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Comparative Risk of Pneumonia Among New Users of Cholinesterase Inhibitors for Dementia

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Abstract

OBJECTIVES—To compare the risk of pneumonia among older patients receiving donepezil, galantamine, or rivastigmine for dementia.

DESIGN, SETTING, AND PARTICIPANTS—Retrospective cohort study of a nationally representative 5% sample of Medicare beneficiaries 65 years or older who newly initiated cholinesterase inhibitor therapy between 2006 and 2009.

MEASUREMENTS—Pneumonia, defined as the presence of a diagnosis code for pneumonia as the primary diagnosis on an inpatient claim or on an emergency department claim followed by dispensing of appropriate antibiotics. We used Cox proportional hazards models to estimate the risk of pneumonia. We conducted secondary analyses and sensitivity analyses using alternative pneumonia definitions and adjustments by high-dimensional propensity scores to test the robustness of the results.

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RESULTS—Among 35,570 new users of cholinesterase inhibitors (30,174 users of donepezil, 1176 users of galantamine, and 4220 users of rivastigmine), mean age was 82 years, 75% were women, and 82% were white. The cumulative incidence of pneumonia was 51.9 per 1000 person-years. Risk was significantly lower by 24% among rivastigmine users compared with donepezil users (hazard ratio [HR], 0.75; 95% CI, 0.60–0.93). Risk among galantamine users (HR, 0.87; 95% CI, 0.62–1.23) was not significantly different from risk among donepezil users. Results of secondary and sensitivity analyses were similar to the primary results.

CONCLUSION—The risk of pneumonia was lower among patients receiving rivastigmine compared with patients receiving donepezil. Additional studies are needed to confirm the findings of pneumonia risk between the oral and transdermal forms of rivastigmine and among users of galantamine.

Keywords

Cholinesterase Inhibitors; Cohort Studies; Dementia; Medicare; Pneumonia

INTRODUCTION

Dementia is a chronic neurodegenerative disorder characterized clinically by deterioration of daily living, behavioral functioning, and global cognitive ability.[1,2] Cholinesterase inhibitors are the cornerstone of medical therapy and are approved for symptomatic treatment of patients with mild to moderate dementia.[2] Because pneumonia is a common cause of death in older patients with dementia,[3,4] the potential risk of pneumonia associated with cholinesterase inhibitors has raised concern.[2,5] Cholinesterase inhibition may lead to over activation of muscarinic receptors and result in bradycardia, bronchospasm, emesis, and diarrhea. Moreover, overstimulation of nicotinic receptors results in fasciculation, muscle weakness, and paralysis that may increase pneumonia risk.[5,6] Although there is no direct evidence of greater pneumonia risk associated with cholinesterase inhibitors, results of randomized clinical trials have suggested the possibility.[7,8] Helou et al[5] found that cholinesterase inhibitor therapy in 183 hospitalized patients with dementia was associated with nearly double the risk of pulmonary disorders, mostly pneumonia.[5]

We evaluated the comparative risk of pneumonia among older patients receiving donepezil, galantamine, or rivastigmine. Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase and has greater selectivity for brain tissue than peripheral tissues.[2,9] Some studies have indicated that rivastigmine has lower affinity for the type 4 globular isoform of acetylcholinesterase than the type 1 isoform, a possible safety improvement because the type 4 isoform predominates in the peripheral nervous system.[10,11] Because the peripheral nervous system regulates involuntary physiological functions such as breathing and digestion, cholinesterase inhibitors with fewer peripheral effects are less likely to cause unintended respiratory outcomes, such as shortness of breath and dyspnea, or unintended digestive outcomes, such as gastro-esophageal reflux or esophageal immotility, which may have a negative impact on pneumonia risk.[5,6,12] However, no evidence exists for the comparative safety of cholinesterase inhibitors with regard to pneumonia risk. We hypothesized that rivastigmine posed a lower risk than donepezil and galantamine, which are acetylcholinesterase inhibitors without selectivity for the type 4 isoform.[10,11]

METHODS

Data Source

We accessed administrative claims data from January 1, 2006, through December 31, 2009, for a nationally representative 5% sample of Medicare beneficiaries. The institutional review board of the Duke University Health System approved the study. The data included inpatient, outpatient, carrier, and prescription drug event claims and corresponding denominator files. Diagnostic and procedural information from the inpatient, outpatient, and carrier files included *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes and Current Procedural Terminology (CPT) codes. We obtained drug information from Medicare Part D claims. Medicare Part D subsidizes the costs of prescription drugs for Medicare beneficiaries. Beneficiaries with Medicare Parts A and B are eligible for Part D. The claims are registered by the date of dispensing, days of supply, dose dispensed, and a National Drug Code for each formulation.

