Effects of the Once-Weekly Glucagon-Like Peptide-1 Receptor Agonist Dulaglutide on Ambulatory Blood Pressure and Heart Rate in Patients With Type 2 Diabetes Mellitus


Abstract—Glucagon-like peptide-1 receptor agonists, used to treat type 2 diabetes mellitus, are associated with small reductions in systolic blood pressure (SBP) and increases in heart rate. However, findings based on clinic measurements do not adequately assess a drug’s 24-hour pharmacodynamic profile. The effects of dulaglutide, a once-weekly glucagon-like peptide-1 receptor agonist, on BP and heart rate were investigated using ambulatory BP monitoring. Patients (n=755; 56±10 years; 81% white; 48% women), with type 2 diabetes mellitus, taking ≥1 oral antihyperglycemic medication, with a clinic BP between 90/60 and 140/90 mm Hg were randomized to dulaglutide (1.5 or 0.75 mg) or placebo subcutaneously for 26 weeks. Ambulatory BP monitoring was performed at baseline and at 4, 16, and 26 weeks. The primary end point was change from baseline to week 16 in 24-hour SBP, with dulaglutide 1.5 mg significantly reduced SBP (least squares mean difference [95% confidence interval], −2.8 mm Hg [−4.6, −1.0]; P≤0.001). Dulaglutide 0.75 mg was noninferior to placebo (1.6 bpm; [0.3, 2.9]; P≤0.02) for 24-hour heart rate (least squares mean difference [95% confidence interval]), but dulaglutide 1.5 mg was not (2.8 bpm [1.5, 4.2]). Dulaglutide 1.5 mg was associated with a reduction in 24-hour SBP and an increase in 24-hour heart rate. The mechanisms responsible for the observed effects remain to be clarified. (Hypertension. 2014;64:00-00.) *Online Data Supplement

Key Words: blood pressure monitoring, ambulatory ■ blood pressure ■ dulaglutide ■ glucagon-like peptide-1 ■ heart rate ■ hypertension ■ type 2 diabetes mellitus

Glucagon-like peptide (GLP-1) is an incretin hormone that stimulates insulin and suppresses glucagon secretion in a glucose-dependent manner, inhibits gastric emptying, and reduces appetite and food intake. Native GLP-1 is short lived, but longer acting GLP-1 receptor agonists that enhance the incretin action and are effective in treating type 2 diabetes mellitus (T2DM) have been developed. Improvements in cardiovascular risk factors (such as decreases in systolic blood pressure [SBP] and body weight) have been reported with GLP-1 receptor agonists. These findings, which are independent of glycemic effects, are important given that T2DM is associated with an increased risk for cardiovascular complications.

A reduction in SBP has been reported with the use of several GLP-1 receptor agonists. In the Liraglutide Effect and Action in Diabetes (1–6) studies, which compared the effects of the once-daily GLP-1 receptor agonist liraglutide with other antidiabetic therapies, liraglutide reduced SBP by 2 to 6 mm Hg. In a post hoc analysis of pooled data from 6 trials, patients treated with twice-daily exenatide had a significant 2.8 mm Hg reduction in mean SBP when compared with placebo (P<0.0002) and a 3.7 mm Hg reduction compared with insulin therapy (P<0.0001). Neither drug had an effect on diastolic blood pressure (DBP), but a small (2–4 bpm) increase in heart rate (HR) has been observed with liraglutide and with a once-weekly formulation of exenatide. However, these studies relied on clinic BP measurements, which may not accurately represent overall blood pressure values. Potentially useful data on hemodynamic effects, such as baseline hypertension status; use and changes in concomitant antihypertensive medications, hypertensive adverse events (AEs), and the timing of BP measurements do not adequately assess a drug’s 24-hour pharmacodynamic profile.
measurements in relation to dosing, were not reported. Despite these omissions, it has become widely accepted that GLP-1 receptor agonists reduce SBP.

