



Early Rhythm Control in Atrial Fibrillation: Reconciling Trial Populations with Clinic Populations

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Received: 07 January 2023; Accepted: 28 April 2023; Published: 29 September 2023

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Abstract

EAST-AFNET 4 established that starting rhythm control -- antiarrhythmic drugs or ablation -- within a year of an atrial fibrillation diagnosis reduces the composite risk of cardiovascular death, stroke, and hospitalisation for heart failure or acute coronary syndrome, in a trial of 2,789 patients with early AF plus cardiovascular risk factors (hazard ratio 0.79). A natural objection to any trial result is that the patients enrolled do not resemble the patients seen in an ordinary clinic. A UK Biobank analysis addressed this directly and found the objection largely does not hold: 80.9% of participants with incident atrial fibrillation would have met EAST-AFNET 4's eligibility criteria, and eligible patients experienced a similar treatment benefit (hazard ratio 0.82) to the trial itself. But a separate real-world analysis of two large cohorts -- 109,739 US claims patients and 11,625 UK Biobank patients -- stratified by comorbidity burden found something more specific: a statistically significant benefit of early rhythm control appeared only in patients with a higher comorbidity burden (CHA2DS2-VASc ≥ 4), not in patients with a lower burden (CHA2DS2-VASc 2-3), in both cohorts independently. This review sets out the trial result, the generalizability finding that broadly supports it, and the comorbidity-stratified finding that narrows it: eligibility for early rhythm control is broad, but the population in whom a real-world benefit signal has actually been demonstrated is narrower than eligibility alone would suggest.

Keywords: Atrial fibrillation; Early rhythm control; EAST-AFNET 4; Generalizability; Comorbidity burden

Introduction

EAST-AFNET 4 gave early rhythm control -- antiarrhythmic drug therapy or catheter ablation started within a year of an atrial fibrillation diagnosis -- one of the clearer positive trial results in this disease area in a decade: a 21% relative reduction in the composite risk of cardiovascular death, stroke, and hospitalisation for heart failure or acute coronary syndrome, in a trial that enrolled 2,789 patients across 135 European sites [1]. Trial results in atrial fibrillation, as in most of cardiology, invite a standing objection: the patients a clinic

sees day to day are not the patients a trial recruits, and a treatment effect measured in the latter may simply not apply to the former.

This review sets out the EAST-AFNET 4 result itself, a UK Biobank analysis built specifically to test whether that generalizability objection holds for this trial, and a further comorbidity-stratified real-world analysis that complicates the reassuring answer the first analysis provides.

Material and Methods

This is a narrative review of the EAST-AFNET 4 primary trial publication, a subsequent UK Biobank generalizability analysis applying the trial's own eligibility criteria to a population-based cohort, and a comorbidity-stratified real-world outcomes analysis across two independent large cohorts, identified through the sources cited above and citation tracking between them, without a pre-registered protocol or systematic search string. All percentages, hazard ratios, and confidence intervals reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated.

Results

EAST-AFNET 4 showed a clear composite benefit for early rhythm control

EAST-AFNET 4 randomised 2,789 patients with early atrial fibrillation (median 36 days since diagnosis) plus at least one cardiovascular risk factor to early rhythm control or usual care, and eligibility required either age over 75, prior stroke or transient ischaemic attack, or two or more additional risk factors from a defined list [1]. The enrolled population had a mean age of 70 years, was 46% female, carried a mean CHA2DS2-VASc score of 3.4, and was already in sinus rhythm in 54% of patients at randomisation, with first-episode AF in 38%, paroxysmal AF in 36%, and persistent AF in the remaining 26% [1]. Figure 1 profiles this enrolled population across five axes at once. The primary composite outcome -- cardiovascular death, stroke, or hospitalisation for worsening heart failure or acute coronary syndrome -- occurred at a rate of 3.9 events per 100 patient-years with early rhythm control versus 5.0 with usual care, a hazard ratio of 0.79 (96% CI 0.66-0.94, $p=0.005$) [1]. Figure 2 sets the primary result out against its individual components: cardiovascular death (HR 0.72), stroke (HR 0.65), heart-failure hospitalisation (HR 0.81), and acute coronary syndrome hospitalisation (HR 0.83) all moved in the same protective direction, while a secondary outcome -- nights spent hospitalised per year -- showed no difference (5.8 versus 5.1 nights, $p=0.23$) [1].

