Selective Serotonin Reuptake Inhibitors and Myocardial Infarction

William H. Sauer, MD; Jesse A. Berlin, ScD; Stephen E. Kimmel, MD, MS

Background—Depression is an independent risk factor for myocardial infarction (MI). Selective serotonin reuptake inhibitors (SSRIs) may reduce this risk through attenuation of serotonin-mediated platelet activation in addition to treatment of depression itself.

Methods and Results—A case-control study of first MI in smokers 30 to 65 years of age was conducted among all 68 hospitals in an 8-county area during a 28-month period. Cases were patients hospitalized with a first MI. Approximately 4 community control subjects per case were randomly selected from the same geographic area using random digit dialing. Detailed information regarding use of antidepressant medication as well as other clinical and demographic data were obtained by telephone interview. A total of 653 cases of first MI and 2990 control subjects participated. After adjustment, using multivariable logistic regression, for age, sex, race, education, exercise, quantity smoked per day, body mass index, aspirin use, family history of MI, number of physician encounters, and history of coronary disease, diabetes, hypertension, or hypercholesterolemia, the odds ratio for MI among current SSRI users compared with nonusers was 0.35 (95% CI 0.18, 0.68; \textit{P}<0.01). Non-SSRI antidepressant users had a nonsignificant reduction in MI risk with wide confidence intervals (adjusted odds ratio 0.48, CI 0.17, 1.32; \textit{P}=0.15). However, analysis of this group was limited by the small number of exposed subjects.

Conclusions—The use of SSRIs may confer a protective effect against MI. This could be attributable to the inhibitory effect SSRIs have on serotonin-mediated platelet activation or possibly amelioration of other factors associated with increased risk for MI in depression. (\textit{Circulation.} 2001;104:1894-1898.)

Key Words: serotonin uptake inhibitors \textbullet} depression \textbullet} epidemiology \textbullet} myocardial infarction \textbullet} drugs \textbullet} platelets

Clinical depression is a risk factor for heart disease\textsuperscript{1,2} and is associated with increased mortality after acute myocardial infarction (MI).\textsuperscript{3} The increased cardiovascular risk among patients with depression has been hypothesized to be attributable to abnormalities in the sympathoadrenal system, the autonomic nervous system, and platelet function.\textsuperscript{4} Selective serotonin reuptake inhibitors (SSRIs) have been demonstrated to be effective for the treatment of depression\textsuperscript{5} and are associated with fewer cardiovascular side-effects compared with other antidepressants.\textsuperscript{6,7} Along with their effect on depression, SSRIs have an inhibitory effect on platelet activation\textsuperscript{8–11} and, therefore, may protect against MI.

Although several studies have examined the cardiac side effects of SSRIs,\textsuperscript{6,7,12,13} only one has examined the possible protective effect against MI.\textsuperscript{14} Although there was a reduced odds of MI in users of SSRIs (odds ratio [OR] 0.8), the study was statistically underpowered to detect a meaningful reduction in risk and could not adjust for potential confounding that might have masked a significant inverse association between SSRI use and MI. Therefore, the specific aim of this study was to examine the possible association between SSRI use and lower risk of first nonfatal MI.

Methods

Source Population and Identification of Subjects

The data were obtained in a case-control study of MI in smokers in the Philadelphia metropolitan area. Patients enrolled were hospitalized at one of the 68 acute care hospitals in an 8-county region that are part of the Delaware Valley Case-Control Network.\textsuperscript{15} The primary objective of the study was to examine the effect of nicotine patch exposure and the risk of MI in smokers.\textsuperscript{15} However, this study also collected detailed information regarding use of antidepressant medication and therefore also assessed the association between MI and this class of drugs.