Dulaglutide is a once-weekly GLP-1 receptor agonist that significantly improves glycemic control in patients with T2DM and has been shown to reduce body weight in many subjects. The present study (NCT01149421) investigated the effects of dulaglutide on BP and HR during 26 weeks using 24-hour ambulatory blood pressure monitoring (ABPM) in patients with T2DM.

Methods

Study Design

The study was a randomized, double-blind, multicenter, placebo-controlled, 26-week trial designed to evaluate the effects of dulaglutide when compared with placebo on BP and HR in patients with T2DM with or without hypertension and BP >140/90 mm Hg. After a 2-week placebo screening and run-in period, eligible patients were randomly assigned using a computer-generated random sequence to injectable placebo or 1.5 or 0.75 mg of dulaglutide (1:1:1) once weekly for 26 weeks and followed up for an additional 4-week off-therapy. Study visits occurred approximately every 4 weeks through 16 weeks, and then at 26 weeks with interim phone follow-up. Randomization was stratified by site and hypertension status (previous diagnosis and the use of antihypertensive medications or a new diagnosis if SBP ≥130 mm Hg or DBP ≥80 mm Hg on ≥2 separate days versus normotensive).

Population

Patients were recruited from 76 centers in Argentina, Brazil, Canada, Czech Republic, Denmark, India, Puerto Rico, and the United States. Men and women ≥18 years of age with T2DM, a glycated hemoglobin A1c ≥7.0% and ≤9.5%, on 1 oral antihyperglycemic medication for ≥3 months, were included. Mean seated BP was required to be between >90/60 and <140/90 mm Hg. Patients with hypertension had to be taking ≥2 classes of antihypertensive medications (same regimen, ≥1 month). Exclusion criteria were a recent (<3 months) major cardiovascular event, mean seated HR <60 or >110 bpm, history of tachyarrhythmia, pancreatitis, clinically significant hepatic disease, renal impairment (estimated glomerular filtration rate ≤30 mL/min per 1.73 m²), and the use of any GLP-1 receptor agonist (past 3 months), any dipeptidyl peptidase-4 inhibitor (past 2 weeks), or insulin. Night or rotating shift workers, pregnant or nursing women, and women of childbearing potential not using approved means of contraception were also excluded. Baseline oral antihyperglycemic medications were continued on study. Dose adjustments were allowed for glycemic management although thiazolidinedione doses could only be decreased; insulin initiation after randomization was permitted. No changes in antihypertensive therapy were allowed. If adjustments to the antihypertensive regimen were required, patients were discontinued from the study. All patients provided written informed consent before initiation of study procedures. The ethics committees or institutional review boards of all participating sites approved the protocol. The trial was conducted in compliance with Good Clinical Practice guidelines and the ethical principles stated in the Declaration of Helsinki.

BP and HR Monitoring Assessments

Clinic BP and HR measurements were taken in triplicate after the patient was seated for 5 minutes using an automated digital BP recorder (Omron HEM 907 XL). The mean of the last 2 clinic readings at screening determined study eligibility; the mean of 3 readings was used for subsequent analyses. Every effort was made to ensure whether the clinic BP readings were taken before any procedures, including venipuncture.

Ambulatory BP measurements were obtained with the SpaceLabs 90207 monitor (SpaceLabs, Inc). All sites were trained and certified in selection of correct BP cuff size and use of the monitoring equipment. ABPM was performed during screening (baseline) and at 4, 16, and 26 weeks. Recordings were obtained 2 to 4 days after injection of study drug (the anticipated time for dulaglutide). BP and HR were measured every 20 minutes between 0700 and 2200 hours and every 30 minutes between 2200 and 0700 hours. ABPM recordings were defined as valid with ≥22.75 hours of monitoring and 80% valid readings. If these criteria were not satisfied, the patient was asked to repeat the procedure, preferably within 24 hours. If the repeat recordings did not satisfy validation criteria, the data were considered nonevaluable. Measurements were blinded after monitor calibration.

