INTRODUCTION

For most patients, achieving blood pressure (BP) targets is often not possible with a single agent. In fact, at least 75% of individuals with hypertension require treatment with at least 2 antihypertensive drugs in order to achieve BP control. Thus, guidelines of the Eighth Joint National Committee (JNC8) recommend an increase in dosage or the addition of a second drug if BP goals are not achieved with a single agent.

Tolerability is an essential factor to consider in the selection of add-on therapies. Although adding a second drug could help patients achieve BP control, the impact on tolerability is unclear. Only half of those who initiate antihypertensive monotherapy maintain treatment after 1 year, with side effects being the most frequently cited reason for discontinuation.

Nebivolol is a highly selective β₁-receptor blocker with nitric oxide-mediated vasodilatory properties. Unlike the nonvasodilatory β-blockers that lower BP by reducing cardiac output, nebivolol decreases peripheral resistance and preserves cardiac output. Data from randomized trials suggest that nebivolol monotherapy is as efficacious as other antihypertensives and better tolerated than other β₁-selective blockers (atenolol, metoprolol, bisoprolol), calcium channel blockers (CCBs), and the angiotensin receptor blocker (ARB) losartan. As an add-on treatment, nebivolol exhibited better efficacy and similar tolerability compared with placebo in a randomized trial among patients who had ongoing treatment with angiotensin-converting enzyme inhibitors (ACEIs), ARBs, diuretics, or a combination of 2 such agents. Nebivolol has been found to be effective and well tolerated in real-world clinical settings.
Postmarketing surveillance studies have suggested that nebivolol is associated with BP reductions, low rates of adverse events, and improvements in metabolic parameters and quality of life. Nevertheless, there is a lack of real-world comparative evidence of the efficacy and tolerability of nebivolol vs other drugs as an add-on treatment.

The purpose of this study was to assess the real-world tolerability and effectiveness of nebivolol as first add-on antihypertensive therapy in comparison to 3 commonly prescribed hypertension drugs: hydrochlorothiazide, metoprolol, and amlodipine.

2 | METHODS

2.1 | Study design and participants

This retrospective medical chart review was conducted by physicians randomly recruited from a nationally representative panel of primary care physicians (PCPs), internists, and cardiologists. These physicians were from geographically diverse sites in the United States and practiced at both private and academic practice settings.

Study participants were selected from all hypertension patients treated by participating physicians. Physicians were paid $40 (US dollars) per patient. Eligible patients were required to have a clinical diagnosis of hypertension and to have initiated nebivolol, hydrochlorothiazide, amlodipine, or metoprolol (study medications) as their first add-on antihypertensive therapy to an existing monotherapy (defined as therapy with no more than 1 active ingredient). The monotherapy was required to be patients' first pharmacological treatment for hypertension (ie, patients could not have a history of switching between monotherapies as their first pharmacological treatment). The initiation of the add-on therapy must have occurred between December 16, 2010 and July 21, 2011, with patients required to be at least 18 years old by the date of initiation. Finally, patients were required to have visited the participating physician at least once in the year prior to chart abstraction, a history of diastolic blood pressure (DBP) > 90 mm Hg or systolic blood pressure (SBP) > 140 mm Hg within 30 days prior to the initiation of study medication, and at least 1 BP measurement at 2, 4, or 6 months after initiation of the study medication. Patients were excluded if they were being treated with β-blockers, CCBs, or diuretics for conditions other than hypertension; had initiated another antihypertensive drug as an add-on therapy at the same time as the study drug; or initiated the add-on therapy as a single-pill combination of the study drug and the first-line monotherapy.

The initiation date of the first add-on antihypertensive therapy was defined as the index date. Patients were followed from index date to chart abstraction date in January 2012 or patient death, whichever came first.

2.2 | Chart abstraction

Each participating physician randomly selected no more than 5 patients who met the selection criteria by matching the first letter of patients' names to a list of random computer-generated letters. Physicians were not aware of the purpose of the chart abstraction. Pilot testing of the chart abstraction form was conducted among 20 physicians, and the form was revised based on feedback regarding data collection and variables of interest. Because this was a retrospective study of deidentified data for both patients and participating physicians, an institutional review board (IRB) exemption was obtained, and ethics committee approval was not required for physicians conducting the chart reviews.

