Author's response to reviews

Title: Cardiovascular Outcomes among Elderly Patients with Heart Failure and Coronary Artery Disease and without Atrial Fibrillation: a Retrospective Cohort Study

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Author's response to reviews:

Reviewer reports:

Wouter Kok (Reviewer 1): The manuscript of "Cardiovascular Outcomes among Patients with Heart Failure and Coronary Artery Disease: a Retrospective Cohort Study" contains information that is pertinent to the present day felt need for additional antithrombotic treatment of patients with heart failure. It is a retrospective study of 22,230 Medicare (age > 65) patients who were admitted to US hospitals for heart failure between January 2007 and December 2013. The selection was 1) patients admitted for heart failure without a prior diagnosis of heart failure, 2) patients with a diagnosis of reduced ejection fraction, and 3) the same patients were admitted without the diagnosis of atrial fibrillation. This selection results in 10% of the hospitalised HF patients that were hospitalised for heart failure in that region. Patients were then followed for endpoints: all-cause mortality, myocardial infarction, and ischemic stroke. To compare the outcomes between patients with previous coronary artery disease (71% of the population) and without previous coronary artery disease, patients were analysed in two propensity score matched groups, correcting for confounders "all demographics, CCI score, CHADS2 score, comorbidities, and prior clinical events", resulting in two groups of 5792 patients each. Mortality rates did not differ after 1 year (34.1% for patients with coronary artery disease versus 35.2% for those without previous coronary artery disease). These mortality rates are quite high, possibly reflecting older age (mean age 80 years !), and are important competing risks for other events;
but here, competing risks seem to be evenly distributed in the two groups, and were analysed using the Gray's test. Myocardial infarction incidence rate at 1 year was 36.1% for coronary artery disease patients versus 9.2%, and ischemic stroke incidence was 11.7% for coronary artery disease, versus 9.4% for those without. These figures indicate a high incidence of event rates, and because of the propensity matching, we are now not aware of the influence of age on these figures; still, we have to keep in mind the mean age of the population: 80 years.

The results are to be summarised as that patients with a prior history of coronary artery disease (CABG, PCI, and previous documented coronary artery disease in ICD code) have a higher burden of myocardial infarction, slightly higher burden of ischemic stroke after discharge from hospital admissions for heart failure, but without much influence on all cause mortality. It would have been interesting to state how many years passed between the prior history and the admission for heart failure, and whether it makes a difference if this was a CABG or a PCI history, or a non-CABG/non-PCI history of coronary artery disease. Also missing are the influence of continued smoking, lipid status. The authors do have the information on diabetes mellitus, but this may be the actual status at presentation, and the type of analysis (propensity score matching) would not have allowed a further discrimination of events by risk factors. So we have to be satisfied with the actual event rates of myocardial infarction and ischemic stroke, that up to now were not well-known. The paper may also be a warning for investigators who would have investigated all-cause mortality as an endpoint in a trial that would investigate additional antithrombotic therapies for those patients at risk, because it would be unlikely that this particular endpoint would change. Rather, endpoints as myocardial infarction and ischemic stroke would be of interest.

Detailed Response to Reviewer 1 Comments:

1) In the discussion, line 220-221, only brief mention is made of the high age in the study groups, and the influence of age on all-cause mortality rates and the other endpoints was not further analyzed. 80 years as mean age is not the mean age of presentation of heart failure patients in most studies, so there has been a selection bias that should be discussed, and if possible also a sensitivity analysis of those patients 65-74, 75-84 and 85+, the way you already divided them in the Table. If this is not possible, then the title may be changed accordingly, for
'elderly' HF patients. I would however be very interested to see the interaction of age on the differences in outcomes between CAD and non-CAD patients.

We agree that the mean age of 80 years in our study is not the mean age of heart failure patients in general. This is because the Medicare population was used for this study which mainly includes elderly patients aged ≥65 years. The generalizability of the results to the overall population has been addressed as a limitation in the discussion section. We agree with the Reviewer’s suggestion and have added “elderly” in the title of the manuscript. We appreciate the Reviewer’s suggestion on providing the results of the interaction of age on the differences in outcomes; however, the data user agreement for this project has expired. Dr. Onur Baser no longer has access to the 5% Medicare data, and considering the time and significant cost associated with renewing the data user agreement, it may not be feasible to perform this analysis.

