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OUTPATIENT CALCIUM CHANNEL BLOCKERS AND THE RISK OF POSTPARTUM HEMORRHAGE: A COHORT STUDY

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Abstract

Objective—To determine whether outpatient exposure to calcium channel blockers (CCBs) at the time of delivery is associated with an increased risk for postpartum hemorrhage (PPH).

Design—Cohort study

Setting—United States

Population or Sample—Medicaid beneficiaries

Methods—We identified a cohort of 9,750 patients with outpatient prescriptions for CCBs, methyldopa, or labetalol for pre-existing or gestational hypertension whose days supply overlapped with delivery; 1,226 were exposed to CCBs. The risk of PPH was compared in those exposed to CCBs to those exposed to methyldopa or labetalol. Propensity score matching and stratification were used to address potential confounding.

Main Outcome Measures—The occurrence of postpartum hemorrhage during the delivery hospitalization.

Results—There were 27 patients exposed to CCBs (2.2%) and 232 patients exposed to methyldopa or labetalol (2.7%) who experienced PPH. After accounting for confounders, there was no meaningful association between CCB exposure and PPH in the propensity score matched

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(odds ratio (OR), 0.77, 95% confidence interval (CI) 0.50 – 1.18) or stratified (OR 0.79, 95% CI 0.53 – 1.19) analyses. Similar results were obtained across multiple sensitivity analyses.

Conclusions—The outpatient use of CCBs in late pregnancy for the treatment of hypertension does not increase the risk of PPH.

Keywords

Postpartum hemorrhage; Hypertensive disorders of pregnancy; Calcium channel blockers

Introduction

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality in both the developed and developing world.^{1–6} The incidence of PPH has increased substantially over the past decade in developed nations, primarily due to an increase in the occurrence of uterine atony.^{3, 7–13} Consequently, identifying modifiable risk factors for PPH in general, and uterine atony particular, is urgently needed.

Calcium channel blockers (CCBs) are frequently prescribed during the third trimester of pregnancy for both hypertension¹⁴ and, off-label, for labor tocolysis^{15, 16}; recent data from the United States suggest that between 1 and 2% of all patients are exposed to CCBs as outpatients during the 3rd trimester.^{17, 18} As the incidence of hypertensive disorders during pregnancy increases,^{19, 20} exposure to CCBs is likely to become increasingly common.

CCBs inhibit the influx of calcium into uterine smooth muscle and prevent uterine contraction²¹; this is the basis for its use in prolonging pregnancy in patients with preterm labor. While this property is useful in the setting of preterm labor, following delivery, effective uterine contraction is required to compress the uterine vasculature and stem the flow of blood to the myometrium.²² In the absence of effective contraction, the atonic uterus can bleed excessively resulting in postpartum hemorrhage. Because of the tocolytic properties of CCBs, several authors have suggested that exposure to CCBs close to the time of delivery may increase the risk of uterine atony and PPH.^{23, 24} To date, however, there are few data examining this risk.

The objective of this study is therefore to examine whether outpatient exposure to CCBs at the time of delivery is associated with an increased risk of PPH. To avoid the potential for confounding by indication²⁵ in this observational study, we focus this study on CCBs prescribed for hypertension and employ an active comparator control group of patients exposed to methyldopa or labetalol, which are first-line agents for the treatment of hypertension in pregnancy^{26–28} and which, to the best of our knowledge, have not been implicated in causing PPH.

Methods

COHORT

The cohort was derived from the Medicaid Analytic eXtract (MAX), an administrative dataset that contains information on Medicaid enrollment and utilization claims. The dataset contains claims for inpatient admissions and outpatient visits, as well as outpatient pharmacy dispensing claims. Using MAX data from 2000 to 2007, a cohort was created for the study of drug utilization and safety in pregnancy.²⁹ Briefly, women with an inpatient or outpatient claim for a delivery were linked to infants within states using the Medicaid Case Number (which is generally shared by families) and the infant's date of birth. Because neither gestational age at birth nor the date of a woman's last menstrual period (LMP) is directly

recorded in the MAX, the LMP was assigned using a validated algorithm that is based on diagnostic codes in the maternal and infant records.³⁰

We then restricted the cohort to women who are eligible for Medicaid continuously from 6 months after the estimated LMP month through the delivery month in order to allow accurate capture of maternal medical and obstetric conditions important in the planned analysis. To ensure complete ascertainment of relevant claims, we restricted our analysis to women with ≥ 28 days of enrollment each month, and without restricted benefits, private insurance, or certain state-specific managed care programs (that underreport claims to MAX). The source cohort included 3,622,489 completed pregnancies.

