Impact of sustained hypertension on new cardiovascular events in patients with type 2 diabetes: KAMOGAWA-HBP study

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Abstract
We have previously shown that masked hypertension (MH) and sustained hypertension (SH) contribute to the progression of diabetic nephropathy. Although the risk of target organ damage and cardiovascular events in MH and SH is significantly higher than that in normotension and white coat hypertension, the role of MH or SH in cardiovascular events has never been reported in studies specific to diabetic patients. Therefore, in this study, we aimed to determine whether blood pressure control status contributes to the development of new cardiovascular events. A longitudinal study of 1082 patients with type 2 diabetes mellitus and no history of cardiovascular events was conducted. Patients were instructed to have their blood pressure measured three times, every morning and evening, for 14 consecutive days. Hypertension status was classified into four groups based on the systolic blood pressure measurements in the clinic and at home. The primary endpoint was the first cardiovascular event. After a median follow-up of 7.0 (interquartile range, 4.0–9.0) years, 119 patients developed cardiovascular events. The hazard ratio (95% confidence interval) for the risk of developing cardiovascular events was significantly higher in the SH group than in the controlled blood pressure group (1.63 [1.02–2.59]). SH is a useful predictor of cardiovascular events. Both at home and in the clinic, blood pressure monitoring should be assessed in routine clinical practice to predict future cardiovascular events in patients with type 2 diabetes.

KEYWORDS
new cardiovascular events, sustained hypertension, type 2 diabetes
The proportion of Japanese individuals with systolic blood pressure (BP) ≥140 mmHg is decreasing, but approximately 9000 patients succumb to hypertensive diseases, including hypertensive heart disease, cardio-renal disease, and other hypertensive diseases, every year. The complication rate of hypertension in diabetic patients is about two times higher than that in non-diabetic patients, and the complication rate of diabetes in hypertensive patients is 2–3 times higher than that in non-hypertensive patients. An essential objective of the treatment of patients with diabetes is to prevent the progression of complications. Diabetes and hypertension together increase micro- and macrovascular complications. Therefore, it is necessary to control the blood glucose level and BP. Studies have suggested that home BP (HBP) control is more effective than that of office BP, as the latter is significantly associated with organ damage. Furthermore, masked hypertension (MH) and white-coat hypertension (WCH) can be detected by measuring HBP. With the KAMOGAWA-HBP study, we previously reported that MH and sustained hypertension (SH) with elevated BP in both ambulatory and home settings contribute to the progression of diabetic nephropathy. The risks of target organ damage and cardiovascular events in MH and SH are significantly higher than those in normotension and WCH. However, none of the cohort studies specific to diabetic patients reported that MH or SH detected by HBP measurement had an impact on cardiovascular events. Therefore, we investigated whether MH or SH contributes to the development of new cardiovascular events in the same cohort of patients with diabetes as shown in the previous study.

2 | METHODS

2.1 | Study design

This study was a longitudinal cohort study. We used data from a KAMOGAWA-HBP study of type 2 diabetic patients visiting the outpatient diabetes clinic of the Kyoto Prefectural University of Medicine Hospital or four other general hospitals.

2.2 | Study population

We recruited 1526 consecutive patients with type 2 diabetes aged 20 years or older who visited the facilities regularly from March 2008 to October 2017. No exclusion criteria were established for the BP level in this study. Patients who failed to have HBP measured (n = 21) were excluded. Additionally, patients with a history of cardiovascular events (n = 391; history of cerebrovascular disease, cardiovascular disease, or atherosclerosis obliterans based on physical examination and clinical history) were excluded. Patients who had missing data (n = 3) and without follow-up (n = 29) were also excluded. Therefore, 1082 patients (574 men and 508 women) were finally included in the study. The diagnosis of type 2 diabetes was based on the American Diabetes Association criteria. All procedures were approved by the local Research Ethics Committee (RBMR-E-349) and carried out following the Declaration of Helsinki. Informed consent was obtained from all the patients.

