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Current Use of Selective Serotonin Reuptake Inhibitors and Risk of Acute Myocardial Infarction

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Abstract

Background: It has been suggested that increased platelet activation increases the risk of acute myocardial infarction (AMI) in patients with depression. Selective serotonin reuptake inhibitors (SSRIs) may attenuate platelet activation by serotonin depletion in platelets. Observational studies have shown discrepant results of AMI risk associated with the use of SSRIs.

Objective: The aim of this study was to evaluate the association of exposure to different groups of antidepressants, including SSRIs, and the risk of AMI. The study also assessed in more detail the influence of timing of the exposure to antidepressants in a general adult population (<90 years of age), with or without diagnosed risk factors for AMI.

Study design/methods: We conducted a population-based case-control analysis on the UK General Practice Research Database (GPRD). The study included 8688 patients (<90 years of age), with a first-time AMI between 1995 and 2001, and 33 923 controls, who were matched by age, sex, calendar time, and general practice. Conditional logistic regression was used to estimate odds ratios (ORs).

Results: Current use of an antidepressant was defined as a supply of the last prescription for an antidepressant that lasted up to the index date or beyond. Recent past use was defined as a supply of the last prescription for an antidepressant that ended 1–29 days before the index date. SSRIs investigated were citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine. Non-SSRIs investigated were amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nefazodone, trazodone and trimipramine. Other antidepressants included were amoxapine, desipramine, lithium, maprotiline, mianserin, moclobemide, nortriptyline and protriptyline. Adjusted ORs (with 95% CI) for the current use of SSRIs, non-SSRIs, or other antidepressants, compared with non-use of antidepressants, were 0.63 (95% CI 0.43, 0.91; p = 0.02), 0.92 (95% CI 0.77, 1.09; p = 0.32) and 0.59 (95% CI 0.29, 1.20; p = 0.14), respectively.

The adjusted OR of recent past use of SSRIs compared with non-use of SSRIs was 1.42 (95% CI 1.02, 1.97; p = 0.04).
Conclusion: The present analysis provides further evidence that the current use of SSRIs is associated with a slightly decreased risk for AMI.

Background

There is substantial evidence from several observational studies that depression is an independent risk factor for cardiovascular disease and acute myocardial infarction (AMI), both aetiologically and prognostically.[1-6] The underlying mechanisms are not well understood yet; however, in addition to abnormalities in the sympathoadrenal system and the autonomic nervous system,[7] enhanced platelet reactivity and an increased risk of thrombus formation may predispose patients with depressive disorders to an increased risk of coronary heart disease.[8-12]

Antidepressants affecting serotonin uptake, especially selective serotonin reuptake inhibitors (SSRIs), may attenuate platelet activation by decreasing platelet serotonin levels.[13-18] This may be associated with a protective effect of SSRIs against AMI.[19] Four recent epidemiological studies have addressed this issue so far,[20-23] including one by our group.[23] The risk estimates for AMI found in these four studies ranged from 0.35 to 0.9 in users of SSRIs compared with non-users. In addition to the different methods used to assess the patient's exposure to antidepressants (e.g. interview-based versus administrative prescription data or electronically recorded prescription information), the differences between these four studies may be partly explained by the different classification of antidepressants regarding serotonin uptake inhibition and different classifications of the timing of antidepressant exposure.

In our previous study, we included only idiopathic cases who were free of diagnosed cardiovascular or metabolic risk factors predisposing for AMI.[23] Patients were classified as current users of antidepressants if the supply of the last prescription for an antidepressant drug exceeded the index date or ended within a period of 30 days before the index date. In that study, we found an adjusted odds ratio (OR) of 0.9 in current SSRI users compared with patients not exposed to antidepressants (95% CI 0.5, 1.8).

The aim of the present study was to further evaluate the association of exposure to different groups of antidepressants, including SSRIs, and the risk of AMI and to assess in more detail the influence of the timing of exposure to antidepressants in a general adult population (<90 years of age) with or without diagnosed risk factors for AMI.

