Antidepressants, autonomic function and mortality in patients with coronary heart disease: data from the Heart and Soul Study

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Background. Antidepressants reduce depressive symptoms in patients with coronary heart disease, but they may be associated with increased mortality. This study aimed to examine whether the use of tricyclic antidepressants (TCA) or selective serotonin reuptake inhibitors (SSRI) is associated with mortality in patients with coronary heart disease, and to determine whether this association is mediated by autonomic function.

Method. A total of 956 patients with coronary heart disease were followed for a mean duration of 7.2 years. Autonomic function was assessed as heart rate variability, and plasma and 24-h urinary norepinephrine.

Results. Of 956 patients, 44 (4.6%) used TCA, 89 (9.3%) used SSRI, and 823 (86.1%) did not use antidepressants. At baseline, TCA users exhibited lower heart rate variability and higher norepinephrine levels compared with SSRI users and antidepressant non-users. At the end of the observational period, 52.3% of the TCA users had died compared with 38.2% in the SSRI group and 37.3% in the control group. The adjusted hazard ratio (HR) for TCA use compared with non-use was 1.74 [95% confidence interval (CI) 1.12–2.69, p=0.01]. Further adjustment for measures of autonomic function reduced the association between TCA use and mortality (HR=1.27, 95% CI 0.67–2.43, p=0.47). SSRI use was not associated with mortality (HR=1.15, 95% CI 0.81–1.64, p=0.44).

Conclusions. The use of TCA was associated with increased mortality. This association was at least partially mediated by differences in autonomic function. Our findings suggest that TCA should be avoided in patients with coronary heart disease.

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Key words: Coronary heart disease, heart rate variability, mortality, norepinephrine, selective serotonin reuptake inhibitors, tricyclic antidepressants.

Introduction

Depressive symptoms occur in 20–40% of patients with coronary heart disease (Allen et al. 2011). Depressive symptoms impair quality of life (Ruo et al. 2003), and are associated with an increased risk for future cardiac events and death (Nicholson et al. 2006; Whooley et al. 2008). Antidepressants reduce depressive symptoms in coronary heart disease patients (Baumeister et al. 2011), and rates of antidepressant use in cardiac patients have risen from less than 5% before 1995 to 10–15% after 2000 (Czarny et al. 2011).

Nevertheless, the use of antidepressants in coronary heart disease patients remains a topic of debate.

Tricyclic antidepressants (TCA) are not recommended as a first-line treatment for depression in coronary heart disease patients because of their unfavourable side-effect profile (Licht et al. 2008, 2010, 2012; Kemp et al. 2010). However, they may still be occasionally prescribed, for example because of treatment resistance to other classes of antidepressants, or because of indications other than depression (e.g. pain syndromes). Selective serotonin reuptake inhibitors (SSRI), on the other hand, are regarded relatively safe in coronary heart disease patients and have even been shown to be associated with reduced mortality (Taylor et al. 2005). However, other studies have raised doubts regarding the safety of SSRI in coronary heart disease patients (O’Connor et al. 2008; Fosbol et al. 2009; Krantz et al. 2009).

Therefore, we examined whether the use of TCA and SSRI is associated with mortality in patients with coronary heart disease over a 7-year observational period.
We further determined whether a potential association is mediated by autonomic function, assessed as heart rate variability (HRV) and norepinephrine (NE) concentrations.

**Method**

**Participants**

Recruitment procedures of the Heart and Soul Study have been previously described (Ruo et al. 2003). The study protocol complied with the Declaration of Helsinki and was approved by the appropriate institutional review boards. All participants provided written informed consent. We used administrative databases to identify out-patients with documented coronary heart disease at two Department of Veterans Affairs medical centres, one university medical centre, and nine public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had at least one of the following: a history of myocardial infarction, angiographic evidence of \( \geq 50\% \) stenosis in one or more coronary vessels, prior evidence of exercise-induced ischaemia by treadmill or nuclear testing, a history of coronary revascularization, or a diagnosis of coronary heart disease documented by an internist or cardiologist.

A total of 1024 participants were enrolled. All participants completed a baseline examination that included an interview, fasting blood draw, questionnaire, echocardiogram, exercise treadmill test, 24-h ambulatory electrocardiogram and 24-h urine collection. Of the 1024 participants who completed the baseline examination, we were not able to contact four participants (<1%) during the follow-up period, and no information on antidepressant use was available for nine participants (<1%). We further excluded patients who used antidepressants other than TCA or SSRI \((n=55)\) because of the large heterogeneity of antidepressants within this group. Thus, 956 subjects were available for this analysis.

