Risk Profile of Cardiac Arrhythmic Events Associated with Cognitive Enhancers in Dementia Patients

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This Certifies that the Master's Thesis of Choi, Yujin is Approved

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Acknowledgement

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가장 먼저, 지도교수인 윤덕용 교수님께 깊은 감사를 전합니다. 교수님의 지도 아래 학문적 지식뿐만 아니라 학문적 태도와 시야까지 배울 수 있었습니다. 바쁘신 일정 속에서도 귀중한 가르침과 따뜻한 격려를 보내주신 김우정 교수님, 최남경 교수님께도 감사드립니다.

무엇보다도, 학위과정에서 만난 연구실 동료들은 가장 소중한 인연이자 든든한 힘이었습니다. 항상 따뜻하게 도움을 주신 찬민쌤, 송수쌤, 창호쌤, 지훈쌤, 재웅쌤, 수연쌤, 인영쌤께 감사의 마음을 전합니다. 각자의 맑은 색으로 연구실 추억을 다채롭게 꾸며준 경빈이, 지안 언니, 유지, 희연이에게도 애정을 담아 고마움을 전합니다. 제가 귀찮게 해도 언제나 기꺼이 도와주셨던 동원쌤과, 그리고 제 연구실 생활의 롤모델이자, 가장 존경하는 유정쌤께 말로 다 전하기 어려운 깊은 감사함의 마음을 전합니다.

또한 오랜 기간 동안 저보다 저를 더 믿어 주고 응원해 준 오랜 친구들에게도 고마움을 전합니다. 그들이 저의 활력소가 되어주었기에, 지치지 않을 수 있었습니다.

마지막으로, 늘 믿음과 지지, 응원을 보내주신 사랑하는 가족에게도 평소에 전하지 못했던 마음을 전합니다. 제 인생의 가장 큰 행운이 되어주셔서 감사합니다.

배움의 과정에서 만난 모든 이에게 다시 한번 감사의 마음을 전합니다. 이곳에서 배운 것을 바탕으로 더욱 성장할 수 있도록 노력하겠습니다.

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ABSTRACT

Risk Profile of Cardiac Arrhythmic Events Associated with Cognitive Enhancers in Dementia Patients

Dementia is a progressive neurodegenerative condition marked by cognitive decline and functional impairment, posing a substantial public health burden with over 50 million cases globally. Cognitive enhancers—including cholinesterase inhibitors (ChEIs: donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine—are widely used to manage symptoms. However, ChEIs have been implicated in cardiac arrhythmias such as bradycardia, QT prolongation, and atrial fibrillation (AFib), likely due to their enhancement of cholinergic transmission and vagal tone. These risks are particularly concerning for elderly patients with dementia, who are more susceptible to conduction abnormalities and their clinical consequences. Despite these known risks, routine electrocardiogram (ECG) monitoring before or during treatment is uncommon in clinical settings. Prior evidence from randomized controlled trials (RCTs) is limited by exclusion of patients with cardiovascular comorbidities or polypharmacy, limiting generalizability. Real-world data is needed to better characterize arrhythmic risk across drug classes, dosage levels, and patient subgroups.

This study aimed to assess the risk of three major cardiac arrhythmic events—bradycardia, QT prolongation, and AFib—identified through ECG records in electronic medical records (EMRs) among users of cognitive enhancers. Specifically, it employed two complementary analytical approaches: (1) a between-subject retrospective cohort design comparing the arrhythmic risk of ChEIs with memantine as the reference; and (2) a within-subject self-controlled risk interval (SCRI) design comparing arrhythmic event rates before and after ChEI initiation, thereby controlling for time-invariant confounders. The study also evaluated dose-response relationships and variations in risk across patient subgroups, stratifying patients by age, sex, baseline cardiovascular comorbidities, and baseline chronotropic medication use using the two study design methods described above.

The study population was derived from Severance Hospital EMRs database, comprising 8,354

patients in the cohort design and 3,364 patients in the SCRI analysis. ChEI use, especially donepezil, was significantly associated with increased bradycardia risk compared to memantine (donepezil HR=1.75, 95% CI: 1.39–2.21; IRR=1.54, 95% CI: 1.39–1.74). Donepezil was also significantly associated with QT prolongation (HR=1.25, 95% CI: 1.02–1.49; IRR=1.46, 95% CI: 1.30–1.61). AFib risk showed no consistent association across drug groups in cohort analyses and SCRI. Dose-response analyses indicated higher bradycardia and QT prolongation risks at increased donepezil doses. Subgroup analysis revealed risk was higher among subgroups with older age, baseline cardiovascular comorbidities, and baseline chronotropic medication use.

By combining between-subject (cohort) comparisons and within-subject (SCRI) analyses, this research provides robust evidence of the arrhythmic risks associated with ChEI use. These findings highlight the importance of individualized cardiovascular risk assessment, routine ECG monitoring before and during treatment, and careful dose titration to improve the safety of dementia pharmacotherapy. Based on these results, this study can also serve as a foundation for developing patient-specific prescribing and safety monitoring strategies to further enhance the safety of dementia treatment.

Key words: Cognitive Enhancers, Cholinesterase Inhibitors, Electrocardiogram, Bradycardia, QT Prolongation, Atrial Fibrillation, Arrhythmia, Real-world Data

1. Introduction

1.1. Background and significance of the research

Dementia is a progressive neurodegenerative disorder characterized by declining cognitive functions, including memory, reasoning, and daily activities. As of 2019, an estimated 50 million individuals worldwide were affected by dementia, with the number expected to rise due to aging populations. This condition poses a significant global health burden, with estimated economic costs reaching approximately $1.3 trillion annually [1]. Pharmacological management of dementia focuses on alleviating cognitive symptoms and maintaining functional independence, with cognitive enhancers playing a key role in clinical practice.

Currently, the most widely approved and clinically used symptomatic treatments for dementia-related cognitive impairment include three cholinesterase inhibitors (ChEIs)—donepezil, rivastigmine, and galantamine—and one N-methyl-D-aspartate (NMDA) receptor antagonist, memantine. Among these, rivastigmine and galantamine are approved for mild to moderate dementia, donepezil for all stages, and memantine for moderate to severe stages. In clinical practice, combination therapy with a ChEI and memantine is frequently prescribed in later stages of the disease, with some evidence suggesting modest benefits over monotherapy [2, 3].

While these agents are effective in improving cognitive symptoms, concerns have emerged regarding their potential to induce cardiovascular events, particularly arrhythmias such as bradycardia, QT prolongation, and atrial fibrillation (AFib) [4, 5]. The arrhythmic risks are especially associated with ChEIs, which enhance cholinergic transmission and may increase vagal tone—potentially leading to suppression of sinoatrial (SA) or atrioventricular (AV) nodal activity. Due to this pharmacologic mechanism, ChEIs have been linked to clinically significant conduction abnormalities [6]. In contrast, memantine acts by modulating glutamatergic neurotransmission through NMDA receptor antagonism. Since NMDA receptors play a minimal role in cardiac electrophysiology, memantine is generally considered to have a lower arrhythmic risk compared to ChEIs [7].

These cardiac risks are of particular concern in elderly dementia patients, who are inherently more vulnerable due to age-related impairments in autonomic regulation and higher baseline susceptibility to conduction disturbances. In such patients, even minor disruptions in cardiac rhythm can lead to serious outcomes such as syncope, falls, or hospitalization, further worsening the overall disease burden and increasing morbidity.

Despite the known risks, routine electrocardiogram (ECG) monitoring—both before and during treatment—remains uncommon in clinical practice. This lack of cardiac assessment may lead to underrecognition of drug-induced arrhythmias, especially among high-risk individuals. Moreover, ChEIs are often prescribed early in the disease course and continued for prolonged periods, increasing the cumulative risk over time. Combination therapy adds further complexity, yet direct comparisons of cardiovascular risk across different treatment strategies are limited.

Additionally, existing safety evaluations are largely derived from randomized controlled trials (RCTs), which frequently exclude patients with cardiovascular comorbidities or polypharmacy [8]. These limitations reduce the generalizability of trial findings to broader dementia populations. Real-world data are therefore needed to enable more accurate stratification of arrhythmic risk across different drug regimens and patient subgroups.

To address these gaps, this study aims to construct a detailed arrhythmic risk profile of cognitive enhancers using real-world data, comparing monotherapy and combination therapy across diverse patient subgroups. By identifying risk factors and characterizing the incidence of bradycardia, QT prolongation, and AFib, this research seeks to inform personalized treatment strategies and proactive monitoring frameworks that enhance the safety of dementia pharmacotherapy in clinical settings.

1.2. Related Studies: Cardiovascular Risks of ChEIs and Memantine

Numerous studies have investigated the potential cardiovascular risks associated with ChEIs in patients with dementia. A systematic review and meta-analysis evaluating 22 longitudinal studies and 9 comparator-based cohort studies reported a significantly increased incidence of bradycardia among users of ChEIs in longitudinal designs (2%, 95% CI = 1–6%, I^2 = 98%), whereas this association was not statistically significant in cohort studies (HR = 1.40, 95% CI = 0.76–2.59, I^2 = 98%) [2]. The discrepancy highlights substantial heterogeneity, suggesting that differences in study design and patient selection may influence observed outcomes.

