Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 56, No. 15, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.03.088

EDITORIAL COMMENT

Coenzyme Q_{10} and Statins in Heart Failure

The Dog That Didn't Bark*

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Detective Gregory: "Is there any other point to which you would wish to draw my attention?"
Holmes: "To the curious incident of the dog in the night-time."
Detective Gregory: "The dog did nothing in the night-time."
Holmes: "That was the curious incident."
—*Silver Blaze*, Sir Arthur Conan Doyle (1)

Coenzyme Q_{10} is an essential cofactor in mitochondrial metabolism and may protect against oxidative stress. Endogenous coenzyme Q_{10} synthesis is blocked by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-coA) reductase inhibitors (statins). These facts have led to questions about whether statin-induced depletion of coenzyme Q_{10} could be a mechanism for statin-induced myopathy, or more importantly, whether depletion of coenzyme Q_{10} by statins could actually worsen heart failure. Supportive evidence for these concerns includes the known relationship between low cholesterol levels and poor outcomes in heart failure (2), as well as a prior publication in the *Journal* reporting that low plasma coenzyme Q_{10} levels were an independent risk factor for worsened outcomes in heart failure (3).

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A Google search combining the search terms "statins," "coenzyme Q_{10}," and "heart failure" results in thousands of links, many asserting a relationship between statin therapy, coenzyme Q_{10} depletion, and heart failure outcomes. Many such sources recommend coenzyme Q_{10} supplementation and/or avoidance of statin drugs for patients with heart failure, and some even attribute the rising prevalence of heart failure to the growing use of statins. Questions from patients about coenzyme Q_{10} supplementation (sometimes accompanied by voluminous pages printed from the Internet) are frequent in clinical practice.

In this issue of the *Journal*, McMurray et al. (4) present the most robust data available to date analyzing the relationship between plasma coenzyme Q_{10} levels, statin therapy, and outcomes in patients with heart failure. In a prospectively defined analysis requested by the Food and Drug Administration, these investigators examined plasma coenzyme Q_{10} levels in 1,191 patients enrolled in the CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) trial, an international randomized trial of rosuvastatin versus placebo in patients with chronic heart failure of ischemic etiology. Notable strengths of this analysis include its prospective design, large sample size, the randomized, double-blind nature of statin treatment, and systematic evaluation of outcomes with regard to both muscle symptoms and cardiovascular events. Although clinical trials typically enroll patients who are younger and have fewer comorbidities than the broader heart failure population, the CORONA study targeted and enrolled an older population with ischemic heart failure, somewhat mitigating this potential limitation. This dataset creates a robust opportunity to address 2 important questions regarding coenzyme Q_{10} and statin therapy in heart failure.

Is coenzyme Q_{10} a prognostic biomarker in heart failure? In the CORONA study, lower coenzyme Q_{10} levels were associated with several other markers of greater disease severity, including older age, higher amino-terminal pro-B-type natriuretic peptide (NT-proBNP), lower ejection fraction, and lower glomerular filtration rate. Although coenzyme Q_{10} levels were associated with adverse outcomes in univariable analysis, a carefully constructed series of multivariable models demonstrated no independent relationship between baseline coenzyme Q_{10} levels and a variety of cardiovascular outcomes. These results stand in contrast to previously published findings examining the relationship between coenzyme Q_{10} and outcomes in heart failure (3). As the authors argue convincingly in their discussion, the CORONA dataset included many more patients and many more events, and thus had the ability to adjust for more covariates and provide more precise estimates of the independent relationship between baseline variables and outcomes. The data from the CORONA study suggest that while low coenzyme Q_{10} appears to be a marker of greater disease severity, it is very unlikely to have utility as a clinically important prognostic biomarker in heart failure.

