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RESEARCH PAPER

Association of rhythm control with incident dementia among patients with atrial fibrillation: a nationwide population-based cohort study

Daehoon Kim[1,†], Pil-Sung Yang[2,†], Seng Chan You[3], Jung-Hoon Sung[2], Eunsun Jang[1], Hee Tae Yu[1], Tae-Hoon Kim[1], Hui-Nam Pak[1], Moon-Hyoung Lee[1], Gregory Y.H. Lip[4,‡], Boyoung Joung[1,‡]

[1]Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea
[3]Department of Preventive Medicine and Public Health, Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK

Address correspondence to: Boyoung Joung, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, Republic of Korea 03722.
Tel: +82-2-2228-8460, Fax: +82-2-393-2041. Email: cby6908@yuhs.ac
[†]The first two authors contributed equally to this work.
[‡]Joint senior authors.

Abstract

Background: Atrial fibrillation (AF) increases the risk of dementia, and catheter ablation of AF may be associated with a lower risk of dementia. We investigated the association of a rhythm-control strategy for AF with the risk of dementia, compared with a rate-control strategy.
Methods: This population-based cohort study included 41,135 patients with AF on anticoagulation who were newly treated with rhythm-control (anti-arrhythmic drugs or ablation) or rate-control strategies between 1 January 2005 and 31 December 2015 from the Korean National Health Insurance Service database. The primary outcome was all-cause dementia, which was compared using propensity score overlap weighting.
Results: In the study population (46.7% female; median age: 68 years), a total of 4,039 patients were diagnosed with dementia during a median follow-up of 51.7 months. Rhythm control, compared with rate control, was associated with decreased dementia risk (weighted incidence rate: 21.2 versus 25.2 per 1,000 person-years; subdistribution hazard ratio [sHR] 0.86, 95% confidence interval [CI] 0.80–0.93). The associations between rhythm control and decreased dementia risk were consistently observed even after censoring for incident stroke (sHR 0.89, 95% CI 0.82–0.97) and were more pronounced in relatively younger patients and those with lower CHA_2DS_2-VASc scores. Among dementia subtypes, rhythm control was associated with a lower risk of Alzheimer's disease (sHR 0.86, 95% CI 0.79–0.95).
Conclusions: Among anticoagulated patients with AF, rhythm control was associated with a lower risk of dementia, compared with rate control. Initiating rhythm control in AF patients with fewer stroke risk factors might help prevent subsequent dementia.

Keywords: atrial fibrillation, dementia, rhythm control, rate control, older people

Key Points

- There is increasing evidence suggesting that atrial fibrillation (AF) contributes to the development of cognitive dysfunction and dementia.
- On top of oral anticoagulation, a rhythm-control strategy was associated with a lower risk of dementia than rate control.

- The beneficial effects of rhythm control were more pronounced in relatively younger patients with fewer stroke risk factors.

Introduction

Approximately 40 million people are living with dementia worldwide, and this number is expected to rise with an increasingly ageing population [1]. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It increases the risk of mortality and morbidity resulting from stroke and congestive heart failure, along with the associated high burden of healthcare costs [2–5]. There is increasing evidence that AF contributes to the development of cognitive dysfunction and dementia [6–8]. Although some observational studies suggest that anticoagulation could decrease the risk of dementia in patients with AF [7, 9], meta-analyses, including one randomised controlled trial and four prospective studies, have failed to provide definitive evidence of cognitive benefits for or harm from anticoagulation [10].

A rhythm-control strategy using anti-arrhythmic drugs, cardioversion and AF ablation improves symptoms and quality of life in patients with symptomatic AF [11, 12]. Previous randomised controlled trials demonstrated no significant difference in cardiovascular outcomes between patients with AF treated with rate control versus rhythm control [13–15]. However, a recent randomised multicenter study of patients with newly diagnosed (i.e. <1 year) AF has demonstrated that an initial rhythm-control strategy was associated with reduced cardiovascular death and stroke rate [16].

Along with the conflicting evidence on the association of rhythm-control strategy with cardiovascular hard outcomes, the effect of the treatment strategy on cognitive outcomes has not been elucidated. A substudy of the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management trial reported that there was no difference in cognitive function between patients having AF treated with rate- or rhythm-control strategies [17]. However, several observational studies have demonstrated improved cognitive function and less dementia following catheter ablation for AF [18–20]. We sought to investigate the association of a rhythm-control strategy for AF with the risk of dementia compared with a rate-control strategy.

Methods

This study is a retrospective analysis based on the national health claims database established by the National Health Insurance Service (NHIS) of Korea. Further details are presented in Appendix Methods. This study was approved by the Institutional Review Board of the Yonsei University Health System (4-2016-0179). The requirement for informed consent was waived because personal identification information was removed after cohort generation, in accordance with strict confidentiality guidelines.

