PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between in-hospital guideline adherence and post-discharge major adverse outcomes of patients with acute coronary syndrome in Vietnam: A prospective cohort study
AUTHORS	Nguyen, Thang; Le, Khanh; Cao, Hoang; Tran, Dao; Ho, Linh; Thai, Trang; Pham, Hoa; Pham, Phong; Nguyen, Thao; Hak, Eelko; Pham, Tam; Taxis, Katja

VERSION 1 - REVIEW

REVIEWER	J. Tra Knowledge Institute of the Federation of Medical Specialists, the Netherlands
REVIEW RETURNED	22-Apr-2017

GENERAL COMMENTS	My compliments for the thoroughly performed research and the clearly written paper. In your research, you looked at the association between receiving medication according to the guidelines and six-month major cardiovascular outcomes and all-cause mortality in two hospitals in Vietnam. Both the research and message of the paper are very relevant: improved guideline adherence is associated with better patient outcomes in patients with ACS. However, there are several possibilities for improving this paper. These are divided between major and minor points. Major points 1. The selection process of the hospitals is not described. It is highly likely that it was a convenience sample, but this should be described in the paper. Please also describe why two hospitals were chosen. Are these all the hospitals in the city? If not, why only these two? Etc. 2. Is verbal consent sufficient for this type of research in Vietnam? On the one hand, the majority of data is collected routinely for which written consent is not always necessary; on the other, patients did receive additional questionnaires and interviews for which written consent is generally required. 3. For the part of missing data, you describe that the impact of attrition bias due to dropouts was analyses using multiple imputation. However, it is not described how missing data from the data at baseline was handled. In your methods section, you

	describe that data at baseline were collected from the patient records. Data from patient records usually has a relatively high percentage of missing data. Please describe how these missing data were handled. In addition, the percentages of missing data should be reported, also for the data at baseline. 4. A vital issue in interpreting the results of your cohort study is the comparability of the guideline adherence group and the non-adherence group on other determinants than medication according to the guidelines. For the majority of factors, you indicate there are no differences (Table 1). One item for which there were differences was treatment with PCI. However, patients in your study were recruited from two different hospitals, of which only one hospital had PCI facilities. It is therefore necessary to look at whether there are differences in guideline adherence and outcomes between the two hospitals. In case there are differences between the hospitals in the (quality of) care other than prescribing the guideline recommended medication, this might influence the results of your study. It is therefore essential to provide information about potential differences. 5. On page 10, line 47/48 it is described that patient who received at least 1 medication had a lower risk of major cardiovascular outcomes in comparison to patients who received no medication according to the guidelines. However, in Table 2 it is reported that only 2 patients did not receive at least 1 medication. Both of these patients were in the group of patients with a major cardiovascular event. This leads to highly unreliable results. This should be avoided, e.g. by defining the groups differently, for example by creating a group with at least 2 medications vs 1 or no medication. 6. There is little attention in both the results and the discussion for the fact that guideline adherence is low (only 31.7% of the patients received all 4 medications according to the guidelines). 7. As it is an exploratory study, many variables are tested for their correlation with the outcomes. However, no interaction terms are tested. Other studies showed that an interaction of e.g. age and sex was correlated with prescribing medication according to the guidelines (https://www.ncbi.nlm.nih.gov/pubmed/25884093). Similar possibilities exist for type of ACS (STEMI/NSTEMI/UA) and treatment (PCI/CABG/medication). Please consider whether testing potentially relevant interactions can contribute to the statistical model. Minor points: 1. In the abstract, the fact that ‘guideline adherence’ only concerns medication in this study is not specified in the Objective. Please also specify the statistical

	methods (at least the Cox regression model). 2. All-cause death is not a major cardiovascular outcome, therefore describe the outcomes as 'hospital readmission due to cardiovascular causes and all-cause mortality during six months after discharge'. 3. On page 8, line 34 the term 'coronary artery disease (CAD) is written in full, however, it is previously described on page 6, line 50 and should be written in full with its abbreviation on first use. 4. On page 10, line 29 it is mentioned that 'The adherence group ad more favourable outcomes compared to the non-adherence group… although these differences were not statistically significant.' Since it is not significant, you can't conclude that one group had more favourable outcomes. 5. Although the general level of English is adequate, there are several possibilities to improve it. For example: - Page 3, line 14: 'reduction' is not the correct word; it implies that results improved over time. - page 11, line 54: 'showed the same benefits' = 'similar benefits' - page 12, line 27: 'his or her spouse or next of kin' = 'informal care provider' - page 13, line 34: 'may have an impact on prescribing guidelines' guidelines are not prescribed; the medication is prescribed according to the guidelines. - page 14, line 23: 'affirm' = 'confirm' 6. The lay-out for the references is inconsistent and for some references incomplete. For example, reference 1 does not include an author, although the factsheet is issued by the WHO. In reference 9, the title is bold (even if this is due to a different type of reference, it looks strange). In reference 22, the title starts with two capital letters. In reference 53, the title is in all capitals and the journal is not abbreviated (JACC). Please check all references carefully. 7. Figure 2 is a dramatization of the results; please use the full range of the y-axis (0-1, not 0.6-1)