2) In the title, no mention is made of the selection of patients without Afib. As the prevalence of AF is about 40% in patients with HF admitted to hospitals, this is a selection that is of importance. The reason for such a selection was not made clear in the introduction or methods, or even in discussion section. The probable reason is that the authors for some reason wished to estimate the impact of adding certain antithrombotics (the NOACs) to these patients, and Afib patients are normally already protected. if this is the reason for selection, please mention this in methods. Also, I would prefer to see 'without Afib' in the title of the manuscript.

Given the limited evidence on the burden of clinical outcomes, as well as the conflicting evidence of the benefit of anticoagulation use in HF patients without AF, we have focused on this population. We have detailed this in the methods section and have added “without AF” in the title of the manuscript. Additionally, the potential benefit of adding antithrombotics to HF patients with sinus rhythm is not well understood, and this study will provide insights about the burden of thrombotic events in this patient population.

3) in the methods section, the propensity score matching was described as matching "all demographics, CCI score, CHADS2 score, comorbidities, and prior clinical events". Here, I would advise to be more precise, matching for age and sex probably, CCI score could only be found in the list of abbreviations in line 307, comorbidities were not defined exactly, and prior clinical events were not defined exactly. I was surprised that 5792 CAD patients could be matched from the 6403 non-CAD patients, or was it done the other way round, that non-CAD patients were matched with the larger population of CAD patients? Then change the sentence.
We have the detailed information regarding demographics, comorbidities, and prior clinical events (including the conditions comprised in each category) in the baseline measures section. Additionally, the CCI was also abbreviated in this section. Since the statistical analysis section followed the baseline measures section, we haven’t added the detailed information again as it would be repetitive. Additionally, we would like to clarify that each CAD patient was matched to a non-CAD patient, during this process about 10,000 CAD patients were dropped.

4) in methods, line 111-112 (and later abstract, results and discussion) LV dysfunction is translated as HFrEF, but at present, HFrEF in the guidelines is defined as HF with LVEF < 40%. This is not what your LV dysfunction definition holds, so please omit the HFrEF definition, and only use LV systolic dysfunction (LVSD for example).

We agree with the Reviewer and have used “HF with LVSD” instead of HFrEF throughout the manuscript.

5) Line 127 and 143, you use competing risk analysis for the endpoints of myocardial infarction and ischemic stroke, and in line 143, Gray's test is mentioned in KM analysis. Please add reference for appropriate use of this Gray's test, for example: Dignam JJ, Kocherginsky MN. Choice and interpretation of statistical tests used when competing risks are present. J Clin Oncol. 2008;26:4027-34.

We have used the log-rank test for the KM analysis comparing the all-cause mortality rates between the two cohorts, and Gray’s test has been used for the competing risk analysis for the endpoints MI and IS. We appreciate the Reviewer’s suggestions and have added appropriate references.

6) in results, line 170, "ACM rate in the CAD cohort was (symbol) about 34% at the end of 1 year" is in fact 34.1%, and I understand that it is in the sentence of figures mentioning 54% and 68%, but you also do not mention 'about' 54% and 68%. So I would advise to only use 34% here, and not 'about' 34%. Same for line 175, 'about 36%', and line 181, 'about 12%'.
We thank the Reviewer for pointing this out and have removed the word “about” from all the places as suggested.