Baseline data collected for each patient included age, sex, existing comorbidities, first-line monotherapy, and the latest BP measurement within 30 days prior to the index date. For the follow-up period, the participating physicians were asked to abstract information related to study medication-related side effects and BP measurements. The abstracted side effects had to be included in the list provided in the chart abstraction form, which was initially compiled by identifying common side effects using study medications’ product labels and was then independently reviewed and approved by 12 physicians. For each abstracted side effect, the physicians were asked for opinion regarding a possible or probable relationship to study medication (with criteria including temporal sequence of events and explicable by other factors) and whether the side effect qualified as serious. Serious side effects were defined as those that were life threatening, required or prolonged hospitalization, or resulted in death, persistent or significant disability, or congenital anomaly. Physicians were also asked to record dose reduction, interruption, or drug discontinuation due to side effects and to indicate whether these events were related to the study medication. BP measurements at approximately 2, 4, and 6 months from the index date were also collected when available.

2.3 | Study outcomes

The primary tolerability outcome was the total occurrence of study medication-related side effects during the follow-up period. Secondary tolerability outcomes included the occurrence of individual side effects related to study medication, any side effects, any serious side effects, serious side effects related to study medication, and dose reductions/interruptions or drug discontinuations due to any side effects and due to side effects related to study medication.

The primary effectiveness outcome was the rate of BP control (SBP/DBP < 140/90 mm Hg in patients < 60 years old or < 150/90 mm Hg in patients 60 years or older) at 2 months following index date. Secondary effectiveness outcomes included change from baseline in BP at 2 months and BP goal achievement at 4 and 6 months.

2.4 | Statistical analysis

Baseline characteristics were compared between the nebivolol group and each of the other treatment groups using the chi-square test for categorical variables and Wilcoxon rank sum tests for continuous variables.
### Table 1: Patient baseline characteristics

| Baseline characteristics | Amlodipine | HCTZ | Metoprolol | Nebivolol |
|--------------------------|------------|------|------------|-----------|
| Patients, n              | 400        | 400  | 400        | 400       |
| Age, y, mean ± SD        | 57.6 ± 11.5** | 54.2 ± 10.5 | 57.7 ± 11.3** | 53.8 ± 10.2 |
| Men, n (%)               | 241 (60.3)** | 208 (52.0)** | 247 (61.8)** | 300 (75.0) |
| White, n (%)             | 266 (66.5)** | 229 (57.3)** | 286 (71.5) | 309 (77.3) |
| SBP, mm Hg, mean (SD)    | 154.0 (11.0) | 152.0 (10.0)* | 152.5 (11.2) | 153.0 (9.4) |
| DBP, mm Hg, mean (SD)    | 90.6 (7.9) | 90.0 (7.5)** | 90.1 (7.6)** | 91.5 (6.5) |
| Follow-up time, wk, mean (SD) | 38.6 (7.3) | 38.1 (7.3) | 38.1 (7.4) | 40.0 (7.5) |
| Hypertension duration, n (%) |            |      |            |           |
| < 1 y                    | 94 (24.5)** | 120 (30.9)** | 112 (28.8)** | 113 (29.3) |
| 1-4 y                    | 163 (42.5) | 176 (45.2) | 170 (43.7) | 206 (53.4) |
| > 4 y                    | 127 (33.1) | 93 (23.9) | 107 (27.5) | 67 (17.4) |
| Treating physician, n (%) |            |      |            |           |
| General/internal         | 319 (79.8) | 326 (81.5) | 310 (77.5) | 307 (76.8) |
| Cardiology               | 81 (20.3) | 74 (18.5) | 90 (22.5) | 93 (23.3) |
| First-line treatment, n (%) |            |      |            |           |
| ACEI                     | 175 (43.8)** | 208 (52.0)** | 177 (44.3) | 170 (42.5) |
| Alpha-agonist            | 4 (1.0) | 4 (1.0) | 1 (0.3) | 3 (0.8) |
| ARB                      | 73 (18.3) | 82 (20.5) | 61 (15.3) | 81 (20.3) |
| Beta-blocker             | 42 (10.5) | 43 (10.8) | 3 (0.8) | 9 (2.3) |
| CCB                      | 5 (1.3) | 54 (13.5) | 30 (7.5) | 27 (6.8) |
| Diuretic                 | 96 (24.0) | 2 (0.5) | 122 (30.5) | 109 (27.3) |
| Renin inhibitor           | 2 (0.5) | 3 (0.8) | 3 (0.8) | 0 (0.0) |
| Vasodilator              | 3 (0.8) | 4 (1.0) | 3 (0.8) | 1 (0.3) |
| High dosage, n (%)c      | 41 (10.3) | 142 (35.5)** | 0 (0.00)** | 52 (13.0) |
| Comorbidities and risk factors, n (%) |            |      |            |           |
| None recorded            | 77 (19.3) | 87 (21.8) | 74 (18.5) | 91 (22.8) |
| Diabetes                 | 91 (22.8)* | 92 (23.0)* | 78 (19.5) | 67 (16.8) |
| Chronic renal disease    | 31 (7.8)* | 11 (2.8) | 21 (5.3) | 15 (3.8) |
| Obesity                  | 130 (32.5) | 163 (40.8) | 117 (29.3)** | 156 (39.0) |
| CAD                      | 38 (9.5) | 23 (5.8) | 86 (21.5)** | 29 (7.3) |
| Heart failure            | 4 (1.0) | 4 (1.0) | 14 (3.5) | 8 (2.0) |
| Arrhythmia               | 8 (2.0) | 3 (0.8)** | 52 (13.0)** | 16 (4.0) |
| Arteriosclerosis         | 19 (4.8) | 13 (3.3) | 21 (5.3) | 14 (3.5) |
| Cerebral ischemia        | 1 (0.3) | 3 (0.8) | 6 (1.5) | 4 (1.0) |
| PVD                      | 20 (5.0)** | 8 (2.0) | 17 (4.3)* | 6 (1.5) |
| Hyperlipidemia           | 200 (50.0) | 181 (45.3) | 179 (44.8) | 190 (47.5) |
| Smoking                  | 91 (22.8) | 100 (25.0) | 89 (22.3) | 103 (25.8) |
| Other                    | 9 (2.3) | 6 (1.5) | 11 (2.8) | 10 (2.5) |
| Unknown (missing data)   | 3 (0.8) | 1 (0.3) | 1 (0.3) | 3 (0.8) |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; PVD, peripheral vascular disease; SBP, systolic blood pressure; SD, standard deviation.

