PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between excessive premature atrial complexes and cryptogenic stroke: results of a case – control study.
AUTHORS	Sajeev, Jithin; Koshy, Anoop; Dewey, Helen; Kalman, Jonathan; Rajakariar, Kevin; Tan, Mae; Street, Maryann; Roberts, Louise; Cooke, Jennifer; Wong, Michael; Frost, Tanya; Teh, Andrew W.

VERSION 1 – REVIEW

REVIEWER	Jelle C.L. Himmelreich Amsterdam UMC, location Academic Medical Center, Amsterdam, The Netherlands
REVIEW RETURNED	05-Feb-2019

GENERAL COMMENTS	Comments to: Sajeev et al., The association between excessive premature atrial complexes and cryptogenic stroke: results of a case – control study. Manuscript ID: bmjopen-2019-029164 Sajeev and colleagues have produced a clearly written piece with an important message, i.e. that frequent PACs and brain ischaemia are associated, and that frequent PACs may be a marker of atrial cardiomyopathy that deserves further study in terms of its ability to predict adverse cardiovascular outcomes, and therefore to guide clinical decision making. I have read the manuscript with interest. However, I do have a number of questions regarding the content of the manuscript. Questions & comments: Major comments 1) Limitations of the study design: Methodologically, the main weakness of the study is its design as a case-control and cross-sectional study. Since there is no follow-up, it is difficult from these data to make inferences on whether frequent PACs were predictive to the outcome stroke, as the authors seem to imply in the discussion ('The current study similarly showed 1.97 times rise in odds for ischaemic stroke.') and by referring here to previous studies that had a longitudinal design and were thus better suited to answer the question of whether

	PACs may predict stroke. The manuscript should contain a more thorough discussion of these limitations and on what can and cannot be concluded from this study. 2) Risk of reverse causality: An interesting aspect of the study is that baseline measurement was performed median 40 days after the index TIA or stroke. Although the observation of frequent PACs is indeed likely related to atrial myopathy and therefore the increased risk of the index event, there remains the risk of reverse causality, where a stroke, through affecting cardiac innervation and subsequent remodelling, may have led to the detection of frequent PACs. In previous studies, patients were screened sooner after index event, or used longitudinal design which allowed for better interferences on the relationship between PACs and future stroke (i.e. the direction of the association). The discussion would gain from a passage on what led to this delay, whether this was intentional or i.e. regular clinical practice, and how this may have affected the outcomes of the study. Minor comments 3) In the stating that 'excessive PACs conferred the highest risk for stroke/TIA' (p 7/24 and in discussion) the authors refer to the point estimate of the OR being highest for excessive PACs. However, the confidence interval overlaps to a large extent with the other variables in the MV analysis. The manuscript could be improved by adding that although the point estimate was highest, this difference was not significant from other factors associated with stroke/TIA, or provide analyses on whether excessive PACs is indeed significantly strongest as a predictor. 4) The authors have selected cut-off for frequent PACs at 200 PACs/24h based on the study by Todo and Engström. Later authors have chosen different cut-offs, and some have tried to homogenise cut-offs, e.g. around 100/24h (1-4) or at '30/h or any run of ≥20 PACs per 24h'(5, 6). The latter definition is also mentioned in the discussion: 'This apparent discrepancy is likely due to a lack of standardised definitions for excessive PACs and treating atrial premature runs ≥20 beats as a standalone variable in the current study, instead of a composite measure' (p. 9/24, line 44). Since the authors are thus aware of this heterogeneity in cut-offs, it would be interesting to present data and show how these previously defined cut-offs fare in the authors' regression analyses, i.e. in supplemental data. 5) The cut-off for long atrial run (≥20) is not mentioned by Todo or Engström. It may help to explicate and/or to add a reference to why this cut-off was chosen. 6) Regarding the statement on p 4/24 line 37 that "no studies have assessed the pathophysiological basis of an increased PAC burden (…)": the review article by Kamel 2016 (7) outlines a possible mechanistic link and therefore pathophysiological basis for PACs as a marker for increased