We then restricted the cohort to those patients that were dispensed as outpatients either a CCB, labetalol, or methyldopa and whose days supply overlapped with the date of delivery. Because we hypothesize that the risk of PPH associated with CCBs derives from direct action of the CCB on the myometrium following delivery, the etiologically relevant window for exposure is the days immediately before delivery. A list of individual medications that comprise the CCBs are included in Appendix S1.

Because confounding by indication is a major threat to the validity of non-randomized studies,²⁵ we selected as a reference group patients exposed to methyldopa or labetalol, which are considered the preferred treatment for hypertension in pregnancy by many guidelines.^{26–28} To ensure the comparability of exposed and reference groups, for the primary analysis we restricted our analysis to those patients who had a diagnosis code for gestational or pre-existing hypertension and further excluded patients with diagnoses other than hypertension which are indications for the prescription of CCBs including preterm labor/threatened labor, preterm delivery, migraine, arrhythmia, angina, and Raynaud's syndrome. We also exclude patients exposed to methyldopa or labetalol in addition to CCBs. Finally, in order to ensure accurate capture of the outcome of PPHs, we excluded patients that did not deliver in the hospital. After these restrictions and exclusions, the primary cohort included 9,750 pregnancies (see Figure 1).

STUDY OUTCOMES

The primary study outcome was the occurrence of PPH during the delivery hospitalization. This was defined based on a diagnostic code of 666 or any subcode thereof, from the *International Classification of Diseases, 9th revision* (ICD 9). Diagnostic codes have been shown to have a high positive predictive value for PPH in administrative data.^{31, 32} As a secondary outcome, we also examined PPH due to uterine atony, as denoted by ICD 9 code 666.1 or any subcode thereof, which mechanistically is the form of PPH most likely to be influenced by CCBs.

COVARIATES

We identified five groups of potential confounders to the planned analysis: patient demographics, medical characteristics, obstetric conditions, medications (which can act as markers of disease and/or disease severity), and measures of medical care utilization during the 3rd trimester; these were selected because they may influence the choice of antihypertensive medication and the risk of PPH. Demographic characteristics analyzed included age and race/ethnicity as reported in the MAX. Maternal medical conditions were identified on the basis of diagnosis codes recorded in patients' inpatient or outpatient claims at any time during the third trimester and included pre-existing hypertension, pre-gestational diabetes, obesity, chronic renal disease, and fibroids. Maternal obstetric conditions/procedures were identified in the same manner and included gestational hypertension, mild preeclampsia (including unspecified hypertensive disorders), severe preeclampsia,

gestational diabetes, previous Cesarean delivery, placenta previa, multiple gestations, cesarean delivery, and induction of labor. Note, while some of these conditions/procedures (e.g., cesarean delivery and induction of labor) will by definition occur after the patient was prescribed the antihypertensive, they may be markers of the severity of important confounding variables (i.e., induction of labor may be a surrogate for severe hypertension) and are thus appropriate to consider as potential confounders in the analysis. However, to ensure that this approach did not introduce selection bias we performed a sensitivity analysis excluding these conditions/procedures in the model used to estimate the propensity score (see below).³³

We also examined measures of medical care utilization during the 3rd trimester which also may serve as markers of comorbid disease/disease severity including number of hospitalizations (including the delivery hospitalization), number of outpatient visits, and number of distinct prescription medications (other than antihypertensives) dispensed.³⁴