* Asterisks represent joint significance for all levels of hypertension.

** Asterisks represent significance for the first-line treatment.

c High dosage was defined as the prescribed dose that was higher than the recommended starting dose from package inserts (nebivolol, > 5 mg/d; HCTZ, > 12.5 mg/d; amlodipine, > 5 mg/d; metoprolol, > 100 mg/d for metoprolol).

*P < .05; ** P < .01 (vs nebivolol); P values were calculated using the chi-square test for discrete variables and Wilcoxon rank sum tests for continuous variables.
For each group, the incidence rate of study medication-related side effects per 100 patients was calculated as the total number of side effects during the follow-up period divided by the number of patients and multiplying by 100. Adjusted incidence rate ratios (IRRs) were calculated to compare the incidence rate of study medication-related side effects between nebivolol and other treatment groups using Poisson regressions. The regressions modeled the total number of study medication-related side effects as a function of a categorical treatment variable (using nebivolol as the reference group), patient characteristics, and other treatment

### TABLE 2  Primary and secondary tolerability outcomes from index date to end of follow-up

| Study medication-related side effects, n (rate per 100 patients) | Amlodipine | HCTZ | Metoprolol | Nebivolol |
|---------------------------------------------------------------|------------|------|------------|-----------|
| Bradycardia                                                  | 0 (0.0)    | 0 (0.0) | 13 (3.3)* | 0 (0.0)   |
| Constipation                                                 | 6 (1.5)*   | 1 (0.3) | 1 (0.3)    | 0 (0.0)   |
| Cough                                                        | 0 (0.0)    | 0 (0.0) | 0 (0.0)    | 1 (0.3)   |
| Depression                                                   | 0 (0.0)    | 0 (0.0) | 1 (0.3)    | 0 (0.0)   |
| Diarrhea                                                     | 0 (0.0)    | 1 (0.3) | 1 (0.3)    | 0 (0.0)   |
| Dizziness                                                    | 4 (1.0)    | 8 (2.0) | 5 (1.3)    | 5 (1.3)   |
| Dry mouth                                                    | 0 (0.0)    | 4 (1.0) | 0 (0.0)    | 0 (0.0)   |
| Dyspnea                                                      | 0 (0.0)    | 0 (0.0) | 0 (0.0)    | 1 (0.3)   |
| Fatigue                                                      | 4 (1.0)*   | 4 (1.0)* | 25 (6.3)  | 13 (3.3)  |
| Headache                                                     | 6 (1.5)    | 2 (0.5) | 3 (0.8)    | 3 (0.8)   |
| Hyperglycemia                                                | 0 (0.0)    | 3 (0.8) | 1 (0.3)    | 0 (0.0)   |
| Hyperuricemia                                                | 0 (0.0)    | 2 (0.5) | 0 (0.0)    | 0 (0.0)   |
| Hypokalemia                                                  | 0 (0.0)    | 10 (2.5)** | 0 (0.0) | 0 (0.0)   |
| Hypotension                                                  | 0 (0.0)    | 1 (0.3) | 0 (0.0)    | 0 (0.0)   |
| Nausea                                                       | 1 (0.3)    | 2 (0.5) | 9 (2.3)    | 2 (0.5)   |
| Peripheral edema                                             | 51 (12.8)** | 0 (0.0) | 0 (0.0)    | 0 (0.0)   |
| Rash                                                         | 0 (0.0)    | 1 (0.3) | 1 (0.3)    | 0 (0.0)   |
| Vomiting                                                     | 0 (0.0)    | 1 (0.3) | 0 (0.0)    | 0 (0.0)   |
| Patients with any side effects, n (%)^a                      | 73 (18.3)  | 41 (10.3) | 45 (11.3) | 27 (6.8)  |
| Patients with serious side effects, n (%)^a,b                | 2 (0.5)    | 3 (0.8) | 1 (0.3)    | 1 (0.3)   |
| Dose change due to side effects, n (%)^a,b                   | 20 (5.0)   | 11 (2.8) | 23 (5.8)  | 5 (1.3)   |
| Discontinuations due to side effects, n (%)^a,b               | 24 (6.0)   | 6 (1.5) | 15 (3.8)  | 4 (1.0)   |

