PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Potential missed opportunities to prevent ischaemic stroke: prospective multicentre cohort study of atrial fibrillation-associated ischaemic stroke and TIA
AUTHORS	Wilson, Duncan; Ambler, Gareth; Shakeshaft, Clare; Banerjee, Gargi; Charidimou, Andreas; Seiffge, David; White, Mark; Cohen, Hannah; Yousry, Tarek; Salman, Rustam; Lip, Gregory Y H; Muir, Keith; Brown, Martin; Jäger, H.R; Werring, David

VERSION 1 - REVIEW

REVIEWER	Wang, Kang-Ling Taipei Veterans General Hospital, Taiwan
REVIEW RETURNED	13-Jan-2019

GENERAL COMMENTS	This is an interesting paper. It shows a great gap between current guideline recommendations and clinical practice in oral anticoagulation in patients with atrial fibrillation. The fact is well known, however, it is rarely reported by a prospective cohort targeting patients with a recent stroke. My comments are: 1. Although I agree with the authors that patients with atrial fibrillation at risk of stroke should be anticoagulated, the European guidelines (both in 2012 and 2016) recommend those with two risk factors other than sex should be anticoagulated (class I recommendation) and those with one risk factor other than sex should consider to receive oral anticoagulants (class IIa recommendation). Therefore, the authors should report their results stratified by sex and by the level of guideline recommendations. 2. In addition, the recent report (PMID: 30605505) suggests the age as the strongest risk driver for stroke in those with only one risk factor other than sex. The authors should compare their patients in this additional method. 3. The missing opportunity in this reported population should not be only refrained to those with stroke with a prior un-anticoagulated atrial fibrillation. It is a tip of the iceberg as it shows a greater proportion of patients with an undiagnosed atrial fibrillation who might be picked by the screening or current technologies. The authors should remind the readers in the discussion.

REVIEWER	Matthew Solomon Kaiser Permanente United States
REVIEW RETURNED	19-Jan-2019

GENERAL COMMENTS	This is a well written study by authors from Europe and the USA that examined patients from the UK who presented with stroke and TIA that were enrolled in a prospective observational study CROMIS-2. Patients were eligible if they had stroke or TIA that was associated with atrial fibrillation (AF), but they also were required not to be on anticoagulation. The goal of the study was to examine the proportion of patients with prior known AF vs newly diagnosed AF after CVA/TIA, and to examine their risk for both stroke and bleeding to identify missed opportunities for anticoagulation treatment that may have prevented the stroke. A strength of the study is the detailed information collected within the CROMIS-2 cohort, to be able to investigate clinical and phenotypic features of this population. As the authors note, the weaknesses of the study include the lack of information about why the patient and MD decided not to anticoagulate patients with known AF. The reasons could be myriad, including patient refusal, of the physician's concern about the ability to comply with warfarin (DOAC use was likely on the lower end during the study period), or MD concern about bleeding risk. Thus, it is not surprising that those with known AF had higher HAS BLED scores in this comparison, because those with known AF had made a decision not to anticoagulate, perhaps due to a high HAS BLED score (or the higher dementia/cognitive impairment). The New AF group is a less selected sample because they never had a reason to be evaluated for anticoagulation; they are younger because the younger Pts with known AF were likely put on anticoagulation (and thus not eligible for the study, even if they had a stroke). So, the two groups are a little bit like apples to oranges; the new AF group is somewhat of a baseline with which to compare the known AF group. But the biggest weakness of the study, to try to answer their research objective, is that, since the only enrolled patients were those with strokes who were not previously on anticoagulation, we do not know the denominator of patients with AF who were not anticoagulated and did not have strokes. We see only the numerator here. Thus, we don't really know the event rates for this population, and what the risks may have been from anticoagulating the entire population non-anticoagulated similar AF patients. Would they have had more intracranial or GI bleeds than strokes (ie, did the MDs and patients make the right decision overall for this population)? The paper states firmly that there were missed opportunities to prevent stroke, but I think that is a strong overstatement and the data do not support that. Perhaps the MDs got the balance correct for this population of patients? We know these patients had strokes, but we don’t know what percentage of the non-anticoagulated AF cohort this represents. This could be more fully explored in the Discussion, to provide balance. Also recommend more information about the neuro imaging findings. I am not sure of the significance of including that in the paper, there is a reference about using those findings as a way to risk stratify on

	the risk for ICH, but it's mentioned only in passing.

