Author’s response to reviews

Title: Cardiac Valvular Abnormalities Associated with Use and Cumulative Exposure of Cabergoline for Hyperprolactinemia: The CATCH Study

Authors:

Amer Budayr (drbudayr.endocrine@gmail.com)

Thida Tan (thida.x.tan@kp.org)

Joan Lo (joan.c.lo@kp.org)

Jonathan Zaroff (jonathan.g.zaroff@kp.org)

Grace Tabada (grace.h.tabada@kp.org)

Jingrong Yang (jingrong.yang@kp.org)

Alan Go (alan.s.go@kp.org)

Version: 1 Date: 11 Jul 2019

Author’s response to reviews:

July 10, 2019

RE: BEND-D-19-00135: “Cardiac Valvular Abnormalities Associated with Use and Cumulative Exposure of Cabergoline for Hyperprolactinemia: The CATCH Study”

Dear Dr. Glynn,

Thank you for the opportunity to submit a response to the Editors and Reviewers, along with our revised manuscript titled, "Cardiac Valvular Abnormalities Associated with Use and Cumulative Exposure of Cabergoline for Hyperprolactinemia: The CATCH Study" (BEND-D-19-00135).

We appreciate the careful review, and we believe the revised manuscript has been strengthened. Thank you for your ongoing publication consideration for BMC Endocrine Disorders.

As per your instructions, we provide a point-by-point response letter that provides a detailed response to each point raised and as appropriate, describing the changes that have been made to the manuscript text and its location using page numbers and continuous page numbers (e.g. Methods section [pg 12 line 5]). We have also uploaded both clean and tracked changes versions of the manuscript.

None of the findings have been previously published and are not being considered for publication elsewhere, in whole or in part. As noted in our submission, all disclosures have been provided, as relevant.
Please do not hesitate to contact me with any additional questions or clarification at Alan.S.Go@kp.org or 510-821-0904.

With best regards,

Alan S. Go, M.D.
Division of Research
Kaiser Permanente Northern California

Editor Technical Comments

1. This study makes an interesting contribution to a controversial area in pituitary endocrinology. However, I do not believe the statistical results support the conclusions – please see the comments of myself and the Reviewer.

We appreciate the comments from the Editor and Statistical Reviewer, and we have clarified our comments in the Abstract (pg 4, line 3-5) and Discussion (pg 13, line 12; pg 14, line 14; pg 15 line 13-15) to emphasize more clearly that we found primarily mild valvular disease.

In addition, we have made clearer results of our analyses examining the association of different dopamine agonist therapies with regurgitation in either ≥1 valve or ≥2 valves, which is a unique strength of our study.

2. In addition, if you wish to resubmit the manuscript for further consideration, I would ask that you separate out those with trivial/mild from those with moderate/severe valve regurgitation for statistical analysis. This will provide a more clinically meaningful analysis for the reader.

Given previous studies have examined “any valvular disease” as an outcome, that was one of our pre-specified outcomes for the study, as we were interested in both ≥1 valve and ≥2 valve abnormalities. However, as noted by the Editor and Reviewers, we only had a single case of moderate or severe valve regurgitation, so we have repeated our analyses excluding this case and reported the findings of this sensitivity analysis in our revised Results section (pg 13, line 1-3), which showed that our results were not materially changed. We have also made a clearer distinction between results for regurgitation for ≥1 valve and regurgitation for ≥2 valves (pg 11-12). As noted above in response #1 to the Editor Technical Comments, we have revised our Abstract and Discussion section accordingly as well.

Editorial comments

1. Abstract: Methods – This is a cross-sectional study; in fact some of the echocardiographic data is retrospective

We thank the Editor for asking about the echocardiographic data collection timeline in respect to when
participants were enrolled into the study. We wish to clarify that this is a cross-sectional study but that all participants except for one had echocardiograms performed at or shortly after the time of enrollment. This has been clarified in the revised Methods section (pg 3, line 7-9).

2. Abstract: Results – why is median cabergoline use presented as a range?

We thank the Editor for this question. The median cabergoline use is presented as a range because we were describing the median use among two sets of participants: (1) cabergoline only patients (median = 2.8 years) and (2) patients exposed to both cabergoline and bromocriptine (median = 3.2 years). We recognize this can be confusing, so we have revised the text to say (pg 3, line 12-13):

“Median cabergoline use was 2.8 years in cabergoline only users and 3.2 years for those exposed to both cabergoline and bromocriptine…”

3. Abstract: Main text - The study was conducted in 2006/2007 – is there a reason that the authors have delayed presentation of the data for over a decade? Is any follow-up data now available for these patients?

We appreciate the Editor’s comment and agree that there has been a delay in publication of these data. To be fully transparent, there were several previous attempts to publish the findings and then the first author retired from our institution, which further contributed to the delay in trying to publish the study results. Funding for this project ended many years ago so we are unable to provide any new follow-up data on these participants. Having said that, however, we believe that there is strong internal validity within this diverse, non-referral, community-based population, and neither the medications nor inclusion criteria for the target population we enrolled have materially changed since we conducted the study, so they remaining applicable to current standard of care choices.