2.3 | HBP and clinic BP measurements

BP was measured by the patients themselves using an automatic BP measuring device (HEM-7080IC, Omron Healthcare Co. Ltd, Kyoto, Japan). Patients were seated at rest for at least 2 min, and their clinic BP was measured by a physician or a nurse on three consecutive occasions. The clinic BP was defined as the mean of three readings for a single day using the HEM-7080IC when we rented the device. Patients were instructed to measure BP three times, every morning and evening, with at least 1 min between recordings, for 14 consecutive days. HBP was measured within an hour of waking up in the morning (after urination, after resting in a sitting position for at least 5 min, before breakfast, and before taking medication) and immediately before bedtime. The HBP value was calculated from the 14-day average of the mean values of the three measurements taken each morning and evening. In this study, the average morning and evening HBP readings were used as the HBP values.

2.4 | Data collection

Blood samples were drawn in the morning. Spot urine samples were collected in the morning and urinary albumin excretion (UAE) was measured using an immunoturbidimetric assay (Autokit Micro Albumin, Wako, Osaka, Japan). The average value for UAE was determined from triplicate urine collections. The characteristics of each patient were obtained from the initial interview and routine physical examination conducted at entry. Nephropathy was classified into three levels according to the level of UAE: normoalbuminuria (<30 mg/g Cr), microalbuminuria (30–300 mg/g Cr), and macroalbuminuria (>300 mg/g Cr). Neuropathy was diagnosed on the basis of the diagnostic criteria for diabetic neuropathy proposed by the Diagnostic Neuropathy Study Group. Retinopathy was classified into three levels: “no diabetic retinopathy,” “simple diabetic retinopathy,” and “proliferative diabetic retinopathy.” Macrovascular complications were defined as the presence of a history of cerebrovascular disease, cardiovascular disease, or atherosclerosis obliterans, based on the patient’s medical history.

2.5 | Definition of hypertension status

Hypertension status was classified into four categories based on BP measurements in the clinic and at home (Figure 1). This was done according to the hypertension diagnostic criteria outlined in the 2019 Japanese Society of Hypertension. According to the guidelines for the management of hypertension, WCH, which includes white-coat uncontrolled hypertension in
patients with antihypertensive treatment, was defined as clinic systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg, with home systolic BP $< 135$ mmHg and diastolic BP $< 85$ mmHg. MH, which includes masked uncontrolled hypertension in patients with antihypertensive treatment, was defined as home systolic BP $\geq$ 135 mmHg and/or diastolic BP $\geq$ 85 mmHg, with clinic systolic BP $< 140$ mmHg and diastolic BP $< 90$ mmHg. SH, which includes sustained uncontrolled hypertension in patients with antihypertensive treatment, was defined as elevated clinic BP (systolic $\geq 140$ mmHg and/or diastolic $\geq 90$ mmHg) and home (systolic BP $\geq 135$ mmHg and/or diastolic BP $\geq 85$ mmHg) and controlled BP, which includes true uncontrolled hypertension in patients with antihypertensive treatment, as low clinic (systolic BP $< 140$ mmHg and diastolic BP $< 90$ mmHg) and home (systolic BP $< 135$ mmHg and/or diastolic BP $< 85$ mmHg). Patients were divided into four groups—controlled BP, WCH, MH, and SH—according to their hypertension status, with or without antihypertensive treatment.13

### 2.6 Definition of composite cardiovascular endpoint

The endpoints were retrospectively referenced to medical records and classified on the basis of the International Classification of Diseases, 10th Edition.14 The cardiovascular composite endpoint was defined based on the patient’s medical history: angina pectoris (I20), cardiovascular death (I00 to I19), transient ischemic attack (G45), nonfatal stroke (I60, I61, I63), nonfatal myocardial infarction (I21), heart failure (I50), unspecified carotid artery occlusion and stenosis (I65), and atherosclerosis obliterans (I73). When assessing outcomes, only the first event was considered.

