PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	DOES A "DIRECT" TRANSFER PROTOCOL REDUCE TIME TO CORONARY ANGIOGRAPHY FOR PATIENTS WITH NON ST-ELEVATION ACUTE CORONARY SYNDROMES?: A PROSPECTIVE OBSERVATIONAL STUDY.
AUTHORS	Gallagher, Sean; Lovell, Matthew; Jones, Dan; Ferguson, Eileen; Akhtar, Abid; Buckhoree, Zia; Wragg, Andrew; Knight, Charles; Mathur, Anthony; Smith, Elliot; Cliffe, Samantha; Archbold, Andrew; Rothman, Martin; Jain, Ajay

VERSION 1 - REVIEW

REVIEWER	David Fitchett St Michael's Hospital University of Toronto Canada
REVIEW RETURNED	24-Mar-2014

GENERAL COMMENTS	I wonder if the situation described in this report still exists today. With the expansion of cardiac services in the UK over the past 10 years it seems amazing that a patient can still wait 9 days for coronary angiography if the truly had an MI This manuscript describes the impact on health care delivery, of a strategy of direct admission to a cardiac centre from district hospital emergency departments compared to the usual strategy of admission to the DGH and subsequent transfer in patients with non-STE ACS. The study compared patients admitted as a result of the direct transfer strategy with patients transferred after DGH admission before the transfer strategy was initiated. The time to angiography (1 vs 7.2 days) and duration of hospital stay 3 vs 9 days) were substantially shortened by the direct admission to the cardiac centre strategy. Comments The criteria for immediate transfer to the cardiac centre were those of compatible symptoms plus either elevated troponin or ECG abnormalities consistent with ACS. These are standard criteria in most parts of the world for coronary angiography referral in NSTE ACS. It is unclear whether there were such criteria for DGH transfer in the Pre-HAC-X. It is possible that different criteria for transfer in the Pre-HAC-X era might explain differences in characteristics. In addition, it would be preferable if the assessment also determined risk using a validated risk table such as GRACE or TIMI. Higher risk patients could be triaged to immediate angiography, whereas lower

	risk patients who probably do not benefit from angiography / revascularization could either be managed medically or undergo later angiography. It is possible that some patients admitted through the DGH were triaged by risk. Consequently it would be valuable to know the TIMI or GRACE risk for the two cohorts of patients. The time to coronary angiography and duration of stay in the Pre-HAC-X group are extraordinarily long for today. It would be useful to know if the current times for such patients are as long. Coronary angiography and revascularization have become more available in many parts of the world, such that times to coronary angiography of 1 day and durations of admission of 2 days in NSTE ACS are not uncommon in many parts of North America and Europe for DGH transfers. It is important that the manuscript discusses the alternative to direct transfer, which is an efficient facilitated access. Clearly the availability of angiographic resources was not a limiting factor during the direct transfer phase, and should not limit access if a more efficient transfer system was devised. Clearly the direct transfer strategy saved and freed resources for other patients. Do the authors believe the direct transfer strategy also reduced ischemic outcomes? The TIMACS study only showed benefit for early angiography in the first 24 hrs vs delayed angiography for high-risk patients. However delayed angiography in that study was only at a median of 50 hours. Do the investigators have any estimates of the recurrent ischemia event rates over the 9 days waiting? The paper indicates 20% of patients did not undergo coronary angiography in the Post-HAC-X group. These patients presumably would not have been seen at the cardiac centre in the Pre HAC-X era. These patients unecessarilty increase the workload burden and cost on the cardiac centre as “unnecessary” transfers. Furthermore most will have diagnoses best managed in the DGH. This discussion should be included in the section on limitations. Do the investigators have any strategies to reduce this burden? It would be useful to know the incidence of “normal” coronary angiograms in the two eras. Clinical trials in NSTE ACS indicate rates as high as 20%. In conclusion this is an interesting observational study that shows direct transfer of NSTE ACS patients shortens time to angiography and hospital stay. However it is unclear whether such a strategy improves outcomes. The alternative of a more efficient referral system resulting in rapid early transfer of more appropriate patients needs to be considered.

