

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Acute rule out of non ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point of care troponin: Rationale and design of the ARTICA randomized trial.
AUTHORS	Aarts, Goaris; Camaro, Cyril; van Geuns, Robert-Jan; Cramer, Etienne; van Kimmenade, Roland; Damman, P.; van Grunsven, Pierre; Adang, Eddy; Giesen, Paul; Rutten, Martijn; Ouwendijk, Olaf; Gomes, Marc; van Royen, Niels

VERSION 1 - REVIEW

REVIEWER	Edd Carlton North Bristol NHS Trust, UK I have received speaker honoraria from Roche diagnostics. I am undertaking a similar study in the UK.
REVIEW RETURNED	28-Oct-2019

GENERAL COMMENTS	<p>Given this is a protocol paper my comments are limited, since in order to obtain funding this project will have undergone peer review. I also note ethical approval has been gained. I do however have some minor comments as follows:</p> <p>I am not sure reference 3 provides original data on the number of patients presenting with chest pain to emergency departments (since it is a guideline). Please provide an alternative reference. Statement around chest pain presentations increasing is not justified from the supplied reference.</p> <p>Statement around crowding closing EDs applies to isolated units in the authors country. I would encourage the authors to explore crowding issues outside of their own country to improve the generalisability of the project.</p> <p>“and even temporary closing of EDs, which is associated with worse patient outcomes.” I am not sure this sentence is correct since the reference provided refers to ED crowding rather than closure of EDs.</p> <p>“health care costs are also increasing,” the reference supplied for this is based on the US healthcare system, which is a fairly unique model. Please provide references pertaining to more generalisable healthcare systems, including your own.</p> <p>“these ED visits often include echocardiography,” This statement is not generalisable and applies to a single US study. Please provide a number of references to support this statement if you still want to include.</p>
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	<p>References 12-15 demonstrate validation in the ED. It would be simpler to reference the recent meta-analysis by Van den Berg which covers the majority of studies rather than selecting a few to cherry pick.</p> <p>“HEART score of 0 to 3 with a negative troponin” This statement really does not make sense. The T of HEART stands for troponin surely? Therefore are you talking about a HEAR score and what does “negative” troponin mean? Do you mean troponin below the 99th percentile for the POC assay? Further to this please explain explicitly that patients who have a HEAR score of 0 but have a troponin above the 99th percentile will be excluded.</p> <p>Patient and public involvement: I think it is vital that there is ongoing patient involvement for the duration of the trial and a patient representative be included on the safety committee and consult in the event of unpredicted adverse events.</p>
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REVIEWER	Erik A. Badings Deventer Hospital, Netherlands
REVIEW RETURNED	15-Nov-2019

GENERAL COMMENTS	<p>well written, clear description of research project.</p> <p>1. Through out the manuscript, HEAR(T) and HEART score is used. Please explain what is meant by HEAR(T). (HEAR score without the Troponin component?)</p> <p>2. please consider to add reference of: van Dongen DN, Ottervanger JP, Tolsma R, et al. In-Hospital Healthcare Utilization, Outcomes, and Costs in Pre-Hospital-Adjudicated Low-Risk Chest-Pain Patients. Appl Health Econ Health Policy. 2019 Aug 6. doi: 10.1007/s40258-019-00502-6. [Epub ahead of print] PubMed PMID: 31388939.</p> <p>3. Please consider to merge results for secondary outcome (incidence of mace) with those of famous triage (ref 20)</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer Edd Carlton: Given this is a protocol paper my comments are limited, since in order to obtain funding this project will have undergone peer review. I also note ethical approval has been gained. I do however have some minor comments as follows:

1. I am not sure reference 3 provides original data on the number of patients presenting with chest pain to emergency departments (since it is a guideline). Please provide an alternative reference.

We thank the reviewer for this comment. We agree that referring to studies with original data on the number of chest pain patients in emergency departments would be more illustrative. Therefore, we replaced the reference with three other references with original data (Mockel et al 2013, Langlo et al 2014 and Pitts et al 2008). (Page 5, lines 103-104)

2. Statement around chest pain presentations increasing is not justified from the supplied reference.

We agree with the reviewer that the reference did not justify the statement. Since the overcrowding of emergency departments worldwide is caused by multiple factors and multiple complaints, not just by chest pain, we decided to change the sentence. Instead of stating that chest pain presentations are increasing, we intended to state that the total number of emergency department presentations is

increasing, leading to overcrowding. Therefore, the reference has been replaced by international references about emergency department presentations and overcrowding. (Page 5, lines 104-106)

3. Statement around crowding closing EDs applies to isolated units in the authors country. I would encourage the authors to explore crowding issues outside of their own country to improve the generalisability of the project.

Again, we would like to thank the reviewer. We totally agree that the potential impact of our study may cross our country borders as overcrowding of EDs is a global phenomenon. We realize that we did not address this issue from that viewpoint. Therefore, we changed our manuscript accordingly, with references that point out that this issue is an international problem not just affecting our countries' EDs. (Sun et al 2013 and Rasouli et al 2019) (Page 5, lines 104-106)

4. "and even temporary closing of EDs, which is associated with worse patient outcomes." I

am not sure this sentence is correct since the reference provided refers to ED crowding rather than closure of EDs.

We like to thank the reviewer for this just comment. The provided reference indeed did not state that the closing of emergency departments is associated with worse outcomes. The added references described in comment 3 concern overcrowding and clearly state that overcrowding is associated with worse outcomes. Together with adjustments made as part of our answer to comment 3, we addressed comment 4 in the same sentence. (Page 5, lines 104-106)

5. "health care costs are also increasing," the reference supplied for this is based on the US healthcare system, which is a fairly unique model. Please provide references pertaining to more generalisable healthcare systems, including your own.