REVIEWER	Heidi Lehtola, MD Oulu University Hospital, Finland
REVIEW RETURNED	21-Jan-2019

GENERAL COMMENTS	The study of Duncan et al., "Missed opportunities to prevent ischaemic stroke: prospective multicentre cohort study of atrial fibrillation-associated ischaemic stroke and TIA" analyzed 1470 patients without previous therapeutic anticoagulation from 79 stroke care units between years 2011-2015. They found that 68% of patients had newly diagnosed AF and 32% had known AF. Study revealed that there still is underanticoagulation, since 86% of patients with known AF had strong indication for anticoagulation (CHA2DS2-VASc ≥2). They conclude that bleeding risk scores should be used to recognise patients with high bleeding risk and treat modifiable risk factors, instead of withdrawal of anticoagulation. I still have minor comments for revision. 1) Ischaemic should be used throughout the manuscript instead of ischemic. 2) How was the atrial fibrillation-associated stroke/TIA defined? Were the neurological symptoms analysed and other possible aetiological factors for ischaemic stroke, e.g. carotid atherosclerosis, excluded? Time causality between ischaemic stroke and afterwords diagnosed AF could be hard to prove. What was the definition of newly diagnosed AF? 3) What means the term "without therapeutic anticoagulation"? Were there warfarin treated patients with poor TTR or does this only mean the patients with antiplatelet treatment, but without DOACs/VKAs? 4) There is some discrepancy in Results section (text and Table 1). Why do you state "other variables ... did not differ significantly, but..." in page 9 lines 42-50 and on next chapter, in age 10, lines 7-10, "the known AF had a significantly higher prevalence of ischaemic heart disease" (it is not mentioned in page 9)? Sentence in page 9 (lines 42-50) is not logical and not in line with the results afterwords. 5) Was any multivariate analysis conducted (in factors mentioned Table1)? 6) Table 1. Is the p-value on CHA2DS2-VASc score correct? 7) Major limitation is that the reasons for withdrawal of anticoagulation were not assessed. Could this be done, since the study design was prospective? There is good discussion about differences in HAS-BLED score and its factors, since CHA2DS-VASc scores were similar and they share partly same risk factors. Duncan et al. showed that ischaemic heart disease and probably therefore antiplatelet medication were higher in patients with known AF than with patients newly diagnosed AF. 8) One would also assume that CHA2DS2-VASc score etc. would have 100% coverage due to study design.

REVIEWER	Ming Liu Department of Neurology, West China Hospital, Sichuan Univeristy, Chengdu, China
REVIEW RETURNED	25-Jan-2019

GENERAL COMMENTS	This was a secondary analysis of data from a subgroup of patients from a prospective multicentre cohort study, the CROMIS-2 study. The aim of current study was to 'identify the frequency and associations of non-anticoagulation prior to ischaemic stroke or TIA associated with atrial fibrillation'. However, the frequency of non-anticoagulation could not be answered by the study design by excluding patients who had previously received therapeutic anticoagulation nor by the stated primary outcome measure 'the proportion of patients with AF known before the index stroke compared to the proportion of patients with AF newly diagnosed after the index stroke'. In general, the outcome measures and data presented in the Results section should be modified to adequately answer the research question. It is confusing that how the comparison between patients with known atrial fibrillation and those with newly-diagnosed atrial fibrillation had revealed the associations of non-anticoagulation prior to ischaemic stroke or TIA. Patients with known AF were more likely to have history of cognitive impairments, hypertension, hyperlipidaemia, and ischaemic heart diseases. These medical conditions might have increase the opportunities to identify AF by medical examinations, which had still not answered the proposed research question of current study. It is very interesting that 73% of patients with known AF and 43% of patients with newly-diagnosed AF (i.e. without previously known AF) were on antiplatelet agents before the incident stroke. Although the authors acknowledged that the use of antiplatelets might be associated with the presence of ischaemic heart diseases, this was only present in about 20% of participants. Other indications for antiplatelets should be explored. In the Discussion section, the authors stated that 'we found that 471 (32%) patients had known AF but were not anticoagulated at the time of their qualifying stroke representing a potential missed opportunity to prevent their ischaemic stroke or TIA'. In fact, it is not 32% of patients with known AF did not receive anticoagulation before incident stroke, but 32% of patients who had AF-associated stroke had known AF but was not on anticoagulation.This relationship should be clarified.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Wang, Kang-Ling

Institution and Country: Taipei Veterans General Hospital, Taiwan Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below This is an interesting paper. It shows a great gap between current guideline recommendations and clinical practice in oral anticoagulation in patients

with atrial fibrillation. The fact is well known, however, it is rarely reported by a prospective cohort targeting patients with a recent stroke.

