PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pre-hospital Triage of Acute Cardiac Patients: Study Protocol of HART-c, a multicenter prospective study
AUTHORS	de Koning, Enrico; Biersteker, Tom; Beeres, Saskia; Bosch, Jan; Backus, Barbra; Kirchhof, Charles; Alizadeh Dehnavi, Reza; Silvius, Helen; Schalij, Martin; Boogers, Mark

VERSION 1 – REVIEW

REVIEWER	ten berg J St Antonius Hospital Nieuwegein the Netherlands
REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	Important study and the methods are sound. I have just 2 suggestions: - introduce stopping rules: define the number of serious adverse events to occur in X number of patients to be left at home making the study to stop - adverse event is any presentation at the ED (and not only for heart failure)

REVIEWER	Dr. Alireza Baratloo Department of Emergency Medicine, Tehran University of Medical Sciences, Tehran, Iran
REVIEW RETURNED	06-Aug-2020

GENERAL COMMENTS	Dear Authors I received your paper as a reviewer. It is a suitable rational paper with the aim of pre-hospital triage of acute cardiac patients. I have just to concern: 1) This intervention has some important ethical considerations, that seems to be approved by expert one in this era and I is assumed that no unethical issue has been left to revise. 2) There are several research on this topic, but I can not properly understand the novelty of your protocol in comparison with others in current literature. I want you to focus on this object both in introduction and discussion. Kind Regards

REVIEWER	D.N. van Dongen Isala Zwolle, the Netherlands
REVIEW RETURNED	07-Aug-2020

GENERAL COMMENTS	Introduction section: - efforts to prevents ED visits are scarce: I wouldn't say these efforts are scarce anymore. There are multiple studies on

	prehospital risk stratification in suspected NSTE-ACS or other suspected cardiac pathology. Those studies should be discussed in the introduction or discussion section. Methods and analysis: in the manuscript the authors speak of a triage protocol. However, it is not very clear what this protocol is beside consultation of a cardiologist. Did the cardiologist make use of a decision aid? The HEAR(T) score (without troponin) was calculated but was the outcome leading in decision making? What decision tool was used in heart failure or for example rhythm disorders? How many triage cardiologists are on call for consultation by paramedics? What if the cardiologist can not be reached in busy shifts? How many cardiologists were involved in the study? What is meant with the describement: Paramedics select low risk patients for the whole pallet of medical specialties, and only transport patients with cardiac complaints when in doubt or if admission is deemed necessary. Please give a reference for the statement: 5% of patients with cardiac complaints aren't referred to a hospital after paramedic assessment. 'An increase in patients not referred to a hospital is possible' --> please use better language. Safety of the HART-c prehospital triage protocol: what will be the comparison? Another interesting endpoint would be the time between first contact with the EMS and admission to the hospital. Will consultation delay or shorten the interval? Statistical analyses: logistic regression analysis is for dichotomous variables. This analyses cannot be used in percentages. The authors state that the study will be underpowered to detect differences in mortality and MACE. However, first: a sample size calculation is not reported, second: shouldn't this be performed with this important outcome measure? Will there also be basic analyses for baseline characteristics like gender, age, comorbidity? What is the dedicated website and e-mail adress? Please decribe the informed consent procedure in more detail. Is the informed consent registered by the paramedic? Is there written informed consent by the patient? And if not: Why not? Discussion What do the authors mean with improved utilization of healthcare resources? Please update the literature in the discussion and contemplate less about the first phase of Famous Triage 1 and more about Famous Triage 2 and 3. As far as I can find on pubmed there are at least 6 publications about those phases. The authors claim that the Hart-C study is unique since it combines since it combines pre-hospital and hospital data and direct consultation with a cardiologist. However, I believe this is already done so in several hospitals in the Netherlands. Please inventarize and please describe other options for AmbuSuite, there are several possibilities for data sharing. For example, AZNConnect.

	With tempus pro monitor no patient specific data are stored on the platform, however, wouldn't it be useful to store this information in the in-hospital patient dossier being accesible for all treating doctors? Please discuss. Please describe the risk of bias by making use of a historic cohort in which paramedics act more autonomously compared to the intervention cohort in which the paramedics are much more likely to discuss every patient case with the triage cardiologist. Figure 1: do ambulance services physically drive to the ED? or do they have to call to inventarize whether there is admission capacity or not.

VERSION 1 – AUTHOR RESPONSE

Reviewers' comments:
Reviewer 1
Important study and the methods are sound
Authors: We would like to thank you for reviewing our manuscript. We find your comments helpful and revised our manuscript accordingly.
I have just 2 suggestions:
- Introduce stopping rules: define the number of serious adverse events to occur in X number of patients to be left at home making the study stop
Authors: We agree stopping rules should be included in the manuscript and added them to the 'safety' section' (page 20, line 139-140): To evaluate safety, a dedicated researcher will contact these patients and their GP and evaluate on a case-by-case basis. If a major adverse event is deemed directly attributable to the triage protocol, the protocol will be adjusted or the study will be terminated prematurely.
- Adverse event presentation at the ED (and not only for heart failure)
Authors: We agree that all cardiac presentations at the ED that are related to the triage advice should be considered an adverse event. We updated Table 2 accordingly. We feel, however, that ED presentations for a non-cardiac complaint should not be considered as an adverse event.

Reviewer 2
Dear Authors
I received your paper as a reviewer. It is a suitable rational paper with the aim of pre-hospital triage of acute cardiac patients.
Authors: Thank you for your insightful comments.
I have just to concern:
1) This intervention has some important ethical considerations, that seems to be approved by expert one in this era and I is assumed that no unethical issue has been left to revise.
Authors: Indeed, ethical considerations have extensively been addressed in the drafting, design and implementation of this protocol and were approved by the regional medical ethics committee.
2) There are several research on this topic, but I can not properly understand the novelty of your protocol in comparison with others in current literature. I want you to focus on this object both in introduction and discussion.
Authors: The current study is the first study that evaluates a prehospital triage protocol using the combination of 1/ prehospital paramedic assessment and, 2/ prehospital expert consultation of cardiologists with direct access to live ambulance data (including ECG readings and vital parameters)

and 3/ a newly developed application showing real-time admission capacity from all regional hospitals and in-hospital patient data. The combination of these 3 factors enables a dedicated evaluation of clinical needs and can guide therapeutic strategies. In addition, with the insight in capacity of regional (cardiac) ED's and cardiac nursing wards, sudden influxes of patient can be coordinated to utilize all available resources without the risk of overcrowding. Lastly, instead of focusing on solely chest pain presentations in previous reports, this study also evaluates patients with other cardiac complaints, including rhythm disturbances and dyspnea. In order to highlight these novelties, we adjusted the introduction (page 14-15, line 24-27) and the discussion section (page 24-25, line 221-233).

Reviewer 3
Authors: Thank you for your helpful and comprehensive critical review of our manuscript. We have adjusted our manuscript after your comments.
Introduction section:
- efforts to prevents ED visits are scarce: I wouldn't say these efforts are scarce anymore. There are multiple studies on prehospital risk stratification in suspected NSTE-ACS or other suspected cardiac pathology. Those studies should be discussed in the introduction or discussion section.
Authors: We agree that various studies address this topic and discussed these studies in the discussion section (page 23, line 188-192). In addition, we changed the wording in the introduction (page 14, line 18-21). Most of the previous studies, however, focus on (pre-hospital) risk stratification and identification of low-risk patients with a suspected NSTE-ACS. The current study is one of the first in which actual decisions are made to prevent ED admissions and leave patients at home based upon a novel prehospital triage protocol.
Methods and analysis: in the manuscript the authors speak of a triage protocol. However, it is not very clear what this protocol is beside consultation of a cardiologist. Did the cardiologist make use of a decision aid? The HEAR(T) score (without troponin) was calculated but was the outcome leading in decision making? What decision tool was used in heart failure or for example rhythm disorders?
Authors: The protocol described is a combination of expert cardiologist and paramedic consultation, insight in live vital parameters through Tempus Monitor and insight in in-hospital capacity and in-hospital data. Based upon clinical cardiac guidelines and expert consensus we have developed decision aids for cardiologists for (1) chest pain, (2) dyspnea and (3) arrhythmia's. However, these are guiding (including the HEAR score) in decision rather than obligated. Accordingly, we included these decision aids as addendum 1, 2 and 3 in this comments letter. If needed, we can add these as addendums to the manuscript as well.
Addendum 1: Decision aid for chest pain
Addendum 2: Decision aid for dyspnea.

