Asymptomatic postprandial hypotension in patients with diabetes: The KAMOGAWA-HBP study

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ABSTRACT
Aims/Introduction: Postprandial hypotension (PPH) refers to a decrease in systolic blood pressure by ≥20 or to <90 mmHg from baseline ≥100 mmHg within 2 h of a meal. Previous studies have reported an association between diabetes and PPH; however, the characteristics of PPH in patients with diabetes remain unclear.

Materials and Methods: We recruited patients with diabetes who regularly attended the diabetes outpatient clinic. Participants were instructed to carry out three sets of blood pressure measurements at six time points: just before and right after, and 30, 60, 90 and 120 min after their main meal of the day. Data on PPH symptoms were collected during an interview. To investigate the relationships between explanatory variables, PPH and associated symptoms, we carried out multiple logistic regression analyses.

Results: We analyzed data from 300 participants. There were 150 (50.0%) participants with PPH. Systolic blood pressure before a meal was significantly associated with PPH (odds ratio [OR] 1.56, 95% confidence interval [CI] 1.30–1.86, \(P<0.001\)), after adjusting for covariates. Furthermore, age (OR 1.08, 95% CI 1.01–1.16, \(P=0.027\)), hemoglobin A1c level (OR 2.39, 95% CI 1.01–5.64, \(P=0.030\)) and coefficients of variation of R-R intervals (OR 0.79, 95% CI 0.65–0.97, \(P=0.032\)) were significantly associated with asymptomatic PPH.

Conclusions: Half of the present study outpatients with diabetes had PPH. High systolic blood pressure before a meal was significantly associated with the risk of PPH. Older adults and patients with higher levels of hemoglobin A1c or an autonomic dysfunction might have difficulties recognizing symptoms of PPH.

INTRODUCTION
Postprandial hypotension (PPH) refers to a decrease in systolic blood pressure (SBP) by ≥20 or to <90 mmHg from a baseline of ≥100 mmHg within 2 h after a meal. It has been associated with syncope, and increased risk of coronary events and mortality. PPH is common among older adults, people with hypertension (HT) and people with neurological disorders; for example, Parkinson’s disease or multiple system atrophy. Furthermore, previous studies with small sample sizes have reported an association between diabetes and PPH. Nevertheless, the characteristics of patients with diabetes and PPH, and the prevalence of the syndrome, remain unclear. The present cross-sectional study involved a large number of outpatients with diabetes, aiming to estimate the prevalence of PPH in this population, and determine factors associated with PPH. We also investigated the prevalence of PPH symptoms, and factors associated with these symptoms.

METHODS
Study design
We sequentially recruited patients with diabetes who regularly attended the diabetes outpatient clinic at the Kyoto Prefectural University of Medicine Hospital, Kyoto, Japan, from January 2016 to December 2019. All procedures were approved by the institutional review board of the Kyoto Prefectural University of
Medicine Hospital (RBMR-E-349-4), and were carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

To be eligible for the present study, patients had to meet the following criteria: confirmed diabetes and age within the range of 20–95 years. Patients were excluded if they refused to provide consent, had secondary or malignant hypertension, had other causes of autonomic dysfunction including Parkinson’s disease or were deemed unsuitable for the study by the attending physician. Secondary hypertension was defined as high blood pressure (BP) that was caused by another medical condition; including the endocrine system. Malignant hypertension was defined as high BP that develops rapidly and causes some type of organ damage.

Data collection
BP was self-measured with an automatic upper arm BP measuring device, using the cuff-oscillometric method to generate a digital display of SBP/diastolic BP and heart rate values. Participants used their own devices or HEM-70801C automatic devices (Omron Healthcare Co., Ltd, Kyoto, Japan), provided by the study lead to participants who did not own one.

Participants were instructed to rest for a few minutes before each BP measurement. The cuff was placed around the upper arm, and its position was maintained at the level of the heart. Participants were instructed to carry out three series of six BP measurements at the following times at their main meal of the day: before a meal, right after a meal, and 30, 60, 90 and 120 min after the meal start. In the case of overlap between measurements right after and 30 min after a meal, the measurement right after a meal was omitted.

