Peer Review File

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Reviewer A

Comment 1:
Excellent summary of current trends in PCI outcomes in management of SIHD in patients with ESKD.

Reply 1:
Thank you for the encouraging feedback.

Reviewer B

I read the manuscript ”Nationwide Trends and Outcomes of Percutaneous Coronary Intervention for Stable Ischemic Heart Disease in End-Stage Kidney Disease: A Longitudinal Study” with great interest. The authors use the United Sates Renal Data System to investigate the annual number of PCI procedures for stable ischemic heart disease in patients with end-stage kidney disease (ESKD) on dialysis. Mortality trends are also investigated at 30 days, 1 year and beyond 1 year. The major findings were that utilization of PCI for stable ischemic heart disease in ESKD patients has declined between 2010 and 2018 with an associated increase in in-hospital mortality, which could partly be attributed to a parallel increase in the comorbidity burden. It is concluded that the results call for cautious patient selection when choosing candidates for PCI. The major strengths include the large number of patients and hard end-point in terms of mortality, but there are also some major issues that should be addressed:

Comment 1:
1) Patients referred for CABG were excluded in this study. This trend and outcome analysis is not complete without also investigating the corresponding trends in ESKD patients who underwent CABG during the same time period. Patients with ESKD are likely to have mutlivessel coronary artery disease with high anatomical complexity. As shown in the present study, the prevalence of diabetes and congestive heart failure are also high among these patients, making CABG a more appropriate revascularization option. In addition, anemia is frequently observed in ESKD patients, why double anti-platelet therapy is less desirable. Thus, several factors support CABG as primary revascularization method for these patients. Has patient referral for CABG been increasing during the corresponding time-period?

Reply 1:
We thank the reviewers for highlighting this important issue. We did investigate the trends in CABG in the ESKD population with stable CAD and this work was recently published in the American Journal of Cardiology (see reference below). We reported that

the trends for CABG in the same patient population is also on a decline over a similar time period with an associated decline in procedural mortality. We hypothesized that this trend reflected the growing preference of physicians to not offer revascularization as often to stable CAD patients. The decreasing mortality trend could possibly be related to more careful selection of patients or better attention to post-operative care. We did not present both CABG and PCI in one manuscript as there was more information here than could fit into one paper and we felt that in a retrospective, administrative database we could not fairly compare the PCI and CABG groups directly as there were many confounders and anatomic variables that were not available. We have now included this in our discussion (see Page 11 Line 236).

Changes in text:
(Page 11 Line 236)
"A recent publication from our group reporting trends of coronary by-pass surgery for SIHD in the ESKD population shows declining trends of by-pass surgery over the years 2009-2017 with an associated decline in post-procedural mortality. (20) This trend could indicate that providers are now more selective in referring ESKD patients for CABG. Subsequently, it is likely that high-surgical risk patients are referred for high-risk PCI, which could also explain the increasing post-PCI mortality trends in our current study."

Reference:
Vasudeva R, Mehta H, Chan WC, Majmundar M, Yarlagadda SG, Downey P, et al. Nationwide Trends and Outcomes for Coronary Artery Bypass Grafting in End-Stage Kidney Disease and Stable Coronary Artery Disease. Am J Cardiol. 2024;210:37-43.

Comment 2:
2) The most important limitation of this study is that vital information, such as number of diseased coronary arteries or number of stents placed during PCI, are not available. Is it possible to obtain this information in some way? It would, for example, be very interesting to know if the number of multivessel-diseased patients with indication for CABG increased from 2010 to 2018. This information should be added to Table 2.

Reply 2:
We agree with the reviewer that having information on coronary anatomy would be useful. Unfortunately, given the administrative nature of the database, specific granular data such as the involvement of specific coronary arteries and the number of stents is not available for analysis.

Comment 3:
3) The results would be more informative if it contained some comparative information. For instance, is it possible to investigate outcome of ESKD patients with stable ischemic heart disease referred for PCI compared to those who are not revascularized? This could indicate if ESKD patients with stable ischemic heart disease benefit from revascularization with PCI. That would support your conclusion of an uncertain benefit of PCI over conservative therapy in

ESKD, which actually is not a valid conclusion since it has not been studied by the authors. Adding the outcome of ESKD patients undergoing CABG and comparing this group to a propensity-score matched cohort of ESKD patients undergoing PCI and conservative care, respectively, would add an extra level to this study.