My comments are:

1. Although I agree with the authors that patients with atrial fibrillation at risk of stroke should be anticoagulated, the European guidelines (both in 2012 and 2016) recommend those with two risk factors other than sex should be anticoagulated (class I recommendation) and those with one risk factor other than sex should consider to receive oral anticoagulants (class IIa recommendation). Therefore, the authors should report their results stratified by sex and by the level of guideline recommendations.

We thank you for your input and suggestion. We have now undertaken this analysis and changed the paper accordingly: abstract (page 3 lines 17-19, and line 24), methods (page 6/7 lines 24/1-2) Results (page 7, lines 8-10), discussion (page 8 lines 12 and 15) and table 1

2. In addition, the recent report (PMID: 30605505) suggests the age as the strongest risk driver for stroke in those with only one risk factor other than sex. The authors should compare their patients in this additional method.

We have added this to table 1. There were no differences and therefore we have not expanded on this in the text.

3. The missing opportunity in this reported population should not be only refrained to those with stroke with a prior un-anticoagulated atrial fibrillation. It is a tip of the iceberg as it shows a greater proportion of patients with an undiagnosed atrial fibrillation who might be picked by the screening or current technologies. The authors should remind the readers in the discussion.

We agree with the reviewer. We have added a sentence into the discussion (page 9 lines 23 to 27).

Reviewer: 2

Reviewer Name: Matthew Solomon

Institution and Country: Kaiser Permanente United States Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below This is a well written study by authors from Europe and the USA that examined patients from the UK who presented with stroke and TIA that were enrolled in a prospective observational study CROMIS-2. Patients were eligible if they had stroke or TIA that was associated with atrial fibrillation (AF), but they also were required not to be on anticoagulation. The goal of the study was to examine the proportion of patients with prior known AF vs newly diagnosed AF after CVA/TIA, and to examine their risk for both stroke and bleeding to identify missed opportunities for anticoagulation treatment that may have prevented the stroke.

A strength of the study is the detailed information collected within the CROMIS-2 cohort, to be able to investigate clinical and phenotypic features of this population. As the authors note, the weaknesses of the study include the lack of information about why the patient and MD decided not to anticoagulate patients with known AF. The reasons could be myriad, including patient refusal, of the physician's concern about the ability to comply with warfarin (DOAC use was likely on the lower end during the study period), or MD concern about bleeding risk.

Thus, it is not surprising that those with known AF had higher HAS BLED scores in this comparison, because those with known AF had made a decision not to anticoagulate, perhaps due to a high HAS BLED score (or the higher dementia/cognitive impairment). The New AF group is a less selected sample because they never had a reason to be evaluated for anticoagulation; they are younger because the younger Pts with known AF were likely put on anticoagulation (and thus not eligible for the study, even if they had a stroke). So, the two groups are a little bit like apples to oranges; the new AF group is somewhat of a baseline with which to compare the known AF group.

But the biggest weakness of the study, to try to answer their research objective, is that, since the only enrolled patients were those with strokes who were not previously on anticoagulation, we do not know the denominator of patients with AF who were not anticoagulated and did not have strokes. We see only the numerator here. Thus, we don't really know the event rates for this population, and what the risks may have been from anticoagulating the entire population non-anticoagulated similar AF patients. Would they have had more intracranial or GI bleeds than strokes (ie, did the MDs and patients make the right decision overall for this population)? The paper states firmly that there were missed opportunities to prevent stroke, but I think that is a strong overstatement and the data do not support that. Perhaps the MDs got the balance correct for this population of patients? We know these patients had strokes, but we don't know what percentage of the non-anticoagulated AF cohort this represents. This could be more fully explored in the Discussion, to provide balance.

We thank the reviewer for their thorough review. We agree that the methodology of our paper prevents us from truly answering this question. However, previous work in atrial fibrillation population studies have firmly answered this question with the European cardiology guidelines presenting Class 1 level A evidence on this1. We have modified the text to highlight the proportion of patients who had class 1 level A or class 2a level b evidence yet were not anticoagulated: abstract (page 3 lines 17-19, and line 24), methods, (page 7 lines 1-4) Results (page 7, lines 14-17), discussion (page 8 lines 11-13 and 15) and table 1. We think presenting these patients as potential missed opportunities to prevent ischaemic stroke is reasonable and have altered the title to reflect this. Although patients with new AF are not a true denominator they do serve as a comparison group to generate hypotheses. We have toned done much of the language throughout (especially discussion, page 8 lines 16-19) to reflect this and listed this as a limitation (page 11 lines 09-12).

