OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: May 27, 2022
To: "Samantha C Do" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-743

RE: Manuscript Number ONG-22-743

Postpartum readmission for hypertension following discharge on labetalol or nifedipine

Dear Dr. Do:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jun 17, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: ONG 22-743

In the manuscript under review, we evaluate the results of a retrospective analysis analyzing the readmission rate for hypertension postpartum for patients on nifedipine or Labetalol. Using data from Optum Clinformatics, the authors identified over 24,000 eligible women. They concluded that patients discharged on Labetalol has increased risk for postpartum readmission.

A few comments on the manuscript are as follows:

ABSTRACT
1. No major issues

INTRODUCTION
2. No clear hypothesis is stated

METHODS
3. Line 70 - Why was this timeline chosen?
4. Line 76-77 if this statement is true, the title of the manuscript should reflect that only pregnancy related hypertension was addressed in this study
5. What type of Nifedipine presentation was evaluated? Extended release or immediate release or both?
6. Were all gestational ages included? Was this analysis limited to singletons?
7. Was any sample size calculated?

RESULTS

8. Line 172-174 if the CI fails to cross one, wouldn't the difference reported here actually be significant rather than "similar"?
9. Do the authors have any data on medication compliance? Nifedipine XR can be once daily while Labetalol given TID.
10. Is there any data on dosing? This is especially important since Labetalol doing can be much more varied than Nifedipine. It's possible that Labetalol was just dispensed at an inadequate dose.

DISCUSSION
11. One could argue that postpartum readmission for hypertension is not a sign of poor control but rather a sign that the safety parameters in place for postpartum women are actually functional. If women fail to appear at their postpartum visit with their health care providers, their severe hypertension could go undetected and therefore they wouldn't be admitted. In this study, the patient described in the scenario above would be cataloged as "adequate blood pressure control". In other words, is postpartum readmission for hypertension a surrogate for poor control?

Reviewer #2:

Lines 44-45 - Is a reference needed for this sentence?

Line 52 - It might be helpful for the reader to mention the class of each of the two anti-hypertensives mentioned here: Nifedipine: a dihydropyridine calcium channel blocker; and labetalol: a beta blocker.

Line 54 - Sentence not clear. What's missing here?

Line 74 - Not sure what the preposition "within" means here.

Line 83 - Were patient admission date and length-of-stay variables in the data set? If so, it might be possible to create a variable that would consistently estimate discharge day.

Line 117 - Was education level used as a measure of SES?

Line 117 - Was missing race/ethnicity (23%) problematic overall in stratifying risk?

Line 206 - ? Subject/verb agreement? (Use of the term "data" requires a plural verb.) Rewrite would include "Otherwise, limited data exist to guide……."

Lines 209-221 - This section of your discussion I find very confusing. I'm not sure I understand your statement that "patients on nifedipine alone had more traditional characteristics associated with an increased risk of admission." Are you saying that contrary to the findings in your analysis, comparable reports on the subject showed that pregnancy-related hypertension patients in the intrapartum period treated with nifedipine alone were more frequently readmitted than those treated with labetalol and that somehow biases in the data or analysis may account for the differences? My sense is that you've shown through adjusted analysis of data that nifedipine treated patients faired better than those on labetalol alone or in combination with nifedipine. How can this be restated so that it is clearer?

Line 243 - See note for line 206 above. The verb "was" should be changed to "were" to assure subject/verb agreement.

Reviewer #3:

THIS IS AN INTERESTING RESEARCH REGARDING Postpartum readmission for hypertension following discharge on labetalol or nifedipine. I HAVE THE FOLLOWING COMMENTS.
1. While in the methods is stated that patients with chronic hypertension are excluded from the study , in the results is obvious that patients with chronic HTN were part of the study (line 142)
2. In the study are included patients which started the treatment up to four days after delivery. Is there a possibility ,more patients that started treatment after birth ere represented in the that in the group that took labetalol was preferred over nifedipine due to the effect of nifedipine on the myometrium.
3.I am concerned by the fact that the readmissions for HTN between the are statistically significant , the readmission for ay other reason are not statistically significant. (line 177) . Iy would be helpful to know which were all the other reasons for readmissions that outbalanced the readmissions for HTN
4. The increased readmission likelihood in the labetalol group maybe just reflects the known rebound phenomenon of the

b-blockers . Do we know if the medication was stopped gradually as indicated.