7) the present sensitivity analysis of patients with inpatient AND outpatient Medicare claims indicates that also in this mixed population of admitted and non-admitted patients with a first presentation of HF and no Afib, results are similar. In discussion line 271, it is mentioned that the incidence of ischemic stroke was not different between the two groups, 'possibly indicating lower risk in outpatients with HF". The incidence of IS in the total population without AF is not lower in CAD patients: 12% vs 11.7% after 1 year in the hospitalised patients, and it is only the difference between CAD and NonCAD that is not as high. Re-phrase your argument ? The purpose of this sensitivity analysis is not very clear, after all, only one sentence is used in discussion on the sensitivity analysis. I would think that results are not very different from hospitalised patients and non-hospitalised patients, and this may be an argument in favor of selecting the riskpatient of previous CAD, with or without HF hospitalisation. There is however a need for timing narrative: how long after their CAD diagnoses were they seen with HF.

We agree with the Reviewers’ comment regarding the argument on ischemic stroke and have updated the statement in the discussion: The main analysis included the hospitalized HF patients, as we have tried to keep the population consistent with that of the COMMANDER HF trial (Zannad et al. EJHF 2015). The sensitivity analysis was performed among the HF patients identified from inpatient or outpatient settings to see if the results, especially the clinical outcomes, differed in between the two populations, considering that the study was performed in the elderly patients aged ≥65 years. Additionally, this sensitivity analysis further demonstrates the robustness of the data in that the risk of these events observed in the broader population remains similar. The rationale for sensitivity analysis has been stated in the methods section.

We appreciate the Reviewer’s suggestion of describing the time from CAD to HF diagnosis; however, as previously stated, the data user agreement for this project has expired. Dr. Onur Baser no longer has access to the 5% Medicare data, and considering the time and significant cost associated with renewing the data user agreement, it may not be feasible to perform this analysis.

8) the poor prognosis (all cause mortality) of the patients is discussed in line 227-230 as compared to patients with cancer. Then the argument is risen that there is a need to focus on further interventions, 'to reduce mortality in HFrEF patients with CAD" . However, the all cause
mortality is NOT what is predicted differently between the CAD and non-CAD patients, and will probably NOT be the focus of further interventions, as these patients may have died from other causes than coronary events or even heart failure. The presence of cancer in these patients was already > 20% in your tables. So the argument is not improving mortality by any proposed intervention in coronary artery disease, but decreasing the risk of myocardial infarction and some ischemic strokes, I would argue, and that these patients have a possible better functional life at this age.

We agree with the Reviewer that the all-cause mortality is not different between the CAD vs non-CAD cohort. However, the overall 1-year mortality is considerably high in our study population (~35%). We have updated the discussion incorporating the Reviewer’s suggestion and acknowledged the presence of cancer in these patients.

9) line 263: COMMANDER-HF trail, should be 'trial'.

We apologize for the typo and have corrected it

10) please add the coronary histories (CABG/ PCI/ CAD disease) in table 1. Now it is unknown what sort of histories how many patients in your cohort of CAD had.

We agree with the Reviewer and have provided the distribution in Table 1.

Susan Stienen (Reviewer 2): Zhao et al. studied the impact of coronary artery disease in newly diagnosed hospitalized heart failure patients with reduced ejection fraction AND without atrial fibrillation in a large retrospective cohort of Medicare patients. After propensity-score matching CV outcomes between patients with and without coronary artery disease (N=5,792 per group) were compared. They observed that mortality rates were equal between groups but that incidence rates of myocardial infarction and ischemic stroke were higher in the group of patients with
coronary artery disease. There is limited real-world data on outcome in this type of HF patients and the research conducted by the authors is therefore relevant. The manuscript is well-written. However, I feel that there are methodological issues that need to be clarified. I have major comments and some suggestions:

Major:

1) Smoking status and heart failure severity are variables associated with prognosis in HF and may differ between CAD and non-CAD patients. Were these variables considered in the matching procedure? If not, it may be possible that CAD patients had more severe HF and therefore were more prone to for example ischemic strokes. Please clarify.

We understand the importance of smoking status and heart failure severity in the prognosis of HF; however, these variables were not included in our study. Since this is a claims-based study using 5% Medicare data, all the diagnoses, including the index diagnosis, were only identified based on the ICD-9 diagnosis codes. In the claims database, smoking status is identified using the ICD-9 codes and is most likely under-reported; further, there are no ICD-9 codes to define the severity of the HF. Therefore, these variables were not included in our study. We have added this in the limitation section.

