Author’s response to reviews

Title: Risk of Venous Thromboembolism after Total Hip and Knee Replacement in Older Adults with Comorbidity and Co-occurring Comorbidities in the Nationwide Inpatient Sample (2003-2006)

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Author’s response to reviews: see over
Editorial Requests:

- Authors' contributions - Please include an Authors' contributions section before the Acknowledgements and Reference list.

For the Authors' contributions we suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

An "author" is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; and 3) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

We have included an author’s contributions section in the revised manuscript. This revision can be found on Page 14.

Author’s Contributions
AK  design, analysis, interpretation, and manuscript write-up
AL  design, analysis, interpretation, and manuscript write-up
MW  analysis and interpretation
JBS interpretation and manuscript write-up
RAS  design, interpretation, and manuscript write-up
EL  design, interpretation, and manuscript write-up
JNK  design, interpretation, manuscript write-up
DB  design, interpretation, and manuscript write-up

Please include the statement on ethics made in your previous cover letter in the methods section of your revised manuscript.

Can you specify for us which of the statements you would like us to retain in the methods, that about not infringing upon any existing copyrights or that about this work not being published elsewhere.
Reviewer 1. Major revisions

Global Response to Reviewer Critique
We would like to thank the reviewer for bringing his / her concerns to our attention. First, we would like to respond by reiterating that the analysis we performed was an administrative data analysis. The administrative data for which we had access, the Nationwide Inpatient Sample (2003-2006), includes primary and secondary diagnosis codes, procedures, patient demographics (gender, age, race, median income, and residence zip code), and hospital characteristics (ownership, size, and teaching status). It does not contain information about medications prescribed and lab tests ordered. To create comorbidities, which we analyzed, we used ICD-9-CM diagnosis codes which have been previously identified by Elixhauser et al [1]. The limitations of our data are offset by the strength of their numbers (more than 300,000 surgical admissions) and the representativeness of the sample (one fifth of all discharges in the U.S. comprising 39 states). The numbers permit measurement of the association between comorbidities and a relatively uncommon but deadly disease such as postoperative venous thromboembolism.

Specific Responses to Reviewer Critique

(1) The quality of this paper is directly related to the quality of the record of the comorbid disease. The exhaustivity of the comorbidity recorded in the NSI is questionable. For example, a prevalence of 0.6 for cerebrovascular disease and 1.2 for congestive heart failure in elderly patients are much below the real prevalence of these diseases in elderly patients receiving orthopedic surgery. How did this information were collected? How was the exhaustivity for the search for these comorbid diseases?

We thank the reviewer for raising these concerns. We decided to group comorbidity exposures into exclusive categories in order to compare each against a common reference population, that is, the group without any of the comorbidities we studied. As such, the population of individuals with CVD alone or CHF alone appears relatively small. In addition, the patients selected for surgery represent a healthier cohort. This issue is discussed more fully in our response to item #5. Overall (including those with condition alone as well as those with it in conjunction with other comorbidities), the range of frequencies of CVD and CHF over the range of frequencies in the hip and knee populations, was 1.3-1.4% and 3.8-4.0% respectively.

On page 7 paragraph 1, we have highlighted the analysis choice:
We created a ten level categorical variable with a separate, mutually exclusive, level for each of nine comorbidities or co-occurring comorbidities (with 1 additional for all other combinations of two or more comorbidities). While this limited the population size for each comorbidity group, it allowed us to compare the risk of VTE for groups of older adults with single or co-occurring comorbidities against a common reference group of older adults without any of the nine comorbidities.
(2) The quality of the results is clearly related to the quality of the capture of the rate of VTE. It is necessary to know how this VTE was diagnosed, how much were symptomatic? How many centers made systematic echography before discharge?

The reviewer identifies an important issue and limitation of administrative data. As mentioned earlier, outcomes were defined by presence of ICD-9 diagnosis codes for VTE. Identification of the outcome is subject to an ascertainment bias where not every event is captured by medical coders. We believe, however, that the direction of this ascertainment bias is non-differential. That is, events identified in individuals with comorbidities and those without comorbidities should occur at the same rate. In a national survey [2], orthopedic surgeons reported changing their prescribing patterns fewer than 10% of the time. We do not, therefore, believe that surgeons are more likely to order diagnostic imaging in individuals with comorbidities and, consequently, believe that the effects estimates that we measured are an accurate representation of the association between comorbidities and postoperative VTE.