Addendum 3: Decision aid for arrhythmia.
How many triage cardiologists are on call for consultation by paramedics? What if the cardiologist cannot be reached in busy shifts? How many cardiologists were involved in the study?
Authors: There are 43 cardiologists from 3 hospitals who are available for the triage schedule and 1 cardiologist is on call every day. The triage cardiologist is not scheduled for any other responsibilities, and if the line is busy paramedics are instructed to call again after 1 minute. If the line is still busy paramedics will transport patients according to their routine clinical care protocol (LPA). The study was designed by 7 cardiologists from 3 different centres (5 of them authors) (page 17, line 62-63).
What is meant with the describment: Paramedics select low risk patients for the whole pallet of medical specialties, and only transport patients with cardiac complaints when in doubt or if admission is deemed necessary.
Authors: This refers to the autonomy of the paramedic as a medical professional and his or her ability to select low-risk patients. In daily practice, well trained, experienced paramedics select low-risk patients from all medical specialties and treat them at home or refer them to their GP (instead presenting them at an ED). We clarified this in the manuscript (page 19, line 107-110).
Please give a reference for the statement: 5% of patients with cardiac complaints aren't referred to a

hospital after paramedic assessment.
Authors: This number is derived from analysis of the historical cohort of cardiac EMS evaluations in the AmbuSuite database. We indicated this in the manuscript (page 19, line 112-115).
'An increase in patients not referred to a hospital is possible' --> please use better language.
Authors: We re-worded this sentence (page 19, line 115-116)
Safety of the HART-c prehospital triage protocol: what will be the comparison?
Authors: As safety data from patients left at home are not available for the historical cohort, a comparison for safety cannot be performed. Instead, safety will be evaluated on a case-by-case basis through contacting all patients who are not transferred to an ED as well as their GPs. For this analysis, the occurrence of pre-defined major and non-major adverse events will be assessed.
Another interesting endpoint would be the time between first contact with the EMS and admission to the hospital. Will consultation delay or shorten the interval?
Authors: We agree this is an interesting endpoint and provide this in our final results (page 20, line 133)
Statistical analyses: logistic regression analysis is for dichotomous variables. This analyses cannot be used in percentages.
Authors: The main outcome will be a dichotomous variable (ED visit or no ED visit) rather than a percentage. We clarified this in the manuscript (page 21, line 149-154).
The authors state that the study will be underpowered to detect differences in mortality and MACE. However, first: a sample size calculation is not reported, second: shouldn't this be performed with this important outcome measure?
Will there also be basic analyses for baseline characteristics like gender, age, comorbidity?
Authors: We have added the baseline characteristics analysis as suggested by the reviewer (page 21, line 151-153)
Differences in mortality and MACE in patients not referred to the hospital are beyond the scope of this study. In line with your suggestion, we consulted a statistician for a possible power analysis and see a very small power for differences in mortality and MACE. For example, since incidence of mortality is estimated to be approximately 1% in the patients not referred to the hospital, 700 patients not transported to the hospital would only have a power of less than 0.20 to detect a reduction of mortality of 50%. A smaller mortality reduction, or fewer subjects per group, would reduce the power even further.
What is the dedicated website and e-mail address?
Authors: The dedicated website is www.hartc.nl and e-mail address is info@hartc.nl. To prevent improper use, we prefer not to include this in the manuscript. However, if the reviewer and editor per se want us to include, we are willing to add this to the manuscript.
Please describe the informed consent procedure in more detail. Is the informed consent registered by the paramedic? Is there written informed consent by the patient? And if not: Why not?
Authors: Informed consent for cardiologist consultation and the HARTc study is given orally by the patient when the paramedic arrives and this is noted in the AmbuSuite database. As agreed upon by the Medical Ethics Committee, requesting written informed consent was not feasible in the urgent paramedic setting. Furthermore, it would potentially delay treatment or transfer to an ED. When contacting patients by phone who were not transported to the hospital, oral informed consent is requested before contacting their GP's (page 22, line 168-170).
Discussion
What do the authors mean with improved utilization of healthcare resources?
Authors: Live insight in the available free ED and hospital capacity in the region enables us to utilize all available healthcare resources. Patient selection in the pre-hospital setting will contribute to better patient-tailored health care as patients are transported to the hospital best suited for solving their problem. Also, transporting patients while aware of ED and nursing ward capacity will lead to improved utilization of existing healthcare resources as overcrowded hospitals are passed and unused beds are used to full capacity. We have expanded our explanation on this part. (page 22-23, line 176-178)

Please update the literature in the discussion and contemplate less about the first phase of Famous Triage 1 and more about Famous Triage 2 and 3. As far as I can find on pubmed there are at least 6 publications about those phases.
Authors: We most extensively discuss the Famous Triage 1 as, in our opinion, this is the most relevant trial for the current rationale and design manuscript. As suggested, we also included the findings from further studies from the Famous Triage study group as well as from the HE-MACS study. The HE-MACS showed ACS could be 'ruled out' in 9.4% of all chest pain patients before arrival at the hospital (page 23, line 185-189). The Famous Triage study showed nicely that pre-hospital risk stratification by ambulance paramedics using the HEART score was accurate in differentiating in low and intermediate to high risk. (page 23-24, line 201-207)
The authors claim that the Hart-C study is unique since it combines pre-hospital and hospital data and direct consultation with a cardiologist. However, I believe this is already done so in several hospitals in the Netherlands. Please inventarize and please describe other options for AmbuSuite, there are several possibilities for data sharing. For example, AZNConnect.
Authors: Indeed, AZNConnect is a platform used for data sharing by the ambulance service and several hospitals in predominantly the northern part of the Netherlands. However, with this platform it is not possible to see live vital parameters as our triage platform does. Our triage platform receives information from AmbuSuite, which the EMS service works with, but is editable by ourselves. Furthermore, to the best of our knowledge no triage protocol or triagist is combined with AZNConnect. We agree that there are other pre-hospital protocols for some (cardiac) patients and, for clarification, we have included a study in pre-hospital logistics for these patients (page 23, line 179-183)
With tempus pro monitor no patient specific data are stored on the platform, however, wouldn't it be useful to store this information in the in-hospital patient dossier being accesible for all treating doctors? Please discuss.
Authors: We agree that this would be incredibly useful, however Dutch (AVG) and European privacy law prohibits us from doing this.
Please describe the risk of bias by making use of a historic cohort in which paramedics act more autonomously compared to the intervention cohort in which the paramedics are much more likely to discuss every patient case with the triage cardiologist.
Authors: We agree that there is risk of bias as this is not a randomized controlled trial, however when analysing the two groups we will assess all cardiac patients who are evaluated by the EMS. So, if the paramedic decides not to call the cardiologist, these patients are still included in the study. We have updated the strengths and limitations section in our article summary.
Figure 1: do ambulance services physically drive to the ED? or do they have to call to inventarize whether there is admission capacity or not.
Authors: This figure shows the option when the ED of 1 one of 3 regional hospitals has capacity and is visited by an ambulance. However, after ED consultation admission is deemed necessary on a cardiac nursing ward. The cardiac nursing ward does not have admission capacity and patient is transferred from the ED to another hospital by another ambulance. When taking nursing ward capacity into account we except less inter-hospital transfers.

VERSION 2 – REVIEW

REVIEWER	Dominique N. van Dongen Isala, the Netherlands
REVIEW RETURNED	27-Sep-2020

GENERAL COMMENTS	Reviewer 3 Authors: Thank you for your helpful and comprehensive critical review of our manuscript. We have adjusted our manuscript after your comments. Thank you for your adjustments and clarifications.