Participant characteristics, including age, duration of diabetes, results of a physiological and biochemical examination, and clinical and medication history, were extracted from medical records. Retinopathy was assessed by the International Clinical Diabetic Retinopathy Disease Severity Scale. Neuropathy was defined by the diagnostic criteria for diabetic neuropathy. A macrovascular complication was defined as the presence of a pre-existing cardiovascular disease, cerebrovascular disease or arteriosclerosis obliterans was confirmed when stated in the clinical history. We measured coefficients of variation of R-R intervals (CVRR) at rest to assess autonomic disorder and ankle brachial pressure index, and pulse wave velocity to assess arteriosclerosis. The lower value of the ankle brachial pressure index and the higher value of pulse wave velocity of results of both sides were selected and used in the present study.

Data on the symptoms of PPH, including sleepiness, dizziness and weakness, were collected during an interview with each patient.

Definition of PPH
In the present study, being PPH-positive was defined as either an SBP fall ≥20 mmHg relative to the pre-meal SBP within 2 h after a meal, or a pre-meal SBP ≥100 mmHg falling <90 mmHg within 2 h after a meal. Datasets without BP before a meal and/or 120 min after a meal, or datasets without more than two BP measurements at 30, 60 and 90 min after meal were excluded. Data from patients who completed fewer than two sets of measurements were excluded.

Sample size
We could not set a sample size before the study, because no reports had provided the relationship between the prevalence of PPH and the factors associated with PPH in patients with diabetes.

Statistical analysis
We used JMP version 13.0 software (SAS Institute, Cary, NC, USA) for statistical analyses. We considered P-values <0.05 as statistically significant. Participants were divided into two groups according to their PPH status. Continuous variables were presented as a median and interquartile range (IQR). Student’s t-test was used for evaluating statistical significance of differences in continuous variables by PPH status. Categorical variables were presented as counts (percentages). The χ²-test was used to evaluate the statistical significance of differences in categorical variables by PPH status.

To investigate the relationship between explanatory variables and PPH, we carried out multiple logistic regression analysis, considering the following factors, which were also included as independent variables in subsequent multiple logistic regression: age, hemoglobin A1c (HbA1c) level, SBP before meal, log urinary albumin : creatinine ratio and CVRR. In addition, because we considered that antihypertensive agents could affect PPH, we carried out the subgroup analysis in patients without antihypertensive medication. We also carried out the subgroup analysis to investigate the relationship between explanatory variables and symptoms of PPH in participants with confirmed PPH. The following factors, which were also included as independent variables in subsequent multiple logistic regression, were considered: age, HbA1c, SBP before a meal, log urinary albumin : creatinine ratio and CVRR.

RESULTS
A total of 353 participants were recruited for the present study. Among them, participants who did not submit their result sheets (n = 28), did not complete their result sheets (n = 16), had duplicate identification (n = 7) or missing identification data (n = 1), or had no diagnosis of diabetes (n = 1) were excluded. Finally, we included data from 300 participants (172 men) in the analysis (Figure 1).

Demographic and clinical characteristics of the participants are provided in Table 1. The median age of the patients was 70.0 years (IQR 64.0–75.0 years), diabetes duration was 14.0 years (IQR 8.0–21.0 years) and HbA1c level was 6.9% (IQR 6.4–7.5 years). Overall, 150 participants (50.0%) were positive for PPH. A total of 15 participants (10.4%) within the
PPH-positive group had symptoms associated with hypotension. Participants in the PPH-positive group had significantly higher values of age, HbA1c, SBP before a meal and UACR than did patients in the PPH-negative group. Finally, SBP before a meal was significantly associated with PPH (odds ratio [OR] 1.56, 95% confidence interval [CI] 1.30–1.86, \( P < 0.001 \)), after adjusting for covariates (Table 2).

Demographic and clinical characteristics of the participants without antihypertensive medication are provided in Table S1. SBP before a meal was significantly associated with PPH (OR 13.02, 95% CI 1.63–103.93, \( P = 0.012 \)), after adjusting for covariates (Table S2).