4. Page 7, line 38 – rephrase – “treated with”

This has been done.

5. Page 8, line 42 – “absence of a pharmacy benefit” What does his mean?

We would like to clarify that our participants were all receiving care within an integrated, capitated insurance model healthcare delivery system in the U.S. In this system, a small percentage of members have insurance plans that do not include a pharmacy benefit which means that they are much less financially incentivized to get their prescription medications from a Kaiser Permanente-owned pharmacy. This would affect our ability to capture comprehensive information on cabergoline and bromocriptine exposure. Therefore, we needed to exclude them from the study. This has been clarified further in the revised Methods section (pg 8, line 19-20).
6. Page 10, line 11: What percentage of the echocardiograms were retrospectively analysed? Why were these performed if the patients were “asymptomatic”

We agree with the Editor about making the timing of echocardiogram ascertainment clearer and the purpose of these tests. First, these were done as research protocol-driven echocardiograms unrelated to the presence or absence of symptoms to avoid ascertainment bias by only looking at patients who may have valvular-related symptoms. Second, nearly all echocardiograms were performed at the time of the study visit, with only one participant having it performed shortly after the study visit and only one participant for whom an adequately performed echocardiogram conducted recently before a study visit was used. In both of the latter two participants, all echocardiograms were read and analyzed together with those ascertained at the study visit by the reader blinded to medication exposure status. This has been clarified in the revised Methods section (pg 10, line 6-9).

7. Page 10, line 20 – What do the authors define as a statistically significant result from Wilcoxon rank sum or chi-squared tests?

A two-sided P value <0.05 was considered significant. We have clarified this in revised Methods section (pg 10, line 12-13).

8. Page 10, line 58 – why is median presented as a range? The median should be presented and the range in parentheses.

We apologize for any confusion. As noted in response #2 to the Editor’s comments, we initially presented median drug exposure as a range because it differed between cabergoline only patients and patients using both cabergoline and bromocriptine. We have now clarified this in the revised Results section (pg 11, line 6-7):

“…median use ranged from 2.8 for cabergoline only users and 3.2 years for those exposed to both cabergoline and bromocriptine;…”

9. The study has no control group which was not exposed to dopamine agonist. This is a major limitation and should be included in the discussion.

While we appreciate the Editor’s comment, the purpose of the study was to determine whether there were differences between patients with hyperprolactinemia who received different treatment options to avoid the potential bias in prior studies given that patients with hyperprolactinemia may have an underlying differential risk of valvular disease regardless of treatment. However, we have added the lack of an unexposed group of hyperprolactinemic patients as a limitation in the revised Discussion section (pg 15, line 13-15).

10. Did any patients have hypertension, a major risk factor for valvular heart disease? Could this have been a confounder?

We appreciate this comment and have now reported on the presence of high blood pressure at the time of the study visit between groups in the revised Table 1 (pg 21) which showed that there were no
significant differences in prevalent high blood pressure between exposure groups. We unfortunately did not collect data on diagnosed hypertension or receipt of antihypertensive medication at the study visit.

Reviewer Comments

Lucio Vilar (Reviewer 1)

There were no comments to respond to for this Reviewer.

Craig Stiles (Reviewer 2)

1. Abstract - echos - mentions 'readings were blinded to type therapy used' does this mean blinded to DA therapy full stop, or blinded to choice between CBG or BC?

We appreciate the opportunity to clarify in the Abstract that the echocardiographer was blinded to the choice and duration of exposure of therapy. We have described this more precisely in the revised Methods section (pg 3, line 8-9).

2. Median cumulative CBG exposure is small (115mg) compared to other studies, exposure time is short at median 2.8-3.2 years

We agree that the duration of cabergoline exposure is smaller than in some other studies and this is expected given our focus on patients with hyperprolactinemia as compared with other patient populations that are exposed to much higher doses over longer periods of time. Our study inclusion required only a minimum of at least 12 months of prescribed dopamine agonist therapy before enrollment which likely contributed to this by enrolling a higher proportion of more newly treated patients. However, while we did discuss this in the original version of the manuscript, we have revised our Discussion section (pg 15 line 10-11) to highlight this issue more explicitly.

3. Page 7 line 38 - 13 studies actually

We thank the Reviewer for noting this and we have updated the revised manuscript accordingly (Introduction, pg 7 line 16).

4. Page 7 line 47 - 3 studies were meta analysed for moderate/severe tricuspid regurg for treatment &gt;12months. More studies were meta analysed for mild tricuspid regurg (non clinically significant) and for other valves

We thank the Reviewer for their comment, and we have revised the Discussion section (pg 14 line 20-21) to note that most studies have included only mild valvular regurgitation. Since prolonged medication exposure or higher total dosage could theoretically worsen existing valvular heart defects, we do believe that there could be a potential longer-term risk that deserves further study to help guide evidence-based, long-term surveillance strategies.
5. Page 8 - line 9-18 what evidence is there to support the statement about the membership of this particular health insurance scheme being highly representative of the local population? I know nothing of the scheme, but one might imagine that a system that involves payments would favour less representation from amongst lower socio economic groups.

