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Association of Amiodarone Use With Acute Pancreatitis in Patients With Atrial Fibrillation: A Nested Case-Control Study

Amiodarone hydrochloride is an antiarrhythmic drug frequently used in the treatment of atrial fibrillation (AF). Isolated reports[1-3] have suggested that use of amiodarone may cause acute pancreatitis. To our knowledge, this potential adverse effect of amiodarone has not been explored in large studies. We assessed whether use of amiodarone or other antiarrhythmic drugs indicated for AF management is associated with developing acute pancreatitis in a large US population.

Methods | We conducted a nested case-control study using the Truven Health MarketScan Commercial and MarketScan Medicare Supplemental Databases for January 1, 2007, through December 31, 2012. These databases include health insurance claims that span all levels of care (inpatient and outpatient services, outpatient pharmacy services) and enrollment data from employers and health plans across the United States that provide private coverage for employees, their spouses, and their dependents and for individuals and their dependents with Medicare supplemental coverage. All patient information was Health Insurance Portability and Accountability Act compliant, deidentified, commercially available secondary data; therefore, the institutional review board at the University of Minnesota deemed this analysis exempt from review.

Case patients were patients with nonvalvular AF (NVAF) admitted to the hospital with a primary diagnosis of acute pancreatitis during the study period (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 577.0). Five control patients with NVAF were matched with each case patient by sex, year of birth, and MarketScan enrollment date selected from individuals enrolled at the time of the pancreatitis hospitalization (index date). Information on use of amiodarone, other medications, and comorbidities before the index date for case and control patients was obtained. We used multivariable conditional logistic regression to estimate odds ratios (ORs) and 95% CIs of acute pancreatitis by use of amiodarone and other antiarrhythmic drugs (each using separate regression models) and time since initiation and cumulative use of amiodarone, adjusting for confounders (**Table 1**).

Results | We included 1686 case patients and 8430 matched control patients (3972 women [39.3%]; mean age, 71 years; Table 1). Ever users had increased odds of acute pancreatitis compared with never users (**Table 2**), particularly when amiodarone therapy was initiated within 12 months before the event date. The multivariable OR was 1.86 (95% CI, 1.41-2.45) vs 1.21 (95% CI, 0.89-1.64) if more than 12 months had elapsed since initiation (P = .04 for the difference between the 2 ORs) com-

Table 1. Selected Characteristics of Case and Control Patients, MarketScan, 2007-2012[a]

Characteristic	Case Patients (n = 1686)	Control Patients (n = 8430)
Age, mean (SD), y	71 (14)	71 (14)
Women	662 (39.3)	3310 (39.3)
History of gallbladder disease	701 (41.6)	306 (3.6)
Alcoholism	87 (5.2)	67 (0.8)
Hypertriglyceridemia	54 (3.2)	121 (1.4)
Prior pancreatic disease	360 (21.4)	48 (0.6)
History of diabetes mellitus	668 (39.6)	2243 (26.6)
Prior use		
Azathioprine	7 (0.4)	23 (0.3)
Mercaptopurine	1 (0.1)	10 (0.1)
Sulfonamides	247 (14.7)	892 (10.6)
Tetracyclines	219 (13.0)	746 (8.9)
Valproic acid	1 (0.1)	6 (0.1)

[a] MarketScan indicates Truven Health MarketScan Commercial and MarketScan Medicare Supplemental Databases. Data are presented as number (percentage) of patients unless otherwise indicated.

