CLINICAL RESEARCH STUDY

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Postponement of Death by Pharmacological Heart Failure Treatment: A Meta-Analysis of Randomized Clinical Trials

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ABSTRACT

BACKGROUND: Outcome postponement has been proposed as an effect measure for preventive drug treatment. It describes the average delay of the investigated unwanted clinical event, achieved by taking medication. The objective was to estimate postponement of death for the following heart failure medications compared to placebo: beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), ARB added to ACE inhibitors, aldosterone antagonists, ivabradine, and renin antagonists.

METHODS: We searched Medline and Embase from inception of databases until October 2017. Eligibility criteria were randomized placebo-controlled heart failure trials, including at least 1000 participants, with survival as a prespecified outcome and a minimum trial duration of 1 year. We calculated the outcome postponement by modeling the area between survival curves. This area was modeled on the basis of the hazard ratio or relative risk, the rate of mortality in the placebo group, and the trial duration. All results were standardized to a 3-year trial duration to ensure comparability between treatments.

RESULTS: We identified 14 eligible trials, with a total of 52,014 patients. The results in terms of postponement of all-cause mortality was: beta-blockers 43.7 days (95% confidence interval [95% CI], 20.8-66.5), ACE inhibitors 41.0 days (95% CI, 18.8-63.3), and aldosterone-antagonists 41.3 days (95% CI, 14.3,68.4).

CONCLUSION: The modeled outcome postponement estimates reiterate beta-blockers, ACE inhibitors, and aldosterone antagonists as the mainstay of heart failure treatment. Furthermore, ivabradine or ARBs added to ACE inhibitors results in no statistically significant gain in survival.

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KEYWORDS: Effect measure; Heart failure; Meta-analysis; Outcome postponement; Randomized Controlled Trial

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INTRODUCTION

Communicating clinical effect and safety of a given intervention to facilitate informed and shared decision making between the patient and the general practitioner is challenging. The effect size of a specific treatment is typically expressed as a relative or absolute risk reduction (RRR and ARR, respectively), or as a number needed to treat (NNT). Patient perception of these measurements are inconsistent, which limits their value in conveying treatment effects.[1,2] Even substantial differences in NNT values do not change the proportion of patients who accept a proposed treatment.[3] Conversely, patients appear to be more responsive to outcome postponement (ie, higher values of outcome postponement are more likely to entail a greater acceptance of treatment).[3,4]

Chronic heart failure is a serious and common condition with a prevalence of 1%-2% among adults living in developed countries.[5] Despite advances in evidence-based therapy, mortality rates remain high at about 50% within 5 years of diagnosis.[5–7] Outcome postponement has not been estimated for the major interventional heart failure trials that form the basis of contemporary guidelines for medical treatment.

We performed a systematic review and identified and analyzed eligible studies. Our aim was to estimate postponement of survival within each trial and to perform a meta-analysis for major drug groups.

CLINICAL SIGNIFICANCE

- Patients have difficulties interpreting effect measures when communicated in relative risk or number needed to treat. An alternative is to convey the treatment effect in terms of postponement of an adverse event, such as death, achieved by taking the drug.
- Heart failure medications postponed death between 4 and 44 days. For drugs with a class I recommendation, death was postponed between 26 and 44 days.

METHODS

In this systematic review, we identified and meta-analyzed large placebo-controlled trials of heart failure medication and calculated the postponement of death.

Eligibility Criteria

We included randomized controlled trials of at least 1000 patients receiving drug intervention for heart failure compared with placebo, with a minimum follow-up of 1 year, and with patients with a left ventricular ejection fraction ≤40%.

Treatment Classes

The following treatments were included: Beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), ARBs added to ACE inhibitors, aldosterone antagonists, ivabradine, renin-antagonists, and neprilysin inhibitors. We did not investigate diuretics or digoxin because these have not been associated with improved survival.[5]

Search Strategy

We searched Medline and Embase from inception of databases until October 2017. For both databases, we used the following search terms as both keywords and MeSH-terms: (Heart failure AND placebo AND random*) AND (ACE inhibitors OR angiotensin II receptor blockers OR Renin-antagonist OR beta-blockers OR ivabradine OR aldosterone-antagonists OR neprilysin inhibitors). Reference lists of included papers was reviewed for additional papers. Two authors (NHP and MB) screened the titles and abstracts independently and, if indicative of an eligible trial, retrieved full text manuscripts. Disagreements were resolved by consensus.

Data Extraction

Trial characteristics and outcome data were extracted from all included trials by 2 independent authors (MRH and MB). Any discrepancies were resolved by consensus. The following trial characteristics were extracted for the mathematical model: number of patients in each arm, trial duration, intervention type, trial follow-up, hazard ratio (HR) or relative risk (RR) with corresponding 95% confidence interval (CI), mortality rate, and cumulative mortality.

We used covidence (www.covidence.org) to organize abstracts and full-text.