Two large population-based cohort studies further explored real-world cardiovascular effects. Gill et al. (2009) reported increased risks of syncope (adjusted HR = 1.76), bradycardia, falls, and pacemaker insertion among ChEI users compared to non-users [3]. Similarly, Hernandez et al. (2009) observed a dose-dependent relationship between ChEI use and bradycardia, with high-dose donepezil users showing the highest risk (adjusted HR = 2.1) [4].

Although memantine's direct cardiac effects have not been thoroughly characterized, available studies suggest a comparatively lower incidence of cardiovascular events, with fewer reports of bradycardia or conduction abnormalities compared to ChEIs [5, 6]. San-Juan-Rodriguez et al. (2019) reported memantine was associated with a lower rate of cardiovascular events compared to ChEI monotherapy or combination therapy. They found no significant difference in cardiovascular event rates between donepezil and rivastigmine, but observed slightly elevated risks particularly with galantamine, whereas memantine maintained relatively lower risks compared to ChEIs [7]. Similarly, Fosbøl et al. (2012) found that ChEIs shared comparable cardiovascular risks, while memantine consistently showed lower adverse event risk [6]. However, both studies were limited in adjusting for clinical variables such as age, comorbidities, and polypharmacy.

Although the existing literature highlights the potential cardiovascular risks of cognitive enhancers, it remains methodologically limited. Most studies adopt a single study design, particularly cohort studies, which are vulnerable to selection bias and often lack comparisons between pre- and post-treatment periods. Furthermore, few studies have evaluated multiple arrhythmia subtypes or conducted subgroup analyses based on clinically meaningful patient

characteristics.

To overcome these limitations, comprehensive comparative evaluations employing both between-subject (cohort) and within-subject (self-controlled) designs are warranted. This approach will facilitate refined, patient-specific arrhythmic risk profiles and support safer, more individualized prescribing strategies in dementia care.

1.3. The objective of the study

This study aims to quantify the risk of arrhythmic events in dementia patients treated with cognitive enhancers. Specifically, it seeks to determine the relative risks of three clinically significant arrhythmias — bradycardia, QT prolongation, and AFib — associated with different cognitive enhancers, as detected through 12-lead electrocardiogram (ECG) monitoring.

Additionally, this study examines dose-response relationships and assesses variations in arrhythmic risk across patient subgroups defined by age, sex, comorbidities, and concomitant medications.

To achieve these objectives, two observational study designs are employed: a between-subject retrospective cohort design to estimate relative arrhythmic risks across drug classes, and a within-subject Self-Controlled Risk Interval (SCRI) design to evaluate short-term risk elevations following treatment initiation, inherently controlling for time-invariant confounding factors [9].

This comprehensive analytical approach enables the construction of detailed arrhythmic risk profiles across drug types, dosages, and patient characteristics. These findings will help inform safer and more individualized prescribing practices in dementia care.

2. Methods

2.1. Data source & study population

This retrospective observational study was conducted using electronic medical records (EMRs) from Severance Hospital (Sinchon and Yongin campuses) in South Korea. The study cohort comprised patients aged 60 years or older who received a clinical diagnosis of dementia between January 2004 and December 2022 and were prescribed at least one cognitive enhancer—donepezil, rivastigmine, galantamine, or memantine.

Dementia diagnoses were identified using the International Classification of Diseases, 10th Revision (ICD-10) codes, including F00.0, F00.1, F00.2, F00.9, F01, F02, F03, F06.7, F10.6, G30.0, G30.1, G30.8, G30.9, G31.00, G31.1, and G31.82. Eligible patients were also required to have at least one 12-lead electrocardiogram (ECG) recorded after treatment initiation.

Patients were excluded if they had a history of major cardiac interventions (e.g., pacemaker implantation, defibrillator placement, cardiac valve surgery) prior to their first cognitive enhancer prescription, received cognitive enhancers for fewer than 14 days, or had invalid ECG results, identified by diagnostic terms such as “expired” or “cannot analyze” in the MUSE system.

For all patients who met the inclusion and exclusion criteria, data on medication prescriptions, diagnosis codes, and ECG parameters were retrieved from structured EMRs encompassing both inpatient and outpatient encounters. The study protocol was approved by the Institutional Review Board (IRB) of Severance Hospital, and all data were de-identified before analysis to protect patient confidentiality.

2.2. Exposure

Patients were categorized into seven treatment groups based on their initial cognitive enhancer: donepezil, donepezil + memantine, rivastigmine, rivastigmine + memantine, galantamine, galantamine + memantine, and memantine. This classification allowed for assessment of individual ChEI risks, as well as potential additive or synergistic effects when used in combination with memantine, accounting for possible drug-drug interactions and clinical practice patterns [10, 11].

Monotherapy groups were defined as patients who were prescribed one of the four cognitive enhancers (donepezil, rivastigmine, galantamine, or memantine) and used it for at least 14 days. The index date for monotherapy was defined as the date of the first prescription of the respective drug.

Combination therapy was defined as concurrent use of a ChEI (donepezil, rivastigmine, or galantamine) and memantine for 14 or more days within the first 60 days after therapy initiation [7]. For these patients, the index date was defined as the first day with an overlapping supply of ChEIs and memantine.

Cognitive enhancer exposure data were extracted from prescription records, including dispensing dates and days of supply. Discontinuation was defined as a gap of 60 days or more following the end of a prescription's days of supply.

For dose-response analyses, each patient was categorized according to the maximum prescribed daily dose prior to any arrhythmic event, as outlined in Table 1. In the case of combination therapy, dose classification was based on the concurrently prescribed ChEI dose.

Table 1. Daily Dose Categories for Cognitive Enhancers

	Donepezil [12]	Rivastigmine [13]	Galantamine [14]	Memantine [15]
Low	≤ 5 mg/day	≤ 1.5 mg/day (oral) ≤ 9 mg/day (patch)	≤ 8 mg/day	≤ 5 mg/day
Medium	7.5–10 mg/day	≤ 9 mg/day (oral) ≤ 18 mg/day (patch)	≤ 16 mg/day	≤ 10 mg/day
High	15–23 mg/day	~12 mg/day (oral) ≤ 27 mg/day (patch)	≤ 24 mg/day	≤ 20 mg/day

2.3. Outcome

Three arrhythmic events were evaluated in this study using serial ECG recordings documented in the EMRs: bradycardia, QT prolongation, and atrial fibrillation (AFib). Bradycardia was defined as a heart rate below 60 beats per minute [16], based on atrial or ventricular rate measurements from standard 12-lead ECGs. QT prolongation was defined as a corrected QT interval (QTc) ≥450 ms in men and ≥460 ms in women [17], calculated using Bazett's formula by the automated MUSE ECG system. AFib was defined by the automated detection of the term "Atrial Fibrillation" in the automated diagnosis text generated by the MUSE ECG system.

To assess potential diagnostic access bias, the frequency of ECG testing per patient was evaluated and compared across each treatment group.

2.4. Covariates

Baseline characteristics included demographic variables, baseline comorbidities, and baseline medication use. These variables were also used as covariates in the main analyses to adjust for potential confounding.

Baseline comorbidities were identified based on diagnosis codes recorded within three years prior to the index date and included angina pectoris, cancer, depression, diabetes mellitus, chronic heart disease, coronary artery disease, heart failure, myocardial infarction, and stroke, as these represent chronic conditions routinely recorded in EMRs (Table 2). Baseline medications were defined as prescriptions filled within six months prior to the index date for drug classes known to affect cardiac electrophysiology, such as beta-blockers, calcium-channel blockers, and antipsychotics (Table 3). These baseline medications were included to characterize patients' underlying cardiovascular risk at treatment initiation and to aid in adjusting for differences in baseline propensity for arrhythmias [18, 19].

In subgroup analyses, patients were stratified by sex, age group, dose category, presence of any baseline cardiovascular comorbidity, and use of any baseline medication with chronotropic effects. These subgroup analyses aimed to evaluate whether certain patient characteristics indicating higher baseline cardiovascular vulnerability were associated with greater arrhythmic risk when using cognitive enhancers. For each stratified analysis, the corresponding stratification variable was excluded from covariate adjustment to avoid overcontrol.

Table 2. Comorbidities. Comorbidities were defined based on diagnoses recorded within 3 years prior to the index date.

Comorbidity	ICD-10 Codes
Angina pectoris	I20.x
Cancer	C00–C97
Depression	F32.x, F33.x
Diabetes Mellitus	E10–E14
Chronic heart disease	I11, I25, I42, I43, I50
Coronary artery disease	I25.x
Heart failure	I50.x
Myocardial infarction	I21.x, I22.x
Stroke	I60–I64

Table 3. Baseline Medications. Baseline medication use was defined as the prescription of the following drugs within 6 months prior to the index date.

