other pathogens, could influence the susceptibility to the atherogenic effect of infection with a particular pathogen like CP. Consequently, this finding suggests that "susceptibility" factors could make subjects more likely to develop CAD when infected with a particular pathogenic agent.

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REPLY

We greatly appreciate the comments of Dr. Auer and colleagues regarding our article recently published in the Journal of the American College of Cardiology (1).

Chlamydia pneumoniae (CP) was often reported to be associated with coronary artery disease (CAD) in seroepidemiologic studies, but the potential contribution of CP to CAD remains controversial. As shown in our article (1), Auer et al. also found no significant difference in the CAD prevalence between patients with and without CP seropositivity. However, CP organism was detected within atheroma by direct immunoﬂuorescence and polymerase chain reaction (PCR), and CP infection was shown to accelerate atherosclerosis in a rabbit model. We agree with Dr. Auer and colleagues that some triggers like cytokine gene polymorphisms or additional exposure to other pathogens could influence susceptibility to the atherogenic effect of CP infection.

Regarding genetic factors for CAD associated with CP infection, we reported that two polymorphisms of interleukin (IL)-1 genes play a role in the development of CAD, especially myocardial infarction, in patients with CP infection (1). However, other cytokine gene polymorphisms, such as IL-6 and IL-10, were also reported to be associated with CAD as well as inflammatory diseases. In addition to the IL-1 gene polymorphisms, they may be contributing to the development of CAD associated with CP infection. We will continue to seek genetic factors influencing the susceptibility to CAD associated with CP or other infections.

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REFERENCE


Patients With CHF and Depression Have Greater Risk of Mortality and Morbidity Than Patients Without Depression

With great respect and interest, we read the recently published study by Vaccarino et al. (1) in the Journal. That study supports our previous findings, presented at the annual meetings of the American Psychiatric Association (2) and the American Heart Association (3) and was just published a day before in the Archives of Internal Medicine this month, that the short-term prognosis of patients with heart failure (HF) and comorbid depression is much worse than that of such patients without depression.

Vaccarino and colleagues assessed the level of depressive symptoms by means of the Geriatric Depression Scale (GDS) on 391 patients aged 50 or older who were hospitalized with HF. They followed the patients for six months and assessed mortality and functional capacity in activities of daily living (ADL). They found that mortality at six months was two to three times higher in patients with greater depressive symptoms than in those with lesser depressive symptoms or those considered to have normal mood. Patients with moderate to severe depressive symptoms also showed significant functional declines during follow-up. Apparently, the covariates of age, gender, race and education were not associated with the relationships of depression to mortality and functional decline; but when the statistical model was adjusted for other variables, such as prior infarction, diabetes, prior admission for HF, certain limiting factors of ADL and several baseline clinical features (systolic blood pressure, serum creatinine, pulse and left ventricular ejection fraction), in addition to these demographic characteristics, the adverse relation between depression and mor-
tality no longer existed. The adverse effects of moderate depression on functional decline were also diminished (see their Table 3 [1]).

These results raise two concerns. First, as the investigators noted in their study, GDS is a valid measure for depressive symptoms among the elderly, but it is not equivalent to a clinical diagnosis of depression through standard diagnostic interviewing. Second, how many variables to include as adjustment factors (given the number of events) and the identification of potentially confounding factors remain as challenges.

We studied 374 hospitalized patients similar to those in the Vaccarino et al. (1) study, except our cohort included subjects ages 18 and up, between March 1997 and June 1998 (4). We used the Beck Depression Inventory (BDI) to screen for the presence of depressive symptoms. Patients with a BDI score $\geq 10$ underwent standardized psychiatric diagnostic interviewing for the clinical diagnosis of major depressive disorder according to DSM-IV criteria. Patients were followed at 3 months and 12 months for repeat hospitalization and mortality. We found that the mortality rate in HF patients with major depression was about 2.5 times higher than in HF patients without depression (BDI score $< 10$) at 12 months, and a similar trend was noted at 3 months. The incidence of repeat hospitalization also followed a similar pattern. The adverse association between depression and HF prognosis was not diminished after adjustment for variables commonly considered to be confounding factors in this population—age, New York Heart Association functional class, baseline ejection fraction, and etiology of HF—suggesting that major depression independently affects prognosis in HF.

We observed that the predictive ability of the BDI score ($< 10$ vs. $\geq 10$) was more powerful at 3 months than at 12 months, when it diminished somewhat. In contrast, the prognostic ability of major depression appeared stronger over time. Given our understanding of HF, and the limited existing knowledge of its interaction with psychiatric disorders, we therefore consider a standardized diagnostic interview to be necessary in addition to self-administered instruments.

We are pleased our findings have been reproduced to a certain degree at different tertiary-care settings. Despite the limitations of both studies, there should be little doubt about the adverse effects of depression on the short-term prognosis of recent inpatients with HF. Whether such an adverse effect carries over to the long term and whether treatment of depression can improve these poorer outcomes demand study. The prognostic association between depression and clinically stable HF also must be examined.

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REPLY

We thank Dr. Jiang and colleagues for their thoughtful comments. We were pleased to read their well-done study (1) published almost concurrently with ours (2). Whereas their study shares a number of similarities with ours, it also presents a number of differences that might explain why the association of depression with mortality was stronger in their study than in ours. First, as these investigators point out, the assessment of depression was different in the two studies.

Second, the populations of heart failure (HF) patients also differed. In the attempt to restrict HF to cases of ischemic or hypertensive etiology, we included predominantly elderly patients (50 years and older), and the mean age of our sample was 73 years. In contrast, Jiang and colleagues enrolled patients 18 years and older. As a result, their population was much younger and most likely it included a broader variety of HF etiology.

Third, while we assessed mortality at six months, Jiang et al. assessed this outcome at three months and one year. The association of depression with death may vary according to length of follow-up. These investigators, for example, observed that major depression was more strongly associated with mortality at one year than at three months. At three months, this association was not significant in their study, and the point estimate was not very different from our estimate for “severe depression” at six months. Therefore, it might be that if a longer follow-up were available in our study, we would have observed a stronger association as well.

Fourth, while Jiang and colleagues adjusted for a number of potential confounders, they did not include in their models a number of covariables that were adjusted for in our study, including race, education, previous hospitalizations for HF, diabetes, systolic blood pressure, serum creatinine and patient’s self-reported disability level (number of limitations in activities of daily living). Our study, therefore, might have obtained a tighter control for potential confounders, especially those factors related to disease severity and comorbidity. We do not believe that model overfitting was a problem in our analysis, because the relative risk estimate declined toward the null with progressive adjustment for potential confounders, and because a reduced model provided similar results.

However, in our study, depression was still associated with substantial (although nonsignificant) mortality risk. Patients with severe depression had 68% higher mortality risk compared with nondepressed patients, and there was a dose-response relationship with mortality according to severity of depressive symptoms. As we pointed out in our study, our main focus was the examination of the association of depression with functional decline. Our study was not powered to examine mortality as a separate end point, and a larger study might have found such a mortality difference to be statistically significant. We concur with Dr. Jiang and colleagues that, based on the results of both studies, depression poses serious adverse effects on the outcomes of patients with HF.