Journal of the American College of Cardiology Vol. 57, No. 14, 2011

ISSN 0735-1097/$36.00

CORRESPONDENCE

Letters to the Editor

Symptoms of Depression But Not Depressive Disorder

I thank Hoen et al. (1) and the Heart and Soul Study for drawing attention to the psychological factors that co-occur with and influence cardiovascular (CV) disease. Hoen et al. (1) reported exciting results with individual symptoms predicting CV events. However, a concern that comes to mind is that the symptoms most significantly associated with CV prognosis are not depression-specific symptoms. The investigators acknowledged this limitation and made efforts to account for it. Yet, despite the acknowledgement, are the researchers really examining depression? These symptoms (i.e., fatigue, appetite problems, and sleeping difficulties) could also be considered symptoms of CV disease, or of any other medical condition (e.g., cancer). This letter is not meant to undermine the importance of these somatic symptoms, as they are important for health, prognosis, and recovery, but rather to bring attention to the fact that this particular investigation does not discuss clinical or diagnosable depression. The investigators' rationale for examining the individual symptoms in light of the heterogeneity of depression and lack of strong treatment effects on CV outcomes is understandable; however, a focus on somatic symptoms may take us away from the original intention: examining depression and CV disease to improve the treatment and outcomes of these patients. In their paper, Hoen et al. (1) include the prevalence of each of the depressive symptoms from the Patient Health Questionnaire, but they do not state the prevalence of meeting criteria for or being clinically relevant and suggestive of major depressive disorder or other depressive disorder on the basis of the scoring and interpretation instructions of the Patient Health Questionnaire (2). The investigators hypothesized in the discussion that the lack of a relationship between cognitive symptoms and CV events may be due to a smaller number of patients reporting cognitive symptoms (p. 843 [1]). The diagnosis of major depressive disorder requires the presence of cognitive symptoms (must have either depressed mood or anhedonia [loss of interest] most of the time for the past 2 weeks), and dysthymic disorder requires depressed mood (3). Thus, by their own admission, the majority of these patients did not have depression. It would be interesting to examine these 3 somatic symptoms (and the other symptoms of depression) and CV outcomes between CV patients who had diagnosed depression and those who did not. There is solid evidence that symptoms of depression (e.g., depressed mood) and diagnosable depression are risk factors for the development and progression of CV disease. Individual symptoms do not "make depression." We do not want to be too hasty to ignore or discredit the cognitive symptoms of depression that exist, individually and as they relate to somatic symptoms and CV events, particularly in patients with CV disease.

***Eva R. Serber, PhD**

*The Miriam Hospital and
The Warren Alpert Medical School of Brown University
Centers for Behavioral and Preventive Medicine
CORO East, Suite 1B
167 Point Street
Providence, Rhode Island 02903
E-mail: eva_serber@brown.edu

doi:10.1016/j.jacc.2010.09.081

REFERENCES

1. Hoen PW, Whooley MA, Martens EJ, Na B, van Melle JP, de Jonge P. Differential associations between specific depressive symptoms and cardiovascular prognosis in patients with stable coronary heart disease. J Am Coll Cardiol 2010;56:838–44.
2. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA 1999;282:1737–44.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th edition. Washington, DC: American Psychiatric Association, 2000.

Reply

In her comments regarding our paper (1), Dr. Serber correctly points out that a diagnosis of major depressive disorder (MDD) requires the presence of at least 1 cognitive symptom (depressed mood or anhedonia). Therefore, somatic symptoms alone do not "make depression." At Dr. Serber's suggestion, we analyzed the effects of individual somatic symptoms on cardiovascular prognosis in patients with and without current MDD (on the basis of the computerized Diagnostic Interview Schedule). Overall, the somatic symptoms were more strongly predictive of cardiovascular events in patients without MDD (n = 795) than in patients with MDD (n = 222). This finding supports Dr. Serber's hypothesis that the cardiotoxicity of the somatic symptoms was not necessarily related to depression. Notably, the increased risk of cardiovascular events in patients with somatic symptoms was independent of several important confounders, including history of myocardial infarction, history of heart failure, and left ventricular ejection fraction. However, although controlling for confounders serves a useful function, it cannot transform observational data into natural experiments (2). Therefore, it remains possible that the association we found between specific symptoms and increased risk of cardiac events was due to worse cardiovascular disease severity that was not otherwise accounted for in our multivariate models. For future studies, it will be important to focus on the relationship between somatic symptoms and cardiovascular disease, including the issue of confounding.

