Author's response to reviews

Title: Changes in Healthcare Utilization and Costs After Beginning Sildenafil for Pulmonary Arterial Hypertension: A Retrospective Cohort Study

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Author's response to reviews: see over
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Mr. Timothy Shipley  
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Dear Mr. Shipley:

Thank you for your interest in our manuscript (MS 1949043407491188, "Changes in Healthcare Utilization and Costs After Beginning Sildenafil for Pulmonary Arterial Hypertension: A Retrospective Cohort Study"). We revised our paper based on the comments we received from the reviewers, as described below.

Reviewer 1: Zhi-Cheng Jing

1. The acronym PAH is not used correctly. ICD-9-CM diagnosis code 416.0 and 416.8 are primary pulmonary hypertension and other chronic pulmonary heart diseases (secondary). Pulmonary hypertension is currently classified into 5 groups (Simonneau G, J Am Coll Cardiol 2009 Jun 30;54(1 Suppl):S43-54.). The use of the most recent and accepted classification will add clarity to the study. And comorbidities in Table 2 should be divided into comorbidities (such as anxiety and atrial fibrillation) and Group of PH (PAH, Group 2 and so on).

   Per the reviewer’s request, we modified the text in the Introduction to include information from the most recent classifications for pulmonary hypertension (i.e., Venice clinical classification [Simonneau 2004], Dana Point classification [Simonneau 2009], guidelines from the European Society of Cardiology and European Respiratory Society [Galie 2009]). We also added language to the Introduction, Methods, and Discussion to clarify the distinction between recent and accepted classifications of pulmonary hypertension and the limitations of our study due to our reliance on outdated ICD-9-CM diagnosis codes for pulmonary hypertension. While we believe that the majority of our study subjects had PAH due to their receipt of sildenafil (which is indicated for PAH, but not Groups 2-5 pulmonary hypertension), we acknowledge that a substantial proportion of study patients may have had non-PAH pulmonary hypertension. In our Discussion, we address the possible impact of including such patients in our analysis.

   Based on our assumption that our case-ascertainment algorithm (i.e., receipt of sildenafil, ≥2 outpatient claims ≥30 days apart [or 1 inpatient claim] with diagnoses of pulmonary hypertension) had high specificity for PAH, and that ICD-9-CM diagnosis codes available at the time our study was conducted cannot...
differentiate between different types of pulmonary hypertension (e.g., Group 1, Group 2), we have not revised Table 2 to display the prevalence of various comorbidities by pulmonary hypertension group.


2. Method, study sample section and results paragraph 1: had all patients done the RHC and have a clear diagnosis? I’m so confused why 86% patients had claims for both primary and secondary pulmonary hypertension. Because of uncertained-diagnosis?

The database does not contain clinical information that one would expect to be found in medical records of patients with PAH, such as 6-minute walk distance and the results of right-heart catheterization (if performed). We therefore had to use case-ascertainment algorithms that relied on information available in health insurance databases (i.e., ICD-9-CM diagnosis codes, prescription dispenses of sildenafil).

3. Results, paragraph 2: The use of PAH-related medications, except for sildenafil, was significant difference between pretreatment and follow-up. Which indicated the reductions in healthcare costs could not be directly attributed to sildenafil. Bosentan, iloprost could also improve 6 MWD and symptom of PAH patients. They treatment effect may also reduce the cost of healthcare. It may difficult to get the conclusion: the cost of sildenafil therapy appears to be partially offset by reduction in other healthcare.

This point is well taken. We now acknowledge in our Discussion additional possible explanations for observed cost offsets (e.g., other PAH-specific therapies received).

4. Results section: did you divided those subjects into subgroup. Were there any differences in the healthcare utilization between severe and non-severe patient, and among PAH, PH Group 2 and PH Group 3?

As noted above (see our response to Comment #1), the database lacked information that would be needed to subdivide patients into meaningful subgroups. Moreover, as we mention in the second sentence of our Results section, 86% of study patients had claims with diagnostic codes for both primary and secondary pulmonary hypertension.

5. Discussion section: the authors discussion was short and did not thoroughly analysis the result. The emphasized two limitations, but did not analysis why total healthcare costs increased among patient with PAH following initiation of sildenafil therapy and how do you find the cost of such therapy appears to be partially offset by reduction in other healthcare costs.

Per the reviewer’s suggestion, we expanded our Discussion section to: (1) provide further explanation of our findings; (2) explain why we would have expected healthcare costs (exclusive of the costs of sildenafil and
other PAH-related medications) to increase over time; and (3) further explain what we mean by a partial offset of healthcare costs.

6. Method, measures and analysis section, paragraph 2: CCB could be also for coronary artery disease, so

In addition to CCBs, which could be used for hypertension or coronary artery disease, several of the other medications we examined also could have been prescribed for indications other than for PAH. We now make note of this in our Methods section. We thought it was important to include not only those medications that are specifically indicated for PAH, but also other medications that might have been prescribed for PAH, and then examine changes in their use/costs between pre-treatment and follow-up. As it turned out, there was little change in the costs of these non-specific medications, while changes in the costs of PAH-specific medications were substantial (Table).