Reply 3:
You raise an important query. The aim of this study is primarily to assess the trends and comment on any change in practice for PCI intervention in patients with ESKD for stable ischemic heart disease. We agree that our statement "uncertain benefit of PCI over conservative therapy in ESKD" can be misleading given that our analysis isn't a comparison. We have excluded this comparative phrase from our text as indicated below (see Page 13 Line 298).

We also do not have a good way to identify stable CAD patients who are managed medically in this database. Since they do not undergo PCI, we may include a lot more patients with mild or uncertain severity of CAD. Using this database, we are also unable to identify patients with abnormal stress tests or abnormal coronary CT scans.

Our other recently published work on CABG trends in the same population provides us a good comparison point as suggested and this has now been included in the discussion text (see Reply 1). However, direct comparison of our outcomes to those undergoing CABG may be misleading since matching will likely be inaccurate as this administrative database did not have access to granular details such as anatomical data for severity of coronary disease and other procedural data.

Changes in text:
(Page 13 Line 298)
"In view of the high overall mortality of ESKD patients and the uncertain benefit of PCI in ESKD, study results call for caution and patient specific clinical decision making when choosing PCI for ESKD patients with SIHD."

Comment 4:
4) Dialysis duration should also be added in Table 2.

Reply 4:
The mean dialysis duration over the study period has now been added to Table 2.

Reviewer C

The topic of this analysis (PCI rates and results in patients with end stage chronic kidney disease) as well as the main findings (decline over time of interventional coronary procedures and increase in both short and long-term mortality) are undoubtledy interesting, even though no answers are given to the obvious questions that these data are prompting .

Comment 1:
There is a progressive increase in number of comorbidities in patients undergoing PCI, but no analysis is performed to account for these risk factors (at least to account for the observed increasing mortality).

Reply 1:
Thank you for your suggestion. Based on this feedback, we conducted additional analysis to account for these risk factors (see Page 7 Line 150). We confirmed for statistical significance in mortality and revascularization trends after adjusting for key clinical variables that showed a consistent increase over the study period – these include age, CHF, COPD, diabetes mellitus, dysrhythmias, liver disease, and cancer.

Adjusted p-valued were estimated as follows:
In-hospital mortality trend– adjusted p <0.0001
30-day mortality trend – adjusted p = 0.0013
1-year mortality trend – adjusted p = 0.0342
1-year repeat revascularization trend – adjusted p = 0.0006.

All outcome trends remained statistically significant after adjusting for the increasing prevalence of co-morbidities described above.

This is added to the text as shown below (see Page 8 Line 180). These findings suggest that the increasing mortality trend is at least in part explained by an increase in comorbidity burden. The retrospective nature of the study and the administrative nature of the database limits the extent to which the impact of additional factors can be assessed. We are unable to comment if an increasing anatomic complexity of coronary artery disease also plays a role in this increasing mortality as the USRDS does not have this information.

Changes in text:
(Page 7 Line 150)
"The Cochran-Armitage test was utilized for trend analysis of the number of PCI procedures and the length of the index hospitalization stay. Logistic regression was performed to identify trends in in-hospital mortality, 30-day mortality, 1-year mortality, and 1-year repeat revascularization rates, adjusting for comorbidities such as age, CHF, COPD, diabetes mellitus, dysrhythmias, liver disease, and cancer."

(Page 8 Line 180)
"These trends remained statistically significant after adjusting for age and other key comorbidities."

Comment 2:
I would suggest to describe the risk profile of patients who died during the early period (years 2010-2013) versus those who died in the late period (2014-2018).

Reply 2:

Table 2 of our manuscript shows a trend of important risk factors, including respective comorbidities and demographics over the study period. However, to address the reviewer's query, we examined patients who died between 2010-2013 and 2014-2018. These comparisons are shown in the table below. Patients who died in 2014-2018 are noted to have a higher Elixhauser Comorbidity Index.

