

FEATURED ARTICLE

# Acetylcholinesterase inhibitors and risk of bleeding and acute ischemic events in non-hypertensive Alzheimer's patients

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## Abstract

**Introduction:** Acetylcholinesterase inhibitors (AChEIs) are commonly used to treat mild to moderate cases of Alzheimer disease (AD). To the best of our knowledge, there has been no study estimating the risk of bleeding and cardiovascular events in patients with non-hypertensive AD. Therefore, this study aimed to estimate the association between AChEIs and the risk of bleeding and cardiovascular ischemic events in patients with non-hypertensive AD.

**Methods:** A nested case-control study was conducted to estimate the risk of bleeding and ischemic events (angina, myocardial infarction [MI], and stroke) in patients with AD. This study was conducted using the UK Clinical Practice Research Datalink and Hospital Episode Statistics (HES) databases. The study cohort consisted of AD patients  $\geq 65$  years of age. The case groups included all AD subjects in the database who had a bleeding or ischemic event during the cohort follow-up. Four controls were selected for each case. Patients were classified as current users or past users based on a 60-day threshold of consuming the drug. Simple and multivariable conditional logistic regression analyses were used to calculate the adjusted odds ratio for bleeding events and cardiovascular events.

**Results:** We identified 507 cases and selected 2028 controls for the bleeding event cohort and 555 cases and 2220 controls for the ischemic event cohort. The adjusted odds ratio (OR) (95% confidence interval [CI]) for the association of AChEI use was 0.93 (0.75 to 1.16) for bleeding events, 2.58 (1.01 to 6.59) for angina, and 1.89 (1.07 to 3.33) for MI. Past users of AChEIs were also at increased risk of stroke (1.51 [1.00 to 2.27]).

**Discussion:** This is the first study assessing the risk of bleeding and cardiovascular events in patients with non-hypertensive AD. Our findings could be of great interest for clinicians and researchers working on AD.

## KEYWORDS

acetylcholinesterase inhibitors, aging, Alzheimer's disease, bleeding, cardiovascular disease, stroke

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## 1 | INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death, contributing to  $\approx 30\%$  of mortality worldwide.<sup>1</sup> There are several known modifiable risk factors for CVD, including smoking, increased plasma low-density lipoprotein cholesterol (LDL-C), sedentary lifestyle,<sup>2</sup> physical inactivity, and arterial hypertension.<sup>3</sup>

Patients living with hypertension are at greater risk for bleeding events, angina, and myocardial infarction (MI).<sup>4</sup> On the other hand, non-hypertensive patients are less exposed to acute ischemic events, including stroke, MI, and angina. The risk of stroke has been found to be significantly higher in hypertensive compared to non-hypertensive individuals (adjusted odds ratio [OR] 2.98, 99% confidence interval [CI] 2.72 to 3.28).<sup>5</sup> Non-hypertensive individuals also have a lower risk of overall cardiovascular diseases (including MI and angina) 46.1% (95% CI 45.5 to 46.8) compared to hypertensive patients 63.3% (95% CI 62.9 to 63.8).<sup>6</sup> Furthermore, it has been suggested that hypertension may reduce the risk of Alzheimer's disease (AD) in patients 60 years of age or older<sup>7</sup> and that individuals with controlled hypertension may be prescribed medications that act similarly to acetylcholinesterase inhibitors (AChEIs); by enhancing cholinergic activity one's risk of CVD could be reduced.<sup>8</sup>

Alzheimer's disease (AD) is the most common type of dementia affecting elderly people. It is characterized by the neurodegeneration of the central nervous system (CNS). It can also be considered as a disease with an essential vascular component. Current evidence emphasizes the role of CVD as a common pathophysiological base for the connection between the CNS and cardiovascular system.<sup>9</sup> Elderly patients with CVD are known to be at higher risk for AD, and the co-existence of both diseases increases patient suffering and treatment expenses.<sup>9</sup> CVDs can cause dementia through cerebral hypoperfusion, emboli, infarction, or hypoxia.<sup>10</sup> Mixed dementia can result from the combination of both cerebrovascular disease and neurodegeneration, and accounts for the majority of cases among the elderly.<sup>11</sup> Considering the evidence presented, there is a tangible and multifaceted association between cardiovascular health and neurological health.