Risk of Bias Assessment

The assessment of bias was performed using Cochrane's risk of bias tool.[8]

Data Analysis: Outcome Postponement Analysis of Individual Trials

Outcome postponement is measured in units of time (eg, days). This relatively novel metric of gained event-free time with intervention can be estimated as the area between the survival curves for patients receiving drug compared with placebo.[9,10] In this systematic review, we used 2 different methods, a mathematical model and pixel counting, to estimate outcome postponement enabling validation of the mathematical model. For our main analysis, we used a mathematical method that models the area between 2 exponential decay functions for the intervention and the control group, using the reported HR, mortality rates, and trial duration. The mathematical model allowed us to calculate

* In the first publication by Hansen et al 2019, this was termed "postponement interval" (PI). A later simulation study demonstrated, as expected, that postponement intervals and confidence intervals are similar (unpublished).

both CIs and to perform a meta-analysis. The underlying assumption of the mathematical model is that the mortality rates are stable in both treatment arms throughout the duration of the trial. The 95% CI for postponement is calculated by substituting the HR in the equation with the upper and lower CI of the reported HR. For our secondary analysis, we used the pixel-counting method, which estimates the area between survival curves by counting the number of pixels between the 2 Kaplan-Meier survival curves. We then used linear regression to compare the model-derived estimate with the estimates derived by pixel counting. These methods are described in detail elsewhere.[11] To increase comparability between outcome postponement in the individual trials, we standardized the result from the mathematical model to a 3-year trial duration.[11] Three years was the median trial duration of the included trials.

Data Analysis: Meta-Analysis

We performed a meta-analysis of all-cause mortality postponement, and of HR using inverse variance weighting and random-effects models (Stata 15, Stata Corp, Texas). We subgrouped trials according to 1) mortality rate in the placebo arm as a proxy for heart failure severity, 2) high versus low overall risk of bias, and 3) type of pharmacological intervention.

We followed PRISMA reporting guidelines for systematic review and meta-analysis.[12]

The systematic review was registered in PROSPERO CRD42018080963.

RESULTS

Our search strategy yielded 2936 potentially eligible trials, of which 14 fulfilled our inclusion criteria (Figure 1). Among the eligible trials, 11 presented Kaplan-Meier survival curves. Furthermore, all trials presented the variables required to model the area between survival curves. The trial characteristics are shown in Table 1. No trials investigating renin-antagonists or neprilysin inhibitors fulfilled the eligibility criteria.

Median outcome postponement across all trials irrespective of follow-up time was 30.6 days using the pixel-counting method and 27.8 days using the mathematical method and original trial durations (eg, nonstandardized to 3 years). We found a fair agreement between the 2 methods with a slope of 0.81 using linear regression. The unadjusted summary estimate across all trials was 24.4 days (95% CI, 14.7-34.1), I^2 = 85.1 (P <0.001). On standardizing to a 3-year trial duration, outcome postponement was 29.5 days (95% CI, 17.5-41.5). Measures of heterogeneity were only marginally affected by standardization (I^2 = 81 (standardized) versus 85.1 (nonstandardized). Results of the primary analysis are presented in Figure 2 and in Table 2. Analyses specified by drug class are shown in Table 3. A forest plot for outcome postponement not standardized to trial duration is presented in Figure 3.

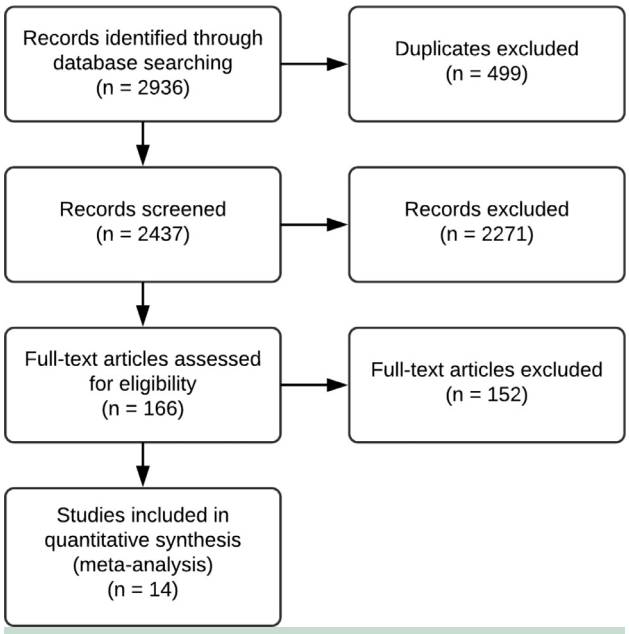

Figure 1 Flowchart of all included studies and exclusion process.

