ABSTRACT

Introduction Non-valvular atrial fibrillation (NVAF) is known as a robust risk factor for stroke. Recent reports have suggested a risk of dementia with NVAF, but much remains unknown regarding the relationship between this mechanism and the potential protective effects of novel anticoagulants (direct oral anticoagulants (DOACs), or non-vitamin K oral anticoagulants).

Methods and analysis This study, the strategy to obtain warfarin or DOAC’s benefit by evaluating registry, is an investigator-initiated, multicentre, prospective, observational, longitudinal cohort study comparing the effects of warfarin therapy and DOACs on cerebrovascular diseases and cognitive impairment over an estimated duration of 36 months. Once a year for 3 years, the activities of daily living and cognitive functioning of non-demented patients with NVAF will be assessed. Demographics, risk factors, laboratory investigations, lifestyle, social background and brain MRI will be assessed.

Ethics and dissemination This protocol has been approved by the ethics committee of the National Center for Geriatrics and Gerontology (No. 1017) and complies with the Declaration of Helsinki. Informed consent will be obtained before study enrolment and only coded data will be stored in a secured database. The results will be published in peer-reviewed journals and presented at scientific meetings to ensure the applicability of the findings in clinical practice.

Trial registration number UMIN000025721.
In patients with non-valvular atrial fibrillation (NVAF), anticoagulant therapy is recommended to prevent stroke. In the past, warfarin was recommended as an anticoagulant, but recently, novel anticoagulants—direct oral anticoagulants (DOACs, or non-vitamin K oral anticoagulants)—have been developed and widely introduced. In particular, we previously revealed that DOACs may be associated with a lower risk of cerebral haemorrhage and haematoma enlargement, and a lower risk of haemorrhagic events after thrombolytic therapy following the onset of ischaemic stroke. A number of studies have reported various new findings concerning the relationship between antithrombotic agents, NVAF, and stroke. Recent reports have suggested a risk of dementia with NVAF and the potential protective effects of DOACs. More specifically, Jacobs et al reported that DOAC use was associated with a lower risk of cerebral ischaemic events and new-onset dementia. Furthermore, in that study, patients taking DOACs had a 51% decreased risk of developing stroke, transient ischaemic attack and dementia than those taking warfarin after multivariable adjustment (HR 0.49). However, the direct relationship between NVAF and dementia has yet to be investigated.

In 2015, we initiated the ‘Organized Registration for the Assessment of dementia on Nationwide General consortium toward Effective treatment in Japan’, otherwise known as the ‘ORANGE Registry’. The aim of the registry is to promote social awareness of dementia, clinical trials and clinical research, and to prepare an infrastructure for implementing measures for dealing with dementia (figure 1). The ORANGE Registry divides the dementia into three stages: the preclinical stage; the mild cognitive impairment (MCI) stage and the dementia care stage. More than 1000 patients with MCI are currently registered and stored data are available on their activities of daily living (ADL) and cognitive function from the ORANGE Registry research consortium.

In the present proposed study, we will investigate the relationship between oral anticoagulants, cerebrovascular diseases and cognitive dysfunction in patients with NVAF using the ORANGE Registry research infrastructure. Our hypothesis is that DOACs decrease the risk of both stroke and cognitive decline in patients without dementia with NVAF compared with warfarin therapy.
METHODS AND ANALYSIS

Study design
This study, the STRAtegy to obtain Warfarin or direct oral anticoagulant’s Benefit by Evaluating RegistRy (Strawberry study), is an investigator-initiated, multicentre, prospective, observational, longitudinal cohort study that will compare the effects of warfarin therapy and DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) on cerebrovascular diseases and cognitive impairment. The study has an estimated duration of 36 months, based on the ORANGE Registry research infrastructure. The Strawberry study is organised by a central coordinating centre located at the National Center for Geriatrics and Gerontology (NCGG), and involves approximately 20 centres located in Japan.