AChEIs are a group of drugs commonly used to treat mild to moderate cases of AD. They stimulate muscarinic cholinergic pathways and thereby could potentially reduce the risk of CVD.<sup>12</sup> As such, AChEIs would counteract the effects of sympathetic activation and thus may reduce blood pressure and platelet aggregation. Platelets, in particular, represent a potential link between vascular inflammation and AD. In AD patients, platelets contribute to amyloid beta ( $A\beta$ ) accumulation in the CNS.<sup>13</sup> Furthermore, patients with coronary artery disease and dementia have shown higher platelet activation compared to those without dementia. As such, platelet activation may bridge the gap between CVD and dementia, and may be considered as an indicator for the severity of dementia and a potential new treatment target in AD patients.<sup>14</sup>

In light of the evidence presented, treating individuals living with AD with AChEIs may thus increase the risk of bleeding events due to the potential inhibition of platelet aggregation. AChEIs have been suggested to increase the risk of gastrointestinal (GI) bleeding in patients

### Research in Context

1. Systematic Review: Patients with Alzheimer's disease and hypertension are more prone to cardiovascular disease (CVD). Previous literature has shown that the use of acetylcholinesterase inhibitors (AChEIs) in AD reduced the risk of such events. However, there is no study assess the risk of bleeding and ischemic events in patients with non-hypertensive AD. This is the first study to assess the risk of bleeding and ischemic events in patients with non-hypertensive AD who are taking AChEIs.
2. Interpretation: Our results showed that the use of AChEIs may not affect the risk of bleeding; however, AChEIs were associated with an increased risk of angina and myocardial infarction (MI) in patients with non-hypertensive AD. The present study controlled for hypertension, which plays a significant role in cardiovascular health and bleeding.
3. Future Directions: This study had small sample size. Large studies with bigger sample sizes are required to further confirm these findings.

with peptic ulcers; however, there is limited evidence on the risk of overall bleeding events, intracranial bleeding, and stroke.<sup>15</sup>

The studies mentioned above suggest that there is a close relationship between one's cardiovascular health and the risk of AD. As such, the aim of the present study is to determine whether there is a relationship between AChEIs and cardiovascular events in non-hypertensive patients. We hypothesize that the use of AChEIs increases the risk of bleeding while reducing the risk of ischemic events (MI, stroke, and angina) in patients with non-hypertensive AD.

## 2 | METHODS

### 2.1 | Study type

A nested case-control study.

### 2.2 | Ethical approval

The study was approved by the Scientific and Ethical Advisory Committee of the Clinical Practice Research Database (CPRD, no. 17\_172), and the ethics review board of the McGill University Health Centre. Patient consent was not required.

### 2.3 | Source of data

We used the data from the Clinical Practice Research Database (CPRD) and Hospital Episode Statistics (HES) database. The CPRD is a large computerized database of longitudinal records from primary care

institutions.<sup>16</sup> The age and sex distribution of patients in the CPRD has been shown to be representative of the UK population.<sup>17</sup> Prescriptions are recorded using a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary. Only data that pass quality control and are considered “up-to-standard” are included in the CPRD database. The CPRD database has a high level of completeness, and has been validated for epidemiological data on patients with bleeding events,<sup>18</sup> CVD,<sup>19</sup> and AD.<sup>20</sup> The recorded information on drug exposure and diagnoses has been validated and shown to be of high quality.<sup>16</sup>