Cases were patients between the ages of 30 and 65 years with a first MI who were hospitalized at one of the hospitals in the Network from September 1995 through December 1997. Acute MI was defined using the criteria from the Minnesota Heart Survey.\textsuperscript{16} Cases were excluded for the following reasons: (1) if they had an MI as a complication of a hospitalization for a different condition (eg, complication of a hospitalization for a different condition (eg,
postoperatively; (2) if they had a history of a prior MI; (3) if they were pregnant or presently nursing (an exclusion criterion used in the primary data set)13; (4) if they did not have telephones or did not speak English; or (5) if they did not live in one of the 8 counties of the Network. Eighty-four percent of potentially eligible cases identified (778 subjects) had their medical records reviewed for confirmation of their MI, and 85% had MIs that met the study criteria. Given this high rate of confirmation, the 140 eligible subjects for whom charts were not available are included in the study analyses examining the association between SSRI use and MI; a separate analysis excluded these subjects with no meaningful change at the results. The participation rate among eligible cases was 68%. The charts of 349 nonparticipant, eligible cases (79% of the known eligible nonparticipants) were reviewed to collect basic demographic information (age, sex, and insurance) on these subjects. The only difference between participants and nonparticipants was insurance status (P<0.01), with nonparticipants more likely to be using medical assistance (13.1% versus 5.1%).13

Control subjects were selected using a telephone survey with sample generated using the single-stage EPSEM random digit dialing method, as implemented within the Genesys sampling system.12 Control subjects met the same inclusion and exclusion criteria as cases. The participation rate among known eligible control subjects was 51%.

Data Collection
Exposure and covariate data were collected using a structured telephone interview for both case and control subjects. The study hypothesis was not revealed to participants at any time. The index date was the date of MI for cases and the date of the telephone interview for control subjects (performed during a separate call subsequent to their initial identification). Detailed information was obtained regarding antidepressant use during the week before the index date, indication for antidepressant use, and other clinical and demographic characteristics. To maximize the validity of exposure information, cases were interviewed only if they could be reached within 6 months of their MI (mean time to interview was 86 days; range, 13 to 178 days; SD, 39 days). Control subjects were also interviewed only within 6 months of being first identified to prevent the potential selection bias that could result if subjects who could not be reached within this time frame differed from those who could. Specific validation methods to verify clinical and demographic data were not used.

Categorization of Antidepressants
Antidepressant medication was categorized into SSRI and other antidepressants.18 The SSRIs represented in the study included were fluoxetine, fluvoxamine, paroxetine, and sertraline. Other antidepressants included tricyclics and atypicals that exhibit nonsellective serotonin uptake inhibition (amitriptyline, clomipramine, doxepin, imipramine, venlafaxine, nefazodone, and trazodone) in addition to other tricyclics (desipramine, nortriptyline, protriptyline, amoxapine, and maprotiline), atypicals (bupropion and mirtazepine), and monoamine oxidase inhibitors (phenelzine and tranylcypromine). To assess the potential for recall bias and for bias attributable to differential use of medical care, we examined the association of anxiolytic exposure, which is not known to affect cardiovascular risk or have an effect on platelets, with MI. Recall bias or bias attributable to differential medical care among SSRI users should be similar to anxiolytic users, making any apparent MI protective effect among anxiolytic users suggestive of bias in the SSRI analysis.

Statistical Analysis
The OR was used to estimate the relative risk of MI from using SSRIs relative to nonusers of any antidepressant. Multivariable logistic regression analysis was used to control for possible confounding. The multivariable model included variables that are known risk factors for MI and any potential confounder that changed the unadjusted OR for SSRI use by >10% after adjustment.19 The variables used in the final model were age, sex, race, education, any degree of exercise within the past year, quantity of cigarettes smoked per day, body mass index, number of physician visits in the prior year, aspirin use for MI prevention, family history, and history of coronary disease, diabetes mellitus, hypertension, and hypercholesterolemia. Other potential confounding variables tested (income, vitamin use, marital status, caffeine and alcohol consumption, type of insurance, prior attempts to quit smoking, use of nicotine replacement therapy, aspirin or β-blocker use, patient worries about MI, season during the index week, and a validated physical activity score20) did not affect any of the analyses and were therefore not included. The analyses examining anxiolytics and non-SSRI antidepressants used the same multivariable model described above. Interactions were tested between each variable and SSRI use; none were significant (P>0.10). Statistical analyses were performed using the SPSS (version 10.0) software program, and statistical significance was defined as a two-sided P value less than 0.05. This study received Institutional Review Board approval at all participating sites.