### 2.7 Statistical analysis

Patient characteristics are described by numbers indicating medians and interquartile ranges (IQRs) or proportions. ANOVA and the $\chi^2$ statistic were used for comparison among the four subgroups. We used Kaplan–Meier and standardized hazard ratios (HRs) were derived from Cox regression analysis to express the risk of developing cardiovascular events in the WCH, MH, and SH groups relative to the controlled BP group. To express the change in risk associated with a 10 mmHg increase in home and clinic BP measurements, we derived standardized HRs from Cox regression. The dependent variable was the number of months between enrollment in the study and the occurrence of the event or the censoring of survivors by December 2018. We set up a multivariate model adjusted for body mass index, age, sex, triglycerides, hemoglobin A1C, and smoking status (model 1); and a multivariate model adding antihypertensive medication status, oral hypoglycemic agent, insulin, and glucagon-like peptide-1 to the variables in model 1 (model 2). Adjusted odds ratios and 95% confidence intervals (CIs) were estimated. Subgroup analysis by age ($\geq 65$ years, <65 years) and by the presence or absence of antihypertensive medication was performed. The SPSS statistical package (version 23.0J, SPSS, Inc., Chicago, IL, USA) was used for statistical analysis, and a two-sided $p < .05$ was considered statistically significant.

### 3 RESULTS

Patients were followed up for a median period of 7.0 years (IQR: 4.0–9.0) and a maximum of 10.4 years. The Kaplan–Meier curves for the entire period without a first cardiovascular event as an endpoint are shown in Figure S1. Baseline characteristics are shown in Table 1. A total of 1082 patients were included in this study. The median age was 65.0 (IQR: 58.0–72.0) years and hemoglobin A1C was 7.1% (IQR: 6.6–7.8). The proportions of patients in the controlled BP, MH, WCH, and SH groups were 44.8%, 12.7%, 9.8%, and 57.9%, respectively. The number (rate) of cardiovascular events in the controlled BP, MH, WCH, and SH groups were 33 (6.8), 20 (14.6), 14 (13.2), and 52 (14.7), respectively. The proportions of patients receiving antihypertensive treatment in those groups were 41.6%, 62.0%, 50.9%, and 57.9%, respectively. The median numbers of days of morning and evening BP measurements per patient were 13.0 (IQR: 12.0–14.0) and 14.0 (IQR: 12.0–14.0) days, respectively.

The adjusted HR (95% CI) of the SH group was significantly higher than that of the controlled BP group (Model 1: 1.71 [1.08–2.73] and Model 2: 1.63 [1.02–2.59], respectively). However, there was no significant increase in the risk of cardiovascular events in the WCH and MH groups, compared with the controlled BP group (Table 2).

The adjusted HR (95% CI) for each 10 mmHg increase in home and clinic systolic BP for cardiovascular events were 1.01 (.79–1.29) and 1.19 (.97–1.46), respectively, and in home and clinic diastolic BP for cardiovascular events were 1.20 (.76–1.90) and .71 (.48–1.03), respectively.

The adjusted HR (95% CI) for cardiovascular events in the SH group with respect to the controlled BP group was 1.75 (.82–3.74) in patients aged < 65 years and 1.45 (.79–2.67) in patients aged > 65 years (Tables S1 and S2). Of the 558 patients aged $\geq 65$ years, 210 (37.6%) were in the SH group, of whom 31 (14.8%) had cardiovascular events. Of the 524
### Table 1: Baseline characteristics of the patients