**Antidepressant use**

All participants brought their medication bottles to the baseline study appointment, and study personnel recorded all medications including antidepressants. Medications were categorized using Epocrates Rx (USA). We grouped participants in users of TCA, SSRI, and non-users of antidepressants.

**Assessment of depressive symptoms**

Depressive symptoms were assessed using the nine-item Patient Health Questionnaire (Kroenke et al. 2001), a self-report instrument that measures the frequency of depressive symptoms corresponding to the nine Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; APA, 1994) criteria for depression. The Patient Health Questionnaire has demonstrated excellent validity when compared with a structured diagnostic interview for depression in patients with coronary heart disease (McManus et al. 2005).

**Assessment of HRV**

Three-channel 24-h ambulatory Holter electrocardiography was used to assess HRV (Gehi et al. 2005). Tapes were scanned at 500 times real time, and electrocardiography data were digitized at a sampling frequency of 128 Hz. Computer software (General Electric Medical System Software for Holter Analysis; GE Healthcare, USA) was used to detect and label each QRS complex using beats that had normal morphological characteristics. An independent and blinded reviewer processed all Holter electrocardiograms and modified any inappropriate computer labels. The standard deviation of NN intervals (SDNN) and the root-mean square of differences between adjacent normal RR intervals (RMSSD) were calculated as time-domain measures of HRV. Frequency-domain parameters of HRV (high-frequency power and low-frequency power) were obtained by power spectral analysis, using a fast Fourier transformation model.

**Assessment of 24-h urinary NE excretion**

Details regarding the analysis of 24-h urinary NE excretion have been described elsewhere in greater detail (Otte et al. 2005). In brief, the participants were instructed to collect all urine for 24 h between the study appointment and the time when a researcher visited their home the next day. Urinary NE was measured with gas chromatography–mass spectrometry at ARUP Laboratories (USA). Since the detection limit was 1.0 mg/dl for NE, levels for participants whose excretion was below this detection limit were coded as 1.0 mg/dl. The inter-assay coefficient of variance was <10%, and the intra-assay coefficient of variance was <8%.

**Assessment of plasma NE levels**

Blood samples were drawn from an intravenous catheter (21-g butterfly), mostly placed in the antecubital fossa. A blood pressure cuff inflated to a maximum pressure of 40 mmHg was used as a tourniquet. After placement of the catheter, the blood pressure cuff was deflated, and subjects rested for 30 min in a quiet windowless room with dimmed lights before blood was drawn. Plasma NE was measured with chromatography at LSM Laboratories.
Plasma NE levels are known to vary depending on situational factors and time of day, and 24-h urinary measurement of NE may thus more accurately reflect overall sympathetic activity during the course of the day. On the other hand, urinary catecholamine levels are considerably influenced by renal metabolism, and plasma NE levels may thus more accurately reflect actual sympathetic activity in the vascular system (Kennedy et al. 2005).

Assessment of mortality

Between the baseline examination and the last day of follow-up, we conducted annual telephone follow-up interviews with participants (or their proxy). If death of the participant was reported, death certificates and coroners’ reports were retrieved and reviewed by two independent blinded adjudicators.

Potential confounding or moderating variables

Age, sex and medical history were determined by self-report questionnaire. We measured height and weight, and calculated body mass index. Smoking and alcohol use were determined by self-report questionnaire. Left ventricular ejection fraction was determined by resting echocardiography. Exercise capacity was measured with a treadmill test according to a standard Bruce protocol and expressed as the total number of metabolic equivalent tasks achieved. To assess medication adherence, we asked, ‘In the past month, how often did you take your medications as the doctor prescribed?’ Possible responses were all of the time (100%), nearly all of the time (90%), most of the time (75%), about half the time (50%), or less than half the time (<50%). We defined medication non-adherence as taking prescribed medications 75% or less of the time (Gehi et al. 2007).

Statistical analysis

Statistical analyses were performed using SAS 9.2 for Windows (SAS Institute, Inc., USA). Baseline differences in characteristics of TCA users, SSRI users and non-users of antidepressants were compared using Kruskal–Wallis tests and χ² tests. We calculated odds ratios (ORs) for being in the lowest tertile of SDNN, and for being in the highest tertile of plasma and urinary NE, each for users of TCA and SSRI compared with non-users of antidepressants. HRV values were log-transformed before the analysis to achieve normal distribution.