Patients discontinued from the study if (1) SBP ≥160 mm Hg or DBP ≥100 mm Hg was confirmed on repeat evaluation in 1 week or (2) SBP ≥140 and <160 mm Hg or DBP ≥90 and <100 mm Hg was confirmed on ≥2 days within 1 month that required additional antihypertensive therapy in the opinion of the investigator.

Additional Assessments

Additional safety measures included AEs, clinical laboratory data, physical examination findings, electrocardiographic data, and weight measurements (using a calibrated electronic scale according to the WHO STEPwise approach http://www.who.int/chp/steps/manual/en/index3.html). Aldosterone, plasma renin activity, metanephrines and normetanephrines, high-sensitivity C-reactive protein, and N-terminal pro–brain natriuretic peptide values were parameters of special interest.

Statistical Analyses

The primary objective was to demonstrate that the changes from baseline in mean 24-hour SBP of patients treated with dulaglutide 1.5 mg and 0.75 mg were noninferior to changes in patients treated with placebo at 16 weeks. The 16-week time point was chosen to minimize any effect of weight reduction on BP. A sequential tree gatekeeping strategy was used to control the family-wise type 1 error rate. Simultaneous noninferiority tests of dulaglutide 1.5 mg and 0.75 mg versus placebo were conducted with a multiplicity adjusted 1-sided α of 0.0135. If noninferiority between dulaglutide and placebo was achieved, then superiority testing was performed. The same strategy was implemented for analyses of mean 24-hour DBP and HR changes from baseline. Other measures were not adjusted for multiplicity and were conducted at a 2-sided α level of 0.05. The primary analysis used a mixed model repeated measure analysis based on the intent-to-treat population with pooled site, treatment, visit, treatment by visit interaction, and stratification variable (diagnosis of hypertension) as fixed effects and baseline mean 24-hour SBP as a covariate. Mixed model repeated measure analysis is a likelihood-based method to handle missing data (early discontinuation). Similar mixed model repeated measure models were implemented to analyze DBP, HR, pulse pressure, diurnal (0800–2100) and nocturnal (0000–0600) data, body weight, and glycated hemoglobin A1c. Categorical variables were analyzed with Pearson χ² test or Fisher exact test. Prespecified subgroup analyses were conducted for baseline categorization of age group (<65 and ≥65 years) and 24-hour ABPM SBP ≥130 mm Hg and DBP ≥80 mm Hg (yes or no).

A post hoc correlation analysis was conducted for the effect of weight on 24-hour mean SBP; in addition, post hoc subgroup analyses were conducted for the effect of use versus nonuse of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, use or nonuse of β-blockers, and use or nonuse of diuretics, and renin inhibitors, on mean 24-hour SBP, DBP, and HR.

All statistical analyses were performed using SAS version 8.2 or higher. Assuming a SD of 10 mm Hg for the mean change from baseline on 24-hour SBP, a 10% dropout rate, and no true treatment difference with a multiplicity adjusted 1-sided α of 0.0135, 693 patients would provide 80% power to demonstrate that dulaglutide 1.5 mg and 0.75 mg were noninferior to placebo using a noninferiority margin of 3 mm Hg. This sample size also provided >80% power to demonstrate that dulaglutide 1.5 mg and 0.75 mg were noninferior to placebo on...
The circadian profile demonstrated a persistent decrease in 24-hour SBP with dulaglutide 1.5 mg at 16 weeks (Figure 1). Between-group comparisons for mean changes from baseline in diurnal (0800–2100) and nocturnal (0000–0600) SBP showed dulaglutide 1.5 mg significantly reduced daytime (Figure 2A) and nighttime SBP when compared with placebo. No significant-group differences were observed for diurnal or nocturnal DBP (Figure 2B). Reductions in mean 24-hour and diurnal and nocturnal pulse pressures were observed in patients treated with dulaglutide when compared with placebo (Figure 2C).