REVIEWER	Hou Tee LU Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, 8 Jalan Masjid Abu Bakar, 80100 Johor Bahru, Johor, Malaysia
REVIEW RETURNED	14-Jun-2017

GENERAL COMMENTS	In Table 3, "Factors associated with six-month major cardiovascular outcome" were calculated using multivariable backward stepwise Cox regression, the variables entered were age, gender, number of CAD risk factors, prior MI/stroke, prior heart failure, Killip class II-IV, renal insufficiency, SBP <100 mmHg, LVEF < 40%, physician

	adherence to guidelines, discharge diagnosis, PCI and health insurance. Comment: ST elevation myocardial infarction (STEACS) is known to have poorer outcome compare to NSTE-ACS. “Type of ACS” (discharge diagnosis) could be a significant covariate affecting the outcomes of ACS. Can author explain the reason why the 'discharge diagnosis' (STEACS, NSTEACS) was not included as one of the covariates in the calculation of multivariable Cox regression analysis?

VERSION 1 – AUTHOR RESPONSE

2.1. Reviewer 1
Reviewer Name: J. Tra
Institution and Country: Knowledge Institute of the Federation of Medical Specialists, the Netherlands
Competing Interests: None declared
General reviewer's comment:
My compliments for the thoroughly performed research and the clearly written paper. In your research, you looked at the association between receiving medication according to the guidelines and six-month major cardiovascular outcomes and all-cause mortality in two hospitals in Vietnam. Both the research and message of the paper are very relevant: improved guideline adherence is associated with better patient outcomes in patients with ACS. However, there are several possibilities for improving this paper. These are divided between major and minor points and can be found in the attached file.
Authors' response:
We thank the reviewer for the compliments. We believe that your thoughtful comments and constructive suggestions help to improve this paper.

2.1.1. Major points
Reviewer's comment 1:
1. The selection process of the hospitals is not described. It is highly likely that it was a convenience sample, but this should be described in the paper. Please also describe why two hospitals were chosen. Are these all the hospitals in the city? If not, why only these two? Etc.
Authors' response 1:
The two hospitals were the largest two hospitals providing care for ACS patients in Can Tho City.

We have chosen the hospitals because they provide the highest level of care. Furthermore, because these were the two largest hospitals to maximize patient numbers in the study. It was outside the scope of our study to collect data in more hospitals. We have amended the methods section to include the information on the selection process and we addressed the limitations of collecting data in only two hospitals in the discussion section.

Reviewer's comment 2:
2. Is verbal consent sufficient for this type of research in Vietnam? On the one hand, the majority of data is collected routinely for which written consent is not always necessary; on the other, patients did receive additional questionnaires and interviews for which written consent is generally required.
Authors' response 2:
We have addressed this comment above.

Reviewer's comment 3:
3. For the part of missing data, you describe that the impact of attrition bias due to dropouts was

analyses using multiple imputation. However, it is not described how missing data from the data at baseline was handled. In your methods section, you describe that data at baseline were collected from the patient records. Data from patient records usually has a relatively high percentage of missing data. Please describe how these missing data were handled. In addition, the percentages of missing data should be reported, also for the data at baseline.
Authors' response 3:
We collected data from medical records in the hospitals prospectively. Therefore researchers asked physicians for missing data. We have amended the methods section to include this information (page 07, lines 27-30). One medical record was not available and we excluded that patient. We have also clarified this point in the paper (page 10, line 10).
Finally, we have amended the discussion section to address this limitation of our study as follows (page 13, lines 27-34): "Sixth, we excluded a substantial proportion of patients at baseline because of pre-defined exclusion criteria. The quality of treatment for these patients, especially for patients who were severely ill or who were transferred to another hospital, could be addressed in future studies."