	stroke risk. Is this what the authors meant by assessing the pathophysiological basis? 7) Ad p 4/24 “no studies have assessed (…) whether individual vascular risk factors that promote stroke independently correlate with excessive PAC burden” and p 10/24 line 39 “this is the first study to evaluate the independent association between specific vascular risk factors and an excessive PAC burden.” Although I grant that previous authors on PACs and stroke have not performed multivariate logistic regression to derive an OR at baseline, a number of previous studies did show baseline differences between those with frequent and infrequent PACs other than ‘PACs status’. I am therefore not certain about the novelty of the findings in the current manuscript. a. Additionally, it is unclear to me how the reference to Tereshchenko 2014 adds to the authors’ argument. 8) On page 3/24 line 9 it says ‘aged match control’, this should be ‘age matched’ 9) Ad p 4/24, line 8: The statement ‘85% of all strokes are ischaemic in nature’ cannot be deduced from the stated reference (Hart & Diener 2014), and the manuscript would benefit from adding a reference for this statement 10) The manuscript must add a reference to the statement in p 4/24, lines 21-25 on equivocal results from anticoagulant trials in all ESUS patients. 11) The reference to Healy 2012 (p 4/24, line 34) on subclinical atrial tachyarrhythmia in my view is not a correct reference to a study that researched the association between frequent PACs and ischemic stroke. The definition provided by Healey et al of subclinical atrial tachyarrhythmia may in some cases include frequent PACs, but likely also incorporates other causes than frequent PACs. The authors could refer to the studies by Binici 2010 (5) and Chong 2012 (2), or to the systematic reviews by Himmelreich 2018 (8) and Huang 2017 (9) to make their case that frequent PACs on Holter have been associated with stroke in stroke-naïve patients (cave: Huang 2017 also (arguably incorrectly) incorporates ECG studies into their meta-analysis, so their conclusion were not solely based on Holter studies), and to the studies by Pinho 2015 (10), Vinther 2016 and 2017(11, 12), and the systematic review by Sejr 2017 (13) for patients selected for stroke history. 12) P 4/24, line 34-37: it is true, that the studies mentioned in the previous sentence of the manuscript did not mention cryptogenic stroke, however there are indeed such studies. The study Pinho 2015 included only cryptogenic TIA and stroke patients, and concluded that frequent PACs were associated with more frequent recurrent stroke in these patients. Although their aim was not as Sajeev et al have done to specifically research whether frequent PACs at baseline could be association with their baseline stroke, it may be good to mention this reference in the introduction, and rewrite this passage accordingly.

13) The study sample consists of 537 consecutive TIA/stroke patients from 3 tertiary centres, included in a 4.5-year period. The authors mention in discussion that there may have been referral bias. For generalizability purposes, it may be helpful to specify whether, and on what grounds, TIA/stroke patients were or were not given Holter, if that information is available.

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REVIEWER	Arwa Younis Sheba Medical Center Tel Aviv University Israel
REVIEW RETURNED	16-Feb-2019

GENERAL COMMENTS	It is an interesting study that might make us reconsider our current notion of APCs as benign conditions. While the actual population with APCs is small, the universe is large, and the implications of the study leading to a closer watch for patients with APCs seems warranted. Clearly the study is based on a very select population with the diagnosis of stroke. Minor comments: 1. How many patients with stroke developed AF during the follow up period, and of those, how many had excessive APCS? 2. Please mention in the limitation section that both groups are highly selected patients, therefore, these findings could not be generalized to other populations and conclusions from this article should not be extrapolated to other populations. 3. The two cohorts are significantly different, and those with the stroke have more risk factors than the other cohort. Despite the use of multivariate analysis, these findings can still influence the results. Would mention that also in the limitation.

VERSION 1 – AUTHOR RESPONSE

Response to reviewers

Reviewer: #1

Reviewer Name: Jelle C.L. Himmelreich
Institution and Country: Amsterdam UMC, location Academic Medical Center, Amsterdam, The Netherlands
Please state any competing interests or state 'None declared': None.
Major comments
1) Limitations of the study design: Methodologically, the main weakness of the study is its design as a case-control and cross-sectional study. Since there is no follow-up, it is difficult from these data to make inferences on whether frequent PACs were predictive to the outcome stroke, as the authors seem to imply in the discussion ('The current study similarly showed 1.97 times rise in odds for ischaemic stroke.') and by referring here to previous studies that had a longitudinal design and were thus better suited to answer the question of whether PACs may predict stroke. The manuscript should contain a more thorough discussion of these limitations and on what can and cannot be concluded from this study.

REPLY: We thank the reviewer for their suggestion to add clarity to our manuscript. A longitudinal study design is certainly more well suited to determine causality. We have amended and added the following sentences to the manuscript, to specifically highlight the study design and to highlight the limitations of inferring causality.

