Letters

TO THE EDITOR

Decreased Mortality With Beta-Blockers in Patients With Heart Failure and Coexisting Atrial Fibrillation

With great interest we read the study by Cadrin-Tourigny et al. (1) in a recent issue of JACC: Heart Failure. In a propensity-matched analysis, these investigators showed that the use of beta-blockers was associated with lower mortality rates, but not with fewer hospitalizations or lower cardiovascular mortality rates, in patients with heart failure (HF) with reduced ejection fraction and atrial fibrillation (AF). Interestingly, these results are in contrast to the findings of 2 meta-analyses of placebo-controlled randomized clinical trials of beta-blockers in HF, in which patients with AF were compared with patients in sinus rhythm. In those 2 meta-analyses, beta-blockers had no effect on mortality rates in patients with HF and AF (2).

The finding that beta-blockers did not improve outcome in patients with HF and AF (2) was somewhat surprising and counterintuitive. Indeed, in the recent European Society of Cardiology HF guidelines, beta-blockers are still recommended for rate control in AF (and HF), but the possibility that they may not improve outcome is also recognized (3). At this time, however, beta-blockers should certainly not be stopped in patients with HF and AF, but new data that may shed additional light on this discussion are more than welcome. The present study by Cadrin-Tourigny et al. (1) may be a new angle to this discussion, and the authors are to be congratulated for their contribution to this clinically relevant field.

Nevertheless, potential limitations of the present data should be noted. First, clearly, beta-blocker use was not randomized in the study of AF and congestive HF and was not included in the matching. The reasons for not using beta-blockers in these patients with HF with reduced ejection fraction would be useful to know because the use of these drugs, as stated earlier, was and still is an important recommendation in current HF guidelines. Second, by using propensity-matched analyses, a reduced sample size is obtained. The patients are matched on baseline characteristics, thus implying that a full dataset is necessary, especially when missing data are not randomly missing, a situation that could introduce a form of selection bias and reduce statistical power. Bias can be caused by incomplete matching in which some treated patients are excluded when no control patients are found. Finally, bias resulting from unmeasured variables may remain after matching. We believe that propensity matching is an interesting way of analyzing data, but it also has significant limitations. Certainly, it may lead to confusion, as was recently shown with 2 subanalyses of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial that examined the efficacy and safety of digoxin and showed significantly different results (4,5).

Therefore, we believe that the present data are intriguing, but they should be interpreted with significant caution. Still they may be valuable because they shed new light on this issue, and we agree with Drs. Piccini and Allen, who wrote the editorial and stated “that we should not bury beta-blockers yet for this indication.”

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REPLY: Decreased Mortality With Beta-Blockers in Patients With Heart Failure and Coexisting Atrial Fibrillation

We appreciate the thoughtful critique of our study from Dr. Mulder and colleagues, which addresses the controversy regarding a survival benefit associated with β-blockers in patients with heart failure with reduced ejection fraction (HFrEF) and concomitant atrial fibrillation (AF) (1).

We generally agree with the limitations raised by Dr. Mulder and colleagues concerning propensity matching in observational research, including the resulting reduction in sample size and potential for residual confounding due to unmeasured variables. We also recognize that bias due to incomplete matching is a valid consideration, although in our particular study, the magnitude of effect was unlikely to be substantial considering most patients without β-blockers (79%) were successfully matched to patients on β-blockers. Similarly, nonrandomly missing data is indeed a theoretical concern with propensity-matched analyses. However, it was unlikely to be a major source of bias in our study considering that the proportion of missing data for all covariates was low (0% to 5%) and that there was no reason to suspect that missing data differed systematically according to exposure status.

Broad categories for the nonuse of β-blockers in the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trial were intolerance (18.2%), pulmonary disease (24.1%), physician discretion (41.6%), and other (16.2%). This type of variable cannot be included in generating a propensity score for matching because it does not apply to patients on β-blockers. We also disagree that including “only patients with (history of) AF” is a potential limitation. External validity is achieved by selecting a study population that is representative of the target population, that is, patients with HFrEF and AF. Every patient in our study had HFrEF and documented adjudicated AF at entry. In contrast, in the meta-analyses by Kotecha et al. (2) and Rienstra et al. (3), only 16.8% and 19.3% of patients with HFrEF were identified as having AF, respectively. These low estimated prevalence rates likely reflect misclassification errors owing to the fact that a single baseline electrocardiogram fails to capture a sizeable proportion of patients with nonpermanent AF. Insensitivity of this screening methodology could potentially yield a nonrepresentative study population.

We commend Dr. Mulder and colleagues for their important and insightful contributions to the debate surrounding β-blockers in patients with HFrEF and concomitant AF. We agree that the diverging observational studies conducted to date (2,3), including our own (1), should be considered hypothesis-generating. Despite lingering uncertainties, it is noteworthy that authors from conflicting studies concur that it could be detrimental to prematurely dismiss potential benefits of β-blockers in patients with HFrEF on the basis of coexisting AF.

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