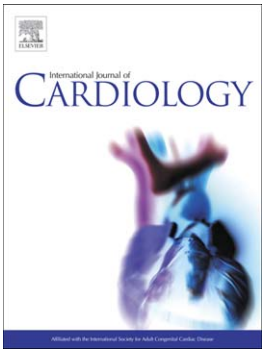
Statins and the risk of dementia in patients with atrial fibrillation

Chao, Tze-fan; Liu, Chia-jen; Chen, Su-jung; Wang, Kang-ling; Lin, Yenn-jiang; Chang, Shih-lin; Lo, Li-wei; Hu, Yu; Tuan, Ta-chuan; Chen, Tzeng-ji; Lip, Gregory; Chiang, Chern-en; Chen, Shih-ann

DOI:
10.1016/j.ijcard.2015.05.159

Document Version
Peer reviewed version

Citation for published version (Harvard):
Chao, T, Liu, C, Chen, S, Wang, K, Lin, Y, Chang, S, Lo, L, Hu, Y, Tuan, T, Chen, T, Lip, GYH, Chiang, C & Chen, S 2015, 'Statins and the risk of dementia in patients with atrial fibrillation: a nationwide population-based cohort study', International Journal of Cardiology, vol. 196, pp. 91-97. https://doi.org/10.1016/j.ijcard.2015.05.159



Statins and the Risk of Dementia in Patients with Atrial Fibrillation: A Nationwide Population-Based Cohort Study

Tze-Fan Chao, Chia-Jen Liu, Su-Jung Chen, Kang-Ling Wang, Yenn-Jiang Lin, Shih-Lin Chang, Li-Wei Lo, Yu-Feng Hu, Ta-Chuan Tuan, Tzeng-Ji Chen, Gregory Y.H. Lip, Chern-En Chiang, Shih-Ann Chen

PII: S0167-5273(15)01261-9
DOI: doi: 10.1016/j.ijcard.2015.05.159
Reference: IJCA 20629

To appear in: *International Journal of Cardiology*

Received date: 29 April 2015
Accepted date: 27 May 2015

Please cite this article as: Chao Tze-Fan, Liu Chia-Jen, Chen Su-Jung, Wang Kang-Ling, Lin Yenn-Jiang, Chang Shih-Lin, Lo Li-Wei, Hu Yu-Feng, Tuan Ta-Chuan, Chen Tzeng-Ji, Lip Gregory Y.H., Chiang Chern-En, Chen Shih-Ann, Statins and the Risk of Dementia in Patients with Atrial Fibrillation: A Nationwide Population-Based Cohort Study, *International Journal of Cardiology* (2015), doi: 10.1016/j.ijcard.2015.05.159

Statins and the Risk of Dementia in Patients with Atrial Fibrillation: A Nationwide Population-Based Cohort Study

Tze-Fan Chao, M.D.[1,2], Chia-Jen Liu, M.D.[3,4], Su-Jung Chen, M.D.[4,5], Kang-Ling Wang, M.D.[1,2], Yenn-Jiang Lin, M.D.[1,2], Shih-Lin Chang, M.D.[1,2], Li-Wei Lo, M.D.[1,2], Yu-Feng Hu, M.D.[1,2], Ta-Chuan Tuan, M.D.[1,2,], Tzeng-Ji Chen, M.D.[6], Gregory Y. H. Lip, M.D.[7], Chern-En Chiang, M.D., Ph.D.[1,2,8,9] and Shih-Ann Chen, M.D.[1,2]

[1]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan. [2]Institute of Clinical Medicine, and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan. [3]Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan. [4]Institute of Public Health and School of Medicine, National Yang-Ming University, Taipei, Taiwan. [5]Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan. [6]Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan. [7]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom [8]General Clinical Research Center, Taipei Veterans General Hospital, Taipei, Taiwan. [9]Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan.

Dr. Tze-Fan Chao and Dr. Chia-Jen Liu contributed equally to this study

Running title: statin and dementia in AF

Total word count: 4,854

Address for correspondence

Chern-En Chiang, M.D., Ph.D., FACC, FESC

General Clinical Research Center, Taipei Veterans General Hospital

No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan.

Tel: 866-2-2875-7774

Fax: 886-2-2874-5422

E-Mail: cechiang@vghtpe.gov.tw

Shih-Ann Chen, M.D.

Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital,

No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan.

Tel: 886-2-2875-7156

Fax: 886-2-2873-5656

E-Mail: epsachen@ms41.hinet.net

Abstract

Background: Atrial fibrillation (AF) is associated with cognitive decline and may contribute to an increased risk of dementia. The goal of the present study was to investigate whether statin use prevented non-vascular dementia in subjects with AF.

Methods: Data from the National Health Insurance Research Database of Taiwan were used in this study. The study group comprised 51,253 AF subjects aged ≥ 60 years who had received statin treatment. For each study patient, four age- and sex-matched AF subjects without statin exposure were selected as the control group (n = 205,012). The risk of non-vascular dementia was compared between the statin and control groups.