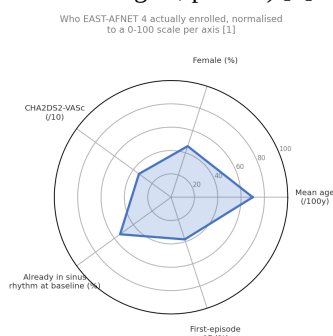


Figure 1: Baseline profile of the EAST-AFNET 4 enrolled population across five characteristics, normalised to a 0-100 scale per axis [1].

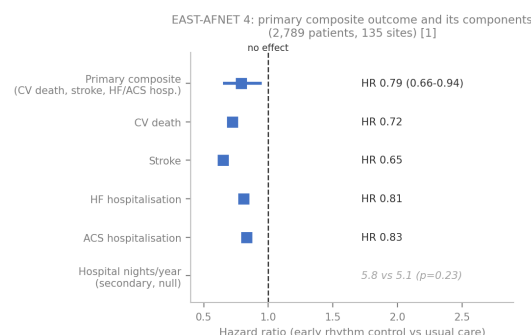


Figure 2: EAST-AFNET 4 primary composite outcome and its individual components, hazard ratios with 96% confidence interval where reported [1].

A UK Biobank analysis found most real-world AF patients would have met trial eligibility

The most direct way to test whether EAST-AFNET 4's eligibility criteria exclude most real-world AF patients is to apply those criteria to a population-based cohort and count. A 2022 analysis did exactly that using UK Biobank: of 502,493 total participants, 35,526 (7.1%) carried an AF diagnosis, and of the 27,186 participants with incident AF, 22,003 -- 80.94% -- met EAST-AFNET 4's eligibility criteria [2]. Figure 3 traces this cascade from the full cohort down to the eligible subset. This is a materially reassuring finding on its own: the trial's inclusion criteria, built around age, prior stroke, and a short list of cardiovascular risk factors, capture the large majority of a real-world AF population rather than a narrow, atypical slice of it, and the eligible subgroup showed a comparable treatment benefit (HR 0.82) to the trial itself [2]. Eligible and ineligible patients were not, however, identical: eligible patients were on average older (70 versus 63 years) and more often female (42% versus 21%) than those the criteria excluded [2]. Figure 4 sets these two differences out directly.

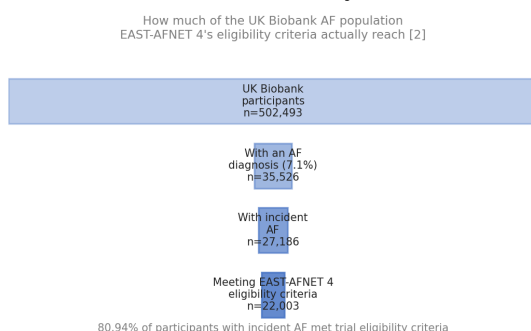


Figure 3: Cascade from the full UK Biobank cohort to the subset meeting EAST-AFNET 4 eligibility criteria [2].

