Comparison of cholinesterase inhibitor safety in real-world practice

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Abstract

Introduction: Cholinesterase inhibitors (ChEIs) are widely used to treat mild to moderate Alzheimer’s disease and related dementia. Clinical trials have focused on placebo comparisons, inadequately addressing within-class comparative safety.

Methods: New users of ChEIs in British Columbia were categorized into five study cohorts: low-dose donepezil, high-dose donepezil, galantamine, rivastigmine patch, and oral rivastigmine. Comparative safety of ChEIs assessed hazard ratios using propensity score adjusted Cox regression.

Results: Compared with low-dose donepezil, galantamine use was associated with a lower risk of mortality (adjusted hazard ratio: 0.84, 95% confidence interval: 0.60–1.18), cardiovascular serious adverse events (adjusted hazard ratio: 0.78, 95% confidence interval: 0.62–0.98), and entry into a residential care facility (adjusted hazard ratio: 0.72, 95% confidence interval: 0.59–0.89).

Discussion: Given the absence of randomized trial data showing clinically meaningful benefit of ChEI therapy in Alzheimer’s disease, our study suggests preferential use of galantamine may at least be associated with fewer adverse events than treatment with donepezil or rivastigmine.

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Cholinesterase inhibitor; Alzheimer’s disease; Dementia; Log-binomial regression; Cox proportional hazard; Propensity score; Epidemiology

1. Introduction

Alzheimer’s disease and related dementia (ADRD) is a growing problem in Canada, affecting an estimated 747,000 people in 2012, with 25,000 new cases diagnosed every year [1]. In British Columbia, cholinesterase inhibitors (ChEIs) are commonly prescribed for treatment of ADRD, where the B.C. Ministry of Health requires a baseline cognitive assessment as part of its Special Authority process [2]. Because little data exist beyond the 6-month to one-year clinical trials and this group of medications is frequently prescribed to patients with ADRD, there is an opportunity for observational data to assess longer-term safety and effectiveness [3].

ChEIs increase cholinergic function by preventing the breakdown of acetylcholine, a neurotransmitter that supports communication among nerve cells when its levels are sufficiently high. Acetylcholinesterase is an enzyme involved in the rapid hydrolysis of acetylcholine. Through inhibition of acetylcholinesterase, ChEIs, such as donepezil, rivastigmine, and galantamine, allow acetylcholine to accumulate. The rationale for prescribing ChEIs for treating symptoms of ADRD is to increase acetylcholine levels, which increases neuronal activity. However, this is a strategy that has low effectiveness [4], and there is no evidence that ChEIs prevent the underlying dementing process [5].

ChEIs have additional pharmacological actions. Rivastigmine inhibits butyrylcholinesterase with a similar
affinity to acetylcholinesterase. The therapeutic effect and resulting clinical consequences of this is unknown [6,7]. Galantamine potentiates the action of acetylcholine on nicotinic receptors, which may influence neuronal processes, such as synaptic efficacy and neuroprotection [8,9]. Evidence suggests the cholinergic adverse effects of these drugs may cause gastrointestinal, neurological, cardiovascular, and urinary disorders [10,11]. In severe instances, these drugs may increase vagal tone and, thereby, precipitate bradycardia [12]. Multiple U.S. Food and Drug Administration safety alerts have raised concerns of increased mortality and serious cardiovascular adverse events in patients taking ChEIs for mild cognitive impairment versus placebo-treated patients [13].

A Cochrane database systematic review (Russ [14]) found no significant difference in progression to dementia between ChEIs and placebo at 12 months. They found ChEIs increased overall adverse events compared with placebo but found no significant differences between the groups for serious adverse events, cardiac problems, depression, or death. Earlier systematic reviews found small improvements or unchanged cognitive benefits with ChEIs versus placebo [15]. In addition, some trials within the systematic reviews showed an unexplained increased death rate.

Effective October 22, 2007, the British Columbia Ministry of Health began providing financial coverage of the ChEIs through the Alzheimer’s Drug Therapy Initiative to address clinical knowledge gaps around the safety and effectiveness of these drugs [16]. Patients receiving a baseline assessment score on the Standardized Mini–Mental State Examination of mild to moderate cognitive impairment are eligible for full financial coverage of a ChEI.