	I think this study is an interesting and relevant study which does include a new pre-hospital approach. However, I still find it hard to figure out what the actual main aim of the study is since the patient group and 'triage' method is very broad and the approach is largely expert opinion based. After reading your answers on my comments, I believe the actual main aim of the study is: to assess the amount of patient left home in usual ambulance care compared to this new pre-hospital consultation approach. I suggest you make this more clear in your abstract. Also because, a clear research question/aim is crucial for a clear results paper in the future. I hope my further questions and suggestions help making the aim and methods of this manuscript more clear. Introduction section: - efforts to prevents ED visits are scarce: I wouldn't say these efforts are scarce anymore. There are multiple studies on prehospital risk stratification in suspected NSTE-ACS or other suspected cardiac pathology. Those studies should be discussed in the introduction or discussion section. Authors: We agree that various studies address this topic and discussed these studies in the discussion section (page 23, line 188-192). In addition, we changed the wording in the introduction (page 14, line 18-21). Most of the previous studies, however, focus on (pre-hospital) risk stratification and identification of low-risk patients with a suspected NSTE-ACS. The current study is one of the first in which actual decisions are made to prevent ED admissions and leave patients at home based upon a novel prehospital triage protocol. The authors made their goal more clear and better explained why their study is relevant. Page 14 line 20, please replace modified HEART by: HEART score Methods and analysis: in the manuscript the authors speak of a triage protocol. However, it is not very clear what this protocol is beside consultation of a cardiologist. Did the cardiologist make use of a decision aid? The HEAR(T) score (without troponin) was calculated but was the outcome leading in decision making? What decision tool was used in heart failure or for example rhythm disorders? Authors: The protocol described is a combination of expert cardiologist and paramedic consultation, insight in live vital parameters through Tempus Monitor and insight in in-hospital capacity and in-hospital data. Based upon clinical cardiac guidelines and expert consensus we have developed decision aids for cardiologists for (1) chest pain, (2) dyspnea and (3) arrhythmia's. However, these are guiding (including the HEAR score) in decision rather than obligated. Accordingly, we included these decision aids as addendum 1, 2 and 3 in this comments letter. If needed, we can add these as addendums to the manuscript as well. Addendum 1: Decision aid for chest pain Addendum 2: Decision aid for dyspnea. Addendum 3: Decision aid for arrhythmia. Thank you for this clear insight. I think that adding those addenda makes the study more clear for readers. However, I do have some questions: Did the authors mention the meaning of the T somewhere? I guess it is troponin, but this should be clarified in the legenda.

	To design decision aids in this broad group of patients is to my opinion very ambitious and difficult. For example the dyspnea decision aid. It is fully concentrated on cardiac reasons for dyspnea, but will there also be investigations on lung disease, for example COPD? Will, for example, all atrial fibrillation patients with hemodynamic instability be transferred to an intervention/ablation center? Probably not, because most decisions will be based on expert consensus, but that is what makes this study difficult to 'measure'. Will the authors decide per included patients whether the guiding aid is followed? Will this be published in the results section? How will you measure whether the protocols did substantially reduce unnecessary ED visits? Is there also a decision aid in heart failure? Or is this included in the dyspnea tool? How many triage cardiologists are on call for consultation by paramedics? What if the cardiologist cannot be reached in busy shifts? How many cardiologists were involved in the study? Authors: There are 43 cardiologists from 3 hospitals who are available for the triage schedule and 1 cardiologist is on call every day. The triage cardiologist is not scheduled for any other responsibilities, and if the line is busy paramedics are instructed to call again after 1 minute. If the line is still busy paramedics will transport patients according to their routine clinical care protocol (LPA). The study was designed by 7 cardiologists from 3 different centres (5 of them authors) (page 17, line 62-63). Thank you for this clarification. Please describe in the proposed results section how many times a cardiologist was consulted when a patient was included and how many times paramedics acted according to their routine LPA. This is important for the feasibility of the approach of your study. What is meant with the describment: Paramedics select low risk patients for the whole pallet of medical specialties, and only transport patients with cardiac complaints when in doubt or if admission is deemed necessary. Authors: This refers to the autonomy of the paramedic as a medical professional and his or her ability to select low-risk patients. In daily practice, well trained, experienced paramedics select low-risk patients from all medical specialties and treat them at home or refer them to their GP (instead presenting them at an ED). We clarified this in the manuscript (page 19, line 107-110). Thank you for this clarification. However, it is still not clear to me why what the reason is for mentioning this. Please give a reference for the statement: 5% of patients with cardiac complaints aren't referred to a hospital after paramedic assessment. Authors: This number is derived from analysis of the historical cohort of cardiac EMS evaluations in the AmbuSuite database. We indicated this in the manuscript (page 19, line 112-115). Thank you for clarifying. To my knowledge, paramedics do not transfer patients in at least 20% of visits. This is based on ambulance data: https://www.ambulancezorg.nl/static/upload/raw/dd0f3beb-7bed-45d3-a7b6-b5e51493726c/AZN+tabellenboek+2018+-+tabellen%2C+grafieken+en+kaarten+-+071019.pdf However, this is the number for all ambulance visits.

	'An increase in patients not referred to a hospital is possible' --> please use better language. Authors: We re-worded this sentence (page 19, line 115-116) Safety of the HART-c prehospital triage protocol: what will be the comparison? Authors: As safety data from patients left at home are not available for the historical cohort, a comparison for safety cannot be performed. Instead, safety will be evaluated on a case-by-case basis through contacting all patients who are not transferred to an ED as well as their GPs. For this analysis, the occurrence of pre-defined major and non-major adverse events will be assessed. Since the aim of your study is: The HART-c study evaluates the efficacy, safety and feasibility of a pre-hospital triage protocol, you should clearify how this will be reported and how a comparison is made. If there is no comparison, can the safety than actually be determined? Or will you base a safety conclusion on for example <1% major adverse events? This should be discussed. Another interesting endpoint would be the time between first contact with the EMS and admission to the hospital. Will consultation delay or shorten the interval? Authors: We agree this is an interesting endpoint and provide this in our final results (page 20, line 133) Statistical analyses: logistic regression analysis is for dichotomous variables. This analyses cannot be used in percentages. Authors: The main outcome will be a dichotomous variable (ED visit or no ED visit) rather than a percentage. We clarified this in the manuscript (page 21, line 149-154). The authors state that the study will be underpowered to detect differences in mortality and MACE. However, first: a sample size calculation is not reported, second: shouldn't this be performed with this important outcome measure? Will there also be basic analyses for baseline characteristics like gender, age, comorbidity? Authors: We have added the baseline characteristics analysis as suggested by the reviewer (page 21, line 151-153) Differences in mortality and MACE in patients not referred to the hospital are beyond the scope of this study. In line with your suggestion, we consulted a statistician for a possible power analysis and see a very small power for differences in mortality and MACE. For example, since incidence of mortality is estimated to be approximately 1% in the patients not referred to the hospital, 700 patients not transported to the hospital would only have a power of less than 0.20 to detect a reduction of mortality of 50%. A smaller mortality reduction, or fewer subjects per group, would reduce the power even further. Thank you for your attempt to explain why a sample size calculation is not reported. However, I do not understand why differences in mortality and MACE are beyond the scope of your study. I do understand that your main interest is to reduce unnecessary ED visits. However, shouldn't the safety of this new approach be analyzed or at least discussed. I think the sample size should be very large to proof non-inferiority and I can understand that this would prevent soon publication of results. However, then the authors should describe that this study is a pilot or proof of concept study for feasibility and efficacy, but not address safety in the abstract or results section.

	What is the dedicated website and e-mail address? Authors: The dedicated website is www.hartc.nl and e-mail address is info@hartc.nl. To prevent improper use, we prefer not to include this in the manuscript. However, if the reviewer and editor per se want us to include, we are willing to add this to the manuscript. Please describe why you are afraid of improper use. Wouldn't it be informative for readers to be able to take a look at the website? It is a well designed website Please describe the informed consent procedure in more detail. Is the informed consent registered by the paramedic? Is there written informed consent by the patient? And if not: Why not? Authors: Informed consent for cardiologist consultation and the HARTc study is given orally by the patient when the paramedic arrives and this is noted in the AmbuSuite database. As agreed upon by the Medical Ethics Committee, requesting written informed consent was not feasible in the urgent paramedic setting. Furthermore, it would potentially delay treatment or transfer to an ED. When contacting patients by phone who were not transported to the hospital, oral informed consent is requested before contacting their GP's (page 22, line 168-170). I suggest you remove the word urgent. One of the main aims of the study is to prevent unnecessary transfers. That is no urgent setting. Furthermore, also STEMI trials and even CPR trials collect (sometimes retrospective) written informed consent. Requesting and collecting informed consent is feasible, however, the need for it can be waived by investigators and medical ethics committees. The authors should explain why this was done so, for example, because usual care is not expected to change significantly (only change of hospital) or risk of study is considered very low or the study is within the scope of usual care, etc. Discussion What do the authors mean with improved utilization of healthcare resources? Authors: Live insight in the available free ED and hospital capacity in the region enables us to utilize all available healthcare resources. Patient selection in the pre-hospital setting will contribute to better patient-tailored health care as patients are transported to the hospital best suited for solving their problem. Also, transporting patients while aware of ED and nursing ward capacity will lead to improved utilization of existing healthcare resources as overcrowded hospitals are passed and unused beds are used to full capacity. We have expanded our explanation on this part. (page 22-23, line 176-178) Thank you for elaborating on this, I think the underlying thought is now more clear. Please update the literature in the discussion and contemplate less about the first phase of Famous Triage 1 and more about Famous Triage 2 and 3. As far as I can find on pubmed there are at least 6 publications about those phases. Authors: We most extensively discuss the Famous Triage 1 as, in our opinion, this is the most relevant trial for the current rationale and design manuscript. As suggested, we also included the findings from further studies from the Famous Triage study group as well as from the HE-MACS study. The HE-MACS showed ACS could be 'ruled out' in 9.4% of all chest pain patients before arrival at the hospital (page 23, line 185-189). The Famous Triage study