Cohort design and study population

This study emulated a randomised controlled trial comparing the effect of rhythm- versus rate-control treatment for AF on the risk of cognitive outcomes. The details of the trial protocol are presented in Appendix Table 1. We identified adults (≥18 years) with AF who were newly treated with rhythm- or rate-control strategies between 1 January 2005 and 31 December 2015. From this population, we enrolled patients meeting at least one of the following criteria: (i) older than 75 years of age, (ii) a history of a transient ischaemic attack or stroke or (iii) two of either age older than 65 years, female sex, heart failure, hypertension, diabetes mellitus, previous myocardial infarction or chronic kidney disease, using similar inclusion criteria as the EAST-AFNET 4 trial [16]. AF was defined according to the International Classification of Disease 10th Revision codes (ICD-10), I48. The diagnosis of AF has previously been validated in the NHIS database with a positive predictive value (PPV) of 94.1% [21]. Details about the study design are presented in Appendix Methods. Rhythm- and rate-control drugs and claim codes for ablation procedures are presented in Appendix Table 2. To minimise the potential for bias from different anticoagulation strategies, this study excluded individuals who did not receive a prescription of more than a 90-day supply of oral anticoagulants within the 180-day period since the initiation of rhythm- or rate-control treatments. Those who died or who were diagnosed with dementia within 180 days of their first record of prescription or procedure were also excluded (Figure 1A).

Outcomes and covariates

The primary outcome was the initial occurrence of all-cause dementia. Secondary outcomes included the development of major dementia subtypes, including Alzheimer's disease and vascular dementia. Diagnosis of dementia was defined using the following ICD-10 codes of dementia (F00 or G30 for Alzheimer's disease, F01 for vascular dementia, F02 for dementia with other diseases classified elsewhere, and F03 or G31 for unspecified dementia) and dementia drugs (rivastigmine, galantamine, memantine or donepezil) (Appendix Table 3). The definition of dementia has previously been validated with a PPV of 94.7% in the NHIS database [22]. Follow-up of the study outcomes was started at 180 days after the first recorded prescription or procedure and lasted until the diagnosis of dementia, death, or at the end of the study period (31 December 2016), whichever came earliest. Details about covariates are presented in Appendix Methods and Appendix Table 2.