Reviewer's comment 4:
4. A vital issue in interpreting the results of your cohort study is the comparability of the guideline adherence group and the non-adherence group on other determinants than medication according to the guidelines. For the majority of factors, you indicate there are no differences (Table 1). One item for which there were differences was treatment with PCI. However, patients in your study were recruited from two different hospitals, of which only one hospital had PCI facilities. It is therefore necessary to look at whether there are differences in guideline adherence and outcomes between the two hospitals. In case there are differences between the hospitals in the (quality of) care other than prescribing the guideline recommended medication, this might influence the results of your study. It is therefore essential to provide information about potential differences.
Authors' response 4:
We agree with the reviewer that differences between hospitals may have an effect on outcomes. However, we did not design our study to test the difference in adherence to guidelines, quality of care or outcomes between the two hospitals. This needs a larger study including more hospitals. We have amended the discussion section to address this point as follows (page 12, lines 54-57; and page 13, lines 3-8): "Differences between hospitals and physicians in the quality of care other than prescribing according to guidelines might also influence our findings. Further studies in a larger number of hospitals should consider the effect of covariates related to hospital and physician characteristics on the association between guideline adherence and patients' major adverse outcomes."
To give the reader more insight into the setting we have included more details on the hospitals in the methods section as follows (page 05; lines 55-58; and page 06, lines 03-06):

"We selected the two largest public hospitals (central and provincial level) in the center of Can Tho City, Vietnam with facilities to treat ACS. Within the region, these two hospitals provide the highest level of care to ACS patients."

Reviewer's comment 5:
5. On page 10, line 47/48 it is described that patient who received at least 1 medication had a lower risk of major cardiovascular outcomes in comparison to patients who received no medication according to the guidelines. However, in Table 2 it is reported that only 2 patients did not receive at least 1 medication. Both of these patients were in the group of patients with a major cardiovascular event. This leads to highly unreliable results. This should be avoided, e.g. by defining the groups differently, for example by creating a group with at least 2 medications vs 1 or no medication.
Authors' response 5:
We agree that these results are unreliable and therefore have deleted the information on patients who received at least 1 medication in the results section, discussion section, Table 2, and Online Appendix A.

Reviewer's comment 6:
6. There is little attention in both the results and the discussion for the fact that guideline adherence is low (only 31.7% of the patients received all 4 medications according to the guidelines).
Authors' response 6:
We have included more information on the fact of low guideline adherence in the results and discussion sections.
RESULTS (page 11, lines 20-23): "31.7% of patients received all 4 medications according to the guidelines (Table 2)."
DISCUSSION (page 14, lines 16-24): "However, less than one-third of eligible patients received all 4 medications according to the guidelines in our study which was lower than in other studies. 46 54 55 Further studies should investigate associated factors and benefits of receiving all 4 medications or beta-blockers in our patient group in Vietnam."

Reviewer's comment 7:
7. As it is an exploratory study, many variables are tested for their correlation with the outcomes. However, no interaction terms are tested. Other studies showed that an interaction of e.g. age and sex was correlated with prescribing medication according to the guidelines (https://www.ncbi.nlm.nih.gov/pubmed/25884093). Similar possibilities exist for type of ACS (STEMI/NSTEMI/UA) and treatment (PCI/CABG/medication). Please consider whether testing potentially relevant interactions can contribute to the statistical model.
Authors' response 7:
We agree with the reviewer that interaction terms could correlate with the outcomes. We did include some interaction terms and have included the information on the interaction terms in the methods section and table 3.
METHODS (page 09, lines 25-32): "Multivariable backward stepwise Cox regression models were used to estimate the association. The first model was adjusted for the covariates and the second model was adjusted for significant associated factors of the first model and interaction terms between these factors and guideline adherence."
Table 3 (page 24, lines 13-19): "a Using multivariable backward stepwise Cox regression models. First model: variables entered at the first step: age, gender, number of CAD risk factors, prior MI/stroke, prior heart failure, Killip class II-IV, renal insufficiency, SBP <100 mmHg, LVEF < 40%, in-hospital guideline adherence, discharge diagnosis, PCI and health insurance. Second model: variables entered at the first step: in-hospital guideline adherence; percutaneous coronary intervention; prior heart failure; renal insufficiency; and interaction terms: in-hospital guideline adherence and percutaneous coronary intervention, in-hospital guideline adherence and prior heart failure, in-hospital guideline adherence and renal insufficiency."

2.1.2. Minor points
Reviewer's comment 1:
1. In the abstract, the fact that ‘guideline adherence’ only concerns medication in this study is not specified in the Objective. Please also specify the statistical methods (at least the Cox regression model).
Authors' response 1:
We have amended the abstract as follows:
ABSTRACT (page 02, lines 07-10): "physician adherence" --> "physician adherence to prescribing guideline-recommended medications during hospitalization".
ABSTRACT (page 02, lines 49-54): Add more "Cox regression models were used to estimate the association between guideline adherence and six-month major adverse outcomes."

Reviewer's comment 2:
2. All-cause death is not a major cardiovascular outcome, therefore describe the outcomes as ‘hospital readmission due to cardiovascular causes and all-cause mortality during six months after

discharge'.
Authors' response 2:
We have changed the words "major cardiovascular outcomes" into "major adverse outcomes" in the whole manuscript.