STATISTICAL ANALYSIS

To adjust for differences between patients treated with CCBs and methyldopa/labetalol, we used two different approaches based on propensity scores. For both of these analyses, a propensity score was estimated using logistic regression with CCB exposure as the dependant variable and all potential confounders described above included without further selection. In the first approach, patients exposed to CCBs were matched on propensity score to those exposed to methyldopa or labetalol in a fixed 1:3 ratio using a nearest neighbor algorithm with a caliper of 0.05 difference in propensity score.³⁵ This resulted in a matched cohort containing 4,900 patients. The odds ratio and 95% confidence interval for PPH or PPH with atony associated with CCB exposure was then estimated directly. In the second approach, all patients with a propensity score value that corresponded to the 2.5 percentile or lower of PS distribution in the CCB exposed and the 97.5 percentile or higher of the PS distribution in the methyldopa/labetalol exposed were identified and excluded from this analysis. Trimming subjects from the tails of the propensity score has been demonstrated to provide an additional reduction in residual confounding.³⁶ In the remaining cohort, propensity score deciles were defined. A logistic regression model was then fit adjusting to deciles of propensity score as a categorical covariate in the model and the odds ratio and 95% CI for PPH and PPH with atony associated with CCB exposure was determined.

SENSITIVITY ANALYSES

Four sensitivity analyses were performed to test the robustness of our findings. First, as the sensitivity of diagnostic codes for hypertensive disorders is imperfect, we repeated our analysis without requiring that patients have a code for pre-existing or gestational hypertension (n=12,298). This was done to ensure that excluding patients without these diagnostic codes did not introduce bias in our analysis. Second, we performed a sensitivity analysis restricting to only those patients that refilled their prescription for CCBs or methyldopa/labetalol at least once during the 3rd trimester (n=7,230). This was intended to reduce misclassification of exposure due to non-compliance based on the assumption that if the patient refilled their prescription at a time point proximate to delivery it is likely that they are taking their antihypertensive medication as prescribed. Third, we performed an analysis that did not include clinical events or conditions that would have developed after the prescription of the antihypertensive in the model used to estimate the propensity score to ensure that we were not adjusting for intermediates in our analysis; these covariates included mild or severe preeclampsia, cesarean delivery, induction of labor, and the number of hospitalizations or outpatient visits during the third-trimester. Fourth, we included the entire cohort prior to any exclusions or restrictions (n=3,622,489). Exposure was defined by prescription for CCB whose day supply overlaps with delivery (as done in the primary

analysis) and the referent included all other patients (with or without hypertension). The propensity score for this sensitivity analysis included the same covariates as in the primary analysis plus variables indicating preterm delivery, preterm labor/threatened labor, migraine, arrhythmia, angina, Raynaud's disease, and in-hospital delivery.

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). Institutional review board approval for this research was in place.

Results

COHORT CHARACTERISTICS

The cohort consisted of 9,750 patients with outpatient prescriptions for CCBs, methyldopa, or labetalol for pre-existing or gestational hypertension whose days supply overlapped with delivery; of these 1,226 were exposed to CCBs (Figure 1), with the balance exposed to methyldopa/labetalol. Overall, 259 (2.7%) of patients in the analytic cohort experienced PPH and 201 had PPH due to uterine atony (2.1%).

There were several important differences in the baseline characteristics of the patients exposed to CCBs compared to those exposed to methyldopa or labetalol (Table 1). Those treated with CCBs were more likely to be Black (and less likely to be White or Hispanic) and to carry a diagnosis of pre-existing hypertension, pre-existing diabetes, or prior cesarean delivery. They were less likely to have gestational hypertension. They are also less likely to deliver via cesarean or to take iron supplements. These imbalances were no longer present in the propensity score matched cohort; the absolute difference in proportions for all covariates considered was 2.0% (Table 2).

ASSOCIATION OF CCB EXPOSURE WITH PPH

Overall, 27 patients exposed to CCBs (2.2%) and 232 patients exposed to methyldopa or labetalol (2.7%) experienced PPH. The unadjusted odds ratio (OR) for PPH associated with CCB exposure was 0.81, 95% confidence interval (CI) 0.54 to 1.21. After adjustment for confounders through propensity score stratification and matching, there was not a meaningful association between CCB exposure and PPH (OR 0.79, 95% CI 0.53 – 1.19 and 0.77, 95% CI 0.50 – 1.18, respectively) (Table 3).