Patient and public involvement
Patients and the public were not involved in the design or conduct of the study. Results of this study will be disseminated to study participants via the project website. Participants will be acknowledged and thanked for their contributions during the publication and distribution of results.

Participants and recruitment
The target population of the Strawberry study is patients diagnosed with NVAF (either paroxysmal, persistent or permanent) who are taking an oral anticoagulant (warfarin or DOAC) at the time of enrolment. Potential participants will be screened by investigators. Patients who have a potential risk of dementia, such as older participants, those having memory problems or those that request medical a check-up regarding memory disorder, will be encouraged to enrol. The study protocol, including potential risks and benefits, will be explained to patients. Those who meet the eligibility criteria will be invited to participate in the study. Figure 2 shows a flow chart of the study design.

Eligibility criteria
Patients with NVAF are eligible for the Strawberry study if they (1) are taking an oral anticoagulant at the time of enrolment, (2) can undergo MRI of the brain at the time of enrolment, (3) can provide informed consent in writing, (4) are aged between 40 and 84 years at the time of enrolment, (5) have a Clinical Dementia Rating (CDR) global score of 0–0.5 and a Mini-Mental State Examination (MMSE) score of 20–30, and (6) are accompanied by a study partner.

We exclude patients if they (1) have valvular AF, (2) are unable to undergo MRI examination, or the MRI cannot be evaluated due to body movement, (3) present with dementia indicated by a CDR global score ≥1 or an MMSE score <20, (4) have a history of stroke within the last 6 months, (5) have ≤6 years of education, (6) have a history of neurodegenerative diseases such as Parkinson’s disease, Huntington’s disease, progressive supranuclear palsy, corticobasal degeneration or multiple system atrophy, (7) have a history of normal pressure hydrocephalus, brain tumours, depression, bipolar disorder, or schizophrenia, or (8) are judged by an investigator to be ineligible to participate as a study subject (figure 2). The presence of cerebral amyloid angiopathy is not an exclusion criterion because this is an important risk factor for dementia.

Observation period
Patient enrolment started in April 2017 and will continue to March 2019. Investigations will be performed annually for 3 years after enrolment and up to March 2022, or until death or informed consent is withdrawn (table 1).
Endpoints

The primary endpoint is the change in MMSE score from the time of enrolment until 3 years after enrolment. Secondary endpoints are as follows: (1) change in the Montreal Cognitive Assessment (MoCA) score from the time of enrolment to 3 years after enrolment; (2) time until occurrence of death, stroke or cardiovascular event; (3) change in CDR global score from time of enrolment until 3 years after enrolment; (4) change in CDR Sum of Boxes score from the time of enrolment to 3 years after enrolment and (5) time until haemorrhagic or ischaemic event. Several exploratory endpoints, such as cognitive function assessment, ADL, brain MRI findings, brain single photon emission CT (SPECT) findings, cardiac function and biomarkers will be analysed after enrolment.

Treatments

Medication with warfarin or DOACs will be freely prescribed by each attending doctor based on the assessment of the condition of each patient and according to the Japanese guidelines for pharmacotherapy of AF and for the management of stroke. Clinical information regarding rate/rhythm control and ablation will be also assessed. Follow-up data will be collected at 12, 24 and 36 months after enrolment. Treatment (drugs, regimen and dosage) for hypertension, dyslipidaemia and diabetes mellitus during the follow-up period should remain the same if possible, but doctors’ discretion to prescribe appropriate treatment will not be restricted in any way. Patients receiving antiplatelet agents are eligible.

Clinical assessment

We assess the following clinical parameters: (1) demographics, such as age, sex and vital signs; (2) risk factors; (3) medical history; (4) medications, including oral anticoagulants and antiplatelets; (5) laboratory findings; (6) physiological tests; (7) brain imaging; (8) comprehensive geriatric assessment; (9) social factors and lifestyle and (10) clinical outcomes. As a physiological test, we assess arterial stiffness using oscillometric devices to measure the Ankle Brachial Index and brachial-ankle pulse wave velocity (PWV) as an indicator of atherosclerosis and the ‘impact’ of the pulse. We calculate the CHADS2 and CHA2DS2-VASC scores based on the data.