We investigated the risk of mortality between the ChEIs for new users during the Alzheimer’s Drug Therapy Initiative. Serious cardiovascular events were investigated as a secondary outcome. We also looked at time to entry into a residential care facility. Supporting people with ADRD to function in their own homes for as long as possible is a stated priority of the B.C. Provincial Guide to Dementia Care [17].

2. Methods

2.1. Data

We obtained access to the B.C. Ministry of Health administrative health claims database through a secure access environment. The database contains linkable, but deidentified, health service records containing all prescriptions dispensed at community pharmacies, physician services, hospital separations, and vital statistics data in British Columbia. We assume that the completeness and accuracy of the data is comparable to other administrative databases [18,19].

2.2. Study design and source population

We conducted a retrospective, propensity score–adjusted cohort study. The source population for the study was all B.C. residents between October 2007 and March 2016 who were registered in the provincial universal medical services plan. Federally insured patients, such as indigenous people, federal police officers, and members of the armed forces and their families, were excluded from the source population because they are not included in the data set. Excluded patients composed about 7% of the provincial population. The source population numbered 4.42 million in 2016 [20].

2.3. Study cohorts

New users of ChEIs were identified during the study period as having no ChEI prescription in the previous 365 days. New users were categorized into 5 exposure groups based on their first prescription: (1) low-dose donepezil (≤7.5 mg/day), (2) high-dose donepezil (>7.5 mg/day), (3) galantamine, (4) rivastigmine patch, and (5) rivastigmine oral. Low-dose donepezil was defined based on receiving a dose equivalent to, or below, the World Health Organization’s Defined Daily Dose. Low-dose donepezil, the most frequently prescribed ChEI, was assigned as the reference drug, providing four comparison cohorts instead of a single multinomial regression approach.

The date of each patient’s first ChEI dispensing was defined as the index date. Patients were excluded from the study cohorts if they were under 50 years old on the index date, in a residential care facility in the 2-year period before index date, did not have continuous medical insurance in the 1-year period before index date, or dispensed more than one ChEI on index date.

2.4. Study outcomes

Our primary outcome was all-cause mortality. Secondary outcomes were (1) composite cardiovascular serious adverse events and (2) entry into a residential care facility. Composite cardiovascular events consisted of a hospital admission for myocardial infarction (ICD-9: 410), coronary artery disease (ICD-9: 411-414), heart failure (ICD-9: 428), arrhythmia (including atrial fibrillation) (ICD-9: 427), and peripheral arterial or vascular disease (ICD-9: 443.9, 440). Entry into a residential care facility was determined by the presence of a government-subsidized prescription under the residential care benefit plan.

2.5. Data analysis

Safety of ChEIs was compared using time-to-event Cox proportional regression. Four drug comparisons were made: (1) low-dose donepezil versus high-dose donepezil, (2) low-dose donepezil versus galantamine, (3) low-dose donepezil versus rivastigmine patch, and (4) low-dose donepezil versus oral rivastigmine. Patient follow-up was censored at the earliest occurrence of our study outcome, death, end of the study period (31 March 2016), emigration from BC, therapy discontinuation, or crossover to another study cohort. Sensitivity analyses used log-binomial regression to
estimate relative risk at 6-month and 12-month fixed follow-up periods [21]. All outcome models were adjusted for history of prior cardiovascular events, smoking, and high-dimensional propensity scores meant to capture other confounding factors. The high-dimensional propensity score methods have been previously described in detail here [22].