Reviewer #4:

Lines 136-143: The stats tests used (Chi-square and ANOVA) compared counts across three categories, so while the counts or proportions in one group may be numerically higher, one cannot "significance" in a statistical sense, to a particular group, unless the Authors were to include pairwise testing in the stats analysis.

General: The use of nifedipine vs labetalol was not randomly assigned. Besides the factors included in the adjustment model, there is no information as to the actual BP measurements of the two cohorts, so the reader cannot judge as to whether the groups had equal risk of readmission for HTN. This should be included as a limitation to generalizing these findings.

The analysis by severity class is helpful, but not as direct or precise as actual BP measurements for the individuals.

In addition, given the many baseline differences among the groups, the Authors need to use a matching algorithm to corroborate their findings of an association of labetalol use with increased odds of readmission.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, describe the reasons that race and ethnicity were assessed in

the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories.

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "Patients with obesity" instead of "obese patients," "Women with disabilities" instead of "disabled women," "women with HIV" instead of "HIV-positive women," "women who are blind" instead of "blind women."

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

8. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting or indicate whether the meeting was held virtually).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."
* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

9. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make sure there are no inconsistencies between the abstract and the manuscript, and that the abstract has a clear conclusion statement based on the results found in the manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. In your abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001").

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available at http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

14. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. Include the digital object identifier (DOI) with any journal article references and an accessed date with website references.

Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the formal reference list. Please cite them on the line in parentheses.

If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

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If your article is accepted, you will receive an email from the Editorial Office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

If you submit a revision, we will assume that it has been developed in consultation with your coauthors and that each author has given approval to the final form of the revision.

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jun 17, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Dwight J. Rouse, MD
Deputy Editor, Obstetrics

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

Dear Editors of *Obstetrics & Gynecology*,

We are pleased to submit our revised manuscript entitled "Rates of postpartum readmission following discharge on labetalol or nifedipine" for your review. Our manuscript is not under consideration elsewhere, and it will not be submitted to other journals unless a final negative decision is made by the Editors of *Obstetrics & Gynecology*.

Nifedipine and labetalol are the most commonly used oral medications for postpartum hypertension. It is unknown if one medication is more effective than the other for postpartum blood pressure control and preventing postpartum readmission for hypertension. Our study sought to evaluate whether nifedipine or labetalol was more effective at preventing postpartum hypertensive readmissions. In our cohort study using data from a national administrative claims database, we found that postpartum readmission for hypertension was more frequent for patients discharged on labetalol compared with nifedipine. Specifically, patients discharged on labetalol were more than twice as likely to be readmitted for hypertension. These findings persisted when adjusting for confounders. Our findings suggest that it will be important to explore whether choice of nifedipine over labetalol for treatment of hypertensive disorders of pregnancy might reduce postpartum readmission rates.

A version of this study was initially submitted to *Obstetrics & Gynecology* in 2021 (Manuscript Number ONG-21-475). After review by the Editorial Board and expert referees, it was deemed that further consideration would be given to a revised version. Unfortunately at the time of revision, the Stanford Research Computing Center environment used for this study, including the study dataset and statistical programs, became permanently inaccessible due to an unexpected collapse of the environment. (Letter from Stanford's Chief Technology Officer explaining this incident is available on request.) This event prompted the withdrawal of our original submission. Since then, we remade our study dataset and conducted analyses largely following our original plan, with some revisions in light of insightful reviewer comments.

We have now revised the current manuscript further in response to helpful reviewer comments to this version of the study (ONG-22-743). Specific point-by-point responses to all of the new reviewer comments are included following this letter.