Characteristic	PCI total (n=23115)	PCI patients who died 2010-2013 (n=5468)	PCI patients who died 2014-2018 (n=10546)	p-value
Male sex	13288 (57.5)	3121 (57.1)	5929 (56.2)	0.2995
Race				<.0001
White	14904 (64.5)	3787 (69.3)	6924 (65.7)	
Black	6815 (29.5)	1429 (26.1)	3025 (28.7)	
Asian / Other	1396 (6.0)	252 (4.6)	597 (5.7)	
Mean Age (SD)	65.1 (11.6)	67.2 (11.3)	66.1 (11.3)	<.0001
Age groups				<.0001
<50	2374 (10.3)	408 (7.5)	908 (8.6)	
50-64	8653 (37.4)	1783 (32.6)	3752 (35.6)	
65-79	9789 (42.3)	2544 (46.5)	4746 (45.0)	
≥80	2299 (10.0)	733 (13.4)	1140 (10.8)	
Dialysis duration (years), mean (SD)	3.5 (3.1)	3.4 (2.9)	3.5 (3.1)	0.5652
Dialysis Modality				0.1820
Hemodialysis	21276 (92.0)	5061 (92.6)	9698 (92.0)	
Peritoneal dialysis	1839 (8.0)	407 (7.4)	848 (8.0)	
Comorbid conditions				
CHF	13603 (58.9)	3375 (61.7)	6495 (61.6)	0.8673
COPD	3315 (14.3)	711 (13.0)	1652 (15.7)	<.0001
CVA / TIA	2805 (12.1)	726 (13.3)	1346 (12.8)	0.3580
Cancer	1392 (6.0)	352 (6.4)	691 (6.6)	0.7801
Diabetes Mellitus	17744 (76.8)	4153 (76.0)	8184 (77.6)	0.0184
Dysrhythmia	6488 (28.1)	1574 (28.8)	3295 (31.2)	0.0013
Hypertension	22569 (97.6)	5388 (98.5)	10181 (96.5)	<.0001
Liver disease	600 (2.6)	107 (2.0)	318 (3.0)	<.0001
PVD	6865 (29.7)	1828 (33.4)	3458 (32.8)	0.4132
Elixhauser comorbidity index, mean (SD)	5.2 (1.9)	4.9 (1.8)	5.5 (2.0)	<.0001

Comment 3:
There are important limitations in this analysis. First of all, the authors do not report separate data for cardiovascular and non-cardiovascular mortality. This information is crucial because a large part of mortality in this population is of non-cardiovascular origin , also among patients with ischemic heart disease .

Reply 3:
We did consider including CV mortality when performing our study analyses. However, since the USRDS database has "unknown" or "missing" data of up to 27% on the cause of mortality (reference below), the estimation of CV mortality will be inaccurate and thus we decided to exclude this outcome.

Reference: **https://usrds-adr.niddk.nih.gov/2023/end-stage-renal-disease/6-mortality**

Comment 4:
There is also a lack of important information about the characteristics of PCI procedures accomplished (number of vessels treated, type and number stents deployed, complexity of coronary artery disease), variables that describe the coronary anatomy and have a relevant bearing on cardiovascular mortality. Data on LV function are also missing.

Reply 4:
Unfortunately, given the administrative nature of the database, specific granular data such as the involvement of specific coronary arteries, the number of stents deployed, coronary anatomy, and LV function is not available for analysis. These would have added valuable insight.

Comment 5:
The Discussion is too long and should be shortened (except for limitations that should probably be expanded). In conclusion this paper stirs curiosity and questions, but does not provide answers.

Reply 5:
We agree with the reviewer that there are limitations in the USRS database such as lack of anatomical data for coronary arteries that we cannot overcome. However, this is the largest and a robust database of ESKD patients in the United States and, thus, has served for decades as a useful resource for assessing trends and major outcomes in this patient population. We hope that our study adds meaningfully to the current literature and raises questions that may be answered in the future. We have further expanded our limitation section as suggested (Page 13 Line 284). We were unable to materially shorten the discussion in part to accommodate suggestions made by other reviewers as well.

Changes in text:
(Page 13 Line 284)
"Several unmeasured confounders and important clinical variables, such as the degree of

chest pain and ischemia, left ventricular systolic function, the coronary anatomy, details of PCI performed such as the number and type of stents deployed, the patient's functional status and quality of life, cannot be accounted for or measured"

Reviewer D

Comment 1:
Good study in an important area where evidence is lacking. Authors mentioned the limitations including the administrative nature of the database. You almost wonder if sometimes unstable CAD is labeled as stable CAD in this special patient population.

Reply 1:
Thank you for your review. The ESKD population is definitely a unique patient population group with frequent masked and atypical presentations for CAD. Unfortunately, miscoding is a commonly known error in administrative datasets such as the USRDS – a limitation that the authors recognize and have indicated in the limitations.