***Petra W. Hoen, BSc**
Mary A. Whooley, MD
Peter de Jonge, PhD

*Interdisciplinary Center for Psychiatric Epidemiology
UMCG, CC72
Hanzeplein 1
9713 GZ Groningen
the Netherlands
E-mail: p.w.hoen@med.umcg.nl

doi:10.1016/j.jacc.2010.11.035

REFERENCES

1. Hoen PW, Whooley MA, Martens EJ, Na B, van Melle JP, de Jonge P. Differential associations between specific depressive symptoms and cardiovascular prognosis in patients with stable coronary heart disease. J Am Coll Cardiol 2010;56:838–44.
2. Christenfeld NJ, Sloan RP, Carroll D, Greenland S. Risk factors, confounding, and the illusion of statistical control. Psychosom Med 2004;66:868–75.

Low Coenzyme Q_{10} Levels and the Outcome of Statin Treatment in Heart Failure

McMurray et al. (1) investigated in a pre-specified substudy of CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) the effect of statin therapy on plasma coenzyme Q_{10} (CoQ_{10}) concentration and the possible relationship between the level of CoQ_{10} and cardiovascular events. Depletion of tissue CoQ_{10}, a powerful natural antioxidant and an essential component of the respiratory chain, might explain at least in part the neutral outcome of the rosuvastatin study. Rosuvastatin treatment at 10 mg/day reduced plasma CoQ_{10} significantly by 39%, down to a median level that was lower than the baseline level of CoQ_{10} in patients classified in tertile 1 (0.48 μg/ml). With a focus on the number of clinical outcomes in patients in tertile 1, more patients in the rosuvastatin group compared with those receiving placebo experienced primary end points (72 vs. 59, respectively); also, greater all-cause mortality (78 vs. 67) and coronary end points (54 vs. 45) were recorded in the rosuvastatin-treated patients. These differences were calculated to be not statistically significant but according to the undersigned clinically relevant. The investigators expressed some caution in their discussion of a possible adverse effect of statin treatment in patients with low CoQ_{10} levels: "We cannot completely exclude an adverse effect," and "we had limited statistical power to exclude this possibility" (1). In a previous study by Molyneux et al. (2), the investigators found low CoQ_{10} concentration to be an independent predictor of mortality in patients with heart failure, and the association was even stronger than with N-terminal pro–B-type natriuretic peptide.

The optimal design of a controlled statin trial in heart failure should have a CoQ_{10} plus statin arm to evaluate outcomes in 2 aspects: 1) to avoid further depletion of the plasma and tissue levels of CoQ_{10} in heart failure (3); and 2) to derive advantage from a possible therapeutic effect of CoQ_{10} in addition to conventional therapy (4).

***Svend Aage Mortensen, MD, DrMedSci**

*Cardiac Transplant Program Heart Centre
Rigshospitalet
Copenhagen University Hospital
Blegdamsvej 9
DK-2100 Ø Copenhagen
Denmark
E-mail: sam@rh.dk

doi:10.1016/j.jacc.2010.10.051

REFERENCES

1. McMurray JJV, Dunselman P, Wedel H, et al. Coenzyme Q10, rosuvastatin, and clinical outcomes in heart failure. J Am Coll Cardiol 2010;56:1196–204.
2. Molyneux SL, Florkowski CM, George PM, et al. Coenzyme Q10: an independent predictor of mortality in chronic heart failure. J Am Coll Cardiol 2008;52:1435–41.
3. Folkers K, Vadhanavikit S, Mortensen SA. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. Proc Natl Acad Sci U S A 1985;82:901–4.
4. Mortensen SA. Overview on coenzyme Q10 as adjunctive therapy in chronic heart failure. Rationale, design and end-points of Q-SYMBIO—a multinational trial. BioFactors 2003;18:79–89.

Reply

Plasma coenzyme Q_{10} (CoQ_{10}) concentration was not an independent predictor of any major clinical outcome in the elderly patients with quite advanced heart failure in CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) (1). Looking at the outcomes that should be most sensitive to any harmful effect of lowering CoQ_{10}, there was no convincing effect of rosuvastatin on either the risk for heart failure hospitalization or the composite of death or heart failure hospitalization. Prior studies of CoQ_{10} supplementation in heart failure have not shown any convincing benefit. Although it would be of interest to study a statin with and without CoQ_{10} supplementation, such a trial is very unlikely to be conducted.

***John J. V. McMurray, MD**

*British Heart Foundation Cardiovascular Research Centre
University of Glasgow
126 University Place
Glasgow G12 8TA
United Kingdom
E-mail: john.mcmurray@glasgow.ac.uk

doi:10.1016/j.jacc.2010.12.018

REFERENCE

1. McMurray JJV, Dunselman P, Wedel H, et al. Coenzyme Q10, rosuvastatin, and clinical outcomes in heart failure. J Am Coll Cardiol 2010;56:1196–204.

Assessment of Psychosocial Risk Factors Is Missing in the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

Despite the amount of evidence supporting significant and independent associations between psychosocial factors and the pathogenesis of cardiovascular disease (1–5), the 2010 American College of Cardiology Foundation/American Heart Association Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults (6) does not consider any of them and does not provide any justification for that decision. This is surprising because many studies have shown that