

# **EAST-AFNET4, Effects of Early Rhythm Control Therapies in Patients with Atrial Fibrillation**

Most strokes related to AF can be prevented with anticoagulation, and rate control often renders patients asymptomatic. In the classic AFFIRM trial comparing rhythm control with rate control, there were no significant differences between the two approaches

at 5 years with respect to mortality or ischemic stroke. **(Ref:1)** Given that rate control tends to be easier to achieve than rhythm control, it should be no surprise that slowing the heart rate became the most common initial therapy.

Yet even with guideline-based management, the rate of stroke, acute coronary syndrome, heart failure (HF),

or CV death is about 5% per year among patients with AF. Moreover, about one-third to one-half of patients with AF who receive adequate anticoagulation are either hospitalized or die within 5 years. That is a lot of morbidity and mortality for a condition with well-established therapies.

Risk of complications is highest during the first year after a diagnosis of AF,

and AF causes atrial damage within a few weeks of onset. Rhythm control is typically delayed unless patients have persistent symptoms on otherwise effective rate control. Given the combination of early risk and early damage, there may be a need to revisit the issue of early rhythm control. It just might reduce or prevent permanent damage, making it more effective.

## **EAST-AFNET 4**

The EAST-AFNET 4 trial investigated whether rhythm control therapy – with antiarrhythmic drugs or ablation – soon after diagnosis improves outcomes compared with usual care. Median time from diagnosis to randomization was 36 days.

A total of 2,789 patients with at least two CV conditions were enrolled from 135 sites in 11 European countries from 2011 to 2016. **(Ref:2)** Concomitant conditions included hypertension, stable HF, valvular heart disease, and chronic kidney disease. Patients were randomized to early rhythm control therapy or usual care.

Almost all patients (94.8%) who were randomly assigned to early rhythm control received an antiarrhythmic drug or underwent ablation, meaning only 5% of patients randomized to rhythm control did not receive rhythm control therapy.

Usual care patients received guideline-recommended therapy, including anticoagulation, but were initially

treated with rate control without rhythm control therapy. Rhythm control was used only to mitigate uncontrolled AF-related symptoms during adequate rate-control therapy (i.e., therapy that maintained the heart rate within guideline-recommended targets).

At 2 years, 65.1% of the early rhythm control group were still receiving rhythm-control therapy, while over the same



period, 85.4% of the usual care arm were still not receiving rhythm control therapy. The trial was stopped for efficacy at the third interim analysis after a median of 5.1 years of follow-up. On an intention-to-treat basis, the early rhythm control strategy was associated with a lower risk of CV outcomes than usual care among patients with early AF and multiple CV conditions (**Table**).

## EAST-AFNET 4: Early Rhythm Control in Patients with Atrial Fibrillation

	<b>Early Rhythm Control</b>	<b>Usual Care</b>	<b>Treatment Effect*</b>
First primary outcome†	3.9%	5.0%	0.79 (0.66-0.94)
Individual components			
CV death	1.0%	1.3%	0.72 (0.52-0.98)
Stroke	0.6%	0.9%	0.65 (0.44-0.97)
Hospitalization (worsening HF)	2.1%	2.6%	0.81 (0.65-1.02)
Hospitalization (ACS)	0.8%	1.0%	0.83 (0.58-1.19)
Nights spent in hospital/year‡	5.8 ± 21.9	5.1 ± 15.5	1.08 (0.93-1.28)

\*Expressed as the median unbiased estimate of the hazard ratio and 96% confidence interval.

†Composite of CV death, stroke, or hospitalization with worsening of HF or ACS.

‡Second primary outcome.

The individual components of the composite primary endpoint were all numerically lower with early rhythm control than with usual care. The authors analyzed 19 predefined subgroups based on variables such as obesity and whether patients did or did not have HF or were symptomatic or asymptomatic. The beneficial effect of early rhythm

control was largely consistent across all subgroups.

The mean number of nights spent in the hospital did not differ significantly between the groups. That is reassuring in view of the excess hospitalizations associated with rhythm control therapy in previous large trials.

As expected, the early rhythm control strategy was associated with more

adverse events related to the rhythm control therapy, but the incidence of the overall safety outcome events was similar.

## **AFFIRMed?**

How is it that these results varied significantly from the 5-year AFFIRM findings? In a commentary accompanying the EAST-AFNET 4

results, authors noted that it is important to remember that rhythm-based treatment for two-thirds of the AFFIRM patients consisted of amiodarone or sotalol. **(Ref:3)**

Also, 38% of the rhythm control arm in AFFIRM crossed over to rate control, primarily because of side effects or the poor efficacy of the drugs. Nevertheless, in a post hoc analysis, the presence of

sinus rhythm was significantly associated with a lower risk of death (hazard ratio, 0.53; 99% confidence interval: 0.39 to 0.72).**(Ref:4)**

Having said that, the strongest predictor of survival in AFFIRM was not the presence of sinus rhythm but the use of warfarin, which was continued in 70% of patients; ischemic strokes in either treatment group largely occurred in

patients in whom anticoagulation was withheld. Back when AFFIRM was conducted, it was common to stop anticoagulation after successful rhythm control.

In EAST-AFNET 4, the use of anticoagulation was common and continued over time (approximately 90% of patients in both groups at 2 years), and the incidence of stroke was



correspondingly low (0.6% of patients assigned to early rhythm control and 0.9% of patients assigned to usual care).

Authors concluded that timing matters, and the results of EAST-AFNET 4 support the use of early rhythm control to reduce adverse clinical outcomes related to AF.

According to the principal investigator of EAST-AFNET 4, all patients with newly diagnosed AF and concomitant CV conditions should be offered rhythm control therapy in addition to anticoagulation and rate control when it is needed to improve outcomes.

According to the PI of the trial , “Rhythm control therapy initiated soon after diagnosis of atrial fibrillation reduces

cardiovascular complications without increasing time spent in hospital and without safety concerns. These results have the potential to completely change clinical practice towards rhythm control therapy early after the diagnosis of atrial fibrillation.”

**Take-home Messages:**

- The risk of severe cardiovascular (CV) complications and death in patients with atrial fibrillation (AF) is highest in the first year after diagnosis, suggesting that early therapy could be most beneficial.
- The EAST-AFNET 4 trial demonstrated that early initiation of rhythm control therapy reduced CV outcomes in patients with early AF

and at least one other cardiovascular condition, without affecting nights spent in the hospital.

- These results have the potential to inform the future use of rhythm control therapy, further improving the care of patients with early AF.

## **COMMENT**

Rhythm control finally wins in minimally symptomatic or asymptomatic AF. Caveats: The rhythm-control strategy was initiated early, before atrial remodeling could occur; most participants remained on anticoagulation therapy; and relatively few participants underwent ablation (about 8% by 1 year, 20% by 2 years). This trial will not dramatically alter the

practice, but its findings and those from CABANA (JAMA 2019; 321:1261) and CASTLE-AF (N Engl J Med 2018; 378:417) show that normal sinus rhythm matters. Editorialists also note that this trial supports both early rhythm control and the comprehensive management with other cardiovascular therapies that participants received.

## **References:**

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- 3. Bunch TJ, Steinberg BA.** Revisiting Rate Versus Rhythm Control in Atrial Fibrillation: Timing Matters. *N Engl J Med* 2020;383:1383-4.
- 4. Corley SD, Epstein AE, DiMarco JP, et al.** Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm

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