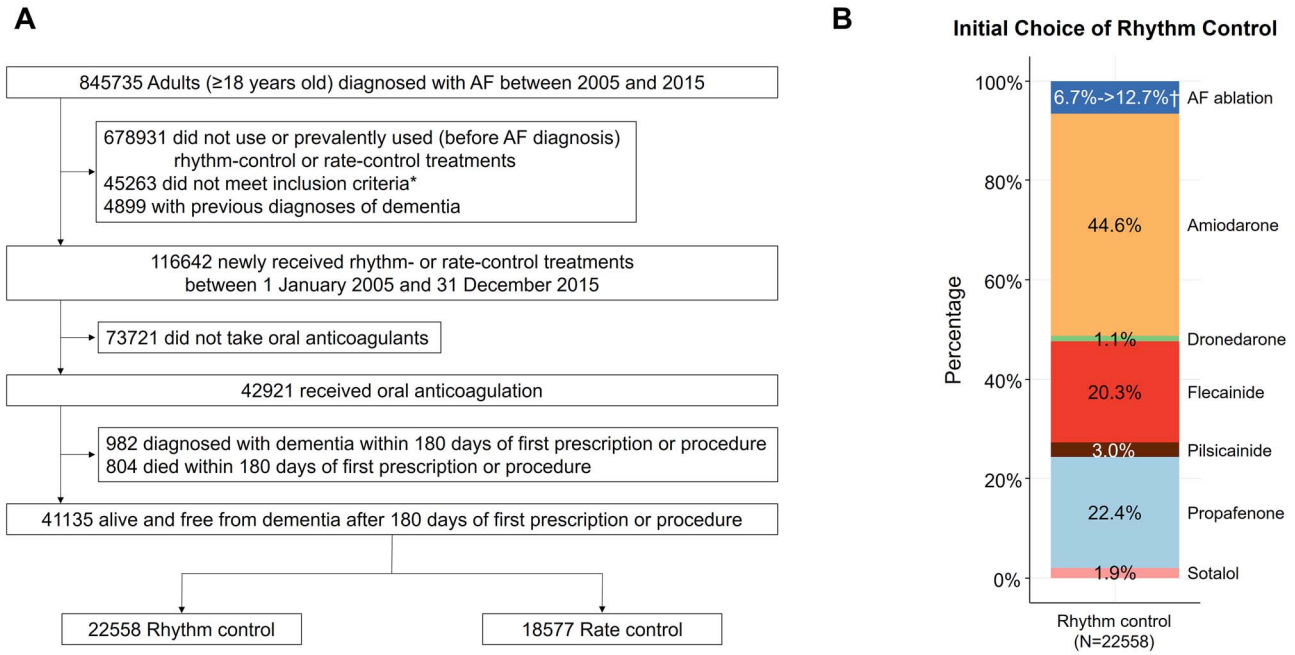

Figure 1. (A) Flowchart of the enrolment and analysis of the study population and (B) initial choice of rhythm-control treatments. ∗Meeting at least one of the following: (i) older than 75 years of age, (ii) had a previous transient ischaemic attack or ischaemic stroke or (iii) met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, previous myocardial infarction or chronic kidney disease. †Eventually performed during follow-up. AF, atrial fibrillation.

Statistical methods

Propensity overlap weighting was used to account for the differences in baseline characteristics between patients who received rhythm-control or rate-control treatments. Propensity scores representing the probability of receiving a rhythm-control treatment were estimated using logistic regression based on sociodemographics; time since AF diagnosis; year of treatment initiation; level of care at which the initial prescription was provided (primary, secondary or tertiary care services); clinical risk scores, including CHA_2DS_2-VASc score, HAS-BLED score, Charlson comorbidity index, and Hospital Frailty Risk score; medical history; and concurrent medication use (listed in Table 1). Continuous variables were modelled as cubic spline functions. The distribution of propensity scores before and after overlap weighting is presented in Appendix Figure 1. The overlap weight was calculated as 1 minus the propensity score for the rhythm-control patients, and the propensity score for the rate-control patients, to obtain estimates representing population average treatment effects with a minimised asymptotic variance of the treatment effect and a desirable exact balance property [23]. The balance between the treatment populations was evaluated by standardised differences of all baseline covariates using a threshold of 0.1 to indicate an imbalance. Weighted incidence rates were calculated as the weighted number of clinical events during the follow-up period divided by 1,000 person-years at risk. We compared the incidence of outcomes using the weighted log-rank test and plotted the weighted failure curves. Competing risk regression by Fine and Gray was used to consider all-cause death as a competing event when estimating the relative hazards of clinical outcomes [24]. Cofactors that had not been balanced by weighting were included as covariates in the competing risk regression. The proportional hazards assumption was tested based on Schoenfeld residuals [25]. We performed subgroup analyses for the primary composite outcome stratified by sex, age, level of care in which the treatment was initiated, time since AF diagnosis, heart failure, hypertension, diabetes, chronic kidney disease, previous myocardial infarction, type of OAC and CHA_2DS_2-VASc score. Interaction tests were performed for all subgroups. The test parameter from the weighting procedure was used to recreate the overlap weighting. The proportional hazards model was fit with new weights, and the interaction term was added for testing. We performed stratified analysis based on whether the rhythm-controlled patients were treated with catheter ablation or anti-arrhythmic drugs, comparing each group with the overall patients undergoing rate control.

To explore the age-dependent effect of rhythm control on primary outcome, a Cox proportional-hazards model was fit to the entire weighted study population using of an interaction term for age at treatment initiation (modelled as a cubic spline) and treatment (rhythm-control or rate-control strategy). Standard errors were computed using 1,000 bootstrap replicates.

Table 1. Baseline characteristics before and after propensity score overlap weighting