Concurrently, subanalysis was carried out on data from 144 patients in the PPH-positive group whose symptom data were obtained. In this group, patients without PPH symptoms were significantly older, and had higher HbA1c and lower CVRR values than patients with PPH symptoms (Table 3). In the PPH-positive group, age (OR 1.08, 95% CI 1.01–1.16, \( P = 0.027 \)), HbA1c (OR 2.39, 95% CI 1.01–5.64, \( P = 0.030 \)) and CVRR (OR 0.79, 95% CI 0.65–0.97, \( P = 0.032 \)) were significantly associated with asymptomatic PPH, after adjusting for covariates (Table 4).

**DISCUSSION**

The present study reported on the prevalence and clinical characteristics of PPH among outpatients with diabetes. Similar previous studies were restricted to a small number of patients\(^5\). This is the first study to report on PPH, based on a large number of patients with diabetes.

In the present study, half of the patients with diabetes had PPH. In previous studies, the reported prevalence of PPH was 27.4% among patients with HT\(^5\), and 18.9% among healthy participants\(^7\). The prevalence of PPH in diabetes patients was reported to be high, 37% among 35 patients\(^8\) or 44% among 16 patients with non-insulin-dependent diabetes mellitus\(^20\), although these studies contained a small number of patients compared with the present study. The present study showed a high prevalence of PPH among a larger number of patients with diabetes. Furthermore, in the present study, SBP before a meal was significantly and independently associated with PPH. This is consistent with previous reports in which uncontrolled HT was associated with PPH among patients with HT\(^21\). It has been suggested that treatment of HT is important to prevent PPH in patients with diabetes.

We considered the effect of antihypertensive medication on PPH; however, there was no association between antihypertensive medication and PPH status. Furthermore, the result of the subgroup analysis for patients without antihypertensive medication was similar to the main result. In the present study, antihypertensive medication might not affect PPH, rather, adequate treatment of HT is recommended.

Although the mechanism of PPH remains unknown, some theories have been proposed. For example, PPH might result from inadequate compensation for the normal physiological postprandial decrease in BP. Patients with stable BP who have splanchnic blood pooling after a meal are able to maintain systemic BP through a sympathetic response; specifically, by increasing their heart rate, peripheral vascular resistance and cardiac output. Concurrently, patients with PPH have a blunted sympathetic response to hypotension. It has been hypothesized that compensatory failure underlies PPH\(^1\).

Diabetes commonly causes autonomic dysfunction\(^22\). There was no association between PPH and CVRR (Table 1), or changes in SBP before and after a meal and CVRR (data are
Table 1 | Demographic and clinical characteristics of participants with diabetes