2) There is no information on medication use in this cohort and it seems that there was no matching for baseline medication. Was the assumption made that by matching patients on medical history in the baseline period medication use (most importantly anticoagulants) was balanced as well?

Yes, since we have matched patient’s medical history in the baseline including the ischemic stroke, TIA, VTE, major bleeding etc, the assumption was that the medication use in the baseline would be taken care of as well.

3) How were the endpoints myocardial infarction and ischemic stroke diagnosed? Also by coding? And what was the timing of collection of the information on the endpoints? This should be clarified (also in the methods section). Moreover, it seems from the Kaplan - Meier curves that there were patients lost to follow-up? Please clarify.
The end points of ischemic stroke and myocardial infarction were captured using the ICD-9 diagnoses codes. They were evaluated in 60-day intervals during the 1-year follow-up period (within 1 year after the index date which is the HF diagnosis date) as well as in each year during the maximum follow-up period of 7 years. We have clarified this in the methods section. Patients were followed until the earliest of death, end of continuous enrollment, or the end of study period, and we agree that there were patients lost to follow-up. However, providing the number of patients is not feasible as the data license agreement has expired.

4) What is the rationale for a sensitivity analysis using a mix of both in- and outpatients. It is clear from previous research that prognosis differs between these types of patients. Moreover, there is no baseline table for this specific population and hence not clear for the reader if they were well-balanced after matching. Also it is not clear what the distribution of in- and outpatients is between CAD and no CAD patients. It is therefore very difficult/impossible to compare results with the primary analyses and likely confuses the reader. However, it may be interesting to study the in- and outpatient populations apart from each other in the primary analyses.

The main analysis included the hospitalized HF patients, as we have tried to keep the population consistent with that of the COMMANDER HF trial (Zannad et al. EJHF 2015). The sensitivity analysis was performed among the HF patients identified from inpatient or outpatient settings to see if the results, especially the clinical outcomes, differed in between the two populations, considering that the study was performed in the elderly patients aged ≥65 years. Although the distribution of the CAD and non-CAD patients in the inpatient (main analysis) and the inpatient or outpatient (sensitivity analysis) samples remained the same, unfortunately, we are not able to provide the distribution of in- and outpatients within each of the CAD and non-CAD cohorts due to the expiry of the data user agreement. Additionally, a table including the baseline characteristics before and after PSM for the sensitivity analysis has been added as supplemental material.

We agree with the reviewer that looking at the distribution of the CAD and non-CAD patients in the inpatient and outpatient populations separately would be of interest; however, the data user agreement for this project has expired. Dr. Onur Baser no longer has access to the 5% Medicare data, and considering the time and significant cost associated with renewing the data user agreement, it may not be feasible to perform this analysis.

5) It was not clear for me from the title and abstract that the authors studied a specific population of HFrEF patients without atrial fibrillation. Also, the exact rationale for excluding these patients should be discussed. From the methods it seems that the presence of atrial
fibrillation was based on an ICD code during the baseline period. However, it is known that atrial fibrillation and HF often co-occur (especially during admission). Were patients with AF during the index admission also excluded? And I feel that the limitations section should mention that an ICD-based AF code does not exclude the possibility that AF patients were included. Also it is possible that AF occurred later during follow-up.

Given the limited evidence on the burden of clinical outcomes, as well as the conflicting evidence regarding the benefit of anticoagulation use in HF patients without AF, we have included these patients. We have detailed this in the methods section and have added “without AF” in the title of the manuscript. We would like to clarify that patients with evidence of ICD-9-CM codes for AF during the 12-months pre-index period, including the index hospital admission, were excluded from the study. We agree that using the ICD-9 codes for AF does not exclude the possibility of AF patients being included in the study and have added this in the limitations. Additionally, it could be possible that the patient has AF in the follow-up period.

6) It is not clear if the CAD diagnosis was based on information solely before the admission or also during the admission. Regular diagnostic work-up in de novo HF patients consists of coronary ischemia detection. Hence, when the period of admission is not considered for this classification it may be that patients were falsely classified as having non-CAD.