Medication Class	Drugs
Antiarrhythmics	Amiodarone, Flecainide, Propafenone, Sotalol, Mexiletine, Dronedarone, Quinidine, Disopyramide
Antipsychotics	Haloperidol, Risperidone, Olanzapine, Quetiapine, Aripiprazole, Clozapine
Beta-blockers	Atenolol, Metoprolol, Bisoprolol, Carvedilol, Propranolol, Esmolol, Nebivolol
Calcium Channel Blockers	Diltiazem, Verapamil, Amlodipine, Nifedipine, Felodipine, Nicardipine
Cardiac Glycosides	Digoxin

2.5. Statistical Analysis

2.5.1. Overview of study design

This study employed both between-subject and within-subject analytical approaches to evaluate the association between cognitive enhancer use and cardiac arrhythmic events. The between-subject analysis used a retrospective cohort design to compare the incidence of arrhythmic events across treatment groups. Complementarily, in the within-subject analysis, a self-controlled risk interval (SCRI) design was implemented to compare event incidence before and after treatment initiation within the same individuals.

The cohort analysis enabled direct comparisons across treatment groups using time-to-event methods. In contrast, the SCRI design inherently adjusted for all time-invariant individual-level confounders by comparing individuals to themselves over time.

Baseline comparability between treatment groups was assessed using standardized mean differences (SMDs) and p-values, with an SMD < 0.1 and $p \geq 0.05$ considered indicative of negligible imbalance [20].

2.5.2. Cohort Study

To estimate the relative risk of arrhythmic events across cognitive enhancers, a retrospective cohort analysis was conducted using Cox proportional hazards regression. Patients with prior arrhythmic events were not excluded to reflect real-world prescribing patterns and maintain generalizability, avoiding selection bias that could arise from excluding higher-risk individuals [21]. Additionally, patients with existing cardiovascular comorbidities or a history of using medications with chronic cardiovascular effects were retained to enable subgroup analyses assessing whether baseline CV risk modifies the association between cognitive enhancer use and arrhythmic events. The primary objective was to compare the incidence of bradycardia, QT prolongation, and AFib among treatment groups, using memantine as the reference (Figure 1).

Follow-up began on the index date and continued until the first occurrence of a arrhythmic event, treatment discontinuation (defined as a gap of ≥60 days in medication supply), or the end of the study period, whichever came first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with adjustment for age, sex, baseline comorbidities, and baseline medication use.

An HR greater than 1 indicated increased risk relative to memantine, and an HR less than 1 indicated decreased risk. The proportional hazards assumption was verified and met in all models.

To account for multiple comparisons across the six treatment groups, the significance threshold was adjusted using the Bonferroni correction [7]. Since each of the six treatment groups was individually compared to memantine, the conventional alpha level of 0.05 was divided by 6, yielding a corrected significance threshold of $p < 0.0083$.

2.5.3. Self-controlled risk interval (SCRI)

To complement the cohort analysis and address residual confounding, a self-controlled risk interval (SCRI) design was employed. As a within-subject analytical approach, SCRI compares risk and control periods within the same individual, thereby minimizing confounding by stable patient characteristics such as demographics, baseline comorbidities, and genetic predisposition.[22, 23]. This design enables a more robust assessment of temporal associations between cognitive enhancer initiation and arrhythmic events, independent of between-person variability.

The SCRI analysis was conducted separately for each arrhythmic event (i.e., bradycardia, AFib, and QT prolongation), and included patients who met the following criteria for the respective event: (1) ECG measurements were recorded both within 12-week periods before and after index date; and (2) at least one corresponding arrhythmic event was detected in either period [23].

SCRI designs can define control periods either before or after exposure, or use bidirectional approaches, to minimize time-varying confounding [22]. However, cognitive enhancers like cholinesterase inhibitors are administered continuously over long durations, leaving little or no unexposed time for a post-exposure control period. Furthermore, ECG monitoring after exposure discontinuation is uncommon, with our dataset showing that ECG records were predominantly clustered around cognitive enhancer initiation. As a result, arrhythmic events would likely go undetected in the period after discontinuation, making the post-exposure control period unsuitable for SCRI in this study.

A symmetric 12-week window was applied for control (weeks –12 to 0) and risk periods (weeks 1 to 12), reflecting a clinically relevant timeframe commonly applied in epidemiologic research [19, 24, 25]. This design helped mitigate potential bias due to non-uniform ECG testing around the time of treatment initiation (Figure 2).

Incidence rate ratios (IRRs) and corresponding 95% confidence intervals were estimated using conditional Poisson regression models. IRRs greater than 1 indicated a higher incidence during the risk period, whereas values less than 1 indicated a lower incidence compared to the control period.

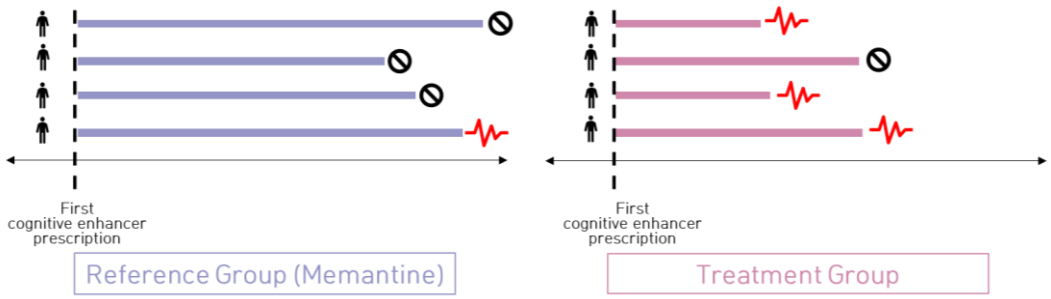

Figure 1. Cohort study design. Conceptual diagram comparing treatment (ChEIs) and reference (memantine) groups. Red ECG symbols indicate arrhythmic events; prohibition signs mark the end of follow-up due to treatment discontinuation or loss to observation.

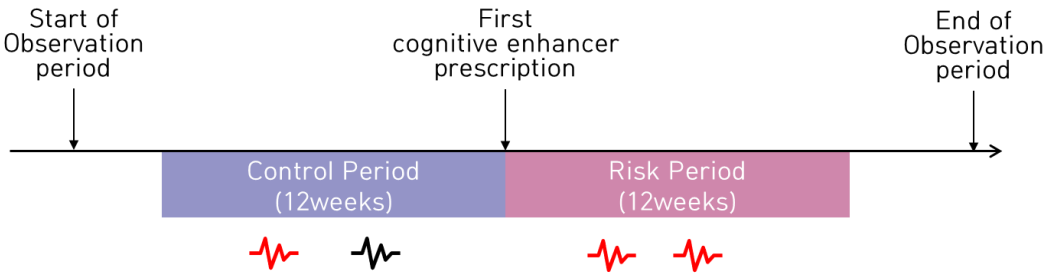

Figure 2. Self-controlled risk interval (SCRI) study design. Conceptual diagram showing fixed 12-week control and risk periods within individuals. Red ECG symbols indicate arrhythmic events observed during each period, illustrating within-person comparison of event incidence before and after exposure.

2.6. Subgroup Analysis

Additional stratified analyses were performed to assess dose-response relationships and identify high-risk patient subgroups. Both cohort and SCRI designs were applied.

To ensure adequate sample size and statistical power, all ChEIs were grouped as a single exposure category in subgroup analyses, reducing small strata and avoiding unstable HR and IRR estimates.

2.6.1. Risk of arrhythmic events by dose level

To evaluate whether higher ChEI doses are associated with increased risk of arrhythmic events, we performed stratified analyses of event incidence by dose level. Patients were categorized into low, medium, or high dose groups based on their maximum prescribed daily dose prior to the first detected cardiac arrhythmic event. For combination therapy cases, dose classification was determined based on the ChEI component. In the cohort analysis, memantine (any dose) served as the reference group.

2.6.2. Risk of arrhythmic events by patient subgroups

Subgroup analyses were conducted to identify high-risk patient subgroups by comparing arrhythmic event risk across categories of age, sex, cardiovascular comorbidities, and baseline medications with chronotropic effects. Age groups included patients in their 60s, 70s, and ≥80 years. Cardiovascular comorbidities included coronary artery disease, chronic heart disease, heart failure, myocardial infarction, or stroke. Chronotropic medications included beta-blockers, calcium channel blockers, antipsychotics, and cardiac glycosides. In the cohort analysis, memantine served as the reference group.

3. Results

3.1. Patient characteristics

A total of 15,561 patients aged 60 years or older who were prescribed at least one cognitive enhancer prescription (donepezil, rivastigmine, galantamine, or memantine) between 2004 and 2022 at Severance Hospital (Sinchon and Yongin campuses) and had at least one ECG measurement were initially identified.

Patients were excluded if they had a history of major cardiac procedures (e.g., pacemaker implantation, defibrillator placement, cardiac valve surgery), received cognitive enhancers for fewer than 14 days, or had invalid ECG results, identified by diagnostic terms such as “expired” or “cannot analyze” in the MUSE system.

After applying these exclusion criteria, the final study cohort consisted of 8,354 patients with at least one valid ECG measurement after cognitive enhancer initiation and no documented history of cardiac surgery. Among them, 3,364 patients who had ECG records available in both the 12-week periods before and after treatment initiation were additionally included in the self-controlled risk interval (SCRI) analysis.