Methods

Study Population and Data Source

The General Practice Research Database (GPRD) is a large and well validated database, which has been previously described in detail.[24-26] Briefly, more than 3 million residents in the UK have been registered with selected general practitioners (GPs) who have agreed to provide data for research purposes to the GPRD. The database has provided the source data for numerous epidemiological studies and the accuracy and completeness of the data have been well documented and validated.[27-29] GPRD data have been used in several recent studies on AMI,[23,30-32] including a study with antidepressant drugs.[23] The age- and sex-distribution of patients in the GPRD is representative of the UK population. The information electronically recorded by GPs includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, clinical diagnoses, referrals to consultants, hospitalisations, and drug prescriptions. Drug prescriptions are recorded in detail using a drug dictionary based on the UK Prescription Pricing Authority codes. For each prescription these codes define the active compound, the route of administration, the dose of a single unit, the number of units prescribed, and, in most instances, the intake

regimen prescribed by the GP (e.g. three tablets per day). Drug prescriptions are generated directly from the computer and are recorded in each patient's computerised profile. On request, hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record.

This study was approved by the Scientific and Ethical Advisory Group of the GPRD.

Case Definition and Ascertainment

We identified potential cases with a first-time diagnosis of AMI via computer-recorded Oxford Medical Information System codes mapped onto International Classification of Diseases codes. We searched for patients <90 years of age who had a first-time AMI between 1995 and 2001. Patients who had been registered on the database for <3 years before the date of the AMI were excluded. We reviewed the computer records of all potential cases, whereby any information on exposure to antidepressants was concealed.

In previous studies using GPRD data, the computer-recorded diagnosis of a first-time AMI was validated for a random sample of approximately 450 patients by reviewing hospital discharge letters. When we selected cases, based on a manual review of computer records and sent for hospital discharge letters, >90% of cases were confirmed by the presence of characteristic diagnostic criteria.[30,31,33] Based on these previous extensive validation procedures, we included all potential cases that we identified through manual review of patient records.

Controls

We identified at random four controls per case, who were matched by age (± 1 year), sex, general practice attended, number of years of recorded history in the database, and calendar time (by using the same index date, i.e. the date of the AMI diagnosis of the corresponding case). Controls with a history of <3 years in the GPRD were excluded.

Exposure Definition

For each case and control, we assessed the exposure history for antidepressants. Antidepressants were classified into three groups according to their inhibitory capacity on serotonin reuptake: (i) SSRIs (i.e. citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine); (ii) non-SSRIs (i.e. amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nefazodone, trazodone, trimipramine); and (iii) a miscellaneous group of 'other antidepressants' (i.e. amoxapine, desipramine, lithium, maprotiline, mianserin, moclobemide, nortriptyline, protriptyline). Based on the number of tablets and the GPs intake regimen of the last prescription for an antidepressant drug prior to the index date, we assessed the number of days between the cessation of an antidepressant and the index date for each case and control patient. According to this time period, a patient was defined as a 'current user' if the supply of the last prescription for an antidepressant lasted up to the index date or beyond. Patients whose antidepressant therapy ended before the index date were categorised according to the time lag between the end of therapy and the index date as 'recent past' or 'past' (i.e. 1–29 days and ≥30 days, respectively).

Statistical Analysis

We conducted a matched analysis (conditional logistic regression model) using the software program SAS, Version 8.1 (SAS Institute Inc., Cary, NC, USA). Relative risk estimates (as odds ratios; ORs) are presented with 95% CIs.

For each case and control patient, the independent effects of various potential confounders on the AMI risk were assessed, such as body mass index (BMI) (<25, 25–29.9, ≥30 kg/m^2, unknown), smoking status (never, ex, current, unknown), number of GP visits in the year prior to the index date (0–4, 5–9, ≥10) as a marker of comorbidity, aspirin (acetylsalicylic acid) use, hypertension, hyperlipidaemia, diabetes mellitus, ischaemic heart disease, other cardiac diseases (arrhythmias or congestive heart failure), arterial vascular diseases (claudication, stroke, transient ischaemic attack, arterial

