PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protective effects of oral anticoagulants on cerebrovascular diseases and cognitive impairment in patients with atrial fibrillation: protocol for a multicenter, prospective, observational, longitudinal cohort study (Strawberry study)
AUTHORS	Saji, Naoki; Sakurai, Takashi; Ito, Kengo; Tomimoto, Hidekazu; Kitagawa, Kazuo; Miwa, Kaori; Tanaka, Yuji; Kozaki, Koichi; Kario, Kazuomi; Eto, Masato; Suzuki, Keisuke; Shimizu, Atsuya; Niida, Shumpei; Hirakawa, Akihiro; Toba, Kenji

VERSION 1 – REVIEW

REVIEWER	Lorenzo Falsetti Azienda Ospedaliero-Universitaria "Ospedali Riuniti" di Ancona, Italy
REVIEW RETURNED	17-May-2018

GENERAL COMMENTS	The study protocol by Saji et al. addresses an important and still unanswered question in the field of the prevention of dementia among subjects with atrial fibrillation. There are several retrospective and prospective studies addressing the role of warfarin or new oral anticoagulants in this setting (i.e. https://www.ncbi.nlm.nih.gov/pubmed/27236255, https://www.ncbi.nlm.nih.gov/pubmed/27402230, etc.). However, this study is interesting because authors add a cognitive, social, and neuroradiological evaluation in a multicenter prospective study. The study methodology is well-written, and I have only some suggestions: - Authors should add a phrase in the introduction and in the discussion sections underlining the difference(s) from the current study and previously published material from other authors (especially from: https://www.ncbi.nlm.nih.gov/pubmed/27236255). Particularly, I suggest to modify the phrase in page 6, lines 6-13: “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 new oral anticoagulants”. Since some authors already underlined that “DOAC use was associated with a lower risk of cerebral ischemic events and new-onset dementia” and that “ patients taking DOAC were 43% less likely to develop stroke/TIA/dementia than those taking warfarin”, authors should take into account previously published papers and comment on the added value of their current study in this field. - In the present paper, authors identify their target population as patients with NVAF without dementia and aim to evaluate the new occurrence of “dementia”. Will they enrol all the dementing patients

	independently of their neuropathology or they refer only to vascular dementia ? This point is very important, because, since they will enrol subjects “from 40 to 84 years” they will find subjects developing familial forms (such as familial Alzheimer’s Disease) as well as patients with senile/vascular/neurodegenerative (as late-onset Alzheimer’s Disease), neurodegenerative/parkinsonian (Parkinson Disease and several parkinsonisms) and pure vascular forms (as vascular dementia). It is possible that a patient with vascular dementia will have a different clinical response to anticoagulants when compared, for example, with a patient with Lewy Bodies disease. Morover, different forms of dementia have a completely different neuroradiology and neuropathology. Will authors attempt a sub-group analysis ? Will authors exclude some specific forms of dementia ? A phrase addressing this specific issue should be added in the methods. - Particularly, authors expect an improvement in their overall population after anticoagulant therapy. This is correct, because several important studies have already associated anticoagulant therapy with a lower progression and incidence of dementia. However, again, some authors doubt on this positive effect in some specific situations: as an example, in Alzheimer’s Disease anticoagulation could impact in a potentially dichotomic way: by inhibiting pro-coagulant activity, it could potentially slow or ameliorate AD, but inhibiting plasma Aβ degradation, it could potentially contribute to brain Aβ accumulation (i.e. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5814162/). Moreover, some authors suggest that a rate/rhythm control strategy could be effective in protecting patients affected by Alzheimer’s disease by reducing chronic cerebral hypoperfusion, and that an anticoagulant therapy could be more effective in patients affected by vascular dementia (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5817903/). I recommend to add a phrase in commenting on this: since authors will investigate all dementias, they should take into account also the fact that specific types of dementia could be associated to different, unexpected outcomes. - Cerebral amyloid angiopathy is common in both vascular dementia and late-onset Alzheimer’s disease and represents a risk factor for local thrombosis as well as for microhaemorrages and major cerebral haemorrages. Will patients with cerebral amyloid angiopathy be treated differently or excluded, since they have a raised risk of major cerebral haemorragic events ? Or will they be excluded from the study ? A short phrase commenting on this aspect should be added. - MMSE is not considered the best tool to screen dementia and, more specifically, to evaluate cognitive deterioration over time. However authors added other cognitive screening tools, as CDR and MoCA to improve neuropsychological evaluation. - Authors should estimate correctly the number of patients potentially developing cognitive deterioration during the study time (3 years). Authors’ estimates are “based on preliminary data from MMSE assessments over time in MCI”. However, the enrolled population is not at higher risk for dementia, as in MCI: this is a general population of patients affected by NVAF. Since they will enrol NVAF patients from 40 to 84 years old, it is very improbable that they will observe any difference among younger patients