Patients were categorized into seven treatment groups based on initial cognitive enhancer exposure: donepezil, donepezil + memantine, rivastigmine, rivastigmine + memantine, galantamine, galantamine + memantine, and memantine. The distribution of patients across these groups is illustrated in Figure 3.

Baseline characteristics are summarized in Table 4. Comparisons were performed using the memantine group as the reference. Compared to other groups, the memantine group exhibited higher baseline proportions of chronic heart disease, calcium channel blocker use, and antipsychotic medication use.

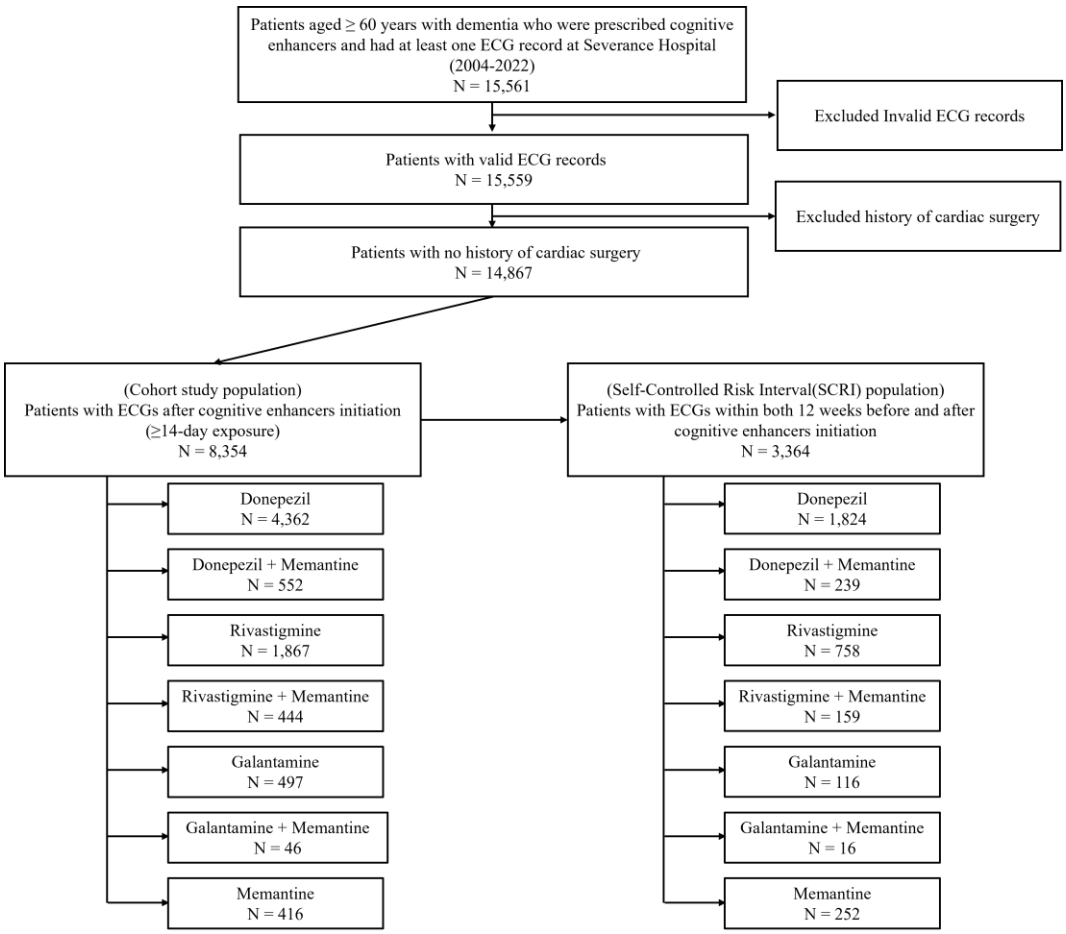

Figure 3. Selection of the Study Sample

Table 4. Baseline characteristics of patients by treatment group. P-values and SMDs are calculated for pairwise comparisons with the memantine group as the reference.

Variable	Memantine (Reference)	Donepezil			Donepezil + Memantine			Rivastigmine			Rivastigmine + Memantine			Galantamine			Galantamine + Memantine		
	(N=416)	(N=4632)	SMD	p	(N=552)	SMD	p	(N=1867)	SMD	p	(N=444)	SMD	p	(N=497)	SMD	p	(N=46)	SMD	p
Demographic																			
Age at index, mean (SD)	68.9 (17.1)	71.9 (14.1)	0.191	<.05	73.8 (13.7)	0.316	<.05	73.9 (11.4)	0.344	<.05	69.6 (11.6)	0.048	0.49	68.6 (14.8)	0.019	0.7889	75.3 (12.5)	0.427	<.05
Male (%)	220 (52.9)	2179 (47.0)	0.117	<.05	275 (49.8)	0.061	0.38	912 (48.8)	0.081	0.15	202 (45.5)	0.148	<.05	197 (49.6)	0.065	0.3897	13 (28.3)	0.501	<.05
Dementia Type N,(%)																			
AD	292 (70.2)	2233 (48.2)	0.447	<.05	333 (60.3)	0.207	<.05	1079 (57.8)	0.258	<.05	279 (62.8)	0.156	<.05	215 (54.2)	0.331	<.05	25 (54.3)	0.327	<.05
Lewy body dementia	7 (1.7)	28 (0.6)	0.101	<.05	6 (1.1)	0.051	0.60	73 (3.9)	0.13	<.05	11 (2.5)	0.056	0.56	2 (0.5)	0.113	0.21	0 (0.0)	0.184	0.80
Mild cognitive disorder	23 (5.5)	366 (7.9)	0.095	0.10	38 (6.9)	0.056	0.47	162 (8.7)	0.123	<.05	26 (5.9)	0.014	0.95	20 (5.0)	0.022	0.88	2 (4.3)	0.055	>.99
Unspecified dementia	69 (16.6)	1028 (22.2)	0.142	<.05	97 (17.6)	0.026	0.75	355 (19.0)	0.063	0.28	82 (18.5)	0.049	0.53	146 (36.8)	0.456	<.05	14 (30.4)	0.327	<.05
Vascular dementia	24 (5.8)	959 (20.7)	0.441	<.05	73 (13.2)	0.254	<.05	56 (3.0)	0.135	<.05	26 (5.9)	0.004	>.99	14 (3.5)	0.107	0.18	5 (10.9)	0.185	<.05
Other dementia	4 (1.0)	19 (0.4)	0.067	0.22	5 (0.9)	0.006	0.99	144 (7.7)	0.331	<.05	20 (4.5)	0.217	<.05	0 (0.0)	0.139	0.14	0 (0.0)	0.139	>.99
Comorbidities N(%)																			
Angina pectoris	40 (9.6)	551 (11.9)	0.074	0.19	63 (11.4)	0.059	0.43	261 (14.0)	0.135	<.05	60 (13.5)	0.122	0.09	27 (6.8)	0.103	0.18	3 (6.5)	0.114	0.67
Cancer	87 (20.9)	699 (15.1)	0.152	<.05	62 (11.2)	0.264	<.05	310 (16.6)	0.11	<.05	62 (14.0)	0.183	<.05	63 (15.9)	0.13	0.08	5 (10.9)	0.275	0.15
Depression	115 (27.6)	1195 (25.8)	0.042	0.44	146 (26.4)	0.027	0.73	379 (20.3)	0.172	<.05	88 (19.8)	0.184	<.05	69 (17.4)	0.246	<.05	9 (19.6)	0.19	0.32
Diabetes Mellitus	155 (37.3)	1654 (35.7)	0.032	0.56	205 (37.1)	0.003	0.99	728 (39.0)	0.036	0.55	151 (34.0)	0.068	0.36	108 (27.2)	0.215	<.05	14 (30.4)	0.144	0.45
CV Comorbidities N(%)																			
Chronic heart disease	37 (8.9)	69 (1.5)	0.334	<.05	10 (1.8)	0.315	<.05	26 (1.4)	0.34	<.05	4 (0.9)	0.37	<.05	4 (1.0)	0.364	<.05	1 (2.2)	0.294	0.20
Coronary artery disease	53 (12.7)	565 (12.2)	0.016	0.80	59 (10.7)	0.064	0.38	250 (13.4)	0.019	0.78	60 (13.5)	0.023	0.81	28 (7.1)	0.19	<.05	3 (6.5)	0.211	0.32
Heart failure	50 (12.0)	361 (7.8)	0.141	<.05	51 (9.2)	0.09	0.20	170 (9.1)	0.095	0.08	30 (6.8)	0.18	0.01	14 (3.5)	0.317	<.05	3 (6.5)	0.19	0.39
Myocardial infarction	10 (2.4)	69 (1.5)	0.066	0.22	7 (1.3)	0.085	0.28	71 (3.8)	0.081	0.22	5 (1.1)	0.097	0.24	9 (2.3)	0.009	0.99	0 (0.0)	0.221	0.60
Stroke	66 (15.9)	926 (20.0)	0.108	<.05	83 (15.0)	0.023	0.79	235 (12.6)	0.094	0.09	64 (14.4)	0.04	0.62	79 (19.9)	0.105	0.16	7 (15.2)	0.018	0.99
Baseline Medication N(%)																			
Antiarrhythmics	8 (1.9)	37 (0.8)	0.097	<.05	4 (0.7)	0.105	0.17	15 (0.8)	0.097	0.07	4 (0.9)	0.087	0.32	0 (0.0)	0.197	<.05	1 (2.2)	0.018	0.99
Antipsychotics	149 (35.8)	862 (18.6)	0.387	<.05	109 (19.7)	0.359	<.05	329 (17.6)	0.411	<.05	81 (18.2)	0.396	<.05	56 (14.1)	0.502	<.05	6 (13.0)	0.53	<.05
Beta-blockers	89 (21.4)	982 (21.2)	0.005	0.976	94 (17.0)	0.111	0.10	351 (18.8)	0.065	0.25	68 (15.3)	0.157	<.05	67 (16.9)	0.115	0.12	7 (15.2)	0.16	0.43
Calcium Channel Blockers	166 (39.9)	1538 (33.2)	0.139	<.05	171 (31.0)	0.187	<.05	562 (30.1)	0.206	<.05	134 (30.2)	0.204	<.05	118 (29.7)	0.214	<.05	14 (30.4)	0.198	0.28
Cardiac Glycosides	7 (1.7)	56 (1.2)	0.04	0.55	9 (1.6)	0.004	0.99	19 (1.0)	0.058	0.37	4 (0.9)	0.069	0.47	8 (2.0)	0.025	0.93	1 (2.2)	0.036	0.99