REVIEWER	Ten Berg, Jurrien st antonius hospital, nieuwegein, the Netherlands
REVIEW RETURNED	28-Mar-2014

GENERAL COMMENTS	**Introduction** This manuscript describes a prospective, observational study about rapid identification of NSTE-ACS patients at the emergency department (ED) of six district general hospitals (without facilities for coronary angiography (CAG) and/or revascularization) in North East London. A protocol, the so-called HAC-X pathway, was designed to

	identify patients with a suspicion of NSTE-ACS within four hours after presentation to the ED and to facilitate a direct transfer from the local ED to the regional interventional cardiac centre for undergoing an invasive management strategy. The manuscript attempts to demonstrate that the HAC-X pathway leads to a better adherence to international cardiology guidelines in terms of reducing the time from hospital admission to coronary angiography (CAG) and a reduced length of hospital stay for NSTE-ACS patients. **Merits** The manuscript concerns a topic that rightfully deserves the attention of the cardiology field. It is known that there is no uniform approach to risk stratification and subsequent management of NSTE-ACS patients. Especially referral for an invasive strategy is not being used optimally in NSTE-ACS, while it is associated with a reduced one-year mortality rate in these patients.[1-2] The article is written in a structural manner and the contents of all the headers are respected accordingly. The first paragraph of the 'Discussion section' highlights the overall conclusion of the study and forms a good starting point for the following discussion. A neat and very comprehensible article. **Critique** 1. In the 'Methods section'; paragraph 'Study protocol', the authors declare that in the post-HAC-X cohort, the diagnosis of NSTE-ACS and the indication for CAG had to be confirmed at the interventional clinic before catheterization took place. In the 'Results section'; paragraph 'Outcome of invasive investigation', we see that this working method led to an approval of the CAG indication in just 80,4% of the referred patients in this cohort, while all referred patients in the pre-HAC-X cohort underwent CAG. This means that in the post-HAC-X cohort, there was a discrepancy between the general and interventional hospital in nearly 20% of the referred patients, concerning the indication for CAG. The pre- and post-HAC-X cohorts do not seem to be equal in their assessment of CAG indication and therefore, it is hard to conclude that the HAC-X protocol (with its reduced time to CAG and length of hospital stay) is completely applicable in a general hospital, because the post-HAC-X patients still needed a second cardiology assessment at the interventional hospital prior to undergoing CAG. The true incremental value of the HAC-X protocol and its applicability at general hospitals should have been investigated, by making the indication for CAG already decisive at the general hospital level (without the confirmation step at the interventional clinic). Perhaps an extra sentence about the applicability of the HAC-X protocol at general hospitals could be added to the Discussion section. 2. <u>Endpoint length of hospital stay:</u> The interventional centre increased its admission capacity prior to introducing the HAC-X protocol, while in the pre-HAC-X cohort, NSTE-ACS patients needed to await their transfer to the interventional clinic that had a smaller admission capacity in their time frame of the study. The interim increase of admission capacity at the interventional hospital could be a serious confounder of the reduced length of hospital stay in the post-HAC-X cohort. Only the economical point of view of the increase in admission capacity at the interventional hospital

is mentioned in the article, but the possible confounding effect regarding the length of hospital stay has not been mentioned in the discussion.

3. In the 'Methods section'; paragraph 'Outcome measures', the chosen primary endpoints of the study are very clear, but are mainly related to an economical point of view. Are there also clinical endpoints (for example: Major Adverse Cardiac Events during a one year follow up)? Besides the economical benefit of the HAC-X protocol, a better clinical outcome in favour of the post-HAC-X cohort could have emphasized the importance of early catheterization.

4. In the 'Results section'; paragraph 'Clinical efficacy of HAC-X pathway', only the results of the post-HAC-X cohort are given. A direct comparison with the numbers of the pre-HAC-X cohort gives the reader a better understanding of the benefit of the HAC-X pathway. In the 'Discussion' it says that a direct comparison is not possible due to the differences between both study cohorts. However, a table comparing the diagnoses (and percentages) of the pre- and post-HAC-X cohorts, gives the reader an extra insight into the clinical efficacy of the HAC-X pathway, while the heterogeneity of both cohorts is also mentioned in the discussion.

