(the inverse of beta-blockers, in which clinicians tend to prescribe to higher risk patients), where propensity-matching was unable to replicate the results of RCTs (4). Confounding may also explain why Cadrin-Tourigny et al found such discrepant findings for death and hospitalization. Furthermore, only 57% of their population was actually in AF at the time of analysis. We have already shown how effective beta-blockers are in preventing AF (and therefore subsequent adverse outcomes) for patients with AF in sinus rhythm (5). A few methodological issues also arise on detailed review, including the divergence in matched groups, omission of paroxysmal versus persistent AF from the standardized difference plot (with clearly >10% difference), and misrepresentation in the abstract about the sample size (n = 655 [not 1,376], with just 95 deaths without beta-blockers and 136 deaths on beta-blockers).

We considered the requirement for AF on the baseline electrocardiography a strength of our previous analysis, which demonstrated a significant interaction in beta-blocker efficacy according to heart rhythm using data from double-blind, placebo-controlled RCTs in patients with HF and predominantly reduced left ventricular ejection fraction (5). Using systematic, carefully checked, and harmonized individual patient data from 10 trials, we identified no significant benefit from beta-blockers in >3,000 patients with concomitant AF, consistent across all outcomes studied and based on a published design paper and pre-specified analysis plan.

Where, as a body of clinical scientists, do we go from here? The answer lies in new RCTs, rather than more analyses of observational data.

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http://dx.doi.org/10.1016/j.jchf.2017.02.013

Please note: Dr. Kotecha is the Chief Investigator for RATE-AF (Rate Control Therapy Evaluation in Permanent Atrial Fibrillation trial; NCT02391337) and the lead for BB-meta-HF (Beta-blockers in Heart Failure Collaborative Group study; NCT00832442); has received research grants from Menarini; has received professional development support from Daiichi-Sankyo; and has received lecture fees from AtriCure. Dr. Flather has received personal fees from AstraZeneca; and has received grants from Novartis, all outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## REPLY: Observational Versus Randomized

### Sliding Toward Nonevidence-Based Medicine

We thank Dr. Kotecha and colleagues for their interest in our study (1). However, we feel obliged to correct several inaccurate and misleading statements, including the catchy but deceptive title. Although Dr. Kotecha and colleagues portrayed their pooled analysis (2) as above the fray of observational research, it should be pointed out that their study was also observational. Despite the care with which it was planned, a post hoc analysis of selected trials is retrospective in nature and subject to several limitations, including search, selection, and publication biases, heterogeneity issues, constraints related to pooling nonuniformly defined variables across studies, and incomplete data. Such limitations have led to the observation that meta-analyses provide discordant results to subsequent large trials in 35% of cases (3).

More specific to the population in question, our AF-CHF (Atrial Fibrillation-Congestive Heart Failure) trial explicitly focused on patients with atrial fibrillation (AF) and heart failure. Inclusion criteria were detailed and AF history was comprehensively characterized. In contrast, studies included in the analysis by Kotecha et al. (2) were not designed to assess a population with AF. As a result, the investigators retrospectively relied on a single nonadjudicated baseline electrocardiogram to define a population with AF. That they consider this “a strength” is misguided, perhaps reflecting an over-simplistic view of a complex entity with a variable disease course. Although all subjects in the AF-CHF trial had electrocardiographically documented and adjudicated AF at entry, the proportion in AF at any given time fluctuated throughout the study.

Another important point of clarification is the suggestion that “confounding may also explain why

the authors…found such discrepant findings for death and hospitalization." It is incongruent to claim that the mortality reduction was driven by residual confounding due to a higher probability that lower risk patients received β-blockers, while simultaneously attributing a lack of reduction in hospitalizations to the same confounding by indication. It would be more logical to expect such a bias to have a similar impact on both outcomes. It is also worth noting that pattern of AF was deliberately omitted from the propensity score (and, hence, standardized difference plot) for the purpose of assessing whether it modulated the effect of β-blockers on outcomes. No such interaction was identified.

We fully support the highest standards of evidence-based medicine and concur that a well-designed randomized trial would be of great value. In the interim, we conclude that it is premature to deny patients with AF and heart failure β-blocker therapy considering the totality of evidence, including the observational study by Dr. Kotecha and colleagues and our own post hoc analysis.

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http://dx.doi.org/10.1016/j.jchf.2017.03.002

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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