

## 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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**R**andomized 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).

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.

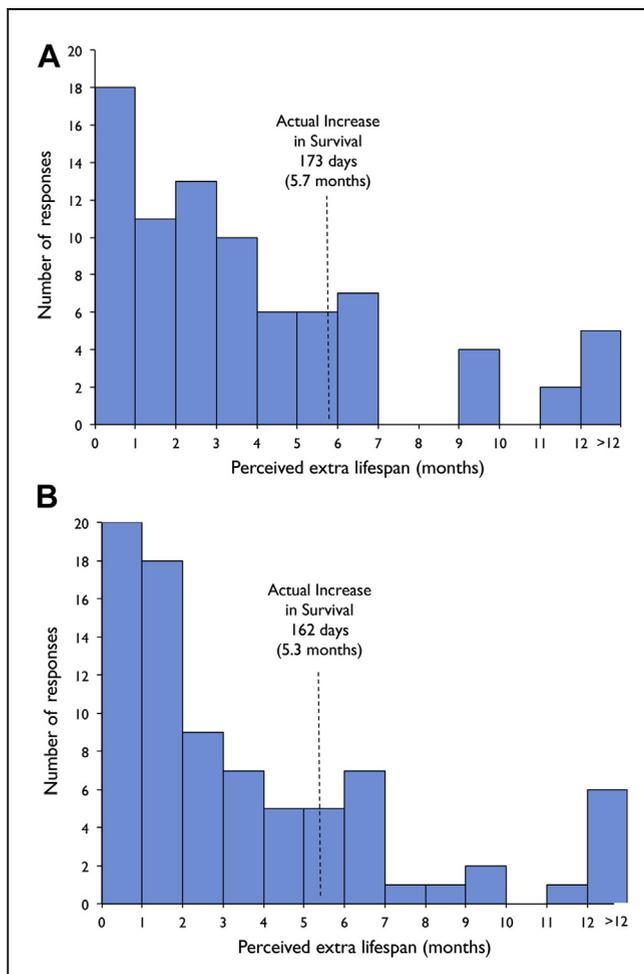
Only 54 (50%) of clinicians explained to patients that they would live longer, and only 8 (7%) estimated the increased lifespan. The reason was not knowing what figure to give (85%) rather than feeling the patient would not want to know (11%). By contrast, the vast majority (85%) reported warning of 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  $\leq 35\%$ . 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



**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.

the recruited cohort for which survival duration could be read from the graph for both arms was 18.8% (IQR: 14.4% to 25.1%).

**LIFESPAN INCREASE FROM DIFFERENT DRUG CLASSES.** For ACE inhibitors (Online Figure 2a), the proportional increase in lifespan ranged from +25% to +175% (weighted mean +48%). For beta-blockers (Online Figures 2b and 2c), the increase was +16% to +152% (weighted mean +44%). For aldosterone antagonists (Online Figure 2d), the increase was +30% to +43% (weighted mean +35%).

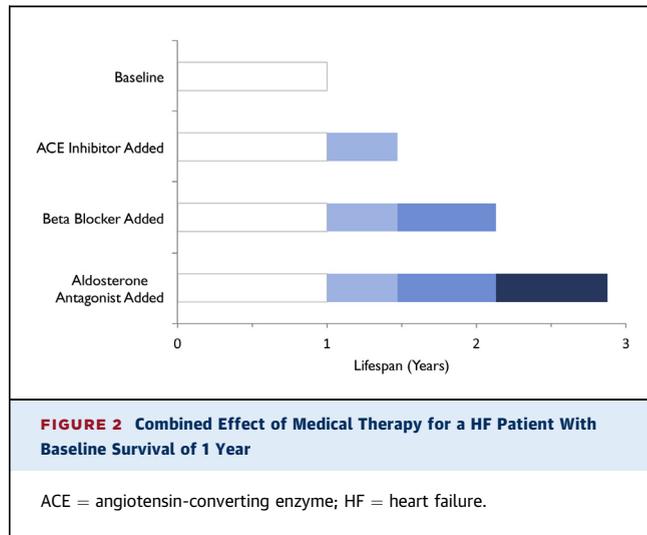
**CALCULATION OF COMBINED EFFECT.** Most trials of an agent had background therapy of the previously recognized prognostically favorable agents (Online Table 1). It is therefore possible to estimate the compounded effect of agents together. The compounding process is multiplicative; for example, to combine +48% and +44%, the calculation is  $1.48 \times 1.44 = 2.13$ , that is, a 2.13-fold expansion of lifespan. On this basis, being prescribed all 3 classes would increase survival from 365 days to 1,049 days; a scale factor of  $\times 2.87$  or almost a tripling (Figure 2).