	showed nicely that pre-hospital risk stratification by ambulance paramedics using the HEART score was accurate in differentiating in low and intermediate to high risk. (page 23-24, line 201-207) Thank you for further discussing the mentioned trials. Since point of care troponin is now available there is no need for a modified HEART score anymore. Furthermore, since POC was not available in the time of Famous Triage 1, this design and results paper is a little outdated. The authors could consider less extensive discussion on this phase. The concept of the Famous study is quite clear if you just mention the goals and the main findings. The most relevant study for this manuscript would be Famous Triage phase 3, since in this study also patients are 'left home'. I suggest you adjust sentence 220 since also Famous and Artica studies leave patients at home after risk assessment and, when needed, hospital/cardiologist consultation. Furthermore, also other hospitals use live monitored patient data via AZN Connect, Corpuls, etc. The authors claim that the Hart-C study is unique since it combines pre-hospital and hospital data and direct consultation with a cardiologist. However, I believe this is already done so in several hospitals in the Netherlands. Please inventarize and please describe other options for AmbuSuite, there are several possibilities for data sharing. For example, AZNConnect. Authors: Indeed, AZNConnect is a platform used for data sharing by the ambulance service and several hospitals in predominantly the northern part of the Netherlands. However, with this platform it is not possible to see live vital parameters as our triage platform does. Our triage platform receives information from AmbuSuite, which the EMS service works with, but is editable by ourselves. Furthermore, to the best of our knowledge no triage protocol or triagist is combined with AZNConnect. We agree that there are other pre-hospital protocols for some (cardiac) patients and, for clarification, we have included a study in pre-hospital logistics for these patients (page 23, line 179-183) I am sorry, but I disagree with the statement that there is no possibility for live vital parameters. I suggest the authors take a look at https://www.aznconnect.nl/ and https://www.corpuls.nl/corpuls-web-live/ to see that that this is in fact possible. With tempus pro monitor no patient specific data are stored on the platform, however, wouldn't it be useful to store this information in the in-hospital patient dossier being accesible for all treating doctors? Please discuss. Authors: We agree that this would be incredibly useful, however Dutch (AVG) and European privacy law prohibits us from doing this. Since the in-hospital dossier and the platform are very well secured and patient information is already shared by paramedics with the consulting cardiologist this is not prohibited by Dutch and European law. Moreover, since you have oral informed consent this should not be a problem. Also, data is already stored on the ambusuite database, is this also actually prohibited? Please describe the risk of bias by making use of a historic cohort in which paramedics act more autonomously compared to the intervention cohort in which the paramedics are much more likely to discuss every patient case with the triage cardiologist. Authors: We agree that there is risk of bias as this is not a randomized controlled trial, however when analysing the two

	groups we will assess all cardiac patients who are evaluated by the EMS. So, if the paramedic decides not to call the cardiologist, these patients are still included in the study. We have updated the strengths and limitations section in our article summary. Thank you for clarifying. Figure 1: do ambulance services physically drive to the ED? or do they have to call to inventarize whether there is admission capacity or not. Authors: This figure shows the option when the ED of 1 one of 3 regional hospitals has capacity and is visited by an ambulance. However, after ED consultation admission is deemed necessary on a cardiac nursing ward. The cardiac nursing ward does not have admission capacity and patient is transferred from the ED to another hospital by another ambulance. When taking nursing ward capacity into account we except less inter-hospital transfers.

VERSION 2 – AUTHOR RESPONSE

Reviewer's comments

Reviewer 3

Thank you for your adjustments and clarifications.

I think this study is an interesting and relevant study which does include a new pre-hospital approach. However, I still find it hard to figure out what the actual main aim of the study is since the patient group and 'triage' method is very broad and the approach is largely expert opinion based.

After reading your answers on my comments, I believe the actual main aim of the study is: to assess the amount of patient left home in usual ambulance care compared to this new pre-hospital consultation approach. I suggest you make this more clear in your abstract. Also because, a clear research question/aim is crucial for a clear results paper in the future.

I hope my further questions and suggestions help making the aim and methods of this manuscript more clear.

Authors (2): Thank you for your continued interest in - and critical review of our study. In line with your suggestion, we adjusted the abstract accordingly (line 5-7 and 14-15).

Introduction section:

- efforts to prevents ED visits are scarce: I wouldn't say these efforts are scarce anymore. There are multiple studies on prehospital risk stratification in suspected NSTE-ACS or other suspected cardiac pathology. Those studies should be discussed in the introduction or discussion section.

Authors: We agree that several studies address this topic and discussed these studies in the discussion section (page 23, line 188-192). In addition, we changed the wording in the introduction (page 14, line 18-21). Most of the previous studies, however, focus on (pre-hospital) risk stratification and identification of low-risk patients with a suspected NSTE-ACS. The current study is one of the first in which actual decisions are made to prevent ED admissions and leave patients at home based upon a novel prehospital triage protocol.

The authors made their goal more clear and better explained why their study is relevant.

Page 14 line 20, please replace modified HEART by: HEART score

Authors (2): We have replaced modified HEART by HEART score (line 20).

Methods and analysis: in the manuscript the authors speak of a triage protocol. However, it is not very clear what this protocol is beside consultation of a cardiologist. Did the cardiologist make use of a decision aid? The HEAR(T) score (without troponin) was calculated but was the outcome leading in decision making? What decision tool was used in heart failure or for example rhythm disorders?

Authors: The protocol described is a combination of expert cardiologist and paramedic consultation, insight in live vital parameters through Tempus Monitor and insight in in-hospital capacity and in-hospital data. Based upon clinical cardiac guidelines and expert consensus we have developed decision aids for cardiologists for (1) chest pain, (2) dyspnoea and (3) arrhythmia's. However, these are guiding (including the HEAR score) in decision rather than obligated. Accordingly, we included these decision aids as addendum 1, 2 and 3 in this comments letter. If needed, we can add these as addendums to the manuscript as well.

Addendum 1: Decision aid for chest pain

Addendum 2: Decision aid for dyspnoea.

Addendum 3: Decision aid for arrhythmia.

Thank you for this clear insight. I think that adding those addenda makes the study more clear for readers.

Authors (2): We have added these decision aids as addenda to our manuscript and have updated our manuscript (lines 69-72).

However, I do have some questions:

Did the authors mention the meaning of the T somewhere? I guess it is troponin, but this should be clarified in the legenda.

To design decision aids in this broad group of patients is to my opinion very ambitious and difficult. For example the dyspnea decision aid. It is fully concentrated on cardiac reasons for dyspnea, but will there also be investigations on lung disease, for example COPD?

Will, for example, all atrial fibrillation patients with hemodynamic instability be transferred to an intervention/ablation center? Probably not, because most decisions will be based on expert consensus, but that is what makes this study difficult to 'measure'. Will the authors decide per included patients whether the guiding aid is followed? Will this be published in the results section? How will you measure whether the protocols did substantially reduce unnecessary ED visits?

Is there also a decision aid in heart failure? Or is this included in the dyspnea tool?

Authors (2):

- The T in this decision aids refers to triage cardiologist consultation. We have explained this in Addendum 1, 2 and 3.

- We agree that the triage method is very ambitious and we see a possibility for the use of this method for other medical specialties in the future. At this point, however, we chose to focus on cardiology patients, in particular patients with chest pain, dyspnoea (with heart failure as suspected origin) and arrhythmias. At this moment, the HARTc protocol is not applied to patients with COPD.

