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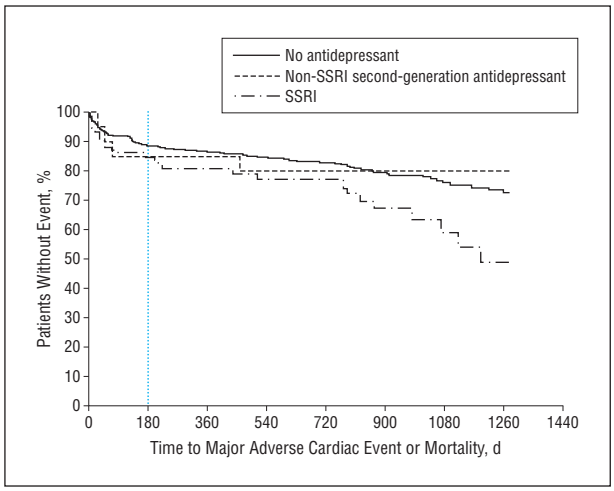

Figure. Event-free survival for combined major adverse cardiac events and mortality in 3 medication groups. Vertical dotted line at 180 days indicates the longest follow-up duration (for adverse cardiac events) in current randomized clinical trials of selective serotonin reuptake inhibitors (SSRIs) in cardiac patients.

Serotonin Reuptake Inhibitor Use, Depression, and Long-Term Outcomes After an Acute Coronary Syndrome: A Prospective Cohort Study

Depression is highly prevalent among patients with coronary heart disease.[1] Selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line antidepressant treatments for this population.[2,3] Whereas there is a long-standing notion that SSRIs may improve cardiac disease prognosis by inhibiting platelet aggregation, SSRI use may also worsen prognosis by increasing bleeding[4] or increasing the risk for arrhythmia.[5]

Only a few small randomized clinical trials with a total of 801 patients have assessed the efficacy of SSRIs in patients with a cardiac condition.[6,7] Although no evidence for harm was detected in 2 meta-analyses, the follow-up periods for adverse cardiac events in these trials did not extend beyond 6 months, and patient samples were highly selected (ie, only patients not already receiving antidepressant therapy in usual care were included, and patients with comorbid conditions were excluded).

In a cohort of patients with acute coronary syndrome (ACS), we evaluated the association of SSRI and non-SSRI second-generation antidepressant use with the occurrence of cardiac events and mortality during a median follow-up period of 40 months.

Methods. Within 1 week of ACS hospitalization, 457 patients completed the Beck Depression Inventory and a diagnostic depression interview (see Davidson et al[8] for details). Antidepressant medication use at hospital admission and discharge was assessed by means of medical record review and self-reports. Medical covariates including a post-ACS prognostic risk score, medical comorbidities, and left ventricular ejection fraction were also assessed. Major adverse cardiovascular events (MACEs, defined as hospitalization for nonfatal myocardial infarction, unstable angina, or urgent and/or emergency percutaneous or surgical coronary revascularization) and mortality were surveyed for up to 42 months.

Three groups were compared according to antidepressant class at admission and/or discharge from index hospitalization[1]: patients not receiving any antidepressant,[2] patients receiving SSRIs only, and patients receiving non-SSRI second-generation antidepressants only (see eFigure 1 for specific antidepressants; http://www.jamainternalmed.com).[3] No patient switched from one to another class during the hospitalization. Because of low numbers (n=21), patients receiving antidepressants in other classes or combinations of antidepressants were excluded. Four additional patients were excluded because they did not complete the depression clinical interview, leaving a sample of 432 patients.

Cox regression analyses were used to estimate differences in time to the first occurrence of either MACE or mortality among the groups (adjusted for age, sex, race, medical covariates [eTable 2], and depression severity or diagnosis of major depressive episode).

Results. Compared with patients not taking any antidepressants (n=354), those receiving antidepressants (n=78) were more likely to be female, to be experiencing a current major depressive episode, and to have increased medical comorbidities and increased depressive symptoms (eTable 1). Compared with patients receiving non-SSRI second-generation antidepressants (n=20), those receiving SSRIs (n=58) were more likely to have a history of major depressive episode ($P=.06$); otherwise, these 2 groups did not differ.

During a median follow-up period of 1192 days (range, 1-1278 days), 101 patients (23.4%) had a confirmed MACE or died. Among users of SSRIs, users of non-SSRI second-generation antidepressants, and patients not receiving any antidepressant, MACE or mortality rates were 36.2%, 20.0%, and 21.5%, respectively.

The **Figure** shows the Kaplan-Meier survival curves in the 3 medication groups. After controlling for demo-

graphics, medical covariates, and depression severity, SSRI use carried an increased risk for first MACE or mortality compared with no antidepressant use (adjusted hazard ratio [HR], 1.83 [95% CI, 1.09-3.06]; $P=.02$); non-SSRI second-generation antidepressant use did not (adjusted HR, 0.86 [95% CI, 0.31-2.42]; $P=.78$) (eTable 2). Compared with non-SSRI second-generation antidepressant users, SSRI users had an increased hazard of MACE and/or mortality but this difference was not statistically significant (age-adjusted and sex-adjusted HR, 1.99 [95% CI, 0.68-5.81]; $P=.21$). When we additionally singly adjusted for smoking, diabetes, hypercholesterolemia, and body mass index, the results were similar.

There was a significant interaction between antidepressant use (yes or no) and timing of antidepressant use initiation (prior to vs only after the ACS; $P=.005$). Among the 78 antidepressant users, 20 initiated use between the date of admission and the time of hospital discharge. These patients had an increased risk for first MACE or mortality compared with patients who did not use antidepressants at all, whereas those who continued to use SSRIs that had been prescribed prior to the ACS were not at increased risk (eFigure 2 and eTable 3).

Discussion. Our study shows that SSRI use may be associated with longer-term risk for adverse prognosis in patients with ACS. Limitations are that these analyses were post hoc and not powered to detect significant associations between antidepressant exposure and rare adverse outcomes (eg, stroke or sudden death). Also, the power for analysis of the effects of non-SSRI second-generation antidepressants was limited by the small number of users. Finally, we could not reliably assess the dosage of antidepressants or the length of time prior to or after the ACS that patients took a prescribed antidepressant.

We conclude that the comparative safety and efficacy of SSRIs and non-SSRI second-generation antidepressants should be investigated in randomized clinical trials with larger samples, in "real world" care settings, and critically, with longer follow-up monitoring. The association between dosage, duration of drug coverage, and adherence to antidepressant medications in relation to adverse events after ACS also needs further investigation.

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