We estimated the risk of death within the observational period associated with the use of TCA or SSRI using Cox proportional hazards models. Non-users of antidepressants served as the reference group. Both unadjusted and adjusted analyses were performed, with variables that differed between the three groups used as covariates. To estimate whether a potential association with increased mortality was mediated by autonomic dysfunction, we additionally adjusted for baseline differences in plasma NE and SDNN.

Results

Patients

Of the 956 patients, 44 (4.6%) used TCA, 89 (9.3%) used SSRI, and 823 (86.1%) did not use antidepressants. Those participants taking a TCA and any other antidepressant were considered TCA users (n=12). Those participants taking an SSRI and any other antidepressant but TCA were considered SSRI users (n=21). Characteristics of the three groups are shown in Table 1. Significant baseline differences were observed with respect to age, sex, body mass index, smoking status, depressive symptoms score, use of renin–angiotensin system inhibitors, and presence of heart failure and diabetes mellitus.

Baseline HRV

TCA users had a significantly lower SDNN, low-frequency power and high-frequency power at baseline compared with controls (Table 2). SSRI users did not significantly differ from controls in any HRV measure. For all further analyses, we used SDNN as an index of HRV because group differences for SDNN were the most pronounced, and previous studies had shown that SDNN predicted mortality in coronary heart disease patients (Janszky et al. 2004).

TCA users had a greater than 1.5-fold increased risk of being in the lowest tertile of SDNN [OR=1.56, 95% confidence interval (CI) 1.24–1.97, p=0.0002; Fig. 1]. Adjustment for age, sex, smoking, body mass index, diabetes, congestive heart failure, use of renin–angiotensin system inhibitors and depressive symptoms did not change the results (OR=1.50, 95% CI 1.17–1.90, p=0.001). SSRI use was not associated with low SDNN (OR=1.07, 95% CI 0.95–1.21, p=0.24; Fig. 1).

Baseline 24-h urinary and plasma NE

TCA users had significantly higher urinary and plasma NE levels compared with controls (Table 2). TCA users had a greater than 1.5-fold increased risk for being in
the highest tertile of 24-h urinary NE (OR=1.52, 95% CI 1.22–1.89, p<0.001; Fig. 1) and a greater than 2-fold increased risk for being in the highest tertile of plasma NE (OR=2.31, 95% CI 1.68–3.19, p<0.001; Fig. 1). Adjustment for age, sex, smoking, body mass index, diabetes, congestive heart failure, use of renin-angiotensin system inhibitors and depressive symptoms did not change the results (OR=1.50, 95% CI 1.19–1.89, p<0.001 for urinary NE; and OR=2.49, 95% CI 1.78–3.49, p<0.001 for plasma NE).

SSRI users did not significantly differ from controls with respect to urinary NE, and they had significantly lower plasma NE levels compared with controls (Table 2). SSRI use was not associated with high