Results: During the follow-up period, 17,201 patients experienced non-vascular dementia. The annual incidence of non-vascular dementia was lower in the statin group than in the control group (1.89% *vs.* 2.20%; $p < 0.001$). Statin use exhibited a protective effect on the occurrence of non-vascular dementia, with an adjusted hazard ratio (HR) of 0.832 (95% confidence interval = 0.801–0.864). Among statin types, the use of rosuvastatin was associated with the largest risk reduction (adjusted HR = 0.661). Statin exposure duration was related inversely to the risk of non-vascular dementia.

Conclusions: In this large-scale nationwide cohort study, statin use was associated with a lower risk of non-vascular dementia in AF. Use of more potent statin and longer exposure time may be associated with greater benefits.

Key words: atrial fibrillation, statin, dementia

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia; its prevalence increases steadily with age and it affects up to 9% of the population aged > 80 years.[1] Worldwide, the number of people aged ≥ 65 years will reach 1.3 billion by 2040,[2] and the incidence of AF is projected to rise continuously over the next few decades due to the aging of the population.[3,4] Similar to AF, the prevalence of dementia, a disorder characterized by memory and cognitive impairments, also increases with age. Recent evidence has demonstrated that AF is associated with an increased risk of cognitive and functional decline and may contribute to the risk of dementia.[2,5-7] In a meta-analysis of eight studies including 77,668 patients, Santangeli et al reported that AF increased the risk of incident dementia by 42%.[7] Thus, how to prevent the occurrence of dementia in patients with AF is an interesting and important issue.

It is generally believed that statins have pleiotropic effects beyond their lipid-lowering activities. The potential benefits of statin use in preventing dementia was first reported in 2000, when two epidemiologic studies reported a lower risk of dementia in statin users.[8,9] Although several subsequent studies reported inconsistent results,[10-13] a recently published meta-analysis that pooled data from eight long-term studies demonstrated a 29% reduction in incident dementia in statin-treated patients.[14] As these previous studies did not focus on the population of patients with AF, whether the use of statin can reduce the risk of dementia in these patients remains unknown.

The objective of the present study was to investigate whether statin use was associated with a lower risk of incident dementia in patients with AF. We tested the hypothesis that statin use would result in less dementia, and second, this would be related to use of more potent statins and longer statin exposure duration.

Methods

Database

Data from the National Health Insurance Research Database (NHIRD), released by the Taiwan National Health Research Institutes, were used in this study. The National Health Insurance (NHI) system is a mandatory universal program that offers comprehensive medical care coverage to all Taiwanese residents. The NHIRD contains detailed health care data from >25 million enrollees, representing >99% of Taiwan's population. In this cohort dataset, the patients' original identification numbers have been encrypted to protect their privacy, but the encryption procedure was consistent, allowing linkage of claims belonging to the same patient within the NHI database and continuous following of patients. The large sample size of this database provided a good opportunity to study the association between statin use and incident dementia in patients with AF.

Study population and definition of study endpoint

The records of 292,029 patients aged ≥ 60 years who were newly diagnosed with AF between 1 January 1996 and 31 December 2011 were retrieved from the NHIRD. AF was diagnosed using the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) codes (427.31). To ensure the accuracy of diagnosis, only patients whose AF was confirmed more than twice in the outpatient department or diagnosed at discharge were included in the AF cohort.[15] The diagnostic accuracy of AF using this definition in NHIRD has been validated previously.[16,17] Each patient's prescriptions for statins available in Taiwan were identified. These drugs included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. Among the AF cohort, 51,253 subjects who had continuously received statins for >30 days and had no past history of dementia

(ICD-9-CM codes 290.0–290.3, 290.4, 294.1x, 294.2x, and 331.0) were identified as the study group (statin users). We defined the date of statin prescription, when each study subject was identified, to be the index date. On the same index date of one study patient, four age- and sex-matched subjects without statin exposure were selected for each included study patient to constitute the control group. The duration between the diagnosis of AF and index date was defined as the "AF duration".

The study endpoint was the occurrence of non-vascular dementia, including pre-senile and senile dementia (ICD-9-CM codes 290.0–290.3) and Alzheimer's disease (ICD-9-CM code 331.0).[18] Vascular dementia (ICD-9-CM code 290.4) was not defined as the study endpoint. All subjects were followed until the study endpoint or for 10 years after enrollment. For each patient in the statin group, the duration of exposure (days) to each type of statin from the time of enrollment to the study endpoint or the end of follow up was calculated. The dominant type of statin treatment was determined based on the longest duration of exposure. The total duration of exposure to statins was defined as the sum of the durations of all statin usages during the follow-up period.

Statistical analysis

Data are presented as mean values and standard deviations for normally distributed continuous variables, medians and interquartile ranges for skewed data, and proportions for categorical variables. The differences between normally distributed continuous values were assessed using unpaired two-tailed *t*-tests. The Mann–Whitney rank-sum test was used for the analysis of skewed variables, and the differences between nominal variables were compared with the chi-squared test. The risk of non-vascular dementia was assessed using Cox regression analysis. An event-free survival curve was plotted using the Kaplan–Meier method with the time zero setting at the index date, and its statistical significance was examined

using the log-rank test. All statistical significance levels were set at $p < 0.05$ and all statistical analyses were performed using SPSS software (ver. 17.0; SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients

The mean age of the study population was 73.2 ± 7.4 years, and 49.7% of patients were men. Hypertension was the most prevalent comorbidity, noted in 92.5% of patients. Baseline characteristics of the statin and control groups are shown in Table 1. Patient age, sex, and CHA_2DS_2-VASc score were matched between the statin and control groups. Patients in the statin-users group had more comorbidities, including diabetes mellitus, previous vascular diseases, end-stage renal disease, chronic obstructive pulmonary disease, autoimmune diseases, thyroid diseases, and sleep apnea, than controls. In contrast, hypertension, congestive heart failure, and liver cirrhosis were more prevalent in the control group. More patients in the statin group than in the control group took aspirin, clopidogrel, warfarin, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. Digoxin was more commonly used in the control group than in the statin group.