- As requested, we added the 3 decision aids as addenda to our manuscript. The decision aids are guidelines/aids for clinical decision making rather than obligated. Accordingly, to analyze per patient whether the guiding aid is strictly followed is beyond the scope of the study.

How many triage cardiologists are on call for consultation by paramedics? What if the cardiologist cannot be reached in busy shifts? How many cardiologists were involved in the study?

Authors: There are 43 cardiologists from 3 hospitals who are available for the triage schedule and 1 cardiologist is on call every day. The triage cardiologist is not scheduled for any other responsibilities, and if the line is busy paramedics are instructed to call again after 1 minute. If the line is still busy paramedics will transport patients according to their routine clinical care protocol (LPA). The study was designed by 7 cardiologists from 3 different centres (5 of them authors) (page 17, line 62-63).

Thank you for this clarification. Please describe in the proposed results section how many times a cardiologist was consulted when a patient was included and how many times paramedics acted according to their routine LPA. This is important for the feasibility of the approach of your study.

Authors (2): Every patient that is consulted from 09.00-17.00 is registered. In patients who are evaluated beyond this time frame, the paramedics follow their routine LPA. We will note how many times a cardiologist will be consulted when a patient is included. Feasibility of the pre-hospital triage method was defined as the absence of technical problems as mentioned (line 146).

What is meant with the describment: Paramedics select low risk patients for the whole pallet of medical specialties, and only transport patients with cardiac complaints when in doubt or if admission is deemed necessary.

Authors: This refers to the autonomy of the paramedic as a medical professional and his or her ability to select low-risk patients. In daily practice, well trained, experienced paramedics select low-risk

patients from all medical specialties and treat them at home or refer them to their GP (instead presenting them at an ED). We clarified this in the manuscript (page 19, line 107-110).

Thank you for this clarification. However, it is still not clear to me why what the reason is for mentioning this.

Author (2): This description refers to our historic control group (regular ambulance care). For comparison reasons, we think it is important to mention this in the manuscript. Patients were already left at home by the ambulance service before starting the prehospital triage, however, due to implementation of our new triage method we expect to increase patients who are left home.

Please give a reference for the statement: 5% of patients with cardiac complaints aren't referred to a hospital after paramedic assessment.

Authors: This number is derived from analysis of the historical cohort of cardiac EMS evaluations in the AmbuSuite database. We indicated this in the manuscript (page 19, line 112-115).

Thank you for clarifying. To my knowledge, paramedics do not transfer patients in at least 20% of visits. This is based on ambulance data: https://www.ambulancezorg.nl/static/upload/raw/dd0f3beb-7bed-45d3-a7b6-b5e51493726c/AZN+tabellenboek+2018+-+tabellen%2C+grafieken+en+kaarten+-+071019.pdf

However, this is the number for all ambulance visits.

Authors (2): Thank you for providing these data. The percentage of 20% accounts for all ambulance rides (for cardiac and non-cardiac complaints). In our historical cohort, from first analysis, approximately 5% of patients with cardiac presentations are left home. However, detailed analysis in our results paper will give us a final number.

'An increase in patients not referred to a hospital is possible' --> please use better language.

Authors: We re-worded this sentence (page 19, line 115-116)

Safety of the HART-c prehospital triage protocol: what will be the comparison?

Authors: As safety data from patients left at home are not available for the historical cohort, a comparison for safety cannot be performed. Instead, safety will be evaluated on a case-by-case basis through contacting all patients who are not transferred to an ED as well as their GPs. For this analysis, the occurrence of pre-defined major and non-major adverse events will be assessed.

Since the aim of your study is: The HART-c study evaluates the efficacy, safety and feasibility of a pre-hospital triage protocol, you should clearify how this will be reported and how a comparison is made. If there is no comparison, can the safety than actually be determined? Or will you base a safety conclusion on for example <1% major adverse events? This should be discussed.

Authors (2): Thank you for pointing out this important issue. As requested, we further clarified the safety endpoint which is a secondary end-point. We will define our study safety endpoint as: <1% major adverse events within 30 days after triage contract, and have added this (line 144-145).

Another interesting endpoint would be the time between first contact with the EMS and admission to the hospital. Will consultation delay or shorten the interval?

Authors: We agree this is an interesting endpoint and provide this in our final results (page 20, line 133)

Statistical analyses: logistic regression analysis is for dichotomous variables. This analysis cannot be used in percentages.

Authors: The main outcome will be a dichotomous variable (ED visit or no ED visit) rather than a percentage. We clarified this in the manuscript (page 21, line 149-154).

The authors state that the study will be underpowered to detect differences in mortality and MACE. However, first: a sample size calculation is not reported, second: shouldn't this be performed with this important outcome measure?

Will there also be basic analyses for baseline characteristics like gender, age, comorbidity?

Authors: We have added the baseline characteristics analysis as suggested by the reviewer (page 21, line 151-153)

Differences in mortality and MACE in patients not referred to the hospital are beyond the scope of this study. In line with your suggestion, we consulted a statistician for a possible power analysis and see a very small power for differences in mortality and MACE. For example, since incidence of mortality is estimated to be approximately 1% in the patients not referred to the hospital, 700 patients not transported to the hospital would only have a power of less than 0.20 to detect a reduction of mortality of 50%. A smaller mortality reduction, or fewer subjects per group, would reduce the power even further.

Thank you for your attempt to explain why a sample size calculation is not reported. However, I do not understand why differences in mortality and MACE are beyond the scope of your study. I do understand that your main interest is to reduce unnecessary ED visits. However, shouldn’t the safety of this new approach be analyzed or at least discussed. I think the sample size should be very large to proof non-inferiority and I can understand that this would prevent soon publication of results.

However, then the authors should describe that this study is a pilot or proof of concept study for feasibility and efficacy, but not address safety in the abstract or results section.

Authors (2): As mentioned before, mortality and MACE rates can unfortunately not be compared with the control group as follow-up is not available for the control group. However, we agree with the reviewer that MACE and mortality rates are of importance. For this reason, we will report the mortality and MACE data in the intervention group. Lastly, we agree that safety of the current study is more a proof-of-concept for pre-hospital triage (safety is defined as <1% MACE rate). Accordingly, this is a secondary end-point rather than a primary study aim. Therefore we have withdrawn the safety endpoint from our abstract (line 19) and methods (line 128) and discussion (line 244).

What is the dedicated website and e-mail address?

Authors: The dedicated website is www.hartc.nl and e-mail address is info@hartc.nl. To prevent improper use, we prefer not to include this in the manuscript. However, if the reviewer and editor per se want us to include, we are willing to add this to the manuscript.

Please describe why you are afraid of improper use. Wouldn't it be informative for readers to be able to take a look at the website? It is a well designed website

Authors (2): We have added the website in our manuscript (line 166-167).

Please describe the informed consent procedure in more detail. Is the informed consent registered by the paramedic? Is there written informed consent by the patient? And if not: Why not?

Authors: Informed consent for cardiologist consultation and the HARTc study is given orally by the patient when the paramedic arrives and this is noted in the AmbuSuite database. As agreed upon by the Medical Ethics Committee, requesting written informed consent was not feasible in the urgent paramedic setting. Furthermore, it would potentially delay treatment or transfer to an ED. When contacting patients by phone who were not transported to the hospital, oral informed consent is requested before contacting their GP's (page 22, line 168-170).

I suggest you remove the word urgent. One of the main aims of the study is to prevent unnecessary transfers. That is no urgent setting. Furthermore, also STEMI trials and even CPR trials collect (sometimes retrospective) written informed consent. Requesting and collecting informed consent is feasible, however, the need for it can be waived by investigators and medical ethics committees. The authors should explain why this was done so, for example, because usual care is not expected to change significantly (only change of hospital) or risk of study is considered very low or the study is within the scope of usual care, etc.

Authors (2): We agree and have adjusted the wording on line 171-174. After extensive discussion with the Medical Ethics Committee the need for written informed consent was waived. Reasons for the waiving of written informed consent were the large group of patients, the fact that patients were transferred to three different hospitals and the setting of enrollment.

Discussion

What do the authors mean with improved utilization of healthcare resources?