### Table 1. Demographic and clinical variables according to AD use

<table>
<thead>
<tr>
<th>Variable</th>
<th>TCA use (n=44)</th>
<th>SSRI use (n=89)</th>
<th>No AD use (n=823)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, years (S.D.)</td>
<td>62.2 (10.8)</td>
<td>64.1 (10.2)</td>
<td>67.8 (10.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>33 (75.0)</td>
<td>65 (73.0)</td>
<td>687 (83.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>27 (61.4)</td>
<td>60 (67.4)</td>
<td>485 (58.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>High school graduate, n (%)</td>
<td>40 (90.9)</td>
<td>79 (88.9)</td>
<td>713 (86.9)</td>
<td>0.66</td>
</tr>
<tr>
<td>Mean body mass index, kg/m² (S.D.)</td>
<td>29.4 (5.5)</td>
<td>29.7 (6.0)</td>
<td>28.2 (5.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Medical conditions, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (81.8)</td>
<td>69 (77.5)</td>
<td>575 (70.1)</td>
<td>0.20</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>26 (52.3)</td>
<td>45 (51.7)</td>
<td>449 (54.9)</td>
<td>0.92</td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (18.2)</td>
<td>17 (19.1)</td>
<td>115 (14.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>Revascularization</td>
<td>6 (13.5)</td>
<td>54 (61.4)</td>
<td>490 (59.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14 (31.8)</td>
<td>12 (13.5)</td>
<td>139 (17.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (52.3)</td>
<td>30 (33.7)</td>
<td>194 (23.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Medication use, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>32 (72.7)</td>
<td>74 (83.2)</td>
<td>592 (71.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>23 (52.3)</td>
<td>60 (67.4)</td>
<td>479 (58.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>Renin-angiotensin system inhibitors</td>
<td>31 (70.5)</td>
<td>47 (52.8)</td>
<td>425 (51.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Other variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular alcohol use, n (%)</td>
<td>11 (25.0)</td>
<td>28 (32.2)</td>
<td>236 (28.9)</td>
<td>0.68</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>16 (36.4)</td>
<td>23 (25.8)</td>
<td>136 (16.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean exercise capacity, MET (S.D.)</td>
<td>6.2 (3.0)</td>
<td>7.2 (2.9)</td>
<td>7.4 (3.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>Mean left ventricular ejection fraction, % (S.D.)</td>
<td>59.0 (9.6)</td>
<td>62.2 (8.8)</td>
<td>61.7 (9.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Medication non-adherence, n (%)</td>
<td>3 (6.8)</td>
<td>11 (12.4)</td>
<td>60 (7.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean PHQ score (S.D.)</td>
<td>7.2 (5.6)</td>
<td>9.6 (6.6)</td>
<td>4.3 (4.9)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

AD, Antidepressants; TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; S.D., standard deviation; MET, metabolic equivalent tasks; PHQ, Patient Health Questionnaire.

### Table 2. Heart rate variability, and urinary and plasma norepinephrine according to AD use

<table>
<thead>
<tr>
<th></th>
<th>TCA use (n=44)</th>
<th>SSRI use (n=89)</th>
<th>No AD use (n=823)</th>
<th>p</th>
<th>TCA v. no AD use: p</th>
<th>SSRI v. no AD use: p</th>
<th>TCA v. SSRI use: p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN, ms</td>
<td>88.6 (38.0)</td>
<td>109.8 (36.1)</td>
<td>110.0 (35.6)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>24.6 (17.7)</td>
<td>28.9 (19.8)</td>
<td>27.6 (16.2)</td>
<td>0.08</td>
<td>0.02</td>
<td>0.99</td>
<td>0.05</td>
</tr>
<tr>
<td>Low-frequency power, ln ms²</td>
<td>3.9 (1.3)</td>
<td>4.4 (1.0)</td>
<td>4.4 (1.0)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.93</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High-frequency power, ln ms²</td>
<td>4.6 (1.3)</td>
<td>5.3 (1.0)</td>
<td>5.3 (1.0)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.94</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24 h urinary norepinephrine, mg/day</td>
<td>81.4 (38.0)</td>
<td>47.0 (24.8)</td>
<td>50.4 (25.0)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.23</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/ml</td>
<td>953.3 (668.4)</td>
<td>389.2 (206.6)</td>
<td>497.4 (285.6)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are given as mean (standard deviation).

AD, Antidepressants; TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; SDNN, standard deviation of NN intervals; RMSSD, root-mean square of differences between adjacent normal RR intervals.
Antidepressants and mortality in coronary heart disease patients

Table 3. Association between antidepressant use and mortality

<table>
<thead>
<tr>
<th>Model</th>
<th>SSRI use v. no antidepressant use</th>
<th>TCA use v. no antidepressant use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>1</td>
<td>1.15 (0.81–1.64)</td>
<td>0.44</td>
</tr>
<tr>
<td>2</td>
<td>1.43 (0.98–2.08)</td>
<td>0.07</td>
</tr>
<tr>
<td>3</td>
<td>1.29 (0.80–2.09)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

SSRI, Selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; HR, hazard ratio; CI, confidence interval.

Discussion

We found that patients with coronary heart disease treated with TCA had a 70% greater risk of mortality during 7 years of follow-up, compared with coronary heart disease patients not using antidepressants. This association remained strong even after adjusting for potentially confounding variables including depressive symptoms. The association between TCA use and mortality was partially mediated by autonomic dysfunction, as indexed by low HRV and high NE concentrations. In contrast, autonomic function was not impaired in SSRI users, and plasma NE concentrations were even lower compared with non-users of antidepressants. However, our data do not suggest a beneficial effect of SSRI on mortality.