Statins and the risk of non-vascular dementia

During the follow-up period, 17,201 (6.7%) patients developed incident non-vascular dementia. The annual incidence of non-vascular dementia was lower in the statin-users group than in the control group (1.89% *vs.* 2.20%; $p < 0.001$; Table 2). Kaplan–Meier survival analysis showed that statin use was associated with a lower risk of incident dementia during the follow-up period (Figure 1). Statin use exhibited a protective effect on the occurrence of non-vascular dementia, with a hazard ratio (HR) of 0.856 (95% confidence interval [CI] = 0.824–0.889; $p < 0.001$) in the univariate regression analysis. After adjustment for age,

gender, and differences in baseline characteristics, the HR was 0.832 (95% CI = 0.801–0.864; $p < 0.001$) (Table 3). In the subgroup analysis, statin use was consistently associated with a lower risk of dementia in different groups of patients (Figure 2). Among patients without previous history of stroke/transient ischemic attack and did not experience stroke during the follow-up period (n = 109,697), the risk of non-vascular dementia was lower in the statin group with a HR of 0.831 (95% CI = 0.795-0.909, $p < 0.001$).

Although the use of anti-thrombotic agents, including warfarin, aspirin and clopidogrel, were significantly different between study and control groups, the risk of dementia was still lower in the statin group for patients without use of these anti-thrombotic drugs (n = 116,727) with an adjusted HR of 0.844 (95% CI = 0.795-0.896, $p < 0.001$)(Figure 2).

Sensitivity analysis

Among the 17,201 patients suffering non-vascular dementia, the diagnoses were made or confirmed by neurologists and psychologists in 8,770 (51.0%) subjects, and 12,820 (74.5%) patients had brain imaging studies, including a computed tomography scan or magnetic resonance imaging. When the study endpoint was defined as non-vascular dementia diagnosed or confirmed by neurologists and psychologists, statin use was still associated with a lower risk of non-vascular dementia with an adjusted HR of 0.781 (95% CI = 0.739-0.824; $p < 0.001$) after adjustment for age, gender, and differences in baseline characteristics. When brain imaging studies were required for the diagnosis of study endpoint in addition to being confirmed by neurologists and psychologists, the risk of non-vascular dementia was also consistently lower in the statin group with an adjusted HR of 0.817 (95% CI = 0.769-0.869; $p < 0.001$). When patients who experienced stroke within 1 year before the non-vascular dementia was diagnosed (n = 688) were further excluded from the clinical endpoint, the HR of non-vascular dementia for statin group was 0.847 (95% CI = 0.798-0.900, p <0.001).

Types of statin, exposure duration, and the risk of non-vascular dementia

In a subgroup analysis of the different types of statin, rosuvastatin was associated with the largest (34%) relative risk reduction for incident dementia, with an adjusted HR of 0.661 (95% CI = 0.602–0.727; $p < 0.001$; Figure 3A). Conversely, fluvastatin and lovastatin exhibited no significant protective effect on the occurrence of non-vascular dementia (Figure 3A). We further divided statin users (n = 51,253) into four groups based on quartile values of statin exposure duration and compared the risk of non-vascular dementia among these groups, with the first quartile group serving as the reference population. As shown in Figure 3B, the risk of non-vascular dementia decreased with increasing duration of statin exposure.

Propensity-matched analysis

Because statin and control groups have different baseline characteristics, we performed a propensity score–matched analysis, in which we calculated a propensity score for the likelihood of using statins by multivariate logistic regression analysis, conditional on the baseline covariates listed in Table 1. After that, we matched each study patient to a control participant on the basis of age, gender, and propensity score (±0.01). The results of the propensity score model about the probability of the use of statins were shown in Supplemental Table 1. Supplemental Figure 1 showed the distributions of propensity scores of study subjects before and after the propensity match. Baseline characteristics of the statin and control groups after propensity match were shown in Supplemental Table 2. Age, gender, comorbidities and medications were not statistically different between patients with and without statin exposure. The risk of non-vascular dementia was significantly lower in the statin group than that of the control group, as demonstrated by the Kaplan–Meier survival analysis (log-rank test, p<0.0001) (Supplemental Figure 2).