	Before overlap weighting			After overlap weighting		
	Rhythm Control ($N = 22,558$)	Rate Control ($N = 18,577$)	ASD, %	Rhythm Control ($N = 22,558$)	Rate Control ($N = 18,577$)	ASD, %
Sociodemographic						
Age, median (IQR), years	67 (58–73)	70 (61–76)	22.3	68 (60–75)	68 (60–75)	<0.1
<65 years, %	41.1	31.7	19.8	36.3	36.3	<0.1
65–74 year, %	38.4	38.0	0.9	38.0	38.0	<0.1
≥75 years, %	20.5	30.4	23.0	25.7	25.7	<0.1
Male, %	54.4	52.1	4.6	54.2	54.2	<0.1
High tertile of income, %	46.3	38.0	16.8	42.3	42.3	<0.1
Number of OPD visits ≥12/year, %	85.4	76.9	21.8	81.1	81.1	<0.1
Living in metropolitan areas, %	48.1	41.9	12.6	45.3	45.3	<0.1
AF duration, median (IQR), months	1.8 (0.0–33.6)	0.0 (0.0–3.9)	36.2	0.8 (0.0–17.7)	0.1 (0.0–16.2)	<0.1
Enrol year, %						
2005	5.6	11.7	21.9	7.6	7.6	<0.1
2006	6.5	9.9	12.5	7.9	7.9	<0.1
2007	6.1	8.1	7.6	7.0	7.0	<0.1
2008	5.7	7.9	8.9	6.9	6.9	<0.1
2009	6.5	6.8	1.5	6.7	6.7	<0.1
2010	7.6	7.2	1.7	7.5	7.5	<0.1
2011	9.2	7.6	5.9	8.2	8.2	<0.1
2012	9.9	8.4	4.9	9.4	9.4	<0.1
2013	11.8	9.7	6.9	11.1	11.1	<0.1
2014	13.8	9.8	12.2	11.9	11.9	<0.1
2015	17.3	12.8	12.7	15.7	15.7	<0.1
Level of care initiating treatment, %						
Tertiary	63.5	42.5	43.1	52.3	52.3	<0.1
Secondary	33.1	48.6	31.8	42.2	42.2	<0.1
Primary	3.3	8.9	23.5	5.4	5.4	<0.1
Clinical risk scores, median (IQR)						
CHA_2DS_2-VASc score,	4 (3–5)	4 (3–5)	9.0	4 (3–5)	4 (3–5)	<0.1
mHAS-BLED score*	2 (2–3)	2 (2–3)	23.6	2 (2–3)	2 (2–3)	<0.1
Charlson comorbidity index	4 (2–6)	2 (1–4)	45.1	3 (2–5)	3 (2–5)	<0.1
Hospital Frailty Risk score	2.0 (0.0–5.4)	1.5 (0.0–5.1)	6.8	1.9 (0.0–5.4)	1.8 (0.0–5.5)	<0.1
Medical history, %						
Heart failure	54.5	53.2	2.6	53.7	53.7	<0.1
Hx of heart failure admission	14.1	15.6	4.1	15.0	15.0	<0.1
Hypertension	88.0	67.6	50.6	81.5	81.5	<0.1
Diabetes	30.3	23.3	15.8	27.8	27.8	<0.1
Dyslipidaemia	82.5	63.8	43.3	75.3	75.3	<0.1
Ischaemic stroke	29.3	32.7	7.3	32.1	32.1	<0.1
Transient ischaemic attack	10.6	7.2	11.9	8.9	8.9	<0.1
Intracranial bleeding	2.2	2.0	1.7	2.2	2.2	<0.1
Myocardial infarction	13.2	8.3	15.7	10.6	10.6	<0.1
Peripheral arterial disease	14.9	9.1	17.9	12.3	12.3	<0.1
Valvular heart disease	17.3	18.1	2.2	17.6	17.6	<0.1
Chronic kidney disease	6.6	3.9	12.5	5.2	5.2	<0.1
Proteinuria	6.6	5.1	6.5	6.1	6.1	<0.1
Hyperthyroidism	16.0	8.5	22.9	11.3	11.3	<0.1
Hypothyroidism	14.3	8.0	20.1	10.6	10.6	<0.1
Malignancy	21.1	17.3	9.8	19.8	19.8	<0.1
COPD	29.9	26.0	8.8	28.6	28.6	<0.1
Liver disease	43.2	31.2	25.1	37.4	37.4	<0.1
Hypertrophic cardiomyopathy	2.7	1.2	10.3	1.8	1.8	<0.1
Osteoporosis	30.4	26.8	7.9	29.0	29.0	<0.1
Sleep apnea	0.6	0.3	5.7	0.4	0.4	<0.1
Concurrent medication, %†						
Oral anticoagulant	100.0	100.0	<0.1	100.0	100.0	<0.1
Warfarin	89.0	93.2	14.9	91.2	91.2	<0.1
NOAC	14.1	9.2	15.6	11.7	11.7	<0.1
Beta-blocker	43.9	64.1	41.2	62.6	62.6	<0.1
Non-DHP CCB	13.3	15.5	6.2	17.0	17.0	<0.1
Digoxin	11.2	43.4	77.7	24.5	24.5	<0.1

(*Continued*)

Table 1. Continued

	Before overlap weighting			After overlap weighting		
	Rhythm Control ($N = 22,558$)	Rate Control ($N = 18,577$)	ASD, %	Rhythm Control ($N = 22,558$)	Rate Control ($N = 18,577$)	ASD, %
Aspirin	26.4	23.6	6.4	25.2	25.2	<0.1
$P2Y_{12}$ inhibitor	9.5	8.1	5.1	9.1	9.1	<0.1
Statin	39.2	34.4	9.9	38.2	38.2	<0.1
DHP CCB	19.5	13.1	17.2	16.0	16.0	<0.1
ACEI/ARB	54.8	56.6	3.6	55.6	55.6	<0.1
Loop/thiazide diuretics	45.4	59.1	27.7	52.2	52.2	<0.1
K^+ sparing diuretics	17.4	26.2	21.3	21.5	21.5	<0.1
Alpha-blocker	2.1	2.5	2.7	2.3	2.3	<0.1