2.6. Confounders

Potential confounders were measured before exposure to a ChEI using hospital and physician diagnostic codes, dispensed prescription records, and patient demographic records. The following covariates were included in the outcome model if they occurred within two years before index date: arrhythmia (ICD-9: 427; ICD-10: I49), myocardial infarction (ICD-9: 410; ICD-10: I21), stroke (ICD-9: 430-434, 436; ICD-10: I60, I61, I64, I63), angina (ICD-9: 413; ICD-10: I20), congestive heart failure (ICD-9: 428; ICD-10: I50), cerebrovascular disease (ICD-10: I60-I69), coronary artery disease (ICD-9: 411, 412, 414; ICD-10: I22-I25, Z95.1, Z95.5, Z98.61), peripheral arterial disease (ICD-9: 440, 443.9; ICD-10: I70, I73.9), or diabetes (ICD-9: 250; ICD-10: E10-E14). Other covariates included sex, age group (50–64, 65–74, 75–84 as reference, 85+), or diabetes (ICD-9: 440, 443.9; ICD-10: I70, I73.9), angina (ICD-9: 413; ICD-10: I20), congestive heart failure (ICD-9: 428; ICD-10: I50), cerebrovascular disease (ICD-10: I60-I69), coronary artery disease (ICD-9: 411, 412, 414; ICD-10: I22-I25, Z95.1, Z95.5, Z98.61), peripheral arterial disease (ICD-9: 440, 443.9; ICD-10: I70, I73.9), or diabetes (ICD-9: 250; ICD-10: E10-E14). Other covariates included sex, age group (50–64, 65–74, 75–84 as reference, 85+), and smoking status (current or past smoker).

The following predefined demographic and diagnostic covariates were incorporated into the high-dimensional propensity score model: age group, sex, family income, index year, time since ADRD diagnosis, more than five distinct medications dispensed in previous year (yes/no), more than five physician visits in previous year (yes/no).

3. Results

There were 34,338 patients from the source population who initiated a ChEI between 22 October 2007 and 31 March 2016. Of those, 29,047 patients remained eligible for the study after exclusions for not meeting medical insurance eligibility criteria (5.4%), resident of a long-term care facility in prior two years (7.9%), initiating more than one ChEI on cohort entry date (1.8%), and age under 50 years (0.4%).

Baseline patient characteristics of the study cohorts (Table 1) were similar for average age of patients (80.5 years). The proportion of female patients was lowest in the oral rivastigmine (48%) cohort and highest in the low-dose donepezil (60%) cohort. Smokers, past or current, ascertained by the presence of a diagnosis of chronic obstructive pulmonary disease or use of a prescription smoking cessation therapy were similar among all cohorts. Galantamine users had the highest proportion of cardiovascular-related hospital admissions in the 2-year period before index date, including stroke, unstable angina, cerebrovascular disease, coronary artery disease, and peripheral arterial disease. Prior medication history was similar, other than prior use of antipsychotics, which was nearly double (19.5%) with oral rivastigmine compared with the low-dose donepezil cohort (10.0%).

Compared with low-dose donepezil, galantamine was associated with a 16% lower 3-year risk of mortality (adjusted hazard ratio [aHR]: 0.84, 95% confidence interval [CI]: 0.60–1.18). High-dose donepezil had similar risk (aHR: 0.97, 95% CI: 0.61–1.54), and the rivastigmine patch had 29% higher risk (aHR: 1.29, 95% CI: 0.93–1.79) (Table 2). The mortality differences were not statistically significant (P < .05).

Compared with low-dose donepezil, galantamine was associated with a lower risk of serious cardiovascular events (aHR: 0.78, 95% CI: 0.62–0.98) and entry into a residential care facility (aHR: 0.72, 95% CI: 0.59–0.89) (Table 2). Comparison with the oral rivastigmine could not be completed due to small-cell data restrictions.

In the 12-month fixed follow-up sensitivity analysis of cardiovascular events, galantamine was associated with an 18% lower risk (adjusted risk ratio [RR]: 0.82 (0.72–0.93) and rivastigmine patch was associated with a 15% higher risk (RR: 1.15 [1.01–1.32]), compared with low-dose donepezil. In the 6-month fixed follow-up analysis of cardiovascular events, there was no significant difference between low-dose donepezil and any of the study medications.

Compared with low-dose donepezil, galantamine was associated with a lower risk of mortality at 6 months (RR: 0.83, 95% CI: 0.69–1.01) and 12 months (RR: 0.82, 95% CI: 0.72–0.93), although the 6-month result was nonsignificant. The rivastigmine patch was associated with an increased risk of mortality at 6 months (RR: 1.21, 95% CI: 0.99–1.49) and at 12 months (RR: 1.15, 95% CI: 1.01–1.32), although the 6-month result was nonsignificant. Both formulations of rivastigmine, patch and oral, were also associated with a 12-month increased risk of entry into residential care (RR: 1.14, 95% CI: 1.03–1.26) and (RR: 1.275, 95% CI: 1.06–1.52), respectively (Tables 3 and 4).

