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 (5), 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.

*Jeffrey S. Borer, MD
Michael Böhm, MD, PhD
Ian Ford, PhD
Michel Komajda, MD
Karl Swedberg, MD, PhD
Luigi Tavazzi, MD

*State University of New York Downstate Medical Center and College of Medicine
Department of Medicine
Division of Cardiovascular Medicine
47 East 88th Street
New York, New York 10128-1152
E-mail: jsborer1@gmail.com

http://dx.doi.org/10.1016/j.jchf.2014.12.004

Please note: Dr. Borer has received fees for consulting from Servier Laboratoires, manufacturer of ivabradine, and Amgen, U.S. licensee of ivabradine; speaker's fees from Servier Laboratoires and Amgen; research funding from Servier Laboratoires; and honoraria and/or consulting fees from Novartis, Pfizer, JenaValve, Takeda USA, Cardiorentis, ARMGO, Celladon, Celgene, and Sanofi. Dr. Böhm has served on the advisory boards of AstraZeneca, Bayer AG, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi, and Servier Laboratoires; and on the Speakers Bureaus of Astra Zeneca, AWD Dresden, Bayer AG, Boehringer Ingelheim, Berlin-Chemie, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi, Servier Laboratoires, Medtronic. Dr. Ford has received committee honoraria, speakers fees, and research funding from Servier Laboratoires; and has served as a consultant for Amgen. Dr. Komajda has served on the advisory boards of BMS and AstraZeneca; has received fees for consulting from Servier Laboratoires; has been on the Speakers Bureaus of Sanofi, BMS, AstraZeneca, MSD, Menarini, and Novartis; and served on the executive committee of the SHIFT trial. Prof. Swedberg has received honoraria and research funding from Servier Laboratoires. Dr. Tavazzi has been on the Speakers Bureau of Servier Laboratoires; and has received research funding from Servier Laboratoires.

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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 I[f] 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

of discharge (e.g., edema). Despite this, their natriuretic peptide levels remain persistently high, which suggests that they are being sent home with relatively high ventricular filling pressures (2). We call this "hemodynamic" congestion, which reflects an increase in intravascular volume. In the first few weeks after discharge, a significant number of patients develop worsening congestion that requires hospitalization. This is due to abnormal hemodynamics, mainly an increase in pulmonary capillary wedge pressure and/or a low cardiac output. Early readmission is often not related to progression of heart failure but to less than optimal treatment of congestion during hospitalization. In patients with left ventricular systolic dysfunction, the maintenance of cardiac output may be achieved by a compensatory increase in heart rate, which is a poor prognostic indicator (3). Thus, elevated heart rate may be a marker rather than a therapeutic target. Accordingly, reducing heart rate that is compensatory may worsen hemodynamics and therefore precipitate clinical congestion. To the best of our knowledge, ivabradine is not known to improve hemodynamics other than by its predominant effect in decreasing heart rate. Alternatively, reduction in heart rate during or early after hospitalization could be of benefit in those patients whose increase in heart rate is not compensatory. We need to keep in mind that the retrospective analysis by Dr. Borer and colleagues was conducted in patients already receiving ivabradine. This is different than starting ivabradine pre-discharge or soon after discharge in the vulnerable phase during which hemodynamics continue to be abnormal and often worsens. We welcome a prospective study assessing the effects of ivabradine started prior to or soon after discharge in patients hospitalized for heart failure. We recommend that congestion during the vulnerable phase be effectively treated with loop diuretic, mineralocorticoid receptor antagonist, and digoxin therapy. In terms of digoxin, it is known to have very little effect on the sinus node, and the decrease in heart rate is secondary to an improvement in hemodynamics that is noted within hours after it is administered (4).

*Mihai Gheorghiade, MD
Muthiah Vaduganathan, MD, MPH
Gregg C. Fonarow, MD
*Center for Cardiovascular Innovation
Northwestern University Feinberg School of Medicine
201 East Huron, Galter 3-150
Chicago, Illinois 60611
E-mail: m-gheorghiade@northwestern.edu
http://dx.doi.org/10.1016/j.jchf.2014.12.010

Please note: Dr. Fonarow has received research support from the Agency for Healthcare Research and Quality and has consulted for Medtronic, Gambro, and Novartis. Dr. Gheorghiade has consulted for Abbott Laboratories, Astellas, Astra Zeneca, Bayer Schering Pharma AG, CorThera, Inc., Cytokinetics, Inc., Debio-Pharm SA, Errekappa Terapeutici (Milan, Italy), GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Otsuka Pharmaceuticals, Pericor Therapeutics, Protein Design Laboratories, Sanofi, Sigma Tau, and Solvay Pharmaceuticals. Dr. Vaduganathan has reported that he has no relationships relevant to the contents of this paper to disclose.

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Coenzyme Q_{10}

Will This Natural Substance Become a Guideline-Directed Adjunctive Therapy in Heart Failure?

Ezekowitz expressed in an editorial comment (1) his opinion about the Q-SYMBIO study (Coenzyme Q10 as adjunctive treatment of chronic heart failure: a randomised, double-blind, multicentre trial with focus on SYMptoms, BIomarker status [Brain-Natriuretic Peptide (BNP)], and long-term Outcome [hospitalisations/mortality]) (2) with the following conclusion: "Heart failure (HF) patients are spending a lot of energy trying to be normal. Let us help them."

Yes. HF is a disabling disease with a poor prognosis despite significant advances in drug and device-based therapies. The results of the Q-SYMBIO study demonstrate that supplementation with coenzyme Q_{10} (CoQ10) in addition to conventional therapy: 1) improves symptoms; 2) improves survival; and 3) reduces hospitalization rate.

Yes. The investigators are encouraged about the study outcomes. The number of patients needed to treat (NNT) for 2 years to prevent 1 death is calculated to 10 based on the hazard ratio (in favor of CoQ10) and the survival rate at 2 years. This estimate of NNT is low compared with NNTs in other HF trials.

Yes. CoQ10 is necessary for the normal function of all cells, and supplementation with CoQ10 has been clinically tested in various disease states in more than