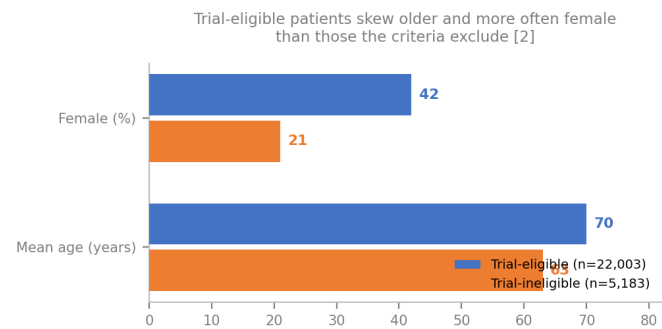


Figure 4: Baseline age and sex differences between trial-eligible and trial-ineligible UK Biobank participants with incident atrial fibrillation [2].

A comorbidity-stratified analysis narrows where the real-world benefit signal actually sits

A separate 2023 analysis approached the generalizability question from a different angle: rather than asking how many real-world patients would have qualified for the trial, it asked whether the treatment benefit itself holds across the full range of comorbidity burden those eligible patients actually carry. Using two independent large real-world cohorts -- 109,739 patients from US claims data (OptumLabs) and 11,625 patients from UK Biobank -- and stratifying by CHA2DS2-VASc score, this analysis found a statistically significant benefit of early rhythm control only in patients with a higher comorbidity burden (CHA2DS2-VASc ≥4): hazard ratio 0.83 in OptumLabs (95% CI 0.72-0.95, p=0.006) and 0.77 in UK Biobank (95% CI 0.63-0.94, p=0.009) [3]. In patients with a lower comorbidity burden (CHA2DS2-VASc 2-3), the point estimates moved in the same direction but were not statistically significant in either cohort: hazard ratio 0.92 in OptumLabs (p=0.767) and 0.94 in UK Biobank (p=0.310) [3]. Figure 5 plots this split for both cohorts side by side, and Figure 6 ties it back to the eligibility cascade from the previous section: broad trial eligibility and a demonstrated real-world benefit are not the same claim, and the second is narrower than the first. Neither cohort showed an excess of serious adverse events with early rhythm control at either comorbidity level [3].

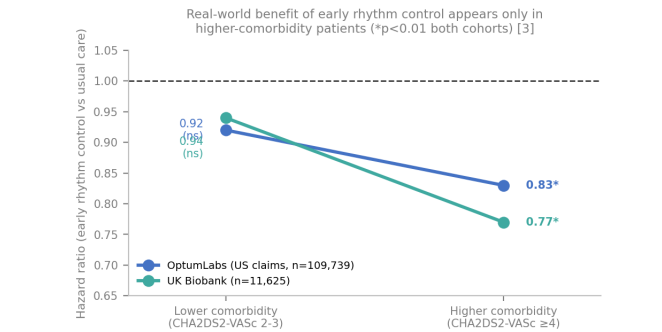


Figure 5: Hazard ratio for early rhythm control by comorbidity burden, plotted separately for two independent real-world cohorts [3].

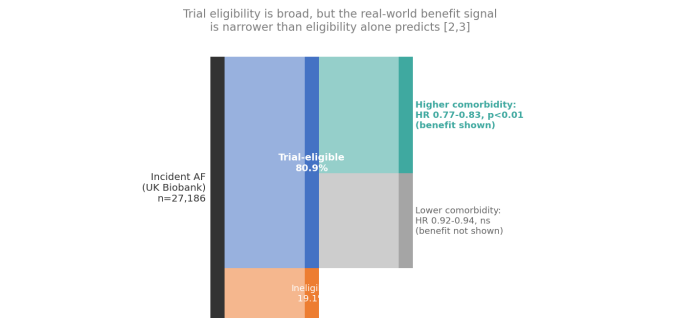


Figure 6: How broad trial eligibility (80.9%) relates to the narrower subgroup, within that eligible population, where a real-world benefit has actually been demonstrated [2,3].