3.2. Risk of arrhythmic events by type of cognitive enhancer

Table 5 and Figure 4 summarize the comparative risks of bradycardia, QT prolongation, and AFib across six treatment groups. Adjusted hazard ratios (HRs) were estimated from the retrospective cohort analysis, while incidence rate ratios (IRRs) were derived from the self-controlled risk interval (SCRI) design. All between-subject comparisons used the memantine monotherapy group as the reference.

Bradycardia

Donepezil was associated with the highest risk of bradycardia, showing statistically significant results in both the cohort (HR = 1.75, 95% CI: 1.39–2.21) and SCRI design (IRR = 1.54, 95% CI: 1.39–1.74).

Galantamine (HR = 1.39, 95% CI: 1.12–1.89) and galantamine + memantine (HR = 2.18, 95% CI: 1.27–3.87) also showed elevated risks in the cohort analysis. Corresponding IRRs from the SCRI analysis for galantamine (IRR = 1.14, 95% CI: 0.70–1.80) and galantamine + memantine (IRR = 1.30, 95% CI: 0.29–5.67) showed a similar increasing trend, although their confidence intervals included unity, indicating no statistical significance in the within-subject comparisons.

When all ChEI users were combined, a consistently elevated bradycardia risk was observed (HR = 1.51, 95% CI: 1.36–1.67; IRR = 1.39, 95% CI: 1.26–1.54), confirming increased risk with ChEI exposure, particularly for donepezil and galantamine.

AFib

AFib risk results were inconsistent across study designs and drug groups. The SCRI analysis revealed a significantly increased AFib risk associated with rivastigmine (IRR = 1.52, 95% CI: 1.12–1.87), while the cohort analysis showed no significant associations.

In contrast, galantamine appeared protective in the SCRI analysis (IRR = 0.31, 95% CI: 0.12–0.85). For most groups, however, HRs and IRRs included unity, indicating inconsistent findings and no robust association between ChEI exposure and AFib risk overall.

QT Prolongation

Donepezil demonstrated a consistently significant association with increased QT prolongation risk across both cohort (HR = 1.25, 95% CI: 1.02–1.49) and SCRI analyses (IRR = 1.46, 95% CI: 1.30–1.61).

Donepezil + memantine also showed elevated risk (HR = 1.20, 95% CI: 1.01–1.47; IRR = 1.52, 95% CI: 1.29–1.80); however, the HR did not meet the stringent Bonferroni-corrected significance threshold ($p < 0.0083$), indicating only modest evidence of increased risk. No other treatment groups exhibited statistically significant associations for QT prolongation.

Overall, elevated risks of arrhythmic events were primarily driven by bradycardia and QT prolongation. Donepezil consistently showed increased risks for both bradycardia and QT prolongation across both analytic methods. Galantamine use was consistently linked to increased bradycardia risk, while associations with QT prolongation and AFib were inconsistent or non-significant. In contrast, the association between ChEI use and AFib risk remained inconsistent and lacked statistical robustness across treatment groups and analytical approaches.

Table 5. Adjusted Hazard Ratios(HR) and Incidence Rate Ratios(IRR) for Arrhythmic Events Across Treatment Groups

	Bradycardia		AFib		QT Prolongation	
	HR(95%CI)	**IRR(95%CI)**	**HR(95%CI)**	**IRR(95%CI)**	**HR(95%CI)**	**IRR(95%CI)**
Donepezil (N = 4,632)	1.75 (1.39–2.21) **	1.54 (1.39–1.74) *	1.05 (0.78–1.50)	1.26 (0.97–1.58)	1.25 (1.02–1.49) **	1.46 (1.30–1.61) *
Donepezil + Memantine(N = 552)	1.63 (1.32–2.02) **	1.21 (1.03–1.42) *	1. 06 (0.73–1.48)	1.22 (0.88–1.67)	1.20 (1.01–1.47) *	1.52 (1.29–1.80) *
Rivastigmine (N = 1,867)	1.09 (0.85–1.40)	1.11 (0.92–1.31)	0.79 (0.58–1.08)	1.52 (1.12–1.87) *	0.83 (0.67–1.03)	0.98 (0.89–1.07)
Rivastigmine + Memantine (N = 444)	0.73 (0.54–1.00)	0.63 (0.36–1.11)	0.79 (0.56–1.14)	1.12 (0.76–1.62)	0.71 (0.56–0.94)	1.24 (0.98–1.48)
Galantamine (N = 397)	1.39 (1.12–1.89) **	1.14 (0.70–1.80)	0.87 (0.57–1.34)	1.95 (0.86–4.47)	0.82 (0.62–1.11)	0.92 (0.71–1.20)
Galantamine + Memantine (N = 46)	2.18 (1.27–3.87) **	1.30 (0.29–5.67)	0.82 (0.29–2.22)	0.31 (0.12–0.85) *	0.51 (0.23–1.07)	0.53 (0.29–0.94) *
Overall(N = 7,938)	1.51 (1.36–1.67) *	1.39 (1.26–1.54) *	0.96 (0.72–1.15)	1.34 (0.98–1.68)	1.06 (0.99–1.13)	1.31 (1.21–1.41) *

Hazard ratios (HRs) are adjusted for age, sex, and the following baseline comorbidities and concomitant medications: angina pectoris, cancer, depression, diabetes mellitus, chronic heart disease, coronary artery disease, heart failure, myocardial infarction, stroke, antiarrhythmics, antipsychotics, beta-blockers, calcium channel blockers, and cardiac glycosides. The reference group for all HR estimates is memantine.