There were 23 patients (1.9%) exposed to CCBs and 178 patients (2.1%) exposed to methyldopa/labetalol who experienced PPH due to uterine atony (unadjusted OR 0.90, 95% CI 0.58 – 1.39). Again, after accounting for confounders through the use of propensity score stratification and matching, there was no meaningful association between CCB exposure and PPH due to uterine atony (OR 0.90, 95% CI 0.58 – 1.41 and OR 0.93, 95% CI 0.58 – 1.49, respectively) (Table 3).

SENSITIVITY ANALYSES

When we performed our analyses without requiring a documented diagnosis of pre-existing or gestational hypertension in the inpatient or outpatient claims, results were comparable to those of the main analysis, with no meaningful association between CCB exposure and either PPH overall or PPH due to uterine atony after accounting for relevant confounders through propensity score matching or stratification. Likewise, there was no association between CCBs and either of these outcomes when we restricted our analyses to those who refilled their antihypertensive medication at least once during the 3rd trimester, when we removed variables from our propensity score model that occurred temporally after the initiation of the antihypertensive, or when we analyzed the entire cohort adjusting for the indications for CCB exposure (Table 4).

Discussion

Main findings

Despite concerns that exposure to CCBs prior to delivery may increase the risk of PPH due to their property of causing uterine relaxation, there has not, to our knowledge, been a large, well-controlled study examining this risk. In this cohort study of 9,750 patients, after careful control of confounding factors and across a range of sensitivity analyses, we did not observe an increase in the risk of PPH or PPH from atony in patients exposed to CCBs at the time of delivery compared to those exposed to methyldopa or labetalol. These data suggest that concern about an increase in the risk of PPH should not affect obstetricians' decision about whether to prescribe a CCB for the control of hypertension in the third trimester.

Strengths and Limitations

Our study should be interpreted in the context of the limitations inherent in its design. First, while we have information on the dispensing of medications which is free from recall bias, we do not have information about whether the patient was compliant and took the medication as prescribed. To help overcome this limitation, we performed a sensitivity analysis including only those patients that refilled their prescription at least once during the third trimester, which strongly suggests that the patient is in fact consuming the medication. This did not tangibly change the results from the main analysis. Another potential limitation is that we do not have direct information on the reason why the CCB was prescribed. We therefore restricted our analysis to those patients that did not have diagnoses for indications for CCBs other than hypertension (preterm labor/threatened labor, arrhythmia, etc) and required a diagnostic code for pre-existing hypertension or gestational hypertension for the primary analysis. While there is still some potential for misclassification of the indication for CCBs, such misclassification is likely to be small and unlikely to significantly alter our results. Further, while we use a sophisticated and rigorous statistical methodology, propensity scores, to account for confounding, we are dependant on recording of claims in the inpatient and outpatient record for demographic and medical conditions; this may result in underascertainment or misclassification of some confounders. We attempted to overcome this potential limitation by minimizing the degree of confounding at the design stage by restricting our analysis to CCBs used for hypertension using an active comparator (treatment with methyldopa/labetalol) as a referent. There is also the potential in drug safety studies, such as the one presented here, for confounding by contraindication (i.e., if clinicians are concerned about the risk of PPH in a patient, they may not prescribe CCBs). However, such bias is unlikely to significantly affect our results, as most of the major risk factors for PPH are measured and adjusted for in our analysis. Further, we do not have direct information on the interval between the last CCB use and delivery. That said, our analysis does capture the effect of outpatient CCB use on the outcome of PPH as CCBs are used in routine practice. Last, after adjusting for relevant confounders, our study cannot exclude up to an 18% increase in the risk of PPH associated with CCB exposure. However, the MAX dataset used for this study is one of the largest of its kind. There were over nine-thousand patients included in the main cohort who were exposed to CCBs, methyldopa, and labetalol and for whom we had longitudinal information from throughout the third-trimester and delivery hospitalization. The failure to show even a trend towards increased risk of PPH associated with CCBs across a range of analytic approaches and sensitivity analyses, suggests that such an increased risk is unlikely to be present.