This study was presented as a poster at the 39th Annual Pregnancy Meeting for the Society for Maternal-Fetal Medicine in Las Vegas, Nevada during the meeting held from February 10-16th, 2019.

This study was reviewed and approved by the Stanford University Institutional Review Board. Each author has contributed substantially to study design, data collection, data analysis and manuscript development. All of the authors approve this submission and report no conflict of interest. The authors have read the Green Journal's Instructions for Authors and followed these guidelines in the composition of this manuscript.

No funding was provided for the study. The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important

aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

We look forward to your response to our manuscript and welcome your feedback.

Sincerely,

Samantha C. Do, MD*

*The manuscript's guarantor

REVIEWER COMMENTS:

Reviewer #1: ONG 22-743

In the manuscript under review, we evaluate the results of a retrospective analysis analyzing the readmission rate for hypertension postpartum for patients on nifedipine or Labetalol. Using data from Optum Clinformatics, the authors identified over 24,000 eligible women. They concluded that patients discharged on Labetalol has increased risk for postpartum readmission.

A few comments on the manuscript are as follows:

ABSTRACT

1. **No major issues**

INTRODUCTION

2. **No clear hypothesis is stated**

Response: We thank the reviewer for their thoughtful reading of our manuscript and their excellent comments. We have added to the end of the introduction the following statement: "We hypothesized that nifedipine would be associated with lower risk of a postpartum readmission for hypertension due to improved renal blood flow and the potential for less frequent dosing with nifedipine." (Line 81-83)

METHODS

3. **Line 70 - Why was this timeline chosen?**

Response: These were the data years available at the time of analysis through the Stanford Center for Population Health Sciences.

4. Line 76-77 if this statement is true, the title of the manuscript should reflect that only pregnancy related hypertension was addressed in this study

Response: Patients with chronic hypertension without superimposed preeclampsia were excluded. Due to character count constraints the title was not updated. If the title may be longer than 100 characters, it could be changed to “Postpartum readmission for hypertension following discharge on labetalol or nifedipine for hypertensive disorders of pregnancy.”

5. What type of Nifedipine presentation was evaluated? Extended release or immediate release or both?

Response: Both extended and immediate release nifedipine were included and this was clarified in the methods with the following sentence added: “Extended release and immediate release formulations of nifedipine were both included.” (Line 107-108)

6. Were all gestational ages included? Was this analysis limited to singletons?

Response: Added to the methods: “Patients with singleton or multifetal deliveries at 20 weeks or greater were included.” (Line 90-91)

7. Was any sample size calculated?

Response: A sample size was not calculated because this was a secondary analysis of a large prospective database and a power calculation after data collection is not advised (Goodman SN, Berlin JA. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. *Ann Intern Med.* 1994;121:200-206).

RESULTS

8. Line 172-174 if the CI fails to cross one, wouldn't the difference reported here actually be significant rather than "similar"?

Response: We wanted to convey that there was not a large difference in absolute rates of readmission between patients discharged on nifedipine and both medications for mild HDP (2.7 vs 2.9%, crude OR 1.06 with 95% CI 0.61-1.85, adjusted OR 0.71 with 95% CI 0.50-1.02, crossing one, not significant) and for patients with severe HDP (3.2 vs 3.3%, crude OR 1.03 with 95% CI 0.65-1.63, adjusted OR 0.80 with 95% CI 0.64-0.99). For patients with severe HDP this did reach statistical significance in the adjusted OR, but a 0.1% absolute difference may not be clinically significant. Thus we have adjusted this sentence to: “The observed hypertensive readmission rate was similar on dual therapy compared to nifedipine alone for patients with mild disease (2.9 vs 2.7%) and for patients with severe disease (3.3 vs 3.2%), although the adjusted odds of hypertensive readmission were significantly lower for dual therapy among patients with severe disease (aOR 0.80, 95% CI 0.64-0.99).” (Line 209-213)