This is in line with the previous comment with regard to the importance of generalisability. Again, we agree that we have used a reference that does not cover the complete picture of the global issue of ED overcrowding. We have explored data on health care expenditure around the world and referred to data from the Organisation for Economic Cooperation and Development (OECD). These data represent health care expenditure in 36 countries, including our own. To address this in our revised manuscript, we changed lines 106-108

(page 5) and added a reference accordingly. (Page 5, lines 106-108)

6. "these ED visits often include echocardiography," This statement is not generalisable and applies to a single US study. Please provide a number of references to support this statement if you still want to include.

We thank the reviewer for this comment. In order to include this statement about additional and possibly unnecessary diagnostic tests in low-risk patients, we have added references from three other studies, two of them are from the Netherlands, and one of them is also from the Unites States. (Page 5, lines 109-111)

7. References 12-15 demonstrate validation in the ED. It would be simpler to reference the recent meta-analysis by Van den Berg which covers the majority of studies rather than selecting a few to cherry pick.

We totally agree with the reviewer and replaced the references with the abovementioned meta-analysis. However, we would still like to refer to the original HEART score study by Six et al, since it has not been included in the abovementioned meta-analysis. (Page 5, lines 112-114)

8. “HEART score of 0 to 3 with a negative troponin” This statement really does not make sense. The T of HEART stands for troponin surely? Therefore are you talking about a HEAR score and what does “negative” troponin mean? Do you mean troponin below the 99th percentile for the POC assay?

With this statement we were referring to a systematic review and meta-analysis, in which the authors state that a modified low-risk HEART score is a HEART score in which patients with a HEART score of 0 to 3 are only classified as low-risk patients if the troponin value is below the 99th percentile. Therefore, the T is for troponin and in the modified low-risk HEART score troponin is determined but found negative according to the 99th percentile of a laboratory based cardiac troponin assay. With regard to your third question, the studies that were included in the meta-analysis only studies troponin levels determined by laboratory based assays used in-hospital. The POC assay is therefore not part of this analysis. We have changed the sentence to explain the modified low-risk HEART score better. (Page 5, lines 117-120)

9. Further to this please explain explicitly that patients who have a HEAR score of 0 but have a troponin above the 99th percentile will be excluded.

In order to clarify the subject of the modified low-risk HEART score in the introduction, we have adjusted the sentence, as described in our answer to ‘comment 8’. In our study, patients with a low HEAR score and an elevated troponin level (≥ 40 ng/L) on the POC assay are not excluded. However, they are transported to the emergency department for further evaluation. We added a sentence in the ‘Methods and analysis’ section regarding the study design. Therefore, we have added a sentence about what happens when a patient is included in the ARTICA trial and the POC troponin value turns out to be elevated. (Page 6, lines 152-154)

10. Patient and public involvement: I think it is vital that there is ongoing patient involvement for the duration of the trial and a patient representative be included on the safety committee and consult in the event of unpredicted adverse events.

We absolutely agree with the reviewer on this subject. The patient representative who was involved during the development of the protocol, is also involved during the duration of the trial. In order to clarify the role of the patient representative, we have added a sentence accordingly. (Page 8, lines 187-188)

Reviewer Erik A. Badings: Well written, clear description of research project:

1. Through out the manuscript, HEAR(T) and HEART score is used. Please explain what is meant by HEAR(T). (HEAR score without the Troponin component?)

We like to thank the reviewer for this comment. Indeed, it is important to further explain the difference between the HEAR score and the HEART score. When screening for eligibility, the HEAR score is calculated, since the troponin level is not yet known. After randomisation, the HEAR score is transformed into a HEART score. Depending on the randomisation group, the T component of the HEART score is added with the POC troponin assay or an in-hospital laboratory based troponin assay. Therefore, we have adjusted the sentence in the “Design and population” section, to clarify that the ambulance paramedics calculate the HEAR score. (Page 6, lines 142-145) Moreover, we have replaced “HEAR(T) score” with “HEAR score” in the “In- and exclusion criteria” section. (Page 8, lines 163-164)

2. please consider to add reference of: van Dongen DN, Ottervanger JP, Tolsma R, et al. In-Hospital Healthcare Utilization, Outcomes, and Costs in Pre-Hospital-Adjudicated Low-Risk Chest-Pain Patients. *Appl Health Econ Health Policy*. 2019 Aug 6. doi: 10.1007/s40258-01900502-6. [Epub ahead of print] PubMed PMID: 31388939.

We thank the reviewer for this suggestion, this study absolutely is of value for our study, so we have added the reference in the introduction. (Page 5, lines 109-112) Furthermore, thanks to this comment and this reference, we have added a statement in the “costeffectiveness” section of the Discussion. (Page 10, lines 239-240)

3. Please consider to merge results for secondary outcome (incidence of mace) with those of famous triage (ref 20)

We agree with the reviewer that merging the results of the ARTICA trial with the results of the Famous Triage studies is of value. We have exchanged contact information with one of the authors and aim to collaborate with the Famous Triage study group.

VERSION 2 – REVIEW

REVIEWER	Edd Carlton North Bristol NHS Trust, UK I conduct research in a related field which has been supported by industry
REVIEW RETURNED	03-Jan-2020

GENERAL COMMENTS	The authors have adequately addressed my previous comments. I look forward to seeing the results of this exciting trial.
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