JACC: HEART FAILURE
VOL. 2, NO. 5, 2014

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2014.04.012

VIEWPOINT

# "Triple Therapy" of Heart Failure With Angiotensin-Converting Enzyme Inhibitor, Beta-Blocker, and Aldosterone Antagonist May Triple Survival Time

## Shouldn't We Tell Patients?

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**ABSTRACT**

Prescription and adherence to medical therapy for heart failure are disappointing despite convincing randomized controlled trial (RCT) evidence for angiotensin-converting enzyme inhibition, beta-blockade, and aldosterone antagonism. In this study, we report an imbalanced approach amongst clinicians, who describe focusing during patient consultations on perceived risks of therapy rather than survival benefits. Only one-half of clinicians mention increased lifespan, and very few suggest to the patient how large this gain might be. We calculate from the available RCT data that, for patients whose lifespan is limited by heart failure, *triple therapy triples lifespan.* (J Am Coll Cardiol HF 2014;2:545–8)
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Randomized controlled trials (RCTs) demonstrate life prolongation by angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and aldosterone antagonists in heart failure. Nevertheless, many patients remain untreated and discontinuation is common (1–3).

For serious diseases, patients are as concerned about life expectancy as they are probability of survival to a fixed time point (4). It is not known whether the magnitude of the increase in life expectancy is provided to patients.

We examined whether clinicians communicate the potential increase in life expectancy when offering treatment to patients with heart failure. We then calculated from the trial data an increase in life expectancy that can be used by clinicians.

## METHODS

**QUESTIONNAIRE.** One hundred ten clinicians looking after patients with heart failure on a regular basis were asked to complete a questionnaire, of whom 107 (97%) accepted. This questionnaire asked:

- How do you explain to a patient why they should take an ACE inhibitor or beta-blocker?
- Do you give them an estimate of how much longer they will live if they take these medications? If not, why not?
- Do you describe adverse effects to patients when prescribing an ACE inhibitor or beta-blocker?

The clinicians were also presented with a hypothetical heart failure patient with an untreated baseline survival of 1 year. We asked them to estimate the

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Manuscript received November 20, 2013; revised manuscript received March 25, 2014, accepted April 3, 2014.

additional lifespan the patient would gain from being prescribed: 1) an ACE inhibitor; and 2) a beta-blocker.

**LITERATURE REVIEW.** Three parallel searches were undertaken for heart failure together with ACE inhibitors, beta-blockers, or aldosterone antagonists. Clinical practice guidelines and existing meta-analyses were also reviewed. When a publication relating to an RCT (follow-up or subgroup analysis) was identified, the original RCT was also reviewed. We included trials of medications licensed in heart failure that compared drug with placebo and presented Kaplan-Meier curves of all-cause mortality. We excluded trials in preserved ejection fraction and those requiring particular comorbidities.

**DATA EXTRACTION AND CALCULATIONS.** The Kaplan-Meier curves were digitized using Engauge (5).

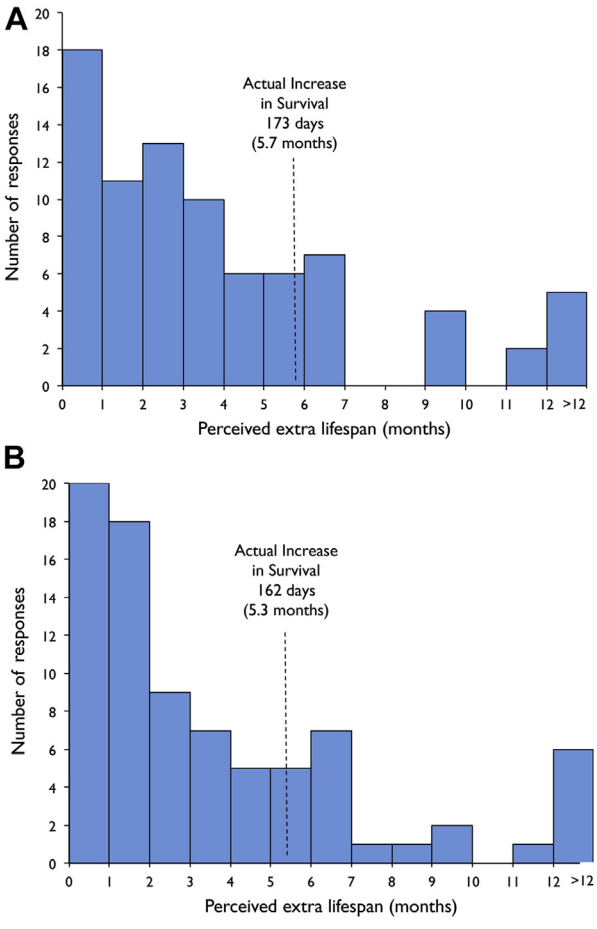


**FIGURE 1 Clinician Estimates of Additional Lifespan**

Clinician estimates of additional lifespan with **(A)** angiotensin-converting enzyme inhibitors and **(B)** beta-blockers for a hypothetical heart failure patient with an untreated survival of 1 year.

Treatment and placebo lifespan values were read at 100 equally spaced intervals as far as data existed for both arms (Online Figure 1). Where a trial included an RCT and open phase, only the RCT phase was analyzed.

We plotted the increase in lifespan against baseline lifespan, and fitted a linear regression through the origin. For example, a slope of +0.3 corresponded to a 30% proportional increase in lifespan. For each drug class, we weighted the trials by the number of deaths.

## RESULTS

**QUESTIONNAIRES ON INTERACTION WITH PATIENT.** Only 54 (50%) of clinicians explained to patients that they would live longer, and only 8 (7%) estimated the increased lifespan. The reason was not knowing what figure to give (85%) rather than feeling the patient would not want to know (11%). By contrast, the vast majority (85%) reported warning of potential adverse effects.

**ESTIMATES OF INCREASED LIFESPAN.** Twenty-five clinicians (23%) were unable to provide an estimate. For an ACE inhibitor, the estimated lifespan increase varied from 7 to 700 days with a median 90 days (interquartile range [IQR]: 50 to 180 days). For a beta-blocker, the estimated lifespan increase varied from 0 to 1,500 days, with a median 90 days (IQR: 37 to 180 days). The distribution of estimates is shown in **Figure 1**.

Substantial underestimation (by more than 2-fold) was more common than overestimation: 37% versus 9% for ACE inhibitors and 48% versus 9% for beta-blockers. Those underestimating the lifespan increase from ACE inhibitors also did so for beta-blockers (Spearman's $\rho = 0.81$, $p < 0.0001$).

**MEASUREMENTS OF LIFESPAN INCREASE FROM TRIALS.** We identified 16 studies in total for the 3 drug classes (Online Table 1). Four studies recruited patients in the post-infarct period. One recruited patients with nonischemic cardiomyopathy. We did not include studies specifically studying preserved systolic function but included the SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure) trial because almost two-thirds of the patients had a left ventricular ejection fraction ≤35%. The BEST (Beta-Blocker Evaluation in Survival Trial) trial was not included because bucindolol is not routinely used for the treatment of heart failure. Many trials were large. Median size was 1,973 (IQR: 567 to 2,589). Median follow-up was 15.6 months (IQR: 9.4 to 21 months). The median proportion of