Improving outcomes in patients with atrial fibrillation: Rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial

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Background Even on optimal therapy including anticoagulation and rate control, major cardiovascular complications (stroke, cardiovascular death, and acute heart failure) are common in patients with atrial fibrillation (AF). Conceptually, maintenance of sinus rhythm could prevent adverse outcomes related to AF. Rhythm control therapy has been only moderately effective in published trials, and its potential benefit was offset by side effects of repeated interventions.

Rationale Rhythm control therapy applied early after the first diagnosis of AF could preserve atrial structure and function and maintain sinus rhythm more effectively than the current practice of delayed rhythm control (when symptoms persist after otherwise effective rate control). Furthermore, catheter ablation and new antiarrhythmic drugs have enhanced the potential effectiveness and safety of rhythm control therapy. The EAST will test whether an early, modern rhythm control therapy can reduce cardiovascular complications in AF.

Design The EAST (Early treatment of Atrial fibrillation for Stroke prevention Trial) will randomize approximately 3,000 patients with recent onset AF at risk for stroke (CHA_2DS_2VASc score ≥ 2) to either guideline-mandated usual care or to usual care plus early rhythm control therapy in a prospective, randomized, open, blinded outcome assessment trial. All patients will be followed up until the end of the trial for the composite primary outcome of cardiovascular death, stroke, worsening of heart failure, and myocardial infarction. Nights spent in hospital will be counted as a coprimary outcome. Usual care will consist of anticoagulation, therapy of underlying heart disease, and rate control as an initial approach. Early rhythm control therapy will consist of usual care plus rhythm control therapy by antiarrhythmic drugs, catheter ablation, and a patient-operated electrocardiographic device to monitor the ongoing rhythm. Key secondary outcomes include cognitive function and quality of life.

Conclusion EAST will determine whether rhythm control therapy, when applied early after the initial diagnosis of AF, can prevent cardiovascular complications associated with AF. (Am Heart J 2013;166:442-8.)

Atrial fibrillation (AF) is the most common sustained arrhythmia in man. In addition to causing discomfort and reduced quality of life in affected patients, AF is associated with approximately every fifth stroke, causes unplanned cardiovascular hospitalizations, and is associated with an increased mortality, independent of other known cardiovascular diseases and risk factors.[1-4] To prevent these complications, to improve the impaired prognosis of patients with AF, and to alleviate suffering, patients with AF receive therapy for concomitant cardiovascular diseases, anticoagulation, and rate control therapy.

Recent developments have refined the management of AF, including the introduction of new fixed dose oral anticoagulants[5-8] and more lenient targets for rate control therapy.[9] Furthermore, vernakalant and dronedarone have been introduced as new antiarrhythmic drugs in Europe, the safe and effective use of "older" antiarrhythmic drugs flecainide[10] and amiodarone[11] has been reinforced in recent trials, and catheter ablation has emerged as an additional rhythm control intervention.[12-15] These findings

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Table I. Annualized rates of stroke, death, and myocardial infarction in >90,000 patients enrolled in controlled trials in atrial fibrillation in the past decade

Trial	No. of patients	Stroke		Death		Myocardial infarction	
		Active group	Comparator	Active group	Comparator	Active group	Comparator
Trials of antithrombotic therapy							
ACTIVE W[19]	6700	2.4	1.4	4	4	0.88	0.55
AMADEUS[20]	4576	0.9	1.3	3.2	2.9	0.8	0.6
ARISTOTLE[7]	18201	1.3	1.6	3.5	3.9	0.5	0.5
AVERROES[8]	5600	0.9	2.5	3.4	4.4	0.7	0.8
RE-LY[5]	18113	1	1.6	3.6	4.1	0.7	0.5
ROCKET AF[6]	14117	2.1	2.4	1.9	2.2	1	1.1
SPORTIF III[21]	3410	1.6	2.3			1.1/0.6	
SPORTIF IV[22]	3922	1.6	1.2	3.6	3.8	1	1.4
Rate and rhythm control trials							
AF-CHF[11]	1376	1.8	1.8	1.8	1.8	9.5	
AFFIRM[23]	4060	1.2	1.2	5	5	5	
ANDROMEDA[24] (terminated early)	627			50	24		
ATHENA[25]	4628	1.2	1.8	2.8	3.4	1.5	2.1
EURIDIS/ADONIS[26]	1237	0.5	0.7	1	0.7		
Flec-SL[10]	635			0	0		
PAFAC[27]	848			1.3			
PALLAS[28]	3236	4.4	1.9	4.7	2.4	0.6	0.4
RACE[29]	522	3.3		3.4			
RACE II[9]	614	1.6	3.9	5.6	6.6		
SAFE-T[30]	665	2	2	4.4	2.8		
SOPAT[31]	1012			1			
Sum	93766	1.5	1.7	3.5	3.5	1.0	0.7

All event rates are given as percentage per year. Although there has been clear improvement in major cardiovascular outcomes in recent trials, including reduced stroke rates, the overall event rate is still high, and mortality seems almost unaltered even in the most recent trials.

are reflected in new and updated practice guidelines for AF in Europe, the United States, and Canada.[13,16-18]

Unmet needs in the management of AF

Even in controlled trials, there is a relevant residual stroke rate in AF patients on optimal anticoagulant therapy (1.5% per year). In addition, 1% of AF patients experience myocardial infarction each year, 3.5% per year die, often of cardiovascular cause, and 4% to 5% suffer from acute decompensation of heart failure in clinical trials (Table I). Furthermore, all available therapies for AF convey risks, for example, bleeding caused by anticoagulants, proarrhythmia caused by antiarrhythmic drugs, bradycardia caused by rate controlling agents, and procedural complications induced by catheter ablation of AF.

Rationale for the EAST trial

Can rhythm control therapy improve outcomes in AF patients?

At present, rhythm control therapy, although potentially capable of eliminating the arrhythmia, is only recommended to alleviate AF-related symptoms,[13,16-18] based on 6 trials comparing the outcomes in patients receiving rhythm control added to rate control therapy to another group receiving rate control therapy alone.[11,29,32-36]

The practice of discontinuing oral anticoagulant therapy in patients with documented sinus rhythm and the limited effectiveness of rhythm control therapy in an era before catheter ablation were important limitations of rhythm control therapy in those trials.[11,32,36-38]

In the ATHENA trial, the antiarrhythmic agent dronedarone reduced the primary outcome of unplanned cardiovascular hospitalizations or all-cause death by 24% compared with placebo (Table I[25]) and reduced stroke and cardiovascular death in secondary, hypothesis-generating analyses.[25,39] To test whether the rate-controlling and/or other effects of dronedarone (rate control, ventricular antiarrhythmic, stroke prevention, blood pressure lowering, or coronary vasodilation) could have mediated the benefits found in ATHENA, the PALLAS trial tested dronedarone in patients with permanent AF (Table I[28]). PALLAS was terminated early because of increased deaths, strokes, and heart failure hospitalizations in patients receiving dronedarone. Taken together, these trials and the prior EURIDIS/ADONIS[26] and ANDROMEDA[24] trials suggest that the benefits of dronedarone in ATHENA were conveyed largely by a long-term atrial rhythm control effect of dronedarone.[25,26] In addition, recent analyses of claims data suggest that rhythm control therapy may be associated with less strokes[40] and even less deaths[41] in the long term, albeit in a nonrandomized setting prone to confounders. Taken together, these data indirectly support the hypoth-