4. Interpretation

This study compares ChEIs in terms of mortality, serious cardiovascular events, and entry into a residential care facility. Donepezil users were divided into low- and high-dose exposure groups based on WHO Defined Daily Dose. Nearly all users of galantamine and rivastigmine (98%) used the single WHO Defined Daily Dose.

The 3-year risk of serious cardiovascular events was 22% lower (aHR 0.78 CI: 0.62–0.98) and all-cause mortality was 16% lower (aHR 0.84 CI: 0.60–1.18) in galantamine versus low-dose donepezil, although the mortality results were not significant at the conventional α level of 0.05. Similar results were seen in both fixed follow-up sensitivity analyses. A Danish cross-national study comparing cardiovascular safety of dementia medications found similar benefits for galantamine (29% lower risk of heart failure [aHR 0.71 CI: 0.46–1.10]) [23].
Table 1
Baseline patient characteristics

| Characteristics | Donepezil (low dose) | Donepezil (high dose) | Galantamine | Rivastigmine (patch) | Rivastigmine (oral) |
|----------------|----------------------|-----------------------|-------------|----------------------|---------------------|
|                | N or mean (n=15,586) | N or mean (n=2519)    | N or mean (n=5926) | N or mean (n=4286)   | N or mean (n=730)   |
| Age (years), mean (IQR) | 80.7 (76-86) | 78.7 (74-85) | 80.8 (77-86) | 80.3 (76-85) | 79.2 (75-84) |
| Female, n (%) | 9366 60 | 1305 52 | 3400 57 | 2319 54 | 347 48 |
| Low family income (< $30k), n (%) | 3469 22 | 507 20 | 1389 23 | 1169 27 | 139 19 |
| Year of study cohort entry, n (%) | | | | | |
| 2007 (Oct 22-Dec 31) | 323 2 | 97 4 | 229 4 | - 0 | 64 9 |
| 2008 | 1763 11 | 437 17 | 1277 22 | 94 2 | 186 25 |
| 2009 | 1767 11 | 371 15 | 1277 22 | 558 13 | 120 16 |
| 2010 | 1966 13 | 375 15 | 1051 18 | 744 17 | 73 10 |
| 2011 | 2241 14 | 360 14 | 787 13 | 791 18 | 59 8 |
| 2012 | 2350 15 | 355 14 | 554 9 | 774 18 | 8 1 |
| 2013 | 2336 15 | 256 10 | 348 6 | 657 15 | 68 9 |
| 2014 | 2182 14 | 215 9 | 315 5 | 536 13 | 8 1 |
| 2015 (up to March 31) | 658 4 | 53 2 | 88 1 | 132 3 | 20 3 |
| Duration of ADRD (years), mean (SD) | 1.04 2.3 | 1.02 2.3 | 1.07 2.4 | 1.10 2.3 | 1.09 2.2 |
| High-dose first prescription, n (%) | - - | - - | 113 1.9 | 23 0.5 | 10 1.4 |
| High-dose second prescription, n (%) | 3471 22 | - - | 134 2.3 | 11 0.3 | 11 1.5 |
| Follow-up time (years), mean (SD) | 3.41 (1.95) | 3.86 (2.05) | 4.14 (2.12) | 3.28 (1.76) | 3.95 (2.26) |
| Smoker (past or current), n (%) | 6955 45 | 1075 43 | 2660 45 | 1967 46 | 311 43 |
| Number of hospital admissions in previous year 0, n (%) | 10,709 69 | 1777 71 | 4080 69 | 2768 65 | 482 66 |
| 1–2, n (%) | 1778 11 | 288 11 | 729 12 | 523 12 | 108 15 |
| 3+, n (%) | 3099 20 | 454 18 | 1117 19 | 995 23 | 140 19 |
| Number of physician visits in previous year, mean (SD) | 21 (18.2) | 20.9 (16.7) | 21 (17.2) | 25.2 (21.6) | 24.1 (19.8) |
| Prior medical history (2 years), n (%) | | | | | |
| Atrial fibrillation or flutter | 2393 15.4 | 336 13.3 | 982 16.6 | 704 16.4 | 105 14.4 |
| COPD, n (%) | 2200 14.1 | 330 13.1 | 871 14.7 | 634 14.8 | 90 12.3 |
| Diabetes mellitus | 3834 24.6 | 621 24.7 | 1467 24.8 | 1160 27.1 | 183 25.1 |
| Myocardial infarction | 218 1.4 | 29 1.2 | 71 1.2 | 62 1.4 | 9 1.2 |
| Hypertension | 9545 61.2 | 1420 56.4 | 3701 62.5 | 2573 60.0 | 441 60.4 |
| Prior hospital admission (2 years), n (%) | | | | | |
| Stroke | 209 1.3 | 34 1.3 | 125 2.1 | 82 1.9 | 10 1.4 |
| Unstable angina | 113 0.7 | 19 0.8 | 54 0.9 | 30 0.7 | 5 0.7 |
| Congestive heart failure | 409 2.6 | 48 1.9 | 159 2.7 | 124 2.9 | 17 2.3 |
| Cerebrovascular disease | 303 1.9 | 55 2.2 | 165 2.8 | 112 2.6 | 19 2.6 |
| Coronary artery disease | 570 3.7 | 91 3.6 | 261 4.4 | 172 4.0 | 31 4.2 |
| Peripheral arterial disease | 70 0.4 | 6 0.2 | 32 0.5 | 11 0.3 | 2 0.3 |
| Prior medication history (1 year), n (%) | | | | | |
| Other anticholinergics, n (%) | 2491 16.0 | 374 14.8 | 952 16.1 | 732 17.1 | 150 20.5 |
| Lipid-lowering agents, n (%) | 6307 40.5 | 995 39.5 | 2546 43.0 | 1804 42.1 | 298 40.8 |
| ACE inhibitors, n (%) | 5146 33.0 | 718 28.5 | 2146 36.2 | 1375 32.1 | 268 36.7 |
| ARBs, n (%) | 2409 15.5 | 365 14.5 | 917 15.5 | 702 16.4 | 102 14.0 |
| Beta-blockers, n (%) | 3944 25.3 | 553 22.0 | 1563 26.4 | 1102 25.7 | 195 26.7 |
| Antidepressants, n (%) | 4898 31.4 | 711 28.2 | 1776 30.0 | 1482 34.6 | 255 34.9 |
| Antipsychotics, n (%) | 1565 10.0 | 235 9.3 | 569 9.6 | 592 13.8 | 142 19.5 |