** Bonferroni-corrected $p < 0.0083$

* $p < 0.05$

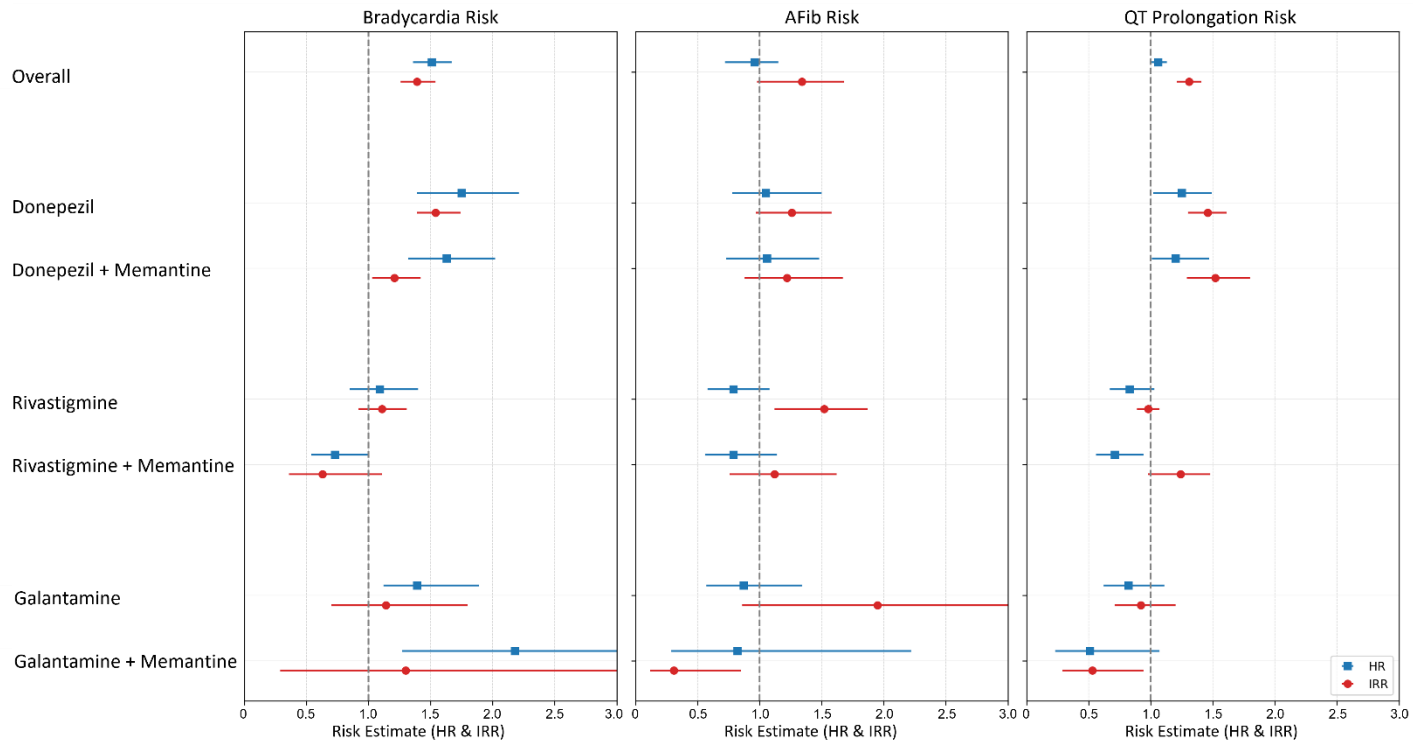

Figure 4. Forest Plots of Adjusted Hazard Ratios(HRs) and Incidence Rate Ratios(IRRs) for Arrhythmic Events Across Treatment Groups

3.3. Risk of arrhythmic events by dose level

To evaluate potential dose-dependent relationships between cognitive enhancer dose and arrhythmic risk, stratified analyses were performed using both between-subject (cohort) and within-subject (SCRI) designs. Table 6 summarizes the adjusted HRs and IRRs for each arrhythmic event across low, medium, and high dose levels in the six treatment groups.

Clear dose-response relationships were observed for donepezil and donepezil + memantine, demonstrating increased risks of both bradycardia and QT prolongation at higher doses.

However, no consistent dose-dependent trends in arrhythmic risk were evident for rivastigmine or galantamine, irrespective of concurrent memantine use. High-dose subgroup estimates lacked statistical power due to small sample sizes, resulting in wide confidence intervals that limited clear interpretation.

To improve statistical power and better characterize dose-response relationships, all cholinesterase inhibitors (ChEIs) were aggregated into a single exposure group. As shown in Figure 5, a clear increasing trend in bradycardia risk was identified with higher cumulative ChEI dosage in both cohort and SCRI analyses. This trend was weaker for QT prolongation and absent for AFib.

Table 6. Adjusted Hazard Ratios (HRs) and Incidence Rate Ratios (IRRs) for Arrhythmic Events by Dose Level Across Treatment Groups

	Bradycardia		AFIB		QT Prolongation	
	HR(95%CI)	IRR(95%CI)	HR(95%CI)	IRR(95%CI)	HR(95%CI)	IRR(95%CI)
Donepezil						
Low	1.67 (1.40–1.98)	1.42 (1.22–1.66)	0.99 (0.41–2.12)	1.09 (0.61–2.43)	0.85 (0.73–0.99)	1.35 (1.25–1.46)
Medium	1.91 (1.6–2.28)	1.46 (1.50–2.00)	1.31 (0.98–1.78)	1.31 (0.92–1.70)	1.2 (1.02–1.4)	1.67 (1.53–1.81)
High	1.68 (0.95–2.97)	1.23 (1.01–1.47)	0.64(0.24-1.73)	1.00 (0.25–4.00)	2.07 (1.29–3.33)	1.23 (0.73–2.06)
Donepezil + Memantine						
Low	1.26 (0.94–1.68)	0.95 (0.52–1.74)	0.85 (0.4–1.45)	2.12 (1.17–3.85)	0.93 (0.7–1.22)	1.64 (1.23–2.20)
Medium	1.88 (1.51–2.35)	0.97 (0.71–1.34)	1.03 (0.71–1.45)	0.98 (0.63–1.52)	1.29 (1.03–1.61)	1.47 (1.20–1.81)
High	1.93 (1.13–3.29)	1.20 (0.52–2.78)	1.21 (0.27–2.86)	0.91 (0.39–2.14)	1.99 (1.25–3.15)	2.80 (1.36–5.76)
Rivastigmine						
Low	1.2 (0.95–1.53)	1.38 (0.87–2.17)	0.88 (0.63–1.22)	1.03 (0.63–1.71)	0.62 (0.47–0.81)	1.03 (0.77–1.38)
Medium	0.98 (0.8–1.18)	1.07 (0.83–1.37)	0.81 (0.63–1.07)	2.02 (1.59–2.57)	0.82 (0.69–0.98)	0.97 (0.87–1.09)
High	1.3 (1.03–1.65)	1.11 (0.79–1.57)	0.71 (0.51–1.09)	1.58 (0.96–2.58)	1.21 (0.98–1.49)	1.01 (0.84–1.20)
Rivastigmine + Memantine						
Low	0.82 (0.56–1.19)	0.75 (0.17–3.35)	0.77 (0.5–1.19)	1.06 (0.54–2.10)	0.58 (0.37–0.92)	4.70 (2.38–9.30)
Medium	0.67 (0.47–0.95)	1.25 (0.34–4.65)	0.61 (0.41–0.92)	4.00 (1.13–14.17)	1.0 (0.77–1.3)	1.74 (1.29–2.34)
High	0.64 (0.47–0.86)	0.48 (0.23–0.98)	1.22 (0.93–1.59)	0.90 (0.54–1.51)	0.89 (0.71–1.11)	0.82 (0.65–1.04)
Galantamine						
Low	1.43 (1.09–1.87)	1.32 (0.76–2.29)	0.44 (0.27–0.7)	NaN	0.55 (0.39–0.77)	0.69 (0.48–0.98)
Medium	1.01 (0.69–1.49)	0.70 (0.27–1.84)	1.16 (0.78–1.74)	1.95 (0.86-4.47)	0.84 (0.59–1.2)	1.09 (0.72–1.64)
High	1.17 (0.54–2.5)	NaN	0.43 (0.11–1.74)	NaN	1.66 (0.78–3.54)	5.00 (1.45–17.27)
Galantamine + Memantine						
Low	2.17 (1.23–3.83)	NaN	0.83 (0.56–1.10)	0.31 (0.12–0.85)	0.76 (0.34–1.72)	0.42 (0.21–0.86)
Medium	1.45 (0.64–3.28)	1.00 (0.20–4.95)	0.81 (0.44–1.35)	NaN	NaN	1.33 (0.30-5.96)
High	1.47 (0.47–4.63)	NaN	NaN	NaN	0.48 (0.07–3.75)	0.40 (0.08–2.06)

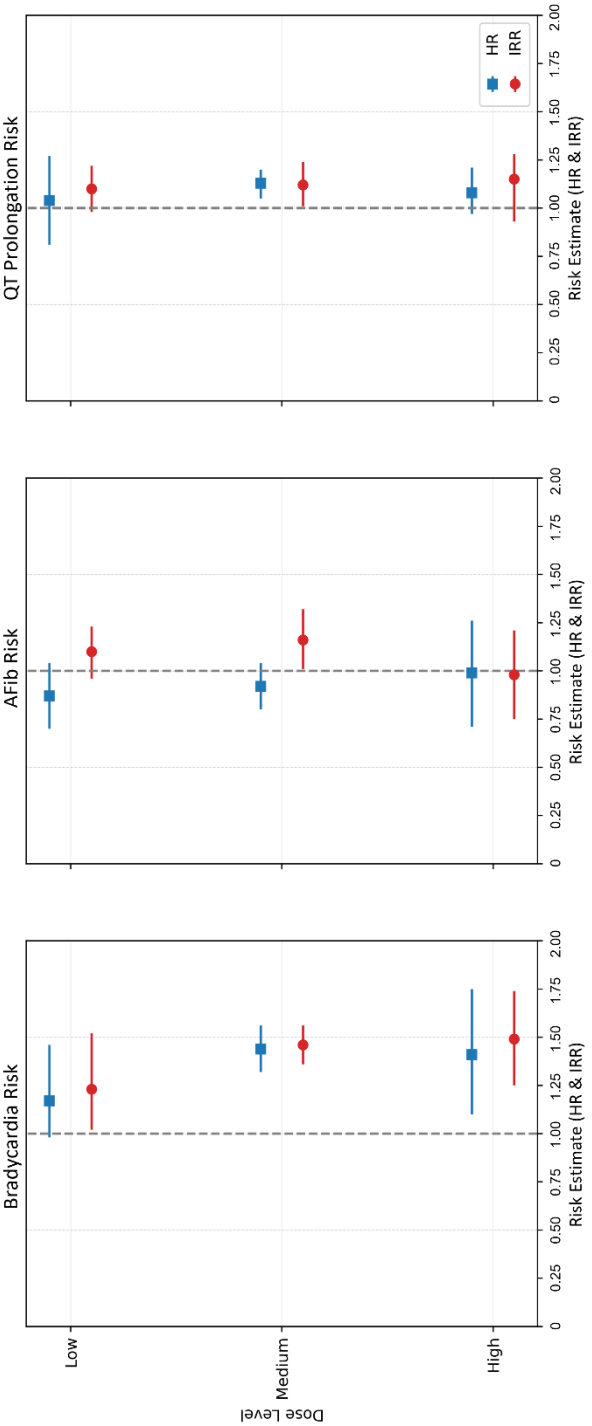

Figure 5. Forest Plots of Adjusted Hazard Ratios (HRs) and Incidence Rate Ratios (IRRs) for Arrhythmic Events by ChEI Dose Levels

3.4. Risk of arrhythmic events by patient subgroups

Figure 6 displays adjusted hazard ratios (HRs) and incidence rate ratios (IRRs) for bradycardia, AFib, and QT prolongation, stratified by various patient subgroups.