Comprehensive geriatric assessment

Comprehensive geriatric assessment, including neuropsychological assessment, is performed at baseline and at 12, 24 and 36 months after enrolment. Fundamental and instrumental scales for ADL (the Barthel Index and GDS, Geriatric Depression Scale; SPECT, Single photon emission CT).
the instrumental ADL scale of Lawton and Brody\textsuperscript{34}), the MMSE, CDR and MoCA are mandatory for annual assessment. The Geriatric Depression Scale\textsuperscript{35} is only mandatory at study enrolment to exclude those with depressive status (defined as a score >9).

**Brain imaging protocol**

Brain MRI scans are performed on a 3 T (if possible) or 1.5 T scanner, depending on the scanner available at each participating institute. The MRI examination comprises standardised sequences used for analysis of the brain. T1-weighted, fluid-attenuated inversion recovery imaging, T2*-weighted gradient echo imaging (susceptibility-weighted imaging), diffusion-weighted imaging and intracranial three-dimensional time-of-flight MR angiography are examined. The presence of cerebral small vessel disease is evaluated by assessing the MRI scans based on the standards for reporting vascular changes in neuroimaging recommendations.\textsuperscript{26}

SPECT of the brain is performed in case of potential cerebral blood flow abnormality due to ischaemic stroke or any causes of cognitive decline, with the agreement of participating doctors and patients, if clinically necessary. Participants and their doctors are notified of any incidental findings of clinical significance.

**Statistics**

The sample size was calculated based on the hypothesis as follows. It is hypothesised that after 3 years, the MMSE score in the DOAC group will be 2.0 points higher than in the warfarin group. Based on preliminary data from MMSE assessments over time in patients with MCI, the SD for the MMSE was estimated to be 5.0. Dropout rates at the months 12, 24 and 36 are set to 5%, 10% and 15%, respectively. The warfarin to DOAC enrolment ratio was established at 2:3. With a two-sided significance level of 5% and a statistical power of 95%, the sample sizes required for the mixed models for repeated measures (MMRM) was calculated as 160 subjects in the warfarin group and 240 in the DOACs group (a total of 400 subjects). The same assumptions were made for the MoCA; therefore, the joint statistical power for detecting the differences between the two groups with respect to both the MMSE and MoCA is approximately 90%.

Data will be presented using the mean, median, SD, range and IQR for continuous and ordinal data, and counts or percentages for categorical data. The normality of variable distribution will be assessed prior to data presentation. The primary endpoint of the change in MMSE between the two groups will be compared using the MMRM analysis with an unstructured covariance structure and adjustment of age, sex, education and known vascular risk factors (such as hypertension, dyslipidaemia, diabetes mellitus, chronic kidney disease, a smoking habit and alcohol consumption). The same analysis will be made for the secondary endpoints of the MoCA score, CDR global score and CDR Sum of Boxes score. We will also perform a propensity score matching analysis for these endpoints. The multivariate Cox regression analysis will be used for the remaining secondary endpoints of time-to-event data. All statistical tests will be two sided and p<0.05 is considered statistically significant. These analyses will be performed using SAS V.9.4 (SAS Institute).

**Data processing**

Standardised processing of files for obtaining informed consent and reporting clinical events in the electronic case report file (eCRF) will be available. Patients’ demographic and clinical data are recorded in an eCRF in a secured electronic data capture system. Patients are assigned an alphanumeric sequential study number to identify all clinical data. After verification of recorded data to source data, recorded data in the eCRF will be exported for further statistical analysis. On completion of the study, the study database will be locked and the data securely archived for 5 years in accordance with a local ethical policy.

Anonymousised MRI scans and biological samples such as plasma, serum and urine will be collected from the participating institutes and stored at the central research office (NCGG). MRI scans will be reviewed by two trained neuroradiologists independent of the recorded clinical data. Stored biological samples will be applied to analyse the biomarkers to identify the risk of clinical outcomes in the future.