9. Do the authors have any data on medication compliance? Nifedipine XR can be once daily while Labetalol given TID.

Response: We agree that medication adherence may contribute to the difference in hypertensive readmission rates we found. We do not have data on medication adherence but we used

medication dispensed rather than prescriptions written to minimize the limitation of not being able to ascertain patient adherence. Additionally, while we do not have data on adherence, this is a “real life” look at outcomes between these two medications. Patients may not be as adherent to labetalol TID as they are to nifedipine XR once daily and this may contribute to the increased risk of hypertensive readmission. We state in the discussion, “Patient adherence may contribute to the lower rate of readmissions. The extended release formulation of nifedipine allows patients to take it one to two times per day. Postpartum regimens for labetalol may be more onerous, requiring patients to take labetalol two to three times per day, which may lead to missed doses and more readmissions.” (Line 245-249). We also discuss the limitation of not having data on medication adherence: “Information on dosages of medication dispensed, duration of medication prescribed and patient adherence to medications was not available. Our approach of utilizing prescriptions filled by the patient (rather than prescriptions ordered by the physician) attempted to minimize the limitation of not being able to ascertain patient adherence.” (Line 298-300)

10. Is there any data on dosing? This is especially important since Labetalol doing can be much more varied than Nifedipine. It's possible that Labetalol was just dispensed at an inadequate dose.

Response: A limitation of the study is that we do not have data on dosing as described in the study limitations. Please see response to Reviewer 1, Comment 9 above.

DISCUSSION

11. One could argue that postpartum readmission for hypertension is not a sign of poor control but rather a sign that the safety parameters in place for postpartum women are actually functional. If women fail to appear at their postpartum visit with their health care providers, their severe hypertension could go undetected and therefore they wouldn't be admitted. In this study, the patient described in the scenario above would be cataloged as "adequate blood pressure control". In other words, is postpartum readmission for hypertension a surrogate for poor control?

Response: We agree with the reviewer that it is possible that postpartum readmission could be a sign that safety parameters are appropriately functioning for people with hypertensive disorders. Despite this, postpartum readmission does still seem to be a surrogate for poor control. A prior study demonstrated a correlation between documented higher blood pressures and increased risk of readmission (Lovgren T, Connealy B, Yao R, et al. Postpartum management of hypertension and effect on readmission rates. Am J Obstet Gynecol MFM 2022;4:100517) without evaluating if labetalol or nifedipine is more effective. Additionally, postpartum readmission has negative implications for patients and health systems (Mogos et al, Hypertensive disorders of pregnancy and postpartum readmission in the United States: national surveillance of the revolving door. J Hypertension, 2018), and postpartum readmissions for hypertension have been investigated in multiple studies. Our study does not capture patients who do not return to care but that is a shared limitation of many studies investigating postpartum hypertension. As our study is not limited to one institution, it does pick up readmissions even if the patient was readmitted to another hospital than where they delivered. In the limitations section, we added a statement acknowledging, “Postpartum readmission is an imperfect indicator of poor blood pressure control, and we cannot assess outcomes among those lost to follow-up. However, higher blood pressures have correlated with an increased risk of postpartum readmission.” (Lines 315-317)

Reviewer #2:

Lines 44-45 - Is a reference needed for this sentence?
Response: Thank you to the reviewer for their reading of our manuscript and feedback. References were added for this sentence (Mogos et al, Stamilio et al).

