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Falling Cardiovascular Mortality in Heart Failure With Reduced Ejection Fraction and Implications for Clinical Trials

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ABSTRACT

OBJECTIVES This study examined the trends in the relative contributions of cardiovascular and noncardiovascular mortality to total mortality according to use of beta-blockers in clinical trials of patients with heart failure with reduced ejection fraction (HF-REF).

BACKGROUND With the increasingly widespread use of disease-modifying therapies, particularly beta-blockers, in HF-REF, the proportion of patients dying from cardiovascular causes is likely to be decreasing.

METHODS In a systematic review, 2 investigators independently searched online databases to identify clinical trials including >400 patients with chronic heart failure published between 1986 and 2014 and that adjudicated cause of death. Trials were divided into 3 groups on the basis of the proportion of patients treated with a beta-blocker (<33% [low], 33% to 66% [medium], and >66% [high]). Percentages of total deaths adjudicated as cardiovascular or non-cardiovascular were calculated by weighted means and weighted standard deviations. Weighted Student *t* tests were used to compare results between groups.

RESULTS Sixty-six trials met the inclusion criteria with a total of 136,182 patients and 32,140 deaths. There was a sequential increase in the percentage of noncardiovascular deaths with increasing beta-blocker use from 11.4% of all deaths in trials with low beta-blocker use to 19.1% in those with high beta-blocker use ($p < 0.001$).

CONCLUSIONS In trials of patients with HF-REF, the proportion of deaths adjudicated as cardiovascular has decreased. Cardiovascular mortality, and not all-cause mortality, should be used as an endpoint for trials of new treatments for HF-REF. (J Am Coll Cardiol HF 2015;3:603–14) © 2015 by the American College of Cardiology Foundation.

The stepwise introduction of several drug and device therapies for patients with heart failure with reduced ejection fraction (HF-REF) has led to incremental improvements in survival in clinical trial cohorts (1) and there have been associated reductions in mortality in individuals with HF in the general population (2,3). By their very nature, treatments for HF are likely to affect mainly cardiovascular (CV) causes of death, particularly death from worsening HF and sudden cardiac death. They should have little impact on non-CV causes of death. As a result, the respective proportions of deaths attributed to CV and non-CV causes in patients with HF has probably changed over recent years, with implications for the design of clinical trials (choice of endpoints and anticipated event rates) and expectations for future treatment effects. To test this hypothesis, we investigated trends in CV and non-CV deaths in patients with HF over the past 3 decades.

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

BB = beta blocker

CV = cardiovascular

HF = heart failure

HF-PEF = heart failure with preserved ejection fraction

HF-REF = heart failure with reduced ejection fraction

NYHA = New York Heart Association

RCT = randomized controlled trial

METHODS

We collected data from randomized controlled trials (RCTs) of patients with chronic HF-REF to examine the respective proportions of deaths by CV and non-CV causes.

LITERATURE SEARCH STRATEGY. We searched the electronic databases Medline and Embase with the terms "heart failure" or "congestive heart failure" as title or keywords. The search, updated until October 2, 2014, was limited to RCTs of adults, with more than 400 participants, published in the English language, between January 1, 1986 and October 1, 2014. Trials were eligible for inclusion in the analysis if both all-cause and CV mortality were adjudicated in the primary results paper or subsequent analyses. We excluded trials in acute HF and those in patients after acute myocardial infarction. Although we did include trials in patients with HF-preserved ejection fraction (HF-PEF), there were many fewer of these than the majority in patients with HF-REF. Bibliographies of guidelines, reviews, and manuscripts identified through the search strategy were also hand-searched for additional eligible trials. Published Food and Drug Administration reports were also searched for CV and total mortality data from trials identified. Abstracts and manuscripts were independently reviewed by 2 readers (C.R. and R.T.C.), with a third reader (J.J.M.) resolving any discrepancies.

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DATA EXTRACTION. Two authors (C.R. and R.T.C.) independently abstracted and tabulated data from manuscripts identified through the search criteria. Relevant endpoints for which data were collected were total mortality, CV mortality, non-CV, and cardiac mortality. Where cardiac mortality was not described, the sum of the individual components commonly used in cardiac mortality (myocardial infarction, HF, sudden cardiac death, arrhythmic death) was used where available. The proportion of deaths classified as unknown was recorded, as was whether the trials reported if these deaths were classified as CV.

DATA SYNTHESIS AND STATISTICAL ANALYSIS. We included all participants regardless of the therapy being investigated. Eligible trials were divided into 3 groups for analysis on the basis of the proportion of patients treated with a beta-blocker (BB) (<33% [low use], 33% to 66% [medium use], >66% [high use]), and also into the decade in which the primary result paper was published (1985 to 1994, 1995 to 2004, 2005 to 2014). The mortality data for each group were analyzed and percentages of total mortality, CV, non-CV, cardiac, and unknown deaths, were calculated as weighted means. Weighted standard deviations were calculated as described by Bland and Kerry (4). The odds of dying from a non-CV cause over time were tested using a grouped logistic regression model. We examined trends adjusting for angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and mineralocorticoid receptor antagonist (MRA) use. In 40% of studies, the proportion of patients receiving a MRA was not reported. Therefore, we examined this association in 2 ways: excluding those trials and after imputing the mean proportion. Analyses were performed using STATA version 12 (Stata Corp., College Station, Texas). As sensitivity analyses, we analyzed the proportion of CV, non-CV, and cardiac deaths by BB group (<33%, 33% to 66%, >66%) and time period (1986 to 1994, 1995 to 2004, 2005 to 2014) in a random effects meta-analysis (using the metaprop command in STATA) (5). Heterogeneity was assessed and interpreted using the I^2 statistic and forest plots (6–8). A p value <0.05 was considered statistically significant.

RESULTS

Our search strategy identified 66 trials that included 136,182 patients and reported 32,140 deaths (9–84). Of the patients enrolled in these trials, 77% were male, the mean age was 65 years, and approximately 90% were in New York Heart Association (NYHA) functional class II or III. The weighted average left ventricular ejection fraction was 27%. More detailed baseline information for each trial is shown in **Tables 1 and 2**.

The trials were divided into 3 groups for analysis on the basis of the proportion of patients treated with a BB. The key baseline characteristics of the 3 groups were, in general, similar except by definition for the treatments prescribed for HF (**Table 3**). The trials with greater use of BB (which were more recent studies) also demonstrated greater use of other disease-modifying therapies (e.g., mineralocorticoid receptor antagonists: used at baseline in 14.4% of patients in trials with <33% BB therapy vs. 44.0% of trials with >66% BB use) and devices (e.g., 1.0% of patients in trials with <33% BB therapy vs. 20.4% of patients in trials with >66% BB use had an implantable cardioverter defibrillator). There was also a greater proportion of patients in NYHA functional class III/IV in the earlier trials with low BB use (49.2%/9.6% vs. 41.1%/4.1%, respectively).

MORTALITY FROM ALL CAUSES. Details of the number and causes of death in each trial are given in **Tables 4**