"Existing longitudinal studies from Engstrom et al. that demonstrated a high PAC burden conferred a 1.9 times higher risk for ischaemic stroke. 19 Despite the differences in methodology, the current study showed a 1.97 times rise in odds for ischaemic stroke."

"The higher burden of PACs were noted in a highly selective patient cohort with ischaemic stroke and a high burden of vascular risk factors. Despite the use of multivariate regression analysis, unrecognised confounders cannot be excluded in a cross-sectional case control study. Further, these findings do not imply causality and should not be extrapolated to other patient cohorts."

2) Risk of reverse causality: An interesting aspect of the study is that baseline measurement was performed median 40 days after the index TIA or stroke. Although the observation of frequent PACs is indeed likely related to atrial myopathy and therefore the increased risk of the index event, there remains the risk of reverse causality, where a stroke, through affecting cardiac innervation and subsequent remodelling, may have led to the detection of frequent PACs. In previous studies, patients were screened sooner after index event, or used longitudinal design which allowed for better interferences on the relationship between PACs and future stroke (i.e. the direction of the association). The discussion would gain from a passage on what led to this delay, whether this was intentional or i.e. regular clinical practice, and how this may have affected the outcomes of the study.

REPLY: Thank you for highlighting this important point. Various cardiac dysfunction has been described in the presence of acute neurological insults such as ischaemic stroke, emotional stress and transient global amnesia. The degree of cardiac dysfunction varies from isolated ECG changes to significant left ventricular dysfunction with concurrent troponin elevation. It is certainly plausible that the same mechanisms could lead to an increase in PACs. We have added the following to the discussion and included the reason for the noted median time to Holter monitoring.

"The time to Holter monitoring following the stroke, based on routine institutional clinical waiting periods, could have introduced unintended variables such as neurologically mediated cardiac modelling with resultant excessive PACs and reverse causality."

Minor comments
3) In the stating that 'excessive PACs conferred the highest risk for stroke/TIA' (p 7/24 and in

discussion) the authors refer to the point estimate of the OR being highest for excessive PACs. However, the confidence interval overlaps to a large extent with the other variables in the MV analysis. The manuscript could be improved by adding that although the point estimate was highest, this difference was not significant from other factors associated with stroke/TIA, or provide analyses on whether excessive PACs is indeed significantly strongest as a predictor.

REPLY: We have amended the following sentences as suggested by the reviewer to clarify this point.
Abstract:
"On multivariate regression, excessive PACs (OR 1.97; 95% confidence interval (CI): 1.29 – 3.02; p <0.01), smoking (OR 1.58; CI: 1.06 – 2.36; p <0.05) and hypertension (OR 1.53; CI: 1.07 – 2.17; p <0.05) were independently associated with ischaemic stroke/TIA."
Discussion:
"Excessive PACs conferred the highest risk for stroke/TIA with an odds ratio of 1.97(CI: 1.29 – 3.02), but the difference was not significant when compared with other risk factors associated with stroke/TIA (Table 2). "

4) The authors have selected cut-off for frequent PACs at 200 PACs/24h based on the study by Todo and Engström. Later authors have chosen different cut-offs, and some have tried to homogenise cut-offs, e.g. around 100/24h (1-4) or at '30/h or any run of ≥20 PACs per 24h'(5, 6). The latter definition is also mentioned in the discussion: 'This apparent discrepancy is likely due to a lack of standardised definitions for excessive PACs and treating atrial premature runs ≥20 beats as a standalone variable in the current study, instead of a composite measure' (p. 9/24, line 44). Since the authors are thus aware of this heterogeneity in cut-offs, it would be interesting to present data and show how these previously defined cut-offs fare in the authors' regression analyses, i.e. in supplemental data.

REPLY: Thank you for the suggestion to include supplementary data based on varying cut offs to define excessive premature complexes. Based on data by Acharya et al. 2015 and Chong et al. 2012, excessive PACs defined as >100 PACs/day yielded an OR for Stroke/TIA of 1.53 (95% Confidence Interval: 1.10 – 2.25; p 0.13).
Based on data by Binici et al. 2010 and Larsen et al. 2015, excessive PACs defined as >30 PACs/hour or an atrial run >20 beats, yielded an OR for Stroke/TIA of 3.21 (95% Confidence Interval: 1.78 – 5.23; p <0.001). This data has been entered in tabular form in the supplemental file.
The following sentence has been added to the results:
"Multivariate analysis with various definitions of excessive PACs based on prior literature yielded similar results, with a significant association between Excessive PACs and stroke/TIA (Supplementary file)."