Interpretation

There are several potential explanations for the lack of association between CCB exposure proximate to the time of delivery and PPH. First, uterotonic agents are routinely administered following delivery as prophylaxis against uterine atony and hemorrhage.³⁷ It is

possible that these agents readily overcome the tocolytic effects of CCBs, which would yield a null result. Second, as our study examines CCBs administered in the outpatient setting, it is possible that for many women plasma levels are relatively low by the time delivery occurs (if the medication was discontinued during labor or if they were transitioned to another medication while in-hospital). Whatever the explanation, it is important that outpatient use of CCBs is not associated with PPH given the frequency with which these medications are prescribed during the third trimester.^{17, 18}

Conclusion

In conclusion, our results suggest that the outpatient use of CCBs in late pregnancy for the treatment of hypertension does not increase the risk of postpartum hemorrhage. An obstetrician or internist's decision about whether to use a CCB or another type of antihypertensive in late pregnancy should not be influenced by this consideration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Patient flow chart

Table 1

Baseline characteristics of patients in the overall cohort.

	CCB, N (%)	Methyldopa or Labetalol, N (%)	Difference (%)
Total	1226	8524	
Age group, y			
15 – 19	89 (7.3)	643 (7.5)	–0.3
20 – 24	298 (24.3)	2119 (24.9)	–0.6
25 – 29	313 (25.5)	2163 (25.4)	0.2
30 – 34	246 (20.1)	1829 (21.5)	–1.4
35 – 39	201 (16.4)	1295 (15.2)	1.2
40 – 44	70 (5.7)	434 (5.1)	0.6
Race			
White	491 (40.1)	4186 (49.1)	–9.1
Black	590 (48.1)	2795 (32.8)	15.3
Asian	13 (1.1)	107 (1.3)	–0.2
Hispanic	58 (4.7)	831 (9.8)	–5.1
Hispanic and other race	15 (1.2)	182 (2.1)	–0.9
Native American	25 (2)	164 (1.9)	0.1
Unknown	27 (2.2)	210 (2.5)	–0.3
Maternal medical conditions			
Pre-existing hypertension	1020 (83.2)	6860 (80.5)	2.7
Pre-gestational diabetes	200 (16.3)	1211 (14.2)	2.1
Obesity	125 (10.2)	870 (10.2)	0
Chronic renal disease	38 (3.1)	197 (2.3)	0.8
Fibroids	20 (1.6)	103 (1.2)	0.4
Maternal obstetric conditions			
Gestational hypertension	587 (47.9)	4379 (51.4)	–3.5
Mild preeclampsia	595 (48.5)	4268 (50.1)	–1.5
Severe preeclampsia	74 (6)	508 (6)	0.1
Gestational diabetes	268 (21.9)	1896 (22.2)	–0.4
Previous cesarean	314 (25.6)	2000 (23.5)	2.2
Placenta previa	16 (1.3)	122 (1.4)	–0.1
Multiple gestation	**	77 (0.9)	–0.3
Cesarean delivery	478 (39)	3557 (41.7)	–2.7
Induction of labor	284 (23.2)	1984 (23.3)	–0.1
Maternal medications			
Heparin	**	51 (0.6)	0.1
LMWH	**	41 (0.5)	0.3
Aspirin	**	48 (0.6)	0.2
Oral hypoglycemics	46 (3.8)	264 (3.1)	0.7

	CCB, N (%)	Methyldopa or Labetalol, N (%)	Difference (%)
Insulin	136 (11.1)	797 (9.4)	1.7
Iron	207 (16.9)	1620 (19)	-2.1
Vitamins	555 (45.3)	3903 (45.8)	-0.5
Medical care utilization			
Number of hospitalizations			
1	1002 (81.7)	7076 (83)	-1.3
2	188 (15.3)	1189 (14)	1.4
3+	36 (2.9)	259 (3)	-0.1
Number of outpatient visits			
0-9	236 (19.3)	1603 (18.8)	0.4
10-13	298 (24.3)	2319 (27.2)	-2.9
14-17	339 (27.7)	2112 (24.8)	2.9
18+	353 (28.8)	2490 (29.2)	-0.4
Number of prescription medications (other than antihypertensives)			
0	558 (45.5)	3953 (46.4)	-0.9
1	412 (33.6)	2709 (31.8)	1.8
2+	256 (20.9)	1862 (21.8)	-1.0