Table I. Characteristics of cases with acute myocardial infarction and controls

Characteristic	No. of cases (%) [n = 8688]	No. of controls (%) [n = 33 923]	Adjusted[a] OR (95% CI)
Age			
<50	662 (7.6)	2 611 (7.7)	
50–69	3681 (42.4)	14 521 (42.8)	
70–89	4345 (50.0)	16 791 (49.5)	
Sex			
male	5463 (62.9)	21 310 (62.8)	
female	3225 (37.1)	12 613 (37.2)	
Smoking status			
non	3952 (45.5)	18 555 (54.7)	1.00 (referent)
current	2192 (25.2)	5 559 (16.4)	2.07 (1.93, 2.22)
ex	1363 (15.7)	4 697 (13.9)	1.31 (1.21, 1.41)
BMI (kg/m^2)			
<25	2376 (27.4)	10 174 (30.0)	1.00 (referent)
25–29.9	2711 (31.2)	10 426 (30.7)	1.06 (0.99, 1.14)
≥30	1219 (14.0)	3 893 (11.5)	1.21 (1.11, 1.32)
Diagnosed risks			
hypertension	3045 (35.1)	9 275 (27.3)	1.26 (1.19, 1.34)
hyperlipidaemia	1957 (22.5)	2 027 (6.0)	4.21 (3.89, 4.55)
diabetes mellitus	1185 (13.6)	2 276 (6.7)	1.84 (1.69, 2.00)
IHD	2616 (30.1)	4 090 (12.1)	2.72 (2.54, 2.92)
arrhythmias/CHF	1691 (19.5)	4 019 (11.9)	1.46 (1.36, 1.57)
arterial thrombosis	1408 (16.2)	3 655 (10.8)	1.25 (1.15, 1.36)
kidney diseases	349 (4.0)	845 (2.5)	1.23 (1.07, 1.43)

a Adjusted for all covariates listed in the table plus acute chest infections, aspirin (acetylsalicylic acid) and NSAID drug use.

BMI = body mass index; **CHF** = congestive heart failure; **IHD** = ischaemic heart disease; **OR** = odds ratio.

thromboembolic events), kidney diseases, acute respiratory tract infection and diseases with systemic inflammation (i.e. rheumatoid arthritis or systemic lupus erythematosus).

Results

We identified 8688 cases with a first-time AMI and 33 923 matched controls. Of the 8688 AMI patients, 1645 (18.9%) died at or shortly after the date the AMI diagnosis was recorded. Table I displays the age and sex distribution of cases and controls, as well as their smoking status, BMI and presence of cardiovascular or metabolic diseases in association with the AMI risk. Case patients were predominantly male (62.9%) and 50% were ≥70 years of age at the date of the AMI. Of the 8688 cases identified, 2124 (24.4%) did not have a computer-recorded diagnosis of a cardiovascular or metabolic disorder prior to the AMI.

In a first analysis, we compared subjects who used SSRIs only (i.e. without previous exposure to non-SSRIs or other antidepressants), subjects who used non-SSRIs only (i.e. without previous exposure to SSRIs or other antidepressants), subjects who used other depressants only (i.e. without previous exposure to SSRIs or non-SSRIs) and the mixed group (i.e. subjects who used a combination of the above) with the reference group of non-users of any antidepressants. The OR of developing a first-time AMI in patients with current exposure to SSRIs was 0.63 (95% CI 0.43, 0.91; p = 0.02), adjusted for hypertension, diabetes, hypercholesterolaemia, ischaemic heart disease, arterial vascular disease, kidney disease, inflammatory diseases, respiratory tract infection, BMI, smoking, number of GP visits in the year prior to the index date, exposure to NSAIDs,

aspirin and/or antipsychotic drugs. This risk reduction was only observed for current not recent past or past SSRIs users (table II). The adjusted ORs for current exposure to non-SSRIs only or other antidepressants only compared with non-use of any antidepressant were 0.92 (95% CI 0.77, 1.09; p = 0.32) and 0.59 (95% CI 0.29, 1.20; p = 0.14), respectively.

In a second analysis, we compared the risk of AMI between users of SSRIs with subjects who had never used SSRIs, adjusting the analysis for use of 'non-SSRIs' and use of 'other antidepressants' (in addition to the covariates described previously). The adjusted OR for current SSRI use, compared with non-use of SSRIs, was 0.71 (95% CI 0.56, 0.89; p = 0.004, table III).

We additionally stratified this analysis by age (<70 years vs ≥70 years); the adjusted ORs for current SSRI use compared with non-users of SSRIs were 0.55 (95% CI 0.39, 0.79; p = 0.001) for patients <70 years of age and 0.85 (95% CI 0.62, 1.17; p = 0.32) for patients ≥70 years of age. Stratification by sex resulted in adjusted relative risk estimates of 0.92 (95% CI 0.67, 1.28; p = 0.62) for women and 0.53 (95% CI 0.38, 0.76; p < 0.0005) for men.

Stratification of current SSRI use by individual SSRIs in the same model yielded the following adjusted ORs compared with non-use of SSRIs: citalopram 0.32 (95% CI 0.11, 0.98; p = 0.04), fluvoxamine 0.27 (95% CI 0.03, 2.57), fluoxetine 0.66 (95% CI 0.45, 0.98), sertraline 0.69 (95% CI 0.38, 1.27), paroxetine 0.80 (95% CI 0.55, 1.18), and venlafaxine 0.95 (95% CI 0.34, 2.62), respectively.