Discussion

The study described in this manuscript was conducted to achieve cost-effective advantages in the management of NSTE-ACS patients. The most recent ESC guidelines concerning NSTE-ACS patients have not been updated since 2011, so the topic of this study is definitely welcome. If the authors would consider applying the suggestions for improvement above, the paper deserves to be published, be it just to create awareness in the field of cardiology regarding an early consideration of catheterization in patients diagnosed with NSTE-ACS.

References

1. Khalill R, Han L, Jing C, et al. The use of risk scores for stratification of non-st elevation acute coronary syndrome patients. Exp Clin Cardiol 2009;14(2):e25-e30.
2. Lee CH, Tan M, Yan AT, et al. Use of cardiac catheterization for non-ST-segment elevation acute coronary syndromes according to initial risk. Reasons why physicians choose not to refer their patients. Arch Intern Med 2008;168:291-6.
3. Hamm CW, Bassand J, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011; 2011;32(23):2999-3054.

Additional comments for authors – textual corrections

	• Page 2; Section: Abstract; paragraph: Objective; In the sentence starting with: 'The objective of this study was **t**o…', the letter 't' is in bold. Please correct this. • Page 5; Section: Introduction; In the middle paragraph the word NSTEACS lacks a score(-). Please correct to NSTE-ACS. • Page 14; Section: Discussion; paragraph: Limitations of study; Please also correct NSTEACS into NSTE-ACS on this page (5th line from the bottom) • Page 26; Figure 2; caption text; 'Beeswarm boxplot demonstrating the time 'the' ED admission to coronary angiography…' Please correct this sentence into: ''Beeswarm boxplot demonstrating the time 'from' ED admission to coronary angiography…'

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

This manuscript describes the impact on health care delivery, of a strategy of direct admission to a cardiac centre from district hospital emergency departments compared to the usual strategy of admission to the DGH and subsequent transfer in patients with non-STE ACS. The study compared patients admitted as a result of the direct transfer strategy with patients transferred after DGH admission before the transfer strategy was initiated. The time to angiography (1 vs 7.2 days) and duration of hospital stay 3 vs 9 days) were substantially shortened by the direct admission to the cardiac centre strategy.

Comments to the Author:

1. **The criteria for immediate transfer to the cardiac centre were those of compatible symptoms plus either elevated troponin or ECG abnormalities consistent with ACS. These are standard criteria in most parts of the world for coronary angiography referral in NSTE-ACS. It is unclear whether there were such criteria for DGH transfer in the Pre-HAC-X. It is possible that different criteria for transfer in the Pre-HAC-X era might explain differences in characteristics.**

Prior to the initiation of the HAC-X transfer protocol, there were no standard criteria for transfer to the cardiac centre for coronary angiography. Patients with suspected ACS were not transferred directly to the cardiac centre from the emergency department (except in cases of STEMI). Patients with suspected NSTE-ACS were admitted to the district hospital for review by a local cardiologist. If the diagnosis of NSTE-ACS was confirmed, and coronary angiography thought to be appropriate then the patients were referred for further treatment to the London Chest Hospital.

We agree with Reviewer 1 that it is possible that the standardized transfer criteria used HAC-X inclusion criteria may explain some of the differences in the clinical characteristics between the pre-HAC-X and post-HAC-X groups. Firstly, the transfer criteria used for the HAC-X pathway, excluded

patients with a major medical comorbidity that would delay coronary angiography. The exclusion criteria included unexplained anaemia and renal dysfunction. These conditions are more prevalent in elderly patients, thus many of these patients may have been ineligible for transfer by the HAC-X pathway. This may partially explain the age difference between the pre-HAC-X cohort and the post HAC-X cohort. Furthermore, the HAC-X inclusion criteria emphasized typical ischaemic symptoms. Older patients presenting 'atypically' may not have been diagnosed with NSTE-ACS whilst in the emergency department. The diagnosis may have become evident at a later time point after the development of typical ECG changes or when troponin assays became positive. If the diagnosis of NSTE-ACS was not evident in the emergency department transfer for coronary angiography by the HAC-X pathway was not possible.