Authors: Live insight in the available free ED and hospital capacity in the region enables us to utilize all available healthcare resources. Patient selection in the pre-hospital setting will contribute to better patient-tailored health care as patients are transported to the hospital best suited for solving their problem. Also, transporting patients while aware of ED and nursing ward capacity will lead to improved utilization of existing healthcare resources as overcrowded hospitals are passed and unused beds are used to full capacity. We have expanded our explanation on this part. (page 22-23, line 176-178)

Thank you for elaborating on this, I think the underlying thought is now more clear.

Please update the literature in the discussion and contemplate less about the first phase of Famous Triage 1 and more about Famous Triage 2 and 3. As far as I can find on pubmed there are at least 6 publications about those phases.

Authors: We most extensively discuss the Famous Triage 1 as, in our opinion, this is the most relevant trial for the current rationale and design manuscript. As suggested, we also included the findings from further studies from the Famous Triage study group as well as from the HE-MACS study. The HE-MACS showed ACS could be 'ruled out' in 9.4% of all chest pain patients before arrival at the hospital (page 23, line 185-189). The Famous Triage study showed nicely that pre-hospital risk stratification by ambulance paramedics using the HEART score was accurate in differentiating in low and intermediate to high risk. (page 23-24, line 201-207)

Thank you for further discussing the mentioned trials. Since point of care troponin is now available there is no need for a modified HEART score anymore. Furthermore, since POC was not available in the time of Famous Triage 1, this design and results paper is a little outdated. The authors could consider less extensive discussion on this phase. The concept of the Famous study is quite clear if you just mention the goals and the main findings. The most relevant study for this manuscript would be Famous Triage phase 3, since in this study also patients are 'left home'. I suggest you adjust sentence 220 since also Famous and Artica studies leave patients at home after risk assessment and, when needed, hospital/cardiologist consultation.

Authors (2): Thank you for providing these suggestions. As requested, we have adjusted line 226-227 as Famous and Artica indeed also have these as outcomes in their studies. Furthermore, we have focused more on FAMOUS 3 (line 208-212).

Furthermore, also other hospitals use live monitored patient data via AZN Connect, Corpuls, etc.

The authors claim that the Hart-C study is unique since it combines pre-hospital and hospital data and direct consultation with a cardiologist. However, I believe this is already done so in several hospitals in the Netherlands. Please inventarize and please describe other options for AmbuSuite, there are several possibilities for data sharing. For example, AZNConnect.

Authors: Indeed, AZNConnect is a platform used for data sharing by the ambulance service and several hospitals in predominantly the northern part of the Netherlands. However, with this platform it is not possible to see live vital parameters as our triage platform does. Our triage platform receives information from AmbuSuite, which the EMS service works with, but is editable by ourselves. Furthermore, to the best of our knowledge no triage protocol or triagist is combined with AZNConnect. We agree that there are other pre-hospital protocols for some (cardiac) patients and, for clarification, we have included a study in pre-hospital logistics for these patients (page 23, line 179-183)

I am sorry, but I disagree with the statement that there is no possibility for live vital parameters. I suggest the authors take a look at https://www.aznconnect.nl/ and https://www.corpuls.nl/corpuls-web-live/ to see that that this is in fact possible.

Authors (2): We have checked the provided websites, and agree that there are other possibilities for data-sharing and insights in pre-hospital parameters. This new market is only expected to grow in the coming years as these are very important new developments.

With tempus pro monitor no patient specific data are stored on the platform, however, wouldn't it be useful to store this information in the in-hospital patient dossier being accesible for all treating doctors? Please discuss.

Authors: We agree that this would be incredibly useful, however Dutch (AVG) and European privacy law prohibits us from doing this.

Since the in-hospital dossier and the platform are very well secured and patient information is already shared by paramedics with the consulting cardiologist this is not prohibited by Dutch and European law. Moreover, since you have oral informed consent this should not be a problem. Also, data is already stored on the ambusuite database, is this also actually prohibited?

Authors (2): Only relevant information for the clinical decision making is available for the consulting cardiologist. Patient’s information which is not useful for cardiac triage will not be available for the consulted cardiologist and these data will not be stored on the digital platform. Informed consent for the triage procedure does not grant us access to all the patient’s medical history.

Please describe the risk of bias by making use of a historic cohort in which paramedics act more autonomously compared to the intervention cohort in which the paramedics are much more likely to discuss every patient case with the triage cardiologist.

Authors: We agree that there is risk of bias as this is not a randomized controlled trial, however when analysing the two groups we will assess all cardiac patients who are evaluated by the EMS. So, if the paramedic decides not to call the cardiologist, these patients are still included in the study. We have updated the strengths and limitations section in our article summary.

Thank you for clarifying.

Figure 1: do ambulance services physically drive to the ED? or do they have to call to inventarize whether there is admission capacity or not.

Authors: This figure shows the option when the ED of 1 one of 3 regional hospitals has capacity and is visited by an ambulance. However, after ED consultation admission is deemed necessary on a cardiac nursing ward. The cardiac nursing ward does not have admission capacity and patient is transferred from the ED to another hospital by another ambulance. When taking nursing ward capacity into account we except less inter-hospital transfers.

VERSION 3 – REVIEW

REVIEWER	D.N. van Dongen Isala, Zwolle, the Netherlands
REVIEW RETURNED	19-Jan-2021

GENERAL COMMENTS	27th of November 2020 Dear Mr. Aldcroft, Thank you for giving us the opportunity to submit a second revised version of the manuscript “Pre-Hospital Triage of Acute Cardiac Patients: Study Protocol of HART-c, a multicenter prospective study”. We appreciate the time and effort you and the reviewers dedicated to providing feedback and are grateful for the insightful comments and improvements to our paper. We incorporated the further suggestions made by the reviewers. Those changes are highlighted in the second revision of this manuscript. We included the reviewer comments immediately after this letter and responded to them individually, indicating how we addressed each comment and describing the changes we have made. We put our answers to the second revision in italic. Page numbers and lines refer to the revised manuscript. We hope the revised manuscript will suit BMJ Open, and we thank you for your continued interest in our research. Yours sincerely, Enrico de Koning Reviewer’s comments Reviewer 3 Thank you for your adjustments and clarifications. I think this study is an interesting and relevant study which does include a new pre-hospital approach. However, I still find it hard to figure out what the actual main aim of the study is since the patient group and ‘triage’ method is very broad and the approach is largely expert opinion based. After reading your answers on my comments, I believe the actual main aim of the study is: to assess the amount of patient left home

	in usual ambulance care compared to this new pre-hospital consultation approach. I suggest you make this more clear in your abstract. Also because, a clear research question/aim is crucial for a clear results paper in the future. I hope my further questions and suggestions help making the aim and methods of this manuscript more clear. Authors (2): Thank you for your continued interest in - and critical review of our study. In line with your suggestion, we adjusted the abstract accordingly (line 5-7 and 14-15). Thank you, this makes the purpose of the manuscript much clearer. I have one 'major' suggestion for your study/paper: perhaps you should switch the term triage protocol to triage approach or triage method. Since the working method presented in your manuscript is more the testing of a new pre-hospital triage method/approach and not really a study on following and testing of a new protocol. Introduction section: - efforts to prevents ED visits are scarce: I wouldn't say these efforts are scarce anymore. There are multiple studies on prehospital risk stratification in suspected NSTE-ACS or other suspected cardiac pathology. Those studies should be discussed in the introduction or discussion section. Authors: We agree that several studies address this topic and discussed these studies in the discussion section (page 23, line 188-192). In addition, we changed the wording in the introduction (page 14, line 18-21). Most of the previous studies, however, focus on (pre-hospital) risk stratification and identification of low-risk patients with a suspected NSTE-ACS. The current study is one of the first in which actual decisions are made to prevent ED admissions and leave patients at home based upon a novel prehospital triage protocol. The authors made their goal more clear and better explained why their study is relevant. Page 14 line 20, please replace modified HEART by: HEART score Authors (2): We have replaced modified HEART by HEART score (line 20). Methods and analysis: in the manuscript the authors speak of a triage protocol. However, it is not very clear what this protocol is beside consultation of a cardiologist. Did the cardiologist make use of a decision aid? The HEAR(T) score (without troponin) was calculated but was the outcome leading in decision making? What decision tool was used in heart failure or for example rhythm disorders? Authors: The protocol described is a combination of expert cardiologist and paramedic consultation, insight in live vital parameters through Tempus Monitor and insight in in-hospital capacity and in-hospital data. Based upon clinical cardiac guidelines and expert consensus we have developed decision aids for cardiologists for (1) chest pain, (2) dyspnoea and (3) arrhythmia's. However, these are guiding (including the HEAR score) in decision rather than obligated. Accordingly, we included these decision aids as addendum 1, 2 and 3 in this comments letter. If needed, we can add these as addendums to the manuscript as well. Addendum 1: Decision aid for chest pain