To assess a potential effect modification by aspirin we stratified current SSRI users into those without aspirin exposure and those who concomitantly used aspirin. The respective adjusted relative risk estimates were 0.66 (95% CI 0.49, 0.88) for those without and 0.73 (95% CI 0.44, 1.20) for those with concomitant aspirin use.

In this analysis, current exposure to non-SSRIs was not associated with a change of the AMI risk compared with patients never exposed to non-SSRIs (adjusted OR 0.97; 95% CI 0.84, 1.13; p = 0.70), and current exposure to other antidepressants yielded a statistically non-significant decreased AMI risk compared with non-use of other antidepressants (adjusted OR 0.70; 95% CI 0.43, 1.12; p = 0.14). In all three groups of antidepressant users, the risk esti-

Table II. Risk of first-time acute myocardial infarction associated with use of antidepressants in mutually exclusive groups

Antidepressant	No. of cases (%) [n = 8688]	No. of controls (%) [n = 33 923]	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Non-exposed	6884 (79.2)	27 652 (81.5)	1.00 (referent)	1.00 (referent)
SSRIs				
current	42 (0.5)	195 (0.6)	0.86 (0.62, 1.20)	0.63 (0.43, 0.91)
recent past (1–29 days)	25 (0.3)	65 (0.2)	1.57 (0.99, 2.50)	1.20 (0.71, 2.01)
past (≥30 days)	168 (1.9)	639 (1.9)	1.06 (0.89, 1.27)	0.90 (0.75, 1.09)
Non-SSRIs				
current	210 (2.4)	797 (2.4)	1.08 (0.92, 1.26)	0.92 (0.77, 1.09)
recent past (1–29 days)	66 (0.8)	204 (0.6)	1.32 (0.99, 1.75)	1.04 (0.76, 1.42)
past (≥30 days)	853 (9.8)	2 866 (8.5)	1.22 (1.12, 1.32)	1.06 (0.97, 1.17)
Other antidepressants				
current	11 (0.1)	58 (0.2)	0.78 (0.41, 1.49)	0.59 (0.29, 1.20)
recent past (1–29 days)	4 (0.1)	6 (0.0)	2.79 (0.79, 9.88)	3.11 (0.78, 12.47)
past (≥30 days)	16 (0.2)	72 (0.2)	0.91 (0.53, 1.57)	0.70 (0.39, 1.25)
mixed antidepressant use	409 (4.7)	1 396 (4.0)	1.22 (1.09, 1.37)	0.98 (0.86, 1.10)

a Adjusted for hypertension, diabetes, hypercholesterolaemia, ischaemic heart disease, arterial vascular disease, kidney disease, inflammatory diseases, respiratory tract infection, body mass index, smoking, number of GP visits in the year prior to the index date, exposure to NSAIDs, aspirin and/or antipsychotic drugs.

GP = general practitioner; **OR** = odds ratio; **SSRIs** = selective serotonin reuptake inhibitors.

Table III. Risk of first-time acute myocardial infarction associated with use of SSRIs compared to non-use of SSRIs

Antidepressant	No. of cases (%) [n = 8688]	No. of controls (%) [n = 33 923]	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Non-use of SSRIs	8079 (93.0)	31 789 (93.7)	1.00 (referent)	1.00 (referent)
SSRIs				
current	108 (1.2)	470 (1.4)	0.90 (0.73, 1.11)	0.71 (0.56, 0.89)
recent past (1–29 days)	71 (0.8)	144 (0.4)	1.96 (1.47, 2.61)	1.42 (1.02, 1.97)
past (≥30 days)	430 (5.0)	1 520 (4.5)	1.13 (1.01, 1.26)	0.92 (0.81, 1.04)
non-use of non-SSRIs	7159 (82.4)	28 712 (84.6)	1.00 (referent)	1.00 (referent)
Non-SSRIs				
current	281 (3.2)	1 038 (3.1)	1.11 (0.97, 1.27)	0.97 (0.84, 1.13)
recent past (1–29 days)	92 (1.1)	267 (0.8)	1.40 (1.10, 1.78)	1.17 (0.89, 1.53)
past (≥30 days)	1156 (13.3)	3 906 (11.5)	1.21 (1.13, 1.30)	1.05 (0.97, 1.15)
non-use of other antidepressants	8577 (98.7)	33 533 (98.9)	1.00 (referent)	1.00 (referent)
Other antidepressants				
current	25 (0.3)	121 (0.4)	0.81 (0.53, 1.25)	0.70 (0.43, 1.12)
recent past (1–29 days)	11 (0.1)	16 (0.1)	2.77 (1.28, 5.96)	2.51 (1.09, 5.78)
past (≥30 days)	75 (0.9)	253 (0.8)	1.18 (0.91, 1.53)	1.00 (0.75, 1.33)

a Adjusted for hypertension, diabetes, hypercholesterolaemia, ischaemic heart disease, arterial vascular disease, kidney disease, inflammatory diseases, respiratory tract infection, body mass index, smoking, number of GP visits in the year prior to the index date, and exposure to NSAIDs, aspirin, antidepressants and/or antipsychotic drugs.

GP = general practitioner; **OR** = odds ratio; **SSRIs** = selective serotonin reuptake inhibitors.

mates suggested a slightly increased AMI risk for subjects whose antidepressant therapy ended within 30 days prior to the index date (i.e. recent past use); the results were statistically significant for patients exposed to SSRIs (adjusted OR 1.42; 95% CI 1.02, 1.97; p = 0.04) and for patients exposed to other antidepressants (adjusted OR 2.51; 95% CI 1.09, 5.78; p = 0.03). Past exposure (last exposure to an antidepressant ≥30 days prior to the index date) was not associated with an altered AMI risk in any of the three antidepressant groups (table III).

In an additional analysis, in which antidepressants were classified according to their affinity for the serotonin transporter (i.e. high affinity [paroxetine, clomipramine, sertraline, fluoxetine], moderate affinity [citalopram, imipramine, fluvoxamine, amitriptyline, venlafaxine], and low affinity [desipramine, nortriptyline, protriptyline, amoxapine, doxepin, trimipramine, trazodone, nefazodone, maprotiline, bupropion, mirtazapine]),[22] the adjusted ORs for current exposure were 0.66 (95% CI 0.47, 0.93; p = 0.02) for antidepressants with high affinity, 0.97 (95% CI 0.76, 1.24; p = 0.82) with moderate affinity, and 0.70 (95% CI 0.40, 1.22; p = 0.21) with low affinity.

Discussion

The results of the present study suggest that current exposure to SSRIs is associated with a significantly decreased risk of AMI compared with non-use of antidepressants or non-use of SSRIs. This is in accordance with other case-control studies[20-22] as well as a randomised controlled trial.[34] In SADHART (Sertraline AntiDepressant Heart Attack Randomized Trial), a randomised trial investigating the safety and efficacy of the SSRI sertraline in patients with major depression hospitalised for AMI or unstable angina and free of other life-threatening medical conditions, the incidence of severe cardiovascular adverse events was non-significantly decreased in patients taking sertraline compared with patients taking placebo (14.5% and 22.4%, respectively); the relative risk of MI in users of sertraline compared with placebo was 0.70 (95% CI 0.23, 2.16).[34]

In a case-control study of 653 myocardial infarction patients and 2990 controls, 30–65 years of age, Sauer et al.[21] used data from another study in which the primary objective was to examine the effect of nicotine patch exposure and the risk of myocardial infarction in smokers.[35] Information on exposure and other covariate data were collected using a structured telephone interview for patients and control subjects. Detailed information was obtained on antidepressant drug exposure during the week before the index date, indication for antidepressant drug use, and other clinical and demographic characteristics. Antidepressant drugs were categorised into SSRIs and other antidepressants (including tricyclic, tetracyclic, atypical antidepressants, and monoamine oxidase [MAO] inhibitors). The risk of AMI in SSRI users compared with non-users of antidepressant drugs (adjusted for age, sex, race, education, degree of exercise within the past year, quantity of cigarettes smoked per day, BMI, number of physician visits in the prior year, aspirin use for myocardial infarction prevention, family history, and history of coronary disease, diabetes, hypertension and hypercholesterolaemia) was significantly decreased (OR 0.35; 95% CI 0.18, 0.68). In users of other antidepressants, the relative risk in comparison with non-users of antidepressants was also reduced but did not reach statistical significance (OR 0.48; 95% CI 0.17, 1.32). In an additional case-control study by the same group,[22] including 1080 myocardial infarction patients and 4256 controls aged 40–75 years, the OR for AMI among current users of antidepressants with high serotonin transporter affinity compared with non-users of antidepressants (after adjustment for age, sex, race, education, physical activity, quantity of cigarettes smoked per day, BMI, aspirin use, family history of myocardial infarction, and history of diabetes, hypertension or hypercholesterolaemia) was 0.59 (95% CI 0.39, 0.91). Increasing serotonin transporter affinity was associated with reduced odds of myocardial infarction among users of all SSRIs but not tricyclic or atypical antidepressants.

Cohen and colleagues[20] performed a retrospective follow-up study in patients aged 25–65 years. Hospitalisation, with a discharge diagnosis of myocardial infarction, or death due to myocardial infarction, was defined as the primary outcome. Using administrative prescription data, exposure information for antidepressant drugs was collected. Antidepressant drugs were categorised in three classes: SSRIs, tricyclic antidepressants, and MAO inhibitors or atypical agents. Furthermore, exposure information on medications indicating other illnesses, including hypertension, hyperlipidaemia, heart disease, diabetes and cancer, was additionally gathered. In a multivariate analysis, the relative risk of myocardial infarction with SSRI use (adjusted for age, sex, exposure to drugs for diabetes, hypertension, heart disease, hyperlipidaemia, anxiety and cancer) was statistically non-significantly decreased to 0.8 (95% CI 0.2, 3.5), while exposure to tricyclic antidepressants was associated with an increased risk (hazard ratio 2.2; 95% CI 1.2, 3.8).

The results of our study underline the importance of appropriate exposure classification. In a previous smaller case-control analysis using GPRD data with 3319 case and 13 139 matched control patients, in which we only included idiopathic cases (i.e. individuals without recorded diagnoses of cardiovascular or metabolic diseases predisposing to ischaemic heart disease prior to the AMI), we defined exposure to SSRIs as ‘current’ if the supply of the last prescription lasted until the index date or ended within a period of 30 days prior to the index date.[23] This classification may have theoretically included individuals with a one-month gap between the last SSRI exposure and the AMI. In that analysis, the OR for current use of SSRIs only was 0.9 (95% CI 0.5, 1.8), adjusted for BMI and smoking, compared with non-use of any antidepressants. If current SSRI use was compared with non-use of SSRIs (adjusting for use of non-SSRIs and other antidepressants, BMI, and smoking), the adjusted OR was 1.1 (95% CI 0.7, 1.6). In the present study, which encompassed 8688 patients with AMI and 33 923 controls, we not only included idiopathic cases but also individuals with pre-existing cardiovascular, metabolic, or inflammatory diseases known to be associated with an increased risk of cardiovascular disease. The re-

duced AMI risk associated with the use of SSRIs, as observed in this study, was restricted to current SSRI users. However, the results of this study suggest that the AMI risk may be increased during the month after cessation of SSRI therapy. This may explain the null finding of our first study in which current SSRI users also included those patients who stopped SSRI therapy the month prior to the event.

The current study cannot answer the question of whether this potential risk reduction may be due to the effects of SSRIs on platelet aggregation or decreasing depressive symptoms. The latter potential mechanism may be supported by the observation that there was also a suggestion of a potentially decreased risk for current users of non-SSRIs (adjusted OR 0.92, 95% CI 0.77, 1.09) as well as for current users of other antidepressants (adjusted OR 0.59, 95% CI 0.29, 1.20), similar to the results of Sauer et al.[21]

The potentially increased cardiac risk in recent past SSRI users might eventually be partly explained by the SSRI discontinuation syndrome. The syndrome is characterised by a variety of symptoms including dizziness, anxiety, fatigue, insomnia, irritability, nausea or emesis, and tremor.[36-38]

Our findings do not imply that the use of SSRIs is without any risk in cardiac patients. It is well known that several SSRIs are moderate-to-strong inhibitors of several cytochrome P450 isoenzymes.[39,40] This may result in increased plasma concentrations of other concomitantly taken drugs, which may ultimately result in a higher risk of concentration dependent adverse drug reactions. Additionally, SSRIs have been associated with various bleeding complications in case reports[41-45] and observational studies have shown an increased risk of gastrointestinal bleeding associated with SSRI use.[46-48] These risks may partly counterbalance the potential positive effects on the risk of AMI.

Some limitations of our study are related to the structure of the database. Information on physical activity or socio-economic status, which may be potential confounders, are not or only unreliably recorded. Additionally, we cannot exclude the possibility that other unrecognised confounding factors may have influenced our results.

Thus, our findings do not conclusively resolve all questions on the complex relationship between depression and cardiovascular disease. Nevertheless, this large case-control analysis suggests that the current use of SSRIs is associated with a decreased risk of AMI.

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