

EDITORIAL COMMENT

## Do Depression or Antidepressants Increase Cardiovascular Mortality?

### The Absence of Proof Might Be More Important Than the Proof of Absence\*

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Major depressive disorder and coronary heart disease (CHD) are 2 of the most important public health problems in the U.S. Depression affects 13 to 14 million U.S. adults per year (1), many of whom have comorbid physical conditions (2). Coronary disease causes over 800,000 deaths/year (3) and is the leading identified pathology (4) for the 300,000 annual cases of sudden cardiac arrest (SCA) in the U.S. (5). Identifying a biological link between depression and coronary disease would therefore have tremendous public health implications, yet remains highly controversial (6). A major challenge is to separate whether depression is related causally to future coronary disease, or related by reverse causality in which individuals with coronary disease are more likely to develop depression (7).

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Observational studies suggest that major depressive disorder does indeed increase the incidence of events due to CHD. Two recent meta-analyses of retrospective studies reported that depression predicted future fatal CHD or myocardial infarction (MI) with a hazard ratio (HR) of 1.81

(95% confidence interval [CI]: 1.53 to 2.15) over 10.8 years in 124,509 individuals (7), and with an HR of 1.64 (95% CI: 1.29 to 2.08) in 36,549 individuals (8). However, these seemingly robust associations must be taken in context. First, depressed patients often exhibit traditional coronary risk factors. Indeed, the HRs in these meta-analyses were substantially attenuated when adjusted by cardiac comorbidities (7,8). Second, meta-analyses adjust only for reported risk factors, yet many of the index studies failed to record serum lipids, body mass index, the metabolic syndrome, or physical inactivity, all of which might contribute to CHD events. Third, the index studies were statistically heterogeneous (7,8) in their definitions of depression, their inclusion of prior CHD (with the concomitant risk of reverse causality), in their duration of follow-up and measured end points, and as is often the case, in under-representing negative studies.

It is in this context that the work by Whang et al. (9) in this issue of the *Journal* is particularly exciting. The authors prospectively studied 63,469 women in the Nurses Health Study without baseline coronary disease, stroke, or malignancy for cardiovascular events on follow-up between 1992 and 2004. The authors found that major depression, defined by a validated 5-point mental health index score (MHI-5) <53 and antidepressant use (in recent cohorts), predicted a combined end point of nonfatal MI, SCA, and fatal CHD events on multivariate analysis. Intriguingly, HRs were stronger for fatal than for nonfatal events and were actually driven by the association with SCA. On stepwise regression analysis, MHI <53 or antidepressant use provided an HR for SCA of 2.33 (95% CI: 1.47 to 3.70,  $p < 0.001$ ). Notably, proportional hazards models showed that antidepressant use alone provided a higher HR for SCA of 3.34 (95% CI: 2.03 to 5.50), but was unrelated to fatal CHD or nonfatal MI.

The authors should be congratulated for these important data on the potential etiologic role of depression and its treatment on cardiovascular outcomes in a very large cohort of healthy individuals. A prospective design with questionnaires administered every 2 years and excellent end point adjudication also allowed the group to demonstrate that depression was predominantly associated with SCA and to provocatively implicate antidepressant drug use in the mechanism for this observation.

These results raise some important questions. The first relates to the accuracy of self-reporting of clinical information from questionnaires. A recent meta-analysis reported that when depression was identified from scores, it was less strongly associated with CHD than when diagnosed by experts (7). This might contribute to the relatively weak adjusted HRs of an MHI score <53 for adverse events (95% CI: 1.13 to 1.49) (Table 2 of Whang et al. [9]) and higher HRs when antidepressant use was added to an MHI score <53 (95% CI: 1.2 to 2.33) (Table 4 of Whang et al. [9]). Because clinical diagnosis is the gold standard for identify-

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ing major depression, some nurses with MHI <53 might therefore have had mild depression or have been misdiagnosed. Self-reporting of nonfatal MI and other cardiac comorbidities is also problematic, because events that were not corroborated by clinical records were still included as “probable.” Because depressed subjects are more likely to report ailments and physical symptoms such as chest pain (10), this might contribute to an alpha error (falsely strengthening the association between depression and cardiac events), although the authors state that results were similar when such cases were excluded. Conversely, although unreported events could not be uncovered, it is unlikely that this population of relatively young nurses would fail to report MI.

Second, multivariate analyses might not fully adjust for important comorbidities. Whang et al. (9) performed a detailed analysis of clinical features omitted from many prior studies (7,8), including serum lipids, body mass index, and physical activity. The results confirm those from smaller prior studies, that depressed individuals were more likely to self-report hypertension, diabetes, and high cholesterol and were more likely to be smokers, obese, and less physically active. Depressed women were also younger and more likely to use regular aspirin and multivitamins, yet less likely to use n-3 fatty acids. However, the use of beta-blockers and other agents linked with depression was not reported. Moreover, baseline electrocardiogram abnormalities, ventricular hypertrophy, or structural heart disease were not reported despite their strong associations with CHD and SCA (11).

