

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

Kirchhof P, et al; EAST-AFNET 4 Trial Investigators. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. N Engl J Med. 2020 Oct 1;383(14):1305-1316. doi: 10.1056/NEJMoa2019422. Epub 2020 Aug 29. PMID: 32865375.

BACKGROUND																																																					
Background	<ul style="list-style-type: none"> Patients with atrial fibrillation are at a higher risk of acute stroke, acute coronary syndrome (ACS), heart failure, and cardiovascular (CV) death compared to patients without atrial fibrillation. Approximately 35-50% of patients with atrial fibrillation require inpatient therapy or die within 5 years despite being on adequate anticoagulation. Currently, it is unclear if rate or rhythm control is superior, especially in newly diagnosed patients. 																																																				
Previous Articles	<ul style="list-style-type: none"> Wyse DG, et al. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002 Dec 5;347(23):1825-33. doi: 10.1056/NEJMoa021328. PMID: 12466506. Hohnloser SH, et al.; ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med. 2009 Feb 12;360(7):668-78. doi: 10.1056/NEJMoa0803778. Erratum in: N Engl J Med. 2009 Jun 4;360(23):2487. Erratum in: N Engl J Med. 2011 Apr 14;364(15):1481. PMID: 19213680. Nattel S, et al. Early management of atrial fibrillation to prevent cardiovascular complications. Eur Heart J. 2014 Jun 7;35(22):1448-56. doi: 10.1093/eurheartj/ehu028. Epub 2014 Feb 16. PMID: 24536084. 																																																				
GENERAL OVERVIEW																																																					
Funding	German Ministry of Education and Research																																																				
Trial design	International, investigator-initiated, parallel-group, open, randomized, blinded-outcome-assessment trial																																																				
Objective	To determine whether a strategy of early rhythm-control therapy (including atrial fibrillation ablation) would be associated with better outcomes in patients with early atrial fibrillation than evidence-based usual care																																																				
METHODS																																																					
Inclusion	Adults with early atrial fibrillation > 75 years old, had a previous transient ischemic attack or stroke, or met two of the following criteria: > 65 years old, female, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease, or left ventricular hypertrophy																																																				
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Statistical analyses	<ul style="list-style-type: none"> Two primary outcomes tested independently Calculated the need for 685 events to show a 20% difference in the event rate for the first primary outcome with a power of 80% Number of patients needed calculated to be 2745 Second primary outcome calculated as the observed sum of nights in the hospital divided by the individual follow-up time 																																																				
RESULTS																																																					
Enrollment period	<pre> graph LR A[2789 135 sites in 11 countries] --> B[1395 early rhythm control] A --> C[1394 usual care] B --> D[1395 included in analysis] C --> E[1394 included in analysis] </pre>																																																				
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Baseline characteristics (%)	Characteristic	Early Rhythm Control N = 1395	Usual Care N = 1394
	Age - yr		70.2±8.4
Female		46.2%	46.5%
Type of atrial fibrillation			
- First episode		38.0%	37.3%
- Paroxysmal		36.0%	35.4%
- Persistent		26.0%	27.3%
Sinus rhythm at baseline		54.9%	53.3%
Median days since atrial fibrillation diagnosis		36.0	36.0
Previous cardioversion		40.0%	39.1%
Previous stroke or TIA		12.5%	11.0%
Blood pressure (mmHg)		136.5±19.4	137.5±19.3
Stable heart failure		28.4%	28.8%
CHAD ₂ DS ₂ -VASc score		3.4±1.3	3.3±1.3
Valvular heart disease		43.8%	46.2%
Medication at discharge			
- Oral anticoagulation		91.2%	89.7%
- Digoxin		3.3%	6.1%
- Beta-blocker		76.2%	85.5%
- Platelet inhibitor		16.5%	16.2%
- Statin		45.2%	40.8%

Summary of outcomes	End Point	Early Rhythm Control	Usual Care	Hazard Ratio (CI)
	Primary Outcomes			
First primary outcome - incidence/100 person-yr		3.9	5.0	0.79 (0.66 to 0.94)
- Death from CV causes		1.0	1.3	0.72 (0.52 to 0.98)
- Stroke		0.6	0.9	0.65 (0.44 to 0.97)
- Hospitalization with worsening HF		2.1	2.6	0.81 (0.65 to 1.02)
- Hospitalization with ACS		0.8	1.0	0.83 (0.58 to 1.19)
Second primary outcome - nights in hospital/yr		5.8±21.9	5.1±15.5	1.08 (0.92 to 1.28)
Secondary Outcomes				
Change in LVEF		1.5±9.8	0.8±9.8	0.23 (-0.46 to 0.91)
Change in EQ-5D score		-1.0±21.4	-2.7±22.3	1.07 (-0.68 to 2.82)
Sinus rhythm		82.1%	60.5%	3.13 (2.55 to 3.84)
Asymptomatic		74.3%	72.6%	1.14 (0.93 to 1.40)
Safety Outcomes and Adverse Events				
Primary composite safety outcome		16.6%	16.0%	
- Stroke		2.9%	4.4%	
- Death		9.9%	11.8%	
- Serious AE related to rhythm-control therapy		4.9%	1.4%	
Hospitalization for atrial fibrillation		0.8%	0.2%	
Drug-induced bradycardia		1.0%	0.4%	

AUTHOR'S CONCLUSIONS

The strategy of initiating rhythm-control therapy in all patients with early atrial fibrillation and concomitant CV conditions was associated with a lower risk for composite of death from CV causes, stroke, or hospitalization for heart failure or ACS when compared to usual care. No difference was found in the number of nights spent at the hospital/year, which was contrasting to previous studies indicating rhythm control led to excess hospitalizations. Previous studies have not shown a better outcomes when comparing rhythm control and rate control, but this study included atrial fibrillation ablation, which might have contributed to the superiority of early rhythm control.

DISCUSSION

Strengths	Randomized, no exclusions, baseline characteristics well matched, variety of antiarrhythmics, ~90% of patients on anticoagulation, majority were treated for CV comorbidities
Limitations	Open-label, not designed to assess the safety and effectiveness of specific components of early rhythm, only included patients with early atrial fibrillation, did not assess cost-effectiveness
Conclusion and Applicability	<ul style="list-style-type: none"> • Patients that are newly diagnosed with atrial fibrillation and are at a higher cardiovascular risk, would likely benefit from initiation with rhythm-control therapy rather than rate-control therapy • Rhythm-control associated with more adverse events related to therapy, but number of nights in hospital did not differ • AHA/ACC/HRS atrial fibrillation guidelines have not been updated since 2019 • Likely to change practice as rate-control is typically first line unless symptomatic