PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Diagnostic yield of chest and thumb-ECG after cryptogenic stroke: Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) – an observational trial
AUTHORS	Magnusson, Peter; Lyren, Adam; Mattsson, Gustav

VERSION 1 - REVIEW

REVIEWER	Tommaso Sanna Fondazione Policlinico Gemelli IRCCS, Rome, Italy Università Cattolica del Sacro Cuore, Rome, Italy
REVIEW RETURNED	28-Mar-2020

GENERAL COMMENTS	The present study was designed to assess the diagnostic yield of a portable device to detect atrial fibrillation (AF) in patients discharged after a cryptogenic stroke (CS). Atrial fibrillation detection after a CS offers the opportunity to reduce the risk of stroke recurrence by initiating anticoagulant treatment. The topic of the manuscript is, therefore, relevant and the subject of extensive research. The device used in the present study is the Coala Heart MonitorTM. No prior research has been indexed on the Pubmed Database utilizing this device, which makes the study of potential interest to the readers of BMJ open. The introduction is clear and reasonably organized. The bibliography regarding the relationship between AF burden and the risk of stroke would probably be further improved by adding the more recent paper from Van Gelder IC et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J. 2017 May 1;38(17):1339-1344. doi: 10.1093/eurheartj/ehx042. The authors state (Page 5, line 29) that “captured episodes often reflect longer and repeated episodes and has become a widely accepted indication to initiate NOAC in newly detected AF” and cite in support of their statement the AF clinical guidelines (references 6 and 7). A generic reference to the guidelines in support of such a specific statement may sound too vague and difficult for the readers to check. I suggest that the investigators be more specific. The authors state (Page 6 Line 18) that “The system offers validated algorithms and the additional chest-ECG, which allows for differentiation between arrhythmias.” I suggest citing a reference in support of this statement. A Pubmed search revealed that the authors of the present

	manuscript published a previous paper describing the study protocol (Magnusson P. et al. A protocol for a prospective observational study using chest and thumb ECG: transient ECG assessment in stroke evaluation (TEASE) in Sweden (NCT03301662) BMJ Open. 2018 Apr 3;8(4):e019933. doi: 10.1136/bmjopen-2017-019933). I wonder why the authors do not mention this paper, which I suggest to reference. Comments about the publication plan of the other endpoints mentioned in the original protocol would be of interest to the readers. The authors state in the Inclusion/Exclusion criteria section (Page 8/25 line 12 “Thus, if outcome is reached the patient should be a candidate for anticoagulation therapy.” This sentence is redundant, and I suggest removing it. The authors state in the Inclusion/Exclusion criteria section (Page 8/25 line 12) “Patients with a TIA were not included, because this diagnosis is often uncertain due to being based solely on patient history”. However, the more recent tissue-based definition of TIA requires neuroimaging in support of the diagnosis reducing uncertainty. I suggest the investigators comment on it and, if deemed appropriate, modify the sentence accordingly The authors state (Page 9/25 Line 25) “The investigators checked all recordings daily. In the case of an atrial tachycardia, a second investigator, an experienced cardiologist within the field of arrhythmia, interpreted the recording. If the outcome was reached, anticoagulation was promptly started”. The primary outcome of the study was “Atrial tachycardia, defined as AF, atrial flutter, or ectopic atrial tachycardia with a duration of at least 30 seconds” (Page 8/25 Line 42). These statements combined imply that anticoagulants could have been prescribed not only after a diagnosis of AF or atrial flutter but also of atrial tachycardia. The authors should either clarify which guideline supports the prescription of anticoagulants after a diagnosis of atrial tachycardia of 30 seconds duration or acknowledge that their approach is investigational. Also, the statement “If the outcome was reached, anticoagulation was promptly started” raises the doubt that it may be considered as an interventional trial and not an observational trial as reported in the title (“Diagnostic yield of chest and thumb-ECG after cryptogenic stroke: Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) – an observational trial”. This may have multiple implications. I would like the authors to comment on this. Not all readers will be familiar with the study device. Supplementary material or a reference describing the study device in more detail would be a appreciated The authors state (Page 10/25 line 6) “As per protocol, 100 patients with a recent history of ischemic stroke were evaluated between October 2017 and October 2019” and then (Page 11/25 line 3) “Among the 111 participants who consented to participate, 11 dropped out because of cognitive or physical impairment that made them unable to handle the technology, or they did not wish to participate”. I suggest reconciling these statements and rephrase the sentence. A possible approach to rephrasing could be a plain description of how many patients were screened, how many accepted to participate, how many signed the informed consent and were enrolled, how many enrolled patients were able and how many failed to complete the study, with motivations.