## 2.4 | Source population

We identified patients 65 years of age or older with a first-time diagnosis of AD according to the International Classification of Diseases, Tenth Revision (ICD-10) coding systems, which were recorded in the computerized database between January 1998 and December 2013. We also identified patients who received a first-time prescription of AChEIs during the same period. We selected 1998 as the beginning of the study period point, as it represents 2 years after the beginning of the commercialization of AChEIs in the UK. An algorithm described by Imfeld et al.<sup>21</sup> was used to identify patients with well-defined AD. The AD patients had to satisfy at least one of the following criteria: (1) a diagnosis of AD followed by at least one prescription for an AD-specific medication, or vice versa; (2) two prescriptions for an AD-specific medication; (3) at least two recordings of an AD diagnosis; (4) an AD diagnosis after a specific dementia test, or (5) an AD diagnosis preceded or followed by any registered dementia symptoms.<sup>22</sup> All participants should have at least two consecutive years of up-to-standard follow-up in the CPRD records before the diagnosis of AD. The cohort was followed until the development of one of the study outcomes (bleeding or ischemic events), end of the study (December 31, 2013), or end of registration with the general practice, whichever happened first.

Patients with clotting or bleeding disorders (ie, hemophilia, thrombocytopenia purpura [TP], and von Willebrand disease) were excluded. Patients diagnosed with conditions that could affect cardiovascular health (ie., Pagett's disease, osteoporosis, osteomalacia,<sup>23</sup> cancer,<sup>23</sup> HIV,<sup>24</sup> congestive heart failure, rheumatoid arthritis,<sup>25</sup> peripheral vascular disease, and alcoholism)<sup>26</sup> as well as patients who used medications known to affect the risk of CVD<sup>27</sup> (ie., corticosteroids, anti-epileptic drugs, anxiolytics, calcium-vitamin D supplements,  $\beta$ -blockers, antihypertensive drugs, and bisphosphonates) prior to the diagnosis of AD were also excluded.

### 2.4.1 | Study series

For our nested case-control study, we used the methodology that has already been published by our research group.<sup>28</sup> We explain the study groups below.

### 2.4.2 | Case series

The case series included all AD subjects registered in the database who had a bleeding event (first case group) or ischemic event (second case group) during the cohort follow-up. All cases should be recorded at least 1 year after the diagnosis of AD (to ensure a sufficient period of exposure to AChEIs) between 1998 and 2013. All cases were required to have no history of bleeding or ischemic events at the time of diagnosis of AD. The date of the diagnosis of a cardiovascular or bleeding event was served as the index date for all cases.

Bleeding was defined based on a comprehensive list of bleeding codes (96 International Classification of Diseases [ICD]-10) and was categorized into intracranial, extracranial bleeding, and GI bleeds. Ischemic events were categorized as stroke, MI, or angina. Angina was categorized as stable and unstable. If a patient had more than one ischemic event, the former was only considered in the analysis.

### 2.4.3 | Control series

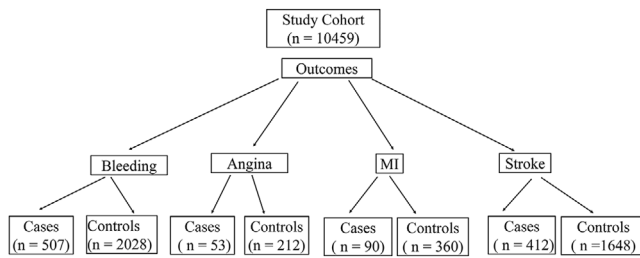
Four matched controls were selected per case by using incidence-density sampling.<sup>29</sup> For each case, the controls were randomly sampled from the set (ie., “risk set”) of AD subjects that are alive and outcome-free on the index date of the matching case. Controls were matched to the cases by age ( $\pm 2$  years), sex, up-to-standard follow-up in the CPRD ( $\pm 1$  year), calendar time (same index date as for cases), and duration of AD ( $\pm 6$  months). The same inclusion/exclusion criteria was also applied to controls.

