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EDITORIAL COMMENT

Nebivolol in Older Adults With Heart Failure

Reduced Rates for Seniors?*

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How old would you be if you didn't know how old you are?

—Satchel Paige (1)

Heart failure constitutes a major growth industry in cardiovascular medicine reflecting the convergence of an aging population with lifesaving pharmacologic, electrical, and mechanical interventions (2). Although age is well recognized as one of the most powerful risk factors for morbid and mortal events, the treatment–risk paradox characterized by under-use of effective therapies in this population is striking (3). Because this paradox seems related to the lack of an evidence base in the oldest patients, the SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) trial has been welcome in addressing this gap (4). The American Heart Association advocates that prospective cardiovascular clinical trials enroll the elderly in proportion to their prevalence among the general treated population to better define the balance between benefit and risk (5). Yet, a closer look at the SENIORS trial yields additional insights into the treatment–risk paradox in older adults.

See page 2150

The SENIORS trial randomly assigned over 2,000 older adults (age ≥70 years) with a history of congestive heart failure to beta-blockers irrespective of ejection fraction (EF) (4). Undertaken in both western and eastern Europe, this study was a placebo-controlled trial of a third-generation beta-1-selective blocker, nebivolol. This agent has vasodilating properties attributed to nitric oxide modulation thought to be potentially advantageous in patients with diastolic dysfunction and heart failure (6). The trial concluded enrollment in December 2002 with a 21-month follow-up and showed a 14% reduction (vs. projected 25% reduction) in the primary composite end point of mortality and cardiovascular hospital readmission from the placebo rate of 35.3%. No influence was evident from subgroup analysis by age, sex, or EF. However, intriguing trends were noted toward less benefit in older adults and more benefit in those with reduced EF and in female subjects (interaction term $p = 0.11$).

Based on the primary SENIORS report, the 2008 European Society of Cardiology Heart Failure guidelines now include nebivolol with the other 3 standard beta-blockers as a Class 1A recommendation in symptomatic heart failure with a left ventricular (LV) EF ≤40% (7). In this issue of the *Journal*, 4 years after their primary report, the SENIORS trial investigators further evaluate the relative efficacy of nebivolol therapy on patients with diminished versus preserved (relatively) EF (>35%) (8). About one-third versus the originally projected one-half of patients had preserved LV function. As previously reported, the modest treatment benefit was equally applicable to those with diminished versus those with preserved EF. When results were further explored as a continuous variable as well as across 4 EF subgroups between ≤30% and ≥46%, no significant interaction between treatment effect and EF was seen.

Does the current study add to our understanding of the mechanism of benefit attributable to nebivolol across differing baseline EFs? Clearly the agent had a larger effect on EF in patients with a baseline ≤35% versus those >35%, although the 5-point absolute parallel increase in EF in the low-EF placebo group suggests caution in attribution of all of this change to study drug. A more modest but statistically significant increase in EF was seen with nebivolol in those with baseline EFs >35%. Previously a small echocardiographic substudy of the SENIORS trial failed to show any improvement in diastolic performance (9). Hence, the mechanism of the benefit attributable to nebivolol in those with preserved LV function remains speculative. Benefit accruing from a reduction in peripheral vascular resistance, myocardial ischemia, or cardiac dysrhythmia are all plausible but unproven. It should be noted that although the primary outcome composite effect was similar in low and preserved EF groups, there was only a 1.1% absolute (difference n = 3) reduction in all-course mortality in those with EFs >35% versus a 2.8% (difference n = 20) absolute difference for those with EFs ≤35%.

Does the current study enhance understanding of nebivolol's mechanism of benefit across the spectrum of age? What potential implications emerge for future studies in the elderly? In the primary SENIORS report, there was a hint of an attenuated treatment effect in those above the cohort median age of 75.2 years: this was even more marked in the very elderly (age >85 years). In general, as risk increases, so should the observed benefit of an agent that directly modifies that risk. Hence the blunting of effect in the oldest

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group, and perhaps also the reduced overall effect in the SENIORS trial compared with that predicted, deserves consideration. First, the benefit of nebivolol use on mortality in older adults may be attenuated by competing contributors to death not modifiable by nebivolol. Although the pre-specified component of the primary end point, that is, cardiovascular hospitalization, was reduced by nebivolol, all-cause hospitalization was unchanged. Second, it was only the highest dose of nebivolol that was associated with event reduction in the SENIORS trial. During the titration phase, 7% of patients could not tolerate any nebivolol, and 33% were not at the dose at which mortality benefit was clear (10). Those unable to tolerate target doses were older and were more likely to be receiving other pharmaceuticals that alter heart rate and conduction (antiarrhythmic agents and calcium blockers). This underscores the challenges of the generalizability of this trial to older adults in clinical practice, where polypharmacy, pre-existing frailty, and conditions affecting tolerability of beta-blockers in maximal doses are more prevalent. Lastly, in older adults, functional outcomes are at least equally as important as mortality benefits. Unfortunately and surprisingly, the pre-specified secondary outcomes of functional capacity by New York Heart Association functional class and 6-min walk test in the SENIORS trial have never been reported: these data would greatly assist clinicians in applying the overall result (11). The net clinical benefit incorporating functional and mortality outcomes to ensure a positive balance from the achieved dose is the desired end point in this population. It is therefore likely that patient-centered, evidence-based medicine operating in the real world explains at least some of the observed treatment–risk paradox in relation to beta-blockers in older heart failure patients. Ironically these end points are well aligned with Satchel Paige's sage query (1) introducing this editorial, as well as a recent Class 1B American College of Cardiology/American Heart Association recommendation articulating that for older patients "decisions on management . . . should be patient centered, with consideration given to general health, functional and cognitive status, comorbidities, life expectancy and patient preferences and goals" (12). We desperately need more and better clinical trials in older adults that reflect new understanding of key definition and design issues. Building these metrics, assessments of variation in older adults using phenotypic and biological constructs, determining relevant net clinical end points, and understanding the selection of patients using registries as shown in Figure 1 will help provide the answers we urgently need for the future. Seniors with heart failure have a reduced rate of beta-blocker usage and reduced rates of inclusion in cardiovascular clinical trial populations relative to their contribution to the mortality and morbidity of the diseases under study. If they have the same or a reduced mortality benefit, then it is vitally important to understand what effect new treatments have on the quality of their remaining life. The future for seniors is now.

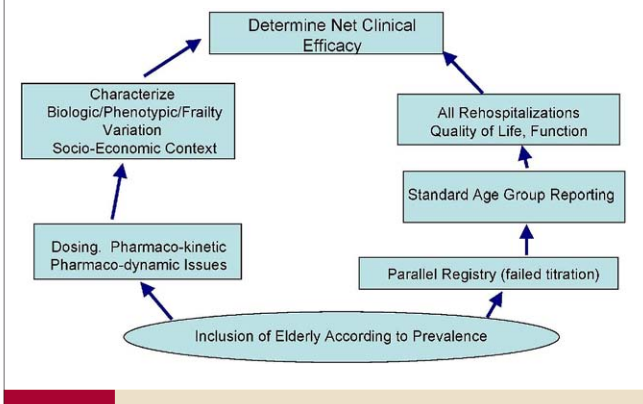

Figure 1 **Winning Clinical Trial in the Elderly**

Starting at the **bottom of the figure**, the upward thrust incorporates key elements especially relevant to clinical trial design in older adults with cardiovascular disease.

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Key Words: heart failure ■ elderly ■ beta-blocker ■ preserved ejection fraction.