Results
Characteristics of Study Participants
A total of 653 cases of first MI and 2990 control subjects participated in the study. Of the 143 SSRI users identified, 125 (87%) reported depression as the indication for use, 5 (3.5%) reported anxiety, and 13 (9.1%) reported an unknown or other indication. There was no difference in indication by case or control status (P=0.3). The distribution of clinical characteristics by SSRI use within the case and control group is shown in Table 1. This comparison assessed the potential for confounding. Compared with non–antidepressant users, control subjects using SSRIs were more likely to have traditional cardiac risk factors, such as hypertension, hypercholesterolemia, diabetes mellitus, and family history. They also were more likely to have preexisting coronary disease and to be heavier smokers and unmarried. On the other hand, they were more likely to be female, white and more educated, use aspirin for primary prevention of MI, have more physician visits per year, exercise, and use vitamins.

Association Between SSRIs and MI protection
The association between SSRI use and MI is presented in Table 2. In unadjusted analysis, there was a significant association between SSRIs and reduced odds of MI. After adjustment with the aforementioned potential confounders, the OR decreased (OR 0.35; 95% CI 0.18, 0.68; P<0.01). Of all the potential confounders tested, only adjustment for sex increased the OR for MI among SSRI users.

Other Psychotropic Medication and MI
Both the unadjusted and adjusted ORs for MI in other antidepressant users are not statistically significant (Table 2), albeit with wide confidence intervals. There were too few users of other antidepressants that exhibit non–selective serotonin uptake inhibition (only 1 exposed case) to compare with SSRI users. Anxiolytic use was not significantly associated with reduced odds for MI (OR 1.04; CI 0.56, 1.95 P=0.90).

Discussion
Study Results
This study demonstrates a statistically significant association between SSRI use and lower odds of MI among smokers. The
small number of users of other antidepressant limits the ability to examine the effects of these drugs with precision. Nonetheless, it is interesting to postulate that the effect of other antidepressants on MI risk may be less than that of SSRIs.

### Non-SSRI Antidepressants and Cardiovascular Disease

Prior investigations have demonstrated an association between cardiovascular events and non-SSRI antidepressant medications.\(^2\) In a small randomized trial comparing the SSRI paroxetine with nortriptyline, there were significantly fewer adverse cardiac events in the SSRI group.\(^6\) Recently, Cohen et al.\(^{14}\) concluded that an excess risk of MI in patients treated with antidepressant medication was specifically associated with the use of tricyclic agents, whereas there was a nonsignificant inverse association between SSRI use and MI (OR 0.8; 95% CI 0.2 to 3.5). This study, however, was limited in its ability to detect a significant reduction in risk.

### TABLE 1. Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SSRI Use</td>
</tr>
<tr>
<td></td>
<td>(n=130)</td>
</tr>
<tr>
<td>Age, y</td>
<td>44.7±7.58</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>32 (24.6)</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>26.6±5.80</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>11 (9.4)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>33 (25.6)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>33 (25.6)</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>55 (42.3)</td>
</tr>
<tr>
<td>Any exercise, n (%)</td>
<td>59 (45.4)</td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>55 (42.3)</td>
</tr>
<tr>
<td>Aspirin use, n (%)</td>
<td>10 (9.0)</td>
</tr>
<tr>
<td>(\beta)-Blocker use, n (%)</td>
<td>6 (4.6)</td>
</tr>
<tr>
<td>History of CAD, n (%)</td>
<td>9 (6.9)</td>
</tr>
<tr>
<td>Medicaid, n (%)</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>108 (83.7)</td>
</tr>
<tr>
<td>Black</td>
<td>14 (10.9)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (5.4)</td>
</tr>
<tr>
<td>College education, n (%)</td>
<td>78 (60.0)</td>
</tr>
<tr>
<td>Income &lt; $30,000, n (%)</td>
<td>42 (33.9)</td>
</tr>
<tr>
<td>Cigarettes smoked/day</td>
<td>20.1±12.00</td>
</tr>
<tr>
<td>Vitamin use, n (%)</td>
<td>55 (42.3)</td>
</tr>
<tr>
<td>Physician visits/year</td>
<td>2.4±0.87</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). AD indicates antidepressant; BMI, body mass index; and CAD, coronary artery disease.