## 2.5 | Exposure assessment

We ascertained the use of AChEIs (ie., donepezil, oral rivastigmine, transdermal rivastigmine, and galantamine) for all cases and controls between the cohort entry and the index date. Patients were classified as current users if the last prescription of AChEIs was within 60 days prior to the index date and past users if it was  $> 60$  days. Patients with no prescription of AChEIs between the cohort entry and index date were considered as non-users. We derived a quantitative measure of the use of AChEIs by calculating the number of days covered by the prescriptions during the year prior to the index date and the Proportion of Days Covered (PDC).<sup>30</sup> PDC adherence were classified into three categories (low  $< 0.20$ , moderate  $0.20 \leq \text{PDC} < 0.80$ , and high  $\geq 0.80$ ).

## 2.6 | Statistical analysis

Previous studies showed that 32% of AD patients had brain bleeds.<sup>31</sup> Based on this information and 95% significant level with an alpha error of 0.05, this study required a minimum sample size of 325 cases and 1300 controls.



**FIGURE 1** Flow chart of cases and controls

We performed simple and multivariable conditional logistic regression analyses to calculate crude and adjusted odds ratios (ORs) estimating rate-ratios (RRs), and the corresponding 95% confidence intervals (CIs). In the multivariable models, the adjusted ORs for stroke, unstable angina, MI, and bleeding events were estimated by adjusting for the following potential confounders: age, body mass index (BMI; <20, 20-24, 25-29, >30 kg/m<sup>2</sup>, and unknown), smoking status (none, current, ex-smokers, unknown), length of stay at hospital, poor mobility (ie, home visits by a general practitioner [GP], or use of walking aid), institutionalization (ie, patient receiving residential care, in a care home, or nursing care), medical conditions increasing the risk of cerebrovascular accident, the use of anticoagulant or anti-platelets drugs (heparin group, platelet aggregation inhibitors excl. heparin, vitamin K antagonists, direct thrombin inhibitors, or direct factor Xa inhibitors), and the use of selective serotonin reuptake inhibitors (SSRIs). All statistical analyses were carried out using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA).

### 3 | RESULTS

A total of 10,459 AD patients who fulfilled the source-cohort criteria were included in the cohort population. There were 507 cases of bleeding events identified over the follow-up, and accordingly, 2028 controls were selected. Their ages ranged from 65 to ≥85 years. A total of 260 cases were AChEI users and 247 cases were non-users. Within the control group, 1030 patients were users of AChEIs and 998 patients were non-users (Figure 1).

#### 3.1 | Bleeding risk

There was no association between AChEI use and bleeding events (adjusted OR = 0.93, 95% CI = 0.75 to 1.16). There was no risk association with either current or past AChEI use. When we assessed adherence to AChEIs, the adjusted OR (95% CI) was 0.91 (0.57 to 1.47) for PDC <0.2, 0.97 (0.70 to 1.34) for PDC 0.2 to 0.8, and 0.92 (0.72 to 1.18) for PDC ≥0.80. There was no risk association concerning the adherence to treatment among current and past users, as well as non-users. A sub-population of intracranial bleeding risk showed no risk association between AChEI users and non-users (adjusted OR = 1.03, 95%

CI = 0.75 to 1.16,  $P = .86$ ). Overall, the results indicate that these drugs may not be associated with the risk of bleeding events (Tables 1 and 2, Tables S1 and S2).

### 3.2 | Ischemic events

#### 3.2.1 | Angina

A total of 53 cases and 212 controls were selected. Among them, 30 angina cases were AChEI users and 23 cases were non-users. For the controls, 100 patients were AChEI users and 112 patients were non-users. Cases were more regularly taking anticoagulants and statins, consistent with their CVD presentation. The use of AChEIs was associated with a higher rate of angina (adjusted OR = 2.58, 95% CI = 1.01 to 6.59). No risk association was found with current usage of AChEI. A high risk was associated with past usage (adjusted OR = 12.22, 95% CI = 2.09 to 71.51).

A high risk was associated with a PDC <0.2 (adjusted OR = 8.29, 95% CI = 1.84 to 37.30) in all users. A high risk of angina risk was also found specifically in current users of AChEIs with a PDC <0.2 (adjusted OR = 7.05, 95% CI = 1.33 to 37.50). However, no risk association was found for a PDC between 0.2 and 0.8 and PDC ≥0.8 (Table 3 and Table S3).