**Secondary use of the data**

After patient registration, the data obtained from this study may be put to a secondary use in a different research study. For example, we will attempt a subgroup analysis stratified by biomarkers indicative of the potential risk of dementia, such as amyloid-\(\beta\) or inflammation. The potential protective effect of both rate/rhythm control and ablation will be also analysed. The central research office and steering committee will manage the details of the secondary use of data.

**Ethics and dissemination**

Informed consent will be obtained from all patients and their study partner (someone familiar with the patient’s living situation such as a relative or caregiver). The participants and their study partners can withdraw their consent at any time point without giving any reason and without any impact on their clinical care. In case of withdrawal, the data collected up to this time point will be used. Clinical care will be provided throughout the study according to standardised local procedures. The study data will be managed confidentially and anonymously and registered along with clinical information via the web-based registration system.

The overview of the Strawberry study is provided on the homepage (URL: https://strawberry.sbscs.jp/e_index.html). The results of this study will be published in peer-reviewed journals and presented at scientific meetings to ensure the applicability of the findings in clinical practice.
DISCUSSION

The mechanism by which NVAF affects brain parenchyma is still unknown. In addition to the comparison between warfarin and DOACs as a primary endpoint, clarification of this mechanism is another key aim of the present study. We speculate that some of the potential mechanisms by which NVAF causes cognitive decline are as follows: (1) brain damage via the onset of cardioembolic stroke; (2) cerebral hypoperfusion caused by low blood pressure and/or bradycardia attributed to chronic heart failure; (3) cerebral microembolism due to insufficient effect of oral anticoagulants; (4) intracranial haemorrhage due to overuse of oral anticoagulants; (5) vascular inflammation and (6) intercalation of common risk factors between stroke and dementia such as hypertension and diabetes mellitus. Although cardioembolic stroke may cause vascular dementia, a previous meta-analysis showed that NVAF decreases cognitive function independent of a history of stroke. Therefore, NVAF per se could be a risk factor for cognitive decline (figure 3). Furthermore, recent work has suggested there to be an association between anticoagulation and amyloid-β metabolism, and that a rate/rhythm control strategy could be effective by reducing the risk of chronic cerebral hypoperfusion.

To clarify these clinical questions, we aim to investigate the association between amyloid-β biomarkers and daily drugs including oral anticoagulants in patients with NVAF.

We also have other research interests. First, NVAF is associated with arterial stiffness indicated by PWV, which is associated with cerebral small vessel diseases and predicts progressive neurological deficits and recurrent stroke. Therefore, variability in the PWV and/or blood pressure due to NVAF may have adverse effects on the brain because increased PWV is suggestive of arteriosclerosis and is also a trigger for brain damage, known as the water hammer effect. Second, provided that NVAF is definitely a risk factor for cognitive decline, patients who have been treated by catheter ablation to terminate NVAF might have a decreased risk of cognitive decline compared with that of patients presenting with NVAF. The assessment items included in the Strawberry study are generally sufficient to clarify these hypotheses.

There are several strengths of our proposed study. First, several novel relationships will be elucidated, because this is a multicentre prospective cohort study design with multilateral evaluations and analyses of cerebrovascular diseases, cognitive decline and social factors. Second, this study is a clinical research study developed based on the infrastructure of a nationwide dementia study in Japan.

Establishment of a nationwide research architecture for studying dementia can accelerate clinical trials and research. Third, the application of a unified comprehensive geriatric assessment as a tool for patient investigation facilitates the research.