Reviewer's comment 3:
3. On page 8, line 34 the term 'coronary artery disease (CAD) is written in full, however, it is previously described on page 6, line 50 and should be written in full with its abbreviation on first use.
Authors' response 3:
The correction has been made.

Reviewer's comment 4:
4. On page 10, line 29 it is mentioned that 'The adherence group ad more favourable outcomes compared to the non-adherence group… although these differences were not statistically significant.' Since it is not significant, you can't conclude that one group had more favourable outcomes.
Authors' response 4:
We have changed the manuscript as follows (page 10, line 54; and page 11, lines 02-06): "Mortality (10.6% vs. 13.1%) and hospital readmission (19.8% vs. 27.0%,) were not statistically significant between the adherence and the non-adherence group."

Reviewer's comment 5:
5. Although the general level of English is adequate, there are several possibilities to improve it. For example:
- Page 3, line 14: 'reduction' is not the correct word; it implies that results improved over time.
- page 11, line 54: 'showed the same benefits' = 'similar benefits'
- page 12, line 27: 'his or her spouse or next of kin' = 'informal care provider'
- page 13, line 34: 'may have an impact on prescribing guidelines' --> guidelines are not prescribed; the medication is prescribed according to the guidelines.
- page 14, line 23: 'affirm' = 'confirm'
Authors' response 5:
The correction has been made as follows:
- Page 03, line 21 and page 15, line 10: "reduction" --> "decrease"
- Page 12, line 23: "the same benefits" --> "similar benefits"
- Page 12, line 54: "his or her spouse or next of kin" --> "informal care provider"
- Page 14, line 25:

"prescribing guidelines" --> "the medication is prescribed according to the guidelines"
- Page 15 line 14: "affirm" --> "confirm"

Reviewer's comment 6:
6. The lay-out for the references is inconsistent and for some references incomplete. For example, reference 1 does not include an author, although the factsheet is issued by the WHO. In reference 9, the title is bold (even if this is due to a different type of reference, it looks strange). In reference 22, the title starts with two capital letters. In reference 53, the title is in all capitals and the journal is not abbreviated (JACC). Please check all references carefully.
Authors' response 6:
We apologize for these errors. The correction has been made in the references section.

Reviewer's comment 7:
7. Figure 2 is a dramatization of the results; please use the full range of the y-axis (0-1, not 0.6-1)
Authors' response 7:
The correction has been made in Figure 2.

2.2. Reviewer 2
Reviewer Name: Hou Tee LU
Institution and Country: Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, 8 Jalan Masjid Abu Bakar, 80100 Johor Bahru, Johor, Malaysia
Competing Interests: None declared
Reviewer's comment:
In Table 3, “Factors associated with six-month major cardiovascular outcome” were calculated using multivariable backward stepwise Cox regression, the variables entered were age, gender, number of CAD risk factors, prior MI/stroke, prior heart failure, Killip class II-IV, renal insufficiency, SBP <100 mmHg, LVEF < 40%, physician adherence to guidelines, discharge diagnosis, PCI and health insurance.
Comment: ST elevation myocardial infarction (STEACS) is known to have poorer outcome compare to NSTE-ACS. “Type of ACS” (discharge diagnosis) could be a significant covariate affecting the outcomes of ACS. Can author explain the reason why the 'discharge diagnosis' (STEACS, NSTEACS) was not included as one of the covariates in the calculation of multivariable Cox regression analysis?
Authors' response:
Several statements that we made were more ambiguous than intended, and we have adjusted the text to be clearer in the methods section and table 3.
METHODS (page 09, lines 25-32): "Multivariable backward stepwise Cox regression models were used to estimate the association. The first model was adjusted for the covariates and the second model was adjusted for significant associated factors of the first model and interaction terms between these factors and guideline adherence."
Table 3 (page 09, lines 25-32): "a Using multivariable backward stepwise Cox regression models. First model: variables entered at the first step: age, gender, number of CAD risk factors, prior MI/stroke, prior heart failure, Killip class II-IV, renal insufficiency, SBP <100 mmHg, LVEF < 40%, in-hospital guideline adherence, discharge diagnosis, PCI and health insurance. Second model: variables entered at the first step: in-hospital guideline adherence; percutaneous coronary intervention; prior heart failure; renal insufficiency; and interaction terms: in-hospital guideline adherence and percutaneous coronary intervention, in-hospital guideline adherence and prior heart failure, in-hospital guideline adhe

rence and renal insufficiency."

VERSION 2 – REVIEW

REVIEWER	Hou Tee Lu Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, 8 Jalan Masjid Abu Bakar, 80100 Johor Bahru, Johor, Malaysia
REVIEW RETURNED	16-Jul-2017

GENERAL COMMENTS	Well done.