ELSEVIER

# A Secondary Analysis of a Duration Response Association Between Selective Serotonin Reuptake Inhibitor Use and the Risk of Acute Myocardial Infarction in the Aging Population

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**PURPOSE:** We assessed the risk of selective serotonin reuptake inhibitor (SSRI) use on the occurrence of acute myocardial infarction (AMI) based on duration of exposure.
**METHODS:** A historical pooled cohort of all elderly, community-dwelling Medicare beneficiaries not enrolled in health maintenance organizations from the 1997 to 2001 Medicare Current Beneficiary Survey was constructed. SSRI users were compared with non-antidepressant users as well as other non-SSRI antidepressant users on their risk of AMI (ICD-9: 410 or 411). Descriptive statistics and binary logistic regression models were used to assess differences between groups.
**RESULTS:** There were 1,052 SSRI users compared with 762 other antidepressant users and 10,856 non-antidepressant users. Logistic regression models revealed that SSRI users were found to have significantly greater odds of AMI compared with nonantidepressant users when controlling for age, gender, race, smoking history and current status, body mass index, depression, anxiety and diabetes (odds ratio 1.85; 95% confidence intervals 1.13–3.04). Stratification by prescription counts revealed those with more than three prescriptions had greater odds of AMI compared with nonusers (odds ratio 2.02, 95% confidence intervals 1.11–3.66).
**CONCLUSIONS:** SSRI use leads to an increased risk of AMI in comparison with nonantidepressant use in an elderly population. The odds of AMI increased in those with more than three prescriptions in the preceding year, indicating a possible duration response relationship.
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KEY WORDS: Acute Myocardial Infarction, Antidepressants, SSRI, Selective Serotonin Reuptake Inhibitor.

## INTRODUCTION

The prevalence of depressive symptoms in the U.S. elderly population is estimated to range from 15% to 30% (1, 2) and the incidence of coronary heart disease (CHD) is estimated to occur at a rate of 22.3 (women) to 39.6 (men) per 1,000 person-years (3). Depression has been established as a risk factor for cardiovascular disease (4–9) through pathophysiology, including abnormalities in the sympathoadrenal system and autonomic nervous system (10), enhanced platelet reactivity, and an increased risk of thrombus formation (11–15). Theoretically, reducing the symptoms of depression should reduce the risk of acute myocardial infarction (AMI); however, antidepressant pharmacological treatment may expose individuals to an increased risk of AMI, independent of depression.

Although all antidepressants have proven efficacy in reducing the symptoms of depression, the pharmacological properties of the various therapeutic classes may increase the risk of cardiovascular disease even though there is a reduction of depressive symptoms. Studies point to changes in 5-HT receptors by antidepressants as the means of mediating atherogenic and prothrombotic mechanisms in the periphery, leading to AMI and other thrombotic events (16–18). Tricyclic antidepressants have been associated with a high incidence of cardiovascular side effects (19). However, selective serotonin reuptake inhibitors (SSRIs) have been associated with a protective effect against AMI (20), hypothesized to be attributable to the reducing platelet activation by the decreasing platelet serotonin levels (11, 21–26).

Six observational studies (20, 27–31) and one clinical trial (32) have evaluated the cardiovascular safety of antidepressants and have found conflicting results. These studies have several limitations that require noting. For one, the only one completed clinical trial evaluating the safety and efficacy of one specific SSRI, of which AMI was measured as an outcome, was unable to assess the independent risk of AMI attributable to SSRI antidepressant use due to sample inclusion restrictions of only including depressed individuals and limiting comparisons to only a placebo group

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**Selected Abbreviations and Acronyms**