We appreciate the Reviewer’s comment, and we now cite findings from a comparison between the Kaiser Permanente Northern California membership with a statewide survey data in California that demonstrates the high level of representativeness (Gordon N; Lin T. The Kaiser Permanente Northern California Adult Member Health Survey. Perm J. 2016 Aug 19;20(4)) that is in addition to the reported that was originally cited (Gordon, N.P.: Characteristics of Adult Health Plan Members in the Northern California Region Membership, as Estimated from the 2011 Member Health Survey. Division of Research, Kaiser Permanente Medical Care Program, Oakland, CA. (2013)).

6. Page 11 line 35 - you claim that 'cabergoline only' exposed patients were more likely to have grade 2+ aortic regurgitation and yet the p value is &gt;0.05!

We apologize for any confusion. We were merely pointing out the higher proportion value and provided the P value that was of borderline statistical significance (0.06). However, we have removed text that suggests statistical significance for this finding in the revised Results section (pg 12 line 1-2).

7. Page 11 line 38 - another claim for something being more likely, but the p value is &gt;0.05!

We apologize for the confusion. As noted in response #6, we were merely pointing out the higher proportion value along with providing the P value that was of borderline statistical significance (0.056), but we have removed text that suggests statistical significance for this finding in the revised Results section (pg 12, line 4).

8. Page 7 line 40 - interesting data, pulmonary valve data is not widely reported elsewhere. I think that this is quite a tricky valve to echo (?) and so how certain can you be about the results here? Were a lot of the mild/moderate calls close? Looking at table 2, it appears that there was some doubt about calling valvular thickening in the pulmonary valve (23 in the inconclusive column - no 'inconclusive' calls in the other valves), which makes me wonder about the accuracy of calling regurgitation in this valve. The tricuspid valve data is consistent with the wider literature. If anything, taking this data at face value reinforces claims for an effect on the right heart from DA drugs - which is logical considering drug absorption from the portal hepatic circulation and therefore probably a greater effect on the right heart as this is where it will be present in greatest concentrations.

We thank the Reviewer for the questions about our assessment of each cardiac valve data capture and the comment about possible effect on right heart valves associated with dopamine agonists. We agree that even with standard research protocols, visualization of the pulmonic valve can be challenging, and in our study, any pulmonic valve result labeled as “Not well seen/visualized” or “Not adequately visualized” by the echocardiographer was considered inconclusive. We have clarified this in the revised Methods section (pg 10 line 3-5).
9. Practically all the results talk about regurgitation scores of 2+ - why not separate into mild (2) and mod (3)/severe (4) - as the latter two are clinically significant. Looking at table 2, the answer probably is because there was only one occurrence of moderate valvular regurgitation - and this was in a mitral valve. 'Mild' regurgitation in one or more heart valve is not necessarily pathologic and is relatively common. This is not to say that the analysis methodology is incorrect, rather it goes towards defining whether cabergoline is causing clinically relevant valvulopathy or not. Nevertheless, the finding mild regurgitation may yet be an interesting finding - all valve lesions that one day become moderate/severe were presumably mild at some point in their evolution.

Please see response to Editor Technical Comment #2. As noted, conducting a sensitivity analysis excluding the 1 moderate regurgitation finding did not materially change the reported findings as shown in Supplementary Tables S4-S7 (pg. 26-27).

10. Page 12 - strictly speaking the statistics quoted here are true. But seeing as there was only one moderate valve lesion in the whole study it feels a little disingenuous to quote 'mild to moderate' persistently.

As noted to the Editor, valvular abnormalities regardless of severity was the pre-specified outcome, and we clearly had no intent to be disingenuous but rather to precise in how we described the results which are accurate. Having said that, we appreciate the comment and have revised the Discussion section to note this more explicitly and to comment on the uncertain clinical significance (pg 15 line 8-11).

11. Page 12 lines 31-61 these patients were on vastly higher doses, 3mg/day compared to 1mg/week. The association between the former dose and valvulopathy is already well proven.

We completely agree with the Reviewer and that is why we conducted our study to evaluate the potential risk of valvulopathy at lower doses of cabergoline and to compare against bromocriptine exposure.

12. Page 13 lines 24-29 yes, but the regurgitation found in your study is non clinically significant.

Please see response to comment #9.

13. Page 13 a table showing the breakdown of the specific valve lesions by drug might still be useful to the reader even without statistical analysis.

We acknowledge the Reviewer’s request for a stratified table of specific valve lesions by drug (Table 2). We have created additional tables stratifying valve lesions by drug and included them as Supplemental Tables S1-S3 (pg 25-26)
Availability of data and materials

We confirm that given the informed consent obtained at the time the study was conducted and corresponding IRB approval constraints, data will not be shared. This has been described as required (pg 6, line 7-9).

Declarations

We have provided requested text that addresses each of the areas: ethics approval and consent to participate, consent to publish, availability of data and materials (see above), competing interests, funding, authors' contributions, acknowledgements and authors' Information (pg 6 line 2-18).