	The results of the study are presented as follows: “In total, the 28-days of scheduled chest and thumb-ECG yielded 9% (n = 9) AF among the participants”. I suggest presenting study results in consistency with the outcomes stated in the methods section. The primary outcome of the study was a composite endpoint: “Atrial tachycardia defined as AF, atrial flutter, or ectopic atrial tachycardia with a duration of at least 30 seconds” and should be presented. It is acceptable, then, to breakdown the single constituents of the composite endpoint, but I wonder whether this approach should have been previously stated in the “methods” section listing them as secondary endpoints. I would like the authors to comment on this. The authors state that (page 11/25 Line 37) “Because we targeted solely patients who were candidates for a change in medication regimen in the presence of AF, this led to an actual benefit in the clinical management of these individual patients”. However, while the diagnosis of AF led the investigators to prescribe anticoagulants, the translation into a clinical benefit is unproven and is currently being investigated in randomized clinical trials. In conclusion (Page 16/25 Line 14) the authors state, “in many stroke survivors this is a feasible approach and can protect them from recurrent stroke by allowing for prompt initiation of NOAC treatment.” I suspect that the findings of the present study do not allow the investigators to conclude that this approach can protect from a recurrent stroke but rather that it could protect from a recurrent stroke, even though prospective studies are required to confirm this hypothesis. My suggestion is to rephrase the conclusions and the abstract accordingly. English is not my first language, and I leave the required comments about whether the standard of written English is acceptable for publication to mother tongue reviewers and the editorial office.

REVIEWER	Jukka Putaala Helsinki University Hospital, Finland
REVIEW RETURNED	01-Apr-2020

GENERAL COMMENTS	This study assessed diagnostic yield of intermittent chest and thumb ECG with Coala ECG device among patients with a recent cryptogenic stroke. The paper is well-written and is of interest to the stroke community.
	
	I have some remarks and concerns to be addressed:
	
	//Abstract:
	- Patient population (cryptogenic strokes) should more explicitly defined in the methods. Embolic neuroimaging pattern, non-lacunar? Apparently ESUS criteria were not followed.
	- Criterion for atrial tachycardia should be stated (at least 30 seconds).
	
	//Introduction:
	- Intro is lengthy. Please revise it more concise, part of if merely

	belongs to discussion.
	
	//Methods:
	- Some details on patients' etiologic work-up should be given, e.g. neurovascular imaging, routine cardiac work-up. Had all patients non-lacunar infarcts?
	- What was the rationale in including ectopic atrial tachycardia among the outcome measures? Although it may be of clinical interest for other reasons, it is not known to significantly elevate stroke risk and induce oral anticoagulation. The message of the paper could be clearer if they only focused on AF and atrial flutter - established causes for oral anticoagulation.
	
	//Results:
	- What proportion of patients with newly diagnosed AF were symptomatic (due to arrhythmia)?
	- Were there any adverse events related to ECG device used?
	
	//Discussion:
	- Overall, the Discussion is lengthy and could be shortened a bit.
	- In the paragraph on comparison to ECG chest belt studies, the authors could broaden the discussion of different post-stroke ECG monitoring solutions, and consider including this recent study utilizing an electrode plaster: Lumikari TJ et al. Continuous 4-week ECG monitoring with adhesive electrodes reveals AF
	in patients with recent embolic stroke of undetermined source. Ann Noninvasive
	Electrocardiol. 2019 Sep;24(5):e12649. doi: 10.1111/anec.12649.
	- Page 13/25, rows 42-43. Please specify the time frame in which the 6.8% and 11.8% AF yield was achieved in that study (ref #30).
	- ESUS criteria were not strictly followed to select patients with cryptogenic stroke and this should be mentioned as a limitation.
	- Page 15/25: The Future perspectives -section of discussion appears to be a bit out of scope in this manuscript. Consider removing this part and stating heart of the matter in Conclusion.
	