Is there a clinically important link between coenzyme Q_{10} levels and the effect of rosuvastatin on clinical outcomes? The most notable findings from the analysis by McMurray et al. (4) are the lack of a significant interaction between low coenzyme Q_{10} levels and the effect of rosuvastatin on a variety of cardiovascular outcomes. Although there were numerically higher numbers of events for rosuvastatin compared to placebo in the lowest coenzyme Q_{10} tertile for most end points, these relationships did not reach nominal statistical significance, whether analyzed within subgroups or based on coenzyme Q_{10}-by-treatment inter-

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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action terms. Although interaction tests generally have low statistical power, it is notable that only 1 of the 19 p values generated for either subgroup analysis within tertile 1 or the interaction across groups (Tables 3 and 4 of McMurray et al. [4]) reach nominal statistical significance, about the same frequency (1 of 20) as would be anticipated by chance alone. A detailed breakdown by type of event showed no difference in heart-failure-related deaths or hospitalizations for rosuvastatin versus placebo, even in the lowest coenzyme Q_{10} tertile. Complaints of muscle pain were no more common among patients with low coenzyme Q_{10} levels, and there was no significant difference in muscle symptoms between patients treated with rosuvastatin or placebo.

Do these findings prove that there is no interaction between low baseline coenzyme Q_{10} levels and the effects of rosuvastatin? Given the logical challenges of "proving a negative," it may be preferable to say that these data strongly suggest that any interactions between coenzyme Q_{10} and the effects of statin therapy in patients with ischemic heart failure are very unlikely to be clinically important. These findings also must be considered in the context of the overall neutral results of the CORONA study (5) and the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico–Heart Failure) trial (6), neither of which demonstrated a substantial beneficial effect of statin therapy on outcomes of patients with systolic heart failure. Despite these neutral studies of heart failure, statin therapy remains indicated for a variety of patient groups that overlap with heart failure, and these data from the CORONA study clearly strengthen the evidence for the safety of these drugs for such patients.

What about the therapeutic use of coenzyme Q_{10} supplements, either as a treatment for heart failure generally or as a therapy to address muscle-related side effects of statins? Neither of these common questions from patients is addressed directly by the data from the CORONA study, and such questions about therapeutic efficacy can only be definitively answered by appropriately designed clinical trials. The efficacy and safety of micronutrients such as coenzyme Q_{10} in heart failure remains unproven and continues to be a subject of debate (7). Similarly, a recent systematic review of the data on coenzyme Q_{10} depletion and statin myopathy did not find definitive evidence for either a causative role or a therapeutic benefit from coenzyme Q_{10} supplements (8). Given the lack of association in the CORONA study, these data do not support an important role of coenzyme Q_{10} as a mediator of either myopathy symptoms or cardiovascular outcomes in patients with heart failure. The coenzyme Q_{10} story demonstrates the potential pitfalls of imputing causation from association. All putative biomarkers should be examined as to whether they are simply associated with greater disease severity ("markers") or, alternatively, play an important mechanistic role in the disease of interest ("mediators"). Coenzyme Q_{10} appears to be a marker, and generally only mediators make intuitive sense as targets for intervention.

Finally, the data from McMurray et al. (4) highlight the potential for substudies of large clinical trials to address important clinical questions. Multicenter clinical trials such as CORONA represent a tremendous investment of time and resources on the part of investigators, study coordinators, sponsors, and most importantly, patients, who agree to participate in human experimentation with the understanding that this participation will help advance human health. In the evolving era of personalized medicine, collection of biologic samples (such as plasma and deoxyribonucleic acid) should not be seen as "ancillary," but rather as a fundamental aspect of clinical trials in cardiovascular disease. Such a framework allows clinical trials to expand beyond answering not only the question "does it work?" but also "why (or why not)?" Like the dog that didn't bark in Arthur Conan Doyle's short story, these data from the CORONA study are most notable for what is absent rather than what is present, and as such represent a "negative" study. Although it is human nature to regard "finding something" with more interest than "finding nothing," often the absence of findings may be of substantial importance. Just ask Sherlock Holmes.

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Key Words: coenzyme Q_{10} ■ heart failure ■ rosuvastatin.