(Continued)
Prior hospital admission for several cardiovascular conditions was highest among galantamine users. Although this usually suggests patients were at a higher risk of future cardiovascular events, an alternative explanation could be that these patients were more closely monitored and more aggressively treated for vascular risk factors, resulting in lower cardiovascular events.

Entry into residential care was studied as a co-secondary outcome as a measure of net benefit over harm. Our results show a 28% lower 3-year risk of entry into a residential care facility with galantamine versus low-dose donepezil (aHR: 0.72 CI: 0.62–0.98). These findings are also consistent with a net benefit of treatment over harm for galantamine and may also be related to a previous finding of longer persistence and better adherence for patients on galantamine versus donepezil [24].

Residual confounding is a possible limitation of our results because of the nonrandomized study design. Baseline characteristics of the study cohorts indicate comparable age, smoking status, and prior medical history. Low-dose donepezil had the highest proportion of females (60%). This was likely due to weight-based dosing. Rivastigmine users had the highest prior use of antipsychotics. There is a positive correlation between cognitive decline, progression of neurodegeneration, and psychosis in patients with ADRD [25]. Previous research has shown that rivastigmine users have a lower rate of antipsychotic prescriptions compared with donepezil patients in a base cohort of antipsychotic naïve patients [26]. These findings may influence physicians to preferentially prescribe rivastigmine over other ChEIs to patients with symptoms of psychosis. In addition, the Alzheimer’s Drug Therapy Initiative required regular cognitive assessments; our study findings may not be generalizable to jurisdictions with alternative health care systems.