Discussion

Main findings

In this nationwide cohort study, we compared the risk of non-vascular dementia in statin users and non-users with AF. The main findings were: (1) Statin use may play a role in preventing incident non-vascular dementia, with a 17% risk reduction in patients with AF aged ≥ 60 years. The association between stain use and a lower risk of dementia was observed consistently in propensity-matched cohorts and when several sensitiviy analyses with different criterions required to define non-vascular dementia were performed. (2) A potent statin such as rosuvastatin was associated with the largest risk reduction, whereas fluvastatin and lovastatin had no protective effects. (3) Statin exposure duration was inversely associated with the risk of non-vascular dementia.

Atrial fibrillation and dementia

Similar to AF, the disease burden of dementia is increasing with the ageing population . Non-vascular dementia, including senile dementia and Alzheimer's disease, is the most common type of dementia in elderly individuals, accouting for 80–90% of cases, with the remainder accounted by vascular dementia.[5,19,20] In addition to age, dementia and AF share some background risk factors such as hypertension, diabetes, smoking, and systemic inflammation.[21,22]

Recent studies have increasingly disclosed important links between AF and dementia.[2,5-7] In a study involving 37,025 patients, Bunch et al. found that AF was independently associated with all forms of dementia, including non-vascular and vascular types.[5] A recent post-hoc analysis of the "ONTARGET" and "TRANSCEND" randomized controlled trials, which involved 31,546 patients (1,016 with AF at baseline and an additional 2,052 participants with AF during follow up), demonstrated that AF was associated with an increased risk of cognitive and functional decline, and the results were consistent among patients with and without stroke.[6] These previous findings suggest that the link between AF and dementia cannot be fully explained by cerebral infarction caused by AF-related thormboembolism.

In addition to an increased risk of dementia in AF patients, the coexistence of AF and dementia also significanlty increases the risk of mortality.[5] Thus, the development of an effective method to reduce the risk of dementia in the AF population is clinically important. Although two epidemiologic studies in the general population initially reported a 60% lower prevalence of dementia in statin users in 2000,[8,9] several subsequent studies yielded inconsistent findings. Rea et al. showed that statin therapy was not associated with a decreased risk of dementia in a community-based cohort of 2,798 subjects aged $\geq$ 65 years.[13] Statin therapy also failed to show benefits in preventing cognitive decline in the PROSPER trial.[23] Given these conflicting results and the lack of studies focusing on patients with AF, a study with a larger population and longer follow-up period is needed to confirm the effects of statin in the prevention of dementia in these patients.

In the present study, we demonstrated that statins may be useful in preventing non-vascular dementia in the AF population. To our knowledge, it is the first large-scale nationwide study to investigate the relationship between statin use and the risk of non-vascular dementia, specifically in subjects with AF.

Statins and the risk of dementia

The mechanism(s) underlying the usefulness of statin in the prevention of dementia remain incompletely understood. Several previous studies showed that atherosclerosis was involved in the pathogenesis of not only vascular, but also non-vascular, dementia, such as Alzheimer's disease, through the promotion of vascular and plaque/tangle pathologies in the brain.[24,25] Thus, statins may prevent dementia *via* anti-atherosclerotic effects. However, as the endpoint of the present study was non-vascular dementia, other effects in addition to the anti-atherosclerotic activity of statins may also be important. Statins possess anti-inflammatory properties and have been demonstrated to reduce high-sensitivity C-reactive protein levels.[26] Several recent studies have even suggested that an increased systemic inflammatory status is associated with accelerated cognitive decline and increased risk of dementia.[27-29] Indeed, there is also plausible evidence demonstrating that inflammation plays an important role in the pathogenesis of AF.[30,31] Accordingly, the use of statins may protect patients with AF from dementia by reducing systemic inflammation.

Clinical implications

The present study shows that statins may be able to prevent non-vascular dementia in patients with AF. The protective effects of statin use were consistently observed in subgroup analyses based on patients' comorbidities and medications. A lower risk of non-vascular dementia was still observed in patients receiving statin treatment compared to matched controls. Use of more potent statins, such as rosuvastatin, atorvastatin and simvastatin, and longer exposure time were associated with an even greater risk reduction in dementia. One exception was pravastatin which exhibited a more obvious protective effect than atorvastatin and simvastatin. However, pravastatin may have different effects from simvastatin on the level of lipoprotein in the cerebrospinal fluid and the expression of dementia-related genes in human astrocytes and neuronal cells.[32,33] However, the precise mechanisms behind the obvious effects of pravastatin in reducing non-vascular dementia were unclear, and the data presented here should be interpreted carefully and further confirmed. Taking these findings together, statins should be considered as a potential treatment for patients with AF aged $\geq$ 60 years to prevent non-vascular dementia in addition to lowering lipid levels.

Study limitations

The strengths of our study include the use of a nationwide dataset, which contained data from a large sample of AF subjects and enabled the continuous tracing of dementia risk in statin users and non-users. However, our study has several important limitations. First, while we reported the significant association between non-vascular dementia and statin use, these results were derived from an observational database. Therefore, we were not able to conclude that statins had directly protective effects against dementia, and only a prospective and randomized trial can answer the question. Second, the diagnosis of dementia was based on the diagnostic codes registered by the physicians responsible for the treatments of patients,

and data about the degree and severity of cognitive impairment were lacking. Third, we defined study endpoint as "non-vascular dementia" and excluded "vascular dementia" using the ICD-9 codes. Therefore, the under recognition of the vascular factors which could cause dementia is possible. However, we have tried to minimize the possibility of misclassification of non-vascular dementia using subgroup and sensitivity analyses. Fourth, multiple baseline characteristics differed between the statin and control groups, as the present study was not a prospective trial. However, age, gender, and CHA_2DS_2-VASc score were matched between these two groups, and the reliability of our findings was further supported by the observed inverse relationship between statin exposure duration and the risk of non-vascular dementia. Lastly, the detailed information about the dose optimization and compliances of statins and other medications was not available in this registry database.

