Should β-Blockers Be Used in Patients With Heart Failure and Atrial Fibrillation?

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ABSTRACT

Purpose: There is overwhelming evidence that β-blockers reduce cardiovascular hospitalizations and mortality in patients with heart failure and a reduced left ventricular ejection fraction provide they are in sinus rhythm. However, a recent meta-analysis of individual patient data provides compelling evidence that β-blockers are not effective in patients with heart failure and atrial fibrillation, although neither did they increase risk. The purpose of this article is to review the evidence, seek possible explanations for this observation, and make recommendations based on the limited evidence available.

Methods: Review and critical analysis of recent publications and meta-analyses on the use of β-blockers and other heart rate–slowing medicines in heart failure.

Findings: The reasons for the lack of effect of β-blockers in patients with heart failure are uncertain. There is a substantial body of evidence to suggest that patients with heart failure and atrial fibrillation who have less stringent ventricular rate control have a better outcome. The most plausible explanation for these findings, in our view, is that β-blockers exert similar benefits through similar mechanisms regardless of intrinsic heart rhythm but that the benefits of β-blockers are neutralized in patients with atrial fibrillation due to the induction of pauses that may impair cardiac function leading to worsening heart failure or cause arrhythmias resulting in death.

Implications: Smaller doses of β-blockers and other rate lowering agents to achieve a resting clinic heart rate in the range of 75-89beats/min might improve outcome. Preventing pauses by pacing or pulmonary vein ablation of atrial fibrillation are strategies that should be researched. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮)

Key words: heart failure, atrial fibrillation, rate control, prognosis, beta-blockers.

INTRODUCTION

Heart failure and atrial fibrillation (AF) have common origins and one often provokes the other.[1] In possibly half or more of patients with heart failure, clinically overt, persistent, or permanent AF will develop during the course of their disease,[2–4] and as many as one half of patients with AF have heart failure.[5] The prevalence of AF varies with and may contribute to the severity of heart failure, from ~10% of those with mild to as many as 50% of those with severe symptoms. Many more patients will have paroxysmal AF that may or may not be clinically apparent.[6] The prevalence of AF is similar or greater in patients with heart failure with a preserved ejection fraction (HFpEF) compared to heart failure with a reduced ejection fraction (HFrEF).[7–9]

β-Blockers in Heart Failure: Effective in Sinus Rhythm But Not in AF

A series of substantial randomized, controlled trials (RCTs) demonstrated that β-blockers could reduce the rate of hospitalization for heart failure as well as cardiovascular and all-cause mortality in patients with HFrEF.[10] Only 1 contemporary trial enrolled a substantial number of patients with HFpEF, with equivocal results in this group of patients.[11] Recently, an individual patient meta-analysis including all the landmark RCTs of HFrEF confirmed the benefits of β-blockers for patients with HFrEF in sinus rhythm but suggested that for patients with AF, β-blockers did not reduce the rate of hospitalization for heart failure or mortality[10] (**Figure 1**). It is possible that this is a chance finding,[12] but it is exceedingly likely that there is a strong association between heart rhythm and the clinical benefits of β-blockers. However, it should be pointed out that β-blockers did