A significant strength of our study was the use of the B.C. Ministry of Health administrative claims database, which captures all prescriptions dispensed at a community pharmacy regardless of payer. Dispensed prescriptions are

### Table 1
Baseline patient characteristics (Continued)

| Characteristics | Donepezil (low dose) | Donepezil (high dose) | Galantamine | Rivastigmine (patch) | Rivastigmine (oral) |
|-----------------|----------------------|-----------------------|-------------|----------------------|---------------------|
| N or mean (n)   | N or mean (n)        | N or mean (n)         | N or mean (n) | N or mean (n)        | N or mean (n)        |
| anxiolytics/sedatives/hypnotics, n (%) | 3717 23.8 | 605 24.0 | 1360 22.9 | 1181 27.6 | 208 28.5 |

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers.

*Net family income in Canadian dollars from the most recent income tax return (1 Canadian dollar = .75 US dollar).

High-dose defined as a dispensed daily dose on the first ChEI prescription that is higher than the WHO Defined Daily Dose (DDD).

Follow-up time shown for primary outcome (mortality).

Smoking status based on history of diagnosed COPD or use of a smoking cessation medication (varenicline, Zyban, or nicotine replacement products).

Hospital separation record or physician visit diagnosis within 2 years before the index date.

### Table 2
Cox proportional hazards for mortality, serious cardiovascular events, and entry into a residential care facility

| All-cause mortality, time-to-event, Cox proportional hazards | N or mean (n) | Cumulative mortality events | Crude rate per 100 PYs | Propensity score–adjusted hazard ratio |
|------------------------------------------------------------|--------------|------------------------------|------------------------|--------------------------------------|
| Low-dose donepezil (reference)                             | 15,586       | 147                          | 5.80                   | 0.97 (0.61–1.54)                      |
| High-dose donepezil                                        | 2519         | 23                           | 5.35                   |                                      |
| Galantamine                                                | 5926         | 51                           | 5.29                   | 0.84 (0.60–1.18)                      |
| Rivastigmine—patch                                         | 4286         | 86                           | 10.82                  | 1.29 (0.93–1.79)                      |
| Rivastigmine—oral                                          | 730          | ^5                           | 0.49 (0.17–1.36)       |                                      |

### Table 2
Cox proportional hazards for mortality, serious cardiovascular events, and entry into a residential care facility

| Serious cardiovascular events, time-to-event, Cox proportional hazards | N or mean (n) | Cumulative mortality events | Crude rate per 100 PYs | Propensity score–adjusted hazard ratio |
|------------------------------------------------------------------------|--------------|------------------------------|------------------------|--------------------------------------|
| Low-dose donepezil (reference)                                         | 15,586       | 331                          | 5.84                   |                                      |
| High-dose donepezil                                                    | 2519         | 50                           | 5.39                   | 1.02 (0.75–1.39)                      |
| Galantamine                                                             | 5926         | 106                          | 5.32                   | 0.78 (0.62–0.98)                      |
| Rivastigmine—patch                                                     | 4286         | 128                          | 10.91                  | 0.98 (0.77–1.25)                      |
| Rivastigmine—oral                                                      | 730          | 16                           | 3.53                   | 0.87 (0.51–1.48)                      |

| Entry into residential care, time-to-event, Cox proportional hazards   | N or mean (n) | Cumulative mortality events | Crude rate per 100 PYs | Propensity score–adjusted hazard ratio |
|------------------------------------------------------------------------|--------------|------------------------------|------------------------|--------------------------------------|
| Low-dose donepezil (reference)                                         | 15,586       | 447                          | 5.86                   | 0.97 (0.74–1.28)                      |
| High-dose donepezil                                                    | 2519         | 66                           | 5.41                   | 0.97 (0.59–0.89)                      |
| Galantamine                                                             | 5926         | 135                          | 5.34                   | 1.16 (0.95–1.42)                      |
| Rivastigmine—patch                                                     | 4286         | 182                          | 10.97                  | 0.88 (0.56–1.37)                      |
| Rivastigmine—oral                                                      | 730          | 22                           | 2.55                   |                                      |
linkable to physician services, hospital discharge abstracts, and client demographic information via an encrypted patient identifier. The comprehensiveness of the databases for the B.C. population reduces the risk of exposure misclassification, which is known to substantially affect risk estimates in observational studies [27] and allows for generalizing results to a wide population.