Our data does not contain information about surveillance echography for the detection of DVT.

On page 11 paragraph 2 we have enhanced our description of the limitation and ascertainment bias issue to include these thoughts: *There are limitations to the work we presented. Due to the nature of the NIS administrative data we have limited ability to capture VTE. A recent study [3], suggests that administrative data capture only 58% of the VTE events. There is no evidence, however, to suggest that the events identified are differentially being diagnosed in individuals with CHF or other comorbidities.*

(3) We do not have any information about VTE appearing after discharge. Medium length of stay was three to four days but the majority of the VTE appear later. How many patients have been re-hospitalized for VTE in the three months after the orthopedic surgery?

The reviewer identifies an important limitation with our data. We do not have information about the events which take place after discharge. Unfortunately, this is an inherent limitation of discharge data such as the NIS dataset. As before, however, we believe the bias in ascertainment to be non-differential. VTE events identified in the group with comorbidities and the group without would occur at roughly the same rate in the hospital and post discharge periods. We acknowledge that the relationships we detected should be confirmed in data with longer follow up available.

On page 12 paragraph 2, we highlight the limitation and our recommendation for confirmation of our findings with alternate data: *We did not have information about events which took place after hospitalization. Given that the median time for development of DVT is 17 days for THR and 7 days for TKR [4]*
and the median length of stay was 3 or 4 days for each surgery in our analysis, the associations we present may not reflect the experience of older adults who develop injury in the post discharge period. Controlling for length of stay would not disentangle the relation between these comorbidities and VTE and we, therefore, did not control for it in our analysis. Length of stay may very well be a surrogate for immobility and stasis which is on the causal pathway of VTE development. Alternatively, increased length of stay may also be associated with VTE because of added time needed to achieve therapeutic levels of warfarin. Even though NIS data does not allow for measurement of the 30 or 90 day incidence of VTE, we believe that post discharge rates of VTE events will be similar for both the groups of individuals with and without comorbidities. In the future, we plan to confirm these associations in data where this information is available.

(4) The results are questionable probably due to a lack of power related to the multiple analysis. In comparison with literature, how could the authors explain a lower risk of VTE in patients with diabetes or cerebrovascular disease compared to patients with no comorbidity

The reviewer suggests that the seemingly paradoxical relationships between CVD or diabetes and postoperative VTE may be related to the lack of sufficient sample to accurately measure the association with VTE. Previous work [5] has suggested that diabetes is associated with a protective effect (OR=0.75 95% CI 0.63 to 0.93). There has been less in the literature about the relationship between CVD and postoperative VTE. As the relationship was not found in both hip and knee cohorts, was of relatively small magnitude (29% reduction in the odds) and was not statistically significant, we defer drawing any firm conclusions.

Starting on page 9 paragraph 2 and continuing to page 10 we highlight the associations we found and the inability to draw any firm conclusions:

After controlling for multiple preoperative and postoperative clinical variables, a multivariate analysis with 76,771 individuals showed that CHF and COPD were not associated with increased rates of VTE. This study supported our findings of the association between diabetes and a slightly lower rate of VTE (OR = 0.75). We also detected a 29% reduction in the risk of VTE in patients undergoing THR with CVD. This result was not statistically significant nor did we detect an association in the knee population. There has been little evidence, however, regarding the relationship between CVD and postoperative VTE. Prior work[6] has suggested a common inflammatory pathway but this has not been evaluated extensively in the postoperative setting. In our study the association was not present for both knee and hip cohorts and was not statistically significant. We plan to re-assess the relationship between CVD and postoperative VTE in our future work.

(5) Why is the risk in case of congestive heart failure lower when this congestive heart failure is associated with coronary artery disease?
We believe that we detected a selection bias where only a healthier subset of older adults with co-occurring comorbidities were selected for surgery compared with a larger pool of patients with CHF alone. The healthier subset of individuals with co-occurring comorbidities likely has a higher functional status than individuals not selected for surgery. In future work we intend to adjust for functional status in data which contains this information in order to validate our contention.

