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Treatment Decisions Based on EF \geq 50% Require More Robust Statistical Validation

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Background

Use of Beta-blocker after myocardial infarction (MI) is a long-standing therapeutic recommendation, but recent individual patient data (IPD) meta-analyses have suggested an ejection fraction (EF) threshold be set at 50%, below which beta-blockers may only be beneficial. Whether this threshold is statistically robust or suitable for informing practice guidelines remains uncertain

Methods

In this paper we performed a two-part evaluation of the proposed EF=50% threshold. Part 1 analyzed published summary data from two contemporary IPD meta-analyses of four randomized trials, applying formal interaction testing, fragility assessment, power calculations, and pooled effect estimation. Part 2 consisted of a simulation study generating 10,000 synthetic meta-analyses structurally matched to the original trials to quantify false-positive rates in threshold detection across six data-generating models.

We compared four analytical approaches: multiple threshold testing, single interaction testing, continuous modeling, and leave-one-trial-out cross-validation

Results

The interaction test between EF 40–49% and EF \geq 50% subgroups was not statistically significant ($p=0.069$), with only 46% power to detect the observed effect difference. The EF 40–49% subgroup result was extremely fragile (fragility index=3 events) and severely underpowered (40% power for HR=0.80). The pooled hazard ratio across EF \geq 40% was 0.94 (95% CI 0.85–1.03).

In simulations with no true threshold, multiple threshold testing produced false-positive thresholds in 46.8% of analyses, while cross-validation reduced false-positives to 1.5%. These patterns were consistent across six alternative true effect models

Conclusions

The proposed EF=50% threshold lacks statistical robustness, biological plausibility, and validation. False-positive threshold detection is common when continuous variables are dichotomized without proper validation. Therefore We believe that the current evidence can not justify EF-stratified beta-blocker recommendations.

Further rigorous validation framework to include: interaction testing, fragility assessment, and cross-validation, should be applied before subgroup findings can directly inform clinical guidelines. Key-

words: myocardial infarction; beta-blockers; ejection fraction; subgroup analysis; fragility index; interaction test; cross-validation; simulation study

Interactive dashboard figures

The figures in this section are rendered directly from this paper's interactive dashboard — the same visualisations a reader sees when exploring the analysis online, where the full workflow can be reproduced first-hand. **Interactive dashboard:** <https://mahmood726-cyber.github.io/betablocker/>

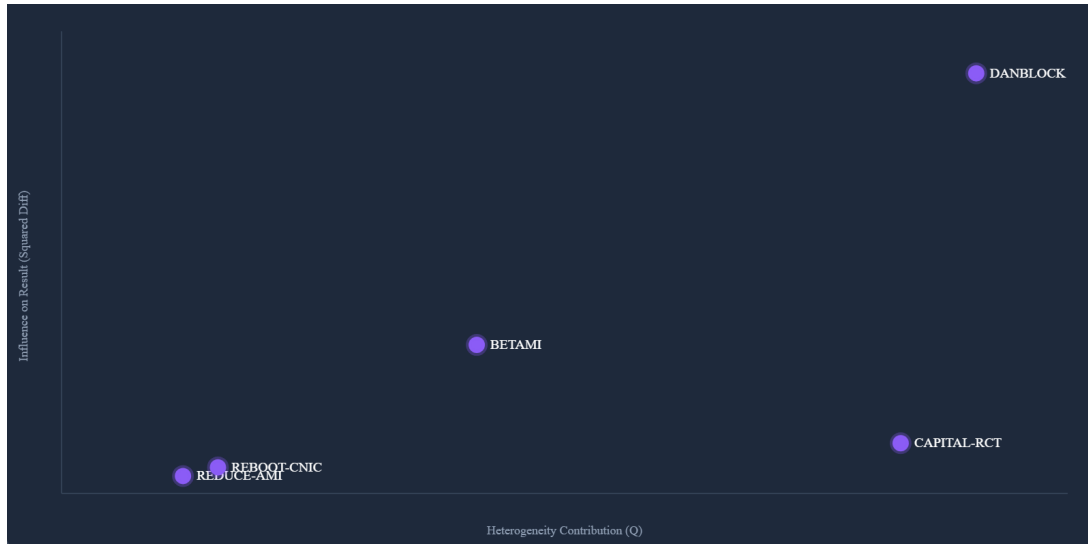


Figure 1. Fragility Diagnostics Dashboard Rendered directly from the article's live interactive dashboard.