These points are explained in the discussion as follows,

> *'There are important differences in the baseline demographics between the patient cohorts. Post-HAC-X patients were younger, more likely to be current smokers and more commonly had a history of hypercholesterolaemia, previous PCI and peripheral vascular disease. There are several potential explanations for these differences in cohort demographics. Firstly, the presence of coronary risk factors or a history of previous PCI in patients presenting to the emergency department with chest pain is likely to stimulate early cardiac investigations. Inclusion criteria for the HAC-X pathway were diagnosis of NSTE-ACS whilst in the Emergency Department. Older patients with a paucity of coronary risk factors and no previous cardiac history may have had a delayed NSTE-ACS diagnosis meaning they could not be transferred directly from the Emergency Department via the HAC-X pathway. Secondly, patients with major medical comorbidities that precluded early angiography were specifically excluded from the HAC-X pathway'.*

> **2. In addition, it would be preferable if the assessment also determined risk using a validated risk table such as GRACE or TIMI. Higher risk patients could be triaged to immediate angiography, whereas lower risk patients who probably do not benefit from angiography / revascularization could either be managed medically or undergo later angiography. It is possible that some patients admitted through the DGH were triaged by risk. Consequently it would be valuable to know the TIMI or GRACE risk for the two cohorts of patients.**

We agree with Reviewer 1 that the addition of a validated risk model would enhance our transfer pathway. It is highly likely that many patients in the pre-HAC-X era were triaged to coronary angiography by their local cardiologist, as they were 'high-risk'. High GRACE score has now been included in subsequent iterations of our HAC-X pathway to trigger transfer for coronary angiography. Unfortunately prior to the initiation of the HAC-X pathway we did not routinely collect GRACE score, and so are unable to present comparative GRACE score data for our two patient cohorts.

3. The time to coronary angiography and duration of stay in the Pre-HAC-X group are extraordinarily long for today. It would be useful to know if the current times for such patients are as long. Coronary angiography and revascularization have become more available in many parts of the world, such that times to coronary angiography of 1 day and durations of admission of 2 days in NSTE-ACS are not uncommon in many parts of North America and Europe for DGH transfers. It is important that the manuscript discusses the alternative to direct transfer, which is an efficient facilitated access. Clearly the availability of angiographic resources was not a limiting factor during the direct transfer phase, and should not limit access if a more efficient transfer system was devised.

We agree with the comments of Reviewer 1. In 2010, the British Cardiovascular Intervention Society (BCIS) National Audit reported that the median wait from admission to coronary angiography was 4.5 days for patients admitted to district hospitals without on-site cardiac catheterization facilities (http://www.bcis.org.uk/resources/BCIS_Audit_2009_data_version_08-10-2010_for_web.pdf). In our Pre-HAC-X group the admission time to coronary angiography was longer than the national average (7.2 days). This delay in treatment for patients with NSTE-ACS was unacceptable and stimulated the design of the HAC-X clinical pathway. As we have detailed in our manuscript, the initiation of the HAC-X pathway has lead to significant reductions in waiting times for coronary angiography in patients with NSTE-ACS, such that in the post-HAC-X group median wait for coronary angiography was only 1 day. Internal audit has confirmed that the HAC-X pathway continues to deliver these impressively short waiting times for coronary angiography in 2012. For comparison, in 2012 the national average wait for coronary angiography for patients with NSTE-ACS was 4.3 days for patients admitted to hospitals without on-site cardiac catheterization facilities and 2.6 days for patients admitted directly to centres with cardiac catheterization facilities (data from BCIS National audit 2012 (http://www.bcis.org.uk/resources/BCIS_Audit_2012_for_web_V2_14-10-20131.pdf).

