE=systemic embolism; TIA=transient ischemic attack.

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Prof. Healey concluded that SCAF is common and is associated with an increased risk of stroke. However, the absolute risk of stroke and the relationship of SCAF with stroke are different than for clinical AF. The role of anticoagulation in SCAF is not known.

FAVORABLE RISK-BENEFIT PROFILE OF NEW ORAL ANTICOAGULANTS IN THE ELDERLY

Michael W. Rich, MD, Washington University School of Medicine, St. Louis, Missouri, USA, presented data on the use of novel oral anticoagulants (NOACs) in elderly patients with AF.

Compared with warfarin, dabigatran 110 mg [RE-LY; Connolly SJ et al. *N Engl J Med* 2009] and rivaroxaban [ROCKET-AF; Patel MR et al. *N Engl J Med* 2011] were noninferior for preventing stroke, while dabigatran 150 mg and apixaban [ARISTOTLE; Granger CB et al. *N Engl J Med* 2011] were superior. Major bleeding rates with dabigatran 150 mg and rivaroxaban were similar to warfarin but were significantly lower than warfarin with dabigatran 110 mg and apixaban. Intracranial hemorrhage was significantly lower with either of the dabigatran doses, rivaroxaban and apixaban when compared to vitamin K antagonist therapy. Subgroup analyses showed no increase in bleeding with rivaroxaban [Goodman SG et al. *J Am Coll Cardiol* 2014] or apixaban [Halvorsen S et al. *Eur Heart J* 2014] among elderly patients. Bleeding complications increased with dabigatran in patients with reduced renal function [Hijazi Z et al. *Circulation* 2014].

In the WOEST trial [Dewilde WJM et al. *Lancet* 2013], patients on oral anticoagulation undergoing PCI were randomized to clopidogrel alone or clopidogrel versus acetylsalicylic acid. At 1 year, any bleeding occurred in 19.4% of patients on double therapy versus 44.4% on triple therapy (HR, 0.36; 95% CI, 0.26 to 0.50; p<0.0001). Death or cardiac event rates were lower with double therapy (HR, 0.60; 95% CI, 0.38 to 0.94; p=0.025).

NOACs have a favorable risk-benefit profile versus warfarin in elderly patients with AF. Existing data suggests that double therapy with clopidogrel and an anticoagulant may be safer than triple therapy with similar efficacy. The decision to use anticoagulants in older patients must be individualized.

STROKE PREVENTION IN ELDERLY PATIENTS

Randall J. Lee, MD, University of California, San Francisco, San Francisco, California, USA, discussed the evidence for using anticoagulation versus an implanted device in elderly patients with AF. Stroke resulting from thrombus formation in the left atrial apendage (LAA) is the most threatening consequence of AF. The primary preventive therapy is anticoagulation. The most commonly used anticoagulant is warfarin, which is not optimal due to its narrow therapeutic window, low compliance, contraindications, and increased risk in the elderly.

The NOACs are noninferior or superior to warfarin for preventing stroke and generally are associated with comparable or lower rates of bleeding.

LAA closure is another option for stroke prevention in patients with AF. The PROTECT-AF trial [Holmes DR et al. *Lancet* 2009] demonstrated noninferiority of the implanted Watchman device compared with warfarin for stroke prevention but periprocedural complications were more frequent than warfarin adverse events.

The LARIAT device is a snare with a pretied suture that is guided epicardially over the LAA. The PLACE II trial [Bartus K et al. *J Am Coll Cardiol* 2013] demonstrated LAA closure with the LARIAT device and no device-related complications. Adverse events included access-related complications (3%), unexplained sudden deaths (2%) and pericardial effusion (1%) but no bleeding.

Dr. Lee concluded that the initial embolic risks and adverse events associated with Watchman device implantation may not outweigh the long-term bleeding risks of NOACs. Observational studies of the Lariat device are promising but randomized trials have not been conducted.