#### 3.2.2 | Myocardial infarction

Ninety cases of MI and 360 controls were selected. A total of 55 MI cases were AChEI users and 35 cases were non-users. For the control patients, 174 patients were AChEI users and 186 patients were non-users. Any use of AChEIs was associated with a higher rate of MI (adjusted OR = 1.89, 95% CI = 1.07 to 3.33). Current users had a higher rate of MI (adjusted OR = 2.07, 95% CI = 1.15 to 3.73). A high risk of MI was found in all users with a PDC between 0.2 and 0.8 (adjusted OR = 2.69, 95% CI = 1.17 to 6.17). A higher rate of MI was also found in current users of AChEIs with a PDC between 0.2 and 0.8 (adjusted OR = 3.74, 95% CI = 1.36 to 10.30). PDC <0.2 and PDC ≥0.8 were not associated with an increased risk of MI (Table 4, Table S4).

#### 3.2.3 | Stroke

Four hundred twelve cases of stroke and 1648 controls were assessed. Among them, 225 stroke cases were AChEI users and 187 cases were non-users. Within the control group, 785 patients were AChEI users and 864 patients were non-users. Past users of AChEIs were at increased risk of stroke (adjusted OR = 1.51, 95% CI = 1.00 to 2.27), whereas current users were not. A high risk was found in only past users with a PDC between 0.2 and 0.8 (adjusted OR = 1.97, 95% CI = 1.13 to 3.41) (Table 5 and Table S5).

**TABLE 1** Crude and adjusted estimates of the odds ratio for the association of adherence with prescribed acetylcholinesterase inhibitors in the year prior to index date with bleeding risk (vs non-use)

Exposure	No. %		Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) <sup>†</sup>
	Cases (n = 507)	Controls (n = 2028)		
<b>AChEI use</b>				
No use	51.28	50.79		
Any use	48.72	49.21	0.98 (0.80-1.20)	0.93 (0.75-1.16)
PDC <0.2	5.52	5.82	0.94 (0.60-1.47)	0.91 (0.57-1.47)
0.2 ≤ PDC <0.8	13.41	13.17	1.01 (0.74-1.38)	0.97 (0.70-1.34)
PDC ≥0.8	29.78	30.23	0.97 (0.77-1.23)	0.92 (0.72-1.18)
<b>Current</b>	39.64	40.68	0.96 (0.78-1.19)	0.93 (0.74-1.17)
PDC <0.2	2.76	3.30	0.80 (0.42-1.52)	0.85 (0.43-1.65)
0.2 ≤ PDC < 0.8	8.68	8.88	0.97 (0.67-1.40)	0.98 (0.67-1.44)
PDC ≥0.8	28.21	28.50	0.98 (0.77-1.25)	0.92 (0.72-1.19)
<b>Past use</b>	9.07	8.53	1.05 (0.74-1.51)	0.95 (0.65-1.38)
PDC <0.2	2.76	2.51	1.09 (0.60-2.00)	0.99 (0.52-1.88)
0.2 ≤ PDC < 0.8	4.73	4.29	1.10 (0.68-1.77)	0.96 (0.58-1.59)
PDC ≥0.8	1.58	1.73	0.91 (0.42,1.98)	0.86 (0.38-1.93)

**TABLE 2** Use of acetylcholine inhibitors and intracranial bleeding risk (vs non-use)

Exposure	No. %		Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) <sup>†</sup>
	Cases (n = 208)	Controls (n = 832)		
<b>AChEI use</b>				
No use	48.08	52.40	1	Ref
Any use	51.92	47.60	1.20 (0.88-1.63)	1.03 (0.73-1.45)
Current	41.35	39.54	1.15 (0.83-1.59)	1.02 (0.71-1.45)
Past use	10.58	8.05	1.44 (0.85-2.44)	1.09 (0.62-1.93)

**TABLE 3** Crude and adjusted odds ratio for the association of adherence with prescribed acetyl cholinesterase inhibitors in the year prior to index date with angina (vs non-use)