Several studies have previously examined the association of antidepressant use and cardiovascular outcomes. However, most studies did not examine

Mortality

At the end of the mean observational period of 7.2 (s.d.=2.6) years, 23 patients (52.3%) in the TCA group, 34 patients (38.2%) in the SSRI group and 306 patients (37.3%) in the control group had died. TCA use was associated with increased mortality compared with controls (Table 3). Adjustment for age, sex, smoking, body mass index, diabetes, congestive heart failure, use of renin–angiotensin system inhibitors and depressive symptoms did not change the results. Additional adjustment for SDNN and plasma NE strongly reduced the association between TCA use and mortality to non-significance (Table 3). In the final adjusted model, age [adjusted hazard ratio (HR)
whether the association between antidepressant use and cardiovascular outcomes was independent of depressive symptoms, which per se are associated with worse cardiovascular outcome (Nicholson et al. 2006; Whooley et al. 2008). Furthermore, many previous studies were not able to differentiate between different classes of antidepressants. Thus, it remained unclear whether an association was driven by use of TCA, SSRI, or use of other antidepressants. Finally, the potential mechanisms linking antidepressant use and cardiovascular outcomes have not been evaluated.

To our knowledge, our study is the first to examine the effects of antidepressants on mortality in patients with stable coronary heart disease. We were able to differentiate effects of TCA versus SSRI while controlling for depression and other potentially confounding variables. Additionally, by implementing measures of autonomic function, we evaluated possible mechanisms linking antidepressant use and mortality.

In line with our results, several studies have found that TCA use, but not SSRI use, was associated with a higher risk of incident cardiovascular disease (Hamer et al. 2011), myocardial infarction (Cohen et al. 2000) and sudden cardiac death (Ray et al. 2004; Honkola et al. 2012). However, none of these studies controlled for the effects of depression.

Among studies examining the association between antidepressants as a group and cardiovascular outcomes, two studies (Tata et al. 2005; Fosbol et al. 2009) observed increased risks of myocardial infarction and mortality in SSRI and TCA users. Again, both studies did not control for depression.

O’Connor et al. (2008) found an association of antidepressant use and increased risk of mortality in heart failure patients, but after controlling for depression this association was no longer significant. Similarly, Sherwood et al. (2007) found an increased risk of mortality associated with antidepressant use in heart failure patients. However, results were not reported according to class of antidepressant. In the Women’s Ischemia Syndrome Evaluation (WISE) Study (Krantz et al. 2009), only the combined use of antidepressants and anxiolytics (but not antidepressants alone) was associated with increased mortality after adjustment for covariates including baseline psychopathology. The Nurses’ Health Study suggested an increased risk of sudden cardiac death but not other cardiovascular events in women without coronary heart disease using antidepressants (Whang et al. 2009). Again, effects were not reported separately for SSRI and ‘other antidepressants’. In the Women’s Health Initiative Study (Smoller et al. 2009), both TCA and SSRI use were associated with an increased risk of all-cause mortality both before and after adjustment for depressive symptoms.

There are also studies specifically examining SSRI use and cardiovascular outcomes. One study found an increased mortality in patients taking SSRI before coronary artery bypass surgery (Xiong et al. 2006). However, this study did not control for depressive symptoms. In contrast, numerous randomized controlled trials showed a favourable safety profile of SSRI in coronary heart disease patients. The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) did not find differences in cardiac safety between sertraline and placebo during 24 weeks in patients after an acute coronary event. The study even found a numerically but non-significantly lower rate of severe cardiovascular events in the sertraline group (Glassman et al. 2002). In the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) Trial, cardiovascular events were not more frequent in patients receiving citalopram during a 12-week observational period (Lesperance et al. 2007). The Enhancing Recovery in Coronary Heart Disease (ENRICHD) Study showed that depressed patients after an acute myocardial infarction who were treated with SSRI even had a lower risk of death or recurrent myocardial infarction within 29 months (Taylor et al. 2005). The Understanding the Prognostic Beneﬁts of Exercise and Antidepressant Treatment (UPBEAT) Study found that 4 months of treatment with sertraline was safe and efficacious in reducing depressive symptoms in coronary heart disease patients (Blumenthal et al. 2012). Finally, the SADHART-CHF (in chronic heart failure) Trial (O’Connor et al. 2010) demonstrated the safety of sertraline in patients with heart failure. Additionally, several case–control studies supported the view that SSRI may have moderate protective effects against incident myocardial infarction, possibly because of inhibitory effects on platelet function (Sauer et al. 2001, 2003; Schlienger et al. 2004). It should be noted, however, that SSRI users in our study did not significantly differ from antidepressant non-users with respect to mortality.