HCTZ, hydrochlorothiazide.

^aCounts represent number of patients experiencing each outcome during the follow-up period. The follow-up period was the time from initiation of add-on therapy to the date physicians took the survey.

^bRelationship of side effect to study medication, side effect severity, and the cause of dose reductions, interruptions, and discontinuations was determined by treating physicians.

^cPatients could have multiple types of study medication-related side effects but not recurrences of the same side effect.

^dA total of 14 patients (5 amlodipine, 7 HCTZ, 2 metoprolol, 0 nebivolol) were reported with side effects classified as “other.” These occurrences are not included in this table, because physicians did not record the type of side effect and its relationship to study medication.

^eP < .05, **P < .01 (vs nebivolol); P values were for study medication-related side effects only, using Fisher’s exact test.
factors that may have affected treatment decisions and onset of side effects. Differences in follow-up duration between patients were accounted for in the model by including an offset term for the duration. Patient characteristics that were controlled for included baseline demographics, baseline BP, duration of diagnosed hypertension, class of first-line antihypertensive treatment, baseline comorbidities (diabetes, chronic renal disease, obesity, coronary artery disease, heart failure, arrhythmia, arteriosclerosis, cerebral ischemia, peripheral vascular disease, hyperlipidemia) and smoking status. Additional treatment factors included specialty of treating physician and dosage of the study medication (high vs low based on the recommended starting dose in adult patients specified in the product labels).

For secondary tolerability outcomes, the proportion of patients experiencing each specific tolerability outcome was calculated. These proportions were compared between the nebivolol group and each of the other treatment groups using Fisher’s exact tests to account for the low number of patients with specific outcomes. The mean change from baseline to 2 months within each treatment combination (first-line plus add-on) was analyzed using an analysis of covariance (ANCOVA) model with baseline BP value and race as covariates. Patients who received first-line and add-on treatments from the same drug class (eg, first-line and add-on were both CCB) were excluded from this analysis. Comparisons between the 10 treatment groups were not performed as the multiple comparisons required would have greatly increased the risk of type I errors. The proportions of patients who achieved BP control at month 2 were calculated and compared between nebivolol and other treatment groups using chi-square tests. In order to compare BP control rates while controlling for confounding factors, adjusted odds ratios (ORs) were calculated using a logistic regression model with the same covariates used for the Poisson regressions. This adjusted analysis was also performed for the secondary effectiveness outcomes.

All hypothesis tests were 2-tailed and conducted at a significance level of $\alpha < 0.05$.

### TABLE 3 Multivariable Poisson regression for the incidence rate of study medication-related side effects ($N = 1548$)