	Addendum 2: Decision aid for dyspnoea. Addendum 3: Decision aid for arrhythmia. Thank you for this clear insight. I think that adding those addenda makes the study more clear for readers. Authors (2): We have added these decision aids as addenda to our manuscript and have updated our manuscript (lines 69-72). However, I do have some questions: Did the authors mention the meaning of the T somewhere? I guess it is troponin, but this should be clarified in the legenda. To design decision aids in this broad group of patients is to my opinion very ambitious and difficult. For example the dyspnea decision aid. It is fully concentrated on cardiac reasons for dyspnea, but will there also be investigations on lung disease, for example COPD? Will, for example, all atrial fibrillation patients with hemodynamic instability be transferred to an intervention/ablation center? Probably not, because most decisions will be based on expert consensus, but that is what makes this study difficult to 'measure'. Will the authors decide per included patients whether the guiding aid is followed? Will this be published in the results section? How will you measure whether the protocols did substantially reduce unnecessary ED visits? Is there also a decision aid in heart failure? Or is this included in the dyspnea tool? Authors (2): - The T in this decision aids refers to triage cardiologist consultation. We have explained this in Addendum 1, 2 and 3. - We agree that the triage method is very ambitious and we see a possibility for the use of this method for other medical specialties in the future. At this point, however, we chose to focus on cardiology patients, in particular patients with chest pain, dyspnoea (with heart failure as suspected origin) and arrhythmias. At this moment, the HARTc protocol is not applied to patients with COPD. - As requested, we added the 3 decision aids as addenda to our manuscript. The decision aids are guidelines/aids for clinical decision making rather than obligated. Accordingly, to analyze per patient whether the guiding aid is strictly followed is beyond the scope of the study. How many triage cardiologists are on call for consultation by paramedics? What if the cardiologist cannot be reached in busy shifts? How many cardiologists were involved in the study? Authors: There are 43 cardiologists from 3 hospitals who are available for the triage schedule and 1 cardiologist is on call every day. The triage cardiologist is not scheduled for any other responsibilities, and if the line is busy paramedics are instructed to call again after 1 minute. If the line is still busy paramedics will transport patients according to their routine clinical care protocol (LPA). The study was designed by 7 cardiologists from 3 different centres (5 of them authors) (page 17, line 62-63). Thank you for this clarification. Please describe in the proposed results section how many times a cardiologist was consulted when a patient was included and how many times paramedics acted according to their routine LPA. This is important for the feasibility of the approach of your study.

	Authors (2): Every patient that is consulted from 09.00-17.00 is registered. In patients who are evaluated beyond this time frame, the paramedics follow their routine LPA. We will note how many times a cardiologist will be consulted when a patient is included. Feasibility of the pre-hospital triage method was defined as the absence of technical problems as mentioned (line 146). Thank you for this clarification. However, you also describe in your manuscript: The HART-c study is designed to evaluate the efficacy and feasibility of a novel comprehensive pre-hospital triage protocol which aims to safely reduce unnecessary ED visits in patients with cardiac complaint. This suggests that the feasibility of implementation of this protocol is tested. This comprehends more than only the technical aspects. If you replace the term protocol to method or approach (like you already do in your clarification above) you partly avoid this 'discussion'. What is meant with the describment: Paramedics select low risk patients for the whole pallet of medical specialties, and only transport patients with cardiac complaints when in doubt or if admission is deemed necessary. Authors: This refers to the autonomy of the paramedic as a medical professional and his or her ability to select low-risk patients. In daily practice, well trained, experienced paramedics select low-risk patients from all medical specialties and treat them at home or refer them to their GP (instead presenting them at an ED). We clarified this in the manuscript (page 19, line 107-110). Thank you for this clarification. However, it is still not clear to me why what the reason is for mentioning this. Author (2): This description refers to our historic control group (regular ambulance care). For comparison reasons, we think it is important to mention this in the manuscript. Patients were already left at home by the ambulance service before starting the prehospital triage, however, due to implementation of our new triage method we expect to increase patients who are left home. Thank you for clarifying. Please give a reference for the statement: 5% of patients with cardiac complaints aren't referred to a hospital after paramedic assessment. Authors: This number is derived from analysis of the historical cohort of cardiac EMS evaluations in the AmbuSuite database. We indicated this in the manuscript (page 19, line 112-115). Thank you for clarifying. To my knowledge, paramedics do not transfer patients in at least 20% of visits. This is based on ambulance data: https://www.ambulancezorg.nl/static/upload/raw/dd0f3beb-7bed-45d3-a7b6-b5e51493726c/AZN+tabellenboek+2018+-+tabellen%2C+grafieken+en+kaarten+-+071019.pdf However, this is the number for all ambulance visits. Authors (2): Thank you for providing these data. The percentage of 20% accounts for all ambulance rides (for cardiac and non-cardiac complaints). In our historical cohort, from first analysis, approximately 5% of patients with cardiac presentations are left home. However, detailed analysis in our results paper will give us a final number.

	:) 'An increase in patients not referred to a hospital is possible' --> please use better language. Authors: We re-worded this sentence (page 19, line 115-116) Safety of the HART-c prehospital triage protocol: what will be the comparison? Authors: As safety data from patients left at home are not available for the historical cohort, a comparison for safety cannot be performed. Instead, safety will be evaluated on a case-by-case basis through contacting all patients who are not transferred to an ED as well as their GPs. For this analysis, the occurrence of pre-defined major and non-major adverse events will be assessed. Since the aim of your study is: The HART-c study evaluates the efficacy, safety and feasibility of a pre-hospital triage protocol, you should clearify how this will be reported and how a comparison is made. If there is no comparison, can the safety than actually be determined? Or will you base a safety conclusion on for example <1% major adverse events? This should be discussed. Authors (2): Thank you for pointing out this important issue. As requested, we further clarified the safety endpoint which is a secondary end-point. We will define our study safety endpoint as: <1% major adverse events within 30 days after triage contract, and have added this (line 144-145). I think that is a good decision. It will help you in your future results paper. Another interesting endpoint would be the time between first contact with the EMS and admission to the hospital. Will consultation delay or shorten the interval? Authors: We agree this is an interesting endpoint and provide this in our final results (page 20, line 133) Statistical analyses: logistic regression analysis is for dichotomous variables. This analysis cannot be used in percentages. Authors: The main outcome will be a dichotomous variable (ED visit or no ED visit) rather than a percentage. We clarified this in the manuscript (page 21, line 149-154). The authors state that the study will be underpowered to detect differences in mortality and MACE. However, first: a sample size calculation is not reported, second: shouldn't this be performed with this important outcome measure? Will there also be basic analyses for baseline characteristics like gender, age, comorbidity? Authors: We have added the baseline characteristics analysis as suggested by the reviewer (page 21, line 151-153) Differences in mortality and MACE in patients not referred to the hospital are beyond the scope of this study. In line with your suggestion, we consulted a statistician for a possible power analysis and see a very small power for differences in mortality and MACE. For example, since incidence of mortality is estimated to be approximately 1% in the patients not referred to the hospital, 700 patients not transported to the hospital would only have a power of less than 0.20 to detect a reduction of mortality of 50%. A smaller mortality reduction, or fewer subjects per group, would reduce the power even further. Thank you for your attempt to explain why a sample size calculation is not reported. However, I do not understand why differences in