Cohort Definition and Exposure

We identified patients 65 years or older who were newly prescribed a cholinesterase inhibitor. We considered the first dispensed cholinesterase inhibitor to be the index medication, and we used the dispensing date as the index date. We included new users who did not receive medication for dementia during the 6 months before the index date. To ensure sufficient data to assess baseline characteristics, we excluded patients with less than 12 months of continuous enrollment in Medicare Parts A and B and less than 6 months of continuous enrollment in Medicare Part D before the index date.

We classified eligible patients into 3 exposure groups by index medication: donepezil, galantamine, and rivastigmine. We defined 3 dosage levels (numbered 1, 2, and 3) based on the last prescription before the end of follow-up.

Outcomes and Follow-up

The outcome of interest was pneumonia, defined as the presence of *ICD-9-CM* codes 480.xx–486.xx as the primary diagnosis on an inpatient claim or on an emergency department claim followed by dispensing of appropriate antibiotics (i.e., erythromycin, clarithromycin, ciprofloxacin, levofloxacin, moxifloxacin, doxycycline, amoxicillin, gemifloxacin, cefpodoxime, cefuroxime, azithromycin, doxycycline, and amoxicillin/clavulanic acid). This identification of an inpatient pneumonia diagnosis has a positive predictive value of 88%.[10] The follow-up period for each patient lasted until the patient received a pneumonia diagnosis, switched from the index medication, discontinued the medication (i.e., no dispensing for more than 30 days after the end date of the previous dispensing), discontinued enrollment in Medicare, or reached the end of the study(December 31, 2009).

Covariates

We assessed demographic characteristics, health services utilization, history of pneumonia, and comorbid conditions during the 12 months before the index date. We also assessed the use of other medications during the 6 months before the index date. We identified history of

pneumonia by the presence of *ICD-9-CM* codes 480.xx–486.xx and 507.xx on inpatient and outpatient claims. We also assessed the use of antipsychotic medications and diagnoses of Lewy body disease (*ICD-9-CM* code 331.82) and Parkinson disease (*ICD-9-CM* code 332.xx). Patients taking antipsychotics have a higher risk of pneumonia.[13] Lewy body disease and Parkinson disease also are known to be associated with greater pneumonia risk.[14]

Statistical Analysis

We report the number of events and the incidence per person-year for the outcomes of interest. We plotted cumulative incidence, which represents the cumulative probability of events over time while accounting for competing risks.[15] We then estimated hazard ratios (HRs) and 95% CIs using Cox proportional hazards models to assess pneumonia risks associated with galantamine and rivastigmine compared with donepezil. We adjusted for demographic characteristics and other covariates to account for potential confounding. We conducted subgroup analyses by stratifying patients by age, sex, race, and history of pneumonia, Parkinson disease (or receiving anti-Parkinson medication), Lewy body disease, and use of antipsychotics.

In secondary and sensitivity analyses, we tested the robustness of the results. We used high-dimensional propensity score estimation to control for confounders and unobserved factors.[16,17] Using a high-dimensional propensity score algorithm, we screened the data to identify covariates that may act collectively as surrogates for unobserved confounding factors.[17] We included the propensity score as a continuous covariate in regression models or matched on the score using a greedy matching method, which reduces bias from incomplete and inexact matching.[18]

We repeated the analyses with various exposure and outcome definitions. Although aspiration pneumonia was coded infrequently, and the accuracy of the coding was unclear, we added aspiration pneumonia (*ICD-9-CM* code 507.xx) to the main outcome definition insensitivity analysis. We varied the grace period for defining discontinuation (0, 7, and 90 days). We also varied the window for capturing antibiotic use for pneumonia identified in the emergency department. To evaluate the impact of censoring, we conducted an intention-to-treat analysis in which we considered patients to be exposed to the index medication until the occurrence of pneumonia, death, or the end of follow-up, regardless of subsequent changes in exposure. We limited the follow-up period to 1 year. We used SAS version 9.3 (SAS Institute, Inc) for all analyses.

