Aspirin to Prevent Stroke in AF Not Supported by Data

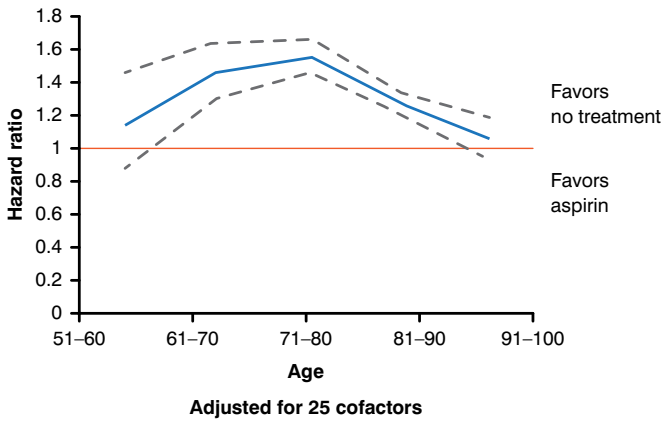
Written by Wayne Kuznar

Leif Friberg, MD, PhD, Karolinska Institute, Stockholm, Sweden, laid out an argument in favor of an oral anticoagulant (OAC) over aspirin for stroke prevention in patients with atrial fibrillation (AF), even among older patients.

The reluctance to use anticoagulants with patients with AF dates back to the 1980s, said Prof. Friberg, when the risk was perceived to be too high in large segments of the population, even in patients with mitral stenosis. During this same period, the utility of aspirin to prevent myocardial infarction was being discovered [Seshasai SR et al. *Arch Intern Med* 2012], and this utility was routinely extrapolated to include stroke prevention by AF as a milder alternative to OACs. The use of aspirin by patients with AF was bolstered by a meta-analysis of a series of small studies, most enrolling <1200 patients, showing it to be superior to placebo in reducing stroke risk in AF. The largest of these studies, the United Kingdom Transient Ischaemic Attack Aspirin trial, in which 2435 patients were enrolled, found no significant effect of aspirin compared with placebo, and a trend toward a negative effect of aspirin on fatal stroke. None of the individual trials, except for the Stroke Prevention in Atrial Fibrillation study [SPAF], achieved significance in favor of aspirin, he noted. Overall, there was no significant effect of aspirin when disabling or fatal strokes were counted.

An analysis of all individuals with a diagnosis of AF from 2005 to 2008 in the National Swedish Patient register, of whom 58,671 were treated with aspirin as monotherapy and 56,514 received no antithrombotic treatment, found no benefit with aspirin in preventing thromboembolism or ischemic stroke, with a mean follow-up of 1.5 years, compared with no treatment [Själander S et al. *Europace* 2014]. Patients on aspirin were older and had more comorbidities, but adjustment for cofactors did not change the results (Figure 1).

Figure 1. Adjusted Rates of Thrombembolism by Aspirin Treatment or No Treatment



Reproduced from Själander S et al. Atrial fibrillation patients do not benefit from acetylsalicylic acid. *Europace* 2014;16:631–638. With permission from the European Society of Cardiology.

A reanalysis of 12 randomized controlled trials found no protective effect of aspirin on ischemic stroke after age 75 years [van Walraven C et al. *Stroke* 2009]. The Copenhagen AFASAK (aspirin vs warfarin standard dose) study found more bleeding events in warfarin-treated patients with AF than in those treated with aspirin, but the warfarin group spent only 42% of the time in the therapeutic range (TTR), defined as an international normalized ratio (INR) of 2.8 to 4.2. The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events trial [ACTIVE W] found that the TTR has to be >65% for warfarin to be superior to aspirin in preventing stroke in AF [The ACTIVE Writing Group. *Lancet* 2006]. This finding is confirmed in the Birmingham Atrial Fibrillation Treatment of the Aged Study, in which patients had a mean age of 81.5 years; their TTR was 67%, with a target INR of 2.0 to 3.0 [Mant J et al. *Lancet* 2007].

Among the new OACs, no significant difference in the rate of major bleeding events was found between apixaban and aspirin [Connolly SJ et al. *N Engl J Med* 2011], noted Prof. Friberg.

These data led the European Society of Cardiology to advise against the use of aspirin for the management of AF and to use anticoagulation in appropriately selected patients at risk for embolic stroke [Camm AJ et al. *Europace* 2012].

RFA or Antiarrythmic Drug Therapy for Symptomatic AF?