Cell count cannot be disclosed in accordance with data use agreement forbidding the reporting of cells with <11 patients; counts for Native Hawaiian, more than one race, age <15 or >44 also not shown due to small cell sizes.

Table 2

Baseline characteristics of patients in the propensity-score match cohort.

	CCB, N (%)	Methyldopa or Labetalol, N (%)	Difference (%)
Total	1225	3675	
Age group, y			
15 – 19	89 (7.3)	292 (8)	–0.7
20 – 24	297 (24.2)	905 (24.6)	–0.4
25 – 29	313 (25.6)	919 (25)	0.5
30 – 34	246 (20.1)	739 (20.1)	0
35 – 39	201 (16.4)	588 (16)	0.4
40 – 44	70 (5.7)	211 (5.7)	0
Race			
White	491 (40.1)	1464 (39.8)	0.2
Black	589 (48.1)	1766 (48.1)	0
Asian	13 (1.1)	38 (1)	0
Hispanic	58 (4.7)	235 (6.4)	–1.7
Hispanic and other race	15 (1.2)	50 (1.4)	–0.1
Native American	25 (2)	51 (1.4)	0.7
Unknown	27 (2.2)	57 (1.6)	0.7
Maternal medical conditions			
Pre-existing hypertension	1019 (83.2)	3062 (83.3)	–0.1
Pre-gestational diabetes	199 (16.2)	607 (16.5)	–0.3
Obesity	125 (10.2)	399 (10.9)	–0.7
Chronic renal disease	37 (3)	120 (3.3)	–0.3
Fibroids	20 (1.6)	61 (1.7)	0
Maternal obstetric conditions			
Gestational hypertension	587 (47.9)	1744 (47.5)	0.5
Mild preeclampsia	595 (48.6)	1779 (48.4)	0.2
Severe preeclampsia	74 (6)	220 (6)	0
Gestational diabetes	267 (21.8)	784 (21.3)	0.5
Previous cesarean	314 (25.6)	896 (24.4)	1.3
Placenta previa	16 (1.3)	37 (1)	0.3
Multiple gestation	**	20 (0.5)	0
Cesarean delivery	478 (39)	1394 (37.9)	1.1
Induction of labor	284 (23.2)	828 (22.5)	0.6
Maternal medications			
Heparin	**	25 (0.7)	0
LMWH	**	28 (0.8)	0
Aspirin	**	24 (0.7)	0.1
Oral hypoglycemics	46 (3.8)	143 (3.9)	–0.1

	CCB, N (%)	Methyldopa or Labetalol, N (%)	Difference (%)
Insulin	135 (11)	417 (11.4)	-0.3
Iron	207 (16.9)	608 (16.5)	0.4
Vitamins	555 (45.3)	1612 (43.9)	1.5
Medical care utilization			
Number of hospitalizations			
1	1001 (81.7)	3029 (82.4)	-0.7
2	188 (15.4)	545 (14.8)	0.5
3+	36 (2.9)	101 (2.8)	0.2
Number of outpatient visits			
0-9	236 (19.3)	697 (19)	0.3
10-13	298 (24.3)	898 (24.4)	-0.1
14-17	338 (27.6)	1028 (28)	-0.4
18+	353 (28.8)	1052 (28.6)	0.2
Number of prescription medications (other than antihypertensives)			
0	558 (45.6)	1712 (46.6)	-1.0
1	411 (33.6)	1215 (33.1)	0.5
2+	256 (20.9)	748 (20.4)	0.5

Cell count cannot be disclosed in accordance with data use agreement forbidding the reporting of cells with <11 patients; counts for Native Hawaiian, more than one race, age <15 or >44 also not shown due to small cell sizes.