RESULTS

Of 35,570 new users of cholinesterase inhibitors, 30,174 were users of donepezil, 1176 were users of galantamine, and 4220 were users of rivastigmine. Table 1 shows the baseline characteristics of the study population. Mean age was 81.6 (SD, 7.3) years, 26,542 (74.6%)of the patients were women, and 29,265 (82.3%) were white. Some patients had a history of pneumonia (13.1%) and chronic obstructive pulmonary disease (28.2%). Galantamine users generally had lower rates of health service utilization. A greater

proportion of rivastigmine users had Parkinson disease (13.9%), Lewy body disease (7.0%), and use of antipsychotics (19.9%) and anti-Parkinson medication (11.8%).

There were 1249 cases of pneumonia during the mean follow-up period of 246.9 days. The cumulative incidence of pneumonia was 51.9 per 1000 person-years. Incidence was highest among donepezil users (52.6 per 1000 person-years), followed by galantamine users (42.9 per 1000 person-years) and rivastigmine users (42.0 per 1000 person-years). The incidence curves in Figure 1 indicate that the rate of pneumonia was significantly lower among rivastigmine users than among donepezil users ($P < .01$). The unadjusted pneumonia risk was lower with rivastigmine (HR, 0.76; 95% CI, 0.62–0.95) and galantamine (HR, 0.76; 95% CI, 0.52–1.10). After multivariable adjustment, pneumonia risk remained significantly lower with rivastigmine (HR, 0.75; 95% CI, 0.60–0.93), whereas the risk was not significantly different between galantamine and donepezil (HR, 0.87; 95% CI, 0.62–1.23). When we assessed pneumonia risk between the oral and transdermal forms of rivastigmine, we observed 39% and 14% lower risks, respectively, compared with donepezil (Table 2).

As shown in Table 2, pneumonia risk increased with advancing age and was greater among men, patients with a history of pneumonia, and patients with heart failure, chronic obstructive pulmonary disease, and previous use of antipsychotics, antidepressants, antiepileptic agents, and loop diuretics.

In secondary analyses and sensitivity analyses, the HRs were similar to those in the primary analysis (Figure 2). We found lower risks of pneumonia among rivastigmine users compared with donepezil users (HRs ranging from 0.38 to 0.95), and the risks were similar between galantamine users and donepezil users (HRs ranging from 0.75 to 1.10). Pneumonia risk was even lower among rivastigmine users compared with donepezil users among those who had Parkinson disease or Lewy body disease (HR, 0.43; 95% CI, 0.22–0.94), whereas it was not significant among those who did not have these conditions (HR, 0.84; 95% CI, 0.67–1.05).

DISCUSSION

In this large retrospective cohort study of a nationally representative sample of Medicare beneficiaries, the rivastigmine group had a higher proportion of patients with Parkinson disease, Lewy body disease, and use of antipsychotics and anti-Parkinson medication, suggesting that rivastigmine users may have a higher baseline risk of pneumonia. Despite the potential for residual confounding due to baseline risk that likely led us to underestimate potential beneficial effects of rivastigmine on pneumonia risk, new users of rivastigmine had significantly lower pneumonia risk compared with new users of donepezil after multivariable adjustment.

Previous research indicated that annual rates of hospital admission in the United States among older persons with pneumonia ranged from 15 to 25 per 1000.[19] The rate of pneumonia in our study was approximately twice that observed in the previous report, suggesting that the study population had higher risk due to underlying disease, dementia, and/or use of cholinesterase inhibitors. Patients with dementia may have higher pneumonia risk because of limited activities of daily living,[5,20] and difficulty swallowing may cause

aspiration pneumonia.[21] This finding addresses questions about whether the increased risk of pneumonia among new users of rivastigmine is caused by dementia or by the medication.[20] In addition to our hypothesis of fewer effects on muscarinic and nicotinic receptors, the lower risk of pneumonia with rivastigmine may be a result of greater effectiveness of the drug. However, evidence from clinical trials that directly compared the efficacy of cholinesterase inhibitors is conflicting.[22–25] Therefore, it is less likely that physicians chose one cholinesterase inhibitor over another for patients with more or less severe dementia.