*Modified HAS-BLED = hypertension, 1 point: >65 years old, 1 point: stroke history, 1 point: bleeding history or predisposition, 1 point: liable international normalised ratio, not assessed: ethanol or drug abuse, 1 point: drug predisposing to bleeding, 1 point. †Defined as a prescription fill of >90 days within 180 days after the first prescription for rhythm- or rate-control drugs or the performance of an ablation procedure for AF. AAD, anti-arrhythmic drug; ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASD, absolute standardised difference; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; OPD, outpatient department.

Two-sided *P*-values <0.05 were considered significant. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of dementia subtypes were interpreted as exploratory. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R version 4.0.1 (The R Foundation, www.R-project.org).

Sensitivity analyses

Details about sensitivity analyses we performed are presented in Appendix Methods, Appendix Figure 2, and Appendix Tables 4–6.

Results

Patient characteristics

Compared with rate-controlled patients, rhythm-controlled patients tended to be younger; have longer median AF duration; live in metropolitan areas; have higher incomes; have higher comorbidity indices; and have more prevalent comorbidities (Table 1). The most commonly used rhythm-control strategy was the class III drug amiodarone (44.6%), followed by class Ic drugs (Figure 1B). Ablation was an initial rhythm-control strategy in 6.7% of patients undergoing rhythm control and was eventually performed during follow-up in 12.7% of the patients. All baseline characteristics were similar between the two groups after propensity overlap weighting (Table 1).

Risk of dementia

During a median (interquartile range) follow-up of 51.7 (27.5–88.8) months, 4,039 patients were diagnosed with dementia. The incidence rates of dementia were 21.2 and 25.2 per 1,000 person-years in the propensity score-weighted rhythm- and rate-control groups, respectively (Table 2). The cumulative incidence of dementia was significantly lower in the rhythm-control group than in the rate-control group (log-rank $P < 0.001$, Figure 2A). After adjusting for the competing risk of mortality, compared with rate control, the risk of all-cause dementia was reduced by 14% in patients with rhythm control (subdistribution hazard ratio [sHR] 0.86, 95% confidence interval [CI] 0.80–0.93, $P < 0.001$) (Table 2). After additionally censoring patients at the time of incident stroke, the incidence rates of dementia were 18.1 and 20.6 per 1,000 person-years, respectively. The risk of overall dementia was still significantly lower in the ablation group than in the rate-control group (sHR 0.89, 95% CI 0.82–0.97, $P = 0.007$) (Table 2). Regardless of the initial choice of rhythm-control treatment (catheter ablation or anti-arrhythmic drugs), rhythm control showed trends towards a lower risk of dementia, compared with rate control (Table 2). The point estimates for all-cause dementia, compared with rate control, was closer to zero in patients initially treated with ablation (sHR 0.59) than in those treated with anti-arrhythmic drugs (sHR 0.86).

Subgroup analyses showed that there were no interactions between the protective association of rhythm control with decreased dementia risk and sex, level of care, time since AF diagnosis, hypertension, diabetes, stroke, chronic kidney disease, previous myocardial infarction, and types of OAC (Appendix Figure 3). Rhythm control was more strongly associated with lower dementia risk in patients who were relatively younger (P for interaction <0.001). The relationship was also more pronounced in those without heart failure (P for interaction = 0.036) and those with lower CHA_2DS_2-VASc scores (P for interaction <0.001).

Age and the association between rhythm control and dementia

Figure 3 shows the relation between age and risk of all-cause dementia comparing rhythm and rate control. The association between rhythm control and lesser dementia risk decreased with advancing age in a linear relation. Initiating

Table 2. Dementia outcomes in weighted patients undergoing rhythm or rate control