Line 52 - It might be helpful for the reader to mention the class of each of the two anti-hypertensives mentioned here: Nifedipine: a dihydropyridine calcium channel blocker; and labetalol: a beta blocker.
Response: We agree this is helpful. The sentence is updated to: "Nifedipine, a dihydropyridine calcium channel blocker, and labetalol, a beta-blocker with alpha blocking activity, are the most commonly used oral medications for postpartum hypertension." (Lines 64-65)

Line 54 - Sentence not clear. What's missing here?
Response: Sentence clarified to: "Postpartum readmission is a surrogate marker for poor control of hypertensive disorders of pregnancy, and associated with severe maternal complications of hypertensive disorders." (Lines 57-58)

Line 74 - Not sure what the preposition "within" means here.
Response: As we were looking at readmissions up to 6 weeks postpartum and we had data through the end of 2017, we limited the date of delivery to 6 weeks prior to the end of 2017 so we would capture all possible readmissions from our deliveries within 2017, the last year we had data for. We clarified the text: "We restricted to delivery dates 1/1/2006-11/16/2017 to capture readmissions up to 6 weeks postpartum in the available data years." (Line 81-82)

Line 83 - Were patient admission date and length-of-stay variables in the data set? If so, it might be possible to create a variable that would consistently estimate discharge day.
Response: We appreciate this suggestion as we agree that those variables would be useful. Unfortunately, our dataset only includes a date for a given diagnosis or procedure, and patient admission and discharge dates and length-of-stay variables are not available.

Line 117 - Was education level used as a measure of SES?
Response: Yes, education level was used as the primary measure of socioeconomic status. Educational attainment is strongly linked to overall socioeconomic advantage and health outcomes (Winkleby MA, et al. Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. *Am J Public Health.* 1992;82(6):816-820) and has been linked to preeclampsia risk (Silva et al, Low socioeconomic status is a risk factor for preeclampsia: the Generation R Study. *J Hypertens*. 2008 Jun;26(6):1200-8.) We therefore felt that this was the most useful proxy for socioeconomic status among available variables.

Line 117 - Was missing race/ethnicity (23%) problematic overall in stratifying risk?
Response: Multiple imputation was used for missing data. We conducted the imputation in the full dataset and then conducted analyses in the full population and stratified by severity of

hypertensive disorder of pregnancy. As shown in the table below for race, missingness was similar across the medication groups. We have revised the relevant sentence in the Methods section to read “In the study sample, 0.2% were missing region, 2% were missing education, and 23% were missing race/ethnicity, which was similar across medication groups.” (Line 128-130)

Frequency Col Pct	Missing covariate	Medication			
		Both	Labetalol	Nifedipine	Total
	No	1041	10709	6881	18631
		76.32	75.89	76.45	
	Yes	323	3403	2120	5846
		23.68	24.11	23.55	
	Total	1364	14112	9001	24477

Line 206 - ? Subject/verb agreement? (Use of the term "data" requires a plural verb.) Rewrite would include "Otherwise, limited data exist to guide……."
Response: Sentence corrected to fix subject/verb agreement: “Otherwise, limited data exist to guide choice…”

Lines 209-221 - This section of your discussion I find very confusing. I'm not sure I understand your statement that "patients on nifedipine alone had more traditional characteristics associated with an increased risk of admission." Are you saying that contrary to the findings in your analysis, comparable reports on the subject showed that pregnancy-related hypertension patients in the intrapartum period treated with nifedipine alone were more frequently readmitted than those treated with labetalol and that somehow biases in the data or analysis may account for the differences? My sense is that you've shown through adjusted analysis of data that nifedipine treated patients faired better than those on labetalol alone or in combination with nifedipine. How can this be restated so that it is clearer?

Response: Compared to patients on labetalol, patients on nifedipine had higher rates of preterm birth and Black race, both of which have been identified as risk factors for postpartum readmission. Despite a higher rate of these risk factors for readmission in the nifedipine group, we found a higher rate of readmissions for patients on labetalol (4.5%) than on nifedipine (2.1%). This section restated to be clearer: “Patients discharged on nifedipine had higher rates of characteristics traditionally associated with increased postpartum readmission, including preterm birth and Black race. Despite this, the observed rate of readmission was lower among those discharged on nifedipine (4.5%) versus labetalol (2.1%), which persisted with confounder adjustment.” (Line 250-253)

Line 243 - See note for line 206 above. The verb "was" should be changed to "were" to assure subject/verb agreement.

Response: Thank you, we have changed the verb to "were."

