Reviewer's report

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

Version: 0 Date: 14 Sep 2018

Reviewer: Wouter Kok

Reviewer's report:

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.

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 analysed. 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.

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.

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.

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).
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.

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%'.

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 A-fib, 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.

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.

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

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.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal