Author's response to reviews

Title: Increased Mortality among Survivors of Myocardial Infarction with Kidney Dysfunction: the Contribution of Gaps in the use of Guideline-Based Therapies

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Author's response to reviews: see over
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Editorial Board, *BMC Cardiovascular Disorders*

To Whom It May Concern:

Thank you for the opportunity to revise manuscript #1381109276209660 according to editorial comments. We appreciate the careful review and have made the suggested changes within the manuscript. Attached, please find our revised manuscript entitled, “Increased Mortality among Survivors of Myocardial Infarction with Renal Dysfunction: the Contribution of Gaps in the use of Guideline-Based Therapies.” Below are point by point responses to the reviewers’ concerns.

To reiterate, the objective of this study was to examine the degree to which differences in guideline-based medical therapy for myocardial infarction contributes to the higher mortality associated with renal dysfunction. In a community-based population of patients with myocardial infarction, we found that renal dysfunction was common, associated with higher mortality and yet lower use of guideline-based medications among eligible patients. However, the higher mortality associated with renal dysfunction is not accounted for by differences in clinical and treatment factors. These results underscore the need for novel therapies specifically targeting the pathophysiologic abnormalities associated with renal dysfunction to improve survival in myocardial infarction patients with renal dysfunction.

This is an original research study which is not under consideration for publication elsewhere. None of the paper’s contents have been previously published.

Eight authors have contributed to this manuscript. Each author contributed significantly to the conception and design or analysis and interpretation of the data, or both; drafting of the manuscript or revising it critically for important intellectual content; and final approval of the manuscript submitted. All authors have read and approved the manuscript. None of the authors have any conflicts of interest to disclose.

Thank you for your consideration. Please do not hesitate to contact me at (303) 436-5663 or Pamela.Peterson@uchsc.edu with any questions.

Sincerely,

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Response to Reviewer Comments, BMC Cardiovascular Disorders, MS: 1381109276209660

First Reviewer’s Comments:

1) Comment: Among the weaknesses is the fact that revascularization is not considered as a guideline-recommended therapy in this report. Undoubtedly, revascularization in both ST and non-ST elevation ACS has a strong impact on mortality. In this case, regarding access to invasive strategy and revascularization/reperfusion, the eligibility of the patients is more difficult to assess because it’s mostly dependent on the subjective judgment of the attending physician. Nevertheless, this represents a huge bias, and it is likely that re-analyzing the data according to the rate of recommended therapies per group, including revascularization/reperfusion would produce slightly different results. Admittedly, no randomized trial has ever been carried out to assess the benefit of revascularization/reperfusion specifically in renal failure in ACS.

Response: The primary aim of the study was to determine the incremental contribution of guideline-based medical therapy in patients with AMI and kidney dysfunction. We agree that revascularization likely has a strong impact on mortality, and thus we accounted for the use of revascularization in our models, removing the potential confounding effects of revascularization on the apparent benefits of evidence-based medical therapy. This is an important strength of our study, as revascularization could be an important confounder. However, we did not want to make the mistake of assuming that by adjusting for revascularization alone, we could presume that this indicated the incremental contribution of revascularization on outcomes. We did not want to make this erroneous assumption because we were unable to determine eligibility for these procedures, which as the reviewer points out, is largely a subjective judgment of the treating physician and therefore difficult to assess. Yet, accounting for eligibility is critical in this analysis because factors related to eligibility may be collinear with treatment, ineligibility for treatment may be a marker for adverse outcomes and eligibility is likely to differ across categories of kidney function. Thus, the failure to account for differences in eligibility would markedly over-estimate the contribution of revascularization to improved survival.

Second Reviewer’s Comments:

1) Comment: The authors considered only the survivors at discharge. We know that in-hospital mortality represents a large proportion of the mortality at one year. Since the quality of management in the acute phase has an impact on the early mortality, and since patients with renal dysfunction less frequently receive reperfusion, angiography, beta-blockers and statins, the selection of survivors after the acute phase is of paramount importance. This selection of patients alive at discharge should be underlined and even announced in the title of the report.