| Covariate               | IRR    | 95% CI      | $P$ value |
|-------------------------|--------|-------------|-----------|
| Age, y                  | 0.99   | 0.97-1.00   | .089      |
| Male                    | 0.74   | 0.55-0.98   | .037*     |
| White                   | 1.09   | 0.81-1.49   | .567      |
| Treatment               |        |             |           |
| Amlodipine              | 2.67   | 1.69-4.21   | <.001**   |
| HCTZ                    | 1.61   | 0.95-2.71   | .075      |
| Metoprolol              | 1.82   | 1.14-2.92   | .012*     |
| Nebivolol               |        |             |           |
| Baseline BP (10 mm Hg)  |        |             |           |
| SBP                     | 0.98   | 0.84-1.13   | .761      |
| DBP                     | 1.11   | 0.90-1.36   | .342      |
| Hypertension duration   |        |             |           |
| 1-4 y                   | 1.53   | 1.04-2.25   | .031*     |
| > 4 y                   | 1.78   | 1.15-2.76   | .009**    |
| < 1 y                   |        |             |           |
| Treating physician      |        |             |           |
| Cardiologist            | 0.72   | 0.49-1.07   | .101      |
| PCP/Internist           |        |             |           |
| First-line treatment    |        |             |           |
| ARB                     | 0.78   | 0.51-1.20   | .254      |
| Beta-blocker            | 0.84   | 0.46-1.53   | .565      |
| CCB                     | 1.17   | 0.66-2.10   | .591      |
| Diuretic                | 1.35   | 0.93-1.94   | .112      |
| Other                   | 0.91   | 0.28-2.92   | .871      |
| ACEI                    |        |             |           |
| Drug dosage$^b$         |        |             |           |
| High                    | 0.86   | 0.54-1.35   | .509      |
| Low                     |        |             |           |
| Comorbidities and risk factors | | |
| Diabetes                | 1.07   | 0.75-1.52   | .700      |
| Chronic renal disease   | 1.41   | 0.81-2.46   | .221      |
| Obesity                 | 1.30   | 0.97-1.74   | .083      |
| CAD                     | 2.98   | 2.03-4.37   | <.001**   |
| Heart failure           | 0.68   | 0.21-2.22   | .525      |
| Arrhythmia              | 1.27   | 0.69-2.34   | .446      |
| Arteriosclerosis        | 0.43   | 0.17-1.08   | .074      |
| Cerebral ischemia       | 0.00   | 0.00-∞      | .978      |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; IRR, incidence rate ratio; PCP, primary care physician; PVD, peripheral vascular disease; SBP, systolic blood pressure; SD, standard deviation.

$^a$The outcome was the count of any study medication-related side effect during the follow-up period. An offset was used to adjust for duration of follow-up. Relationship of side effect to study medication was determined by physicians. Patients with missing data on the outcome or any of the covariates were excluded from the analysis.

$^b$High dose was defined as the prescribed dose that was higher than the recommended starting dose from package inserts (nebivolol, > 5 mg/d; HCTZ, > 12.5 mg/d; amlodipine, > 5 mg/d; metoprolol, > 100 mg/d for metoprolol).

$^*P < .05; ^{**}P < .01; P$ values were calculated using the Wald test.
3 | RESULTS

3.1 | Baseline characteristics

In total, 396 physicians participated in the study and contributed a total of 1600 patient records (400 patients per group). Baseline demographic characteristics of study patients are summarized in Table 1. The entire study sample had a mean age of 56 years, with 62% men and 68% white patients. The majority of patients received their initial diagnosis of hypertension within the past 4 years and used an ACEI (45.6%) or a diuretic (20.6%) as their first-line anti-hypertensive medication. The most common baseline comorbidities or relevant risk factors included hyperlipidemia (47%), obesity (35%), smoking (24%), and diabetes (21%). The majority of patients (79%) were treated by PCPs or internists, and the remainder were treated by cardiologists. Patients treated with nebivolol tended to be younger and were more likely to be male or white than patients treated with the other study medications (Table 1). The mean duration of follow-up for the entire study population was 38.7 weeks (range 38.1-40.0 weeks) and was similar between treatment groups.

3.2 | Tolerability outcomes

Incidence rates of study medication-related side effects among patients treated with amlodipine, hydrochlorothiazide, metoprolol, and nebivolol were 18.8, 10.5, 15.0, and 7.0 per 100 patients, respectively (Table 2). The percentage of patients treated with amlodipine, hydrochlorothiazide, metoprolol, and nebivolol who experienced at least 1 study medication-related side-effect was 16.25%, 7.75%, 10.25%, and 5.25%, respectively.

Compared with the nebivolol group, the amlodipine group had a 167% higher rate of study medication-related side effects (IRR = 2.67, \( P < .001 \)), and the metoprolol group had an 82% higher rate (IRR = 1.82, \( P = .012 \)) after adjustment (Table 3). The diuretic group had a 61% higher rate than that observed in the nebivolol group, but the difference was not statistically significant.

