Author's response to reviews

Title: How low should we target the LDL goal to improve survival for Acute Coronary Syndrome patients in Hong Kong?

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Author's response to reviews: see over
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Editor-in-Chief,
BMC Cardiovascular Disorders

Dear Editor-in-Chief:

Revised Manuscript Titled: How low should we target the LDL goal to improve survival for Acute Coronary Syndrome patients in Hong Kong?

I would like to submit my manuscript to you for publication in the “BMC Cardiovascular Disorders”. I have submitted the manuscript entitled “How low should we target the LDL goal to improve survival for Acute Coronary Syndrome patients in Hong Kong?” The manuscript was revised based on the valuable comments from the reviewers. We have addressed all the comments and prepared a point-by-point response in this cover letter.

Referee(s)' Comments to Author:

Reviewer 1

Comments to the Author
1. There were patients who did not get the LDL-C test during hospitalization. Did they have prior test? Would that affect the statin prescribing? Did the patient’s characteristics differ from patients who received the LDL-C test?
Response: Thank you for your comment. Those patients who did not get the LDL-C test during hospitalization may have prior test. However, if the prior test was done prior to our study period, the data was not collected. The lack of LDL-C testing should not affect statin prescribing since ACS patients should be on lipid lowering drugs according to the ACC/AHA guidelines. The patient’s characteristics were not different from patients from patients who received the LDL-C test.
2. The authors demonstrated that the LDL-C level at 6 months independently associated with mortality. The authors should include serum creatinine or estimated GFR in the prognostic model because renal function has been shown as important independent prognostic factors in several cohorts.

Response: Thank you for your comment. We totally agree with the reviewer's comment. Unfortunately, the serum creatinine was not recorded in the data collection process. Therefore, we are not able to input the renal function in the prognostic model.

3. The authors should mention number of patients attaining LDL-C goal (2.8 and 1.8 mmol/l) because limited sample size may cause inconclusive findings.

Response: Thank you for your comments. Table 2 has been added listing the LDL-C levels and statin utilization of patients at various time points.

4. Should the author discuss the different of K-M survival curve which was separated very early between patients receiving or not receiving statin while the curve separated later between patients who attained and did not attain LDL-C goal.

Response: Thank you for your comments. The major reason that the K-M survival curve was separated very early for patients with or without statin versus patients who were on statins but with or without target goal attained was that statin demonstrated positive clinical survival outcomes particularly in the high risk cardiovascular patients. Our findings echoed the value of statins as in published data.

5. The title of the manuscript and the conclusion in the abstract are not supporting each other.

Response: Thank you for your comment. The title has been revised as “How low should we target the LDL goal to improve survival for Acute Coronary Syndrome patients in Hong Kong?”

Minor compulsory revisions
1. Did the authors do the K-M survival curve adjusted for the patients' characteristics?

Response: Since our sample size was so small, we did not adjust for the patients' characteristics. This is one of the limitations of our study. Thank you for your comment. We have added this limitation in the discussion section.

2. Please add “number at risk” in the K-M curve.

Response: Thank you for your comment. The exact number of all-cause mortality for each K-M curve was listed under figure 2.

Reviewer 2
Comments to the Author
The current study demonstrates that stains were underutilized for patients with myocardial infarction (MI) in the local hospital in Hong Kong, and that lower LDL-C, especially with a cut-off value less than 2.4 mmol/L, is a significantly independent predictor for mortality in MI patients. The current finding reveals the significance to achieve lower LDL-C in the specific race after the occurrence of MI. Thus, this paper is worthy. The biggest question for this reviewer is about the statin usage and LDL-C value. After multivariate analyses, statin is not an independent predictor for mortality, suggesting that statin usage and LDL-C may be confounding factors. The other lipid-lowering drugs rather than statins or life-style change may be more important. Thus, please provide more information on medications.
Response: Thank you for your comment. We totally agreed with the reviewer’s comments. The following information was added in the manuscript. Among those patients discharged with statins \((n = 298)\), majority of our patients were on monotherapy lipid lowering agent (mainly statin) at discharge. There were 268 (90%) patients who were prescribed with simvastatin, Rosuvastatin, atorvastatin and lovastatin were prescribed in 24 (8.1%), 5 (1.7%) and 1 (0.3%) patients respectively. We excluded patients with combination therapy of lipid-lowering agents or non-statin therapy. There were 6 patients being excluded: 3 patients on monotherapy gemfibrozile 1200 mg/day, 1 patient with gemfibrozil 600 mg/day plus simvastatin 40 mg, 2 patients with ezetimibe 10 mg/day plus atorvastatin 80 mg.