CHD = coronary heart disease
AMI = acute myocardial infarction
SSRI = selective serotonin reuptake inhibitor
CMS = Centers for Medicare and Medicaid Services
MCBS = Medicare Current Beneficiary Survey
BMI = body mass index
DCG-HCC = Diagnostic Cost Grouper – Hierarchical Coexisting Conditions
OR = odds ratio
95% CI = 95% confidence interval

rather than to other antidepressant groups (such as tricyclic antidepressant users) (32). The authors of only one cohort study evaluated the risk of AMI in SSRI antidepressant users, and their findings were not significant (27). The authors of three case-control studies (20, 28, 29) have shown that SSRIs provide a protective effect against AMI, whereas the author of another study (30) has shown that stopping SSRI use within 30 days of an AMI increases the risk substantially. The most recent study found an increased risk of AMI within the first 7 days of taking an SSRI (31). Further, previous studies have not evaluated a duration response relationship by SSRI antidepressant use in the elderly population, and no studies have evaluated the marginal risk or attributable risk of AMI by SSRI antidepressants, independent of depression. Well-designed cohort studies that assess SSRI antidepressant use when controlling for depression in the elderly are needed to determine the attributable risk of SSRI antidepressant use because of the high incidence of cardiovascular events and high prevalence of depression in the elderly.

We pooled data to conduct a historical cohort study to estimate the risk associated with SSRI use in the elderly population using nationally representative data collected by the Center for Medicare and Medicaid Services (CMS) to compare the risk of AMI in elderly patients on SSRI therapy when controlling for depression, anxiety, other antidepressant use and other key cardiovascular risk factors. We hypothesized that elderly patients taking SSRI antidepressants have a greater risk of AMI than elderly patients not taking SSRI antidepressants, and elderly patients with more than three SSRI antidepressant prescriptions annually will have a greater risk of AMI than elderly patients taking three or fewer SSRI antidepressant prescriptions. Findings from this study will help physicians and providers better monitor elderly adults taking SSRI antidepressants for thrombotic events.

## METHODS

### Data Source

The study used the Medicare Current Beneficiary Survey (MCBS), which is considered to be the premier source of information on elderly and disabled Medicare beneficiaries. The survey is administered by the CMS, the federal agency responsible for the payment of services for all Medicare and Medicaid beneficiaries. The study used data spanning from 1997 through 2001. The MCBS uses a nationally representative sampling frame, which allows for generalizing study results to the whole population of Medicare beneficiaries. The survey also uses a longitudinal rotating panel design, every year, one round is retired and another round begins, giving the survey a cumulative sample size of three 4,000 beneficiary cohorts totaling approximately 12,000 beneficiaries in any given year. The survey collects information on beneficiaries' demographic characteristics, medical history, prescription drug use, insurance coverage, and death. Prescription mentions are ascertained through MCBS interviewers visiting enrolled beneficiaries and visibly verifying the beneficiary received a prescription for the corresponding medication. Follow-ups of medication detail ascertainment of beneficiaries are then continued by phone verification.

The survey is linked to the Medicare part A and B claims files, which includes diagnoses, utilization, and payment data. The MCBS typically has limited loss to follow-up, ranging from approximately 8% to 10% (33).

### Sample

The primary sample for the study consisted of Medicare beneficiaries enrolled in the MCBS in from 1997 to 2001. The inclusion criteria restricted the sample to beneficiaries who are 65 years of age or older residing in the community. Exclusions to the sample included those beneficiaries who were lost to follow-up as well as those beneficiaries participating in Medicare Plus Choice. Medicare Plus Choice beneficiaries were excluded from the sample because their claims are managed by managed care plans and not available in the Medicare claims files, which are required to identify AMI and to measure the outcome variables. Beneficiaries who were lost to follow-up before completing 2 years in the MCBS were also removed from the sample because 2 complete years of observation are required to assess the exposure in the first year and the outcomes in the second year. Individuals included in our study sample were designated as SSRI antidepressant users if they received an SSRI in the baseline year. If an individual did not receive an SSRI in the baseline year, but received another antidepressant, they were classified as an "other antidepressant" user. All those not included in the prior groups were defined as nonantidepressant users.

## MEASURES

### Variables of Interest

The dependent variable in the study is a binary measure of acute myocardial infarction, which is defined by at least