Our study found that galantamine has a superior safety profile compared with low-dose donepezil and was associated with a lower risk of entry into a residential care facility. The rivastigmine patch was associated with a higher risk of mortality and a higher risk of entry into a residential care facility. High-dose donepezil had a similar safety and effectiveness profile compared with low-dose donepezil. Given the absence of significant differences in the safety profiles of the three cholinesterase inhibitors, clinicians may consider patient preference and cost when choosing a treatment option.

Table 3
Six-month fixed follow-up log-binomial regression

| N  | Number of outcomes | Crude risk ratio (95% confidence interval) | Age-sex adjusted | Fully adjusted |
|----|-------------------|----------------------------------------|------------------|----------------|
|    |                   |                                        | Risk ratio (95% confidence interval) | P-value         | Risk ratio (95% confidence interval) | P-value         |
|   |                   |                                        | P-value          |                 | P-value          |                 |
| Crude and adjusted odds ratio, all-cause mortality, 6-month fixed follow-up |
| Low-dose donepezil (reference) | 15,586 | 440 |
| High-dose donepezil | 2519 | 53 | 0.75 (0.56-0.99) | 0.81 (0.61-1.08) | 0.147 | 0.83 (0.62-1.11) | 0.209 |
| Galantamine | 5926 | 150 | 0.90 (0.75-1.08) | 0.89 (0.74-1.06) | 0.194 | 0.83 (0.69-1.01) | 0.066 |
| Rivastigmine—patch | 4286 | 158 | 1.31 (1.09-1.56) | 1.31 (1.09-1.56) | 0.003 | 1.21 (0.99-1.47) | 0.062 |
| Rivastigmine—oral | 730 | 17 | 0.82 (0.51-1.33) | 0.88 (0.54-1.41) | 0.585 | 0.74 (0.45-1.22) | 0.243 |

Crude and adjusted odds ratios, cardiovascular events, 6-month fixed follow-up

| N  | Number of outcomes | Crude risk ratio (95% confidence interval) | Age-sex adjusted | Fully adjusted |
|----|-------------------|----------------------------------------|------------------|----------------|
|    |                   |                                        | Risk ratio (95% confidence interval) | P-value         | Risk ratio (95% confidence interval) | P-value         |
|   |                   |                                        | P-value          |                 | P-value          |                 |
| Crude and adjusted odds ratios, entry to residential care, 6-month fixed follow-up |
| Low-dose donepezil (reference) | 15,586 | 920 |
| High-dose donepezil | 2519 | 108 | 0.73 (0.60-0.88) | 0.81 (0.67-0.99) | 0.037 | 0.82 (0.67-1.01) | 0.058 |
| Galantamine | 5926 | 298 | 0.89 (0.79-1.00) | 0.89 (0.78-0.99) | 0.032 | 0.80 (0.70-0.92) | 0.001 |
| Rivastigmine—patch | 4286 | 329 | 1.19 (1.05-1.35) | 1.22 (1.08-1.39) | 0.002 | 1.19 (1.03-1.36) | 0.015 |
| Rivastigmine—oral | 730 | 63 | 1.46 (1.15-1.87) | 1.62 (1.27-2.06) | 0.0001 | 1.26 (0.98-1.63) | 0.077 |

Bold values indicate a confidence interval that does not include 1.