Bradycardia risk was consistently elevated and statistically significant across most patient subgroups, as indicated by hazard ratios (HRs) and incidence rate ratios (IRRs) exceeding unity. Specifically, older adults (≥80 years), males, and patients with cardiovascular comorbidities or baseline medications with chronotropic effects were identified as having notably increased bradycardia risk following ChEI initiation.

In contrast, the AFib risk associated with ChEI use showed different patterns between analytic approaches. Although hazard ratios (HRs) generally indicated no statistically significant associations, incidence rate ratios (IRRs) demonstrated a consistent tendency towards increased risk across most patient subgroups, with several subgroups showing statistically significant elevations. This discrepancy suggests a potential short-term elevation in AFib risk detectable in within-subject comparisons, despite the absence of significant between-subject comparisons.

For QT prolongation, increased risk estimates were identified in older adults and female patients; however, these associations were generally weaker and less consistent compared to bradycardia.

Formal statistical evidence for effect modification was limited, but consistent trends of modestly elevated arrhythmic risk were noted among patients with cardiovascular comorbidities or baseline medications with chronotropic effects, particularly for bradycardia.

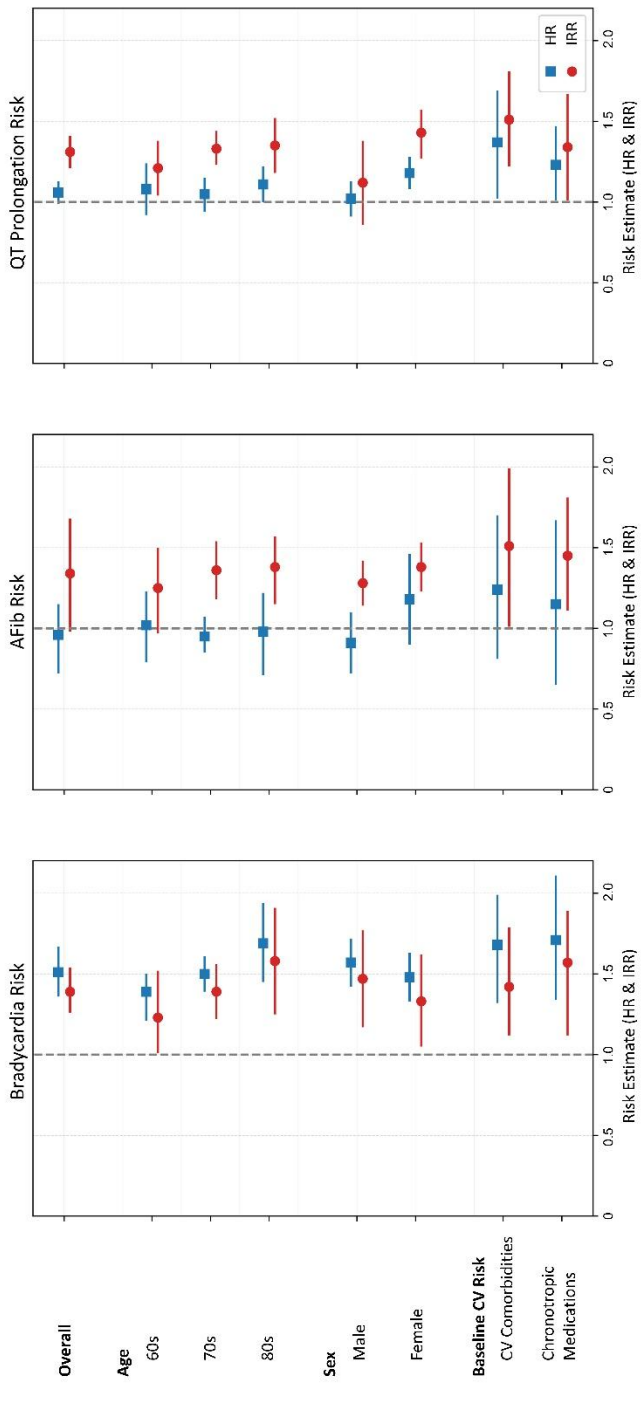

Figure 6. Forest Plots of Adjusted Hazard Ratios (HRs) and Incidence Rate Ratios (IRRs) for Arrhythmic Events by Patient Subgroups

4. Discussion

We conducted a large EMR-based study of older adults with dementia to evaluate the association between cognitive enhancers and arrhythmic events. Using both retrospective cohort and self-controlled risk interval (SCRI) designs, we aimed to compare arrhythmia risks across treatment strategies and to assess short-term within-person risk changes following drug initiation.

Across both designs, donepezil consistently demonstrated the highest risk of bradycardia (HR = 1.75, 95% CI: 1.39–2.21; IRR = 1.54, 95% CI: 1.39–1.74). Galantamine also showed elevated bradycardia risk in the cohort analysis (HR = 1.39, 95% CI: 1.12–1.89), although SCRI estimates were less precise, with wide confidence intervals crossing unity. QT prolongation risk was most prominent with donepezil across both designs (HR = 1.25, 95% CI: 1.02–1.49; IRR = 1.46, 95% CI: 1.30–1.61), consistent with known pharmacologic effects [26]. For AFib, most ChEIs did not show significant associations in cohort analyses, but rivastigmine was associated with a short-term risk increase in SCRI (IRR = 1.52, 95% CI: 1.12–1.87), suggesting a possible transient elevation immediately after initiation.

Dose-stratified analyses demonstrated a clear dose-response relationship for bradycardia, particularly with donepezil, where higher prescribed doses were associated with increased event rates. QT prolongation also showed a weaker but notable dose-response pattern, especially at higher donepezil doses. This supports the concept of cumulative cholinergic burden contributing to conduction abnormalities.

In subgroup analyses, bradycardia risk was elevated among older adults, those with cardiovascular comorbidities, and patients receiving baseline chronotropic medications. Notably, bradycardia risk was higher among males, while QT prolongation risk was higher among females. For AFib, subgroup analyses revealed no significant associations in the cohort analysis but demonstrated statistically significant increases in IRRs in the SCRI analysis, suggesting that ChEI initiation may confer a short-term AFib risk in susceptible populations.

The higher QT prolongation risk observed with donepezil may be due to differences in its overall pharmacologic effects. Donepezil is the only cholinesterase inhibitor currently recognized

as having a known risk for QT prolongation [26], which is consistent with our results.

When interpreting the results, it is important to consider the potential influence of diagnostic access bias in both study designs, which may have affected the magnitude of risk estimates in opposite directions. In the cohort analysis, HRs may have been underestimated because ECG testing was performed most frequently among memantine users, who served as the reference group. This higher likelihood of arrhythmia detection in the reference group could have biased the comparison, leading to attenuated hazard ratios. In contrast, the SCRI design may have overestimated IRRs, as ECG testing was generally more frequent after treatment initiation than before, increasing the chance of detecting arrhythmic events in the risk window. Furthermore, the SCRI analysis included only individuals with ECG data both before and after treatment, which may have resulted in overrepresentation of patients with higher baseline cardiovascular risk.

To address these limitations, we applied both retrospective cohort and self-controlled risk interval (SCRI) designs. Taken together, potential underestimation of HRs in the cohort analysis and overestimation of IRRs in the SCRI design should be considered when interpreting the results. In this context, consistent findings across both designs support a robust association, while discrepancies warrant cautious interpretation.

A key strength of this study is the application of two complementary observational designs to evaluate the association between cognitive enhancers and arrhythmic events. The cohort design enabled long-term follow-up and comparison of arrhythmia risk across treatment groups using memantine as a reference, while the SCRI design allowed for within-person comparisons immediately following treatment initiation, thereby reducing confounding from stable individual characteristics.

In addition, to better reflect real-world clinical practice and avoid underestimating risk, we did not exclude patients with a history of arrhythmia prior to cognitive enhancer initiation. This decision was based on two key considerations. First, cholinesterase inhibitors increase vagal tone by elevating acetylcholine levels, which can exacerbate pre-existing conduction abnormalities [27]. Second, randomized controlled trials often exclude high-risk patients, limiting generalizability [21]. Including patients with prior arrhythmia allowed for a more comprehensive risk assessment and enabled subgroup analyses in clinically vulnerable populations.

These two approaches have different sources of bias, and their combined use provided a more balanced and robust assessment of arrhythmic risk by enabling evaluation across both treatment arms and temporal risk windows.