Exposure	No. %		Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) <sup>†</sup>
	Cases (n = 53)	Controls (n = 212)		
<b>AChEI use</b>				
No use	43.40	52.83		
Any use	56.60	47.17	1.52 (0.80-2.89)	2.58 (1.01-6.59)
PDC <0.2	13.21	8.49	1.97 (0.72-5.41)	8.29 (1.84-37.30)
0.2 ≤ PDC < 0.8	11.32	8.96	1.61 (0.57-4.55)	2.84 (0.65-12.35)
PDC ≥0.8	32.1	27.9	1.34 (0.62-2.88)	1.49 (0.48-4.62)
<b>Current</b>	47.19	41.51	1.44 (0.74-2.81)	2.11 (0.79-2.66)
PDC <0.2	9.43	5.19	2.30 (0.68-7.77)	7.05 (1.33-37.50)
0.2 ≤ PDC < 0.8	7.55	6.60	1.43 (0.43-4.78)	1.67 (0.30-9.48)
PDC ≥0.8	30.19	29.72	1.26 (0.57-2.74)	1.29 (0.39-4.34)
<b>Past use</b>	9.43	5.66	2.12 (0.66-6.81)	12.22 (2.09,71.51)
PDC <0.2	3.77	3.30	1.42 (0.28-7.20)	9.82 (0.96-100.21)
0.2 ≤ PDC < 0.8	3.77	2.36	1.94 (0.33-11.33)	7.32 (0.52-103.97)
PDC ≥0.8	1.89	0.00	-----	-----

**TABLE 4** Crude and adjusted odds ratio for the association of adherence with prescribed acetyl cholinesterase inhibitors in the year prior to index date with MI (vs nonuse)

Exposure	No. %		Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) <sup>†</sup>
	Cases (n = 90)	Controls (n = 360)		
<b>AChEI use</b>				
No use	38.89	51.67		
Any use	61.11	48.33	1.69 (1.05-2.72)	1.89 (1.07-3.33)
PDC <0.2	5.56	5.83	1.19 (0.41-3.47)	1.26 (0.38-4.19)
0.2 ≤ PDC < 0.8	18.89	12.22	2.25 (1.08-4.67)	2.69 (1.17-6.17)
PDC ≥0.8	36.67	30.218	1.63 (0.94-2.82)	1.73 (0.91-3.30)
<b>Current</b>	55.56	40.00	1.86 (1.14-3.04)	2.07 (1.15-3.73)
PDC <0.2	3.33	3.33	1.24 (0.30-5.13)	1.49 (0.32-7.04)
0.2 ≤ PDC < 0.8	15.56	8.61	3.01 (1.26-7.18)	3.74 (1.36-10.3)
PDC ≥0.8	36.67	2.06	1.71 (0.99-2.96)	1.81 (0.95-3.47)
<b>Past use</b>	5.56	8.33	0.91 (0.33-2.47)	1.08 (0.34,3.39)
PDC <0.2	2.22	2.50	1.22 (0.26-5.82)	1.14 (0.17,7.52)
0.2 ≤ PDC < 0.8	3.33	3.61	1.23 (0.33-4.63)	1.46 (0.34-6.19)
PDC ≥0.8	0.0	2.22	0.00-----	0.0-----

**TABLE 5** Crude and adjusted odds ratio for the association of adherence with prescribed acetyl cholinesterase inhibitors in the year prior to index date with Stroke (vs nonuse)

