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Risk factors for cardiovascular events of antidementia drugs in Alzheimer's disease patients

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ABSTRACT

Background: Antidementia drugs have been associated with an increased risk of cardiovascular events. The objective of this study was to identify the predictors for cardiovascular events among patients with Alzheimer's disease (AD) on antidementia drugs, mining large longitudinal claims data.

Methods: Using 2006–2011 claims from a 5% random sample of Medicare beneficiaries, I identified patients with AD who filled a prescription for an antidementia drug between 2007 and 2011. I followed them from the initiation of the antidementia drug until a cardiovascular event or December 31, 2011, censored by death or discontinuation of antidementia drugs. The outcome was the incidence of cardiovascular events, which include acute myocardial infarction, bradycardia, syncope, atrioventricular block, QT prolongation, and ventricular tachycardia. Covariates included predefined patient characteristics and empirical attributes identified from the claims, including *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis codes, Healthcare Common Procedure Coding System codes, and therapeutic classes of all prescriptions filled. After using feature selection to choose the top covariates, a logistic regression with multivariate variable selection was constructed.

Results: With an accuracy of 83.9% and a sensitivity of 93.3%, the algorithm identified 22 predictors for cardiovascular events, including a history of ischemic heart disease, congestive heart failure, syncope, stroke or transient ischemic attack, diabetes, number of other comorbidities, and procedures including venipuncture and radiologic examinations.

Conclusion: The results of this study can help clinicians identify AD patients with a higher risk of cardiovascular events who therefore should be prescribed antidementia drugs cautiously.

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive impairment affecting primarily those 65 years of age and older. The prevalence of AD among Medicare beneficiaries has been estimated at 5.1% in 2011.[1] As the number of older adults grows, the prevalence of AD will increase. Although there is no cure for AD, four medications are available to delay the cognitive impairment associated with AD, i.e., rivastigmine, galantamine, and donepezil—all acetylcholinesterase inhibitors (AChEIs), and the *N*-methyl-D-aspartic receptor antagonist memantine.

Four antidementia drugs have been associated with an increased risk of cardiovascular events. In particular, there is evidence of increased risk of syncope, bradycardia, QT interval prolongation, ventricular tachycardia, and atrioventricular block with AChEIs.[2–8] Moreover, memantine has been associated with an increased risk of myocardial infarction,[9] among other cardiovascular events.[10] Despite the severity of these events, most observational studies on the cardiovascular safety of antidementia drugs are case or case series reports[8,11–13] and therefore, it remains unknown which factors place a higher risk for experiencing cardiovascular events while taking antidementia drugs.

Identifying clinical predictors for such events is of high relevance for three reasons. First, most prescribers are not aware of these events when prescribing antidementia drugs.[3] Second, these events occur in aged patients with a high burden of comorbidities and who are at high risk for complications. Third, because there is only limited evidence on the effectiveness of these

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medications,[14–16] the benefit/risk ratio of using antidementia drugs for each patient is especially sensitive to the risk of adverse events.

As a result, it is important to use real-world data to identify the risk factors for cardiovascular events in patients with AD taking antidementia drugs. In this paper, I leveraged large longitudinal claims data to identify predictors for cardiovascular events among patients with AD and on antidementia drugs.

2. Methods

2.1. Data source and study population

Pharmacy and medical claims in 2006–2011 for a 5% random sample of Medicare beneficiaries were obtained from the Centers for Medicare and Medicaid Services (CMS). First, patients diagnosed with AD were identified by using the CMS Chronic Condition Warehouse indicator that traces the first diagnosis date back to January 1, 1999. The diagnosis of AD was defined as having one claim with primary or secondary *International Classification of Diseases, Ninth Revision* (ICD-9) code 331.0.[17] Second, individuals who filled at least one prescription for donepezil, rivastigmine, galantamine, or memantine between January 1, 2007 and December 31, 2011 were selected. Index date was defined as the date of the first prescription filled for an antidementia drug after January 1, 2007. The study sample included 109,331 donepezil patients, 15,021 rivastigmine patients, 2535 galantamine patients, and 33,209 memantine patients. Each individual was followed from index date until cardiovascular event or December 31, 2011, censored by discontinuation of antidementia drugs for > 45 days or death. The study was declared by the Institutional Review Board at the University of Pittsburgh, Pittsburgh, PA, USA as exempt because it used existing deidentified data.