Outcome	Number of events	Person-years	Event rate*	Number of events	Person-years	Event rate*	Absolute rate difference per 1,000 person-years* (95% CI)	Subdistribution hazard ratio (95% CI)	*P* value
Rhythm versus Rate control	Rhythm control (*N* = 22,558)			Rate control (*N* = 18,577)					
Including stroke									
All-cause dementia	1718	93,631	21.2	2,321	83,397	25.2	−4.0 (−6.5 to −1.5)	0.86 (0.80–0.93)	<0.001
Alzheimer's disease	1,167	94,949	14.2	1,580	85,301	16.7	−2.6 (−4.6 to −0.5)	0.86 (0.79–0.95)	0.002
Vascular dementia	392	96,584	4.7	516	87,616	5.5	−0.8 (−1.9 to 0.4)	0.88 (0.75–1.04)	0.126
Censoring for stroke									
All-cause dementia	1,400	89,706	18.1	1788	78,055	20.6	−2.5 (−4.9 to −1.7)	0.89 (0.82–0.97)	0.007
Alzheimer's disease	998	90,499	12.8	1,297	79,101	14.7	−2.0 (−3.9 to 0.0)	0.88 (0.79–0.97)	0.013
Vascular dementia	263	91,947	3.3	322	80,981	3.7	−0.4 (−1.4 to 0.6)	0.91 (0.74–1.11)	0.340
Ablation versus Rate control	Ablation (*N* = 1,508)			Rate control (*N* = 18,577)					
Including stroke									
All-cause dementia	49	7,672	9.1	2,321	83,397	17.9	−7.8 (−14.6 to −1.0)	0.59 (0.35–1.01)	0.053
Alzheimer's disease	36	7,721	7.6	1,580	85,301	10.6	−3.1 (−8.7 to 2.5)	0.78 (0.42–1.45)	0.437
Vascular dementia	13	7,756	1.5	516	87,616	4.2	−2.7 (−5.9 to 0.4)	0.39 (0.11–1.33)	0.133
AAD versus Rate control	AAD (*N* = 21,050)			Rate control (*N* = 18,577)					
Including stroke									
All-cause dementia	1,669	85,959	21.5	2,321	83,397	25.4	−3.8 (−6.4 to −1.3)	0.86 (0.78–0.96)	0.009
Alzheimer's disease	1,131	87,228	14.4	1,580	85,301	16.9	−2.5 (−4.6 to −0.4)	0.87 (0.76–0.99)	0.036
Vascular dementia	379	88,828	4.81	516	87,616	5.51	−0.7 (−1.9 to 0.5)	0.89 (0.71–1.12)	0.318

*Weighted incidence rate (per 1,000 person-years) comparing rhythm- and rate-controlled patients after overlap weighting was applied. AAD, anti-arrhythmic drug; CI, confidence interval.

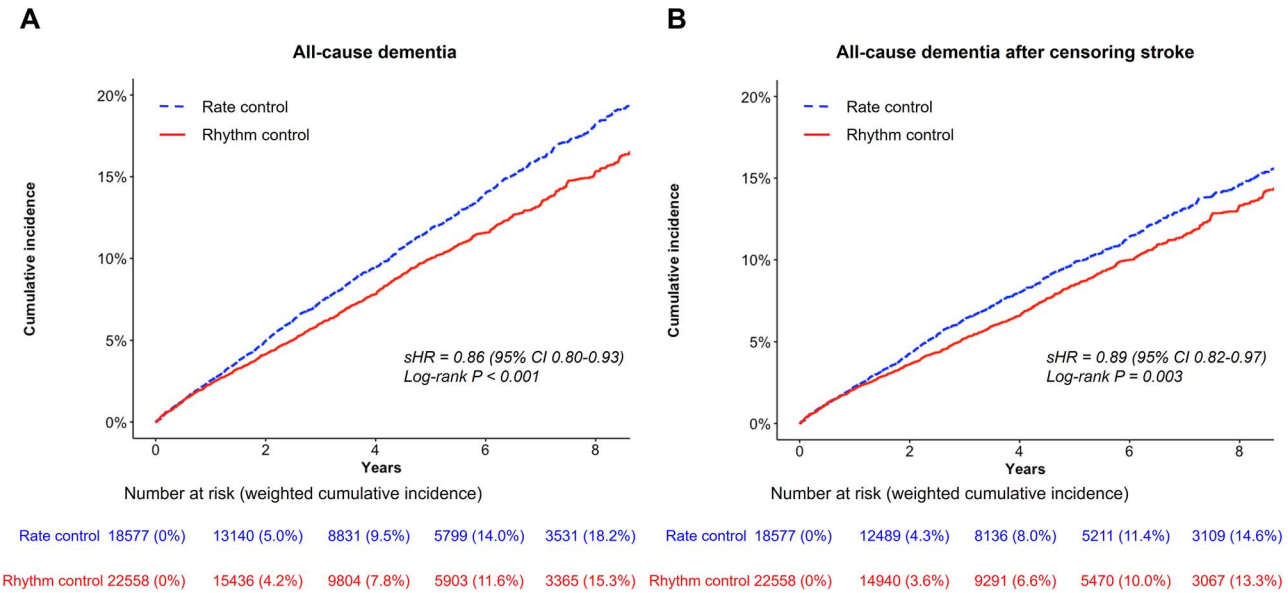

Figure 2. Weighted cumulative incidence curves for all-cause dementia in (A) overall and (B) after censoring stroke. CI, confidence interval; sHR, subdistribution hazard ratio.

rhythm-control treatments in those with younger age was associated with a lower risk of all-cause dementia compared with rate control and the point estimate exceeded 1 between the age of 80 and 90 years.