On page 10 paragraph 2 we elaborate our interpretation of this result:

*The association of CHF and VTE may relate to blood flow stasis as discussed earlier. Alternatively, CHF may indicate a degree of immobility that was not measured in the data we analyzed. Other comorbidities may also contribute to the development of postoperative VTE but their effects may have been attenuated by a selection bias. Surgeons may select only the healthiest subset of older adults with comorbidities for surgery. The absence of positive interactions between frequently co-occurring comorbidities (especially CAD and CHF) also suggests a selection bias. Older adults with co-occurring comorbidities deemed to be suitable surgical candidates are presumably healthier in other ways than other older adults with the same comorbidities.*

(6) Why some very well-known risk factors like COPD increase the risk of VTE after knee surgery but not after hip surgery?

We hypothesize that COPD is a weaker predictor of VTE compared with CHF. We only detected this effect in the knee cohort. It is unclear what the interaction between COPD and knee surgery might be. Factors such as postoperative mobility may be higher in the case of knee surgery and therefore the effects of other factors like COPD may be detectable in a population with fewer competing risks. Further evaluation with data in which patient mobility is available will help better understand the independent effect of COPD.

Page 10 paragraph 3:

*In the case of COPD, we only detected an increase in risk for older adults undergoing knee surgery. This could be explained by the generally weak predictor effect of COPD on VTE or it could be related to the inherent differences between hip and knee surgery. Postoperative mobility may be significantly less for hip surgery and the effect of immobility in this group may dwarf other predictors such as COPD. Future work should examine the interaction between mobility and surgery type in data where this information is available.*

(7) Why is the age a risk factor after hip surgery but not knee surgery? All these results are in opposition with the previous literature.
The effect in the hip population aged 80 and above is still relatively small (30% increase in the odds). We therefore defer attributing any biological explanation for an interaction between age and surgery type. Although age has historically been considered a predictor of VTE in the general medical setting, we identified several papers [7-10] in the postoperative setting in which it was a major predictor. This is one of the critical lesions we have learned working in this area. Age alone is not a major predictor of postoperative VTE but associated comorbidities contribute substantially.[5, 11, 12] The relative risk / odds ratio estimates for age span the range of 1.3 to 2.6. By comparison, those for comorbidities (save for diabetes) span a range of not being significant in Schiff et al.[8] to odds ratios of 7.7 for previous acute myocardial infarction in Kikura et al[11]

(8) More precise results are needed: in table 1, we need to know the frequency of the comorbid diseases for each different group of age. In table 2, we need the absolute number of events (VTE).

In light of the reviewer’s request, we have created a new table. The new Table 2 contains the frequency of comorbid disease by age group and procedure. The new table Table 3 includes the absolute number of events (VTE = yes and VTE = no) in addition to the adjusted odds ratios.

Reviewer 1. Minor revisions

(1) It is important to know how many patients receive a prophylaxis for a deep vein thrombosis prevention in the whole population, in the population with comorbidity, in the population with comorbidity and VTE.

Medication information including prophylaxis chosen in each surgery is not available in NIS. In the previously mentioned survey by Markel et al[2], prophylaxis choice by orthopedic surgeon varied less than 10% of the time based on cardiopulmonary comorbidities.

We discuss the limitation on page 9 paragraph 3:
In addition, we did not have access to medication information including prophylaxis agent. A recent study by Cohen et al. in 2008[13] indicated that in the United States, only 48% of medical patients are receiving the recommended ACCP prophylaxis and only 71% of surgical patients are receiving prophylaxis [13]. If comorbidities prompted physicians to prescribe more potent prophylaxis in older adults with CHF or other comorbidities, however, the effects we observed would represent an underestimate of the true effect.

(2) Why did comorbidities considered in this paper were limited to coronary artery disease, congestive heart failure, COPD, diabetes and cerebrovascular disease?
We chose the comorbidities which have been previously identified in the literature and also by the expertise of our co-authors. These variables also comprised those for which for which icd-9 codes have previously been assessed and felt to be accurate compared with chart abstraction [14]. The majority of these are cardiopulmonary comorbidities as identified by the reviewer. Based on later suggestions we also examined chronic kidney disease, cancer, and other hypercoagulable states as potential confounders of the main associations which we examined. As none of these other health conditions changed our main effects significantly, we do not present their effects in the results.