Written by Jill Shuman

Radiofrequency ablation (RFA) has emerged as an effective therapy for patients with paroxysmal atrial fibrillation (PAF) [Stabile G et al. *Eur Heart J* 2006], and at least 1 international consensus document concludes that ablation is an acceptable first option for patients with symptomatic PAF [Caulkins H et al. *Europace* 2012]. However, limited data are available comparing this technology with antiarrhythmic drug (AAD) therapy as first-line treatment for patients with PAF.

Jens Cosedis Nielsen, MD, Aarhus University Hospital, Skejby, Denmark, reported 24-month outcomes from the Medical Antiarrhythmic Treatment or Radiofrequency

Ablation in Paroxysmal Atrial Fibrillation trial [MANTRA-PAF; Cosedis Nielsen J et al. *N Engl J Med* 2012]. The trial was designed to compare the efficacy of RFA with AADs in relatively young male symptomatic patients [Jons C et al. *Europace* 2009]. Eligibility criteria included ≥2 symptomatic episodes of AF with an indication for rhythm control within the preceding 6 months and no episodes of AF lasting >7 days. Baseline characteristics of the patients are described in Table 1.

Table 1. Baseline Characteristics

Characteristic	Ablation (n=146)	Drug Therapy (n=148)
Age, years	56±9	54±10
Male sex	100 (68)	106 (72)
Medical history		
Hypertension	43 (29)	53 (36)
Previous stroke or TIA	6 (4)	5 (3)
Diabetes mellitus	6 (4)	10 (7)
Left atrial size, parasternal long axis, mm	40±6	40±5
Left ventricular ejection fraction, number		
>60%	116	121
40%-60%	29	26
NYHA functional class		
I	131	128
II	15	19
III	0	1
$CHADS_2$ score		
0	92	80
1	37	49

Values in n (%) or mean±SD.
NYHA=New York Heart Association; TIA=transient ischemic attack.

A total of 294 patients were randomly assigned to undergo first-line treatment of catheter ablation (n=146) or medical therapy (n=148) [Cosedis Nielsen J et al. *N Engl J Med* 2012]. The preferred medical agents were flecainide or propafenone. If these 2 were contraindicated, patients could receive either amiodarone or sotalol. Follow-up included 7-day Holter monitoring at 3, 6, 12, 18, and 24 months. If drug therapy failed, patients were offered supplementary RFA as clinically indicated. The primary end points were the cumulative burden of AF (the percentage of time spent in AF) and the AF burden at each 7-day Holter recording; follow-up was completed in May 2011.

Table 2. Selected Serious Adverse Events

Event	Number of Events	
	Ablation	Drug Therapy
Death	3	4
Stroke	1	0
Pulmonary vein stenosis	1	0
Tamponade	3	0
Pericardial effusion, no puncture	0	1
Atrial flutter or atrial tachycardia	3	3
Bradycardia with the need for a cardiac pacemaker	0	1

Dr. Nielsen reported that at 2 years, there was no significant cumulative difference between the 2 treatment groups in either cumulative AF burden or that at 7-day Holter monitoring. In both groups, the burden of AF was significantly lower at each follow-up than at baseline ($p<0.001$ for all comparisons). The only significant difference reduction in AF burden was noted in the ablation group at 24 months ($p=0.007$). Twenty patients in the RFA group and 16 patients in the AAD group suffered adverse events, which was not significantly different ($p=0.45$; Table 2).

Dr. Nielsen then turned to a comparison of the costs for each procedure. Data from MANTRA-PAF were analyzed to determine the cost-effectiveness of RFA compared with medical therapy as a first-line treatment for PAF [Aronsson A et al. *Eur Heart J* 2013]. While RFA was associated with some clinical improvement in the overall population, the benefits occurred primarily in the youngest quartile of patients. RFA was almost cost neutral in patients aged ≤50 years as compared with patients aged >50 years. For example, the incremental cost-effectiveness ratio for a 45-year-old patient was €3434 per quality-adjusted life year (QALY) gained, compared with €108,937 per QALY gained for patients aged >65 years.

Dr. Nielsen closed his presentation with some caveats. It may be that no differences were noted in the 2 groups because RFA techniques have improved since the study began. Additionally, it is important to remember that RFA should be used only for patients with symptomatic AF and that RFA does carry a risk of serious adverse events. Perhaps most important is that the relatively young patients in this trial do not represent the true AF cohort in the population and that the results should not be extrapolated to the broader (older) population with AF.