Advances in heart failure (HF) drug and device therapies over the past 3 decades have made major inroads into the lethality of this disease. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), as well as device-based approaches including cardiac resynchronization therapy and implantable cardioverter defibrillator therapy, have resulted in substantial mortality, morbidity and quality of life (QoL) benefits to such patients, particularly those with HF and reduced ejection fraction (HFREF).

Beta-blockers are arguably the most potent therapy in reducing mortality in HF. Mortality reductions in mild to moderate as well as advanced HFREF in the pivotal trials additional to background ACE inhibitors and diuretics were consistently of the order of 30% (1–3). This was accompanied by improvements in cardiac remodeling parameters, HF symptoms, and QoL measures.

In this issue of JACC: Heart Failure, Rush et al. (4) have reviewed the totality of HF randomized controlled trials in the past 3 decades, evaluating cardiovascular (CV) mortality according to beta-blocker usage in the trials. The authors have been meticulous in including all of the major, predominantly HFREF, randomized control trials over this period. The analysis included 66 trials, including 136,182 participants and 32,140 deaths, with participants mostly with New York Heart Association (NYHA) functional class II and III symptoms and a weighted average left ventricular ejection fraction of 27%. The trials were divided into 3 groups according to the proportion of patients treated with a beta-blocker. The proportion of CV deaths decreased from 87% with low beta-blocker use to 80% with high beta-blocker use. Non-CV deaths rose from 11.4% to 19.1% with high beta-blocker therapy, representing a proportional increase of two-thirds in non-CV deaths. The reduction in CV mortality was associated with a rise in non-CV deaths, which was due mostly to malignancy.

This analysis confirms what we have known for some time, which is that mortality rates are falling with modern HF treatment; these data allow us to go some way in quantifying the major therapeutic advances that have been made in this field. This analysis examines background beta-blocker use within these trials, and as the authors acknowledge, concomitant with increased beta-blocker use over recent years has been increased use of ACE inhibitor/ARB, rapid uptake of MRAs following the RALES study (Randomized Aldactone Evaluation Study) (5) and the EMPHASIS-HF study (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) (6) as well as the advent of devices, and it is therefore impossible to attribute improved CV mortality (and accompanying relative increase in non-CV mortality) entirely to beta-blocker therapy alone. However, a sensitivity analysis adjusting for ACE inhibitor/ARB use and adjusting for MRA use, and also using a meta-analytic approach, demonstrated that beta-blockers contributed most to the reduction in CV deaths.

This analysis includes the individual study outcomes of the placebo group and the intervention group. Many of these interventions are of novel agents that turned out to result in neutral or even adverse clinical outcomes. Examples include the BEST The Beta-Blocker Evaluation of Survival Trial study (7), in which bucindolol failed to improve...
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The Digitalis Investigation Group trial (9), which is shifting the cause of death. This was seen in CV mortality may be a safety signal that the treatment in all-cause mortality in the presence of a reduction in the addition of beta-blockers to our clinical armamentarium. However, these major gains cannot be seen in isolation from the contribution of other therapies to improvements in HF mortality. Beta-blockers continue to be underprescribed in HF, and this continues to be a major challenge going forward. Additionally, this analysis demonstrates that improvements in HF mortality forecast increasing difficulty demonstrating improved outcomes in future trials, and work is needed to develop appropriate clinical endpoints in contemporaneous HF trials. This endpoint evaluation work is urgently needed to optimize evaluation of new treatments to reduce the still unacceptably high mortality and morbidity associated with the condition.

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