Also recommend more information about the neuro imaging findings. I am not sure of the significance of including that in the paper, there is a reference about using those findings as a way to risk stratify on the risk for ICH, but it's mentioned only in passing.

We did not wish to focus on these findings as the evidence for using neuroimaging to guide treatment is not proven. We briefly mentioned these in case previous imaging was being incorrectly used as a reason for clinicians to avoid anticoagulation

Reviewer: 3

Reviewer Name: Heidi Lehtola, MD

Institution and Country: Oulu University Hospital, Finland Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below The study of Duncan et al., "Missed opportunities to prevent ischaemic stroke: prospective multicentre cohort study of atrial fibrillation-associated ischaemic stroke and TIA" analyzed 1470 patients without previous therapeutic anticoagulation from 79 stroke care units between years 2011-2015. They found that 68% of patients had newly diagnosed AF and 32% had known AF. Study revealed that there still is underanticoagulation, since 86% of patients with known AF had strong indication for anticoagulation (CHA2DS2-VASc ≥2). They conclude that bleeding risk scores should be used to recognise patients with high bleeding risk and treat modifiable risk factors, instead of withdrawal of anticoagulation.

I still have minor comments for revision.

1) Ischaemic should be used throughout the manuscript instead of ischemic.

Thank you for pointing this out; this has now been changed.

2) How was the atrial fibrillation-associated stroke/TIA defined? Were the neurological symptoms analysed and other possible aetilogical factors for ischaemic stroke, e.g. carotid atherosclerosis, excluded? Time causality between ischaemic stroke and afterwords diagnosed AF could be hard to prove. What was the definition of newly diagnosed AF?

We thank the reviewer for pointing out this distinction. Patients were included if they had and ischaemic stroke AND atrial fibrillation which required anticoagulation. Stroke were defined locally by each enrolling centre. We have changed the wording in the article to reflect this (abstract page 3 line 10) and added a note in the limitations (page 11 lines 15-16).

3) What means the term "without therapeutic anticoagulation"? Were there warfarin treated patients with poor TTR or does this only mean the patients with antiplatelet treatment, but without DOACs/VKAs?

We have changed this to ‘previous anticoagulation’ throughout the manuscript to avoid confusion.

4) There is some discrepancy in Results section (text and Table 1). Why do you state "other variables ... did not differ significantly, but..." in page 9 lines 42-50 and on next chapter, in age 10, lines 7-10, "the known AF had a significantly higher prevalence of ischaemic heart disease" (it is not mentioned in page 9)? Sentence in page 9 (lines 42-50) is not logical and not in line with the results afterwords.

We thank the reviewer for pointing out these inconsistencies and have corrected these within the text (results page 7 lines 19 to 26).

5) Was any multivariate analysis conducted (in factors mentioned Table1)?

No. As our comparator group (patients with newly diagnosed AF) is not a true comparator group (see reviewer 2 and reviewer 4’s concerns) we did not think it wise to take the statistical analysis any further. We rather used the two groups to generate new hypotheses.

6) Table 1. Is the p-value on CHA2DS2-VASc score correct?

Yes, although the medians and IQRs are the same there is a statistical difference.

7) Major limitation is that the reasons for withdrawal of anticoagulation were not assessed. Could this be done, since the study design was prospective?

This was not asked unfortunately (as it was not the primary research question in CROMIS-2) and would require further ethical approval to do so. We are thus not able to provide this information.

There is good discussion about differences in HAS-BLED score and its factors, since CHA2DS-VASc scores were similar and they share partly same risk factors. Duncan et al. showed that ischaemic heart disease and probably therefore antiplatelet medication were higher in patients with known AF than with patients newly diagnosed AF.

8) One would also assume that CHA2DS2-VASc score etc. would have 100% coverage due to study design.

Unfortunately, some centres were unable to provide some of the relevant variables for patients.

