Biomarkers predict early rhythm control benefit in AFib

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Early rhythm control strategies reduce cardiovascular events in patients with atrial fibrillation (AF) and comorbidities. But the consistency of this effect across varying severities of AF-associated conditions has remained unclear, leaving clinicians to wonder which patients benefit most from an aggressive approach. A new exploratory analysis from the EAST-AFNET 4 biomolecule study offers some clarity, identifying specific blood biomarkers that predict a greater treatment effect.

KEY TAKEAWAYS

- The Pivot: Early rhythm control's efficacy in AFib is not uniform; it is modulated by baseline levels of specific cardiac and inflammatory biomarkers.
- The Data: Patients with NT-proBNP in the highest quartile saw a 70% relative risk reduction (HR 0.30; 95% CI, 0.17-0.53; P<.001) in the primary outcome with early rhythm control.
- The Action: Consider baseline NT-proBNP and hs-cTnT levels when assessing the potential benefit of early rhythm control in AFib patients, particularly those with higher values.

Atrial fibrillation management has long debated the optimal timing for rhythm control. The EAST-AFNET 4 trial previously established that early rhythm control, initiated within one year of AF diagnosis, significantly reduced a composite primary outcome of cardiovascular death, stroke, hospitalisation for heart failure, or acute coronary syndrome in patients with AF and cardiovascular comorbidities.1 This benefit was observed irrespective of symptom severity or AF duration, challenging prior assumptions that a 'wait and see' approach was acceptable for less symptomatic patients.1 The current exploratory analysis, published in Europace, examined the interactions of early rhythm control with various blood biomolecules.1 Researchers from the German Centre for Cardiovascular Research (DZHK) and the University Medical Center Hamburg-Eppendorf, including lead author C. Al-Taie, aimed to determine if the treatment effect of early rhythm control varied based on baseline levels of specific biomarkers.1 The EAST-AFNET 4 trial enrolled 2,789 patients, randomising them to either early rhythm control or usual care.1 The biomolecule substudy included 2,076 patients with available baseline blood samples, representing a substantial cohort for this type of analysis.1

Biomarkers and the Primary Outcome

The analysis focused on the primary composite outcome of cardiovascular death, stroke, hospitalisation for heart failure, or acute coronary syndrome.1 Early rhythm control consistently reduced this outcome across all biomarker subgroups, but the magnitude of the benefit varied considerably.1 For instance, patients with baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in the highest quartile (≥000 pg/mL) experienced a pronounced reduction in the

primary outcome with early rhythm control, cutting the risk by 70% (HR 0.30; 95% CI, 0.17-0.53; P<.001).1 This effect was less pronounced, though still present, in the lowest NT-proBNP quartile (HR 0.73; 95% CI, 0.49-1.08; P=.11).1 High-sensitivity cardiac troponin T (hs-cTnT) also showed a significant interaction.1 Patients with hs-cTnT in the highest quartile (≥4 ng/L) saw a 56% reduction in the primary outcome (HR 0.44; 95% CI, 0.28-0.69; P<.001) with early rhythm control.1 In contrast, those in the lowest quartile (<6 ng/L) had a more modest 27% risk reduction (HR 0.73; 95% CI, 0.52-1.01; P=.06).1 These findings suggest that patients with higher baseline cardiac stress and injury markers derive a greater absolute benefit from early rhythm control, which aligns with the understanding that these markers reflect underlying cardiovascular disease burden.

Other biomarkers explored included high-sensitivity C-reactive protein (hs-CRP), growth differentiation factor 15 (GDF-15), and galectin-3.1 While early rhythm control generally reduced the primary outcome across all quartiles of these biomarkers, the interaction P-values for hs-CRP (P=.09), GDF-15 (P=.07), and galectin-3 (P=.06) did not reach statistical significance, indicating that the treatment effect did not differ significantly across their respective quartiles.1 This contrasts with the clear interaction observed for NT-proBNP and hs-cTnT, highlighting their specific utility in risk stratification for early rhythm control. For a deeper understanding of how systemic factors influence AF, consider our previous coverage on atrial fibrillation and cardio-kidney-metabolic risk.