| Characteristics                                      | All (1082) | Controlled BP group (485) | WCH group (137) | MH group (106) | SH group (354) |
|------------------------------------------------------|------------|---------------------------|-----------------|----------------|----------------|
| Male                                                 | 574 (53.0) | 255 (52.6)                | 70 (51.1)       | 61 (57.5)      | 188 (53.1)     |
| Age, years                                           | 65.0 (58.0-72.0) | 63.0 (57.0-69.0) | 65.0 (59.5-72.0)* | 66.0 (58.8-73.0) | 67.0 (60.0-74.0)** |
| Duration of diabetes mellitus, years                 | 9.0 (5.0-16.8) | 8.0 (4.0-15.0)          | 10.0 (4.0-18.0) | 11.5 (5.0-19.8) | 10.0 (5.0-18.0) |
| Body mass index, kg/m2                               | 23.4 (21.4-25.7) | 22.9 (21.1-25.0)       | 23.5 (21.3-25.4) | 23.9 (21.3-26.3) | 23.9 (21.9-26.6)** |
| Hemoglobin A1C, %                                    | 7.1 (6.6-7.8) | 7.0 (6.1-7.2)          | 6.5 (6.0-7.4)   | 6.9 (6.3-7.5)** | 6.8 (6.4-7.6)** |
| Hemoglobin A1C, mmol/mol                              | 54.1 (48.6-61.7) | 53.0 (43.2-55.2)       | 47.5 (42.1-57.4) | 51.9 (45.3-58.5)** | 50.8 (46.4-59.5)** |
| Total cholesterol, mg/dl                             | 191.0 (170.5-214.0) | 189.0 (170.0-213.0) | 186.0 (167.5-204.0) | 193.5 (181.8-216.5) | 194.0 (170.2-216.0) |
| Triglycerides, mg/dl                                 | 116.0 (81.0-173.0) | 110.0 (75.0-158.0)     | 108.0 (80.0-158.0) | 124.0 (91.8-185.0) | 127.0 (87.0-193.0)** |
| Creatinine, mg/dl                                    | .7 (.6-.9) | .7 (.6-.9)                | .7 (.6-.9)       | .8 (.6-10)** | .7 (.6-.9)     |
| Clinic systolic blood pressure, mmHg                 | 136.2 (124.7-150.3) | 126.7 (117.3-136.0)    | 144.7 (140.3-150.9)** | 135.3 (128.7-143.3)** | 151.3 (143.0-164.0)** |
| Clinic diastolic blood pressure, mmHg                | 76.0 (69.3-84.3) | 73.7 (67.3-80.3)       | 80.3 (73.3-86.6)** | 76.0 (70.0-83.0) | 83.2 (74.5-90.8)** |
| Home systolic blood pressure, mmHg                   | 133.4 (122.2-144.3) | 120.0 (113.1-127.0)    | 128.7 (124.3-132.3)** | 139.3 (136.4-142.7)** | 146.5 (139.7-154.9)** |
| Home diastolic blood pressure, mmHg                  | 74.4 (67.5-81.2) | 67.9 (63.3-73.0)       | 70.8 (65.0-76.2)** | 76.5 (69.7-82.4)** | 78.1 (71.6-87.2)** |
| Smoking status                                        |             |                          |                 |                 |                |
| Current                                              | 195 (18.0) | 81 (16.7)                | 15 (10.9)       | 20 (18.9)      | 79 (22.3)      |
| Past                                                 | 267 (24.7) | 117 (24.1)               | 38 (27.7)       | 29 (24.7)      | 83 (23.4)      |
| Alcohol consumption status                           |             |                          |                 |                 |                |
| Daily                                                | 242 (22.4) | 98 (20.2)                | 35 (25.5)       | 22 (20.8)      | 87 (24.6)      |
| Social                                               | 229 (21.2) | 110 (22.7)               | 30 (21.9)       | 12 (11.3)      | 77 (21.8)      |
| Nephropathy (UAE 30–300)                             | 315 (29.1) | 113 (23.3)               | 32 (23.4)       | 31 (29.2)      | 139 (39.2)**   |
| Retinopathy                                           |             |                          |                 |                 |                |
| SDR                                                  | 163 (15.1) | 62 (12.7)                | 19 (13.9)       | 18 (17.0)      | 64 (18.1)      |
| PDR                                                  | 108 (10.0) | 36 (7.4)                 | 23 (16.8)       | 12 (11.3)      | 37 (10.5)      |
| Neuropathy                                           | 334 (30.9) | 129 (26.6)               | 45 (32.8)       | 34 (32.1)      | 126 (35.6)     |
| Antihypertensive medication                          | 546 (50.5) | 202 (41.6)               | 85 (62.0)**     | 54 (50.9)      | 205 (57.9)**   |
| Hypoglycemic treatment                               |             |                          |                 |                 |                |
| diet/OHA/insulin/GLP-1                                | 182/795/237/23 | 85/359/102/12         | 29/95/32/2      | 16/79/26/3     | 52/262/77/6    |
| First onset of cardiovascular events                  | 119 (11.0) | 33 (6.8)                 | 20 (14.6)**     | 14 (13.2)      | 52 (14.7)**    |

Note: For categorical variables, n (%) is presented. For continuous variables, the median (interquartile range) is presented. Abbreviations: BP, blood pressure; GLP-1, glucagon-like peptide-1; MH, masked hypertension; OHA, oral hypoglycemic agent; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy; SH, sustained hypertension; UAE, urinary albumin excretion; WCH, white-coat hypertension.

*p < .05, **p < .0001, ***p < .01, for difference versus Controlled BP group; ANOVA or χ² test for comparison among the four subgroups.