We also agree with Reviewer 1 that there are alternatives to a direct transfer system to reduce waiting times for coronary angiography for patients with NSTEMI. Despite the availability of angiographic resources not being a limiting factor for our centre, access to inpatient beds frequently delayed transfer of patients for coronary angiography. Larger institutions in America or Europe with more inpatient beds may not face these bed capacity challenges and may be able to deliver rapid transfer and coronary angiography for all patients with NSTE-ACS. That we increased our bed capacity, by providing a dedicated 6-bed ward for patients admitted via the HAC-X pathway was central to our ability to deliver the pathway (please see response to Reviewer 2 Question 2). However, more efficient facilitated transfer systems, with more efficient bed usage, may have proved similarly effective in reducing time to coronary angiography. For example, Bellenger et al described the development of a regional transfer unit created to expatiate access of NSTE-ACS patients referred from district hospitals (Bellenger N, Wells T, Hitchcock R, Watkins M, Duffet C, Jewell D, Palliser D, Shapland L, Curtis R, Scrase S, Burns R, Curzen N. Reducing transfer times for coronary angiography in patients with acute coronary syndromes: one solution to a national problem. Postgrad Med J 2006; 82:411-413). The transfer unit received patients for same day angiography, and the patients were then discharged within 24 hours of their procedure; either home, or back to the referring district hospital. The establishment of this transfer unit led to a reduction in the mean waiting time from referral to angiography from 20 to 8 days. Another alternative to direct transfer is immediate retransfer of patients with NSTE-ACS to their referring hospitals post PCI. This has been shown to be safe and feasible at the Oslo University Hospital (Andersen J, Klow N, Johansen O. Safe and feasible immediate retransfer of patients to the referring hospital after acute coronary angiography and

percutaneous coronary angioplasty for patients with acute coronary syndrome. Eur Heart J Acute Cardiovasc Care 2013; 2:256-261). This system would allow for more efficient bed usage at the interventional cardiac centre. However, as mentioned in the manuscript, the HAC-X pathway has an additional cost benefit as it avoids local health care commissioners from having to fund 2 admission tariffs for the same NSTE-ACS admission. Prior to the initiation of the HAC-X the local health care commission was paying admission tariffs to both the DGH, and the regional cardiac centre. Both the regional transfer unit and immediate retransfer strategies described above would necessitate 2 admission tariffs for the admission.

We have expanded our discussion to include these points as follows,

> *'Alternative transfer strategies for patients with NSTE-ACS, such as regional transfer units, and same day 'repatriation' of patients to the referring hospital after PCI, have been described, and result in more efficient bed usage and reduced time to angiography in patients with NSTE-ACS. However, these management strategies require admission tariffs at both the referring DGH and also the cardiac centre'.*

> **4. Clearly the direct transfer strategy saved and freed resources for other patients. Do the authors believe the direct transfer strategy also reduced ischemic outcomes? The TIMACS study only showed benefit for early angiography in the first 24 hrs vs delayed angiography for high-risk patients. However delayed angiography in that study was only at a median of 50 hours. Do the investigators have any estimates of the recurrent ischemia event rates over the 9 days waiting?**

This was an observational study monitoring a novel change in practice designed to reduce waiting times for coronary angiography in patients with NSTE-ACS, rather than an outcome study of patients with NSTE-ACS. At study conception we hoped to show the feasibility of the HAC-X pathway, and we did not plan to collect clinical outcome data upon our patients. Unfortunately we have no estimates of the rates of recurrent ischaemia in the pre-HAC-X cohort whilst these patients were waiting for coronary angiography. We have clearly highlighted the lack of clinical outcome data as a limitation of this study (please see response to Reviewer 2 Question 3).