	(except for patients with some familial forms of dementia). I recommend reviewing this statistical/methodological point.

REVIEWER	Atul Verma Southlake Regional Health Centre, Newmarket, Ontario, Canada
REVIEW RETURNED	15-Jul-2018

GENERAL COMMENTS	Saji et al. present the protocol of an observational, prospective cohort study that intend to evaluate the potential protective effect on dementia of DOACs compared with warfarin in patients with atrial fibrillation, with a follow up of 36 months. The cognitive impairment will be evaluated annually with MMSE, CDR and MoCA scales, as well as with fundamental and instrumental scales for ADL. 400 subjects will be enrolled in the trial with a 2:3 ratio for warfarin to DOAC. The primary endpoint is a change in MMSE with the other scales being secondary endpoints. In order to elucidate the mechanisms of the relationship between AF and dementia, two brain MRI will be performed in every patient enrolled to assess repetitive microemboli and microbleeds as a potential cause. In addition, a brachial-ankle pulse wave velocity will be measured to assess the variability in pulse and cerebral vascular perfusion. Common risk factors will be analyzed and laboratory tests will be performed to assess perpetuation of an inflammatory state related to AF. This protocol is compelling and opportune considering the literature recently published on the relationship between dementia and AF. More specifically, there is controversy over whether anticoagulation can reduce this risk of dementia. A recent metanalysis (Cheng et al, 2018) already supports the protective effect of DOAC over warfarin. A study like the Strawberry trial can definitely shed light on this issue. However, there are a few concerns that need to be addressed: Major concerns: - This study has the limitations of a cohort observational study where adjustment between both cohorts cannot neutralize unknown confounding factors. Propensity matching will be performed, but there are no details on the statistical methods that will be used to compare the primary and secondary endpoints. Will they use a chi-square analysis, or a logistic regression, or a GEE model? The authors need to provide further detail on how the primary and secondary endpoints will be compared. - Considering that the Guidelines for Pharmacotherapy of Atrial Fibrillation in Japan (JSC 2013) recommend DOAC over warfarin in patients with NVAF, yet the authors think that 40% of patients enrolled in this study will be on warfarin. Are you sure that so many patients will still be on warfarin? Given the reduction in ICH with DOACs, I would have thought that most patients are being changed from warfarin to DOAC. And of the patients that remain on warfarin, maybe they have co-morbidities that prevent the use of a DOAC (like CKD) in which case, they may do worse cognitively not because of the difference in oral anticoagulation, but because of their different co-morbidity status. Even propensity matching cannot correct for all of these differences.

	- Considering that patients over 40 can be enrolled in the study with a mean follow up of 3 years, the likelihood of developing dementia is low with such a short follow up in relatively young population. Previous studies failed to demonstrate a relationship between dementia and AF with such a short follow up. (Tilvis et al., Peters et al, Marengoni et al…). Why would you not include more high risk patients? Minor concerns: - The authors mention that depressive status is an exclusion criteria although it was not included in the eligibility criteria. They should clarify if a score > 9 in Geriatric Depression Scale is an exclusion criteria. - MMSE cut-off used in this study as an exclusion criteria is < 20 instead of < 24. Why did the authors chose this cut off? By choosing 20, patients with mild cognitive impairment can be included in this study. Meranus et al. (2013) reported a higher risk of dementia in patients with mild cognitive impairment using anticoagulation which is paradoxical to the findings in patients without cognitive impairment. This may be due to a higher incidence of cerebral microbleeding. - The treatment received for AF is not mentioned in the protocol (rate vs rhythm control, ablation). These can have substantial impacts on cognitive function if the AF burden is minimized. There also has to be some assessment of AF incidence during the follow up. Since most of the hypothesis that correlate dementia and AF assume the patients are in AF (microemboli, pulse wave variability) how can the authors infer a causative effect from the results if some patients no longer have AF?

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1

The study protocol by Saji et al. addresses an important and still unanswered question in the field of the prevention of dementia among subjects with atrial fibrillation. There are several retrospective and prospective studies addressing the role of warfarin or new oral anticoagulants in this setting (i.e. https://www.ncbi.nlm.nih.gov/pubmed/27236255, https://www.ncbi.nlm.nih.gov/pubmed/27402230, etc.). However, this study is interesting because authors add a cognitive, social, and neuroradiological evaluation in a multicenter prospective study. The study methodology is well-written, and I have only some suggestions:

Thank you for your thorough review of our manuscript and thoughtful comments and suggestions. We have revised our manuscript according to the recommendations provided, and our point-by-point responses are provided below. We greatly appreciate your review of our manuscript.

Points/Content of the Revision

- Authors should add a phrase in the introduction and in the discussion sections underlining the difference(s) from the current study and previously published material from other authors (especially from: https://www.ncbi.nlm.nih.gov/pubmed/27236255). Particularly, I suggest to modify the phrase in page 6, lines 6-13: “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 new oral anticoagulants". Since some authors already underlined that "DOAC use was associated with a lower risk of cerebral ischemic events and new-onset dementia" and that "patients taking DOAC were 43% less likely to develop stroke/TIA/dementia than those taking warfarin", authors should take into account previously published papers and comment on the added value of their current study in this field.

Thank you for your comment. According to your suggestion, we have cited the recommended article and have revised this section, as shown below.

Page 5, Line 22
Recent reports have suggested a risk of dementia with NVAF16-19 and the potential protective effects of DOACs.20 More specifically, Jacobs et al. reported that DOAC use was associated with a lower risk of cerebral ischemic events and new-onset dementia.20 Furthermore, in that study, patients taking DOACs had a 51% decreased risk of developing stroke, transient ischemic attack, and dementia than those taking warfarin after multivariable adjustment (hazard ratio 0.49). However, the direct relationship between NVAF and dementia has yet to be investigated.

- In the present paper, authors identify their target population as patients with NVAF without dementia and aim to evaluate the new occurrence of "dementia". Will they enroll all the dementing patients independently of their neuropathology or they refer only to vascular dementia? This point is very important, because, since they will enroll subjects "from 40 to 84 years" they will find subjects developing familial forms (such as familial Alzheimer's Disease) as well as patients with senile/vascular/neurodegenerative (as late-onset Alzheimer's Disease), neurodegenerative/parkinsonian (Parkinson Disease and several parkinsonisms) and pure vascular forms (as vascular dementia). It is possible that a patient with vascular dementia will have a different clinical response to anticoagulants when compared, for example, with a patient with Lewy Bodies disease. Moreover, different forms of dementia have a completely different neuroradiology and neuropathology. Will authors attempt a sub-group analysis? Will authors exclude some specific forms of dementia? A phrase addressing this specific issue should be added in the methods.

Thank you for your insightful comment. Based on the inclusion criteria, we include patients with a CDR global score of 0 to 0.5 and an MMSE score of 20 to 30, independent of their neuropathology. However, we will exclude patients if they have neurodegenerative diseases such as Parkinson's disease, Huntington's disease, progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy. Furthermore, patients with a history of normal pressure hydrocephalus, brain tumors, depression, bipolar disorder, and schizophrenia are unsuitable for this study.

It is difficult to determine the neuropathology of dementia before the onset of dementia, because amyloid-PET and tau-PET are not applied in the usual clinical situation in Japan. However, some biomarkers such as amyloid-β may be indicative of the neuropathology of dementia. Therefore, we will attempt a sub-group analysis using these biomarkers after the patient registration.

According to your suggestion, we have revised our manuscript, as shown below.

Page 8, Line 15
"We exclude patients if they (1) have valvular atrial fibrillation, (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 tumors, depression, bipolar disorder, or schizophrenia, or (8) are judged by an investigator to be ineligible to participate as a study subject (Fig. 2). The presence of cerebral amyloid angiopathy is not an exclusion criterion because this is an important risk factor for dementia.26"

Page 13, Line 22
"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 sub-group analysis stratified by biomarkers indicative of the potential risk of dementia, such as amyloid-β or inflammation. The potential protective effect of both rate/rhythm control and ablation will be also analyzed. The central research office and steering committee will manage the details of the secondary use of data."

- Particularly, authors expect an improvement in their overall population after anticoagulant therapy. This is correct, because several important studies have already associated anticoagulant therapy with a lower progression and incidence of dementia. However, again, some authors doubt on this positive effect in some specific situations: as an example, in Alzheimer's Disease anticoagulation could impact in a potentially dichotomic way: by inhibiting pro-coagulant activity, it could potentially slow or ameliorate AD, but inhibiting plasma Aβ degradation, it could potentially contribute to brain Aβ accumulation (i.e. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5814162/). Moreover, some authors suggest that a rate/rhythm control strategy could be effective in protecting patients affected by Alzheimer's disease by reducing chronic cerebral hypoperfusion, and that an anticoagulant therapy could be more effective in patients affected by vascular dementia (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5817903/). I recommend to add a phrase in commenting on this: since authors will investigate all dementias, they should take into account also the fact that specific types of dementia could be associated to different, unexpected outcomes.

Thank you for your comment and the two article suggestions. As you mentioned, Alzheimer's disease is a main topic of dementia research. We are willing to investigate the association between Alzheimer's disease and anticoagulation in patients with NVAF. According to your suggestion, we have cited the two articles and have revised the discussion section, as shown below.

Page 16, Line 14
"Furthermore, recent work has suggested there to be an association between anticoagulation and amyloid-β metabolism,37 and that a rate/rhythm control strategy could be effective by reducing the risk of chronic cerebral hypoperfusion.38 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."

- Cerebral amyloid angiopathy is common in both vascular dementia and late-onset Alzheimer's disease and represents a risk factor for local thrombosis as well as for microhaemorrages and major cerebral haemorrages. Will patients with cerebral amyloid angiopathy be treated differently or excluded, since they have a raised risk of major cerebral haemorragic events? Or will they be excluded from the study? A short phrase commenting on this aspect should be added.

Thank you for your comment. Patients with cerebral amyloid angiopathy will be included in this study and treated equally. However, as the both reviewers have mentioned, the recent guideline in Japan indicates the superiority and safety of DOACs compared to warfarin. Therefore, such patients will be

more likely to be treated by DOACs according to the attending doctor's treatment policy. We have therefore revised the Eligibility criteria part, as shown below.

Page 9, Line 1
"The presence of cerebral amyloid angiopathy is not an exclusion criterion because this is an important risk factor for dementia.26"

- MMSE is not considered the best tool to screen dementia and, more specifically, to evaluate cognitive deterioration over time. However authors added other cognitive screening tools, as CDR and MoCA to improve neuropsychological evaluation.

Thank you for your comment. We entirely agree with you. In the clinical situation of a dementia clinic in Japan, the MMSE or Hasegawa dementia rating scale-revised (HDS-R) are widely used as screening tools. Therefore, we adopted the MMSE as a screening scale and added the MoCA and CDR to improve the cognitive screening test of this study.

- Authors should estimate correctly the number of patients potentially developing cognitive deterioration during the study time (3 years). Authors' estimates are "based on preliminary data from MMSE assessments over time in MCI". However, the enrolled population is not at higher risk for dementia, as in MCI: this is a general population of patients affected by NVAF. Since they will enroll NVAF patients from 40 to 84 years old, it is very improbable that they will observe any difference among younger patients (except for patients with some familial forms of dementia). I recommend reviewing this statistical/methodological point.

Thank you for your comment. We should have explained this point more carefully to avoid any misunderstanding. We are enrolling patients who have a potential risk of dementia, such as older patients, those complaining of memory disorder (but who do not have dementia), or those that request a medical check-up regarding memory disorder. In fact, the data from the enrolled patients (n = 100) in this study show that the mean age is 76 years (IQR 73-79, range 47-84). Of those 100 patients, 98 are over 65 years old. Furthermore, the distribution of CDR global scores show that the half of the enrolled patients have a score of 0.5 (55.4%). This indicates that half of the enrolled patients have MCI. Therefore, although this study enrolls a general population of patients with NVAF that are aged from 40 to 84 years old, the population actually enrolled is at a higher risk for both dementia and stroke. To clarify this, we have revised the Participants and recruitment part, as shown below.