We did not observe a significant effect of depressive symptoms on mortality in our fully adjusted model. It was previously shown that depressive symptoms were associated with an increased rate of adverse cardiac events in patients from the Heart and Soul Study. However, the effect was no longer significant after adjustment for behavioural mediators (Whooley et al. 2008). Thus, it is likely that variables, which were previously shown to partially mediate the depression–cardiovascular risk association (e.g. smoking), decreased the strength of association in our fully adjusted model.

We identified decreased HRV and elevated NE concentrations as mechanisms that may be responsible for
the association between TCA use and mortality. Reduced HRV and elevated NE were shown to predict mortality in cardiac patients (Anand et al. 2003; Janszky et al. 2004), rendering autonomic dysfunction a likely mechanism of adverse TCA effects. Indeed, adverse effects of TCA on HRV, plasma NE levels and sympathetic control have been previously described (Veith et al. 1983; Licht et al. 2008, 2012; Kemp et al. 2010), but had so far never been tested as mediators of increased mortality associated with TCA use. Low cardiac vagal tone increases the risk for cardiac arrhythmias and sudden cardiac death (Odemuyiwa et al. 1991), but has also been shown to be associated with increased inflammation, insulin resistance, dyslipoproteinemia and other cardiovascular risk factors (Thayer & Lane, 2007). NE has been shown to have direct toxic effects on cardiocytes (Mann et al. 1992) as well as pro-arrhythmgogenic (Meredith et al. 1991) and pro-aggregatory effects (Benedict et al. 1996). Apart from autonomic side effects, other factors such as unfavourable drug interactions or metabolic changes may additionally contribute to the adverse effect of TCA use on mortality.

In contrast to TCA, SSRI use was not associated with lower HRV in our study. While our finding is in line with a previous meta-analysis (Kemp et al. 2010), data from the Netherlands Study of Depression and Anxiety (NESDA) suggest unfavourable effects of both SSRI and TCA on HRV (Licht et al. 2008, 2010). Prospective data from SADHART, however, showed better HRV in coronary heart disease patients treated with sertraline, although this difference primarily resulted from decreased HRV in the control group (Glassman et al. 2007). Additionally, the UPBEAT Study found that 4 months of treatment with sertraline improved HRV compared with placebo (Blumenthal et al. 2012). Our finding of decreased plasma NE levels in patients treated with an SSRI is in line with the finding that SSRI treatment reduced cardiac sympathetic control (Licht et al. 2012).

Several limitations of our study must be acknowledged. First, our study has an observational character and was not a randomized controlled trial of antidepressant use. Therefore, inferences about causality are limited. Second, because our study comprised predominantly male and white participants, the results may not generalize to other populations. Third, the study population consisted of patients with stable coronary heart disease, and our findings may not apply to patients with chronic heart failure or acute cardiac events. Fourth, the number of subjects who used antidepressant medication was relatively low. Nevertheless, we were able to demonstrate a significant association between TCA use and mortality, even after adjustment for potential confounders. Fifth, we were not able to take into account the duration of antidepressant treatment or potential changes of antidepressants. Given the relatively long duration of follow-up, it is possible that a proportion of deaths occurred after discontinuation or change of treatment, which may have influenced the results. Further, antidepressants are also used in anxiety disorders such as panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder as well as pain syndromes or sleep disorders. Therefore, we cannot completely rule out that these potentially underlying conditions may have in part contributed to our findings of adverse effects of TCA. However, we controlled for depression in our analyses, which still appears to be the most likely cause of antidepressant use. Finally, TCA users were more affected by somatic co-morbidities such as heart failure or diabetes. Although we adjusted our analyses for these factors, it is possible that residual confounding might have contributed to the between-group differences regarding mortality.

Conclusions

In summary, we found that the use of TCA, but not SSRI, was associated with increased mortality in coronary heart disease patients. The harmful effects of TCA appeared to be partially mediated by autonomic dysfunction. In conclusion, our findings support previous evidence that TCA should be avoided in coronary heart disease patients.

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.
Declaration of Interest

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References