> **5. The paper indicates 20% of patients did not undergo coronary angiography in the Post-HAC-X group. These patients presumably would not have been seen at the cardiac centre in the Pre HAC-X era. These patients unecessarilty increase the workload burden and cost on the cardiac centre as "unnecessary" transfers. Furthermore most will have diagnoses best managed in the DGH. This discussion should be included in the section on limitations.**

Pre-HAC-X the diagnosis of NSTE-ACS was confirmed at the district hospital by a local cardiologist

prior to coronary angiography. As a result all patients in the pre-HAC-X cohort underwent angiography. The post-HAC-X cohort consisted of patients with cardiac symptoms and either an abnormal ECG or positive troponin. The diagnosis of NSTE-ACS was not confirmed by a cardiologist until after transfer to the cardiac centre. In the post HAC-X cohort 250 of 311 (80.4%) patients transferred underwent angiography. The remaining 61 patients did not undergo coronary angiography for a variety of reasons. Most commonly this was that another 'non-coronary' diagnosis became apparent after clinical review at the cardiac centre. This included patients with non-coronary' but cardiac diagnoses who were often best managed in the cardiac centre, with access to advanced cardiac imaging modalities to aid diagnosis, but also patients with non-cardiac diagnoses. Usually these patients could be treated and discharged rapidly from the cardiac centre, and consequently were not a large burden upon resources. Patients with a 'non-cardiac diagnosis who could not be managed at the cardiac centre may have be 'repatriated' to the district hospital if it was thought to be best for their further care.

We have amended our discussion to include this point,

> *'In patients in whom myocardial infarction was suspected at presentation, the rapid access to coronary angiography and early demonstration of unobstructed coronary arteries allowed other cardiac diagnoses to be considered. In patients with a 'non-coronary' cardiac diagnosis, such as myocarditis, the early access to advanced non-invasive cardiac imaging at the cardiac centre undoubtedly streamlined their hospital admission, allowing earlier diagnosis and treatment. The small proportion of patients transferred with a non-cardiac diagnosis could be treated then discharged rapidly and safely from the cardiac centre, meaning that they were little burden upon our resources. Although we strived to manage the vast majority of post HAC-X patients exclusively at the cardiac centre, a small proportion of patients with a non-cardiac diagnosis were 'repatriated' to their district hospital for specialized further management of their condition.*
>
> *'*

6. It would be useful to know the incidence of "normal" coronary angiograms in the two eras. Clinical trials in NSTE ACS indicate rates as high as 20%.

Unfortunately we are unable to provide this data. The incidence of normal coronary arteries was not a pre-specified end-point of this study and so the data was not collected prospectively. We have recorded the number of patients who after angiography were managed medically. This group obviously includes those patients with normal coronary arteries, those with minor non-obstructive coronary artery disease and those with diffuse extensive coronary artery disease that is not amenable to revascularization. A recent change in our angiographic archiving system means that retrospective review of the angiographic images for these patients is not possible. As individual angiographers report 'normality' differently, often reporting 'unobstructed coronary arteries' to mean either truly normal coronary arteries or minor coronary artery disease it is impossible to differentiate the incidence of normal coronary angiograms merely from the retrospective review of the angiographic reports.

In conclusion this is an interesting observational study that shows direct transfer of NSTE ACS patients shortens time to angiography and hospital stay. However it is unclear whether such a strategy improves outcomes. The alternative of a more efficient referral system resulting in rapid early transfer of more appropriate patients needs to be considered.

Reviewer: 2

This manuscript describes a prospective, observational study about rapid identification of NSTE-ACS patients at the emergency department (ED) of six district general hospitals (without facilities for coronary angiography (CAG) and/or revascularization) in North East London. A protocol, the so-called HAC-X pathway, was designed to identify patients with a suspicion of NSTE-ACS within four hours after presentation to the ED and to facilitate a direct transfer from the local ED to the regional interventional cardiac centre for undergoing an invasive management strategy. The manuscript attempts to demonstrate that the HAC-X pathway leads to a better adherence to international cardiology guidelines in terms of reducing the time from hospital admission to coronary angiography (CAG) and a reduced length of hospital stay for NSTE-ACS patients.

Merits

The manuscript concerns a topic that rightfully deserves the attention of the cardiology field. It is known that there is no uniform approach to risk stratification and subsequent management of NSTE-ACS patients. Especially referral for an invasive strategy is not being used optimally in NSTE-ACS, while it is associated with a reduced one-year mortality rate in these patients. The article is written in a structural manner and the contents of all the headers are respected accordingly. The first paragraph of the 'Discussion section' highlights the overall conclusion of the study and forms a good starting point for the following discussion. A neat and very comprehensible article.