	//Table 1:
	- There is no reason to display proportions for "Stroke" since all of the patients had a stroke. Instead, replace it by a variable "Previous stroke" depicting stroke history prior the index stroke.
	- Table title should describe the patient population.
	
	//Figure 1:
	- Please also provide an example of a clear sinus rhythm produced by Coala Heart Monitor.

VERSION 1 – AUTHOR RESPONSE

Questions/remarks	Comments/changes to the manuscript
Reviewer 1	We are thankful for this constructive review. It will definitely improve the paper.
#2. The present study was designed to assess the diagnostic yield of a portable device to detect atrial fibrillation (AF) in patients discharged after a cryptogenic stroke (CS). Atrial fibrillation detection after a CS offers the opportunity to reduce the	Thank you for recognizing the novelty of the paper.

risk of stroke recurrence by initiating anticoagulant treatment. The topic of the manuscript is, therefore, relevant and the subject of extensive research. The device used in the present study is the Coala Heart Monitor™. No prior research has been indexed on the Pubmed Database utilizing this device, which makes the study of potential interest to the readers of BMJ open.	
#3. The introduction is clear and reasonably organized. The bibliography regarding the relationship between AF burden and the risk of stroke would probably be further improved by adding the more recent paper from Van Gelder IC et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J. 2017 May 1;38(17):1339-1344. doi: 10.1093/eurheartj/ehx042.	Agree. Reference 17 was already part of the ASSERT study but your suggestion is better and therefore we have replaced it. Van Gelder IC, Healey JS, Crijns HJGM, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J 2017;38(17):1339-1344. Page 5, line 5.
#4. The authors state (Page 5, line 29) that "captured episodes often reflect longer and repeated episodes and has become a widely accepted indication to initiate NOAC in newly detected AF" and cite in support of their statement the AF clinical guidelines (references 6 and 7). A generic reference to the guidelines in support of such a specific statement may sound too vague and difficult for the readers to check. I suggest that the investigators be more specific.	Guidelines are appropriate in this case as it summarizes the expert consensus rather than opinion based on separate papers.
#5. The authors state (Page 6 Line 18) that "The system offers validated algorithms and the additional chest-ECG, which allows for differentiation between arrhythmias." I suggest citing a reference in support of this statement.	Agree. Since we submitted the paper an expert opinion review about the Coala Heart Monitor™ has been published. This reference is added. Insulander P, Carnlöf C, Schenck-Gustafsson K, et al. Device profile of the Coala Heart Monitor for remote monitoring of the heart rhythm: overview of its efficacy. Expert Rev Med Devices. 2020;17(3):159-165. Page 6, line 8.
#6. A Pubmed search revealed that the authors of the present manuscript published a previous paper describing the study protocol (Magnusson P. et al. A protocol for a prospective observational study using chest and thumb ECG: transient ECG assessment in stroke evaluation (TEASE) in Sweden (NCT03301662) BMJ Open. 2018 Apr 3;8(4):e019933. doi: 10.1136/bmjopen-2017-019933). I wonder why the authors do	Agree. We already referred to the study protocol that was registered at Clinical Trial Registration NCT03301662. We tried to limit the number of references but based on your suggestions we have added the previous publication of the protocol in BMJ Open. "Magnusson P, Koyi H, Mattsson G. A Protocol for a Prospective Observational Study Using Chest and Thumb ECG: Transient ECG Assessment in Stroke