### TABLE 4

| Treatment (first-line, add-on) | N   | SBP, LS mean ± SE, mm Hg | \( P \) value\(^b\) | DBP, LS mean ± SE, mm Hg | \( P \) value\(^b\) |
|-------------------------------|-----|-------------------------|---------------------|--------------------------|---------------------|
| CCB                           |     |                         |                     |                          |                     |
| Nebivolol                     | 24  | −15.9 ± 2.1             | <.0001              | −8.2 ± 1.4               | <.0001              |
| HCTZ                          | 48  | −15.2 ± 1.7             | <.0001              | −5.5 ± 1.1               | <.0001              |
| Metoprolol                    | 23  | −16.9 ± 2.2             | <.0001              | −10.4 ± 1.5              | <.0001              |
| Diuretic                      |     |                         |                     |                          |                     |
| Nebivolol                     | 100 | −17.9 ± 1.3             | <.0001              | −8.1 ± 0.9               | <.0001              |
| Metoprolol                    | 102 | −15.2 ± 1.3             | <.0001              | −7.5 ± 0.9               | <.0001              |
| Amlodipine                    | 81  | −14.8 ± 1.4             | <.0001              | −7.8 ± 0.9               | <.0001              |
| RAS\(^c\)                     |     |                         |                     |                          |                     |
| Nebivolol                     | 223 | −17.9 ± 1.1             | <.0001              | −8.2 ± 0.7               | <.0001              |
| HCTZ                          | 245 | −15.9 ± 1.1             | <.0001              | −7.2 ± 0.7               | <.0001              |
| Metoprolol                    | 203 | −14.7 ± 1.1             | <.0001              | −8.0 ± 0.7               | <.0001              |
| Amlodipine                    | 220 | −17.5 ± 1.1             | <.0001              | −8.6 ± 0.7               | <.0001              |

CCB, calcium channel blocker; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; ITT, intent-to-treat; LS, least squares; RAS, renin-angiotensin system; SBP, systolic blood pressure; SE, standard error.

\(^a\)Seven patients who received first-line and add-on treatments from the same drug class were excluded from this analysis: 2 received a diuretic plus HCTZ and 5 received a CCB plus amlodipine.

\(^b\)Calculated via analysis of covariance (ANCOVA) model with baseline BP value and race as covariates.

\(^c\)Includes angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs).

### FIGURE

Blood pressure control rates around month 2 using JNC8 goal BP levels. Blood pressure control rates measured at around 2 mo following the initiation of the first antihypertensive add-on therapy. BP control was defined according to JNC8 criteria (SBP/DBP < 140/90 mm Hg for patients < 60 y old; < 150/90 mm Hg for those age 60 and above). Pairwise \( P \) values were calculated using the chi-square test. BP, blood pressure; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure.

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Sex, hypertension duration, and presence of coronary artery disease or peripheral vascular disease at baseline were factors found to be significantly associated ($P < .05$) with study medication-related side effects.

The most frequently reported individual study medication-related side effects were peripheral edema in the amlodipine group (12.8%), hypokalemia in the hydrochlorothiazide group (2.5%), and fatigue in the metoprolol and nebivolol groups (6.3% and 3.3%, respectively; Table 2). Amlodipine, hydrochlorothiazide, and metoprolol treatment groups also had a higher proportion of patients experiencing any side effects (18.3%, 10.3%, and 11.3%, respectively) compared with the nebivolol group (6.8%).

Serious side effects were experienced by a total of 7 patients (Table 2): 2 (0.5%) in the amlodipine group (hospitalization due to hypotension, disability due to peripheral edema), 3 (0.8%) in the hydrochlorothiazide group (hospitalizations due to hypokalemia and hypotension, disability from impotence), 1 (0.3%) in the metoprolol group (hospitalizations due to hyperglycemia and bradycardia), and 1 (0.3%) in the nebivolol group (hospitalization due to nausea).

Nebivolol-treated patients had a lower rate of dose reductions or interruptions due to side effects (1.3%) than those treated with amlodipine (5.0%), hydrochlorothiazide (2.8%), or metoprolol (5.8%), as well as a lower rate of discontinuations due to side effects (1.0% vs 6.0%, 1.5%, and 3.8%, respectively) (Table 2). Results for outcomes related to study medication were similar.

### 3.3 | Effectiveness outcomes

At 2 months, all treatments significantly reduced SBP and DBP from baseline ($P < .0001$, all; Table 4). In unadjusted analyses on BP control, the nebivolol group had a significantly higher proportion of patients achieving control at 2 months ($P < .05$, all; Table 4). Significant differences were maintained after statistical adjustments (OR for amlodipine vs nebivolol: 0.51, $P < .001$; hydrochlorothiazide: 0.66, $P = .046$; metoprolol: 0.34, $P < .001$; Table 5).