### Table 2: Adjusted hazard ratios for cardiovascular events in patients with type 2 diabetes

| Group (number of events/total patients) | * Model 1 | * Model 2 |
|----------------------------------------|-----------|-----------|
|                                        | Adjusted HR (95% CI) | p value | Adjusted HR (95% CI) | p value |
| Controlled BP group (33/485)            | 1         | 1         |
| WCH group (20/137)                      | 1.75 (.97-3.16) | .063      | 1.61 (1.89-2.92) | .119  |
| MH group (14/106)                       | 1.52 (.79-2.92) | .210      | 1.47 (.76-2.83) | .248  |
| SH group (52/354)                       | 1.71 (1.08-2.73) | .023      | 1.63 (1.02-2.59) | .042  |

Abbreviations: BP, blood pressure; CI, confidence interval; GLP-1, glucagon-like peptide-1; HR, hazard ratio; MH, masked hypertension; OHA, oral hypoglycemic agent; SH, sustained hypertension; WCH, white-coat hypertension.

* Model 1: Odds ratios were adjusted for sex, age, body mass index, hemoglobin A1C, triglyceride and smoking status.

* Model 2: Odds ratios were adjusted for the variables in Model 1 with additional adjustment for antihypertensive medication use, OHA, insulin and GLP-1.
patients aged < 65 years, 144 (27.5%) were in the SH group, of whom 21 (14.6%) had cardiovascular events.

Furthermore, the adjusted HR (95% CI) for cardiovascular events in the SH group with respect to the controlled BP group was 1.42 (.63–3.19) in patients who did not use antihypertensive medications and 1.79 (.99–3.25) in patients who used antihypertensive medications (Tables S3 and S4). In the present study, 149 (27.8%) of the 536 patients not using antihypertensive medication were in the SH group, of whom 14 (9.4%) had cardiovascular events. Of the 546 patients using antihypertensive medication, 205 (37.5%) were in the SH group, of whom 38 (18.5%) had cardiovascular events.

4 | DISCUSSION

In the KAMOGAWA-HBP cohort study of 1082 patients with type 2 diabetes, for a median period of 7.0 years, we examined the relationship between BP control status and incidence of new cardiovascular events. The present study showed that patients in the SH group, but not the WCH and MH groups, had a significantly higher risk of developing new cardiovascular events than those in the controlled BP group.

A meta-analysis of seven studies not specific to diabetes showed that composite cardiovascular events were significantly lower in MH patients than in SH patients. On the other hand, other previous reports have also found MH to be a significant predictor of target organ damage and cardiovascular outcomes. There are several possible reasons to explain the discrepancy between previous reports and the present findings. There are differences in the method of measuring BP (HBP measurement or ambulatory BP monitoring). Furthermore, different study endpoints may also affect the outcome. The Japan Morning Surge–Home Blood Pressure study of outpatients with a history or risk of cardiovascular disease indicated that SH and MH are associated with an increased risk of stroke events but not with an increased risk of coronary heart disease. In the present study, when coronary heart disease events (cardiovascular death, angina pectoris, nonfatal myocardial infarction, or heart failure) and carotid cerebrovascular events (unspecified carotid artery occlusion and stenosis, nonfatal stroke, or transient ischemic attacks) were separately evaluated, the adjusted HR (95% CI) for the risk of coronary heart disease events was 1.63 and that for the risk of carotid cerebrovascular events was 2.20 in the SH group. Other previous reports were not specific to diabetic patients, and the higher home systolic BP values in the MH group compared to the controlled BP group, compared to the present study, may have influenced the study results. Furthermore, the fact that all patients were essential hypertension and had an increased risk of coronary heart disease. In the present study, when coronary heart disease events (cardiovascular death, angina pectoris, nonfatal myocardial infarction, or heart failure) and carotid cerebrovascular events (unspecified carotid artery occlusion and stenosis, nonfatal stroke, or transient ischemic attacks) were separately evaluated, the adjusted HR (95% CI) for the risk of coronary heart disease events was 1.63 and that for the risk of carotid cerebrovascular events was 2.20 in the SH group. Other previous reports were not specific to diabetic patients, and the higher home systolic BP values in the MH group compared to the controlled BP group, compared to the present study, may have influenced the study results.