Beyond the study design itself, our analysis benefited from the inclusion of multiple treatment groups and arrhythmic outcomes. The study examined not only individual cholinesterase inhibitors but also combination therapies, which is particularly important given that combining ChEIs with memantine is common in advanced dementia stages. This enables evaluation of potential additive or synergistic effects and reflects real-world prescribing practices. Importantly, while randomized controlled trials often assess the safety of individual ChEIs, they rarely evaluate arrhythmic risk when used in combination with memantine even though such combination therapy is frequently prescribed for patients with more advanced dementia. Given the pharmacodynamic interactions and the potential for additive cholinergic effects when ChEIs are combined with memantine, careful monitoring is warranted [10, 11]. This study therefore aimed to address this gap by conducting a large-scale, real-world analysis to evaluate the comparative arrhythmic risk of combination therapy versus monotherapy, providing clinically relevant safety data to inform prescribing decisions in this vulnerable population.

In parallel with the comprehensive treatment group evaluation, the study assessed three distinct arrhythmic outcomes: bradycardia, QT prolongation, and atrial fibrillation (AFib), offering a detailed profile of drug-associated cardiac risks. This comprehensive and stratified approach allowed us to evaluate associations across specific drug-event pairs with greater confidence, addressing the complexity of arrhythmia risk in this population.

Another further strength lies in the use of clinically recorded, routinely collected ECG data, which offers objective and time-stamped physiological measurements. Unlike diagnosis codes or claims data that may miss subclinical or asymptomatic events, ECG records enable the detection of subtle or borderline arrhythmias such as mild QT prolongation or bradycardia [28]. This reduces misclassification bias, enhances the sensitivity of arrhythmia detection, and allows for more precise temporal alignment between drug exposure and outcome occurrence. By using real-world ECG measurements, our study aims to provide enhanced clinical granularity and support a more valid assessment of cardiac safety in dementia patients.

Several limitations should be considered when interpreting the findings of this study. First, the analysis was limited to patients with ECG measurements following cognitive enhancer initiation, which may have led to a study population skewed toward individuals with higher baseline cardiovascular risk. As a result, the findings may not be fully generalizable to all users of these medications. Moreover, ECGs were not performed at regular intervals for all patients, and the frequency of measurements varied depending on clinical context such as inpatient admission or outpatient visits. As a result, differences in monitoring intensity may have led to unequal opportunities for event detection across patients.

In addition, concomitant medication use after ChEI initiation was not incorporated as time-varying covariates, which may have introduced residual confounding in some comparisons. Other important clinical factors, such as dementia severity, caregiving status, frequency of outpatient visits, or patients' adherence to prescribed medications, were also not captured in our data and may have influenced both treatment selection and arrhythmia risk.

Another important limitation relates to the imbalance in treatment group sizes, with donepezil being prescribed far more frequently than galantamine or memantine. This discrepancy may have reduced statistical power to detect meaningful differences involving the less commonly used drugs. For similar reasons, subgroup analyses combined all ChEIs into a single exposure category rather than analyzing individual agents separately, as sample sizes within each subgroup were insufficient. While this approach improved analytic feasibility, it limited the ability to evaluate agent-specific risks. Additionally, stratified analyses by cardiovascular comorbidities or baseline medication use were constrained, highlighting the need for future studies with larger and more balanced samples to explore potential effect modification across specific subgroups.

Finally, the study covered a long observation period, during which external changes such as evolving clinical guidelines, advances in ECG technology, or shifts in healthcare policy and utilization patterns may have occurred. These changes could have affected the conditions under which ECGs were performed, the frequency of testing, and the precision of recorded measurements, but were not fully addressed in our analysis.

These findings have important clinical implications for the management of dementia in older adults, particularly in those with elevated cardiovascular risk. Our results emphasize the need for

individualized risk assessment when prescribing cognitive enhancers, especially donepezil, which was associated with higher rates of bradycardia and QT prolongation. Clinicians should consider baseline ECG evaluations prior to initiating cognitive enhancer therapy, carefully review baseline cardiovascular comorbidities and use of chronotropic medications, and adopt conservative dose titration or escalation strategies. Such risk-based approaches are particularly relevant for older patients and those with pre-existing cardiac conditions.

Routine or targeted ECG assessment before starting cognitive enhancer therapy may facilitate early identification of high-risk individuals, enabling proactive intervention before clinically significant arrhythmias occur. Implementing such strategies in real-world clinical practice has the potential to reduce adverse cardiac events and improve the safety profile of dementia pharmacotherapy.

In conclusion, this study reliably evaluated the arrhythmic risks associated with the use of cognitive enhancers by applying multiple study designs based on real-world clinical data. The findings provide clinical evidence that may serve as a foundation for developing prescribing strategies and ECG monitoring protocols in the treatment of patients with dementia.

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Abstract in Korean

치매환자의 인지기능개선제 사용과 관련된 부정맥 발생 위험 프로파일 분석

치매는 인지 저하와 기능적 장애를 특징으로 하는 진행성 신경퇴행성 질환으로, 전 세계적으로 5천만 명 이상의 환자가 존재하는 심각한 공중보건 부담을 초래한다. 치매 증상 완화 치료 약제로는 콜린에스테라아제 억제제(ChEI: 도네페질, 리바스티그민, 갈란타민)와 NMDA 수용체 길항제인 메만틴이 널리 사용된다. 그러나 ChEI는 콜린성 신경전달을 촉진하고 부교감신경의 활성도를 증가시켜 서맥, QT 간격 연장, 심방세동(AFib)과 같은 심장 부정맥을 유발할 수 있는 것으로 알려져 있다. 이러한 위험은 특히 부정맥으로 인한 임상적 결과에 더 취약한 고령의 치매 환자에서 임상적으로 중요한 문제로 지적된다. 그럼에도 불구하고 임상 현장에서는 치료 전후 심전도(ECG) 모니터링이 의무화되어 있지 않다. 또한 기존 무작위 대조시험(RCT)은 심혈관 동반질환이나 고위험군 환자를 제외하는 경우가 많아, 실제 임상 환경에서의 일반화 가능성이 제한적이다. 이러한 배경에서 치매 환자의 인지기능개선제 사용과 관련된 부정맥 발생 위험을 보다 정밀하게 평가할 수 있는 대규모 실제 데이터(real-world data) 기반의 프로파일링 연구가 필요하다.

본 연구는 치매 환자의 인지기능개선제 사용과 관련된 세 가지 주요 심장 부정맥 사건(서맥, QT 간격 연장, 심방세동)의 위험을 전자의무기록(EMR)의 심전도(ECG) 기록을 활용해 평가하고자 하였다. 이를 위해 (1) ChEI 사용군과 메만틴 단독군을 비교한 환자군 간 후향적 코호트 연구 설계와, (2) ChEI 시작 전후의 부정맥 발생률을 동일 환자 내에서 비교함으로써 시간 불변 교란 요인을 통제한 자기대조 위험구간(SCRI) 설계의 두 가지 상보적 분석 접근법을 사용하였다. 또한 두 설계법을 동일하게 적용하여 연령, 성별, 기저 심혈관 동반질환, 기저 심박수 조절 약물 사용에 따른 하위집단별 위험과 용량-반응 관계를 평가하였다.

연구 대상자는 세브란스병원의 전자의무기록에서 추출되었으며, 코호트 연구 설

계에는 총 8,354명이 포함되었고 이 중 3,364명이 SCRI 분석에 포함되었다. ChEI, 특히 도네페질은 메만틴 대비 서맥 위험 증가와 유의하게 관련되었다(HR=1.75, 95% CI: 1.39–2.21; IRR=1.54, 95% CI: 1.39–1.74). 도네페질은 QT 간격 연장 위험도 유의하게 증가시켰다(HR=1.25, 95% CI: 1.02–1.49; IRR=1.46, 95% CI: 1.30–1.61). 반면, 심방세동 위험과 ChEI의 연관성은 두 연구디자인에서 일관되게 관찰되지 않았다. 용량-반응 분석에서는 도네페질 용량이 증가할수록 서맥 및 QT 연장 위험이 높아졌으며, 하위집단 분석에서도 고령, 기저 심혈관 동반질환, 기저 심박수 조절 약물 사용군에서 위험이 더 컸다.

본 연구는 환자 간 비교(코호트 연구)와 환자 내 비교(SCRI 연구) 분석을 병행하여 ChEI 사용과 관련된 부정맥 위험에 대한 견고한 근거를 제시한다. 이러한 결과는 치매 약물 치료의 안전성을 향상시키기 위해, 개별화된 심혈관 위험 평가, 치료 전후의 정기적인 심전도(ECG) 모니터링, 그리고 용량 조절의 중요성을 강조하며, 이를 바탕으로 향후 치매 약물 치료의 안전성을 개선하기 위한 환자 맞춤형 처방 및 안전 모니터링 전략 개발의 근거로 활용될 수 있을 것으로 기대된다.

핵심 되는 말 : 인지기능개선제, 콜린에스테라아제 억제제, 심전도, 서맥, QT 간격 연장, 심방세동, 부정맥, 실제 임상 데이터