Risk of Alzheimer's disease and vascular dementia

Of the study population, 2,747 and 908 patients were diagnosed with Alzheimer's disease and vascular dementia. Rhythm control, compared with rate control, was related to a lower risk of Alzheimer's disease (14.2 and 16.7 per 1,000 person-years, sHR 0.86, 95% CI 0.79–0.95, $P = 0.002$) and there was a non-significant trend towards a lower risk of vascular dementia in rhythm-controlled patients (4.7 and 5.5 per 1,000 person-years, sHR 0.88, 95% CI 0.75–1.04, $P = 0.126$) (Table 2). The cumulative incidences of Alzheimer's disease (log-rank $P < 0.001$) were significantly

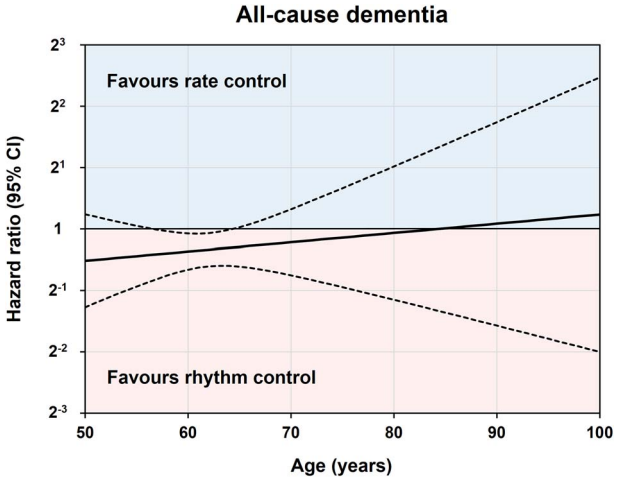

Figure 3. Relation between age at treatment initiation and risk of dementia for rhythm control or rate control. The *x*-axis shows the age at the time of treatment initiation; the *y*-axis, hazard ratios (HRs) associated with rhythm control compared with rate control. The grey horizontal line indicates HR = 1, which corresponds to an equal risk of outcomes in patients treated with rhythm and rate control. Dashed black lines show the 95% confidence interval (CI).

lower in the rhythm-control group than in the rate-control group (Appendix Figure 4).

Sensitivity analyses

All the results from the sensitivity analyses were generally consistent with the main findings (Appendix Figure 5 and Appendix Tables 7–15). Some patients switched between treatment strategies: 1,848 (9.9%) patients from rate control switched to rhythm control, whereas 11,260 (49.9%) patients switched from rhythm control to rate control during follow-up (Appendix Table 7). The results from the on-treatment approach in which patients were censored at the time of crossover between treatment arms or discontinuation of treatment were consistent with the main findings (Appendix Table 8). Time-varying regression analyses also revealed consistent findings (Appendix Table 9).

Discussion

In this study, our principal finding was that among anticoagulated patients with AF, the rhythm-control strategy was associated with a lower risk of dementia, compared with the rate-control strategy, even after adjusting for variations in background characteristics and competing for risk of death. This association was consistently evident after censoring for incident stroke. The association between rhythm control and lower dementia risk was more pronounced among patients who were relatively younger and those with fewer stroke risk factors.

Among the treatment modalities of rhythm control for AF, catheter ablation has been associated with a lower risk of dementia, in comparison with medical therapy [19, 20]. Recent prospective studies demonstrated an improvement in cognitive function among well-anticoagulated, ablated patients with AF [18, 23]. A recent observational study showed that ablated patients were at 27% lower risk of overall dementia, compared with medically treated patients (incidence rate per 1,000 person-years: 8.1 in the ablated patients versus 5.6 in the anti-arrhythmic or rate-control drug users) [19]. We enrolled an older population with more prevalent risk factors than the previous study (median age: 68 versus 60 years; median CHA_2DS_2-VASc score: 4 versus 2 points), which could explain the higher dementia incidence observed in this study. This study showed that rhythm-control therapy mainly based on anti-arrhythmic drugs was also associated with a lower risk of all-cause dementia, compared with rate control. Integrated AF management with the control of risk factors is also related to the reduced risk of dementia in patients with AF [26]. Among mid-life patients with AF, minimising the burden of hypertension has been suggested to be helpful in preventing dementia [22].