Exposure	No. %		Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) <sup>†</sup>
	Cases (n = 412)	Controls (n = 1648)		
<b>AChEI use</b>				
No use	45.39	52.37		
Any use	54.61	47.63	1.33 (1.07-1.66)	1.22 (0.97-1.54)
PDC <0.2	5.58	6.13	1.04 (0.63-1.72)	1.00 (0.59-1.68)
0.2 ≤ PDC < 0.8	15.53	13.11	1.36 (0.98-1.89)	1.23 (0.87-1.73)
PDC ≥0.8	33.50	30.218	1.38 (1.07-1.79)	1.26 (0.96-1.65)
<b>Current</b>	44.42	28.40	1.29 (1.02-1.62)	1.17 (0.91-1.49)
PDC <0.2	3.16	3.70	0.93 (0.48-1.80)	0.89 (0.45-1.77)
0.2 ≤ PDC < 0.8	9.95	9.77	1.14 (0.77-1.68)	1.00 (0.67-1.50)
PDC ≥0.8	31.31	26.64	1.40 (1.08-1.83)	1.28 (0.97-1.70)
<b>Past use</b>	10.19	7.52	1.59 (1.08-2.36)	1.51 (1.00-2.27)
PDC <0.2	2.43	2.43	1.17 (0.57-2.40)	1.10 (0.52,2.32)
0.2 ≤ PDC < 0.8	5.58	3.34	2.03 (1.20-3.43)	1.97 (1.13-3.41)
PDC ≥0.8	2.18	1.76	1.45 (0.67-3.12)	1.33 (0.60-2.95)

## 4 | DISCUSSION

The findings of our study showed no association between AChEI use and bleeding in patients with non-hypertensive AD. These results are in accordance with the cohort-study conducted by Thavorn et al., in which they found no association between the use of AChEIs and upper GI bleeding in an elderly population.<sup>15</sup> In addition, this was in agreement with our in vivo study, in which we showed that the AChEI, donepezil, did not affect hemostasis and platelet function.<sup>32</sup> Thus AChEI use does not appear to be associated with increased bleeding risk.

This study also showed that AChEI users were at increased risk of ischemic events (MI, angina, and stroke) in patients with non-hypertensive AD. Past use of AChEIs was associated with angina and stroke, whereas, current use was associated with MI and angina. These differences could be attributed to the adverse effects of these drugs, or occur simply because the patient was not adherent to their medications. These findings contradict those reported by Nordstrom et al., who found a reduced risk of MI among AChEI users.<sup>33</sup> A study conducted by Pariente et al., observed an increased risk in MI in patients concomitantly consuming AChEIs and anti-psychotics.<sup>34</sup> Our study did

not control for the consumption of anti-psychotics; therefore a drug interaction remains a possibility. It has been shown that anti-psychotics increase the risk of cardiometabolic disturbances, probably by increasing levels of triglycerides and low-density lipoprotein (LDL).<sup>35</sup>

Furthermore, the results of this study demonstrate an increased risk in stroke in past users only without a change in risk in current users. These results are not in accordance with those found by Lin et al., in which they found a reduced risk of stroke among AChEI users compared to non-users.<sup>36</sup> The studies mentioned above did not control for physical activity, or BMI, thus drawing different conclusions on MI and stroke risk. BMI is an independent predictor of CVD seeing as it is a measure of obesity, and thus metabolic syndrome, ultimately influencing the results of the studies mentioned above.<sup>37</sup> Lifelong physical activity is a strong predictor of cardiovascular health, and thus could have contributed to differences between studies.<sup>38</sup> The studies by Nordstrom et al. and Tan et al. used a Swedish database to obtain the results for their analyses. The Sweden population was among the most physically active in all of Europe (87.2%).<sup>39</sup> Drawing a comparison to the UK, from which our source population was extracted, 75.8% is adequately active.<sup>39</sup> Our study also controlled for confounding variables for CVD such as hypertension and smoking, which were not controlled for in the studies mentioned above.

The results from this study reveal that patient adherence to AChEIs is an important contributor to the risk of cardiovascular events. Compliance with medication remains a problem in patients living with AD. According to the literature, one of the main reasons for not adhering to the treatment regimen is the perception of a lack of benefits and forgetfulness.<sup>40</sup> This will effectively result in the worsening of cognitive function and may have a deleterious effect on cardiovascular health.<sup>41</sup> Based on the results of the study, although one can infer that a lack of adherence to AChEIs may be associated with an increased risk of cardiovascular events, the evidence remains limited. Nevertheless, a possible mechanism of this association can be extracted from Umegaki et al., in which they discovered that acute administration of donepezil was associated with an increase in sympathetic nervous system activation, whereas long-term consumption attenuates sympathetic activity allowing the parasympathetic system to predominate.<sup>42</sup> To further corroborate these findings, it is important to acknowledge that a lack of drug adherence may also be a signal for poor adherence to a healthy lifestyle, further impacting cardiovascular health.