Conclusion

In this large-scale cohort study, statin use was associated with a 17% reduction in the risk of non-vascular dementia among patients with AF aged ≥ 60 years. Use of more potent statin and longer exposure time resulted in greater benefits. A prospective randomized trial is needed to confirm these findings.

Acknowledgments

This work was supported in part by grants from the National Science Council (NSC98-2410-H-010-003-MY2, NSC102-2628-B-075-004-MY3), and Taipei Veterans General Hospital (V99C1-140, V99A-153, V100D-002-3, V101D-001-2, and V102B-025).

Disclosures

None.

References

1. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol* 2009;104:1534-1539.

2. Dublin S, Anderson ML, Haneuse SJ, et al. Atrial fibrillation and risk of dementia: a prospective cohort study. *Journal of the American Geriatrics Society* 2011;59:1369-1375.

3. Potpara TS, Lip GY. Lone atrial fibrillation: what is known and what is to come. *Int J Clin Pract* 2011;65:446-457.

4. Tse HF, Wang YJ, Ahmed Ai-Abdullah M, et al. Stroke prevention in atrial fibrillation--an Asian stroke perspective. *Heart Rhythm* 2013;10:1082-1088.

5. Bunch TJ, Weiss JP, Crandall BG, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm* 2010;7:433-437.

6. Marzona I, O'Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *CMAJ : Canadian Medical Association journal* 2012;184:E329-336.

7. Santangeli P, Di Biase L, Bai R, et al. Atrial fibrillation and the risk of incident dementia: a meta-analysis. *Heart Rhythm* 2012;9:1761-1768.

8. Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Archives of neurology* 2000;57:1439-1443.

9. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. *Lancet* 2000;356:1627-1631.

10. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.

11. Rodriguez EG, Dodge HH, Birzescu MA, Stoehr GP, Ganguli M. Use of lipid-lowering drugs in older adults with and without dementia: a community-based epidemiological study. *Journal of the American Geriatrics Society* 2002;50:1852-1856.

12. Zandi PP, Sparks DL, Khachaturian AS, et al. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Archives of general psychiatry* 2005;62:217-224.

13. Rea TD, Breitner JC, Psaty BM, et al. Statin use and the risk of incident dementia: the Cardiovascular Health Study. *Archives of neurology* 2005;62:1047-1051.

14. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects. *Mayo Clin Proc* 2013;88:1213-1221.

15. Chen SJ, Liu CJ, Chao TF, et al. Dental scaling and atrial fibrillation: a nationwide cohort study. *Int J Cardiol* 2013;168:2300-2303.

16. Lin LJ, Cheng MH, Lee CH, Wung DC, Cheng CL, Kao Yang YH. Compliance with antithrombotic prescribing guidelines for patients with atrial fibrillation--a nationwide descriptive study in Taiwan. *Clin Ther* 2008;30:1726-1736.

17. Chang CH, Lee YC, Tsai CT, et al. Continuation of statin therapy and a decreased risk of atrial fibrillation/flutter in patients with and without chronic kidney disease. *Atherosclerosis* 2014;232:224-230.

18. Chen PL, Lee WJ, Sun WZ, Oyang YJ, Fuh JL. Risk of dementia in patients with insomnia and long-term use of hypnotics: a population-based retrospective cohort study. *PloS one* 2012;7:e49113.

19. Caselli RJ. Current issues in the diagnosis and management of dementia. *Seminars in neurology* 2003;23:231-240.

20. Morris JC. Dementia update 2003. *Alzheimer disease and associated disorders* 2003;17:245-258.

21. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005;64:277-281.

22. Schram MT, Euser SM, de Craen AJ, et al. Systemic markers of inflammation and cognitive decline in old age. *Journal of the American Geriatrics Society* 2007;55:708-716.

23. Trompet S, van Vliet P, de Craen AJ, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *Journal of neurology* 2010;257:85-90.

24. Roher AE, Esh C, Kokjohn TA, et al. Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arterioscler Thromb Vasc Biol* 2003;23:2055-2062.

25. Yarchoan M, Xie SX, Kling MA, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. *Brain : a journal of neurology* 2012;135:3749-3756.

26. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001;286:64-70.

27. Komulainen P, Lakka TA, Kivipelto M, et al. Serum high sensitivity C-reactive protein and cognitive function in elderly women. *Age and ageing* 2007;36:443-448.

28. Xu G, Zhou Z, Zhu W, Fan X, Liu X. Plasma C-reactive protein is related to cognitive deterioration and dementia in patients with mild cognitive impairment. *J Neurol Sci* 2009;284:77-80.

29. Wersching H, Duning T, Lohmann H, et al. Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. *Neurology* 2010;74:1022-1029.

30. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. *J Am Coll Cardiol* 2007;50:2021-2028.

31. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol* 2012;60:2263-2270.

32. Vuletic S, Riekse RG, Marcovina SM, Peskind ER, Hazzard WR, Albers JJ. Statins of different brain penetrability differentially affect CSF PLTP activity. *Dementia and geriatric cognitive disorders* 2006;22:392-398.

33. Dong W, Vuletic S, Albers JJ. Differential effects of simvastatin and pravastatin on expression of Alzheimer's disease-related genes in human astrocytes and neuronal cells. *Journal of lipid research* 2009;50:2095-2102.

Table 1 Baseline characteristics of the subjects

Variables	Statin group (n=51,253)	Control group (n=205,012)	P value
Age, years	73.2 ± 7.4	73.2 ± 7.4	0.999
Age ≥ 65 years, n (%)	44,068 (86.0)	176,272 (86.0)	1
Gender (male), n (%)	25,490 (49.0)	101,960 (49.0)	1
CHA_2DS_2-VASc score, median (inter-quartile range)	5 (4-6)	5 (4-6)	1
AF duration, years	2.01 ± 2.47	2.09 ± 2.42	<0.001
Medical history (components of CHA_2DS_2-VASc score)			
Hypertension	46,337 (90.4)	190,622 (93.0)	<0.001
Diabetes mellitus	25,091 (49.0)	98,564 (48.1)	<0.001
Congestive heart failure	25,749 (50.2)	109,528 (53.4)	<0.001
Previous stroke/TIA	24,444 (47.7)	98,044 (47.8)	0.596
Previous vascular diseases	26,610 (51.9)	95,998 (46.8)	<0.001
Medical history			
End-stage renal disease	1,095 (2.1)	2,633 (1.3)	<0.001
COPD	4,944 (9.6)	19,087 (9.3)	0.020
Malignancy	2,859 (5.6)	11,597 (5.7)	0.491
Autoimmune diseases	1,351 (2.6)	4,608 (2.2)	<0.001
Thyroid diseases	1,567 (3.1)	5,278 (2.6)	<0.001
Liver cirrhosis	743 (1.4)	5,258 (2.6)	<0.001
Sleep apnea	908 (1.8)	3,319 (1.6)	0.015
Medications			
Aspirin	24,521 (47.8)	81,145 (39.6)	<0.001
Clopidogrel	5,409 (10.6)	100,81 (4.9)	<0.001
Warfarin	6,752 (13.2)	23,274 (11.4)	<0.001
Digoxin	11,935 (23.2)	52,131 (25.4)	<0.001
ACEIs/ARBs	20,330 (39.7)	69,531 (33.9)	<0.001

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II-receptor blocker; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack.

Table 2 Incidence (per 100 person-years) of non-vascular dementia in patients with and without statin use

Groups	Number of events	Number of Patients	Person-years	Incidence*
Statin	3,342	51,253	177,271	1.89
Control	13,859	205,012	630,737	2.20

*Number of ischemic strokes per 100 person-years of follow-up

Table 3 Cox regression models on the relationship between stain use and risk of non-vascular dementia

Models	HR (statin versus control group)	95% CI	P value
Model 1: unadjusted regression analysis	0.856	0.824-0.889	<0.001
Model 2: adjusted for age, gender	0.835	0.804-0.867	<0.001
Model 3: adjusted for age, gender and CHA_2DS_2-VASc score	0.828	0.797-0.860	<0.001
Model 4: adjusted for age, gender, CHA_2DS_2-VASc score and AF duration	0.826	0.795-0.858	<0.001
Model 5: adjusted age, gender, AF duration, hypertension, diabetes mellitus, heart failure, vascular diseases, end-stage renal disease, COPD, autoimmune diseases, thyroid diseases, liver cirrhosis and sleep apnea	0.829	0.798-0.861	<0.001
Model 6: adjusted for all variables in model 5, and the use of aspirin, clopidogrel, warfarin, digoxin and ACEI/ARB	0.832	0.801-0.864	<0.001