|                               | PPH +       | PPH −       | P-value  |
|-------------------------------|-------------|-------------|----------|
| **n**                         | 150 (50.0)  | 150 (50.0)  | –        |
| **Age (years)**               | 70.0 (64.4–76.0) | 69.0 (62.8–73.3) | 0.050*   |
| **Female**                    | 63 (42.0)   | 65 (43.3)   | 0.815    |
| **Body mass index (kg/m²)**   | 22.6 (20.8–25.0) | 23.3 (21.0–25.8) | 0.136    |
| **Hemoglobin A1c (%) (mmol/mol)** | 7.1 (6.5–7.6)/54 (48–60) | 6.8 (6.4–7.3)/51 (46–60) | 0.032*   |
| **Duration of diabetes (years)** | 15.0 (9.0–20.0) | 13.0 (7.0–22.0) | 0.746    |
| **SBP before a meal (mmHg)**  | 144.0 (133.8–156.3) | 131.5 (122.0–143.0) | <0.001*  |
| **DBP before a meal (mmHg)**  | 78.0 (72.0–86.0) | 75.0 (69.0–82.0) | 0.074    |
| **Estimated glomerular filtration rate (mL/min/1.73 m²)** | 70.1 (51.9–81.6) | 69.0 (53.3–84.2) | 0.355    |
| **Urinary albumin : creatinine ratio (mg/g)** | 29.3 (9.5–114.8) | 18.0 (8.3–52.0) | 0.014*   |
| **Pulse wave velocity (m/s)** | 1,746.0 (1,557.0–2,044.0) | 1,784.5 (1,572.0–2,030.8) | 0.687    |
| **Ankle-brachial pressure index** | 1.12 (1.06–1.16) | 1.13 (1.05–1.17) | 0.286    |
| **Coefficient of variation of R-R intervals (%)** | 2.57 (1.63–3.26) | 2.73 (1.77–3.84) | 0.394    |
| **Retinopathy (SDR/PPDR and PDR)** | 22 (14.7)/17 (11.3) | 21 (14.1)/19 (12.8) | 0.830    |
| **Neuropathy**                | 56 (37.3)   | 54 (36.2)   | 0.353    |
| **Macroangiopathy**           | 42 (28.0)   | 37 (24.7)   | 0.512    |
| **Smoking status (current smoker/past smoker)** | 17 (11.3)/60 (40.0) | 16 (10.7)/53 (35.6) | 0.369    |
| **Alcohol consumption status (daily/social)** | 25 (16.7)/35 (23.3) | 33 (22.2)/25 (16.8) | 0.381    |
| **Medication for diabetes**   | 141 (94.0)  | 132 (88.0)  | 0.069    |
| **Sulfonylureas**             | 46 (30.7)   | 108 (72.0)  | 0.612    |
| **Glinide**                   | 18 (12.0)   | 24 (16.0)   | 0.318    |
| **α-Glucosidase inhibitor**   | 22 (14.7)   | 31 (20.7)   | 0.173    |
| **Biguanide**                 | 49 (32.7)   | 59 (39.3)   | 0.229    |
| **Thiazolidinediones**        | 4 (2.7)     | 9 (6.0)     | 0.156    |
| **DPP-4 inhibitor**           | 89 (59.3)   | 86 (57.3)   | 0.725    |
| **SGLT2 inhibitor**           | 22 (14.7)   | 18 (12.0)   | 0.497    |
| **GLP-1 receptor agonist**    | 8 (5.3)     | 11 (7.3)    | 0.477    |
| **Insulin**                   | 48 (32.0)   | 37 (24.7)   | 0.159    |
| **Medication for diabetes**   | 141 (94.0)  | 132 (88.0)  | 0.069    |
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| **Insulin**                   | 48 (32.0)   | 37 (24.7)   | 0.159    |
| **Antihypertensive medication** | 85 (56.7)   | 84 (56.0)   | 0.907    |
| **RAS inhibitor**             | 72 (48.0)   | 71 (47.3)   | 0.908    |
| **CCB**                       | 53 (35.3)   | 46 (30.7)   | 0.39     |
| **Diuretics**                 | 15 (10.0)   | 14 (9.3)    | 0.845    |
| **β-Blocker**                 | 12 (8.0)    | 7 (4.7)     | 0.236    |
| **α-Blocker**                 | 19 (12.7)   | 10 (6.7)    | 0.079    |
| **Symptoms**                  | 15 (10.4)   | 8 (5.5)     | 0.120    |

For categorical variables, count (%) is presented. For continuous variables, median (interquartile range) is presented. The difference between groups was analyzed with the Student’s t-test (*P < 0.05). CCB, calcium channel blocker; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PPH, postprandial hypotension; RAS, renin–angiotensin system; SBP, systolic blood pressure; SDR, simple diabetic retinopathy; SGLT2, sodium–glucose transporter 2.

Table 2 | Crude and adjusted odds ratios for postprandial hypotension

|                               | Unadjusted OR (95% CI) | P-value  | Adjusted OR (95% CI) | P-value  |
|-------------------------------|------------------------|----------|----------------------|----------|
| **Age (years)**               | 1.02 (1.00–1.05)       | 0.049*   | 1.00 (0.97–1.03)     | 0.834    |
| **Hemoglobin A1c (%)**        | 1.34 (1.02–1.76)       | 0.031*   | 1.29 (0.94–1.75)     | 0.108    |
| **SBP before a meal (10 mmHg)** | 1.62 (1.38–1.91)      | <0.001*  | 1.56 (1.30–1.86)     | <0.001*  |
| **Log UACR (mg/g)**           | 1.24 (1.06–1.45)       | 0.006*   | 1.06 (0.88–1.27)     | 0.559    |
| **α-Glucosidase inhibitor**   | 2.03 (0.91–4.53)       | 0.077    | 2.23 (0.80–6.20)     | 0.114    |