ABLATION FOR ATRIAL FIBRILLATION IN THE ELDERLY

Thomas M. Munger, MD, Mayo Clinic, Rochester, Minnesota, USA, discussed AF ablation versus atrioventricular node ablation (AVNA) with permanent pacemaker implantation in patients aged >75 years old. The 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society Consensus Statement on catheter and surgical ablation of atrial fibrillation [Calkins H et al. *Heart Rhythm* 2012] summarized the results of eight randomized studies on AF catheter ablation. At 1 year, ablation was superior to antiarrhythmic drugs or rate control (66% to 89% vs 9% to 58% freedom from AF).

A study of long-term outcomes of AF catheter ablation reported a 47% recurrence rate at 3 years [Wokhlu A et al. *J Cardiovasc Electrophysiol* 2010]. Univariate predictors for ablation failure included hypertension, diabetes, persistent pattern, family history, and large atria. In the MAZE III study [Stulak JM et al. *Ann Thorac Surg* 2007] of surgical ablation for AF, 64% of patients with paroxysmal AF and 62% of those with persistent AF were free from AF at 10 years post ablation. A wide variety of complications are associated with AF catheter ablation, including silent microemboli (7% to 38%) [Calkins H et al. *Heart Rhythm* 2012].

Results of AVNA trials in patients with AF are shown in Table 2.

Table 2. Atrioventricular Nodal Ablation Trials

Study	Design	Results
AVNA long-term survival [Ozcan C et al. *N Engl J Med* 2001]	▪ 350 AF patients with AVNA and PPM from 1990–1998 ▪ 2 control groups: age and sex-matched controls; AF patients on drug therapy ▪ Endpoint long-term survival compared with age and sex-matched controls ▪ Mean follow-up 37±27 months	▪ Overall survival significantly worse than expected (p<0.001) ▪ Survival in patients without underlying heart disease similar to expected survival (p=0.43)
AVNA in AF [Chatterjee N et al. *Circ Arrhythm Electrophysiol* 2012]	▪ Efficacy review (meta-analysis): 5 studies, 314 patients ▪ Effectiveness review (pooled outcomes, observational studies): 11 studies, 810 patients ▪ Safety review: 47 studies, 5632 patients ▪ AVNA vs drug therapy	▪ Efficacy (reduced EF): significant EF increase with AVNA (+4%; 95% CI, 3.11–4.89) ▪ Efficacy (normal EF): no significant change in EF (−2.07%; 95% CI, −7.95 to 3.81) ▪ Effectiveness (reduced EF): significant EF increase after AVNA (+7.44%; 95% CI, 5.40–9.48) ▪ Effectiveness (normal EF): no significant change in EF (+1.94%; 95% CI, −2.90 to 6.77%) ▪ Safety: procedural death, 0.27%; left-sided ablation, 6.9%; re-do ablation, 2.9%; lead failure, 0.23%; stroke, 0.19%; SCD at 30 months, 2.1%
AVNA meta-analysis [Ganesan AN et al. *J Am Coll Cardiol* 2012]	▪ Patients with CHF and AF receiving CRT ▪ AVNA vs rate-controlling drugs	▪ All-cause mortality: significant reduction with AVNA (RR, 0.42; 95% CI: 0.26–0.68; p<0.001)
CERTIFY study [Gasparini M et al. *JACC Heart Fail* 2013]	▪ CRT outcomes in AF patients with AVNA or rate-slowing drugs ▪ Control: patients in SR ▪ Endpoint, total mortality	▪ Total mortality, AF + AVNA vs control: (HR, 0.93, 95% CI, 0.74–1.67) ▪ Total mortality, AF + drugs vs AF + AVNA and control: (HR, 1.52, 95% CI, 1.26–1.82; p<0.001)

AF=atrial fibrillation; AVNA=atrioventricular nodal ablation; CHF=congestive heart failure; CRT=cardiac resynchronization therapy; EF=ejection fraction; PPM=permanent pacemaker; SCD=sudden cardiac death.

According to Dr. Munger, virtually no studies have compared AF ablation and AVNA ablation. There is a need for head-to-head trials and ablation registry studies, especially in the elderly. Future studies should include single procedure results, primary outcomes of freedom from AF without antiarrhythmic drugs, AF burden assessment at various points, and cost analyses.