Letters to the Editor

Health Care System for Reducing Readmissions for Heart Failure

We have read with interest the editorial of Vaduganathan et al. (1). We strongly agree with the authors regarding the importance for our patients and our health care system of reducing readmissions for heart failure among those initially admitted to hospital, as well as reducing initial admissions. In addition, we recognize the appropriateness of the authors’ recognition of the importance for our patients and our health care system for reducing readmissions for heart failure among those initially admitted to hospital, as well as reducing initial admissions. In addition, we recognize the appropriateness of devices, educational initiatives and other nonpharmacological approaches when drugs also are used. Nonetheless, given recent publications in this field, including our own, we believe the authors may wish to reconsider some of their statements about strategies for reduction in early readmissions.

First, the authors indicate that the use of ivabradine, which we have specifically assessed in the 6,505-patient SHIFT (Systolic Heart Failure treatment with the If inhibitor ivabradine Trial), had no impact on early readmissions. They inferred this from “inspection of the survival curves” in the initial SHIFT study report by Swedberg et al. (2). However, this publication is not at all relevant to the readmission issue because it presents only time-to-first-event analyses of the primary composite endpoint (cardiovascular mortality or heart failure hospitalizations) and of the secondary endpoint of heart failure hospitalizations alone, both of which were marked and significantly reduced by ivabradine (hospitalizations by 26%). No data of any kind about readmissions were presented. Nonetheless, based on the same concern about the need to reduce readmissions indicated by Vaduganathan et al. (1), more than a year ago we published a post-hoc analysis of the SHIFT study data focusing specifically on hospital readmissions among the 1,186 patients who, throughout the full duration of the SHIFT study, were admitted to the hospital for worsening heart failure at least once (3). This study revealed a 34% reduction in second heart failure hospitalizations among those who were admitted once and a 29% reduction in readmissions among those who, despite the initial benefit, were admitted twice. All-cause and cardiovascular hospitalizations were reduced in parallel. Moreover, in addition to assessing admissions using a “total time” approach encompassing all admissions for all patients throughout the trial, we also specifically evaluated time to a second admission with a “gap time” approach, encompassing only patients who had both a first and second admission during the trial. This analysis revealed a 17% increase in time to a second hospitalization associated with ivabradine versus placebo, although, of course, from the total time analysis, highly significantly fewer patients who suffered a first admission ever suffered a second admission when ivabradine was used instead of placebo. Clearly, these analyses indicate the benefit of therapeutic heart rate slowing with ivabradine, on a background of beta-blockade, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors; mineralocorticoid receptor antagonists (MRAs); and diuretics (background therapy mandated, when possible, by the trial protocol), in reducing early, as well as later, readmissions. Indeed, the use of all admissions in analyses like ours from the SHIFT study add considerable and critically important data not available from time-to-first-event analyses like that referenced by Vaduganathan et al. (1). Review of several trials, indicates that more than one-half the admissions data are lost when time to first event, alone, is considered.

Regarding the possible synergy of digoxin and other drugs, suggested by Vaduganathan et al. (1), this is difficult to assess for ivabradine because only 32% of patients in the SHIFT study readmission analysis were receiving digitalis compounds at the time of study entry, and digitalis was not added to the regimen during the study. However, approximately 70% of patients were receiving MRAs at entry (again, none was added during the trial); thus, we cannot assess the possible synergy on readmissions between ivabradine and MRAs, although the clear and significant effect of ivabradine on readmissions irrespective of digitalis or MRA administration argues in favor of a highly significant independent effect of ivabradine for this outcome. The latter inference is consistent with the recent analyses demonstrating a parallel effect of ivabradine on outcome among those patients in the SHIFT study who were receiving MRAs and those who were not.

We did not study the effects of digitalis compounds in the SHIFT study, and we agree that Vaduganathan et al. (1) raise an interesting hypothesis about the potential benefits of digitalis compounds, specifically in preventing early readmissions. However, we would note the recent article of Freeman et al. (4) who analyzed the effects of de novo use of digoxin in adults with incident systolic heart failure between 2006 and 2008 in the database of the Kaiser Permanente Northern California system. These authors adjusted for medical history, laboratory results, concomitant medications, heart failure severity, and...
the propensity for digoxin use and found that during a median 2.5 years, digoxin was associated not only with higher rates of death (14.2 vs. 11.3 per 100 person-years) but also specifically with higher rates of heart failure hospitalization (28.2 vs. 24.4 per 100 person-years) than nonuse. In addition, it may be relevant to note that, in the now relatively old DIG (Digitalis Investigation Group) trial (3), digoxin reduced heart failure readmissions but significantly increased other cardiovascular hospitalizations (hazard ratio: 1.20; 95% confidence interval: 1.05 to 1.38). By contrast, as noted in the preceding text, in the SHIFT study, ivabradine reduced all-cause and cardiovascular hospitalization, as well as heart failure hospitalizations. Finally, because of the relatively small number of events within 30 days of initial admission and the lack of power to assess the significance of any difference, we did not include information about readmissions specifically within 30 days in our 2012 publication on ivabradine’s effects on heart failure readmissions (3). However, we did collect these data, and they were consistent with a clear benefit of ivabradine in preventing early readmission: thus, among those patients who suffered a first hospitalization during the SHIFT study, readmission occurred within 30 days in 21 of the 514 patients (4.1%) randomized to ivabradine versus 42 of the 672 patients (6.3%) randomized to placebo.

In summary, the editorial by Vaduganathan et al. (1) raises important and thought-provoking hypotheses. However, until these are formally tested in appropriately designed trials, it seems reasonable to infer from firm data that therapeutic heart rate slowing with ivabradine, on a background of beta-blockade, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors; MRAs; and diuretics, is highly likely to reduce both early and late readmission rates for systolic heart failure.

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REFERENCES

REPLY: Effect of Ivabradine on Early Readmissions After Hospitalization for Worsening Heart Failure

We agree with Dr. Borer and colleagues that the retrospective analysis of the SHIFT (Systolic Heart failure treatment with the IF inhibitor ivabradine Trial) showed a significant reduction in readmissions in response to ivabradine therapy; however, this reduction occurred over a relatively long period of time in patients already receiving this medication. In our paper (1), we are referring to a specific time frame soon after hospitalization, which in the past, we called “the vulnerable phase.” Simply defined, the vulnerable phase is the immediate postdischarge period. Although morbidity and mortality during hospitalization may still occur, a substantial number of patients are readmitted for worsening heart failure within 30 days after discharge. Available data suggest that the congestion manifested by dyspnea most likely due to high left ventricular filling pressures is the main reason for hospitalization and rehospitalization. Most patients admitted with worsening chronic heart failure improve in response to diuretic therapy with minimal clinical congestion at the time