	mortality and MACE are beyond the scope of your study. I do understand that your main interest is to reduce unnecessary ED visits. However, shouldn't the safety of this new approach be analyzed or at least discussed. I think the sample size should be very large to proof non-inferiority and I can understand that this would prevent soon publication of results. However, then the authors should describe that this study is a pilot or proof of concept study for feasibility and efficacy, but not address safety in the abstract or results section. Authors (2): As mentioned before, mortality and MACE rates can unfortunately not be compared with the control group as follow-up is not available for the control group. However, we agree with the reviewer that MACE and mortality rates are of importance. For this reason, we will report the mortality and MACE data in the intervention group. Lastly, we agree that safety of the current study is more a proof-of-concept for pre-hospital triage (safety is defined as <1% MACE rate). Accordingly, this is a secondary end-point rather than a primary study aim. Therefore we have withdrawn the safety endpoint from our abstract (line 19) and methods (line 128) and discussion (line 244). Thank you What is the dedicated website and e-mail address? Authors: The dedicated website is www.hartc.nl and e-mail address is info@hartc.nl. To prevent improper use, we prefer not to include this in the manuscript. However, if the reviewer and editor per se want us to include, we are willing to add this to the manuscript. Please describe why you are afraid of improper use. Wouldn't it be informative for readers to be able to take a look at the website? It is a well designed website Authors (2): We have added the website in our manuscript (line 166-167). Please describe the informed consent procedure in more detail. Is the informed consent registered by the paramedic? Is there written informed consent by the patient? And if not: Why not? Authors: Informed consent for cardiologist consultation and the HARTc study is given orally by the patient when the paramedic arrives and this is noted in the AmbuSuite database. As agreed upon by the Medical Ethics Committee, requesting written informed consent was not feasible in the urgent paramedic setting. Furthermore, it would potentially delay treatment or transfer to an ED. When contacting patients by phone who were not transported to the hospital, oral informed consent is requested before contacting their GP's (page 22, line 168-170). I suggest you remove the word urgent. One of the main aims of the study is to prevent unnecessary transfers. That is no urgent setting. Furthermore, also STEMI trials and even CPR trials collect (sometimes retrospective) written informed consent. Requesting and collecting informed consent is feasible, however, the need for it can be waived by investigators and medical ethics committees. The authors should explain why this was done so, for example, because usual care is not expected to change significantly (only change of hospital) or risk of study is considered very low or the study is within the scope of usual care, etc. Authors (2): We agree and have adjusted the wording on line 171-174. After extensive discussion with the Medical Ethics Committee

	the need for written informed consent was waived. Reasons for the waiving of written informed consent were the large group of patients, the fact that patients were transferred to three different hospitals and the setting of enrollment. Thank you for removing the word urgent. I will rest my case here and have no further questions about the informed consent procedure. However I still have to say that the group size, the fact that several hospitals are involved and the setting of enrolment are absolutely no legitimate reasons for waiving a written informed consent . Check some large anticoagulation trials for instance :) Discussion What do the authors mean with improved utilization of healthcare resources? Authors: Live insight in the available free ED and hospital capacity in the region enables us to utilize all available healthcare resources. Patient selection in the pre-hospital setting will contribute to better patient-tailored health care as patients are transported to the hospital best suited for solving their problem. Also, transporting patients while aware of ED and nursing ward capacity will lead to improved utilization of existing healthcare resources as overcrowded hospitals are passed and unused beds are used to full capacity. We have expanded our explanation on this part. (page 22-23, line 176-178) Thank you for elaborating on this, I think the underlying thought is now more clear. Please update the literature in the discussion and contemplate less about the first phase of Famous Triage 1 and more about Famous Triage 2 and 3. As far as I can find on pubmed there are at least 6 publications about those phases. Authors: We most extensively discuss the Famous Triage 1 as, in our opinion, this is the most relevant trial for the current rationale and design manuscript. As suggested, we also included the findings from further studies from the Famous Triage study group as well as from the HE-MACS study. The HE-MACS showed ACS could be 'ruled out' in 9.4% of all chest pain patients before arrival at the hospital (page 23, line 185-189). The Famous Triage study showed nicely that pre-hospital risk stratification by ambulance paramedics using the HEART score was accurate in differentiating in low and intermediate to high risk. (page 23-24, line 201-207) Thank you for further discussing the mentioned trials. Since point of care troponin is now available there is no need for a modified HEART score anymore. Furthermore, since POC was not available in the time of Famous Triage 1, this design and results paper is a little outdated. The authors could consider less extensive discussion on this phase. The concept of the Famous study is quite clear if you just mention the goals and the main findings. The most relevant study for this manuscript would be Famous Triage phase 3, since in this study also patients are 'left home'. I suggest you adjust sentence 220 since also Famous and Artica studies leave patients at home after risk assessment and, when needed, hospital/cardiologist consultation. Authors (2): Thank you for providing these suggestions. As requested, we have adjusted line 226-227 as Famous and Artica indeed also have these as outcomes in their studies. Furthermore, we have focused more on FAMOUS 3 (line 208-212).

	Thank you, your discussion is now more up-to-date. Furthermore, also other hospitals use live monitored patient data via AZN Connect, Corpuls, etc. The authors claim that the Hart-C study is unique since it combines pre-hospital and hospital data and direct consultation with a cardiologist. However, I believe this is already done so in several hospitals in the Netherlands. Please inventarize and please describe other options for AmbuSuite, there are several possibilities for data sharing. For example, AZNConnect. Authors: Indeed, AZNConnect is a platform used for data sharing by the ambulance service and several hospitals in predominantly the northern part of the Netherlands. However, with this platform it is not possible to see live vital parameters as our triage platform does. Our triage platform receives information from AmbuSuite, which the EMS service works with, but is editable by ourselves. Furthermore, to the best of our knowledge no triage protocol or triagist is combined with AZNConnect. We agree that there are other pre-hospital protocols for some (cardiac) patients and, for clarification, we have included a study in pre-hospital logistics for these patients (page 23, line 179-183) I am sorry, but I disagree with the statement that there is no possibility for live vital parameters. I suggest the authors take a look at https://www.aznconnect.nl/ and https://www.corpuls.nl/corpuls-web-live/ to see that that this is in fact possible. Authors (2): We have checked the provided websites, and agree that there are other possibilities for data-sharing and insights in pre-hospital parameters. This new market is only expected to grow in the coming years as these are very important new developments. With tempus pro monitor no patient specific data are stored on the platform, however, wouldn't it be useful to store this information in the in-hospital patient dossier being accesible for all treating doctors? Please discuss. Authors: We agree that this would be incredibly useful, however Dutch (AVG) and European privacy law prohibits us from doing this. Since the in-hospital dossier and the platform are very well secured and patient information is already shared by paramedics with the consulting cardiologist this is not prohibited by Dutch and European law. Moreover, since you have oral informed consent this should not be a problem. Also, data is already stored on the ambusuite database, is this also actually prohibited? Authors (2): Only relevant information for the clinical decision making is available for the consulting cardiologist. Patient's information which is not useful for cardiac triage will not be available for the consulted cardiologist and these data will not be stored on the digital platform. Informed consent for the triage procedure does not grant us access to all the patient's medical history. Maybe you can suggest it would be helpful if pre-hospital information like ECG will be integrated in the hospital EPD in the future. Please describe the risk of bias by making use of a historic cohort in which paramedics act more autonomously compared to the

	intervention cohort in which the paramedics are much more likely to discuss every patient case with the triage cardiologist. Authors: We agree that there is risk of bias as this is not a randomized controlled trial, however when analysing the two groups we will assess all cardiac patients who are evaluated by the EMS. So, if the paramedic decides not to call the cardiologist, these patients are still included in the study. We have updated the strengths and limitations section in our article summary. Thank you for clarifying. Figure 1: do ambulance services physically drive to the ED? or do they have to call to inventarize whether there is admission capacity or not. Authors: This figure shows the option when the ED of 1 one of 3 regional hospitals has capacity and is visited by an ambulance. However, after ED consultation admission is deemed necessary on a cardiac nursing ward. The cardiac nursing ward does not have admission capacity and patient is transferred from the ED to another hospital by another ambulance. When taking nursing ward capacity into account we except less inter-hospital transfers. Ok, thank you for clarifying.

VERSION 3 – AUTHOR RESPONSE

Reviewer 3 comment: I have one ‘major’ suggestion for your study/paper: perhaps you should switch the term triage protocol to triage approach or triage method. Since the working method presented in your manuscript is more the testing of a new pre-hospital triage method/approach and not really a study on following and testing of a new protocol.
Author's response: We have changed the wording in our manuscript from 'triage protocol' to triage method.

Reviewer 3 comment: This suggests that the feasibility of implementation of this protocol is tested. This comprehends more than only the technical aspects. If you replace the term protocol to method or approach (like you already do in your clarification above) you partly avoid this ‘discussion’.
Author's response: We agree and have changed the wording accordingly.

Reviewer 3 comment: Maybe you can suggest it would be helpful if pre-hospital information like ECG will be integrated in the hospital EPD in the future.
Author's response: We have included a statement suggesting future integration of pre-hospital data in in-hospital electronic patient dossiers on line 235-236.