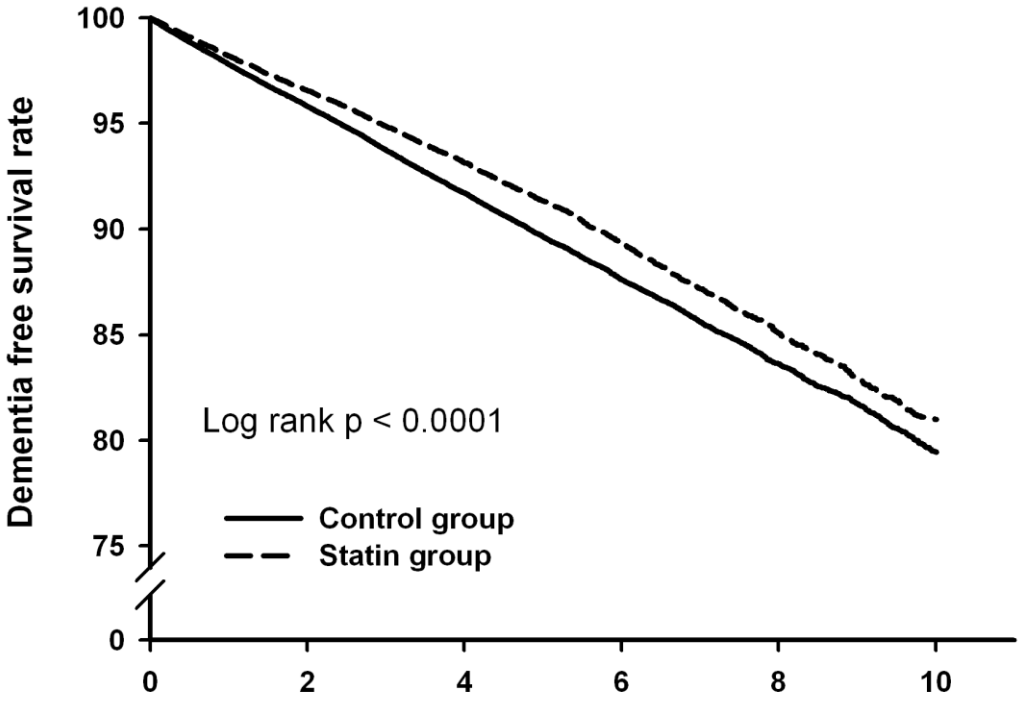
ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II-receptor blocker; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio

Figure Legends

Figure 1 Statin use and the risk of dementia. Kaplan–Meier survival analysis showed that statin use was associated with a lower risk of dementia during the follow-up period.

Figure 2 Statin use and the risk of dementia in different groups of patients. In the subgroup analysis, statin use was consistently associated with a lower risk of dementia in different groups of patients. *Adjustment for age, gender, AF duration, hypertension, diabetes mellitus, heart failure, vascular diseases, end-stage renal disease, COPD, autoimmune diseases, thyroid diseases, liver cirrhosis, sleep apnea and the use of aspirin, clopidogrel, warfarin, digoxin and ACEI/ARB. ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II-receptor blocker; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; TIA = transient ischemic attack.

Figure 3 Types of statin, exposure duration, and the risk of dementia. (A) Rosuvastatin was associated with the lowest risk of dementia compared with statin non-users. Conversely, fluvastatin and lovastatin did not significantly protect patients with AF from dementia. (B) Among statin users, a longer duration of statin exposure was associated with a lower risk of dementia. *Adjustment for the same variables in Figure 2.Abbreviations as in Figure 2.



Number at risk						
Control	205012	114318	62587	30360	12265	3662
Statin	51253	31704	18498	9549	4041	1273

