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).

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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

200 randomized controlled trials (RCT) as listed on Medline. None of these trials have reported serious adverse effects. A few incidences of mild gastrointestinal discomfort have been registered, probably due to the vegetable solvent in the capsule and not by CoQ10 per se. The 42% lower all-cause mortality in the CoQ10 group in the Q-SYMBIO study compared with placebo is indicative of the safety profile.

The preparation used in the Q-SYMBIO trial (Myoqinon) is a licensed medicinal product in Hungary, a European Union Member, for adjunctive treatment of HF, which further supports the safety of CoQ10.

Ezekowitz (1) questions whether the results of the Q-SYMBIO study would be replicable in a larger study. It is unlikely to be a large-scale trial, as funding is difficult when using a nonpatentable substance. A confirmatory trial with CoQ10 could be done, but then the important question would be, is it ethical to wait for the results of a new trial with the present survival data in Q-SYMBIO study?

RCTs with a similar size as the Q-SYMBIO study have been guideline changing in HF. The CONSENSUS I (Cooperative North Scandinavian Enalapril Survival Study) (3) from 1987 with enalapril of 253 patients changed clinical practice in HF. Also, the initial beta-blocker trials had fewer patients enrolled compared with the Q-SYMBIO study, for example, the PRECISE trial (4) with 278 patients.

CoQ10 was acknowledged in a previous American College of Cardiology/American Heart Association HF guidelines from 2005 (5) to have a possible effect in some studies, but supplementation was not recommended until more data were available. The positive survival data from the Q-SYMBIO study and the meta-analyses of RCTs regarding ejection fraction and/or New York Heart Association classification give us a more robust documentation for CoQ10 treatment in HF.

Unlike current pharmacological interventions, CoQ10 supplementation restores a deficiency state that may otherwise contribute to symptoms and reduced survival in patients with HF.

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REPLY: Coenzyme Q_{10}

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

Dr. Mortensen raises a number of points that need clarification and context.

First, the references to current therapeutics (angiotensin-converting enzyme inhibitor and beta-blocker) success in smaller clinical trials are taken out of context. A practice change and recommendations occurred *after* the confirmatory adequately powered randomized controlled trials (RCTs) were complete. Other therapies have not made it by this necessary hurdle as a result of lack of efficacy or safety. On the basis of Dr. Mortensen's rationale, many nonefficacious and potentially toxic medications would be on the market and in patient pill bottles had the adequately powered RCT not been done.

Second, although promising, safety is not established (1). Lack of reporting to regulatory authorities does not mean lack of safety events, because coenzyme Q_{10} (CoQ10) is not subject to any rigorous reporting such as post-marketing surveillance. Clinical trials are only 1 method to review safety and an imperfect one given the narrow inclusion and broad exclusion criteria. In the PubMed search of the same articles mentioned, which includes many single-arm noncontrolled studies, safety assessment is of mixed reporting quality.

Third, other nonpatentable intervention trials have been completed and successfully changed clinical practice, so as originally stated, it behooves the clinical and scientific community to seek appropriate funding for the adequately powered RCT. Much like the trials of statins that were said to be "unethical" because of fixed beliefs that statins improve outcomes in patients with HF, it was ethical, and statins did not reduce clinical events (2). Perhaps the ethical dilemma of recommending a therapy without proven