

Mortality Still Matters in Clinical Trials for Heart Failure

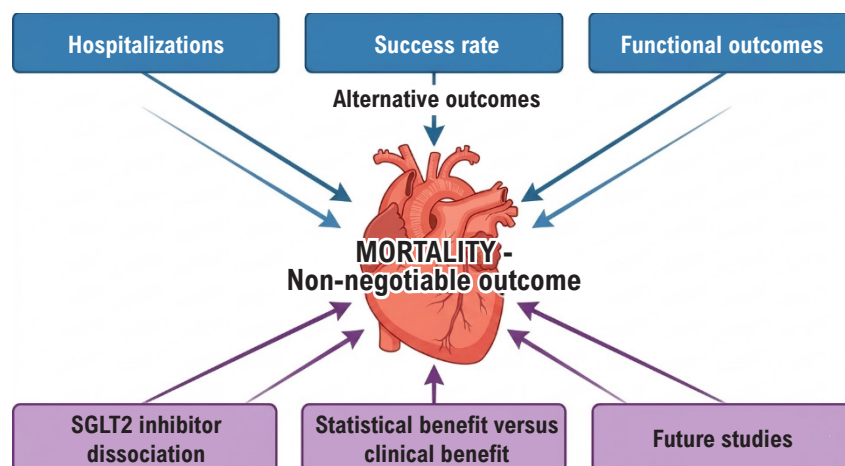
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Central Illustration: Mortality Still Matters in Clinical Trials for Heart Failure



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Heart failure (HF) remains one of the leading causes of mortality and healthcare costs worldwide. In the ESC HF III Registry, one-year mortality after hospitalization ranged from 16% to 22%,¹ while in the United States it reaches 35.2% among patients ≥ 65 years.² Even so, only 1 in 8 post-2015 trials in HF with reduced ejection fraction (HFrEF) demonstrated a reduction in cardiovascular death, in contrast with 13 of 16 pre-2015 trials.³ This misalignment has driven an increasing reliance on alternative endpoints.

Having participated in the Brazilian coordination of international acute myocardial infarction trials – including ISIS-4, ASSENT-2, and ASSENT-4 PCI⁴⁻⁶ – all of which used mortality as the central endpoint, it was possible to witness an era in which the primary clinical question was whether a treatment did or did not reduce death. This viewpoint

argues that mortality remains the principal endpoint for clinical inference in HF and should not be abandoned in the design of contemporary trials.

Mortality in HF: a persistent reality

A population-based Australian and New Zealand study including 283,048 patients demonstrated a median survival of only 2.8 years after hospitalization for acute HF, with just 17.1% of patients alive at 10 years.⁷ In a Danish cohort of 194,997 patients followed for 25 years, the reduction in 5-year mortality was substantially smaller among individuals ≥ 80 years compared with younger patients.⁸ A meta-analysis across 38 countries involving 1.5 million patients reported one-year mortality of 23.3% and rehospitalization rates of 35.7%.⁹ These data reinforce that mortality continues to represent the final clinical expression of HF progression.

Modern trials: why has mortality disappeared as a primary endpoint?

Mortality was the primary endpoint in 9 of 16 pre-2015 HFrEF trials, but in none of the pivotal trials published after 2015.³ Optimization of background therapy substantially reduced fatal events: comparative analyses estimated a 50% reduction in cardiovascular mortality with quadruple therapy,¹⁰ while a contemporary meta-analysis confirmed an estimated gain of 5.3 years of life.¹¹

Moreover, event-driven trials use shorter follow-up periods, during which hospitalizations occur earlier than deaths.³ The

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progressive reduction in the death-to-hospitalization ratio also makes demonstrating survival benefit more difficult.³ Another relevant factor is the use of run-in periods that exclude higher-risk patients, as seen in PARADIGM-HF.¹²

Beyond clinical and methodological aspects, the shift toward alternative endpoints likely also reflects economic and operational constraints of modern trials. As demonstrating mortality reduction became more challenging, clinical trials began to require larger samples, longer follow-up, and substantially higher costs – making non-fatal endpoints and analytical methods with greater statistical efficiency progressively more attractive.³⁻²⁰

Alternative endpoints: statistical efficiency and clinical benefit are not equivalent

Methods for recurrent event analysis, the *win ratio*, and the *estimand* framework have become pragmatic alternatives to increase analytical efficiency in contemporary HF trials. However, gains in statistical efficiency do not necessarily correspond to demonstrating clinical benefit of greater prognostic relevance.³

In an analysis of four SGLT2 inhibitor trials, recurrent-event models produced wider confidence intervals and lower statistical significance than traditional Cox models in three of the four studies.¹³ The *win ratio* incorporates clinical hierarchy by prioritizing death over hospitalization, but may yield results similar to those obtained with first-event analyses.¹³

The *estimand* framework proposed by ICH E9(R1) represents an important methodological advance, but does not eliminate limitations in statistical power to detect differences in mortality.¹⁴ Strategies such as *while on treatment* and *hypothetical* have also been criticized for potentially reducing the use of information from randomized participants after intercurrent events.¹⁵

In contemporary practice, meta-analyses and evidence-grading systems such as GRADE have increasingly supported therapeutic recommendations predominantly based on non-fatal endpoints – even in the absence of robust demonstration of mortality benefit.^{3,18}

The example of the iSGLT2 inhibitors

SGLT2 inhibitors clearly illustrate this dissociation between endpoints. A meta-analysis of five randomized trials demonstrated a 28% reduction in HF hospitalizations, whereas the effects on cardiovascular death and all-cause mortality were proportionally smaller.¹⁶ In HFrEF, a meta-analysis of DAPA-HF and EMPEROR-Reduced confirmed a 14% reduction in cardiovascular mortality.¹⁷ In HFpEF, the benefit was predominantly driven by reductions in hospitalizations, with a borderline effect on cardiovascular death.¹⁶ An additional systematic review classified the evidence for mortality as low certainty, despite high certainty for hospitalizations.¹⁸ Taken together, these findings show that consistent reductions in non-fatal endpoints may occur even in the absence of proportional benefit in mortality, reinforcing the importance of continuing to evaluate survival as a central endpoint in HF trials.

Implications for future studies

Future HF trials should be designed to evaluate mortality more consistently, with adequate follow-up, inclusion of mortality as a primary or co-primary endpoint, and selection of populations with higher baseline risk. The ratio between mortality and hospitalization may help estimate the feasibility of demonstrating survival benefit. Alternative outcomes, particularly functional, symptomatic, and patient-centered ones, remain relevant for quantifying clinical burden and therapeutic benefit. However, their interpretation should occur within the context of the most clinically relevant and irreversible outcomes, especially mortality, and should be considered preferably complementary, not substitutes, for survival assessment. Not surprisingly, the FDA, EMA, and PMDA continue to separately evaluate the most clinically relevant components of composite outcomes, paying particular attention to the effects on mortality and other irreversible outcomes.^{3,19,20}

Conclusion

Alternative endpoints are important for assessing clinically relevant aspects such as symptom burden, hospitalizations, and quality of life. However, in a chronic disease with high lethality such as HF, benefits in non-fatal endpoints do not necessarily translate into proportional reductions in mortality. Therefore, demonstrating survival benefit remains essential for evaluating the overall clinical impact of therapeutic interventions.^{3,19,20}

Mortality still matters – and will always matter – in clinical trials in heart failure (Central Illustration).

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Availability of Research Data

The underlying content of the research text is contained within the manuscript.



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