Our findings contradicted our initial hypothesis, which was based on the mechanism by which sympathetic hyperactivity increased platelet activation. This would imply that by increasing the concentration of acetylcholine, through the use of AChEIs, the sympathetic nervous system would be attenuated, thereby reducing platelet activation. Ozdemir et al. demonstrated that there was an enhanced mean platelet volume with sympathetic over-activity, demonstrating the presence of platelet activation.<sup>43</sup> Furthermore, Bennett et al. revealed that carbachol, an analog of acetylcholine, inhibits platelet activation through the attenuation of thrombin receptor.<sup>44</sup> In addition, AChEIs have been reported as having an anti-platelet effect in the endothelial cells, which play an essential role in ischemic stroke development.<sup>36</sup> These differences could be due to a different population being

studied, seeing as we placed an emphasis on non-hypertensive AD patients.

#### 4.1 | Strengths and limitations

Our study was the first to determine the risk of bleeding and cardiovascular events in non-hypertensive AD patients. The present study controlled for hypertension, which has a significant role in cardiovascular health and bleeding. Another strength of this study was the ability to stratify the results based on patient adherence.

Limitations potentially affecting the findings of the present study are associated with the risk of selection bias among both cases and controls. Measures were put in place to reduce the risk of selection bias by stratifying the variables that could have ultimately affected the outcomes measured. The variables included are age, BMI, smoking status, hospitalization duration, morbidity, institutionalization, medical conditions, and medications known to affect bleeding or cardiovascular health.<sup>45</sup> In addition, this study used information extracted from the Clinical Practice Research Database (or CPRD), a high-quality population-based database. It contains a diverse population of participants and their associated outcomes and exposures, which helped reduce likelihood of selection bias.<sup>16</sup> In addition, four controls were matched per selected case using incidence-density sampling, which is considered one of the most effective ways to reduce bias in selecting a control group sample.<sup>29</sup> Furthermore, this study strictly included well-defined AD patients, following a validated algorithm conducted by Imfeld et al.<sup>46</sup> Another limitation is that the sample size of this case-control study was limited by our restrictive inclusion criteria that aimed to minimize the risk of selection bias. Therefore, future studies with larger sample sizes are ideal in order to corroborate our findings. Another limitation is the drug tolerance that may develop when patients are consuming highly reversible drugs such as donepezil and galantamine, but this may not be the case with slowly reversible drugs such as rivastigmine. As such, if patients consume these drugs consistently, their effects may quickly diminish, and the dose would therefore need to be adjusted.

## 5 | CONCLUSION

The use of AChEIs may be associated with a modest increase in the risk of MI and angina in patients with non-hypertensive AD; however, it does not affect the risk of bleeding events. Future large-sampled well-controlled studies are required to confirm these findings.

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## CONFLICTS OF INTEREST

None.

## AUTHOR CONTRIBUTIONS

Data curation, Faez Saleh Al-Hamed and Iskandar Tamimi; Formal analysis, Abbas Kezouh; Methodology, Marie Lordkipanidzé, Igor Karp, Belinda Nicolau, and Faleh Tamimi; Project administration, Faleh Tamimi; Resources, Faleh Tamimi; Software, Abbas Kezouh; Supervision, Faleh Tamimi; Visualization, Abbas Kezouh; Writing of original draft, Faez Saleh Al-Hamed and Stamatis Kouniaris; Writing and review & editing, Faez Saleh Al-Hamed, Stamatis Kouniaris, Iskandar Tamimi, Marie Lordkipanidzé, Sreenath Arekunnath Madathil, Igor Karp, Belinda Nicolau, and Faleh Tamimi.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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