In addition, the authors mentioned that the patients who did not take statins at discharge had significantly less PCI treatment and lower LDL-C level during hospitalization. However, lower LDL-C is also shown to be a significantly independent predictor, but statin usage is not. This patient group may have achieved the goal of LDL-C cut-off value, but had worse clinical outcome. Please clarify and comment on this inconsistency.

Response: Thank you for pointing this out. We found that there were statistically significant differences between the statin group versus non-statin group in terms of baseline characteristics. The patients who did not take statins at discharge were older (average age: 70 years old versus 79 years old; \(p < 0.001\)), with more previous ischemic heart disease/acute coronary syndrome (19.8% versus 32.7%; \(p = 0.007\)), cerebrovascular accident (8.4% versus 14.4%; \(p = 0.077\)), heart failure (9.4% versus 30.8%; \(p < 0.001\)) and poorer creatinine kinase levels (3.0% versus 8.9%; \(p = 0.023\)) as well as liver function (0.7% versus 3.9%; \(p = 0.041\)). Therefore, although the patients who did not take statins may have achieved the LDL-C goal, they had poorer clinical outcomes due to other co-existing conditions.

Please discuss the reasons why all-cause mortality and hospitalization are significantly reduced in patients with statins compared to those without statins regardless of similar revascularization rate between two groups. Is cardiovascular disease-associated mortality rate also reduced by statin? If possible, please provide the information on causes of death.

Response: Thank you for your kind comments. Unfortunately, our system did not record the cause of death.

Specific comments:
The detailed data regarding coronary artery disease (culprit lesion, multi-vessel disease, etc) and revascularization method (DES, graft etc) is missing.

Response: Thank you for your comments. We agreed that the specific details of the coronary artery disease and revascularization method. Unfortunately, when we designed the study, we did not include the collection of these data.

Please describe the diagnostic definition of heart failure, hypertension, and diabetes.

Response: Thank you for your comments. We have added the definition in the methods section. The diagnostic definition of the diseases were as followed:

Heart failure – Patients with positive cardiac echocardiography findings and confirmed diagnosis by cardiologists.

Hypertension – Patients with at least 2 consecutive blood pressure measurements that exceed the target range according to the Joint National Committee VII Report on Hypertension.

Diabetes – Patients with hemoglobin A1C greater than 7%.
Please describe the method to prescribe statins. Is there a criterion?

Response: Thank you for your comments. Since our patients were high-risk cardiovascular patients, they were required to be put on lipid-lowering agents according to the American Heart Association and the European Cardiology Society. Therefore, all our ACS patients were expected to have lipid-lowering agent. We have added this criterion in the manuscript.

What kinds of statins were prescribed in this cohort? What was the dosage?

Response: Thank you for your comments. Among those patients discharged with statins (n = 298), majority of our patients were on monotherapy lipid lowering agent (mainly statin) at discharge. There were 268 (90%) patients who were prescribed with simvastatin, Rosuvastatin, atorvastatin and lovastatin were prescribed in 24 (8.1%), 5 (1.7%) and 1 (0.3%) patients respectively. The equipotency dosage has been listed in Figure 1. We excluded patients with combination therapy of lipid-lowering agents or non-statin therapy. There were 6 patients being excluded: 3 patients on monotherapy gemfibrozil 1200 mg/day, 1 patient with gemfibrozil 600 mg/day plus simvastatin 40 mg, 2 patients with ezetimibe 10 mg/day plus atorvastatin 80 mg.

Minor comments:
Page 10, line 168-172; the data regarding hospitalization and revascularization is missing.

Response: Thank you for your comments. The number of patients and percentage for hospitalization and revascularization were added in the manuscript.

Were there any side effects of statins reported during follow-up?

Response: Thank you for your comments. We did not detect any side effects related to statins during the follow up period. However, 3 patients were excluded from data analysis due to unsuitability for statins therapy because of elevation of liver function tests or elevation of creatinine kinase with complain of myalgia because of statin use at baseline. The side effects and exclusion data were added to the manuscript.

Please do not hesitate to contact me if further information is needed. My email address is vivianlee@cuhk.edu.hk. I am looking forward to your favorable reply.

Thank you for your kind attention.

Best regards,

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