Reviewer: 4

Reviewer Name: Ming Liu

Institution and Country: Department of Neurology, West China Hospital, Sichuan Univeristy, Chengdu, China Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below This was a secondary analysis of data from a subgroup of patients from a prospective multicentre cohort study, the CROMIS-2 study. The aim of current study was to 'identify the frequency and associations of non-anticoagulation prior to ischaemic stroke or TIA associated with atrial fibrillation'. However, the frequency of non-anticoagulation could not be answered by the study design by excluding patients who had previously received therapeutic anticoagulation nor by the stated primary outcome measure 'the proportion of patients with AF known before the index stroke compared to the proportion of patients with AF newly diagnosed after the index stroke'. In general, the outcome measures and data presented in the Results section should be modified to adequately answer the research question.

It is confusing that how the comparison between patients with known atrial fibrillation and those with newly-diagnosed atrial fibrillation had revealed the associations of non-anticoagulation prior to ischaemic stroke or TIA. Patients with known AF were more likely to have history of cognitive impairments, hypertension, hyperlipidaemia, and ischaemic heart diseases. These medical conditions might have increase the opportunities to identify AF by medical examinations, which had still not answered the proposed research question of current study.

Thank you for your review. We agree with the reviewer that our study was not designed to answer this question. We have modified the wording in our manuscript to more clearly outline the aims and findings to work within the limitations of our methodology: (discussion, page 8 lines 11-13) and reflect on this by listed this as a limitation (page 11 lines 9-16).

It is very interesting that 73% of patients with known AF and 43% of patients with newly-diagnosed AF (i.e. without previously known AF) were on antiplatelet agents before the incident stroke. Although the authors acknowledged that the use of antiplatelets might be associated with the presence of ischaemic heart diseases, this was only present in about 20% of participants. Other indications for antiplatelets should be explored.

As CROMIS-2 was not specifically designed to answer this clinical question we did not collect detailed information regarding reasons for antiplatelet therapy. We have added in 'known peripheral vascular disease' to table 1 (no difference between the groups) although there were only 31 patients, so this is unlikely to account for the antiplatelet use in the majority of cases. We have listed this within the limitations (page 11 line 13/14)

In the Discussion section, the authors stated that 'we found that 471 (32%) patients had known AF but were not anticoagulated at the time of their qualifying stroke representing a potential missed opportunity to prevent their ischaemic stroke or TIA'. In fact, it is not 32% of patients with known AF

did not receive anticoagulation before incident stroke, but 32% of patients who had AF-associated stroke had known AF but was not on anticoagulation. This relationship should be clarified.

Thank you for making this important point. We have modified the text accordingly

VERSION 2 – REVIEW

REVIEWER	Wang, Kang-Ling Taipei Veterans General Hospital, Taiwan
REVIEW RETURNED	13-Mar-2019

GENERAL COMMENTS	This revised manuscript reflects more accurately what the study was designed for. I only have one minor suggestion: 1. In the abstract section, the distribution of each HAS-BLED score, namely IQR, can be removed for the streamline and more intuitive presentation.

REVIEWER	Heidi Lehtola Oulu University Hospital, Finland
REVIEW RETURNED	24-Mar-2019

GENERAL COMMENTS	I thank for Duncan et al. for resubmission, where my previous questions are answered thoroughly and corrections are made accurately. This study clearly shows underanticogulation of AF patients suffering ischaemic stroke/TIA (between years 2011-2015). The main limitation of the study still remains, that this study was not originally designed to answer the question for the reasons to withdraw anticoagulation. Large proportion of patients on antiplatelet treatment during the stroke is also surprising in both study groups (43% vs 73%), since the number of previous ischaemic strokes (10% vs 10%), ischaemic heart disease (14% vs 22%) and especially known peripheral vascular disease (2% vs. 3%) were relatively small. Unfortunately, reasons for antiplatelet use were not assessed. The limitations of this study are now clarified in the Discussion section and study design corrected in the Methods section.

REVIEWER	Ming Liu Department of Neurology, West China Hospital, Sichuan University, Chengdu, China
REVIEW RETURNED	27-Mar-2019

GENERAL COMMENTS	Major point: Further to my previous concerns on the study design to answer the proposed research question, the current reported methods still could not achieve the study aim to 'identify the frequency and associations

	of non-anticoagulation prior to ischaemic stroke or TIA associated with atrial fibrillation' (as stated in abstract) nor to determine 'the proportion of patients with AF already known before the index stroke' (as stated in introduction)'. For the associations of non-anticoagulation prior to ischaemic stroke, the study to compare between patients who had received anticoagulation and those who did not; however, in the current study patients previously treated with oral anticoagulation had been excluded. For the proportion of patients with AF already know before the index stroke, the population of interest should be all patients who had AF and stroke, not only those who did not receive anticoagulation. Also, as only patients who had not received anticoagulation were included and the denominator of this population is unknown, the statement 'Our finding that large proportions of patients with AF at risk of ischaemic events are not anticoagulated…' in the discussion is not supported by the results. Indeed, data presented in the results section answered the question 'any demographic, clinical, or radiological differences between patients with known (and not treated) and patients with newly diagnosed AF'. So the findings of current study is mainly to answer why patients with AF have not been diagnosed prior to the incident stroke/TIA. Minor point: Study objectives stated in abstract and introduction are inconsistent.