2.2. Outcome

Medical claims of study participants were collected during the follow-up period with primary or secondary ICD-9 codes for the following events: acute myocardial infarction (ICD-9 code 410), bradycardia (ICD-9 = 427.89), syncope (ICD-9 = 780.2), atrioventricular block (ICD-9 = 426.0), QT interval prolongation (ICD-9 = 426.82), and ventricular tachycardia (ICD-9 = 427.1). The outcome was an indicator variable for the occurrence of any of these cardiovascular events.

2.3. Covariates

Covariates included demographic variables, predefined clinical characteristics, and empirical attributes from the medical and pharmacy claims of each study participant. The demographic variables and predefined clinical characteristics were measured at baseline, and the empirical attributes were measured both at baseline and during follow-up period.

The demographic variables included age, race, and Medicaid eligibility. The predefined clinical factors included congestive heart failure, hypertension, chronic kidney disease, diabetes, a history of the following events: acute myocardial infarction, bradycardia, syncope, QT prolongation, ventricular tachycardia, atrioventricular block, stroke or transient ischemic attack (TIA), CMS priority types of cancer, and number of other CMS priority comorbidities. To identify a history of acute myocardial infarction, a history of stroke or TIA, congestive heart failure, hypertension, chronic kidney disease, diabetes, a history of CMS priority types of cancer, and the number of other CMS priority comorbidities (listed in Table 1), I used CMS Chronic Condition Warehouse indicators that trace the first diagnosis of these conditions date back to January 1, 1999.[17]

Table 1
Baseline characteristics of the study participants, by incidence of cardiovascular event.

Variable (%)	Free of cardiovascular event (N = 128,398)	Experiencing cardiovascular event (N = 31,698)	p
Age (y)			<0.001
<65	4.15	3.69	
65–79	34.12	33.14	
>80	61.73	63.17	
Male	27.76	30.06	<0.001
Race			<0.001
White	76.03	75.59	
Black	9.63	12.27	
Asian	2.67	2.54	
Hispanic	10.61	8.48	
Native American	0.27	0.26	
Other	0.69	0.86	
Medicaid eligibility	41.96	50.20	<0.001
History of myocardial infarction	4.07	7.26	<0.001
History of bradycardia	5.85	13.47	<0.001
History of syncope	10.32	22.66	<0.001
History of QT prolongation	0.04	0.09	<0.001
History of ventricular tachycardia	0.93	2.67	<0.001
History of atrioventricular block	0.6	2.74	<0.001
History of stroke or TIA	21.71	33.01	<0.001
Ischemic heart disease	46.38	67.21	<0.001
Congestive Heart Failure	31.50	46.43	<0.001
CMS priority cancer[a]	10.14	12.82	<0.001
Other CMS comorbidities[b]			<0.001
0–1	37.53	20.25	
2–3	38.23	45.72	
≥4	24.25	34.03	

CMS = Centers for Medicare and Medicaid Services; TIA = transient ischemic attack.
[a] CMS priority types of cancer include breast cancer, colorectal cancer, endometrial cancer, and lung cancer.
[b] The number of other CMS priority comorbidities was calculated as the sum of history of cataract, chronic obstructive pulmonary disease, depression, glaucoma, knee or hip replacement, osteoporosis, and rheumatoid arthritis or osteoarthritis.

Indicator variables were defined for each condition (the indicator equaled 1 if the first diagnosis happened prior to the index date, 0 otherwise). To identify a history of bradycardia, syncope, QT prolongation, ventricular tachycardia, and atrioventricular block, I collected the medical claims for study participants made during the year prior to the index date and identified whether they had at least one claim with primary or secondary ICD-9 codes for any of these events (ICD-9 codes are listed in section “Outcome”).

The empirical attributes included therapeutic class of any medication used, an indicator of surgery, the first three digits of the ICD-9 diagnosis codes, and the first three digits of the Healthcare Common Procedure Coding System (HCPCS) codes. To identify the therapeutic class of any medication used, the National Drug Code for all medications from the pharmacy claims were extracted and linked with the First Data Bank Enhanced Therapeutic Classification System, which includes 242 therapeutic classes of drugs. I extracted all inpatient claims for each study participant and created an indicator variable representing whether the patient had surgery. In addition, I collected all medical claims and created indicator variables for each of the unique first three digits of ICD-9 diagnosis codes and unique first three digits of the HCPCS codes. All empirical attributes were identified in two time dimensions: first, from the claims made during the year prior to the initiation of an antidementia drug; second, from the claims made during follow-up period. I included empirical attributes measured during follow-up period as covariates to enable the detection of possible interactions between other therapeutic classes of drugs or clinical

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