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pre-Index</th>
<th>Post-Index</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH-specific medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase type-5 inhibitors</td>
<td>2 (0, 4)</td>
<td>5236 (4963, 5510)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prostaglandin/prostacyclin analogues</td>
<td>1569 (934, 2204)</td>
<td>2271 (1574, 2969)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>4686 (4009, 5363)</td>
<td>5613 (4867, 6359)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Medications with other uses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>79 (66, 92)</td>
<td>71 (59, 83)</td>
<td>0.14</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>31 (26, 36)</td>
<td>41 (35, 47)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diuretics</td>
<td>61 (52, 71)</td>
<td>75 (64, 87)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>4 (3, 5)</td>
<td>5 (4, 6)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Unless otherwise noted, all values are mean (95% CI) costs ($); all information is set forth in Table 4 of the manuscript.

7. The author used the ratio of a patient’s total healthcare costs during pretreatment to mean total pretreatment healthcare costs as a proxy for disease severity, but there was no relative result.

Because we did not use this ratio in any of our analyses, we have omitted the sentence concerning this measure from our Methods section. We apologize for this oversight.

8. Healthcare utilization may also be influenced by Coverage type and the reimbursement. High cost and low reimbursement rate may also reduce the healthcare utilization. If the database contain the relative information, it better to show.

We agree that plan type (e.g., health maintenance organization) and reimbursement structure (e.g., copays, co-insurance) can influence both the utilization and costs of healthcare services. Unfortunately, the database does not contain health plan identifiers, so we could not to stratify/adjust for these potentially important confounders. On the other hand, given our study design (i.e., each patient served as his/her own “control”), we believe that the impact of these considerations on our findings is probably minimal (i.e., while they would undoubtedly influence overall levels of healthcare utilization and cost, we think their
impact on changes in these measures between pre-treatment and follow-up is probably much less). No further action has been taken on this comment.

Reviewer 2: Qayyim Said

1. Background: The description of clinical classification of pulmonary hypertension seems confusing. The authors refer to WHO classification. However, the WHO classification was updated by more recent classifications (Venice classification 2003, and Dana Point classification 2009). It is not clear why there was no mention of these more recent clinical classifications, and why these classifications were not used by the authors. As an example, please see: “Simonneau G, et al. Clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol 2004, 43:5S-12S”.

As noted above (please see response to Comment #1 by Reviewer #1), differences between recent classifications of pulmonary hypertension and the outdated ICD-9-CM diagnosis codes available to us are now more thoroughly discussed throughout the paper; problems of interpretation posed by our use of ICD-9-CM diagnosis codes also are more fully discussed throughout the manuscript.

2. Study sample was identified by PAH diagnosis the date of first claim for Revatio was designated as index date. However, it was not made clear if the index date occurred after the diagnosis for PAH, and if so, how was it made sure that it did indeed occur after PAH diagnosis. I would suggest authors included a schematic figure using a timeline to show when each of the event occurred.

Given that Revatio is indicated only for PAH, we assumed that its use would be limited to patients with confirmed PAH. Accordingly, we did not require that one of the “mandatory” claims with a PAH diagnosis (i.e., ≥2 outpatient claims, ≥1 inpatient claims) occur prior to initiation of Revatio. We have not added a schematic along the lines suggested, as we do not believe that it would help to shed light on our sample-selection algorithm. We have, however, added text to our Sample Selection section to more fully explain our methods.

3. Patients who received Viagra in the post-treatment period were excluded. However, it appears that those receiving Viagra in the follow-up period were not excluded. If that is the case then some of the benefit of reduction in resource utilization can be attributed to Viagra as well. Please clarify this point.

We now explain in our Methods section that patients receiving Viagra in the follow-up period were not excluded, and we note in our Results section that this was a rare occurrence.

4. The pretreatment and follow-up period were restricted to 6 months only. PAH being a progressive, it might be better to have 12 months of follow-up period.

While we agree that use of a 12-month follow-up period would have provided additional insight into relatively long-term patterns of healthcare utilization and cost following initiation of Revatio for PAH, we opted for the shorter 6-month period for two principal reasons—it increased our sample size substantially, and also seemed to us a more plausible time period over which to examine the impact of Revatio on
patterns of healthcare utilization and cost, which we presumed to be more proximal to the initiation of such therapy. No further action has been taken on this comment.

5. While identifying co-morbidities, the authors imposed the restriction of two or more outpatient claims at least 30 days apart. This restriction of two claims instead of one may have led to under-identifying of comorbid conditions. Common practice in such studies is to just look for one claim for identifying comorbidities. Please explain why this restriction was imposed.

We respectfully disagree with the reviewer on this point. ICD-9-CM diagnosis codes in administrative databases sometimes can be wrong due to coding errors—and more important, often are (incorrectly) used when a test is ordered to rule out a particular disease (Fisher 1992, Jollis 1993, Quam 1993). While use of a single claim only might increase sensitivity, we think it would have a deleterious effect on specificity as a result of misclassification. No further action has been taken on this comment.


6. One major limitation of the study is that it does not have a control group. Having a control group would have allowed a more rigorous difference-in-difference analysis. Please include this point as a limitation.

We agree that a cohort of patients who did not initiate therapy with Revatio might have been included. Such a comparison, however, undoubtedly would be subject to confounding by indication and possibly other factors. Without effective control for these potential sources of confounding, we would not be able to determine if observed differences were attributable to Revatio or uncontrolled confounders. Regardless, we have added text to our Discussion section describing this limitation.

We thank you again for your interest in our manuscript. Please feel free to contact me if you have any additional questions or concerns. My colleagues and I look forward to hearing from you soon.

Sincerely,

Ariel Berger, M.P.H.