5) The cut-off for long atrial run (≥20) is not mentioned by Todo or Engström. It may help to explicate and/or to add a reference to why this cut-off was chosen.

REPLY: The missing reference for long atrial runs cut-off by Larsen et al. has been added
"Based on prior literature, we defined excessive PAC burden as ≥ 200 PACs/24 hours and a long atrial run as ≥20 beats.9 14 15"
6) Regarding the statement on p 4/24 line 37 that "no studies have assessed the pathophysiological basis of an increased PAC burden (…)": the review article by Kamel 2016 (7) outlines a possible mechanistic link and therefore pathophysiological basis for PACs as a marker for increased stroke risk. Is this what the authors meant by assessing the pathophysiological basis?
&
7) Ad p 4/24 "no studies have assessed (…) whether individual vascular risk factors that promote stroke independently correlate with excessive PAC burden" and p 10/24 line 39 "this is the first

study to evaluate the independent association between specific vascular risk factors and an excessive PAC burden." Although I grant that previous authors on PACs and stroke have not performed multivariate logistic regression to derive an OR at baseline, a number of previous studies did show baseline differences between those with frequent and infrequent PACs other than 'PACs status'. I am therefore not certain about the novelty of the findings in the current manuscript.
a. Additionally, it is unclear to me how the reference to Tereshchenko 2014 adds to the authors' argument.

REPLY: Thank you for requesting further clarity on these sentences and for highlighting the review article by Kamel 2016. The review outlines the evidence for atrial substrate as a driver for cardioembolic stroke in the absence of AF. They list electrocardiographic abnormalities such as elevated PTFV1 and PAC burden as potential electrocardiographic markers of abnormal atrial substrate and risk marker for stroke. However, it is unclear if specific vascular risk factors drive an atrial myopathy with resultant electrical abnormalities. As the reviewer has outlined, authors have previously provided baseline differences between patients with and without infrequent PACs. The baseline odds ratio provided following regression analysis in the current manuscript is additive information and may indicate that certain risk factors preferentially contribute to adverse atrial remodelling. Risk factor driven electroanatomic substrate abnormalities have been previously demonstrated and excessive PACs maybe just one manifestation of these changes. These findings add to and corroborate pathophysiological mechanisms postulated by Kamel et al. We have removed the reference to Terenshchenko 2014 and changed the wording of the sentence in the introduction to reflect the reviewer's suggestion.
"In addition, it is unclear whether vascular risk factors that promote stroke, independently and uniformly lead to atrial remodelling that result in excessive PAC burden."
Removed the following sentence:
"To our knowledge, this is the first study to evaluate the independent association between specific vascular risk factors and an excessive PAC burden."

8) On page 3/24 line 9 it says 'aged match control', this should be 'age matched'

REPLY: This has been corrected as per the reviewer's suggestion.

9) Ad p 4/24, line 8: The statement '85% of all strokes are ischaemic in nature' cannot be deduced from the stated reference (Hart & Diener 2014), and the manuscript would benefit from adding a reference for this statement.

REPLY: Thank you for highlighting this omission. The statement has been updated with a reference to the "Heart disease and stroke statistics- 2017 update."

10) The manuscript must add a reference to the statement in p 4/24, lines 21-25 on equivocal results from anticoagulant trials in all ESUS patients.

REPLY: The statement has been updated with a reference to the NAVIGATE ESUS trial manuscript.

11) The reference to Healy 2012 (p 4/24, line 34) on subclinical atrial tachyarrhythmia in my view is not a correct reference to a study that researched the association between frequent PACs and ischemic stroke. The definition provided by Healey et al of subclinical atrial tachyarrhythmia may in some cases include frequent PACs, but likely also incorporates other causes than frequent PACs. The authors could refer to the studies by Binici 2010 (5) and Chong 2012 (2), or to the systematic reviews by Himmelreich 2018 (8) and Huang 2017 (9) to make their case that frequent PACs on Holter have been associated with stroke in stroke-naïve patients (cave: Huang 2017 also

(arguably incorrectly) incorporates ECG studies into their meta-analysis, so their conclusion were not solely based on Holter studies), and to the studies by Pinho 2015 (10), Vinther 2016 and 2017(11, 12), and the systematic review by Sejr 2017 (13) for patients selected for stroke history.

REPLY: Thank you for highlighting studies that provide better evidence for the included statements. We have updated the references for this sentence, by removing Healy 2012 and by adding the meta-analysis by Sejr 2017 and Himmelreich 2018.