Response: This study was designed to ascertain long term outcomes in patients AMI among a representative sample of patients surviving AMI. As a result, patients who died during hospitalization were not considered in the analytic cohort. However, only a very small proportion of patients died (17 of out of the original cohort of 2,498 patients enrolled). We agree that it is important to make it very clear that this is a study of survivors of AMI hospitalization. We have added a flow chart of patient accounting (new figure 1) which indicates the number of patients who died in the
hospital. Additionally, the title has been revised to indicate that this is a study of AMI survivors:

"Increased Mortality among Survivors of Myocardial Infarction with Kidney Dysfunction: the Contribution of Gaps in the use of Guideline-Based Therapies"

2) Comment: The authors should provide details of the study population, showing (in a flow chart for example) the number of patients admitted, the % of in-hospital death, % of patients who refused to participate, or who had incomplete data or lost to follow-up.
Response: A flow chart has been added (new figure 1) to provide details of the study population.

Figure 1. Patient accounting.

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Total MI Patients
n=3953

Enrolled in PREMIER
n=2498

GFR known
n=2475

GFR < 150
n=2443

Discharged alive
n=2426

2-year Vital Status Known
n=2,386

1455 unable to or refused consent

23 cannot calculate GFR
(9 creatinine missing)
(14 race missing)

32 GFR >= 150

17 died in hospital

40 vital status unknown
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3) Comment: As acknowledged in the discussion, the authors only recorded the treatment at discharge and not during follow-up. Nevertheless, it is likely that, over a two year period the treatment was modified: either a reduction in treatment, for example because of side effects or non-adherence, or an increase in treatment because of progressive introduction of drugs or changes in guidelines. Thus it seems difficult to support the hypothesis of having the same treatment over two years and draw definitive conclusions on the impact on mortality.

Response: We recognize that it is possible that treatment was modified over the two year follow-up period. However, studies suggest that the failure to implement therapy for patients with cardiovascular disease in the inpatient setting is a strong marker of the lack of outpatient therapy.[1] Additionally, no landmark clinical trials or revisions in guidelines were published during the study period. Thus, patient eligibility and recommended treatment should not have changed. We recognize the absence of follow-up medication data a limitation and have included it in the limitations section of the discussion as follows:

"We did not include follow-up medication data. Patients may have been started on guideline-based therapy after discharge from the hospital, or conversely, medications prescribed at the time of discharge may have been discontinued after discharge. This misclassification would tend to underestimate the relationship between therapies and outcomes. However, several studies suggest that the failure to implement therapy for patients with cardiovascular disease in the inpatient setting is a strong marker of the lack of outpatient therapy."

4) Comment: The authors provide data on eligibility for treatments, and this is an important point. Nevertheless, the definition of contra-indication is not detailed in the paper. In addition, from table 2, it appears that the authors did not consider that patients with renal dysfunction had an indication for ACEI or ARB.

Response: It is difficult to clearly define all contraindications to therapy because there are numerous nuances to identifying patients who are eligible. Therefore, we used the clinician’s judgment regarding the presence of contraindications and prospectively collected the presence of any contraindication based on documentation in the clinical record by the treating clinician. Furthermore, the lack of specificity regarding contraindications does not influence the eligibility of patients for therapy and thus findings of this study.

Because the focus of this study was on the use of guideline-based therapies for acute MI, patients considered eligible for ACE-inhibitor or ARB were those with at least moderate left ventricular systolic dysfunction. While we recognize that renal dysfunction in and of itself is an indication for treatment with an ACE-inhibitor or ARB, for the purposes of this study, renal dysfunction alone was not considered an indication.

5) Comment: In the discussion section, the authors should compare their results to another registry study showing that renal dysfunction was an independent predictor of one year mortality even after adjustment on the rate of use of guideline-recommended treatment (AHJ 2006; 151:661-7)

Response: We believe that the study cited by the reviewer is important, but addresses a different issue than that addressed in our paper. Schiele et al evaluated the relationship between renal function and mortality among a community-based cohort of patients admitted with AMI in France. They found that renal function remained an independent predictor of mortality independent of initial risk and acute
management and that guideline recommended therapies were underused in patients with impaired renal function. The authors conclude that renal function parameters should be incorporated into risk assessment and that patients with impaired renal function should benefit from greater application of guideline recommended therapies. In contrast, our study addresses a fundamentally different question, namely the incremental contribution guideline-based medical therapy in patients with AMI and kidney dysfunction. We believe that this is why this study is an important contribution to the existing literature. In response to this comment, we have revised the discussion of our manuscript to reflect these contrasts:

"Indeed, multiple studies have demonstrated under use of guideline based therapies in patients with impaired renal function. While elevating the care for patients with kidney disease is an important goal, our results suggest that lower treatment rates alone do not account for excess mortality."

Reference List