Page 7, Line 19
"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 enrollment. Potential participants will be screened by investigators. Patients who have a potential risk of dementia, such as older participants, those complaining of memory problems, or those that request medical a check-up regarding memory disorder, will be encouraged to enroll. 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 flowchart of the study design."

Response to Reviewer #2

Saji et al. present the protocol of an observational, prospective cohort study that intend to evaluate the potential protective effect on dementia of DOACs compared with warfarin in patients with atrial fibrillation, with a follow up of 36 months. The cognitive impairment will be evaluated annually with

MMSE, CDR and MoCA scales, as well as with fundamental and instrumental scales for ADL. 400 subjects will be enrolled in the trial with a 2:3 ratio for warfarin to DOAC. The primary endpoint is a change in MMSE with the other scales being secondary endpoints. In order to elucidate the mechanisms of the relationship between AF and dementia, two brain MRI will be performed in every patient enrolled to assess repetitive microemboli and microbleeds as a potential cause. In addition, a brachial-ankle pulse wave velocity will be measured to assess the variability in pulse and cerebral vascular perfusion. Common risk factors will be analyzed and laboratory tests will be performed to assess perpetuation of an inflammatory state related to AF. This protocol is compelling and opportune considering the literature recently published on the relationship between dementia and AF. More specifically, there is controversy over whether anticoagulation can reduce this risk of dementia. A recent metanalysis (Cheng et al, 2018) already supports the protective effect of DOAC over warfarin. A study like the Strawberry trial can definitely shed light on this issue.
However, there are a few concerns that need to be addressed:

Thank you for your thorough review of our manuscript and the thoughtful comments and suggestions. We have revised our manuscript according to the recommendations provided, and our responses to your comments are provided in more detail below. We greatly appreciate your review of our manuscript.

Major concerns:

- This study has the limitations of a cohort observational study where adjustment between both cohorts cannot neutralize unknown confounding factors. Propensity matching will be performed, but there are no details on the statistical methods that will be used to compare the primary and secondary endpoints. Will they use a chi-square analysis, or a logistic regression, or a GEE model? The authors need to provide further detail on how the primary and secondary endpoints will be compared.

Thank you for your insightful comment. Based on your comment, we have added some additional details concerning the statistical analyses that will be employed to compare primary and secondary endpoints between the two groups, as follows:

“Data will be presented using the mean, median, standard deviation, range, and interquartile range 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, dyslipidemia, 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 $P < .05$ is considered statistically significant. These analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).”

- Considering that the Guidelines for Pharmacotherapy of Atrial Fibrillation in Japan (JSC 2013) recommend DOAC over warfarin in patients with NVAF, yet the authors think that 40% of patients enrolled in this study will be on warfarin. Are you sure that so many patients will still be on warfarin? Given the reduction in ICH with DOACs, I would have thought that most patients are being changed from warfarin to DOAC. And of the patients that remain on warfarin, maybe they have co-morbidities that prevent the use of a DOAC (like CKD) in which case, they may do worse cognitively not because

of the difference in oral anticoagulation, but because of their different co-morbidity status. Even propensity matching cannot correct for all of these differences.

Thank you for your insightful comment, which we agree with. This is a valid point, especially considering that, compared with the planning period of this study (2015-2016), some patients have certainly switched to DOACs from warfarin treatment. The patient enrollment will end in March 2019, after which we will be able to verify the ratio of anticoagulants. Furthermore, the presence of renal dysfunction or other potential risk factors may also affect the selection of the anticoagulants. We agree that these potential comorbidities should be acknowledged as potential limitations of the study. Although there might be some limitations (e.g. potential lack of warfarin users) regarding this study protocol, it has enough worth to warrant being carried out. According to these points, we have revised the limitations part as shown below.

Page 4, Line 8
“Strengths and limitations of this study
• Potential lack of warfarin users because prescription of warfarin may have been partly replaced by direct oral anticoagulants (DOACs)

Page 4, Line 8
“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.”

- Considering that patients over 40 can be enrolled in the study with a mean follow up of 3 years, the likelihood of developing dementia is low with such a short follow up in relatively young population. Previous studies failed to demonstrate a relationship between dementia and AF with such a short follow up. (Tilvis et al., Peters et al, Marengoni et al…). Why would you not include more high risk patients?