Impact on Individual Components and Safety

The analysis also examined the effect of early rhythm control on individual components of the primary outcome.1 For cardiovascular death, early rhythm control reduced the risk by 48% (HR 0.52; 95% CI, 0.32-0.85; P=.009) in patients with NT-proBNP in the highest quartile.1 Similarly, hospitalisation for heart failure was reduced by 74% (HR 0.26; 95% CI, 0.12-0.54; P<.001) in this same group.1 These specific reductions make the point about the particular benefit for patients with elevated natriuretic peptides, which are well-established markers of heart failure severity.

But the study also noted that the interaction for stroke, while showing a trend, did not reach statistical significance (P=.13 for NT-proBNP interaction).1 This suggests that while early rhythm control is broadly beneficial, its impact on stroke risk may be less modulated by these specific biomarkers compared to its effect on heart failure hospitalisations or cardiovascular death. Clinicians often rely on comprehensive guides for managing complex cardiac conditions, and a resource like the Oxford Handbook of Cardiology can be invaluable for navigating these nuances.

The safety profile of early rhythm control, including serious adverse events related to antiarrhythmic drugs or ablation, did not show significant interactions with any of the tested biomarkers.1 This indicates that while the efficacy of early rhythm control varies, its safety risks remain consistent across different biomarker profiles. This is an important consideration, as clinicians must weigh both benefit and risk when initiating aggressive rhythm management strategies. The overall incidence of serious adverse events was low, at 1.5% per year in the early rhythm control group versus 0.9% per year in the usual care group, consistent with the main EAST-AFNET 4 trial findings.1

Where the Analysis Falls Short

This was an exploratory, post-hoc analysis of the EAST-AFNET 4 trial, which means the findings, while compelling, should be interpreted with caution.1 The study was not powered to detect differences in treatment effect within specific biomarker subgroups, and the P-values for interaction, while statistically significant for NT-proBNP and hs-cTnT, do not constitute definitive proof of differential efficacy.1 Future prospective trials specifically designed to stratify patients by

these biomarkers would be necessary to confirm these observations. Still, the consistency of the findings across multiple endpoints and the biological plausibility of the interactions lend considerable weight to the results.

The study population consisted of patients with recently diagnosed AF and cardiovascular comorbidities.1 Whether these biomarker interactions hold true for patients with long-standing AF, different comorbidity profiles, or those without significant structural heart disease remains an open question. The generalizability of these findings is therefore limited to a similar patient population. Also, the study did not explore the dynamic changes in biomarkers over time in response to early rhythm control, which could offer further insights into treatment response. For more on the complexities of AF management, our article on integrated pathways in atrial fibrillation provides additional context.

The analysis also did not account for all potential confounders or other biomarkers that might influence treatment effect.1 The choice of biomarkers was based on their known association with cardiovascular disease and AF, but other inflammatory or fibrotic markers could also play a role. The study provides a valuable step towards personalised AF management, but it is not the final word. The next step would be to see if these biomarkers can guide treatment selection in a randomised fashion, moving beyond observational associations to direct clinical utility. Understanding the nuances of AF ablation, for example, requires considering more than just AF type, as discussed in our piece AFib ablation: Stop assuming success based on AFib type alone.

CLINICAL IMPLICATIONS

This exploratory analysis from EAST-AFNET 4 offers a practical lens through which to view early rhythm control in atrial fibrillation. The data indicates that patients with higher baseline NT-proBNP and hs-cTnT levels are precisely the ones who stand to gain the most from an aggressive rhythm strategy. This is not a subtle effect; a 70% relative risk reduction in the highest NT-proBNP quartile is substantial.

Clinicians should consider these biomarkers not just as diagnostic or prognostic tools, but as potential guides for treatment intensity. For patients presenting with AF and elevated NT-proBNP or hs-cTnT, an early rhythm control approach appears particularly warranted, shifting the conversation from a blanket recommendation to a more stratified one. This moves us closer to truly personalised medicine in cardiology.

The implication for guideline developers is clear: incorporate these biomarker thresholds into future recommendations for AF management. While this was an exploratory analysis, the consistency and magnitude of the effect for these specific markers are difficult to ignore. It suggests that a simple blood test could help identify a subgroup of patients who will derive disproportionate benefit from early intervention.

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