Table 2. Acute Pancreatitis by Previous Use of Selected Antiarrhythmic Drugs in Patients With Nonvalvular Atrial Fibrillation, MarketScan, 2007-2012[a]

Drug	No. (%) of Patients With Acute Pancreatitis		Odds Ratio (95% CI)
	Case Patients (n = 1686)	Control Patients (n = 8430)	
Amiodarone hydrochloride	245 (14.5)	758 (9.0)	1.53 (1.24-1.88)
Dronedarone	38 (2.3)	186 (2.2)	0.97 (0.61-1.53)
Sotalol hydrochloride	103 (6.1)	457 (5.4)	0.95 (0.71-1.27)
Flecainide	56 (3.3)	286 (3.4)	0.88 (0.60-1.29)
Propafenone	59 (3.5)	262 (3.1)	1.18 (0.80-1.74)
Dofetilide	10 (0.6)	65 (0.8)	0.46 (0.17-1.22)

[a] MarketScan indicates Truven Health MarketScan Commercial and MarketScan Medicare Supplemental Databases. Conditional logistic regression adjusted for matching factors, age at index date, history of gallbladder disease, alcoholism, hypertriglyceridemia, diabetes mellitus, other pancreatic or cholestatic disease, and prior use of azathioprine, mercaptopurine, sulfonamides, tetracyclines, or valproic acid.

pared with never users. Cumulative use was not associated with increased odds of acute pancreatitis (*P* for trend among users = .49). Use of other antiarrhythmic drugs was not associated with acute pancreatitis (Table 2).

Discussion | In this study of health care utilization data, use of amiodarone but not of other antiarrhythmic drugs was associated with a 50% increased odds of acute pancreatitis among patients with NVAF. The odds were almost doubled in the 12 months after amiodarone therapy initiation and did not depend on cumulative use of amiodarone. Considering an incidence of acute pancreatitis of 3 to 4 cases per 10 000 adults per year,[4] the observed association would result in approximately 1 to 2 additional cases of acute pancreatitis per 10 000 amiodarone users per year. A few isolated case reports of acute pancreatitis possibly linked to amiodarone use have been described in the literature.[1-3] The mechanisms responsible for this association are unknown, although direct cytotoxicity or immune-mediated pathways, as described for amiodarone-related pulmonary toxic effects, could be potential explanations.[5]

Strengths of our study include the prospective assessment of medication use, the large sample size, and the availability of information on comorbidities and use of other medications potentially associated with increased risk of acute pancreatitis. Limitations are related to the use of health care utilization data: limited information on the validity of claims for acute pancreatitis, absence of clinical variables that characterize severity of the episode (eg, blood markers of acute pancreatitis), and the select group of patients included in this database.

Our results indicate that acute pancreatitis could be an adverse effect of amiodarone use, an effect that may not be shared by other antiarrhythmic drugs. Even though the absolute risk of acute pancreatitis in the general population is low, health care professionals should be aware of this potential association in the treatment of patients with NVAF or acute pancreatitis. Further research should replicate our findings and determine potential mechanisms.

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Falls and Fractures With Atypical Antipsychotic Medication Use: A Population-Based Cohort Study

Antipsychotic medications are commonly used in elderly persons to treat dementia and other behavioral disturbances.[1] Several articles have linked these medications to an increased risk of fracture.[2,3] It is unclear whether this fracture risk is limited to older conventional antipsychotic medications or if the risk extends to newer atypical antipsychotics[4] because the newer drugs remain associated with orthostatic hypotension, gait abnormalities, and sedation (all of which may increase the risk of falling).[5] We conducted a population-based study to better understand the risk of falls and fracture associated with atypical antipsychotic medications.

Methods | We used linked health care administrative databases housed at the Institute for Clinical Evaluative Sciences in the province of Ontario, Canada, which provides universal health care for its citizens. Hwang et al[6] recently examined the association between the use of atypical antipsychotics and kidney injury (the study methods are fully described in that article); we used this same cohort for the current study. In brief, adults 65 years and older who received a new outpatient prescription for an oral atypical antipsychotic (quetiapine, risperidone, or olanzapine) between June 1, 2003, and December 31, 2011, were matched 1 to 1 with individuals who did not receive such a prescription. The cohort was followed up for 90 days to assess fracture and fall outcomes with hospital presentation, identified by diagnosis and procedure codes in hospital discharge, same-day surgery, and ambulatory care databases. We followed a prespecified protocol that was approved