On page 6 paragraphs 1 and 2 we discuss our approach and enhance the write-up of how we chose the variables which we did:

We included specific comorbidities based on evidence of associations with VTE documented in the literature or a known biological link to the outcomes. These included CAD, CHF, COPD, CVD, and diabetes. Comorbidities and presence of obesity were coded as by Elixhauser et al. (Appendix II). Multiple publications [15-17] have supported the use of the Elixhauser comorbidity coding algorithms rather than the earlier Charlson comorbidity index, including those looking at discrete surgical procedures [18, 19]. The accuracy of coding of the comorbidities has been validated in multiple publications [20, 21].

Consistent with previous work [14, 15, 23], we evaluated the effects of potentially confounding factors, i.e. race, insurance status, hospital surgical volume, obesity, bilaterality (two primary procedures during the same surgery), chronic kidney disease, and hypercoagulable state (including cancer and genetic predisposition), by adding them, one at a time, to the crude model (with comorbidity exposure, age group, and sex). If the addition of a given factor did not change the odds ratios for the comorbidity exposure by more than 10%, it was deleted from the final model.

COPD and congestive heart failure are already well-known as risk factors for VTE. Arterial diseases are not. Then the results in table 2 are clearly in relation with the previous data and this paper does not add any new epidemiological information.

The reviewer is correct in iterating that our analysis confirmed the relationship between CHF and COPD with VTE. We did not find an association with arterial disease but reports have conflicted. At least one report [11] demonstrated an association in the postoperative setting and other recent accounts in non-surgical settings have shown atherosclerosis to be a predictor of venous thromboembolism sparking our interest in the analysis we performed. We improve upon previous measurements in the literature by analyzing more than 300,000 surgeries affording us the ability to examine the risk associated with relatively uncommon but important combinations of comorbidities in older adults. Our work has also helped elucidate a path for future work which will allow us to hone the relationships we found and diminish the uncertainties related to absence of follow up, medication, and functional status information.
The ENDORSE study published by Alexander Cohen (Lancet 2008; 371: 387-94) has to be discussed and to be listed in the references. The ENDORSE Study is discussed in the revised manuscript and has been added as a reference on page 11 paragraph 3. A recent study by Cohen et al. in 2008[13] indicated that in the United States, only 48% of medical patients are receiving the recommended ACCP prophylaxis and only 71% of surgical patients are receiving prophylaxis [13].

On page 9, the number of patients included in the study by Gangireddy and by Kikura has to be given. We have added the requested data from Gangireddy (page 9 paragraph 2) and Kikura (page 10 paragraph 2). Gangireddy et al. [5] conducted one of the largest studies to date using data from the Veterans Affairs National Surgical Quality Improvement Program (NSQIP), which included veterans undergoing nine different surgeries, including THR, between 1996 and 2001. After controlling for multiple preoperative and postoperative clinical variables, a multivariate analysis with 76,771 individuals showed that CHF and COPD were not associated with increased rates of VTE. Kikura et al. [11] examined 21,903 Japanese patients of multiple ages and multiple surgery types and found that history of acute myocardial infarction (AMI) was significantly related (OR = 7.7, 95%CI 1.7-34.7) to the development of postoperative thrombotic events (including repeat AMI).

The title of this study might be more informative, saying that only cardiovascular comorbidity were studied. We appreciate the reviewer’s intention to more precisely describe the comorbidities which we analyzed. Our main analysis, however, also looked at CVD and diabetes. Moreover, we also examined the role of chronic kidney disease, cancer, and hypercoagulable state; although none materially changes the main effects, we feel the restriction in the title would undersell the scope of our analysis and efforts.

Reviewer 2.

Minor comments: abbreviations in the Tables should be explicited. We have revised Table 1 to include explicit names for the comorbidities. In Tables 2 and 3 we have used abbreviations but have listed them explicitly in the legends.
References