Critique

1. **In the 'Methods section'; paragraph 'Study protocol', the authors declare that in the post-HAC-X cohort, the diagnosis of NSTE-ACS and the indication for CAG had to be confirmed at the interventional clinic before catheterization took place. In the 'Results section'; paragraph 'Outcome of invasive investigation', we see that this working method led to an approval of the CAG indication in just 80,4% of the referred patients in this cohort, while all referred patients in the pre-HAC-X cohort underwent CAG. This means that in the post-HAC-X cohort, there was a discrepancy between the general and interventional hospital in nearly 20% of the referred patients, concerning the indication for CAG. The pre- and post-HAC-X cohorts do not seem to be equal in their assessment of CAG indication and therefore, it is hard to conclude that the HAC-X protocol (with its reduced time to CAG and length of hospital stay) is completely applicable in a general hospital, because the post-HAC-X patients still needed a second cardiology assessment at the interventional hospital prior to undergoing CAG. The true incremental value of the HAC-X protocol and its applicability at general hospitals should have been investigated, by making the indication for CAG already decisive at the general hospital level (without the confirmation step at the interventional clinic). Perhaps an extra sentence about the applicability of the HAC-X protocol at general hospitals could be added to the**

Discussion section.

Patients with suspected NSTE-ACS (diagnosed in the district hospital emergency department on the basis of symptoms, and/ or ECG changes or positive troponin) were transferred to the regional cardiac centre via the HAC-X protocol. These patients were not seen by a cardiologist until they arrived at the cardiac centre. Subsequently, not all of the patients transferred were confirmed as having a NSTE-ACS and as a result they did not undergo coronary angiography.

Pre-HAC-X all patients were seen by a cardiologist and the diagnosis of NSTE-ACS was confirmed prior to transfer. All of these patients underwent coronary angiography.

It is not that the post-HAC-X patients needed a second cardiology review, rather they received their first cardiology review after arrival at the cardiac centre instead of at the district hospital. It seems likely that before the initiation of the HAC-X a number of patients would have been admitted to the district hospital with an initial diagnosis of suspected NSTE-ACS, only for another diagnosis to be suggested after local cardiology review. These patients were not referred for coronary angiography and are not represented in this study. This is an important limitation in our analysis that has been highlighted by Reviewer 2 and we have amended the discussion section of our manuscript to emphasize this point as follows,

> *'Inclusion to the study occurred once patients were transferred to the cardiac centre (for coronary angiography in pre-HAC-X patients, and with suspected NSTE-ACS for assessment and/or coronary angiography in post-HAC-X patients) rather than at the district hospital. As a result, a proportion of patients in the post-HAC-X group, after review at the cardiac centre were thought to have a non-coronary diagnosis, and did not undergo coronary angiography. Undoubtedly, before the initiation of the HAC-X pathway a number of patients were admitted to the district hospital with suspected NSTE-ACS, but this diagnosis was discounted after local cardiology review. These patients initially suspected to have NSTE-ACS, but later proven to have a non-coronary diagnosis, whilst still in their district hospital, were not included in the pre-HAC-X cohort.'*

> **2. Endpoint length of hospital stay: The interventional centre increased its admission capacity prior to introducing the HAC-X protocol, while in the pre-HAC-X cohort, NSTE-ACS patients needed to await their transfer to the interventional clinic that had a smaller admission capacity in their time frame of the study. The interim increase of admission capacity at the interventional hospital could be a serious confounder of the reduced length of hospital stay in the post-HAC-X cohort. Only the economical point of view of the increase in admission capacity at the interventional hospital is mentioned in the article, but the possible confounding effect regarding the length of hospital stay has not been mentioned in the discussion.**

We agree with this concern raised by Reviewer 2 and have acknowledged this as a limitation of our

study as follows,

> *'Thirdly, the cardiac centre increased bed capacity, providing a dedicated 6 bed ward for patients admitted via the HAC-X pathway. The small increase in the total bed capacity of the hospital coupled with more efficient utilization of inpatient beds allowed the HAC-X pathway to function. Potentially, these changes may confound our results, as they may influence both time to coronary angiography and length of hospital stay'.*

3. In the 'Methods section'; paragraph 'Outcome measures', the chosen primary endpoints of the study are very clear, but are mainly related to an economical point of view. Are there also clinical endpoints (for example: Major Adverse Cardiac Events during a one year follow up)? Besides the economical benefit of the HAC-X protocol, a better clinical outcome in favour of the post-HAC-X cohort could have emphasized the importance of early catheterization.