The magnitude of outcome postponement was more pronounced among trials with the highest mortality rate (62.6 days [95% CI, 37.0-88.1]) than among trials with the lowest rate (6.2 days [95% CI, -4.3 to 16.7]; Figure 4). As all trials were characterized as having a low risk of bias, no subgroup analysis by risk of bias was performed. Funnel plots were symmetrical (Figure 5), and all trials but 2 had predefined mortality as outcome in their study protocol (no protocol was accessible or the remaining 2 trials). A meta-analysis of HRs is presented in Figure 6.

We investigated statistical heterogeneity and found considerable I^2 among the trials. We found an I^2 for beta-blockers on 65, ACE inhibitors on 57, ARBs added to ACE inhibitors on 45, aldosterone antagonist on 78, and ivabradine on 69. Because of the low number of trials among the individual drug classes, we were not able to perform subgroup analysis within individual drug classes. However, we performed an overall subgroup analysis according to baseline mortality rate in the placebo group; here we demonstrated that the heterogeneity disappeared in the 2 middle stratas: Q2 (0.11-0.11) and Q3 (0.12-0.17) (Figure 4).

DISCUSSION

Our study demonstrated a postponement of all-cause mortality by approximately 1 month, but with variation, among the use of conventional heart failure medication (ie, ACE inhibitors/ARBs, beta-blockers, or aldosterone antagonists) in patients with chronic heart failure. Outcome postponement appeared to be larger in individuals at higher baseline risk of death.

Table 1 Characteristics of the Included Trials, Including Type of Heart Treatment, the Year of Publication, NYHA Class at Baseline, Number of Patients in Each Group and Trial Duration.

Type of heart failure treatment	Trial name	Publication year	NYHA Class	Drug	Number of patients		Trial duration (year)
					Active	Placebo	
Beta-blockers	BEST[24]	2001	3-4	Bucindolol	1354	1354	3.5
	CIBIS-II[25]	1999	3-4	Bisprolol	1327	1320	2.0
	MERIT-HF[26]	1999	2-4	Metropolol	1990	2001	1.6
ACE inhibitors	AIRE[27]	1993	NA	Ramipril	1014	992	2.5
	SOLVD (1991)[28]	1991	1-4	Enalapril	1285	1284	4.0
	TRACE[29]	1995	(1)	Trandolapril	876	873	4.1
ARB	CHARM altern[30]	2003	2-4	Candesartan	1013	1015	3.5
ARB added to ACE inhibitors	CHARM added[31]	2003	2-4	Candesartan	1276	1272	3.5
	VAL-HeFT[32]	2001	2-4	Valsartan	2511	2499	2.2
Aldosterone antagonists	EMPHASIS[33]	2011	2	Eplerenone	1364	1373	3.1
	EPHESUS[34]	2003	NA	Eplerenone	3313	3319	2.5
	RALES[35]	1999	(2)-4	Spironolactone	822	841	2.9
Ivabradine	BEAUTIFUL[36]	2008	1-3	Ivabradine	5479	5438	2.0
	SHIFT[37]	2010	2-4	Ivabradine	3268	3290	2.5

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CI = confidence interval; NA = not available; NYHA = New York Heart Association.