Population / stratum	Hazard ratio (95%/96% CI)	Significant?
EAST-AFNET 4 trial (primary composite)	0.79 (0.66-0.94)	Yes, p=0.005
UK Biobank, trial-eligible subset	0.82	Yes
OptumLabs, CHA2DS2-VASc ≥4	0.83 (0.72-0.95)	Yes, p=0.006
UK Biobank cohort, CHA2DS2-VASc ≥4	0.77 (0.63-0.94)	Yes, p=0.009
OptumLabs, CHA2DS2-VASc 2-3	0.92	No, p=0.767
UK Biobank cohort, CHA2DS2-VASc 2-3	0.94	No, p=0.310

Table 1: Hazard ratios for early rhythm control across the trial and both real-world comorbidity strata [1-3].

Discussion

Taken together, these three sources answer the generalizability objection more precisely than either a simple defence ("the trial result applies broadly") or a simple dismissal ("trial patients aren't real patients") would allow. The eligibility question and the benefit question turn out to have different answers. On eligibility, EAST-AFNET 4's criteria are genuinely broad: four in five real-world patients with incident atrial fibrillation would have qualified, and among those who did, the treatment effect looked similar to the trial's own result [2]. On benefit, the picture across the full range of comorbidity those eligible patients carry is less uniform: a statistically significant advantage for early rhythm control has been demonstrated, independently, in two large real-world cohorts, specifically among patients with a higher comorbidity burden, while lower-comorbidity patients -- who make up a substantial share of any eligible population, since eligibility itself can be satisfied by age alone or by a smaller number of risk factors -- have not shown a significant benefit in either cohort [3].

This is not evidence that early rhythm control fails to help lower-comorbidity patients; both point estimates in that stratum still favoured treatment, and the trials and cohorts examined here were not necessarily powered to detect a smaller true effect in a lower-risk subgroup with fewer

competing events. It is, however, a reason to be precise about what "this trial generalizes" actually means in clinical terms: it means the enrolled population is broadly representative of who a clinic will see, not that the demonstrated real-world benefit currently extends with equal certainty across every comorbidity level within that eligible population. A clinician deciding how strongly to recommend early rhythm control to a lower-comorbidity, otherwise eligible patient is working with a positive but statistically unconfirmed signal, not the same evidentiary footing as for a higher-comorbidity patient in whom the benefit has been shown twice, independently, in cohorts an order of magnitude larger than the trial itself [1-3].

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and it draws on three sources with different designs: one randomised trial and two observational analyses that cannot fully eliminate residual confounding despite propensity weighting [1-3]. The generalizability analysis and the comorbidity-stratified analysis used overlapping but not identical UK Biobank cohorts and outcome ascertainment windows, and neither analysis reports results for a combined age-and-comorbidity stratification that might further refine which specific patients show the clearest real-world benefit [2,3]. The OptumLabs cohort is a US claims-based population with its own selection characteristics distinct from either the European trial population or the UK Biobank cohort, which limits how directly its hazard ratios can be pooled with the other two sources rather than considered alongside them [3]. Finally, none of the three sources examined here reports long-term outcomes beyond the follow-up windows used in each original publication, so durability of the comorbidity-stratified benefit beyond those windows remains unaddressed by this review.

Conclusion

EAST-AFNET 4 demonstrated a clear composite benefit for early rhythm control in atrial fibrillation, and a population-based generalizability analysis found that most real-world patients would have qualified for the trial and experienced a similar benefit. A separate comorbidity-stratified analysis across two independent real-world cohorts narrows that reassurance: a statistically significant benefit has so far been demonstrated specifically in patients with a higher comorbidity burden, not yet in patients with a lower burden. Reconciling trial and clinic populations, for this treatment, means recognising that broad eligibility and a confirmed real-world benefit are related but distinct claims, and that the second claim currently applies to a narrower group than the first.

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Cite this article: Bencivenga A, Ravensbergen M, Radvilas T. Early Rhythm Control in Atrial Fibrillation: Reconciling Trial Populations with Clinic Populations. *J Heart Cardiovasc Sci*. 2023; 4: 001-006.

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