not mention this paper, which I suggest to reference. Comments about the publication plan of the other endpoints mentioned in the original protocol would be of interest to the readers.	Evaluation (TEASE) in Sweden. BMJ Open 2018;8(4):e019933." The study protocol was registered at Clinical Trial Registration NCT03301662 and published.[28] Page 9, line 4.
#7. The authors state in the Inclusion/Exclusion criteria section (Page 8/25 line 12 "Thus, if outcome is reached the patient should be a candidate for anticoagulation therapy." This sentence is redundant, and I suggest removing it.	We think it should be stressed that the principle is that if outcome is reached it will have clinical implication for the individual patient. Thus we would like to keep the sentence.
#8. The authors state in the Inclusion/Exclusion criteria section (Page 8/25 line 12) "Patients with a TIA were not included, because this diagnosis is often uncertain due to being based solely on patient history". However, the more recent tissue-based definition of TIA requires neuroimaging in support of the diagnosis reducing uncertainty. I suggest the investigators comment on it and, if deemed appropriate, modify the sentence accordingly.	Agree. We do agree that the more recent tissue-based definition of TIA utilizing magnetic resonance diffusion weighted imaging improves the diagnostic accuracy. However, this supports the statement that a diagnosis of TIA based on only clinical history is unreliable. We thus still believe that including only patients with ischemic stroke reduced the risk of including patients without a true cerebrovascular event. We have made changes to the text to clarify that more accurate diagnostic methods are sometimes used. "Patients with a TIA were not included, because this diagnosis is often uncertain whendue to being based solely on patient history.[25] While the more recent tissue-based definition of TIA utilizing magnetic resonance diffusion weighted imaging improves the diagnostic accuracy, this is not always done in routine clinical practice.[27]" Page 7, line 8-12.
#9. The authors state (Page 9/25 Line 25) "The investigators checked all recordings daily. In the case of an atrial tachycardia, a second investigator, an experienced cardiologist within the field of arrhythmia, interpreted the recording. If the outcome was reached, anticoagulation was promptly started". The primary outcome of the study was "Atrial tachycardia, defined as AF, atrial flutter, or ectopic atrial tachycardia with a duration of at least 30 seconds" (Page 8/25 Line 42). These statements combined imply that anticoagulants could have been prescribed not only after a diagnosis of AF or atrial flutter but also of atrial tachycardia. The authors should either clarify which guideline supports the prescription of anticoagulants after a diagnosis of atrial tachycardia of 30	Agree. Thank you for letting us clarify this. From an electrophysiological point of view the concept of atrial tachycardia include atrial fibrillation, atrial flutter, and ectopic atrial tachycardia. However, atrial flutter and ectopic atrial tachycardia may be impossible to differentiate with surface-ECG. Atrial flutter is sometimes described as atypical atrial flutter that cannot be distinguished from ectopic atrial tachycardia. In the study it was only atrial fibrillation and no other arrhythmias of relevance for the outcome. Because atrial fibrillation and atrial flutter are established indication for anticoagulation while ectopic atrial tachycardia is not we have rewritten this. "Atrial tachycardia was defined as AF, atrial flutter, or ectopic atrial tachycardia Atrial fibrillation or atrial flutter with a duration of at least 30 seconds."

seconds duration or acknowledge that their approach is investigational. Also, the statement “If the outcome was reached, anticoagulation was promptly started” raises the doubt that it may be considered as an interventional trial and not an observational trial as reported in the title (“Diagnostic yield of chest and thumb-ECG after cryptogenic stroke: Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) – an observational trial”. This may have multiple implications. I would like the authors to comment on this.	Page 7, line 20-21. “The endpoint was 28-day cumulative incidence of atrial fibrillation or atrial flutter. tachycardia.” Page 8, line 1-2. “In the case of an arrhythmia that would imply outcome atrial tachycardia, a second investigator, an experienced cardiologist within the field of arrhythmia, interpreted the recording.” Page 8, line 14.
#10. Not all readers will be familiar with the study device. Supplementary material or a reference describing the study device in more detail would be a appreciated	Agree. As stated in #5: Since we submitted the paper an expert opinion review about the Coala Heart Monitor™ has been published. This reference is added. “Insulander P, Carnlöf C, Schenck-Gustafsson K, Jensen-Urstad M. Device profile of the Coala Heart Monitor for remote monitoring of the heart rhythm: overview of its efficacy. Expert Rev Med Devices. 2020;17(3):159-165.” Page 6, line 8.
#11. The authors state (Page 10/25 line 6) “As per protocol, 100 patients with a recent history of ischemic stroke were evaluated between October 2017 and October 2019” and then (Page 11/25 line 3) “Among the 111 participants who consented to participate, 11 dropped out because of cognitive or physical impairment that made them unable to handle the technology, or they did not wish to participate”. I suggest reconciling these statements and rephrase the sentence. A possible approach to rephrasing could be a plain description of how many patients were screened, how many accepted to participate, how many signed the informed consent and were enrolled, how many enrolled patients were able and how many failed to complete the study, with motivations.	We made changes to the manuscript to highlight the fact that 100 patients completed the study as per protocol out of 111 patients who were included. “As per protocol, 100 patients with a recent history of ischemic stroke were evaluated (out of 111 who consented to participate) between October 2017 and October 2019” Page 9, line 8.
#12. The results of the study are presented as follows: “In total, the 28-days of scheduled chest and thumb-ECG yielded 9% (n = 9) AF among the participants”. I suggest presenting study results in consistency with the outcomes stated in the methods section. The primary outcome of the study was a composite endpoint: “Atrial	Agree. We have rewritten this. See #9.