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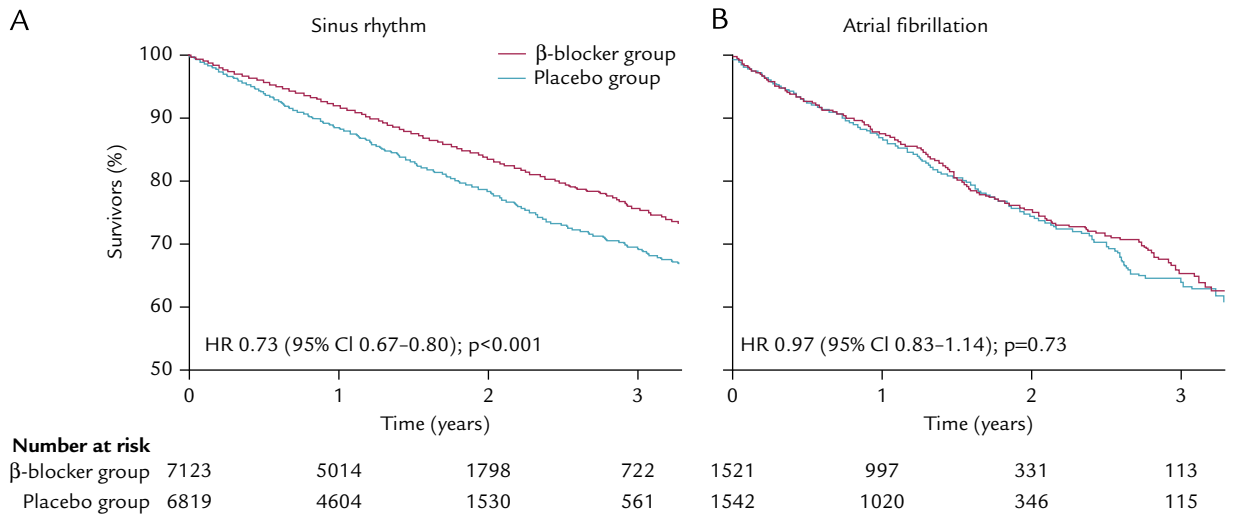

Figure 1. All-cause mortality in patients with sinus rhythm and atrial fibrillation in an individual patient data meta-analysis of landmark randomized, placebo-controlled trials of β-blockers in heart failure. HR = hazard ratio. Reproduced with permission.[10]

not increase risk in patients with AF. Interestingly, an analysis of the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure trial suggested that the benefits of nebivolol were also confined to patients in sinus rhythm, even in those with a left ventricular ejection fraction >35%.[13] Thus, heart rhythm rather than left ventricular ejection fraction may be the key determinant of the benefits of β-blockers in patients with heart failure. For patients in sinus rhythm, the reduction in mortality, hospitalization for heart failure, and their composite was ~30% ($P < 0.001$), an effect that might have been even larger had follow-up been censored for patients who developed AF, which presumably would have led to a loss of further benefit from β-blockers, although because the incidence of AF in these studies was only 5%, this effect would not be large. Information on the persistence and duration of AF before enrollment was not available, and assessment at a single point in time might not be robust.[10] However, such inaccuracies in data acquisition only serve to dilute observed effects. Although β-blockers do reduce the risk of the development of AF,[14] the annual incidence remains ~5%.[15]

Why Do β-Blockers Not Improve Outcomes in AF?

Understanding why β-blockers do not improve outcome in patients with heart failure and AF is hampered by uncertainty about the mechanism by which β-blockers mediate their benefits. β-Blockers block adrenergic receptors in a variety of tissues, including cardiovascular, brain, and adiposetissue. Some β-blockers are selective for particular receptors, and others have partial agonist activity. Changes in β_1- and β_1-receptor regulation and intracellular signaling and activating antibodies may be important and specific mechanisms for the effect of β-blockers.[16] However, β-blockers also have nonspecific effects, including slowing heart rate, leading to reductions in myocardial oxygen demand and the propensity to ischemia. This may divert adenosine triphosphate from consumption in the actin-myosin cycle to other important cellular functions that improve calcium handling, increase ryanodine channel stability, and reduce apoptosis. Improved cell and whole-organ function may reduce supraventricular and ventricular arrhythmias. How much these effects depend on heart rate reduction, which could be achieved by other means, and how much on adrenergic receptor blockade independent of heart rate reduction are uncertain. A study of β-blockers in patients with HFrEF who had pacemakers suggested that the improvement in cardiac function with β-blockers was lost when the pacing rate was increased from 60 to 80 beats/min (Table).[17]

In sinus rhythm, heart rate is strongly associated with survival, although evidence that the relationship