### TABLE 2. Association Between SSRI Use and MI

<table>
<thead>
<tr>
<th>Cases</th>
<th>Control Subjects</th>
<th>Bivariable OR (95% CI)</th>
<th>Multivariable OR (95% CI)*</th>
<th>(P)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AD use</td>
<td>635</td>
<td>2820</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>All SSRI users</td>
<td>13</td>
<td>130</td>
<td>0.45 (0.25–0.80)</td>
<td>0.35 (0.18–0.68)</td>
</tr>
<tr>
<td>No AD use</td>
<td>635</td>
<td>2820</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Other AD users</td>
<td>5</td>
<td>47</td>
<td>0.49 (0.19–1.22)</td>
<td>0.48 (0.17–1.32)</td>
</tr>
<tr>
<td>No AD or anxiolytic use</td>
<td>610</td>
<td>2739</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>No AD use, anxiolytic users</td>
<td>25</td>
<td>81</td>
<td>1.58 (0.94–2.64)</td>
<td>1.04 (0.56–1.95)</td>
</tr>
</tbody>
</table>

AD indicates antidepressant.

*Adjusted for age, sex, race, education, any degree of exercise within the last year, quantity of cigarettes smoked per day, body mass index, number of physician visits in the prior year, aspirin use for MI prevention, family history, and history of coronary disease, diabetes, hypertension, and hypercholesterolemia.

†\(P\) value for multivariable OR.
because adjustment for confounding was limited to variables available in an administrative database and the number of events was small.

Although there were too few users of non-SSRI antidepressants to accurately measure the odds of MI with precision, the nonsignificant protective effect in this study is apparently contradictory to the prior studies mentioned above. In light of the previous studies demonstrating an increase in odds of MI for this group, the lower point estimate in the non-SSRI users is likely attributable to chance or bias. Bias could be from misclassification, because this group included tricyclic, atypical, and other non-SSRI antidepressants, each of which may have different effects on MI risk. Some atypical and tricyclic antidepressants demonstrate serotonin uptake inhibition (in addition to other properties), which may affect platelets and reduce the observed odds of MI for this group. Second, because we only examined first non-fatal MI, potential cases taking tricyclic agents (which have class I antiarrhythmic properties) may have died from sudden cardiac death, thereby causing a false association with MI protection. Finally, because of the known association these agents have with cardiovascular complications, there may have been a potential for confounding by indication (ie, lower cardiovascular risk individuals may have been more likely to use these agents, whereas higher-risk individuals were prescribed SSRIs). Nonetheless, any conclusions drawn from the analysis of these agents in this study would be speculative because of the small number of exposed subjects.

Depression, SSRIs, and Platelet Function

One of the hypotheses explaining why patients with depression are at an increased risk for MI is related to abnormalities in platelet function.\(^{5,22}\) This may be attributable to the upregulation of platelet imidazoline\(^{23}\) and serotonin\(^{24}\) receptors and enhanced intraplatelet calcium mobilization\(^{25}\) seen in patients with depression.

SSRIs may reverse these sequelae and reduce MI risk by affecting serotonin-mediated platelet activation.\(^{4,8,9}\) This was the a priori hypothesis of our study. SSRIs inhibit serotonin uptake into platelets,\(^{11,26,27}\) block intracellular calcium mobilization,\(^{28}\) and are associated with an increase in bleeding time.\(^{13,29}\) These are the proposed mechanisms for the reduced platelet activity\(^{10,11}\) and the increased bleeding risk observed with SSRI therapy.\(^{30–33}\) Our results are, within the study’s degree of precision, consistent with the effect of other antiplatelet agents on nonfatal myocardial infarction.\(^{34}\)