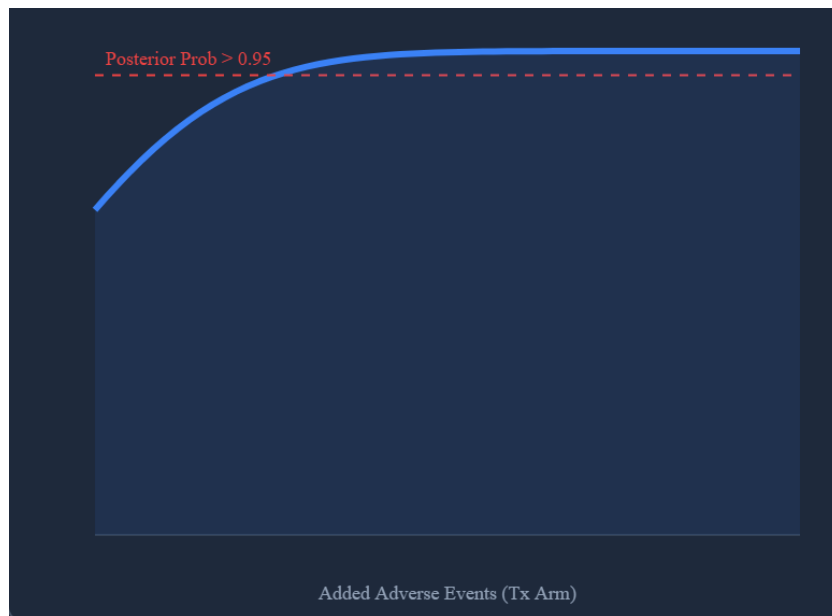


Figure 2. Fragility Diagnostics Dashboard Rendered directly from the article's live interactive dashboard.

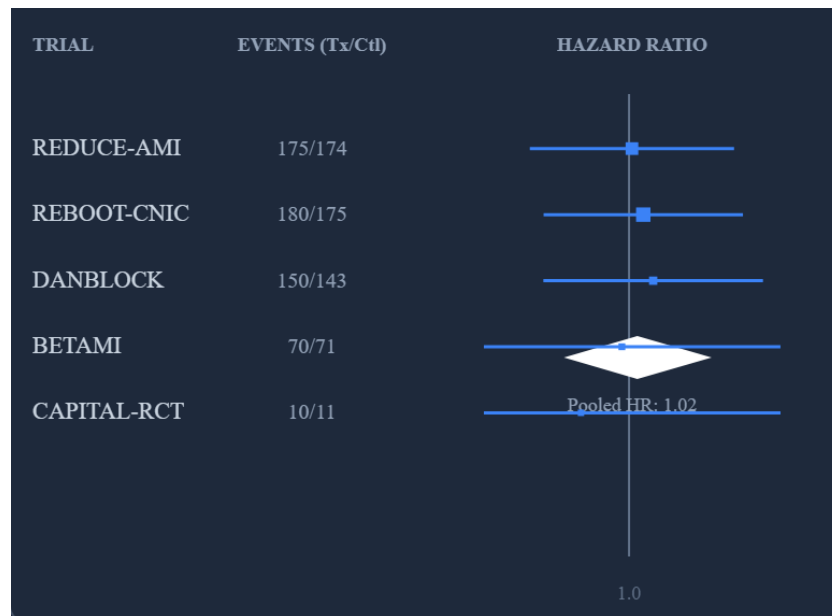


Figure 3. Fragility Diagnostics Dashboard Rendered directly from the article's live interactive dashboard.

HOW TO CITE

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