Factors significantly associated with BP control included age, baseline blood pressure, treatment by cardiologist vs PCP/internist, choice of first-line drug, and presence of diabetes or chronic renal disease.

| Covariate                              | Odds ratio | 95% CI    | P value |
|----------------------------------------|------------|-----------|---------|
| Diabetes                               | 0.69       | 0.49-0.98 | .036*   |
| Chronic renal disease                  | 0.44       | 0.22-0.87 | .018*   |
| Obesity                                | 0.79       | 0.60-1.04 | .091    |
| CAD                                    | 0.85       | 0.53-1.37 | .500    |
| Heart failure                          | 0.93       | 0.34-2.69 | .892    |
| Arrhythmia                             | 2.89       | 1.48-5.96 | .003**  |
| Arteriosclerosis                       | 0.80       | 0.41-1.59 | .524    |
| Cerebral ischemia                      | 4.53       | 0.72-47.40| .146    |
| PVD                                    | 0.43       | 0.20-0.92 | .031*   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; PCP, primary care physician; PVD, peripheral vascular disease; SD, standard deviation. $a$BP control was defined according to JNC8 criteria (SBP/DBP < 140/90 mm Hg for patients < 60 y old; < 150/90 mm Hg for those age 60 and above). $b$High dose was defined as the prescribed dose that was higher than the recommended starting dose from package inserts (nebivolol, > 5 mg/d; HCTZ, > 12.5 mg/d; amlodipine, > 5 mg/d; metoprolol, > 100 mg/d for metoprolol). $c$P < .05; $**$P < .01; $P$ values were calculated using the Wald test.

### Table 5 (Continued)

| Covariate                              | Odds ratio | 95% CI    | P value |
|----------------------------------------|------------|-----------|---------|
| Diabetes                               | 1.11       | 0.84-1.47 | .477    |
| Smoking                                | 0.81       | 0.60-1.11 | .186    |
| Other                                  | 3.75       | 1.38-11.58| .014*   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; PCP, primary care physician; PVD, peripheral vascular disease; SD, standard deviation. $a$BP control was defined according to JNC8 criteria (SBP/DBP < 140/90 mm Hg for patients < 60 y old; < 150/90 mm Hg for those age 60 and above). $b$High dose was defined as the prescribed dose that was higher than the recommended starting dose from package inserts (nebivolol, > 5 mg/d; HCTZ, > 12.5 mg/d; amlodipine, > 5 mg/d; metoprolol, > 100 mg/d for metoprolol). $c$P < .05; $**$P < .01; $P$ values were calculated using the Wald test.

The most frequently reported individual study medication-related side effects were peripheral edema in the amlodipine group (12.8%), hypokalemia in the hydrochlorothiazide group (2.5%), and fatigue in the metoprolol and nebivolol groups (6.3% and 3.3%, respectively; Table 2). Amlodipine, hydrochlorothiazide, and metoprolol treatment groups also had a higher proportion of patients experiencing any side effects (18.3%, 10.3%, and 11.3%, respectively) compared with the nebivolol group (6.8%).

Serious side effects were experienced by a total of 7 patients (Table 2): 2 (0.5%) in the amlodipine group (hospitalization due to hypotension, disability due to peripheral edema), 3 (0.8%) in the hydrochlorothiazide group (hospitalizations due to hypokalemia and hypotension, disability from impotence), 1 (0.3%) in the metoprolol group (hospitalizations due to hyperglycemia and bradycardia), and 1 (0.3%) in the nebivolol group (hospitalization due to nausea).

Nebivolol-treated patients had a lower rate of dose reductions or interruptions due to side effects (1.3%) than those treated with amlodipine (5.0%), hydrochlorothiazide (2.8%), or metoprolol (5.8%), as well as a lower rate of discontinuations due to side effects (1.0% vs 6.0%, 1.5%, and 3.8%, respectively) (Table 2). Results for outcomes related to study medication were similar.
disease at baseline. Adjusted analyses for BP control at months 4 and 6 found no statistically significant differences in the odds of BP goal achievement associated with nebivolol vs amlodipine at months 4 and 6 (Table 6).

4 | DISCUSSION

To our knowledge, this is the first study to compare the real-world tolerability and effectiveness of nebivolol as first add-on therapy with hydrochlorothiazide, metoprolol, and amlodipine. Results suggest that add-on nebivolol is associated with better tolerability than amlodipine and metoprolol and better BP control than hydrochlorothiazide, metoprolol, and amlodipine 2 months after initiation. Tolerability is a critical factor in treatment decision making and side effects from medications can negatively affect treatment adherence and persistence, which are essential to achieving and maintaining BP control.\(^5\) Our data are largely consistent with previous findings indicating that the tolerability of nebivolol monotherapy is superior to that of CCBs\(^6\) and the nonvasodilatory \(\beta\)-blockers atenolol, bisoprolol, and metoprolol.\(^7\) Furthermore, randomized studies have shown that nebivolol is well tolerated when added to ongoing ACEI, ARB, or diuretic therapy\(^8,12\) or when used in combination with an ACEI\(^13\) or diuretic.\(^14\) The favorable tolerability profile of nebivolol in this study also is consistent with results of a large retrospective claims database study in which nebivolol was associated with significantly greater persistence than other \(\beta\)-blockers, including metoprolol.\(^15\)