It is also possible that SSRIs prevent MI through reduction of other depression-mediated mechanisms. Treatment of depression could lead to reversal of the abnormal platelet function, modification of lifestyle, and better compliance with medication, diet, and exercise. Because we did not identify untreated patients with depression and because of the small number of other antidepressant users, we are unable to distinguish between the relative benefit of the treatment of depression itself versus the drug’s potential antiplatelet action on MI risk. However, the aforementioned studies\(^{9–11,26–28,33}\) and case reports describing bleeding complications\(^{30–32}\) suggest that platelet inhibition may be the mechanism for a protective effect and that other antidepressants may not have a beneficial effect on MI risk.\(^{2,14,21}\)

Potential Limitations

The potential limitations of observational research must be considered in interpreting the results of this study. Because this study only included cases with non-fatal MI, a false-negative association could be created if users of SSRIs were more likely to develop sudden death after an MI. This bias is unlikely, because SSRIs do not have arrhythmogenic properties.\(^{7,12}\) Unlike tricyclic antidepressants, SSRIs do not have class I antiarrhythmic properties, a characteristic associated with increased mortality post-MI.\(^{35}\) In addition, SSRIs do not alter intraventricular conduction times or QT intervals.\(^{6,7}\)

A low participation rate could have created a false association if nonparticipant cases were more likely to use SSRIs for treatment of depression. However, nonparticipant cases were less likely to have private medical insurance and perhaps therefore less likely to have received an SSRI. This would, if anything, bias the results toward the null. A false association could also have been created if nonparticipant control subjects were less likely to use SSRIs compared with participants. However, the 4.35% exposure rate seen in our control group is similar to the 4.05% prevalence of SSRI use in the general population during the same time period.\(^{36}\) In addition, even if SSRI use among the potentially eligible control subjects who did not participate was one third of the participant’s, there would still be a significant association between SSRIs and reduced MI risk (OR 0.56, \(P=0.05\)).

Differential recall of SSRI use could create a false inverse association if control subjects were more likely than cases to accurately report SSRI exposure. Although the OR of 0.5 for users of non-SSRI antidepressants could reflect differential recall, it also may be attributable to chance or bias, as previously discussed. In addition, the fact that anxiolytic use was not associated with MI suggests that differential recall of medications was unlikely to have produced our results.

Uncontrolled confounding is another potential limitation of our study. If SSRIs users are a low risk group because of other unmeasured unique characteristics, there would be a false association between SSRIs and lower risk for MI. Because SSRIs require a doctor’s prescription as well as adequate follow-up to monitor progress, it also is possible that better medical attention and treatment of modifiable risk factors for MI could account for the protective effect seen. However, SSRIs users had more traditional risk factors for MI, and adjustment for all known potential risk factors (except sex), including variables related to access to medical care, strengthened rather than weakened the inverse association between SSRI use and MI. In addition, use of anxiolytics, which also require a prescription and medical follow-up, was not associated with MI protection, making this bias unlikely. Finally, confounding by indication (ie, if SSRIs were used for a condition that is itself associated with lower MI risk) could not explain these results, because the indication for SSRIs, depression, should, if anything, increase the risk of MI.\(^{1,2}\) This would bias the results toward a falsely harmful effect of SSRIs.

Because we only recorded current use within the index week, some SSRI users may not have received the duration of...
therapy studied for treatment of depression. However, our a priori hypothesis is that platelet inhibition, which has been demonstrated with short-term exposure, is the mechanism for reduced odds of MI. In addition, any misclassification of chronic SSRI exposure (ie, classifying chronic, prior users incorrectly as nonusers or present, short-term users incorrectly as users) would bias toward no effect of chronic SSRI use on MI and could not explain these results.

Finally, the results may not be applicable to nonsmokers. Smokers may represent a high-risk group with altered platelet function and, therefore, may be more sensitive to the effect of SSRIs. However, the effects of SSRIs on platelet inhibition and treatment of depression are not restricted to smokers and therefore would be expected to affect MI risk for nonsmokers as well.

Conclusions

Current use of SSRIs in patients with depression is associated with a reduced odds of MI. This may be attributable to the inhibitory effect that SSRIs have on serotonin-mediated platelet activation or perhaps amelioration of other mechanisms of increased adverse cardiovascular risks associated with depression not specific to SSRI therapy. Additional investigation is needed to confirm these findings and to determine if other serotonergic antidepressants have similar effects.

Acknowledgments

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References

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