tachycardia defined as AF, atrial flutter, or ectopic atrial tachycardia with a duration of at least 30 seconds" and should be presented. It is acceptable, then, to breakdown the single constituents of the composite endpoint, but I wonder whether this approach should have been previously stated in the "methods" section listing them as secondary endpoints. I would like the authors to comment on this.	
#13. The authors state that (page 11/25 Line 37) "Because we targeted solely patients who were candidates for a change in medication regimen in the presence of AF, this led to an actual benefit in the clinical management of these individual patients". However, while the diagnosis of AF led the investigators to prescribe anticoagulants, the translation into a clinical benefit is unproven and is currently being investigated in randomized clinical trials.	We decided to include patients in whom the detection of atrial fibrillation/flutter would imply initiation of NOAC, thus a potential clinical benefit for the individual undergoing the investigation. We clarified this. "Because we targeted solely patients who were candidates for a change in medication regimen in the presence of AF, this led to a potentialan actual benefit in the clinical management of these individual patients." Page 11, line 5. Anticoagulation in stroke survivors is warranted even though a large scale RCT is lacking. We addressed this in the limitation section.
#14. In conclusion (Page 16/25 Line 14) the authors state, "in many stroke survivors this is a feasible approach and can protect them from recurrent stroke by allowing for prompt initiation of NOAC treatment." I suspect that the findings of the present study do not allow the investigators to conclude that this approach can protect from a recurrent stroke but rather that it could protect from a recurrent stroke, even though prospective studies are required to confirm this hypothesis. My suggestion is to rephrase the conclusions and the abstract accordingly.	Indeed this a prospective study. We also state "can", not "will", which is deemed likely based on the vast experience of NOAC in the prevention of stroke. In secondary stroke prevention it is even a stronger reason to advocate treatment with NOAC.
#15. English is not my first language, and I leave the required comments about whether the standard of written English is acceptable for publication to mother tongue reviewers and the editorial office.	Agree. Neither are we native speakers and therefore consulted a professional language editor with vast experience. In the Acknowledgements section this is stated: The authors acknowledge editing by Jo Ann LeQuang of LeQ Medical who reviewed the manuscript for American English.
Reviewer 2	We are thankful for this constructive review. It definitely improved the paper.
#16. //Abstract: - Patient population (cryptogenic strokes) should more explicitly defined in the	Cryptogenic stroke was defined as described using a pragmatic approach in the clinical setting. Thus for example neuroimaging such as MRI was not always