Results of a meta-analysis of 29 randomized trials showed that the extent of BP reduction, not the use of any particular drug class, is the key determinant in reducing cardiovascular morbidity and mortality.\(^16\) Evidence from randomized trials is relatively sparse but suggests that the antihypertensive effect of nebivolol monotherapy may be similar to or stronger than that of some other drugs or drug classes\(^6\) and that adding nebivolol to other drugs provides additional efficacy.\(^8,12,14\) Meta-analyses also indicate that \(\beta\)-blockers are associated with worse prevention rates of stroke compared with other antihypertensive drug classes,\(^17,18\) but those data were mostly obtained from atenolol trials. Head-to-head randomized trials have shown that vasodilatory \(\beta\)-blockers, including nebivolol, may have superior hemodynamic properties (eg, a greater effect on central and pulse pressure) vs traditional, nonvasodilatory \(\beta\)-blockers (atenolol, metoprolol) even though brachial BP reductions are similar.\(^19,20\) Consistent with these findings, our data suggest similar reductions in brachial BP but greater BP control with add-on nebivolol compared with metoprolol.

Although the results presented in this paper are based on an assessment of BP goal achievement defined in the JNC8\(^21\) guidelines, the results were robust to the previous definition (JNC7).\(^2\) That a greater proportion of nebivolol-treated patients achieved BP control after 2 months compared with patients treated with the other 3 drugs suggests a potentially greater reduction of cardiovascular risk with nebivolol. The VALUE trial has shown that faster achievement of BP control is associated with greater cardiovascular risk reduction with a significant effect observed after 1 month.\(^22,23\) However, these findings should be confirmed in randomized prospective trials.

This study has several limitations inherent to retrospective chart reviews. First, patients within each treatment group received different classes of first-line antihypertensive treatment. This may not have been adjusted for completely in the regression analyses because of possible interaction effects or difficulty in controlling for individual drugs within each class. Second, patients may have experienced side effects that were not reported; however, this is likely to occur in all treatment groups and is not likely to bias comparisons of rates. Third, assessment of the relationship between adverse effects and the study drug was performed by treating physicians and thus may not have been consistent across physicians. As with underreporting of side effects, this limitation is less likely to bias comparisons across the treatment groups. The robustness of the conclusions is bolstered by the fact that results for any side effects, which are not subject to physician’s subjective assessment, were similar to those for medication-related side effects. Lastly, hypertension is a chronic disease that often requires lifelong treatment. Therefore, the maximum follow-up period of 1 year in this study does not provide evidence of comparative long-term effectiveness.

This real-world study of nebivolol as first add-on therapy suggests that nebivolol could be well tolerated and effective compared with add-on amlodipine, metoprolol, or hydrochlorothiazide. Although this study indicates that nebivolol could potentially be a good candidate

### Table 6 Logistic regression for the odds ratio of blood pressure goal achievement at months 4 (\(N = 1111\)) and 6 (\(N = 1350\)) based on JNC8 goal BP levels\(^a\)

| Covariate | Month 4 | | | Month 6 | | |
|-----------|---------|---|---|---------|---|
| Treatment | OR (95% CI) | \(P\) value | | OR (95% CI) | \(P\) value |
| Amlodipine | 0.91 (0.58-1.44) | .693 | | 0.69 (0.41-1.17) | .172 |
| HCTZ | 1.13 (0.70-1.85) | .615 | | 0.63 (0.36-1.11) | .112 |
| Metoprolol | 0.64 (0.40-1.02) | .064 | | 0.51 (0.30-0.87) | .013* |
| Nebivolol | - | - | | - | - |

CI, confidence interval; HCTZ, hydrochlorothiazide; OR, odds ratio.

\(^a\)BP control was defined according to JNC8 (SBP/DBP < 140/90 mm Hg for patients < 60 y old; < 150/90 mm Hg for those age 60 and above). Separate regressions were conducted at month 4 and month 6. Results are obtained from multivariable regressions adjusting for the same set of covariates as for the month 2 regression (Table 5).

\(^*P < .05; **P < .01; \(P\) values were calculated using the Wald test.\)
for first add-on hypertension therapy in general, the relative tolerability and effectiveness of nebivolol compared with hydrochlorothiazide, metoprolol, or amlodipine when added on to a specific monotherapy remains unclear. Further studies should compare different combinations and identify optimal combinations for each patient type.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed extensively and equally to the material presented in this manuscript. All authors had equal opportunity to review and edit the manuscript and give approval prior to submission.

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