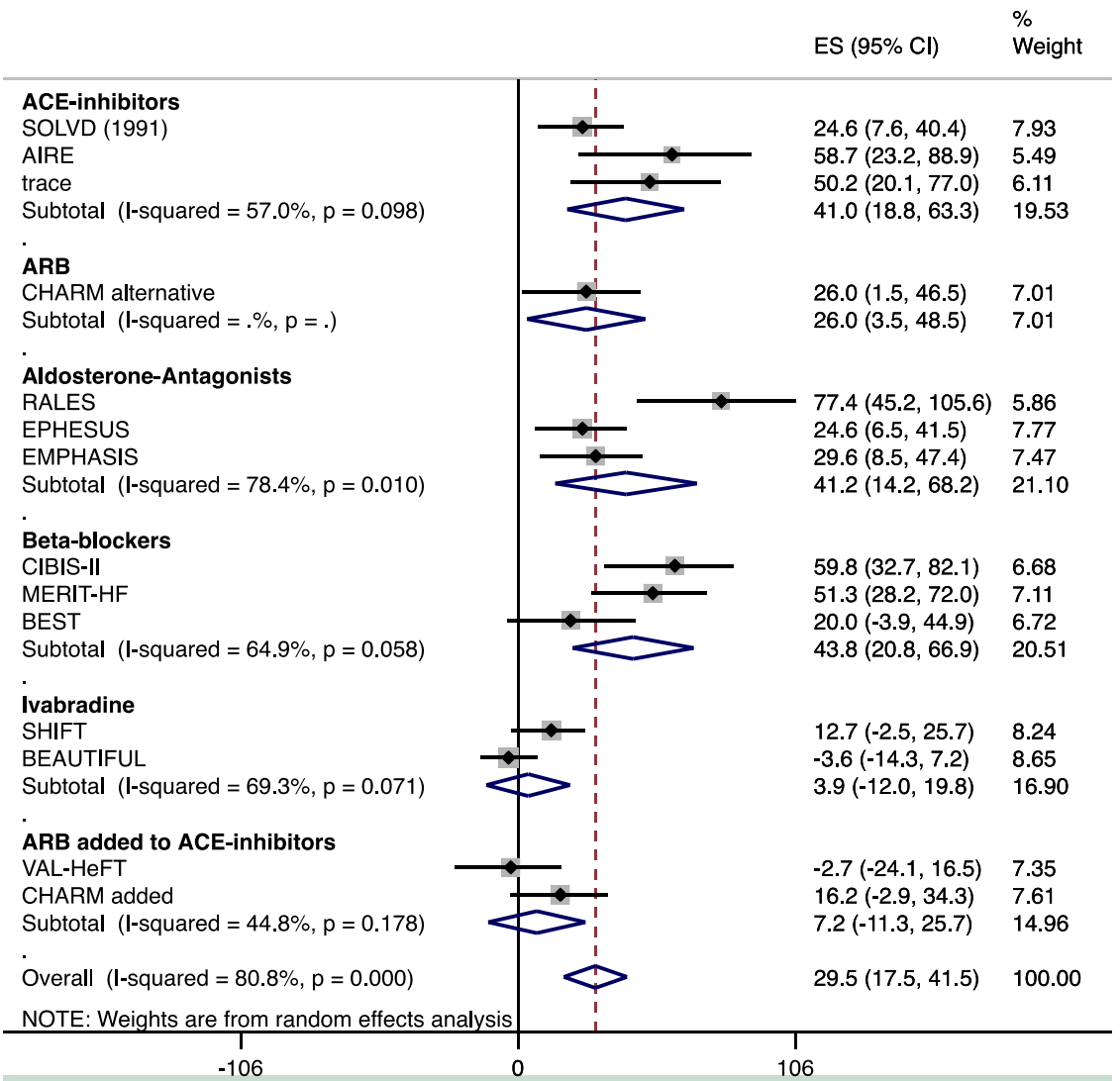

Figure 2 Forest plots of postponement of all-cause mortality in days, results standardized to 3 years of trial duration.

Table 2 Results of Outcome Postponement Calculations from Pixel Counting, the Mathematical Model Standardized to 3 Years of Trial Duration and Nonstandardized Results

Type of heart failure treatment	Trial name	HR/RR (95% CI)	Mortality rate in placebo arm	Trial duration (year)	Postponement based on Kaplan-Meier survival curves, days	Modeled postponement, days (95% CI)	Modeled postponement standardized to 3 years, days, (95% CI)
Beta-blockers	BEST[24]	0.90 (0.78-1.02)	0.17	3.5	30.6	25.9 (-5.1 to 58.3)	20.0 (-3.9 to 44.9)
	CIBIS-II[25]	0.66 (0.54-0.81)	0.13	2.0	28.6	29.6 (16.3-40.5)	59.8 (32.7-82.1)
	MERIT-HF[26,*]	0.66 (0.53-0.81)	0.11	1.6	27.9	15.2 (8.4-21.2)	51.3 (28.2-72.0)
ACE inhibitors	AIRE[27]	0.73 (0.60-0.89)	0.18	2.5	46.8	42.8 (17.0-64.7)	58.7 (23.2-88.9)
	SOLVD (1991)[28,*]	0.84 (0.74-0.95)	0.12	4.0	59.8	40.8 (12.5-67.3)	24.6 (7.6-40.4)
	TRACE[29]	0.78 (0.67-0.91)	0.20	4.1	.	84.5 (33.5-130.5)	50.2 (20.1-77.0)
ARB	CHARM altern[38]	0.83 (0.70-0.99)	0.11	3.5	.	34.2 (2.0-61.4)	26.0 (1.5-46.5)
ARB added to ACE inhibitors	CHARM added[31]	0.89 (0.77-1.02)	0.11	3.5	.	21.3 (-3.8 to 45.2)	16.2 (-2.9 to 34.3)
	VAL-HeFT[32,*]	1.02 (0.88-1.18)	0.10	2.2	0.0	-1.6 (-14.3 to 9.7)	-2.7 (-24.1 to 16.5)
Aldosterone antagonists	EMPHASIS[33]	0.76 (0.62-0.93)	0.09	3.1	32.4	31.6 (9.1-50.7)	29.6 (8.5-47.4)
	EPHESUS[34,*]	0.85 (0.75-0.96)	0.13	2.5	20.9	17.7 (4.7-29.8)	24.6 (6.5-41.5)
	RALES[35,*]	0.70 (0.60-0.82)	0.23	2.9	102.2	73.9 (43.2-100.8)	77.4 (45.2-105.6)
Ivabradine	BEAUTIFUL[36]	1.04 (0.92-1.16)	0.06	2.0	.	-1.7 (-6.6 to 3.3)	-3.6 (-14.3 to 7.2)
	SHIFT[37]	0.90 (0.80-1.02)	0.09	2.5	11.4	9.1 (-1.8 to 18.3)	12.7 (-2.5 to 25.7)

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CI = confidence interval; HR = hazard ratio; RR = relative risk.
*RR used instead of HR.