In addition, psychiatric confounders such as anxiety disorders are highly comorbid with depressive disorders yet were not considered in the analyses. For instance, a recent prospective study from the Women’s Health Initiative (WHI) observational study found an association between panic attacks and incident cardiovascular events (12). Another recent prospective study (led by 1 of the coauthors of the present report) from the Normative Aging Study found that 1 specific anxiety disorder, post-traumatic stress disorder (PTSD), was associated with incident CHD even after controlling for depressive symptoms (13). These factors do not invalidate these results but rather suggest that a wider array of neuropsychiatric disorders might affect cardiovascular outcomes.

Third, reverse causality must be considered. A recent meta-analysis suggested reverse causality between coronary disease and depression in 17,842 patients with an HR of 1.8 for adverse outcome (7). Whang et al. (9) used a time-varying analysis of interim nonfatal MI to show that the duration of time since nonfatal MI did not impact future CHD events. The authors use these data to exclude reverse causality, although they did not analyze whether subjects had angina, heart failure, or other cardiac diseases other than nonfatal MI. In addition, the study examined only women, and future work should also examine men.

This leads us to examine the final conclusion of this study, that the use of antidepressant medications was

associated with an elevated risk of SCA, and that this explained most of the CHD events associated with major depression. The relationship between antidepressant use and SCA remained after adjusting for clinical confounders (Table 4 in Whang et al. [9]), whereas the relationship between antidepressant use and nonfatal MI or fatal CHD was less clear.

This surprising result merits scrutiny. Numerous pharmaceutical agents might contribute to arrhythmic mortality, often by blocking repolarizing currents that exaggerate ventricular repolarization dispersion and may prolong the electrocardiographic QT interval (14). The report by Whang et al. (9) agrees with a recent study of 2,228 SCA victims and 4,164 age- and sex-matched control subjects showing that depression was more prevalent in SCA victims than control subjects (15). Depression in that study was also defined by antidepressant use as well as clinical history, although the predictive value of antidepressant use alone was not analyzed (15). In the study by Whang et al. (9), 61% of subjects using antidepressants used selective serotonin reuptake inhibitors (SSRIs), whereas 39% used “other” (nonspecified) agents. The authors stated no difference in the results for SSRI or non-SSRI agents, although CIs for the association with non-SSRI agents crossed unity.

It is unclear whether SSRI agents might cause SCA. While cardiac events are well documented with the use of non-SSRIs such as tricyclic antidepressants (16), evidence for a link with SSRIs is mixed (17). On one hand, SSRI agents have been linked with ventricular arrhythmias (18) and increased mortality (19) in small clinical and animal studies. On the other hand, recent studies suggest that SSRIs might prevent future CHD events and MI (20,21), and 1 trial (22) reported that the SSRI sertraline did not prolong QT or elevate morbidity or mortality in patients with acute coronary syndrome, albeit with relatively preserved left ventricular ejection fraction (52%) on short follow-up (24 weeks).

Moreover, it is quite possible that antidepressant use merely indicates that depression is of sufficient severity to merit treatment. It is well established that patients with depression after acute coronary syndrome, for example, are less likely to adhere to their cardiac medication regimens (23), although treating the depression improves adherence (24). In addition, a recent prospective study of patients with heart failure, albeit in a smaller population, reported that depression but not antidepressant use was associated with increased mortality (25). Additional studies are clearly necessary to resolve this controversy.

In conclusion, Whang et al. (9) present exciting results that major depressive disorder was associated with an increased risk of nonfatal MI, SCA, and fatal CHD in relatively healthy women with no prior coronary disease. Surprisingly, adverse outcomes consisted mostly of SCA that, in turn, was most strongly associated with antidepressant use. Clearly, the burden of proof rests on confirming this association. The authors conclude that, at the present

time, the benefits of appropriately prescribed antidepressants likely outweigh the risk of SCA. We agree. There are abundant data attesting to the safety and efficacy of SSRIs in particular, and a relative paucity of data showing adverse cardiac effects. Moreover, if antidepressant use merely indicates severe depression, these results could suggest that depression should actually be treated more aggressively. Thus, at the present time, the absence of proof that antidepressants might cause cardiac events is more relevant than conclusive proof that this effect is absent. Nevertheless, these findings are sufficiently sobering to warrant heightened clinical surveillance and to initiate studies to definitively address this relationship.

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