Author's response to reviews

Title: Surgical revascularization versus amputation for peripheral vascular disease in dialysis patients: a cohort study

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Version: 4 Date: 12 January 2005

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Responses

Reviewer: Paul Eggers

*The major concern I have is the length of follow-up in the analyses. 30 days (essentially peri-operative mortality) seems to be very short period of time on which to judge the relative merits of one procedure versus another. Did you consider using a one-year follow-up time?*

We thank Dr. Eggers for his thoughtful comments. We added the data on 1-year post procedure mortality in Table 3 of the manuscript and as well as presented it in the table below.

**Table 1. 1-year post-procedure mortality in amputation versus revascularization groups in the entire cohort and subgroups of likelihood of amputation**

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort (n = 3,942)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.67</td>
<td>1.48 – 1.90</td>
</tr>
<tr>
<td>Adjusted**</td>
<td>1.46</td>
<td>1.25 – 1.71</td>
</tr>
<tr>
<td>Subgroup analyses by likelihood for amputation***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low likelihood group (n= 1,314)</td>
<td>1.61</td>
<td>1.14 – 2.26</td>
</tr>
<tr>
<td>Moderate likelihood group (n= 1,314)</td>
<td>1.55</td>
<td>1.22 – 1.96</td>
</tr>
<tr>
<td>High likelihood group (n= 1,314)</td>
<td>1.23</td>
<td>0.92 – 1.63</td>
</tr>
</tbody>
</table>

* reference revascularization group  
** adjusted for propensity scores, demographics (age, sex, race), dialysis modality, comorbid conditions (diabetes, coronary artery disease, congestive heart failure, cerebrovascular disease and malignancy), clinical indications (intermittent claudication, resting pain, ulcer, gangrene or other/unknown), hematocrit, nutritional status (BMI and serum albumin) and functional status (required assistance to transfer or ambulate).  
*** adjusted for all above variables except propensity scores

As seen above, the results are very similar to 30-day mortality. In unadjusted analysis, the amputation group still had 67% higher odds of dying in 1 year compared to the 2 fold higher odds within 30 days of the procedure. When adjusted for propensity scores and clinical variables, amputated group had 46% higher odds of dying within 1 year compared to the 85% higher odds of 30-day mortality. In subgroup analyses by likelihood of undergoing amputation, amputation procedure was associated with the highest odds of dying in 1 year in patients with low likelihood of undergoing amputation, reduced but still significant odds in patients with moderate likelihood of undergoing amputation similar to the 30 day mortality models.
It seems to this reviewer that ‘indication bias’ is still a potential problem with respect to the large percentage difference in gangrene cases. I would feel better if the authors recommendations reflected more caution on this note.

We have added a statement on residual bias in the limitation section (page 14) and have revised our conclusions accordingly to “We conclude that amputation might carry significant morbidity and mortality in dialysis patients compared to revascularization procedures” (page 15).

**Reviewer: Bernard Jaar**

We appreciate Dr.Jaar’s insightful review of our manuscript.

1. **One obvious limitation is the retrospective nature of the study. In that setting, there is significant selection bias. However, to their credit, the authors attempt to address this issue by using a propensity score. In my opinion, it would be important to address the limitations of the study design in the discussion section.**

We agree with Dr.Jaar that the retrospective aspect of our study introduces some amount of selection bias. However, it should be noted that selection bias is a common limitation to all previously published studies of USRDS database. We have added a statement on limitations of using existent databases to perform retrospective analyses (page 15).

2. **The authors use Medicare patients who underwent surgical revascularization or amputation within 6 months of initiation of dialysis. How do they account for patients not yet covered by Medicare, since there is a few months lag time before patients younger than 65 years are covered by Medicare?**

This is an inherent limitation of the USRDS database. We concur with Dr.Jaar that this would introduce some amount of selection bias and have included a statement regarding this issue in the limitations section (page 15).

3. **Peripheral vascular disease (PVD) starts well before the initiation of dialysis and many patients undergo PVD-related procedures before state of dialysis. How did the authors account for these procedures before initiation of dialysis? For example, it is possible that a patient had a revascularization for PVD before starting dialysis and a few months later while on dialysis they undergo a major amputation. I believe the authors should clarify this point.**

Similarly, this is a major shortcoming in the database. We have mentioned the lack of data on pre-dialysis PVD-related procedures in the methods section.

4. **Another limitation of the study is the use of the Medical Evidence (Form 2728) form. This form has limited sensitivity although high specificity. Again the authors should address this issue in their limitation.**
We are grateful for the reference and have added it to the limitation section (page 15).

5. *There is a risk of misclassification by using the ICD-9 codes. Procedure code 39.29 is also used for dialysis access. How did the authors differentiate between PVD and dialysis access procedures? I concur that 39.25 mostly represent PVD-related revascularization.*

As procedure code 39.25 might have included upper limb revascularization procedures, we repeated the analyses with including only procedure code 39.29 (proximal bypass procedures involving the aorta-iliac-femoral-popliteal vessels) in sensitivity analyses and the results were the same.

6. *I would suggest testing for interaction by race, diabetes mellitus status. It had been reported that African-American were more likely to undergo amputation for example.*

We concur with the reviewer that African-Americans and Diabetics are at increased risk of amputation. As shown in table 2, African-Americans had 52% higher odds of amputation compared to Caucasians and diabetics had 66% higher odds of amputation.

7. *How do the authors explain the increased risk of death in the “healthier” patients?*

The “healthier” patients mentioned in paragraph 1 of page 13 refers to the patients with low or moderate likelihood of amputation. Our results indicate that when patients with low likelihood of amputation undergo amputation instead of revascularization, there is an increased risk of death within 30 days and 1 year associated with amputation.

8. *The authors could present the number procedures by ICD-9 codes. How may had a code 39.25 versus 39.29?*

We have included these numbers in the results section (page 10 second paragraph).

9. *One suggestion would be to look at specific cause of death. Is there more cardiovascular death after amputation versus revascularization?*

This is an interesting issue raised by the reviewer. When we analyzed cardiovascular causes of death, 323 (8.2%) patients died within 30 days of procedure and 1,231 (31.2%) died within 1 year of procedure due to cardiovascular causes. The following table shows the odds of post-operative cardiovascular mortality –

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day mortality Unadjusted</td>
<td>2.07</td>
<td>1.62 – 2.63</td>
</tr>
</tbody>
</table>

**Table 2. Post-procedure cardiovascular mortality in amputation versus revascularization groups**
As shown above, the odds of post-operative cardiovascular mortality were higher in patients with amputation compared to revascularization.

10. If possible, the authors should consider other confounders in their analyses, such as: facility characteristic. Are large medical centers more likely to do better after amputation or revascularization because of the large volume of cases, their expertise? What about regional (geographic) variations?

We agree with the reviewer that variations in amputation by facility characteristics and geographic locations will be interesting to study. We plan to address these in future studies.