EDITORIAL COMMENT

Treatment of the Heart Failure Patient With Atrial Fibrillation

A Major Unmet Need*

Michael R. Bristow, MD, PhD,†‡
Ryan G. Aleong, MD†

Aurora, Colorado

Treatment of chronic heart failure (HF) in patients with reduced left ventricular (LV) ejection fractions (HFREF) has markedly improved in the last 20 years. Beginning with the success of neurohormonal inhibition in the 1990s and 2000s, the introduction of cardiac resynchronization therapy in the mid-2000s and, most recently, demonstration that heart rate (HR) slowing with ivabradine therapy (1) has beneficial effects additive to other therapies. Despite these achievements, much remains to be done, as HF continues to extract large societal tolls in terms of mortality, major morbidity, and healthcare economics.

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Treatment of atrial fibrillation (AF), the other common cardiac disorder that is steadily increasing in prevalence (2), has also shown progress. The introduction of new anticoagulants for stroke prevention (3) is an improvement on warfarin therapy, and approval of dronedarone as an AF prevention antiarrhythmic agent with an adverse event profile superior to that of amiodarone offers advantages for some patients (4).

However, all is not so sanguine at the intersection of AF and HFREF, which occurs commonly (5) due to overlap in their underlying pathophysiologies (6). One such example of therapeutic dissonance is described in the report by Rienstra et al. (7), which indicates that β-blockade, a cornerstone of HFREF treatment, is of little or no benefit in HFREF patients with AF. These authors performed a meta-analysis of the effects of β-blockers in patients with AF across four large phase 3 HFREF trials involving four different compounds approved for the

treatment of HF in at least some countries and found no benefit in outcomes compared to substantial benefits for patients in sinus rhythm (SR) (7). Given that AF is common (19% in the four trials examined by Rienstra et al. [7] and up to 40% in other reports) in HFREF patients and that pharmacologic effects of β-blockers could be different in AF, this issue deserves further attention. Cardiac resynchronization therapy and ivabradine, the latter targeting sinus node funny current I(f) channels (1) that are of lower density and importance in the AV node, are other effective SR-HFREF therapies that are less or not effective in AF-HFREF patients.

Analogously, there is also trouble in the use of antiarrhythmic drugs to prevent AF or control ventricular rate response in HFREF patients, in whom proarrhythmia is common and adverse effects on LV function may also compromise treatment. The most recent victim of these realities is dronedarone, which increases mortality in HFREF patients at risk for AF (8) or in both HF and non-HF patients in permanent AF (9). The clinician is thus faced with a relative lack of therapeutic options in the AF-HFREF patient. Based on the relatively high prevalence of AF and evidence that it worsens mortality rate in HF patients (5), treatment of AF-HFREF is a major unmet need in cardiovascular therapies.

Taking data from the report by Rienstra et al. (7) at face value, why would β-blockers not be effective in HFREF patients with AF? AF-HFREF patients tend to be older and have longer durations of HF than their SR counterparts, although in the analysis by Rienstra et al. (7), age was not different in every study and duration of HF was not reported. These characteristics could have diminished the response to β-blockers, but a metaregression analysis using age and additional factors that could affect outcomes did not diminish the effect of AF (7). In addition, the site of pharmacologic effect of β-blockers on HR slowing, an important component of the mechanism of action of β-blockers (1,10), in SR is different from that in AF. In SR, the predominant site of action is on sinus node β_1-adrenergic receptors (AR) and on β_2-ARs to a lesser extent, whereas in AF, the predominant impact is on atrioventricular (AV) nodal β-ARs that are $\sim$50% β_2 (11). This raises the question of whether the selective β_1-AR blocking agents used in three of the the four studies analyzed by Rienstra et al. (7) would effectively block the AV node and lower HR in high-adrenergic drive AF-HFREF patients. However, the degree of HR lowering appeared to be similar in AF and SR patients, with respective average reductions compared to placebo of 9.1 versus 10.5 beats/min (p = 0.17 by test for interaction) (7), so differential effects on HR do not obviously explain these results. Another possible explanation for ineffectiveness of β-blockers in AF-HFREF is that AF patients have higher levels of adrenergic drive than their SR counterparts (12), and it is possible that the degrees of competitive β-AR antagonism used in the 4 trials were inadequate to substantially antagonize β-adrenergic signaling in AF patients. That HR lowering

was similar in AF and SR patients (7) would argue against this, although HR is a poor surrogate measure of cardiac adrenergic activity.

The meta-analysis by Rienstra et al. (7) used four major β-blocker trials: CIBIS II (Cardiac Insufficiency Bisoprolol Study II, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure), MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure, and SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) and the US-Carvedilol Trial, which allowed for analysis of the currently available β-blockers approved in HFREF treatment. These trials were said to have used similar β-blocker "doses," by which the authors meant doses that would be expected to produce similar degrees of β-blockade. However, there are two noteworthy databases that were not used in the analysis: the BEST (13) and COPERNICUS (14) trials, which enrolled patients with more advanced HF and LV dysfunction. It is possible that inclusion of these latter trials would have impacted the level of interaction between β-blocker and baseline rhythm. In the case of the COPERNICUS trial (14), data for patients in AF at the time of study entry have not been reported and are apparently unavailable, whereas BEST trial AF data have been reported as a propensity score analysis (15) or are in press (12). Data from the BEST trial, which investigated the pharmacogenetically modulated β-blocker/sympatholytic agent bucindolol, do appear to be different from those reported by Rienstra et al. (7) for bisoprolol, metoprolol CR/XL, carvedilol, or nebivilol in that there is evidence of efficacy in the AF subset as well as efficacy enhancement in patients with the β_1389 arginine homozygous genotype (12). These differences could be the result of either bucindolol's unique mechanisms of action or the more advanced HF in the BEST patient population, and they raise the question of heterogeneity of β-blocker effectiveness in HFREF patients with AF.

One acknowledged weakness of the study by Rienstra et al. (7) is the lack of data for type of AF, and a maldistribution of AF duration between the β-blocker and placebo treatment arms could have affected the results. For this and other reasons related to retrospective analyses, the current meta-analysis (7) is meant to be hypothesis-generating, and prospective studies are needed. In that regard, it would appear to be ethical to compare placebo to a β-blocker in AF-HFREF patients in that available data support equipoise. At a minimum, data from the study by Rienstra et al. (7) suggest that AF-HFREF treatment should be approached differently from that for SR-HFREF, via therapies uniquely suited to dealing with this important subpopulation.

Reprint requests and correspondence: Dr. Michael Bristow, CU Cardiovascular Institute, 12700 East 19th Avenue, P-15, Room 8003, Campus Box B-139, Aurora, Colorado 80045. E-mail: michael.bristow@ucdenver.edu.

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