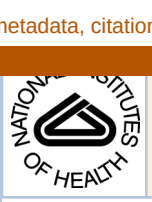

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Exposure to Tricyclic Antidepressants is Associated with an Increased Risk of Incident CHD Events in a Population-based Study

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Abstract

PURPOSE—The purpose of this study was to assess the association between antidepressant use and incident coronary heart disease (CHD) events in a sample of individuals without known baseline heart disease.

PARTICIPANTS AND METHODS—We studied a group of 970 randomly-selected community-dwelling adults in the 1995 Nova Scotia Health Survey, who were followed for up to ten years. Antidepressant usage was classified according to class. Primary outcomes were acute coronary syndrome hospitalizations or cardiac death, determined by centralized, standardized ratings.

RESULTS—During a follow-up period of ten years, there were 147 incident CHD events (139 acute coronary syndromes and 8 cardiac deaths) during the 8,129 person-years of observation (incidence rate = 18.1 events/1000 person years). In a model controlling for age, sex, Framingham risk score, time to last annual exam, aspirin exposure, and depressive symptoms, an increased risk of CHD events was associated with tricyclic antidepressant exposure (adjusted hazard ratio, 2.10; 95% confidence interval, 1.09–4.06; p=0.027).

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CONCLUSION—In this prospective population-based study, exposure to tricyclic antidepressants was associated with higher risk of first CHD events.

INTRODUCTION

Depression has been associated with worse prognosis in individuals with established coronary heart disease and with the development of coronary heart disease.1 However, there have been few population-based investigations testing the impact of antidepressant use on long-term CHD incidence.2,3,4,5 In this report we present the results of a prospective analysis of the relationship between antidepressant medication use and risk of incident CHD during 10-year follow-up of a population-based cohort.

METHODS

SUBJECTS

The study sample included patients enrolled in the 1995 Nova Scotia Health Survey study, a population-based survey by Heart Health Nova Scotia in partnership with the Nova Scotia Department of Health. The targeted population consisted of all non-institutionalized Nova Scotians age 45 and older, known to be CHD-free, whose names were listed in the Medical Service Insurance register, the government-sponsored, universal health insurance plan. We defined the period of follow-up for each participant as starting at the participant's age at baseline and extending until either his/her age at first CHD event or age on March 31, 2005 for those who did not have an event during the follow-up period.

At the home visit, the nurse requested all prescription and nonprescription medications and supplements, and recorded the generic drug name, the brand name, the number of pills in the bottle, the date of the prescription, and the dosing instructions. Drugs were coded using the World Health Organization Nordic Anatomical, Therapeutic, and Chemical code classification valid in 1995.6

The main outcome variable was incidence of nonfatal or fatal CHD, as categorized by the International Classification of Diseases.7 All deaths are reported to provincial offices, which in turn notify the national census bureau, Statistics Canada, which applies a nationally consistent process of determining the underlying cause of death. Nonfatal CHD was assessed by primary discharge hospital code, collected in the centralized, computerized, single-payer medical system.

Depressive symptoms were assessed at baseline with the Center for Epidemiological Studies Depression Scale.

Nurses visited the subjects at home for the baseline measures and recorded all prescription medications. Antidepressants were categorized as TCAs, SSRIs and Others.

STATISTICAL ANALYSIS

Baseline characteristics of the participants were compared by use of antidepressant medications and by drug class. Data are expressed as means and standard deviations, or percentages. Multivariable proportional hazards models were used to estimate the hazard ratio associated with antidepressant use, with adjustment for possible confounders including Framingham risk score and depressive symptoms. All statistical analyses were performed using SPSS statistical software version for Windows 16.0 (Chicago, IL).

RESULTS

Of the 970 patients, 40 (4%) possessed at least one prescription for an antidepressant at baseline (1995), and 930 did not. Baseline clinical characteristics are shown in Table 1. Length of follow-up did not vary for the antidepressant class and nonuser categories. Of the 40 participants using an antidepressant, 14 were on selective serotonin reuptake inhibitors (SSRIs), 25 were on tricyclic antidepressants (TCAs), and one patient was taking both. During follow-up of ten years, there were 147 incident CHD events (139 acute coronary syndromes and 8 cardiac deaths) during the 8,129 person-years of observation (incidence rate = 18.1 events/1000 person years). In a proportional hazards model controlling for age, sex, Framingham risk score, time to last annual exam, aspirin exposure, and baseline depressive symptoms, TCA exposure predicted a higher risk of 10-year incident CHD events (adjusted hazard ratio, 2.10; 95% confidence interval, 1.09–4.06; $p<0.05$) (Table 2). After adjustment for the same factors, the association of SSRI exposure with CHD events was not significant (relative risk 1.33, 95% CI 0.49–3.64).

DISCUSSION

In this population-based survey we found a statistically significant association between TCA use and risk of 10-year incident CHD events. The relation between tricyclic use and incident CHD events persisted after multivariable adjustment for possible confounders, including annual visit, use of another cardioprotective medication (aspirin), the Framingham risk score and depressive symptoms. As antidepressant use can be viewed as a marker for depressive symptoms, our data support the existing evidence linking the presence of depression to development of coronary heart disease. However, our data are also consistent with cardiovascular harm associated with tricyclic use, this time with long-term follow-up.

Our findings substantiate the results of a previous study of 2247 union health plan members, 8 which reported a relative risk for myocardial infarction of 2.2 (95% CI 1.2–3.8) among TCA users, although this study did not adjust for depressive symptoms. Our findings support another observation of this study that identified no increased risk of MI with SSRI exposure. Other similar investigations have been limited by short follow-up periods, usually not more than 8 weeks in duration.9

In this observational study of 970 Nova Scotians without pre-existing CHD, we observed an association between exposure to TCAs and incident CHD over a ten-year follow-up period. This increased risk suggests a mechanism of cardiotoxicity independent of the well-known arrhythmogenic effects of TCAs. Further research is indicated to determine the underlying pathways between tricyclic exposure and increased incidence of CHD seen in long-term follow-up in a general population.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.10

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Table 1

Baseline Variables for the Canadian, Population-based Sample (N=970)

Variable	Mean(SD)	N
Age, y	61 (11.20)	
Female, %		516 (53.2)
Framingham Risk Score	7.96 (3.88)	
Time to last annual exam 1 year, %		709 days (73.1)
2 year, %		149 days (15.4)
3 year, %		112 days (11.5)
SSRI exposure, %		15 patients (1.4)
Tricyclic exposure, %		26 patients (2.8)
Aspirin exposure, %		59 (6.1)

Table 2

Predictors of Incident Coronary Heart Disease

Predictor	Category of Exposure	Bivariate Hazard Ratio (95%CI)	Adjusted* Bivariate Hazard Ratio (95%CI)
Sex of Participant	Female (vs Male)	1.69(1.21–2.34)	-
Age	Per SD (1 SD = 11.20 yrs)	1.66 (1.42–1.93)	-
Risk Score	Per SD (1 SD = 3.88 points)	1.83 (1.57–2.13)	-
SSRI		1.35 (0.43–4.23)	1.33(0.49–3.64)
Tricyclic Antidepressants		2.88(1.46–5.68)	2.10(1.09–4.06)
Aspirin exposure		1.37(0.76–2.47)	1.13(0.65–1.96)