CORRESPONDENCE

Letters to the Editor

Treatment-Resistant Depression and Sudden Cardiac Death

Whang et al. (1) recently reported some very interesting data from the Nurses’ Health Study showing that depression predicts cardiac-related mortality and that a proxy indicator of clinical depression (either scoring in the depressed range on the Mental Health Index-5 using antidepressant medication) predicted sudden cardiac death in a large cohort of female nurses. The authors are to be commended for their outstanding work. The key question is how to interpret their findings.

Recent clinical trials in patients after acute coronary syndrome suggest that depression that does not respond to standard treatments is associated with a particularly high risk of cardiac morbidity and mortality (2). Thus, it is not being on an antidepressant per se that increases risk, but rather being on an antidepressant and remaining depressed. Treatment-resistant depression might also confer a higher risk of sudden cardiac death in individuals without initial clinical evidence of heart disease.

Possible support for this conclusion is evident in Figure 3 of the paper by Whang et al. (1). It shows 4 Kaplan–Meier curves of time to sudden cardiac death, defined by combinations of the presence or absence of clinical depression and whether or not the individual was taking an antidepressant. One group, those who remained depressed despite taking an antidepressant, seems to be at much higher risk for sudden cardiac death than the other 3 groups.

We encourage the authors to compare the nondepressed/no antidepressant reference group with each of the other 3 groups. If the patients on antidepressants who remain clinically depressed are at the highest risk of sudden cardiac death, the results would support our interpretation. This would be strengthened if it could be established that these individuals had received a therapeutic dose of the antidepressant agent for sufficient duration to classify them as treatment nonresponders.

Regardless, depression that does not respond to treatment is associated with cardiac morbidity and mortality in post-acute coronary syndrome patients and may be the most plausible explanation for the findings by Whang et al. (1). It is not known why treatment-resistant depression confers a high risk for cardiac-related mortality or sudden cardiac death. A variety of factors that have been associated with treatment resistance are also risk factors for cardiac events, including elevated inflammatory markers, hypothalamic–pituitary–adrenal axis dysregulation, and low thyroid hormone levels (2). However, further research is needed to definitively explain this relationship.

We thank Drs. Carney and Freedland for their perspective on our study (1). We performed the analyses that they suggested by estimating separate hazard ratios for 4 categories of women from the Nurses’ Health Study according to presence of severe depressive symptoms (Mental Health Index-5 score <53) and/or reported use of antidepressant medications. In multivariable analyses, the hazard ratios associated with each category are listed in Table 1. The risk of sudden cardiac death was significantly elevated among women treated with antidepressants regardless of whether they continued to show severe depressive symptoms. Although the hazard ratio was slightly higher among those who showed severe depressive symptoms, confidence intervals overlapped. Also, we did not find evidence for an interaction between the Mental Health Index 5 score category and antidepressant use in separate multivariable models that used a cross-product term. Therefore, we were unable to find strong evidence in support of the hypothesis of Drs. Carney and Freedland in our data; however, we strongly agree that further research into the prognosis of depression and treatment-resistant depression, and the underlying mechanisms, is needed.

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Table 1 Hazard Ratios for Sudden Cardiac Death Associated With Each Category

<table>
<thead>
<tr>
<th>Category</th>
<th>Hazard Ratio (95% Confidence Interval) p Value</th>
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</thead>
<tbody>
<tr>
<td>MHI-5 score ≥53, no antidepressant</td>
<td>Referent</td>
</tr>
<tr>
<td>MHI-5 score &lt;53, no antidepressant</td>
<td>0.76 (0.24–2.43) 0.64</td>
</tr>
<tr>
<td>MHI-5 score ≥53, antidepressant use</td>
<td>3.11 (1.80–5.36) &lt;0.001</td>
</tr>
<tr>
<td>MHI-5 score &lt;53, antidepressant use</td>
<td>3.99 (1.69–9.42) 0.002</td>
</tr>
</tbody>
</table>

MHI-5 = Mental Health Index-5.

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doi:10.1016/j.jacc.2009.03.081

Please note: The authors are supported in part by grant RO1 HL-76808 from the National Heart, Lung, and Blood Institute, and by the Lewis and Jean Sachs Charitable Lead Trust. Dr. Carney receives Zoloft from Pfizer, Inc., for a National Institutes of Health-funded clinical trial.
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