In a Japanese study, a sub-analysis of the Hypertension Objective Treatment Based on Measurement by Electrical Devices Blood Pressure trial (HOMED-BP) examined the predictive power of home and clinic BP on long-term cardiovascular outcomes in hypertensive patients with and without impaired glucose metabolism, baseline HBP significantly predicted cardiovascular events in the impaired glucose metabolism group (HR 1.68, 95% CI 1.26–2.26), whereas clinic BP was not. Similar results were obtained in the present study specifically for diabetic patients, and it is recommended that HBP be referenced to predict future cardiovascular events.

When the risk of cardiovascular events was evaluated by age, the adjusted HR of cardiovascular events in the SH group was similar between patients aged < 65 years and those aged > 65 years. This may be attributed to the fact that the incidence of cardiovascular events in the SH group was similar between patients aged ≥65 years and those aged < 65 years.

However, when the risk of cardiovascular events was evaluated in the presence or absence of antihypertensive medication, the adjusted HR for cardiovascular events in the SH group tended to be slightly higher in patients using antihypertensive medication than in those not using them. The incidence was higher in patients using antihypertensive medication. This may be due to the fact that patients using antihypertensive medications had higher HBP levels than those not on antihypertensive medications in our study (data not shown) and are at higher risk for cardiovascular events.

One of the strengths of this study was the use of a BP measurement device that saves the measurements, which allowed for accurate analysis. Furthermore, the HBP measurement period in the present study was 14 consecutive days; we have previously reported that monitoring for 14 days can help predict target organ damage. This study has a few limitations. First, ambulatory BP monitoring was not used, and BP variability at home was unknown during the night and day. Therefore, some of the MH cases may have been misinterpreted as those of controlled BP. However, HBP measurement was reported to be a more reliable method than ambulatory BP monitoring in diagnosing hypertension and detecting MH in untreated and treated patients. Second, it is uncertain whether the results of the present study can be generalized to other ethnic groups with different diets, environmental conditions, and genetics. Third, this study analyzed only BP values at study entry, and we were unable to examine the reproducibility of HBP after a median period of 7.0 years follow-up and its relationship with HBP at the onset of cardiovascular events. In the future, it is necessary to examine the reproducibility of HBP and HBP values at the onset of cardiovascular events in order to examine target BP values that prevent cardiovascular events. Fourth, in this study, there was no significant association between MH and cardiovascular events. This may be partly due to the small sample size and small number of events, which resulted in low statistical power. We would like to revisit this issue with a larger sample size in the future. Last, in this study, event adjudication was done by retrospectively referring to the medical record. In clinical practice, hypertensive patients tend to be overestimated and hypotensive patients underestimated, and the possibility of bias in event determination cannot be ruled out.

5 | CONCLUSION

In conclusion, a retrospective cohort study of the KAMOGAWA-HBP in patients with type 2 diabetes revealed that SH is a valuable predictor
of cardiovascular events. Therefore, in patients with type 2 diabetes, both clinic BP and HBP should be evaluated in daily clinical practice to predict future cardiovascular events.

AUTHOR CONTRIBUTIONS

Takashi Yoshimura designed the study, contributed to the collection of research data, analyzed, and interpreted data, and drafted and revised the manuscript. Emi Ushigome, Shinnosuke Hata, Maya Takegami, Goji Hasegawa, Toru Tanaka, Masayoshi Ohnishi, Sei Tsunoda, Hidetaka Ushigome, Nobuko Kitagawa, Mai Asano, Masahide Hamaguchi, Masahiro Yamazaki, and Michiaki Fukui collected, analyzed, and interpreted the data and revised the manuscript. Toru Tanaka was the principal investigator of the Kyoto First Red Cross Hospital. Goji Hasegawa was the principal investigator of the Kyoto Second Red Cross Hospital. Masayoshi Ohnishi was the principal investigator of the Osaka General Hospital of West Japan Railway Company. Isao Yokota supervised data analysis and revised the manuscript. All authors approved the final version of the manuscript. Emi Ushigome is the main study physician responsible for the KAMOGAWA-HBP study in the Kyoto Prefectural University of Medicine, Graduate School of Medical Science and the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

The authors declare no competing interests related to this study.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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