Previous meta-analyses have investigated the effects on death of various heart failure medications, obtaining results similar to our conventional HR-based estimates. A 2009 meta-analysis of 23 beta-blocker trials by McAlister et al found a risk ratio of 0.76 (95% CI 0.68-0.84).[13] Extracting data from 34 trials, Garg et al found a significant reduction in all-cause mortality with the use of ACE inhibitors (odds ratio, 0.77 (95% CI, 0.67-0.88)).[14] However, Tai et al failed to show a risk reduction with ARBs (6 trials, RR 0.98 [95% CI, 0.90-1.07]).[15] Conversely, in a meta-analysis including 15 trials on aldosterone antagonists, Berbenetz et al demonstrated a decline in all-cause mortality (RR, 0.83 [95% CI, 0.77-0.88]).[16] Finally, Narayanan et al examined the effect of ivabradine. The summary estimate was based on 6 trials, and did not show a reduction in all-cause mortality (RR, 0.98 [95% CI, 0.89-1.15]).[17]

The postponements in all-cause mortality, seen with beta-blockers, aldosterone antagonists, and ACE inhibitors, are large and thus supportive of contemporary North American and European guidelines for heart failure. In these, ACE inhibitors/ARBs, beta-blockers, and aldosterone antagonists all receive a class I recommendation, whereas the strength of recommendation for ivabradine is lower (class IIa).[5,18,19] Of note, the European guidelines only recommend ARBs as an alternative for patients who cannot tolerate an ACE-inhibitor.[5,18,19] Furthermore, both guidelines state that the combination of an ACE inhibitor and an ARB should only be considered among patients who already are on a beta-blocker and are unable to tolerate an aldosterone antagonist (class IIb).[5,18,19]

We found that beta-blockers provided the highest point estimate of postponement of all-cause mortality, followed by ACE inhibitors and aldosterone antagonists. However, it should be noted that the study populations are not directly comparable and, to a large extent, reflect the order in which the mainstay treatments were established. ACE inhibitors were typically tested in patients who only received diuretics and digoxin. Beta-blockers were tested later in patients who typically already received ACE inhibitors. Aldosterone antagonists were typically tested in patients who received both ACE inhibitors and beta-blockers. All things being equal, it is conceivable that the added value of a given intervention decreases if the patients are already extensively treated by other inventions, although we are not aware of any studies formally addressing this notion.

In a previous publication, our group investigated outcome postponement on all-cause mortality provided from statin treatment over a 5-year trial duration.[11] We found that statins only postponed death with 13 days within 5 years of trial duration. In comparison, all heart failure medications that are class I recommended postponed all-cause mortality with about 40 days, during just 3 years of trial duration.

Outcome postponement has previously been appraised as a useful tool for communicating the effect of treatment to patients, and it has shown improved perception among patients, as compared with traditional effect measures (ie,

Table 3 Meta-Analyses of Postponement of All-Cause Mortality Both Standardized to 3 Years of Trial Duration, Nonstandardized and Regular HR-Based, According to Drug Class (Random Effects Meta-Analysis).

Drug class	Number of trials	Outcome postponement, days (95% CI)	I^2	Outcome postponement standardized to 3 years, days (95% CI)	I^2	HR all-cause mortality (95% CI)	I^2
Beta-blockers	3	21.7 (10.4-32.9)	55	43.9 (20.8-66.9)	65	0.74 (0.59-0.93)	79
ACE inhibitors	2	48.4 (28.3-68.4)	24	41.0 (18.8-63.3)	57	0.80 (0.73-0.87)	0
ARBs	1	34.2 (4.5-63.9)		26.0 (3.5-48.5)		0.83 (0.70-0.99)	
ARBs added to ACE inhibitors	2	7.3 (-14.6 to 29.1)	63	7.2 (-11.3 to 25.7)	45	0.95 (0.83-1.09)	42
Aldosterone-antagonist	3	38.6 (9.7-67.5)	84	41.2 (14.2-68.2)	78	0.77 (0.68-0.88)	47
Ivabradine	2	7.3 (-14.6 to 29.1)	72	3.9 (-12.0 to 19.8)	69	0.97 (0.84-1.12)	65

ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; CI = confidence interval; HR = hazard ratio.

