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EDITORIAL COMMENT

Understanding Mechanisms of Action of Beta-Blockers in Heart Failure With Reduced and Preserved Ejection Fraction*

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Heart failure (HF) is a global health challenge due to ageing populations and increasing burden of disease (1). Older HF patients have higher rates of preserved ejection fraction (HFpEF) and higher numbers of females and comorbidities (2). There are uncertainties in diagnosis of HF in the elderly, who may present with atypical symptoms, and the evidence base for conventional treatments is weaker especially for HFpEF (3).

The exact pathophysiologic mechanisms responsible for HFpEF are not clear. The condition is thought to be mediated by diastolic dysfunction (including myocardial hypertrophy, increased ventricular stiffness, and prolonged ventricular relaxation), but a simple and universal definition of HFpEF is lacking (4). Unfortunately, the therapeutic paradigm that has been successful in heart failure with reduced ejection fraction (HFrEF) has yet to be convincingly demonstrated in HFpEF. Without effective therapies, hospitalizations for HFpEF have increased, and risk of death and hospitalization appear similar to those of HFrEF (5). As a result, a dichotomy in outcomes has emerged between these 2 seemingly related pathophysiological states.

The physiological mechanisms of beta blockers appear to be well understood in HFrEF, blocking sympathetic neural activity, preventing catecholamine elevation, reducing heart rate, and reducing proapoptotic and cardiotoxic effects of cyclic adenosine monophosphate-mediated calcium overload (6). Several large trials and an individual patient data meta-analysis confirm an overall absolute reduction in the risk of death with beta blockers compared to placebo (7). However there was little evidence of benefit in patients with atrial fibrillation (hazard ratio: 0.97 compared to 0.73 for sinus rhythm). The apparent benefit of the composite of all-cause mortality and cardiovascular hospitalization in the SENIORS trial in patients with EF >35% (mean EF: 49%) was found to be similar to that in patients with EF ≤35% (mean: 28%), but mortality benefits appeared to be attenuated with higher EF (8). Other subgroups in whom there are doubts about efficacy of beta blockers are the elderly, women, and those with diabetes, and further analyses from the Beta Blockers Heart Failure Collaborative Group will help to clarify effects in these important subgroups.

CIBIS-ELD (Comparison of Bisoprolol and Carvedilol in elderly heart failure [HF] patients: a randomised, double-blind multicentre study; ISRCTN34827306) randomized 883 patients (mean: 73 years of age; 39% women; mean EF: 42%) to receive bisoprolol or carvedilol, to assess safety and tolerability over a 12-week titration period (9). Only one-fourth of patients in both groups achieved the target (10 mg of bisoprolol or 25 mg of carvedilol [which was twice the daily carvedilol dose]) with approximately 90% of subjects tolerating the starting or a higher dose. Adverse bradycardia was more common with bisoprolol, whereas pulmonary events were more common with carvedilol.

The paper by Edelman et al. (10) in this issue of *JACC: Heart Failure* extended these findings by

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stratifying the CIBIS-ELD cohort into HFpEF (EF: >45%) and HFrEF (10). HFpEF was diagnosed in 29% of patients with a mean EF of 59% compared to 35% in HFrEF. HFpEF patients were slightly older, more likely to be female, have lower heart rate, higher systolic BP, higher body mass index and less likely to have atrial fibrillation compared to the HFrEF group. Overall tolerability and safety of bisoprolol and carvedilol were similar in the 2 groups, but there were more likely to be delays to increased titration in the HFpEF group. Although

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there were similar reductions in heart rate from baseline to end of titration in both groups (approximately 7 beats/min), HFpEF patients showed greater reductions in systolic blood pressure while N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations showed elevation compared to HFrEF patients, who showed no detectable changes. Increases in New York Heart Association functional class, 6-min walk test results, and SF-36 questionnaire responses were greater in HFrEF patients than in HFpEF patients, and echocardiographic measurements, including EF and end-systolic and end-diastolic results, were improved in HFrEF patients, with no observable change in HFpEF patients (10).

CIBIS-ELD was a well conducted study and one of the few direct comparisons of beta-blockers in HF (9). The current analysis stratified by EF is important for several reasons. First, HFrEF patients tolerate speedier up-titration of beta-blockers than HFpEF, which seems counterintuitive. Second, there are differential mechanistic effect of beta-blockers in HF stratified by EF, as HFrEF responds better in terms of cardiac function, walking ability, and subjective measurements assessed by SF-36. Third, there is evidence that NT-proBNP shows little change or a potential rise in response to beta-blockers in HF, which again is counterintuitive but has been seen in previous studies (11). This opens up the question of the role of NT-proBNP in monitoring response to beta-blocker therapy in HF. These findings also suggest that HFpEF is a heterogeneous and poorly understood condition with various definitions in clinical trials. The analysis presented is not randomized and we should be cautious about overinterpretation. However the study provides a sound basis for future randomized trials of beta-blockers in elderly patients with HFpEF, to resolve an unmet need.

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REFERENCES

1. Chaudhry SI, Wang Y, Gill TM, Krumholz HM. Geriatric conditions and subsequent mortality in older patients with heart failure. J Am Coll Cardiol 2010;55:309–16.

2. Montero-Perez-Barquero M, Manzano L, Formiga F, et al., for the RICA investigators. Utility of the SENIORS elderly heart failure risk model applied to the RICA registry of acute heart failure. Int J Cardiol 2015;182:449–53.

3. Yancy CW, Jessup M, Bozkurt B, et al., for the Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association. J Am Coll Cardiol 2013;62:1495–539.

4. Abbate A, Arena R, Abouzaki N, et al. Heart failure with preserved ejection fraction refocusing on diastole. Int J Cardiol 2015;179:430–40.

5. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.

6. Satwani S, Dec GW, Narula J. Beta adrenergic blockers in heart failure: review of mechanisms of action and clinical outcomes. J Cardiovasc Pharmacol Ther 2004;9:243–55.

7. Kotecha D, Holmes J, Krum H, et al., for the Beta-Blockers in Heart Failure Collaborative Group. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384:2235–43.

8. van Veldhuisen DJ, Cohen-Solal A, Böhm M, et al., for the SENIORS Investigators. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction. J Am Coll Cardiol 2009;53:2150–8.

9. Düngen HD, Apostolovic S, Inkrot S, et al. Titration to target dose of bisoprolol versus carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. Eur J Heart Fail 2011;13:670–80.

10. Edelmann F, Musial-Bright L, Gelbrich G, et al. Tolerability and feasibility of beta-blocker titration in HFpEF Versus HFrEF: insights from the CIBIS-ELD trial. J Am Coll Cardiol HF 2016;4:140–9.

11. Taneja AK, Gaze D, Coats AJ, et al., for the SENIORS Investigators. Effects of nebivolol on biomarkers in elderly patients with heart failure. Int J Cardiol 2014;175:253–60.

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