Table 3

Odds ratios of postpartum hemorrhage in patients treated with pre-existing to gestational hypertension calcium channel blockers as compared with patients treated with methyldopa or labetalol

	CCB	Methyldopa/Labetalol	Odds ratio (95% CI)
Postpartum hemorrhage (overall)			
Unadjusted	27/1226	232/8524	0.81 (0.54 – 1.21)
Propensity score stratified	27/1182	228/8072	0.79 (0.53 – 1.19)
Propensity score matched	27/1225	105/3675	0.77 (0.50–1.18)
Postpartum hemorrhage from uterine atony			
Unadjusted	23/1226	178/8524	0.90 (0.58 – 1.39)
Propensity score stratified	23/1182	175/8072	0.90 (0.58 – 1.41)
Propensity score matched	23/1225	74/3675	0.93 (0.58–1.49)

Table 4

Sensitivity analysis (1) without restricting to those with diagnosis of pre-existing and gestational hypertension and (2) those who refilled the medication of interest at least once during the third trimester, (3) excluding from propensity score model clinical conditions or events that occur after the initiation of the medication, and (4) including the entire cohort without restriction.

	CCB	Methyldopa/Labetalol	Odds ratio (95% CI)
Without restricting to those with diagnosis of pre-existing to gestational hypertension			
Postpartum hemorrhage (overall)			
Unadjusted	43/1947	268/10351	0.85 (0.61 – 1.18)
Propensity score stratified	43/1865	260/9860	0.88 (0.63 – 1.23)
Propensity score matched	32/1545	106/4635	0.90 (0.61 – 1.35)
Postpartum hemorrhage from uterine atony			
Unadjusted	31/1947	210/10351	0.78 (0.53 – 1.14)
Propensity score stratified	31/1865	203/9860	0.85 (0.57 – 1.25)
Propensity score matched	25/1545	79/4635	0.95 (0.60 – 1.49)
Restricting to those with diagnosis of pre-existing or gestational hypertension and who refilled the medication of interest at least once during the third trimester			
Postpartum hemorrhage (overall)			
Unadjusted	22/915	161/6315	0.94 (0.60–1.48)
Propensity score stratified	22/883	159/5994	0.94 (0.60 – 1.49)
Propensity score matched	22/909	70/2727	0.94 (0.58 – 1.53)
Postpartum hemorrhage from uterine atony			
Unadjusted	19/915	126/6315	1.04 (0.64 – 1.70)
Propensity score stratified	19/883	124/5994	1.05 (0.64 – 1.73)
Propensity score matched	19/909	57/2727	1.00 (0.59 – 1.69)
Excluding from propensity score model clinical conditions or events that occur after the initiation of the medication			
Postpartum hemorrhage (overall)			
Unadjusted	27/1226	232/8524	0.81 (0.54 – 1.21)
Propensity score stratified	27/1189	228/8143	0.81 (0.54 – 1.21)
Propensity score matched	27/1226	96/3678	0.84 (0.55 – 1.29)
Postpartum hemorrhage from uterine atony			
Unadjusted	23/1226	178/8524	0.90 (0.58 – 1.39)
Propensity score stratified	23/1189	175/8143	0.92 (0.59 – 1.43)
Propensity score matched	23/1226	75/3678	0.92 (0.57 – 1.47)
Including the entire cohort, without restriction			
	CCB	Unexposed to CCB	
Postpartum hemorrhage (overall)			
Unadjusted	380/15052	84836/3607437	1.08 (0.97 – 1.19)
Propensity score stratified	269/9680	59814/2315606	1.06 (0.94 – 1.20)
Propensity score matched	380/15052	1117/45156	1.02 (0.91 – 1.15)
Postpartum hemorrhage from uterine atony			

	CCB	Methyldopa/Labetalol	Odds ratio (95% CI)
Unadjusted	280/15052	67003/3607437	1.00 (0.89 – 1.13)
Propensity score stratified	196/9680	47575/2315606	1.03 (0.90 – 1.19)
Propensity score matched	280/15052	823/45156	1.02 (0.89 – 1.17)