There are several potential limitations. First, even though we plan to survey patients with NVAF, a comparison between patients with and without NVAF would also be useful to assess the risk of NVAF. Such assessment may be feasible using the ORANGE Registry data as a secondary analysis source. Second, there is still the possibility of unrecognised confounders despite the multicentre design. The duration of oral anticoagulant use may introduce bias, because patients who have recently started taking them might have different outcomes from those who have received long-term treatment. Third, there is a potential lack of participants because prescription of warfarin may have been partly replaced by DOACs. Finally, patients taking warfarin may have comorbidities that prevent the use of DOACs, such as renal dysfunction. Such factors may increase the risk of stroke and may result in a worse cognitive performance, not because of the difference in oral anticoagulants, but because of their different comorbidity status. Even propensity matching cannot correct for all of these differences.

Dealing with dementia and stroke is a pressing issue for Japan and its ageing society. We hope that our study will contribute to a better understanding of the association between dementia and stroke in patients with NVAF.

CONCLUSIONS

The Strawberry study has the potential to reveal the association between cognitive impairment and NVAF. If the results support the efficacy of DOACs in preventing cognitive decline, independent of stroke, this will be of great interest to both patients and clinicians from the viewpoint of dementia prevention.

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3. Kimura K, Kazui S, Minematsu K, et al. BMJ Open 2018;8:e021759. doi:10.1136/bmjopen-2018-021759

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Contributors

NS is the principle investigator and contributed to the concept, drafting and design of the protocol. TS, KI, HT, KK, KM, YT, KK, ME, KS, SN, AH and KT contributed to the design of the study and reviewed the manuscript for intellectual content.

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Disclaimer

The sponsors have no role in the study design and conduct; the collection, management, analysis and interpretation of the data; or the preparation and approval of the manuscript.

Competing interests

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Patient consent

Not required.

Ethics approval

The study was approved by the Institutional Review Board of the National Center for Geriatrics and Gerontology (No. 1017). This study was registered with the UMIN Clinical Trials Registry (UMIN000025721).

Provenance and peer review

Not commissioned; externally peer reviewed.

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REFERENCES

1. Iguchi Y, Kimura K, Aoki J, et al. Prevalence of atrial fibrillation in community-dwelling Japanese aged 40 years or older in Japan: analysis of 41,436 non-employee residents in Kurashiki-city. Circ J 2006;70:909–13.

2. Inoue H, Fujii A, Origasa H, et al. Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. Int J Cardiol 2009;137:102–7.

3. Kimura K, Kazui S, Minematsu K, et al. Analysis of 16,922 patients with acute ischemic stroke and transient ischemic attack in Japan. A hospital-based prospective registration study. Cerebrovasc Dis 2004;18:47–56.

4. Maeda K, Toyoda K, Minematsu K, et al. Effects of sex difference on clinical features of acute ischemic stroke in Japan. J Stroke Cerebrovasc Dis 2013;22:1070–5.

5. Kimura K, Minematsu K, Yamauchi T, et al. Atrial fibrillation as a predictive factor for severe stroke and early death in 15,831 patients with acute ischaemic stroke. J Neurol Neurosurg Psychiatry 2005;76:679–83.

6. Toyoda K. Epidemiology and registry studies of stroke in Japan. J Stroke 2013;15:21–6.

7. Kirchhof P, Benussi S, Kotecha D, et al. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.

8. Xian Y, Wu J, O’Brien EC, et al. Real world effectiveness of warfarin among ischemic stroke patients with atrial fibrillation: observational analysis from Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) study. BMJ 2015;351:h3786.

9. Odutayo A, Wong CX, Hsiao AJ, et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ 2015;354:i4482.

10. López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017;359:j5058.

11. Saji N, Kimura K, Aoki J, et al. Intracranial Hemorrhage Caused by Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)- Multicenter Retrospective Cohort Study in Japan. Circ J 2015;79:1018–23.

12. Saji N, Kimura K, Tateishi Y, et al. Safety and efficacy of non-vitamin K oral anticoagulant treatment compared with warfarin in patients with non-valvular atrial fibrillation who develop acute ischemic stroke or transient ischemic attack: a multicenter prospective cohort study (dAVinci study). J Thromb Thrombolysis 2016;42:453–62.