To our knowledge, our study is the first to assess the comparative risk of pneumonia among cholinesterase inhibitors. Despite the higher incidence of Parkinson disease and other comorbid conditions that might have resulted in worse outcomes among rivastigmine users, this group had lower risk of pneumonia compared with the donepezil group. Rivastigmine provides functional inhibition of both acetylcholinesterase and butyrylcholinesterase, whereas donepezil provides no functional inhibition of butyrylcholinesterase. Butyrylcholinesterase inhibition yields cognitive improvements inpatients with dementia.[9,26–28] Furthermore, the preferential affinity of rivastigmine for the type 1 globular isoform of acetylcholinesterase over the type 4 isoform may contribute to improved safety, because the type 4 isoform predominates in the peripheral nervous system.[29,30] As we hypothesized, the risk of pneumonia among rivastigmine users was lower than among donepezil users, which may be a result of reduced effects of rivastigmine on the peripheral nervous system. In addition, rivastigmine is not substantially metabolized by the hepatic microsomal cytochrome P450 system. It also has a low protein binding affinity, so it is less likely to compete with a high protein binding drug.[9] Therefore, the increased risk of pneumonia may also result from unintended fluctuation in plasma concentration of donepezil due to drug-drug interaction.[31] It is noteworthy that, compared with donepezil, the risk of pneumonia among rivastigmine users with Parkinson disease (or patients receiving anti-Parkinson medication) or Lewy body disease was lower than the risk among rivastigmine users without these conditions in sensitivity analysis. This finding may suggest greater effectiveness of rivastigmine in patients with dementia and Parkinson disease,[32–34] leading to a greater protective effect, especially for patients with those conditions.

Galantamine is a tertiary alkaloid compound with efficacy comparable to donepezil.[23] Because donepezil is an older drug, physicians are more familiar with it, which may help to explain its higher use. In addition, it was the first drug to have a generic equivalent. The relatively short half-life of galantamine requires twice-daily administration, which may partially explain the lower use of galantamine compared with the other medications. Galantamine users had a slightly lower risk of pneumonia compared with donepezil users, although this finding was not statistically significant, partly due to the smaller cohort size. Although Meguro et al[12] found that donepezil had a positive effect on life expectancy, this finding may be related to the lower mortality rate from pneumonia or respiratory failure compared with the galantamine or memantine group. We were unable to differentiate the effects of galantamine from memantine. In summary, the comparative risk of pneumonia between galantamine and donepezil remains inconclusive based on current evidence.

After stratifying by the oral and transdermal patch formulations of rivastigmine, we found a smaller, non significant reduction in pneumonia among users of the patch. With its introduction to the United States in 2007, the patch offered a more favorable gastrointestinal tolerability profile and steadier drug plasma concentration than oral rivastigmine.[35] Treatment adherence may be improved by transdermal delivery, imparting clinical benefits and fewer side effects such as pneumonia. Patch users may have more advanced dementia than oral rivastigmine users, so possible confounding by indication should be noted. Although we performed a series of adjustments to minimize bias, future studies with more precise assessments of pneumonia risk between the oral and patch formulations are warranted.

Our findings are consistent with previous reports of risk factors associated with pneumonia risk.[36–38] The association between antipsychotics and pneumonia risk maybe explained by the mechanism of action on neurotransmitters.[39,40] Also, antipsychotic use may be a surrogate for more severe dementia; we were unable to directly measure and account for dementia severity in our data set.[11] We also found that the use of antiepileptic medication increased the risk of pneumonia. Although there is no direct evidence for this association, Yang et al[41] noted that concomitant use of antiepileptic medication with antipsychotics would significantly increase pneumonia risk compared with use of antipsychotics alone.[41] One study found that pneumonia was 3 times as likely afterhospitalization for depression, implying that antidepressants may also increase pneumonia risk.[42] We found that the use of antidepressants was associated with pneumonia risk, but the risk was much lower after multivariable adjustment.[43]