Figure 1

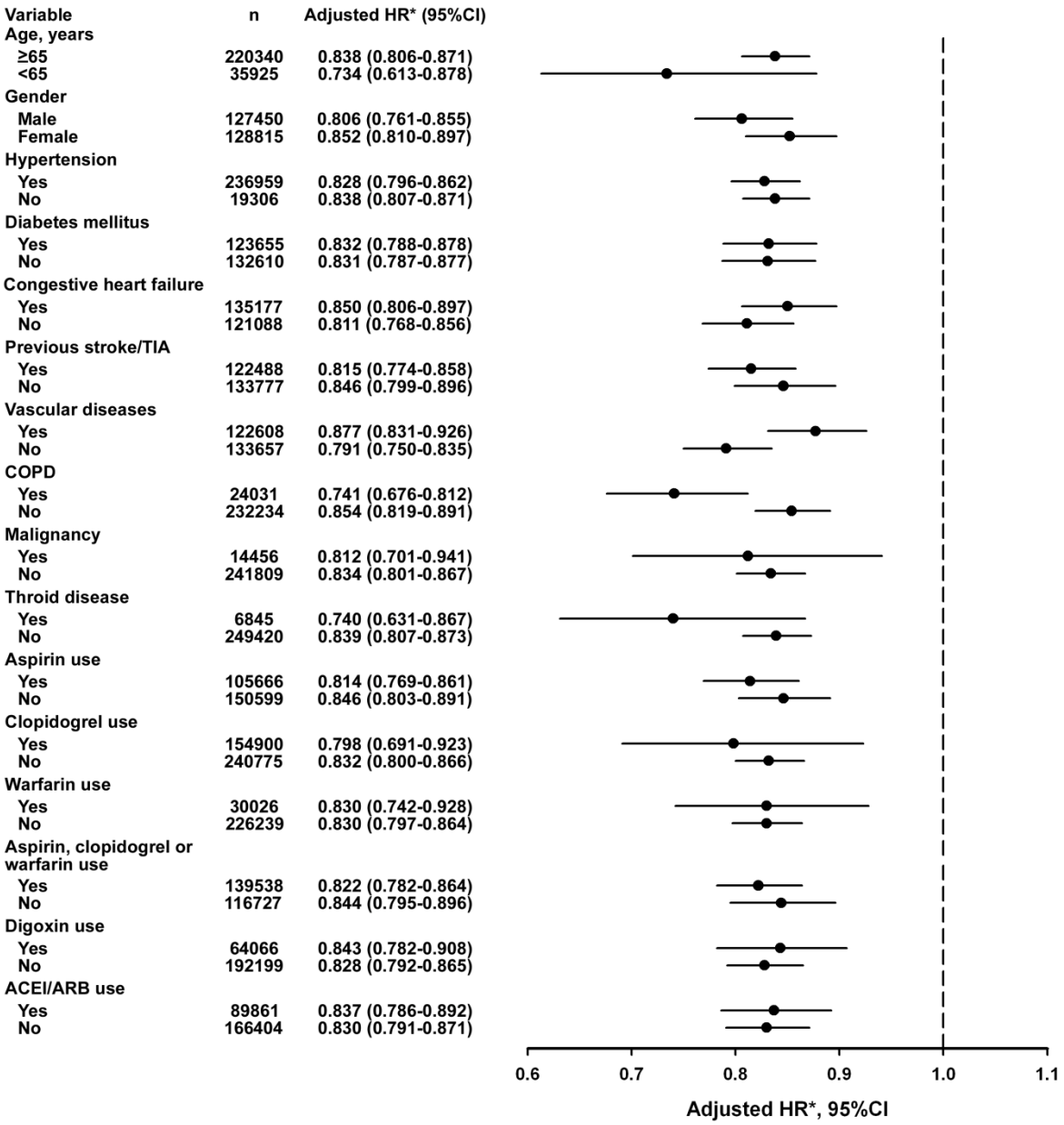


Figure 2

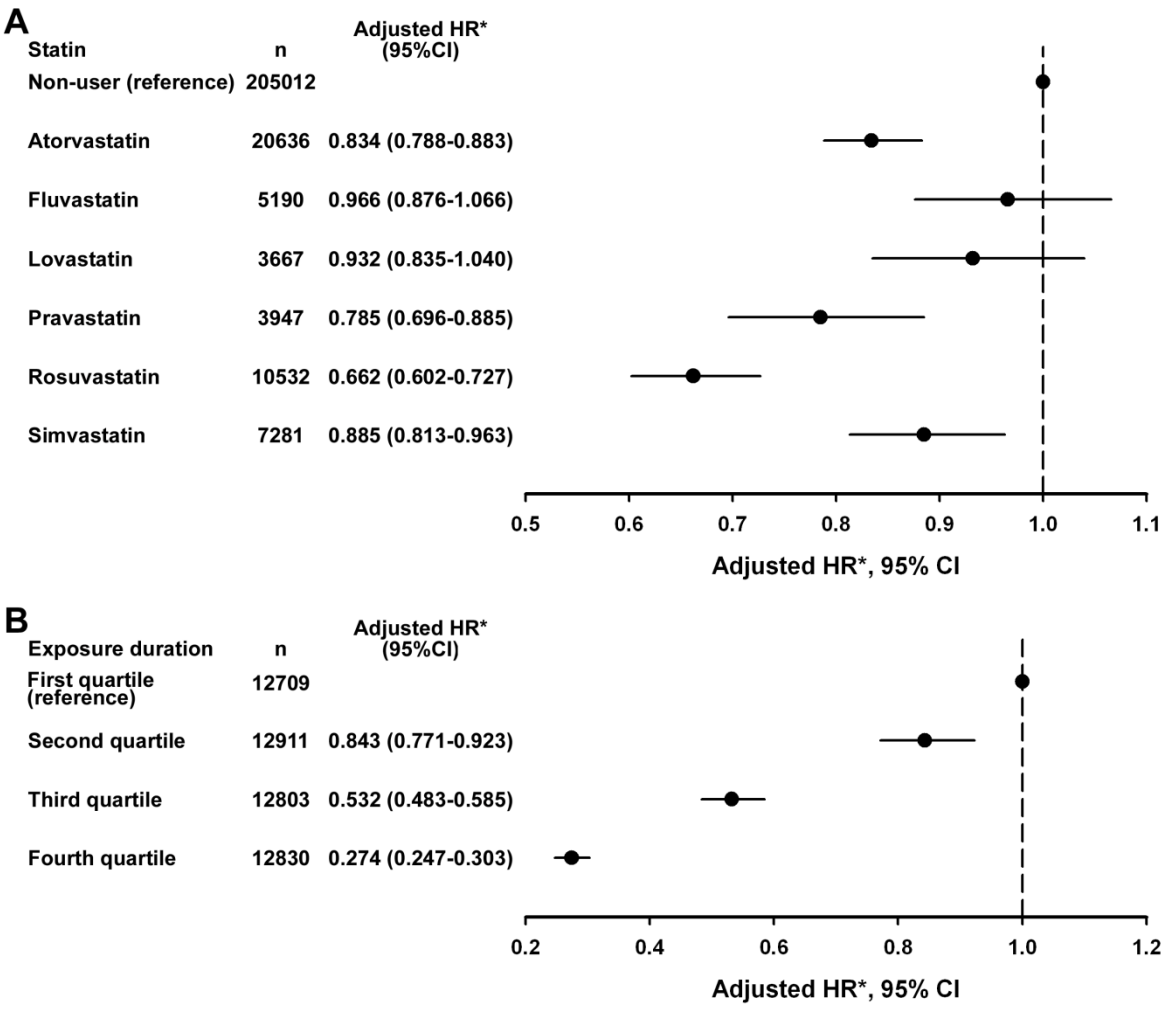


Figure 3