We apologize for the confusion. Patients with CAD were identified based on the presence of the criteria for CAD any time in the 12-month pre-index period which included the index hospital admission. We have clarified the same in the methods section.

7) A large part of the discussion consists of the authors stating the necessity of exploring treatment options for HF patients with CAD without atrial fibrillation. However, they do not discuss the results of one of the latest landmark trials in this field: the COMMANDER-HF (Zannad et al. NEJM 2018). Please update the discussion in light of these results.

As the results of the COMMANDER-HF trial have not be published until recently, these were not provided in our discussion. We thank the Reviewer for pointing this out and have updated the discussion including the results from this latest trial.
8) An interesting finding of this study are the equal mortality rates in CAD and non-CAD patients. Previous studies observed a higher mortality risk in CAD patients; can the authors elaborate on this finding? In my opinion, this should be mentioned in the discussion section.

We agree with the Reviewer that the equal mortality rates of the two groups in our study is contrary to other studies. However, the average 1-year mortality rate of the total hospitalized HF patients is consistent with a previous study by Hernandez et al. which has been described in the discussion section. Additionally, the reason for observing the similar mortality rate in both CAD and non-CAD cohorts could be attributed to the older age of patients in both the cohorts (mean age is 80 years) and the higher prevalence of cancer in the baseline period. We have added more information on this in the discussion section.

Minor:

9) The number of patients with CAD is quite high (~70%) compared to other studies (for example Rusinaru et al Eur J HF 2014 which had ~40% of patients with CAD). Are there differences in CAD definition? Were patients with stable angina pectoris included in this study?

We thank that Reviewer for pointing this out. We would like to highlight the following difference in methodology – this is a claims-based study in which the presence of CAD was defined as an evidence of previous documented CAD (identified using ICD-9-CM codes), history of prior coronary artery bypass graft, or percutaneous coronary intervention with or without stent (identified using CPT codes) at any time in 12-month pre-index period including the index HF hospital admission. Whereas, Rusinaru et al. was a registry study in which CAD was defined by the presence of documented history of acute coronary syndromes, significant CAD previously confirmed by coronary angiography (reduction of the normal diameter ≥50% for the left main coronary artery and of ≥70% for the right coronary, left anterior descending, and circumflex arteries), or history of coronary revascularization before the index admission of HF.

10) Patients with evidence for HF in the baseline period were excluded. How was this defined?

We apologize for the confusion and would like to clarify that the patients with evidence of HF (ICD-9CM code: 428.xx) in the 12 months prior to the index hospital admission were excluded from the study and have clarified the same in the methods section.
11) The CHADS2 score was amongst others used for matching. To my knowledge, the CHADSVASC score is validated in a HF population in sinus rhythm but not the CHADS2 score. What was the reason for determining the CHADS2 score and not the CHADSVASC?

We thank the Reviewer for providing this suggestion. However, our study has included the CHADS2 score in the PSM, and we believe that the results might not differ significantly by using the CHADSVASc score. We will keep this suggestion as a reference for future studies.

12) Suggestion to clarify in Figure 1 which part is for the sensitivity analyses and which part for the primary analysis. Also, in case of patients lost to follow-up, please depict this in the flow diagram.

We have added symbols and the footnotes corresponding to these symbols indicating the final sample size used for the main analysis as well as the sensitivity analysis. We appreciate the Reviewer’s suggestion to add the number of patients lost to follow-up in the flow diagram. However, the data user agreement for this project has expired and Dr. Onur Baser no longer has access to the 5% Medicare data. While considering the time and significant cost associated with renewing the data user agreement, it may not be feasible to provide this number. Additionally, we would like to clarify that the patients lost to follow up wouldn’t change significantly between the two samples as the identification period remained the same.

13) Reference 9 seems not correct (different article?), and ref 18 is not about HFrEF but HFP EF patients. Moreover, ref 13 refers to previous guidelines (2012), please update.

We thank the Reviewer for point this out and have updated the references as suggested.