12) P 4/24, line 34-37: it is true, that the studies mentioned in the previous sentence of the manuscript did not mention cryptogenic stroke, however there are indeed such studies. The study Pinho 2015 included only cryptogenic TIA and stroke patients, and concluded that frequent PACs were associated with more frequent recurrent stroke in these patients. Although their aim was not as Sajeev et al have done to specifically research whether frequent PACs at baseline could be association with their baseline stroke, it may be good to mention this reference in the introduction, and rewrite this passage accordingly.

REPLY: We have added a sentence to take into account the study by Pinho that looked for stroke recurrence in patients with excessive PAC burden.
"While another study has shown an elevated risk for recurrent stroke in patients with excessive PACs, following a cryptogenic stroke15."

13) The study sample consists of 537 consecutive TIA/stroke patients from 3 tertiary centres, included in a 4.5-year period. The authors mention in discussion that there may have been referral bias. For generalizability purposes, it may be helpful to specify whether, and on what grounds, TIA/stroke patients were or were not given Holter, if that information is available.

REPLY: Thank you for this suggestion on improving the manuscript. The following sentence has been added to the discussion

" All patients included in the study had guideline-based referral for Holter monitoring. However, as Holter monitoring was an inclusion criterion, we do not have data on patient who may have received their Holter monitoring at an external institution."

Reviewer # 2
Reviewer Name: Arwa Younis
Institution and Country: Sheba Medical Center
Tel Aviv University
Israel
Please state any competing interests or state 'None declared': None

It is an interesting study that might make us reconsider our current notion of APCs as benign conditions. While the actual population with APCs is small, the universe is large, and the implications of the study leading to a closer watch for patients with APCs seems warranted.
Clearly the study is based on a very select population with the diagnosis of stroke.
Minor comments:
1. How many patients with stroke developed AF during the follow up period, and of those, how many had excessive APCS?
REPLY: Thank you for asking for clarification. We have added the following sentence to the manuscript.
"23 out of 537 (4.2%) patients had AF identified on Holter monitoring and were excluded. Four patients with AF had an excessive PAC burden (17%). "

2. Please mention in the limitation section that both groups are highly selected patients, therefore, these findings could not be generalized to other populations and conclusions from this article should not be extrapolated to other populations.
&
3. The two cohorts are significantly different, and those with the stroke have more risk factors than the other cohort. Despite the use of multivariate analysis, these findings can still influence the results. Would mention that also in the limitation.
REPLY: Thank you for raising these points and for the suggestion on improving the manuscript. We have added the following sentences to the manuscript, as per the reviewer's suggestion.

"The higher burden of PACs was noted in a highly selective patient cohort with ischaemic stroke and a high burden of vascular risk factors. Despite the use of multivariate regression analysis, unrecognised confounders cannot be excluded in a cross-sectional case control study, therefore these findings should not be extrapolated to other patient cohorts."

VERSION 2 – REVIEW

REVIEWER	Jelle C.L. Himmelreich Amsterdam UMC, location AMC, Amsterdam, The Netherlands Recently published a systematic review and meta-analysis on this subject, however no commercial interests.
REVIEW RETURNED	17-May-2019

GENERAL COMMENTS	Sajeev and colleagues have an important message, i.e. that frequent PACs and brain ischaemia are associated, and that frequent PACs may be a marker of atrial cardiomyopathy that deserves further study in terms of its ability to predict adverse cardiovascular outcomes, and therefore to guide clinical decision making. I have read the revised manuscript with interest. The authors have been responsive to the questions brought up by myself and other commenters, and have in my opinion substantially improved the manuscript. I have no further substantial comments. My only minor comment refers to the reference to Himmelreich et al, 2018, as referenced in the reviewed manuscript. This was an ePub ahead of publication, and has since been published as: Frequent premature atrial contractions are associated with atrial fibrillation, brain ischaemia, and mortality: a systematic review and meta-analysis. Jelle C L Himmelreich Wim A M Lucassen Martijn Heugen Patrick M M Bossuyt Hanno L Tan Ralf E Harskamp Faridi S van Etten-Jamaludin Henk C P M van Weert. EP Europace, Volume 21, Issue 5, May 2019, Pages 698–707, https://doi.org/10.1093/europace/euy276

REVIEWER	Arwa Younis Sheba Medical Center, affiliated with the Tel-Aviv university.
REVIEW RETURNED	16-Mar-2019

GENERAL COMMENTS	No further comments