Model 1: crude odds ratios (ORs). Model 2: ORs adjusted for age, hemoglobin A1c, systolic blood pressure (SBP) before a meal, log urinary albumin : creatinine ratio and α-glucosidase inhibitor. *P < 0.05.
not shown) in the present study, although we speculate that the high prevalence of PPH among diabetes patients in the present study might be due to a higher rate of autonomic dysfunction among these patients. It has been reported that intraduodenal glucose might cause a decrease in postprandial BP among older adults; however, it does not correspond to a difference in the magnitude of heart rate response or muscular sympathetic nerve activity. These findings suggest that there are other mechanisms that are likely responsible for PPH. For example, a previous study has reported that neuropeptide Y and insulin have vasodilatory effects and are related to PPH.

### Table 3 | Demographic and clinical characteristics of postprandial hypotension-positive participants with diabetes

| Symptom + | Symptom - | \( P \)-value |
|-----------|-----------|--------------|
| \( n \)   | 15 (10.4) | 129 (89.6)   | –            |
| Age (years) | 67 (63.0–71.0) | 70 (65.0–76.0) | 0.012*       |
| Female     | 4 (26.7)  | 57 (44.2)    | 0.194        |
| Body mass index (kg/m\(^2\)) | 248 (226–273) | 225 (207–249) | 0.113        |
| Hemoglobin A1c (%/mmol/mol) | 6.7 (6.3–7.1)/50 (45–54) | 7.1 (6.6–7.6)/54 (49–60) | 0.022*       |
| Duration of diabetes (years) | 140 (1.0–170) | 150 (90–208) | 0.228        |
| SBP before a meal (mmHg) | 1440 (1310–1580) | 1420 (1335–1560) | 0.645        |
| DBP before a meal (mmHg) | 780 (760–860) | 780 (690–860) | 0.845        |
| Urinary albumin : creatinine ratio (mg/g) | 39.0 (8.2–175.6) | 28.0 (9.0–102.3) | 0.448        |
| Pulse wave velocity (m/s) | 1,704.0 (1,434.0–1,813.5) | 1,746.0 (1,559.5–2,091.0) | 0.262        |
| Ankle-brachial pressure index | 1.13 (1.05–1.17) | 1.12 (1.06–1.16) | 0.868        |
| Coefficient of variation of R-R intervals (%) | 3.02 (2.89–3.92) | 2.40 (1.60–3.23) | 0.029*       |
| Retinopathy (SDR/PPDR and PDR) | 3 (20.0)/2 (13.3) | 19 (14.7)/15 (11.6) | 0.926        |
| Neuropathy | 6 (40.0)  | 49 (38.0)    | 0.935        |
| Macroangiopathy | 4 (26.7)  | 38 (29.3)    | 0.822        |
| Smoking status (current smoker/past smoker) | 0 (0.0)/8 (53.3) | 16 (12.4)/49 (38.0) | 0.540        |
| Alcohol consumption status (daily/social) | 4 (26.7)/5 (33.3) | 18 (14.0)/30 (23.3) | 0.501        |
| Medication for diabetes | 14 (93.3) | 122 (94.6) | 0.843        |
| Sulfonylureas | 4 (26.7)  | 41 (31.8)    | 0.686        |
| Glimepiride | 1 (6.67)  | 16 (12.4)    | 0.515        |
| a-Glucosidase inhibitor | 2 (13.3)  | 20 (15.5)    | 0.825        |
| Biguanide | 7 (46.7)  | 42 (32.6)    | 0.275        |
| Thiazolidinediones | 0 (0.0)  | 4 (3.1)      | 0.489        |
| DPP-4 inhibitor | 8 (53.3)  | 76 (58.9)    | 0.678        |
| SGLT2 inhibitor | 4 (26.7)  | 17 (13.2)    | 0.161        |
| GLP-1 receptor agonist | 2 (13.3)  | 6 (4.7)      | 0.165        |
| Insulin | 5 (33.3)  | 42 (32.6)    | 0.952        |
| Antihypertensive medication | 9 (60.0)  | 73 (56.6)    | 0.801        |

For categorical variables, count (%) is presented. For continuous variables, median (interquartile range) is presented. The difference between groups was analyzed with the Student’s \( t \)-test \(( \* P < 0.05)\). DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; SBP, systolic blood pressure; SDR, simple diabetic retinopathy; SGLT2, sodium–glucose transporter 2.