VERSION 2 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Wang, Kang-Ling

Institution and Country: Taipei Veterans General Hospital, Taiwan

Please state any competing interests or state 'None declared': None

This revised manuscript reflects more accurately what the study was designed for.

I only have one minor suggestion:

1. In the abstract section, the distribution of each HAS-BLED score, namely IQR, can be removed for the streamline and more intuitive presentation.

Thank you for your re-review. We have made the change as suggested

Reviewer: 3

Reviewer Name: Heidi Lehtola

Institution and Country: Oulu University Hospital, Finland

Please state any competing interests or state ‘None declared’: 'None Declared'

I thank for Duncan et al. for resubmission, where my previous questions are answered thoroughly and corrections are made accurately.

This study clearly shows underanticogulation of AF patients suffering ischaemic stroke/TIA (between years 2011-2015). The main limitation of the study still remains, that this study was not originally designed to answer the question for the reasons to withdraw anticoagulation. Large proportion of patients on antiplatelet treatment during the stroke is also surprising in both study groups (43% vs 73%), since the number of previous ischaemic strokes (10% vs 10%), ischaemic heart disease (14% vs 22%) and especially known peripheral vascular disease (2% vs. 3%) were relatively small. Unfortunately, reasons for antiplatelet use were not assessed.

The limitations of this study are now clarified in the Discussion section and study design corrected in the Methods section.

Thank you for your further review. We are glad you are satisfied with our changes.

Reviewer: 4

Reviewer Name: Ming Liu

Institution and Country: Department of Neurology, West China Hospital, Sichuan University, Chengdu, China

Please state any competing interests or state ‘None declared’: None declared

Major point:

Further to my previous concerns on the study design to answer the proposed research question, the current reported methods still could not achieve the study aim to ‘identify the frequency and associations of non-anticoagulation prior to ischaemic stroke or TIA associated with atrial fibrillation’ (as stated in abstract). For the associations of non-anticoagulation prior to ischaemic stroke, the study to compare between patients who had received anticoagulation and those who did not; however, in the current study patients previously treated with oral anticoagulation had been excluded

Thank you for your further review. We agree with your point and have changed the wording in the objective to adhere to what we can achieve within the limits of our study (page 3 lines, 5 and line 13,

page 5 lines 11-15 as well as highlighting this as a weakness in the general weaknesses of the study (bullet points page 4 lines 24) and discussion (page 10 lines 5-7)

Further to my previous concerns on the study design to answer the proposed research question, the current reported methods still could not determine 'the proportion of patients with AF already known before the index stroke' (as stated in introduction)'. For the proportion of patients with AF already know before the index stroke, the population of interest should be all patients who had AF and stroke, not only those who did not receive anticoagulation. Also, as only patients who had not received anticoagulation were included and the denominator of this population is unknown.

Thank you for your further review. Once again, we agree with you and have further modified our wording to adhere with what the methodology of our study allows (page 5 lines 11-15) as well as highlighting this as a weakness in the general weaknesses of the study (bullet points page 4 lines 24) and discussion (page 10 lines 5-7)

The statement 'Our finding that large proportions of patients with AF at risk of ischaemic events are not anticoagulated…' in the discussion is not supported by the results. Indeed, data presented in the results section answered the question 'any demographic, clinical, or radiological differences between patients with known (and not treated) and patients with newly diagnosed AF'. So the findings of current study is mainly to answer why patients with AF have not been diagnosed prior to the incident stroke/TIA.

Thank you for your further review. Once again, we agree we are unable to comment on the proportions of patients with AF who are not anticoagulated. We have further modified our wording to adhere with what the methodology of our study allows (page 9 lines 4-6) and highlighted this as a weakness within the discussion.

Minor point:

Study objectives stated in abstract and introduction are inconsistent.

These are now consistent