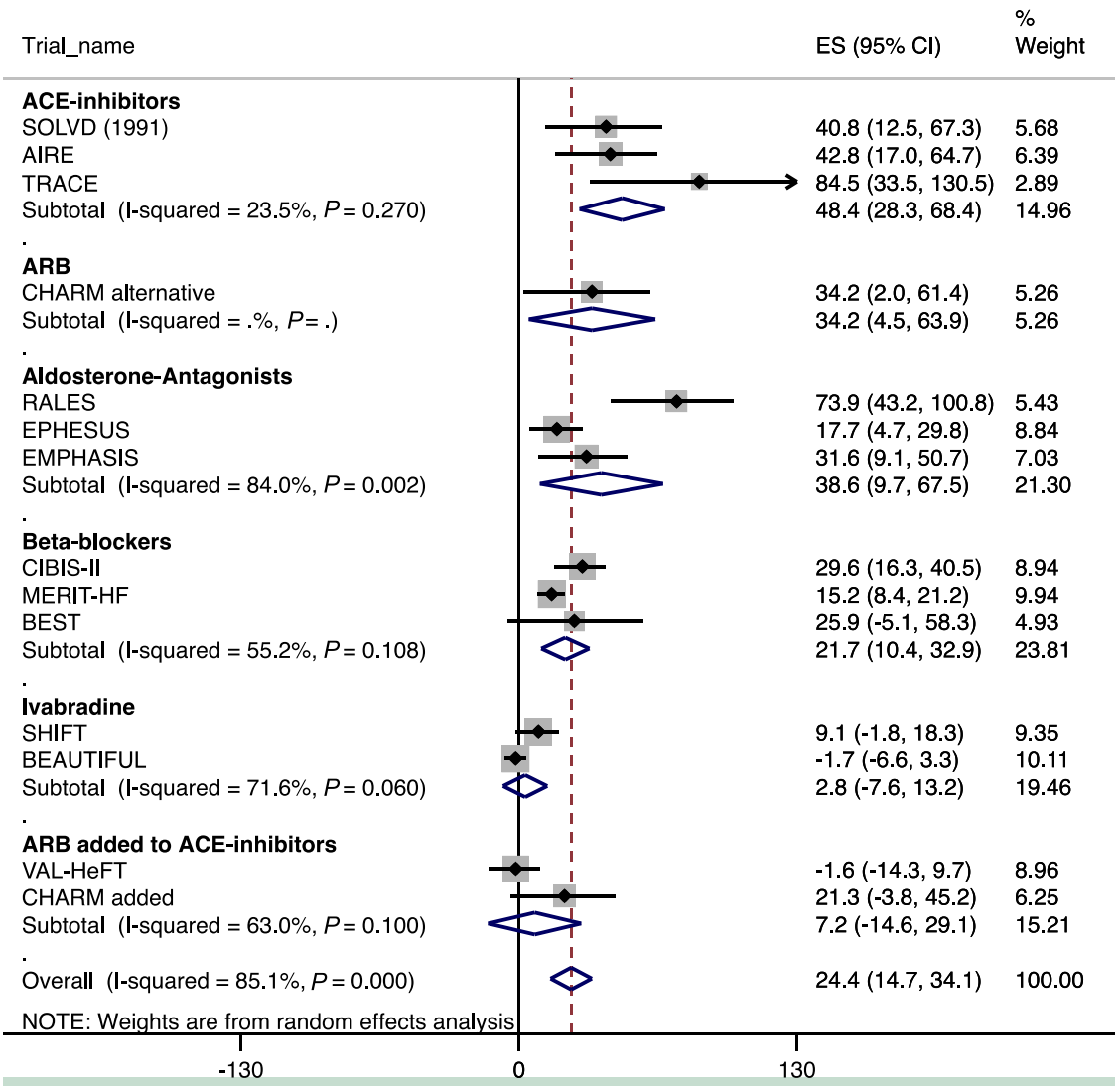

Figure 3 Forest plots of postponement of all-cause mortality in days, results non-standardized.