methods. Embolic neuroimaging pattern, non-lacunar? Apparently ESUS criteria were not followed. - Criterion for atrial tachycardia should be stated (at least 30 seconds).	used when the diagnosis was obvious. "…but no other significant atrial arrhythmias (>30 seconds) was diagnosed." Page 2, line 17.
#17. //Introduction: - Intro is lengthy. Please revise it more concise, part of if merely belongs to discussion.	There is a balance what should be part of Introduction and what is part of Discussion. We find the current organization of the paper appropriate in that regard.
#18. //Methods: - Some details on patients' etiologic work-up should be given, e.g. neurovascular imaging, routine cardiac work-up. Had all patients non-lacunar infarcts? - What was the rationale in including ectopic atrial tachycardia among the outcome measures? Although it may be of clinical interest for other reasons, it is not known to significantly elevate stroke risk and induce oral anticoagulation. The message of the paper could be clearer if they only focused on AF and atrial flutter - established causes for oral anticoagulation.	Regarding stroke evaluation see the response under #20 about the ESUS criteria not being used. Regarding atrial tachycardia see the answer and changes made under #9.
#19. //Results: - What proportion of patients with newly diagnosed AF were symptomatic (due to arrhythmia)? - Were there any adverse events related to ECG device used?	Agree. We added this to the manuscript. "Out of 9 patients with detected atrial fibrillation, 1 patient had come into contact with health care due to the episode, he reported that he experienced symptoms in the form of palpitations and dizziness the night before atrial fibrillation was detected. He had experienced similar symptoms previously but this time after seeing that the automated report of the scheduled ECG in the morning was abnormal he went to the emergency department and was admitted due to rapid atrial fibrillation. Out of the other 8 patients with detected atrial fibrillation; 1 reported feeling palpitations, 1 reported feeling stressed as well as dizzy and 6 reported feeling well with no symptoms in conjunction with the episode." Page 10, line 3-11. "There was no adverse event related to the use of the ECG device." Page 10, line 12.
#20. //Discussion: - Overall, the Discussion is lengthy and could be shortened a bit. - In the paragraph on comparison to ECG	The Discussion is 1,315 words which is quite typical for a paper in the field. We added the suggested reference which further

chest belt studies, the authors could broaden the discussion of different post-stroke ECG monitoring solutions, and consider including this recent study utilizing an electrode plaster: Lumikari TJ et al. Continuous 4-week ECG monitoring with adhesive electrodes reveals AF in patients with recent embolic stroke of undetermined source. Ann Noninvasive Electrocardiol. 2019 Sep;24(5):e12649. doi: 10.1111/anec.12649. - Page 13/25, rows 42-43. Please specify the time frame in which the 6.8% and 11.8% AF yield was achieved in that study (ref #30). - ESUS criteria were not strictly followed to select patients with cryptogenic stroke and this should be mentioned as a limitation. - Page 15/25: The Future perspectives - section of discussion appears to be a bit out of scope in this manuscript. Consider removing this part and stating heart of the matter in Conclusion.	improve the Discussion. “Lumikari TJ, Putaala J, Kerola A, et al. Continuous 4-week ECG Monitoring With Adhesive Electrodes Reveals AF in Patients With Recent Embolic Stroke of Undetermined Source. Ann Noninvasive Electrocardiol 2019;24(5):e12649.” “In patients not eligible for thumb ECG, a device with adhesive electrodes would be an alternative.[35]„ Page 14, line 17-18. We inserted “for 30 days”: “In another post stroke/TIA study (n=249) using thumb-ECG twice daily for 30 days, the yield was 6.8% and 11.8% in patients aged 75 years and older.[30]“ Page 12, line 20. “We used a pragmatic approach based on current practice, even though a more detailed classification, based on imaging, of cryptogenic stroke has been suggested.[27]“ The following reference was added: ”Hart RG, Catanese L, Perera KS, et al. Embolic stroke of undetermined source: A systematic review and clinical update. Stroke 2017 48(4), 867– 72.” Page 14, line 4-6. The Future perspective serve as a beneficial part of the Discussion to guide future directions for research.
#20. //Table 1: - There is no reason to display proportions for "Stroke" since all of the patients had a stroke. Instead, replace it by a variable "Previous stroke" depicting stroke history prior the index stroke. - Table title should describe the patient population.	The reason to report “stroke” in Table 1 is to summarize the components of the CHA_2DS_2-VASc score for the cohort. Previous stroke would be somewhat confusing as this would be different from previous stroke in the CHA_2DS_2-VASc score which was a criteria that all patients necessarily fulfilled.
#21. //Figure 1: - Please also provide an example of a clear sinus rhythm produced by Coala Heart Monitor.	Agree. Figure 2 has been added as well as a figure caption. An example of AF is shown in Figure 1 (as a comparison sinus rhythm is shown in Figure 2). Page 9, line 19-20. “● Figure 2. Example of an ECG transmission from a Coala Heart Monitor™ showing normal sinus rhythm.” Page 23, 9-10.

VERSION 2 – REVIEW

REVIEWER	Jukka Putaala Helsinki University Hospital, Helsinki, Finland
REVIEW RETURNED	23-Jun-2020

GENERAL COMMENTS	The authors have adequately responded to my concerns.