### Table 4 | Crude and adjusted odds ratios for asymptomatic postprandial hypotension in the postprandial hypotension-positive group

| Model 1 | Model 2 |
|---------|---------|
| Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
| \( P \)-value | \( P \)-value |
| Age (years) | 1.07 (1.01–1.14) | 1.08 (1.01–1.16) |
| Hemoglobin A1c (%) | 2.60 (1.17–5.75) | 2.39 (1.01–5.64) |
| SBP before a meal (10mmHg) | 0.93 (0.67–1.28) | 0.77 (0.54–1.08) |
| CVRR (%) | 0.83 (0.68–1.00) | 0.79 (0.65–0.97) |

Model 1: crude odds ratios (ORs). Model 2: ORs adjusted for age, hemoglobin A1c, systolic blood pressure (SBP) before a meal and coefficient of variation of R-R intervals (CVRR). CI, confidence interval. \( \* P < 0.05 \).
Although the prevalence of PPH was high in the present study, just 10.4% of the included patients with PPH were aware of symptoms associated with BP decrease after a meal. Furthermore, older age and higher HbA1c and lower CVRV values in the PPH-positive group were significantly associated with lack of PPH symptoms. The present findings suggest that older patients, or patients with poor glycemic control or an autonomic dysfunction might have difficulties recognizing symptoms, such as sleepiness, dizziness and weakness, when their BP has fallen, and that they might be at a higher risk of sudden syncope or falling. This concept is similar to “hypoglycemia unawareness,” which refers to a lack of subjective hypoglycemia symptoms. One of the causes of hypoglycemia unawareness is a decrease in the sympathetic nerve response.

The present study had several limitations. First, the devices used to measure BP in this study were not standardized. However, BP-measuring devices available in Japan have been validated and approved by the Ministry of Health, Labor and Welfare of Japan, and comply with the USA27 or European standards.28 Furthermore, each patient carried out a series of BP measurements using the same device; it is likely that BP fluctuation of each patient was accurately evaluated. Second, the type, volume, content and timing of the meals designated for BP measurements were not standardized. A previous study has reported that the amount of rice consumed might affect the type, volume, content and timing of the meals designated for PPH. A decrease in the sympathetic nerve response26. Therefore, differences in meals might affect the present findings. However, the present study protocol for evaluating PPH closely reflects real-world circumstances associated with meal consumption. Third, diagnostic criteria for PPH, based on home measurements have not been established; it is not clear whether three sets of measurements are sufficient. Future studies should consider what the appropriate number of measurements might be, alongside the desired measurement sensitivity. Fourth, as the present study only included patients capable of measuring and recording their own BP, older adult patients with disorders, such as dementia or cerebrovascular disorders, were excluded. These groups of patients are at high risk of PPH. Therefore, the prevalence of PPH reported in the present study might be underestimated. Fifth, symptoms of PPH were collected during interviews with patients. In addition, the symptoms cannot be determined to be as a result of hypotension. Finally, the present study was restricted to Japanese participants. The generalizability of our findings to non-Japanese populations is unclear.

In the present study, half of the participating outpatients with diabetes had PPH, and high SBP before a meal was associated with PPH. In addition, “PPH unawareness” was likely present. Patients with diabetes need to be monitored for HT to prevent the development of complications and PPH. Furthermore, treatment of older adults with diabetes, patients with uncontrolled diabetes or diabetes-related autonomic nervous system disorders should include PPH monitoring, even when subjective symptoms have not been reported.

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DISCLOSURE

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Characteristic of participants with no antihypertensive medication.

**Table S2** | Unadjusted and adjusted odds ratios for PPH in participants with no antihypertensive medication.