Pneumonia is one of the most life-threatening complications of Parkinson disease and Lewy body disease.[14,44] We observed small but non significant increases in pneumonia risk. This finding can be explained by our combined definition of “Parkinson disease or Lewy body disease,” resulting in low statistical power and misclassification bias toward the null. On the other hand, use of angiotensin-converting enzyme (ACE) inhibitors was associated with lower pneumonia risk. ACE inhibitors are known to enhance the cough reflex and protect the tracheobronchial tree by avoiding exposure of the respiratory tree to oropharynx secretions, which may reduce the incidence of pneumonia.[45]

Our study has limitations. First, Medicare data do not include information on dementia severity. Donepezil may be used for moderate to severe dementia; thus, residual confounding by severity is possible. However, we believe the confounding effect was relatively small when compared among users of cholinesterase inhibitors, because prescribers may pay more attention to patients’ situations when choosing a cholinesterase inhibitor rather than pay attention to labeled indication relative to severity. Second, the dose of last prescription may reflect the most recent status of drug level before the pneumonia event. Although we did not observe a dose-response relationship, inclusion of last dose in the regression models may partially adjust for the most recent status of the patient, such as health, disease, or drug tolerability status. Third, the diagnosis reported in emergency department claims has not been validated. Although we used the dispensing of appropriate antibiotics to increase the validity of the diagnosis, we could not eliminate the possibility of misclassification. Fourth, we included only new users in an attempt to create a relatively homogenous cohort. Also, the

data indicate that the rivastigmine group had conditions associated with higher risk of pneumonia, in that the group had a higher proportion of patients with Parkinson disease, Lewy body disease, and the use of antipsychotics and anti-Parkinson medication. Nonetheless, we used multivariable adjustment and high-dimensional propensity score estimation to control for factors that may have been surrogates for disease severity. Fifth, the mortality rate was high, which may have introduced competing risks for pneumonia outcomes. We used the cumulative incidence function to address competing risks, and the results remained robust. Finally, we only assessed comparative safety among users of cholinesterase inhibitors, and we did not include a non treatment group because such patients were uncommon and may not be comparable to those receiving cholinesterase inhibitors due to different baseline risk of pneumonia. No inference can be made about risks associated with cholinesterase inhibitors compared with no treatment.

CONCLUSION

Rivastigmine posed a lower risk of pneumonia compared with donepezil in patients with dementia who newly initiated cholinesterase inhibitor therapy. Additional studies are needed to confirm the findings, including more precise assessments of pneumonia risk between the oral and transdermal forms of rivastigmine and among users of galantamine.

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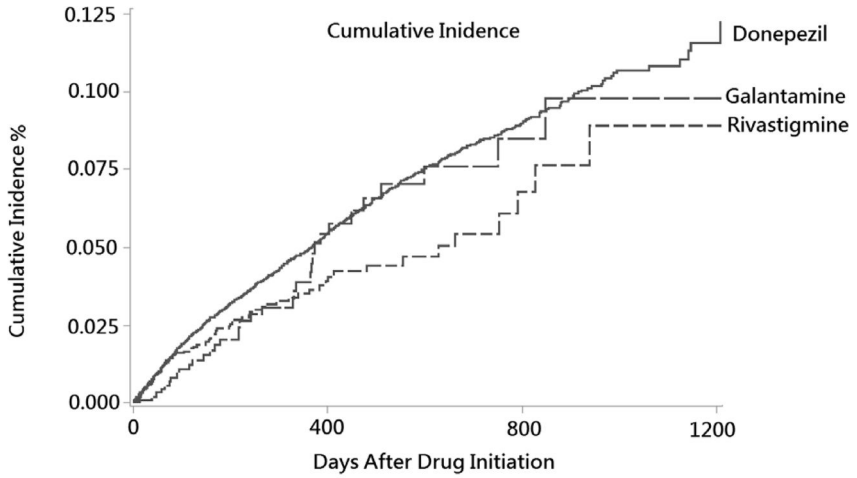

Figure 1.

Cumulative Incidence of Pneumonia Risk Among New Users of Cholinesterase Inhibitors

Note: $P < .01$ for comparisons between the index medications.