This study was an observational study monitoring a novel change in practice designed to reduce waiting times for coronary angiography in patients with NSTE-ACS, rather than an outcome study of patients with NSTE-ACS. At study conception we hoped to show the feasibility of the HAC-X pathway, and we did not plan to collect clinical outcome data upon our patients. We agree that analysis of clinical outcomes would yield important and interesting data, and although, all patients undergoing coronary revascularisation (either PCI or surgical) in our unit have prospective clinical, surgical and 30-day complication data recorded, we do not routinely record data upon patients who do not receive coronary revascularization. Of 702 patients in our study cohort, 346 (49.3%) did not undergo coronary revascularization. We have chosen not to present clinical outcome data upon the 50.7% of patients who were revascularised as we feel that these were select patients, and thus their outcome data would not be reflective of the cohort as a whole.

We have added this point as a limitation in our discussion section as follows,

> *'this was an observational study designed to evaluate the feasibility of a novel change in practice to reduce waiting times for coronary angiography in patients with NSTE-ACS. We did not collect clinical outcome data upon the entire cohort and so can only speculate as to whether the initiation of this pathway provided clinical benefit to the patients presenting with NSTE-ACS.'*

4. In the 'Results section'; paragraph 'Clinical efficacy of HAC-X pathway', only the results of the post-HAC-X cohort are given. A direct comparison with the numbers of the pre-HAC-X cohort gives the reader a better understanding of the benefit of the

HAC-X pathway. In the 'Discussion' it says that a direct comparison is not possible due to the differences between both study cohorts. However, a table comparing the diagnoses (and percentages) of the pre- and post-HAC-X cohorts, gives the reader an extra insight into the clinical efficacy of the HAC-X pathway, while the heterogeneity of both cohorts is also mentioned in the discussion.

Not all patients transferred to the cardiac centre were eventually diagnosed with NSTE-ACS. The purpose of the 'Clinical efficacy of HAC-X pathway' sub-section was to detail the accuracy of the inclusion criteria of the HAC-X pathway for diagnosing NSTE-ACS. Pre-HAC-X patients were confirmed as having had a NSTE-ACS prior to transfer and so a similar analysis for these patients would be inappropriate. The differences in inclusion in to the study groups has been explained in more detail in our response to Reviewer 2 Question 1 and our manuscript text changed accordingly.

Additional comments for authors,

1. Page 2; Section: Abstract; paragraph: Objective; In the sentence starting with: 'The objective of this study was to…', the letter 't' is in bold. Please correct this.

This typographical error has been corrected.

2. Page 5; Section: Introduction; In the middle paragraph the word NSTEACS lacks a score(-). Please correct to NSTE-ACS.

This typographical error has been corrected.

3. Page 14; Section: Discussion; paragraph: Limitations of study; Please also correct NSTEACS into NSTE-ACS on this page (5th line from the bottom)

This typographical error has been corrected.

4. Page 26; Figure 2; caption text; 'Beeswarmboxplot demonstrating the time 'the' ED admission to coronary angiography. Please correct this sentence into: ''Beeswarm boxplot demonstrating the time 'from' ED admission to coronary angiography'

This typographical error has been corrected.

VERSION 2 – REVIEW

REVIEWER	Ten Berg, Jurrien st antonius Hospital Nieuwegein the netherlands
REVIEW RETURNED	23-May-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	David Fitchett St Michaerl's Hospital University of Toronto Canada
REVIEW RETURNED	02-Jun-2014

GENERAL COMMENTS	The authors have satisfactorily answered my comments and I have nothing further to add