Reviewer #3:

THIS IS AN INTERESTING RESEARCH REGARDING Postpartum readmission for hypertension following discharge on labetalol or nifedipine. I HAVE THE FOLLOWING COMMENTS.

1. While in the methods is stated that patients with chronic hypertension are excluded from the study , in the results is obvious that patients with chronic HTN were part of the study (line 142)

Response: Thank you to the reviewer for their helpful comments. As stated in the methods in line 84-85, "To examine those with an obstetric cause for hypertension, patients with chronic hypertension without superimposed preeclampsia were excluded." Patients with chronic hypertension with superimposed preeclampsia were included. There were 3,477 patients with chronic hypertension without superimposed preeclampsia who were excluded as shown in Figure 1. The patients referenced in the results are patients with chronic hypertension and superimposed preeclampsia. To clarify this, we added to the methods: "Patients with chronic hypertension with superimposed preeclampsia were included." (Line 85-86)

2. In the study are included patients which started the treatment up to four days after delivery. Is there a possibility ,more patients that started treatment after birth ere represented in the that in the group that took labetalol was preferred over nifedipine due to the effect of nifedipine on the myometrium.

Response: There were more patients on labetalol than nifedipine (14,112 vs 9,001 patients). It is a limitation of our study that we do not know the reason more patients were treated with labetalol than nifedipine, but our sensitivity analysis suggests that the timing of prescriptions postpartum does not account for the higher readmission rate with labetalol than nifedipine (Appendix 4). Our sensitivity analysis included patients who were dispensed treatment up to 3 days after delivery instead of up to 4 days after delivery as in the main analysis. The sensitivity analysis also demonstrated significantly more hypertensive readmissions for patients on labetalol compared to nifedipine.

3.I am concerned by the fact that the readmissions for HTN between the are statistically significant , the readmission for ay other reason are not statistically significant. (line 177) . Iy would be helpful to know which were all the other reasons for readmissions that outbalanced the readmissions for HTN

Response: The structure of the dataset does not permit a ranking or general query of reasons for a readmission. We identify all claims for a hypertensive condition, and then select for claims that occur among patients with a recent delivery claim. Labetalol compared to nifedipine was associated with significantly higher overall readmission risk in the subgroup analyses looking at patients with mild hypertensive disorders of pregnancy and those with severe hypertensive

disorders of pregnancy, supporting a link between the medication and postpartum hypertension and readmission (Appendix 5).

4. The increased readmission likelihood in the labetalol group maybe just reflects the known rebound phenomenon of the b-blockers . Do we know if the medication was stopped gradually as indicated.

Response: It is not known from our dataset if labetalol was tapered off. However, most readmissions for hypertension occur in the first week postpartum and often blood pressure medications are not tapered and discontinued until 2 or more weeks postpartum. In the study by Stamilio et al (Risk factors for postpartum readmission for preeclampsia or hypertension before delivery discharge among low-risk women: a case-control study, Am J Obstet Gynecol MFM 2021;3:100317.), the median time to readmission was 6 days. In the study by Lovgren et al (Lovgren T, Connealy B, Yao R, et al. Postpartum management of hypertension and effect on readmission rates. Am J Obstet Gynecol MFM 2022;4:100517.), the median time to readmission was 3 days. A multistate analysis found that median time to postpartum readmission for any indication was 7 days (Clapp MA, Little SE, Zheng J, Robinson JN. A multi-state analysis of postpartum readmissions in the United States. American Journal of Obstetrics & Gynecology. 2016;215(1):113.e1-113.e10.) With most readmissions for hypertension occurring early, it is less likely that blood pressure medication was tapered and discontinued in this time frame; as such, a rebound phenomenon of beta-blockers would not be expected to significantly contribute to our results.

Reviewer #4:

Lines 136-143: The stats tests used (Chi-square and ANOVA) compared counts across three categories, so while the counts or proportions in one group may be numerically higher, one cannot "significance" in a statistical sense, to a particular group, unless the Authors were to include pairwise testing in the stats analysis.