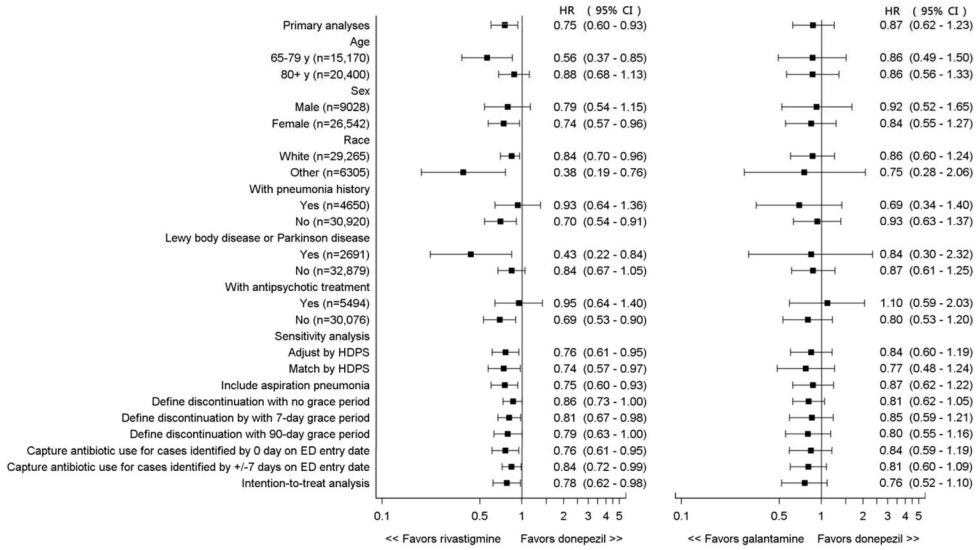

Figure 2.

Secondary and Sensitivity Analyses of Pneumonia Risk Among New Users of Cholinesterase Inhibitors

Note: High-dimensional propensity scores were generated by donepezil-galantamine group and donepezil-rivastigmine group, respectively.

Table 1

Baseline Characteristics of the Study Population (N = 35,570)

Characteristic	Donepezil (n = 30,174)	Galantamine (n =1176)	Rivastigmine (n = 4220)	
			Oral (n =1157)	Transdermal (n =3063)
Age, mean (SD), y	81.6(7.2)	81.0(6.9)	80.8(7.3)	81.6(7.3)
Age group, No. (%)				
65–74 y	5448(18.1)	219(18.6)	251(21.7)	556(18.2)
75–84 y	13,618(45.1)	566(48.1)	521(45.0)	1390(45.4)
85–94 y	10,247(34.0)	368(31.3)	357(30.9)	1024(33.4)
≥ 95 y	861(2.9)	23(2.0)	28(2.4)	93(3.0)
Men, No. (%)	7536(25.0)	366(31.1)	344(29.7)	782(25.5)
White race, No. (%)	24,794(82.2)	1019(86.6)	921(79.6)	2531(82.6)
Lewy body disease, No. (%)	857(2.8)	53(4.5)	118(10.2)	178(5.8)
History of pneumonia, No.(%)	3979(13.2)	132(11.2)	139(12.0)	400(13.1)
Health service use				
Hospital admissions, mean (SD)	0.8(1.2)	0.6(1.1)	0.7(1.1)	0.8(1.2)
Outpatient clinic visits, mean (SD)	17.9(14.2)	19.5(14.8)	18.0(14.6)	20.8(15.8)
Emergency department visits, mean (SD)	1.9(4.8)	1.5(3.8)	1.6(2.5)	2.0(5.3)
Skilled nursing facility, No. (%)	8800(29.2)	253(21.5)	346(29.9)	891(29.1)
Prescriptions, mean (SD)	27.1(20.4)	25.3(19.4)	26.5(21.0)	31.2(21.1)
Last prescription before end of follow-up[a]				
Dosage level 1, No. (%)	18(0.1)	0	0	201(6.6)
Dosage level 2, No. (%)	17,107(56.7)	587(49.9)	450(38.9)	1423(46.5)
Dosage level 3, No. (%)	13049(43.2)	589(50.1)	707(61.1)	1439(47.0)
Comorbid conditions, No. (%)				
Arrhythmia	10,001(33.1)	357(30.4)	344(29.7)	1041(34.0)
Cancer	3825(12.7)	156(13.3)	125(10.8)	376(12.3)
Cerebrovascular disease	11,660(38.6)	458(38.9)	438(37.9)	1318(43.0)
Chronic obstructive pulmonary disease	8489(28.1)	311(26.4)	312(27.0)	908(29.6)
Depression	6576(21.8)	242(20.6)	247(21.3)	713(23.3)
Diabetes mellitus	10,581(35.1)	389(33.1)	419(36.2)	1096(35.8)