Our study shows that the rhythm-control strategy for AF was associated with a lower risk of Alzheimer's dementia, even after censoring for stroke. Alzheimer's disease is the most common type of dementia, and AF has been identified as a risk factor for Alzheimer's disease [7, 8]. Cerebral hypoperfusion due to a reduced cardiac output and a higher flow variability in AF could be a plausible mechanism for the AF-related cognitive impairment [27–29]. In the majority of cases, the brains of patients with Alzheimer's disease show vascular microinfarcts, white matter lesions, or vessel wall alterations [30]. Vascular risk factors correlated with a higher risk of Alzheimer's dementia in many epidemiological studies [30]. These vascular attributes might help to explain the association between AF and the increased risk of Alzheimer's disease or between rhythm control and a decreased risk of Alzheimer's disease. The relationship between rhythm control and lower dementia risk was more pronounced in younger patients with lower CHA_2DS_2-VASc scores. These findings suggest that the effect of rhythm control on dementia risk might be maximised in patients with AF without multiple risk factors, whereby electrophysiological remodelling could be partially reversed with rhythm control, rather than the substrate remodelling seen with ageing and comorbidities. In new AF guidelines, such characterisation of AF is advocated using the 4S-AF scheme (Stroke Risk; Symptoms; Severity of Burden; Substrate) for a more structured characterisation of AF to incorporate specific domains with treatment and prognostic implications [3, 31].

In this study, the point estimates for the risks of all-cause dementia and each subtype were closer to 1 after censoring patients at the time of incident stroke, suggesting that the reduction of dementia in this study might be partly attributable to the reduction of stroke by rhythm-control therapy. Given the relationship between AF and stroke, vascular dementia, encompassing both multi-infarct

and small vessel disease dementia, might be considered as an obvious contributory factor for cognitive decline in the AF population [6, 32]. A post-hoc analysis of the ATHENA trial demonstrated that dronedarone was associated with a significant reduction in the risk of ischaemic and haemorrhagic stroke [33]. Tsadok *et al.* reported in a population-based observational cohort that, in comparison with rate control, rhythm control was associated with lower rates of stroke/TIA among patients with AF, particularly among those with a moderate and high risk of stroke [34].

Study limitations

The present study has several limitations. In this claims-based database, the burden of AF was not evaluated, and its role as a contributor to outcomes remains unknown. Since we defined AF diagnoses and ablation cases only with ICD-10 or claim codes, data regarding types or symptoms of AF (paroxysmal versus non-paroxysmal; symptomatic versus non-symptomatic) were not available. Our observational study findings cannot be used to establish causal relationships, and residual confounding may persist even after propensity score weighting or matching (e.g. quality of anticoagulation and baseline cognitive function). However, the results from the falsification analysis revealed that the presence of significant systematic bias is less likely. We identified sufficient overlaps of propensity scores between the groups, which represents the existence of equipoise between the two treatment strategies [35]. We were unable to assess the effects of modifiable risk factors for Alzheimer's disease such as obesity, smoking, depression, cognitive inactivity and physical activity [36]. The occurrence of mild cognitive impairment was not compared, and dementia outcomes were ascertained by clinical diagnosis and associated medication use (a high-specificity assessment method). As such, milder cases may have remained undetected. However, the association between treatment and outcome is unlikely to be biased or overestimated by underascertainment of the outcome [37]. Although the subtypes of dementia were assessed using different ICD-10 codes, patients with dementia often exhibit a mixture of both pathologies [38]. When a diagnosis of a specific dementia type is made by physicians, they could be affected by the presence of AF and prevalent vascular risk factors or medication use associated with AF. Therefore, caution is warranted when interpreting associations according to dementia subtypes. Due to the active-comparator design of this study, asymptomatic patients with AF who did not require treatment could have been excluded. In addition, owing to the new user design in which prevalent drug users at the time of AF diagnosis were excluded, the proportion of treatment strategies chosen among patients with AF in this study cannot fully reflect the preferences in real-world clinical practice.

Conclusions

A rhythm-control strategy was associated with a lower risk of dementia than rate control in AF patients taking oral anticoagulants. The association was more pronounced in relatively younger patients with fewer stroke risk factors. It suggests that early initiation of a rhythm-control strategy on top of optimal anticoagulation in selected patients with AF might help prevent subsequent dementia.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: Gregory Y.H. Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees have been received directly or personally. Boyoung Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo and received research funds from Medtronic and Abbott. No fees have been received directly or personally. The remaining authors have nothing to declare.

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