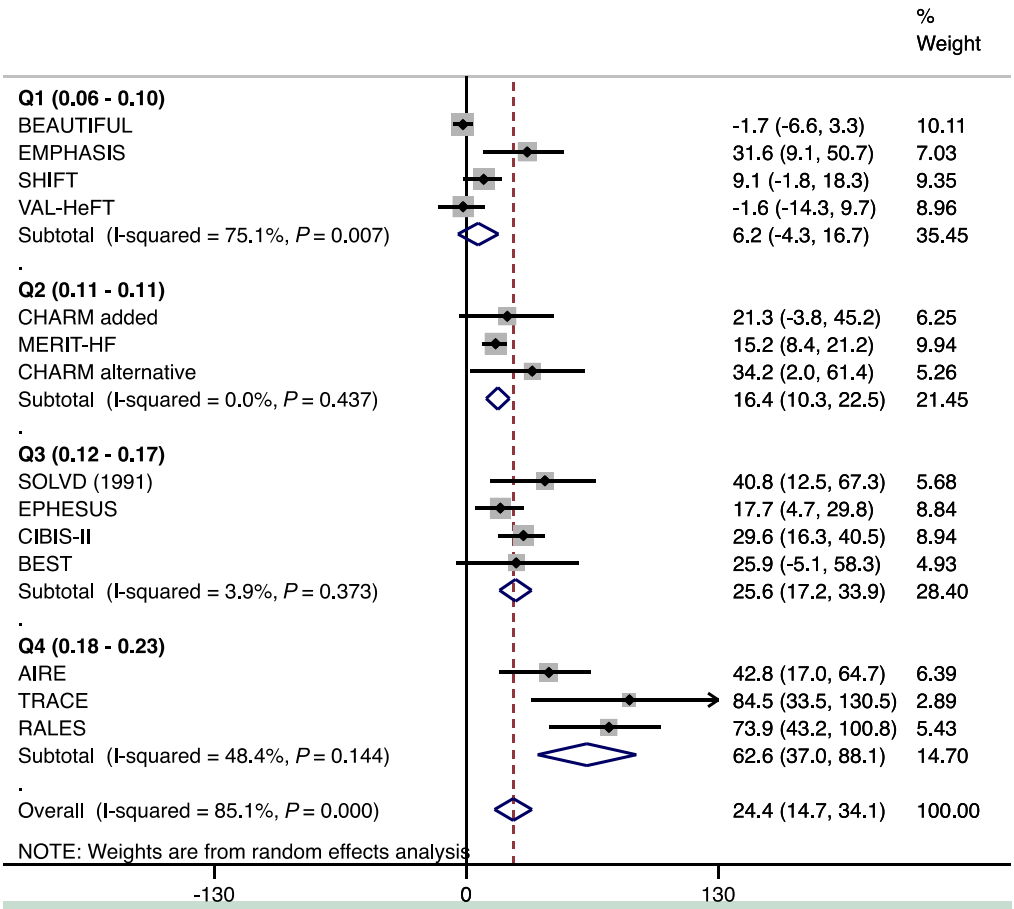

Figure 4 Forest plots of postponement of all-cause mortality in days, results ranked according to mortality rate in placebo group and grouped in 4 quartiles.

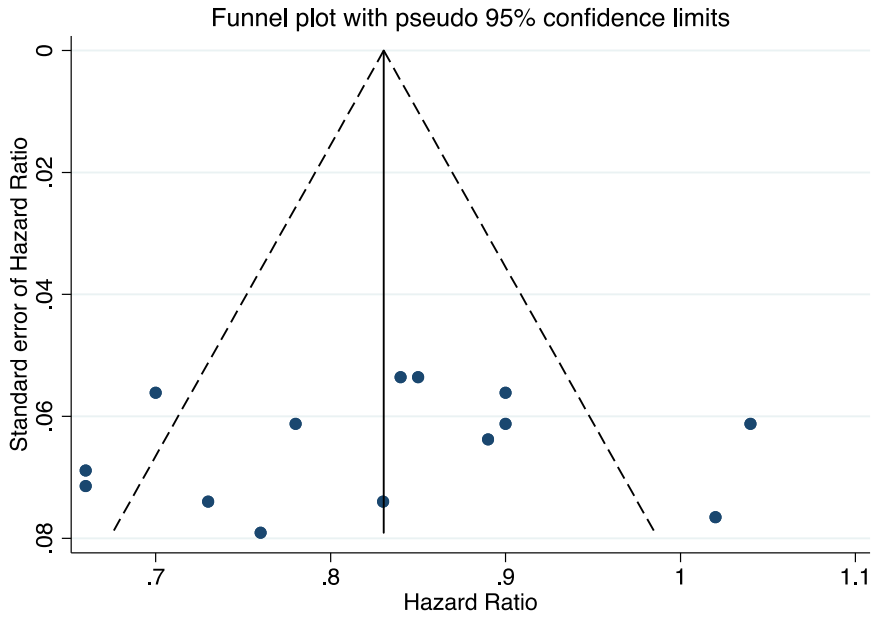

Figure 5 Funnel plots for investigation of publication bias.