Characteristic	Donepezil (n = 30,174)	Galantamine (n =1176)	Rivastigmine (n = 4220)	
			Oral (n =1157)	Transdermal (n =3063)
Dyslipidemia	18,366(60.9)	719(61.1)	684(59.1)	1911(62.4)
Heart failure	7503(24.9)	243(20.7)	288(24.9)	757(24.7)
Hypertension	25,416(84.2)	931(79.2)	956(82.6)	2633(86.0)
Liver disease	1356(4.5)	52(4.4)	48(4.1)	134(4.4)
Mood disorder	3427(11.4)	140(11.9)	158(13.7)	409(13.4)
Myocardial infarction or ACS	3161(10.5)	80(6.8)	118(10.2)	314(10.3)
Parkinson disease	1551(5.1)	88(7.5)	185(16.0)	401(13.1)
Renal disease	4753(15.8)	121(10.3)	172(14.9)	544(17.8)
Schizophrenia	568(1.9)	30(2.6)	29(2.5)	58(1.9)
Medications, No. (%)				
ACE inhibitor	9128(30.3)	309(26.3)	305(26.4)	804(26.2)
Antidepressive agent	12,783(42.4)	518(44.0)	509(44.0)	1421(46.4)
Antidiabetic agent	6412(21.3)	240(20.4)	237(20.5)	645(21.1)
Antiepileptic agent	3424(11.3)	120(10.2)	164(14.2)	395(12.9)
Antihyperlipidemic non-statin	2088(6.9)	85(7.2)	78(6.7)	245(8.0)
Antihyperlipidemic statin	12,161(40.3)	480(40.8)	431(37.3)	1242(40.5)
Anti-infective agent	13,672(45.3)	492(41.8)	514(44.4)	1504(49.1)
Anti-Parkinson agent	1338(4.4)	77(6.5)	161(13.9)	337(11.0)
Antipsychotic agent	4450(14.7)	205(17.4)	257(22.2)	582(19.0)
β-Blocker	12,308(40.8)	424(36.1)	437(37.8)	1307(42.7)
Calcium channel blocker	8847(0.3)	285(0.2)	326(0.3)	932(0.3)
Loop diuretic	7176(23.8)	234(19.9)	265(22.9)	758(24.7)
Thiazide diuretic	3418(11.3)	121(10.3)	105(9.1)	298(9.7)

Abbreviations: ACE, angiotensin-converting-enzyme; ACS, acute coronary syndrome.

[a]We defined dosage level 1 as donepezil 5 mg, galantamine 4 mg, oral rivastigmine 3 mg, and transdermal rivastigmine 4.6 mg; dosage level 2 as donepezil 10 mg, galantamine 24 mg, oral rivastigmine 12 mg, and transdermal rivastigmine 9.5 mg; and dosage level 3 as donepezil > 10 mg, galantamine > 24 mg, oral rivastigmine > 12 mg, and transdermal rivastigmine > 9.5 mg.

Table 2

Cox Proportional Hazards Regression Model for Risk of Pneumonia Among New Users of Cholinesterase Inhibitors