13. Verheugt FW, Granger CB. Oral anticoagulants for stroke prevention in atrial fibrillation: current status, special situations, and unmet needs. Lancet 2015;386:305–10.

14. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955–62.

15. Toyoda K, Arihiro S, Todo K, et al. Trends in oral anticoagulant choice for acute stroke patients with nonvalvular atrial fibrillation in Japan: the SAMURAI-NVAF study. Int J Stroke 2015;10:386–42.

16. Cao L, Pokorney SD, Hayden K, et al. Cognitive Function: Is There More to Anticoagulation in Atrial Fibrillation Than Stroke? J Am Heart Assoc 2015;4:e001573.

17. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370–5.

18. Horstmann S, Rizos T, Rauch G, et al. Atrial fibrillation and prestroke cognitive impairment in stroke. J Neurol 2014;261:546–53.

19. Bunch TJ, May HT, Bair TL, et al. Atrial Fibrillation Patients Treated With Long-Term Warfarin Anticoagulation Have Higher Rates of All Dementia Types Compared With Patients Receiving Long-Term Warfarin for Other Indications. J Am Heart Assoc 2016;5:6003932.

20. Jacobs V, May HT, Bair TL, et al. Long-Term Population-Based Cerebral Ischemic Event and Cognitive Outcomes of Direct Oral Anticoagulants Compared With Warfarin Among Long-Term Anticoagulated Patients for Atrial Fibrillation. Am J Cardiol 2016;118:210–4.

21. Saji N, Sakurai T, Suzuki K, et al. ORANGE’s challenge: developing wide-ranging dementia research in Japan. J Cardio 2016;15:661–2.

22. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011;7:270–9.

23. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–92.

24. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2413–4.

25. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

26. Wardlaw JM, Smith EE, Biessels GJ, et al. Standards for Reporting Vascular changes on Neuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–38.
27. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.

28. JCS Joint Working Group. Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013). *Circ J* 2014;78:1997–2021.

29. Shinohara Y, Yamaguchi T. Outline of the japanese guidelines for the management of stroke 2004 and subsequent revision. *Int J Stroke* 2008;3:55–62.

30. Saji N, Kimura K, Yamaguchi T, et al. Comparison of arteriosclerotic indicators in patients with ischemic stroke: ankle-brachial index, brachial-ankle pulse wave velocity and cardio-ankle vascular index. *Hypertens Res* 2015;38:323–8.

31. Saji N, Toba K, Sakurai T. Cerebral small vessel disease and arterial stiffness: tsunami effect in the brain? *Pulse* 2016;3:182–9.

32. Mahoney FI, Barthel DW, Callahan JP. Rehabilitation of the hemiplegic patient: a clinical evaluation. *South Med J* 1955;48:472–80.

33. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–86.

34. Lesher EL, Berryhill JS. Validation of the geriatric depression scale-short form among inpatients. *J Clin Psychol* 1994;50:256–60.

35. Kalantarian S, Stern TA, Mansour M, et al. Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med* 2013;158:338–46.

36. Yang L, Bhattacharya A, Li Y, et al. Anticoagulants inhibit proteolytic clearance of plasma amyloid beta. *Oncotarget* 2018;9:5614–26.

37. Ihara M, Washida K. Linking atrial fibrillation with alzheimer’s disease: epidemiological, pathological, and mechanistic evidence. *J Alzheimers Dis* 2018;62:61–72.

38. Chen SC, Lee WH, Hsu PC, et al. Association of brachial-ankle pulse wave velocity with cardiovascular events in atrial fibrillation. *Am J Hypertens* 2016;29:348–56.

39. Saji N, Kimura K, Kawarai T, et al. Arterial stiffness and progressive neurological deficit in patients with acute deep subcortical infarction. *Stroke* 2012;43:3088–90.

40. de Roos A, van der Grond J, Mitchell G, et al. Magnetic resonance imaging of cardiovascular function and the brain: is dementia a cardiovascular-driven disease? *Circulation* 2017;135:2178–95.