Thank you for this comment, which was also raised by Reviewer 1. We have indeed set a wide inclusion criteria; however, the enrolled patients so far (n = 100) are older and therefore more likely to have MCI. We are enrolling patients who have a potential risk of dementia, such as older patients, those complaining of memory disorder (but who do not have dementia), or those that request a medical check-up regarding memory disorder. Data from the enrolled patients (n = 100) in this study show that the mean age is 76 years (IQR 73-79, range 47-84). Of those 100 patients, 98 are over 65 years old. Furthermore, the distribution of CDR global scores show that the half of the enrolled patients have a score of 0.5 (55.4%). This indicates that half of the enrolled patients have MCI. Therefore, although this study enrolls a general population of patients with NVAF that are aged from 40 to 84 years old, the population actually enrolled is at a higher risk for both dementia and stroke. To clarify this, we have revised the Participants and recruitment part, as shown below.

Page 7, Line 19
“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 enrollment. Potential participants will be screened by investigators. Patients who have a potential risk of dementia, such as older participants, those complaining of memory problems, or those that request medical a check-up regarding memory disorder, will be encouraged to enroll. 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 flowchart of the study design.”

Minor concerns:

- The authors mention that depressive status is an exclusion criteria although it was not included in the eligibility criteria. They should clarify if a score > 9 in Geriatric Depression Scale is an exclusion criteria.

Thank you for your comment. We have revised this point, as shown below.

Page 8, Line 15
Eligibility criteria
We exclude patients if they (1) have valvular atrial fibrillation, (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 tumors, depression, bipolar disorder, or schizophrenia, or (8) are judged by an investigator to be ineligible to participate as a study subject (Fig. 2). The presence of cerebral amyloid angiopathy is not an exclusion criterion because this is an important risk factor for dementia.26

Page 11, Line 5
Comprehensive geriatric assessment
The Geriatric Depression Scale35 is only mandatory at study enrollment to exclude those with depressive status (defined as a score >9).

- MMSE cut-off used in this study as an exclusion criteria is < 20 instead of < 24. Why did the authors choose this cut off? By choosing 20, patients with mild cognitive impairment can be included in this study. Meranus et al. (2013) reported a higher risk of dementia in patients with mild cognitive impairment using anticoagulation which is paradoxical to the findings in patients without cognitive impairment. This may be due to a higher incidence of cerebral microbleeding.

Thank you for your comment. In this study, we also aim to compare the patients with MCI and those without MCI regarding their clinical outcomes such as stroke and cognitive decline. This comparison will clarify the clinical question as mentioned above. Therefore, we aim to enroll patients presenting with a high-risk of dementia. The main targets are elderly patients presenting with MCI. Hence, we set the cut-off MMSE score as 20 to include such patients.

- The treatment received for AF is not mentioned in the protocol (rate vs rhythm control, ablation). These can have substantial impacts on cognitive function if the AF burden is minimized. There also has to be some assessment of AF incidence during the follow up. Since most of the hypothesis that correlate dementia and AF assume the patients are in AF (microemboli, pulse wave variability) how can the authors infer a causative effect from the results if some patients no longer have AF?

Thank you for your insightful comment. Indeed, we aim to investigate important issues such as rate/rhythm control and ablation, because these issues could indeed affect the outcomes. Clinical information regarding rate/rhythm control and ablation will be surveyed and will be analyzed. It would also be interesting to compare patients with AF and patients who had received treatment for AF by ablation. After the ablation therapy, the risk of dementia might decrease; however, this has not yet

been verified. If the number of the patients treated by ablation is sufficient, we will address this clinical question in a secondary use of the study data. However, this might be an exploratory analysis. We have included this point in the revised manuscript, as shown below.

Page 9, Line 21
“Treatments
Medication with warfarin or DOACs will be freely prescribed by each attending doctor based on assessment of the condition of each patient and according to the Japanese guidelines for pharmacotherapy of atrial fibrillation28 and for the management of stroke.29 Clinical information regarding rate/rhythm control and ablation will be also assessed.”

Page 13, Line 22
“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 sub-group analysis stratified by biomarkers indicative of the potential risk of dementia, such as amyloid-β or inflammation. The potential protective effect of both rate/rhythm control and ablation will be also analyzed. The central research office and steering committee will manage the details of the secondary use of data.”