Parameter	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Index medication		
Donepezil	1.00 [Reference]	1.00 [Reference]
Galantamine	0.76(0.52–1.10)	0.87(0.62–1.23)
Rivastigmine[a]	0.76(0.62–0.95)	0.75(0.60–0.93)
Oral rivastigmine	0.70(0.48–1.03)	0.61(0.41–0.89)
Transdermal rivastigmine	0.85(0.65–1.11)	0.85(0.66–1.10)
Age (per 1 year)	1.03(1.02–1.03)	1.03(1.02–1.03)
White race	1.02(0.89–1.17)	1.04(0.91–1.20)
Male sex	1.39(1.24–1.56)	1.59(1.43–1.78)
Last prescription before end of follow-up[b]		
Dosage level 1	1.00 [Reference]	1.00 [Reference]
Dosage level 2	0.38(0.09–1.52)	0.94(0.85–1.04)
Dosage level 3	0.89(0.80–0.99)	0.44(0.11–1.79)
Parkinson disease or Lewy body disease	1.16(0.97–1.40)	1.15(0.92–1.44)
History of pneumonia	3.21(2.87–3.60)	1.66(1.46–1.88)
Health service use		
Hospital admission	1.34(1.30–1.38)	1.13(1.08–1.18)
Outpatient clinic visit	1.00(1.00–1.01)	1.00(0.99–1.00)
Emergency department visit	1.02(1.02–1.02)	1.00(1.00–1.01)
Skilled nursing facility admission	1.85(1.67–2.06)	0.93(0.82–1.05)
Prescription	1.01(1.01–1.01)	1.00(1.00–1.01)
Comorbid conditions		
Arrhythmia	1.54(1.38–1.71)	0.99(0.89–1.11)
Cancer	1.02(0.87–1.20)	0.87(0.75–1.01)
Cerebrovascular disease	1.21(1.09–1.34)	0.92(0.82–1.02)
Chronic obstructive pulmonary disease	2.53(2.28–2.81)	1.72(1.54–1.91)
Depression	1.21(1.08–1.36)	0.89(0.78–1.01)
Diabetes mellitus	1.21(1.09–1.34)	0.94(0.81–1.09)
Dyslipidemia	0.76(0.68–0.84)	0.79(0.71–0.88)
Heart failure	2.16(1.95–2.41)	1.20(1.07–1.35)
Hypertension	1.37(1.17–1.60)	0.97(0.83–1.14)
Liver disease	1.32(1.05–1.66)	1.07(0.86–1.33)
Mood disorder	1.21(1.05–1.41)	0.88(0.75–1.02)
Myocardial infarction or ACS	1.54(1.33–1.79)	0.95(0.81–1.10)
Renal disease	1.67(1.47–1.89)	0.97(0.85–1.11)
Schizophrenia	1.16(0.84–1.61)	0.91(0.66–1.26)
Medications		
ACE inhibitor	1.00(0.89–1.12)	0.90(0.80–1.00)

Parameter	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Antidepressive agent	1.43(1.28–1.58)	1.19(1.06–1.33)
Antidiabetic agent	1.23(1.09–1.38)	1.14(0.97–1.35)
Antiepileptic agent	1.52(1.32–1.75)	1.15(1.00–1.32)
Antihyperlipidemic non-statin	0.84(0.67–1.05)	0.85(0.68–1.07)
Antihyperlipidemic statin	0.85(0.77–0.95)	0.98(0.86–1.11)
Anti-infective agent	1.63(1.47–1.81)	1.21(1.08–1.34)
Anti-Parkinson agent	1.05(0.84–1.31)	0.83(0.63–1.10)
Antipsychotic agent	1.49(1.32–1.68)	1.13(1.00–1.28)
β-Blocker	1.06(0.95–1.17)	0.87(0.78–0.97)
Calcium channel blocker	1.21(1.09–1.36)	1.06(0.95–1.19)
Loop diuretic	1.78(1.60–1.98)	1.14(1.01–1.29)
Thiazide diuretic	0.97(0.82–1.15)	1.07(0.91–1.25)

Abbreviations: ACS, acute coronary syndrome; ACE, angiotensin-converting-enzyme; HR, hazard ratio.

[a] We separated the use of rivastigmine by formulations and repeated the analysis.

[b] We defined dosage level 1 as donepezil 5 mg, galantamine 4 mg, oral rivastigmine 3 mg, and transdermal rivastigmine 4.6 mg; dosage level 2 as donepezil 10 mg, galantamine 24 mg, oral rivastigmine 12 mg, and transdermal rivastigmine 9.5 mg; and dosage level 3 as donepezil > 10 mg, galantamine > 24 mg, oral rivastigmine > 12 mg, and transdermal rivastigmine > 9.5 mg.