Response: We thank the reviewer for their comments. The text in this location has been updated to remove the word “significant” and thus it is descriptive of the counts and proportions differing between groups without claiming statistical significance. It now reads: “Patients discharged on both labetalol and nifedipine were older than patients discharged on either monotherapy and more likely to have underlying chronic hypertension, chronic renal disease, cesarean delivery and deliver preterm than patients on monotherapy.”

General: The use of nifedipine vs labetalol was not randomly assigned. Besides the factors included in the adjustment model, there is no information as to the actual BP measurements of the two cohorts, so the reader cannot judge as to whether the groups had equal risk of readmission for HTN. This should be included as a limitation to generalizing these findings.

Response: We agree with this limitation and have added to the limitations section: “Blood pressure measurements were unavailable and thus could not be adjusted for. Analysis by disease severity attempted to address this limitation.” (Line 298-300) We also added to the methods our reason for performing the analysis stratified by disease severity: “Analysis of readmission rates by disease severity attempted to decrease biasing of results by potential differences in severity of

hypertensive disorder for patients treated with labetalol vs nifedipine." (Line 135-137). However, severity of hypertensive disorders of pregnancy did not appear to account for differences in prescribing patterns with nifedipine prescribed to 29% of patients with mild versus 30% of patients with severe hypertensive disorders. This is not a randomized trial and thus we acknowledge that despite the logistic regression analysis and the propensity score matching analysis there still may be unaccounted for factors influencing our results. As we state in the conclusion (line 320), our study may be useful to inform future investigational trials where randomization could more fully remove confounding.

The analysis by severity class is helpful, but not as direct or precise as actual BP measurements for the individuals.

Response: As actual BP measurements for the individuals were not available in the dataset, analysis by severity class was used to demonstrate increased risk of hypertensive readmission for labetalol compared to nifedipine regardless of disease severity. The absence of BP measurements has been added to the limitations as above.

In addition, given the many baseline differences among the groups, the Authors need to use a matching algorithm to corroborate their findings of an association of labetalol use with increased odds of readmission.

Response: We have replicated the analyses using a doubly robust matching procedure. We have described this approach and the results in manuscript and added 3 supplemental tables to the appendix (Appendices 5-7).

Methods: "We used a doubly robust matching procedure to estimate adjusted associations between medication dispensed and postpartum readmission for hypertension. We calculated propensity scores and then used greedy nearest neighbor matching with "method nearest" in the MatchIt package in R, which matches patients on a given medication regime with patients on the comparison medication regime based on their baseline covariates. We then included the covariates in the final outcome model in the matched dataset. These analyses were conducted among patients with complete covariate data." (Line 142-148)

Results: "We also replicated analyses using a doubly robust matching procedure to adjust for confounders (Appendices 5-7). The pattern of results was similar in these analyses, although the magnitude of the association between labetalol and readmission was larger than in the main analysis (aOR 2.29, 95% CI 1.43-1.85) and the association between dual therapy and readmission was null (aOR 0.95, 95% CI 0.57-1.58)." (Line 223-228)

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Not applicable.

*** Name the IRB or Ethics Committee institution in the Methods section (if applicable).**

Updated in the text. “The Stanford University Research Compliance Office provided ethics approval for the study.” (Line 86-87)

*** Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.**

Not applicable.

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Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

Response: Explanation for the use of race/ethnicity and the way it was collected and the amount of missing information was all included in the text. From the methods: “Race/ethnicity was included as an imperfect surrogate for other sociologic determinants of health that were not available and should not be construed as a biologic indicator. Race/ethnicity was categorized as Black, White, Hispanic, Asian or unknown and based on Optum’s proprietary algorithms relying on the policyholder’s zip code in combination with the individual’s first, middle, and last names, public records, and self-reported surveys.”

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Person first language is used.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

ReVITALize definitions were followed where applicable.

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Odds ratios are used for our primary outcome data.

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