## DISCUSSION

Clinicians are much more likely to convey perceived adverse effects than an increase in lifespan, even when many commonly listed adverse effects are no more likely to occur with treatment (6). Trainees specializing in heart failure follow curricula (7-9) that contain no direction to either estimate or communicate the magnitude of survival benefit.

There is no proof that provision of this information would translate into better concordance and outcomes. Nevertheless, although undertreatment of chronic conditions is multifactorial (10), when we preferentially tell patients of perceived harm rather than survival benefit, we may be missing a very cost-effective opportunity to improve survival. Although there are many barriers to initiation and long-term adherence with prognostically beneficial agents, imparting a simple memorable phrase to alert patients to the potential benefits of therapy may be helpful and is unlikely to cause harm. Direct testing of the usefulness of providing this information would be difficult, because such a trial would have to deliberately withhold information on survival benefit from 1 arm.

Most trials showed greater lifespan gain in patients with a better baseline survival. Whereas trials may report primarily the vertical distance between survival curves (reduction in risk of death), another



aspect of benefit is the horizontal distance between the same curves (lifespan gained).

**STUDY LIMITATIONS.** First, our calculation is correct only for the type of patient that enters a trial and dies within the trial duration, that is, those in whom heart failure is the dominant disease. For patients whose heart failure is milder, or who have extensive comorbidities (under-represented in trials), competing risks mean that the scaling up of lifespan from heart failure therapies will be smaller (11).

Second, the most formal way to calculate the lifespan gain would be to obtain data from trials that maintain randomization for the whole of patients' lives, and then conduct meta-analyses for each added class. If such trials are unavailable, one could conduct a forward-projection analysis using a competing risks model as we have done for cardiac resynchronization therapy (11). However, readers might require specialized software to replicate these calculations. Our simplified approach can be replicated by any clinician from publically available Kaplan-Meier curves.

A third limitation is that our analysis could only use trials that provided Kaplan-Meier curves of all-cause mortality. However, meta-analyses (12-14) show that the trials meeting our eligibility criteria were not outliers in terms of mortality effect size.

Fourth, some clinicians prefer to cross-check the results of RCTs against models including observational data, or against pairs of cohorts drawn from different generations. Models from observational data are often unreliable for evaluating interventions because confounding influences on decision making can so easily distort the results (15). The Seattle

Heart Failure model (16) might be suitable, however, because it draws heavily upon RCTs. In this model, the combined coefficients for ACE inhibitor, beta-blocker, and aldosterone antagonist provide a 2- to 3-fold increase in life expectancy. A suitable cross-generational comparison might be the treatment arm of the EMPHASIS (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) trial (which had ACE inhibitor, beta-blocker, and aldosterone antagonist, versus the placebo arm of the SOLVD (Studies of Left Ventricular Dysfunction) trial, which had almost none. This shows a 2.52-fold increase in survival duration.

Fifth, it should be remembered that dosing in clinical practice might not reach the level in trials. However, explaining lifespan gain to patients is unlikely to inhibit up-titration or promote abandonment.

## CONCLUSIONS

Clinicians behave asymmetrically when discussing prognostic agents in heart failure. There is focus on describing perceived harm even if not different from placebo (6), rather than confirmed increase in lifespan versus placebo. This article provides an estimate of lifespan benefit using a method that any clinician can replicate. A memorable summary for use in discussion of life-prolonging therapy might be “*triple therapy triples lifespan.*”

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**KEY WORDS** adrenergic, aldosterone antagonists, angiotensin-converting enzyme inhibitors, beta-blockers, heart failure, life expectancy

**APPENDIX** For supplemental figures and a table, please see the online version of this paper.