Table 4
Twelve-month fixed follow-up log-binomial regression

| N  | Number of outcomes | Crude risk ratio (95% confidence interval) | Age- and sex-adjusted | Prop. Score adjusted |
|----|-------------------|----------------------------------------|------------------|----------------|
|    |                   |                                        | Risk ratio (95% confidence interval) | P-value         | Risk ratio (95% confidence interval) | P-value         |
|   |                   |                                        | P-value          |                 | P-value          |                 |
| Crude and adjusted odds ratio, all-cause mortality, 12-month fixed follow-up |
| Low-dose donepezil (reference) | 15,586 | 990 |
| High-dose donepezil | 2519 | 134 | 0.84 (0.70-0.99) | 0.90 (0.76-1.07) | 0.244 | 0.93 (0.77-1.11) | 0.408 |
| Galantamine | 5926 | 298 | 0.85 (0.75-0.97) | 0.86 (0.78-0.99) | 0.032 | 0.82 (0.72-0.93) | 0.002 |
| Rivastigmine—patch | 4286 | 329 | 1.21 (1.07-1.36) | 1.21 (1.07-1.36) | 0.002 | 1.15 (1.01-1.32) | 0.031 |
| Rivastigmine—oral | 730 | 48 | 1.04 (0.78-1.37) | 1.08 (0.82-1.43) | 0.589 | 0.97 (0.72-1.29) | 0.815 |

Crude and adjusted odds ratios, cardiovascular events, 12-month fixed follow-up

| N  | Number of outcomes | Crude risk ratio (95% confidence interval) | Age- and sex-adjusted | Prop. Score adjusted |
|----|-------------------|----------------------------------------|------------------|----------------|
|    |                   |                                        | Risk ratio (95% confidence interval) | P-value         | Risk ratio (95% confidence interval) | P-value         |
|   |                   |                                        | P-value          |                 | P-value          |                 |
| Crude and adjusted odds ratios, entry to residential care, 12-month fixed follow-up |
| Low-dose donepezil (reference) | 15,586 | 914 |
| High-dose donepezil | 2519 | 125 | 0.85 (0.71-1.02) | 0.90 (0.75-1.08) | 0.264 | 0.96 (0.80-1.16) | 0.708 |
| Galantamine | 5926 | 300 | 0.86 (0.76-0.98) | 0.86 (0.75-0.97) | 0.016 | 0.83 (0.73-0.95) | 0.007 |
| Rivastigmine—patch | 4286 | 240 | 0.95 (0.83-1.10) | 0.96 (0.84-1.10) | 0.560 | 0.94 (0.81-1.09) | 0.434 |
| Rivastigmine—oral | 730 | 40 | 0.93 (0.69-1.27) | 0.98 (0.72-1.33) | 0.898 | 0.85 (0.61-1.16) | 0.305 |

Crude and adjusted odds ratios, entry to residential care, 12-month fixed follow-up

| N  | Number of outcomes | Crude risk ratio (95% confidence interval) | Age- and sex-adjusted | Prop. Score adjusted |
|----|-------------------|----------------------------------------|------------------|----------------|
|    |                   |                                        | Risk ratio (95% confidence interval) | P-value         | Risk ratio (95% confidence interval) | P-value         |
|   |                   |                                        | P-value          |                 | P-value          |                 |
| Low-dose donepezil (reference) | 15,586 | 1702 |
| High-dose donepezil | 2519 | 218 | 0.79 (0.69-0.91) | 0.88 (0.77-1.00) | 0.051 | 0.90 (0.78-1.03) | 0.117 |
| Galantamine | 5926 | 659 | 1.02 (0.94-1.11) | 1.02 (0.94-1.11) | 0.566 | 0.95 (0.87-1.04) | 0.284 |
| Rivastigmine—patch | 4286 | 529 | 1.13 (1.03-1.24) | 1.16 (1.06-1.27) | 0.001 | 1.14 (1.03-1.26) | 0.011 |
| Rivastigmine—oral | 730 | 113 | 1.42 (1.19-1.69) | 1.54 (1.30-1.83) | <.0001 | 1.27 (1.06-1.52) | 0.011 |

Bold values indicate a confidence interval that does not include 1.
of randomized trial data showing clinically meaningful benefit of ChEI therapy in ADRD, our study suggests that preferential use of galantamine may at least be associated with fewer adverse events than treatment with donepezil or rivastigmine and may also be associated with longer independent living before requiring a residential care facility.

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Disclaimer: All inferences, opinions, and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the Data Stewards.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2019.09.011.

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