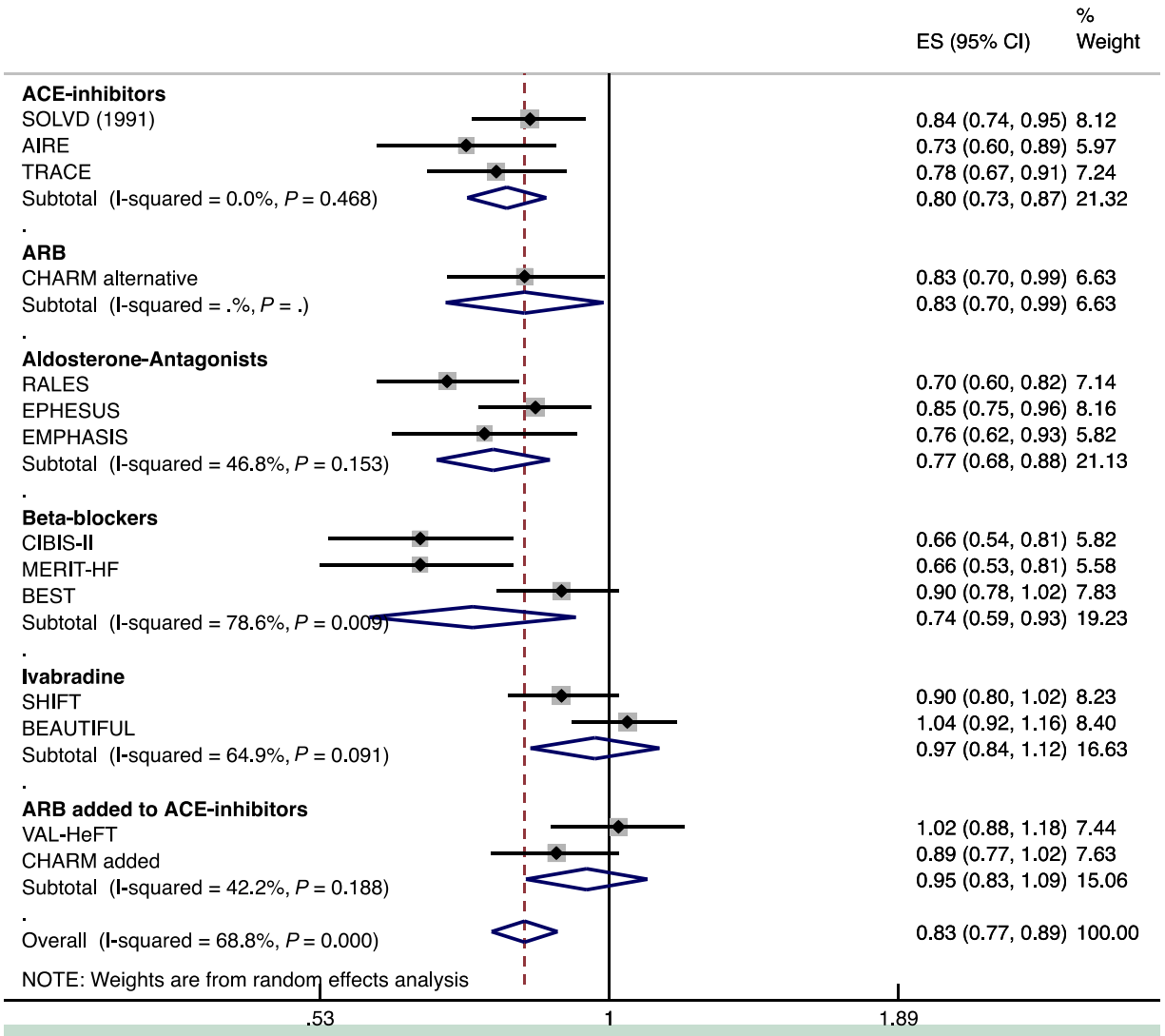

Figure 6 Forest plot of hazard ratios of all-cause mortality in the trials.

RR, ARR, and NNT).[3,4] Because our results emphasize which of the heart failure medications are associated with the largest improvements in prognosis, presenting the benefits of evidence-based, guideline-recommended heart failure therapy using these measures may help ensure improved adherence in daily clinical practice. An additional methodological strength is our previous validation of this model against the actual area between survival curves, measured by pixel counting, which accounts for the potential limitation of the survival curve not conforming to an exponential decay function.[11]

The main limitation of outcome postponement is that only the accrued survival benefit during trial duration can be estimated. The survival benefit will continue to rise as long as the survival curves are separated. Unfortunately, this added survival benefit is difficult to estimate, and estimates vary considerably according to the given assumptions.[20-22] Although such limitations are universal for all effect measures derived from survival analyses, caution is advised when interpreting a specific measure.[11]

Modeling the effect of continued intervention relies on assumptions that are impossible to test. Extrapolations have yielded highly variable results.[11] As an example, Claggett et al found a survival benefit of 1-2 years with sacubitril-valsartan compared with enalapril when extrapolating from the available follow-up data and using actuarial estimates from *the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure*.[23] However, optimal use of this otherwise promising method requires availability of individual-level patient data. In an attempt to estimate lifelong benefit from ACE inhibitors, we have calculated the outcome postponement from the 12-year follow-up of TRACE trial, finding a value of 204 days for all-cause mortality. Given the high mortality for heart failure patient, 12 years would seem as a realistic proxy for lifelong treatment duration.

CONCLUSION

We found that after standardization to a 3-year trial duration, all-cause death was postponed from 4 to 44 days for different heart failure medications. However, for drugs with a class I recommendation in contemporary guidelines, death was postponed between 26 and 44 days. Outcome postponement appears to be affected by the underlying baseline risk.

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