### Findings by Age, Baseline BP, and Body Weight

No differences with regard to age (<65 and ≥65 years) were observed relative to treatment effects on mean 24-hour SBP or DBP (interaction P value, 0.271 and 0.555, respectively). When mean baseline 24-hour ABPM was dichotomized into BP ≤130/80 versus >130/80 mm Hg, there was no subgroup by treatment interaction effect (interaction P values, 0.290 and 0.777, respectively).

At 16 weeks, body weight (least squares mean±SE) was reduced −1.8±0.2 kg in the dulaglutide 1.5 mg group and −0.8±0.2 kg in the 0.75 mg group when compared with −0.1±0.2 kg in the placebo group (P ≤0.005 for each group).
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Comparison). A post hoc analysis found no correlation at 16 weeks between change in mean 24-hour SBP and change in body weight ($r^2=0.09$, $r^2=0.04$, and $r^2=0.00$ for dulaglutide 1.5 mg, 0.75 mg, and placebo, respectively).

**Changes in 24-Hour HR**

The effects of dulaglutide and placebo on ambulatory HR are shown in the Table. Treatment comparisons of the changes from baseline in mean 24-hour HR showed that only dulaglutide 0.75 mg was noninferior to placebo at 16 and 26 weeks. A least squares mean increase in HR of 3 to 4 bpm versus placebo was observed with dulaglutide 1.5 mg. Similarly, small increases in diurnal and nocturnal HR were seen with dulaglutide 1.5 mg when compared with placebo (Figure 2D).

Treatment comparisons between dulaglutide 0.75 mg and placebo were significant at all time points during the nocturnal period but only at 4 weeks during the diurnal period (Figure 2D). At 16 weeks, no correlation was observed between change in mean 24-hour SBP and change in HR ($r^2=0.01$, $r^2=0.00$, and $r^2=0.04$ for dulaglutide 1.5 mg, 0.75 mg, and placebo, respectively).

**Findings by Baseline Antihypertensive Agent**

A post hoc subgroup analysis demonstrated no subgroup by treatment interaction effect on mean 24-hour SBP, DBP, or HR in patients taking or not taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (SBP: $P=0.684$; DBP: $P=0.279$; HR: $P=0.966$), beta blockers...
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No significant changes from baseline were observed within or between the dulaglutide and placebo groups for serum aldosterone, plasma renin activity, plasma metanephrines and normetanephrines, or N-terminal pro–brain natriuretic peptide. There were no correlations between changes in 24-hour SBP and these analytes at 16 weeks. Changes from baseline in high-sensitivity C-reactive protein levels at 16 weeks were −0.98, −0.08, and 0.62 mg/L for dulaglutide 1.5 mg (P<0.001 versus placebo), dulaglutide 0.75 mg, and placebo, respectively. The mean (SD) glycated hemoglobin A1c at baseline was 7.9±0.8% for all treatment groups combined. Glycated hemoglobin A1c was reduced −1.1±0.1% and −1.0±0.1% in the dulaglutide 1.5 mg and 0.75 mg groups at 16 weeks, respectively, when compared with −0.1±0.1% in the placebo group (least squares mean±SE; P<0.001 each comparison).

Discussion

This prospective, randomized clinical study used ABPM to assess the effects of an investigational once-weekly GLP-1 receptor agonist, dulaglutide, on BP and HR in patients with T2DM during 26 weeks of treatment. Enrollment was stratified for diagnosis of hypertension and, when present, hypertension was required to be controlled (BP value between 90/60 and 140/90, taking 3 or fewer antihypertensive medications). Dulaglutide doses of 1.5 mg and 0.75 mg, the same doses tested in phase 3 efficacy and safety trials, were shown to be noninferior to placebo for reductions in mean 24-hour SBP and DBP. Dulaglutide 1.5 mg also significantly reduced mean 24-hour SBP by ≥3 mm Hg, an effect that persisted throughout the 26-week treatment period. The lowering in SBP was evident at 4 weeks, the earliest time point measured, and a time when dulaglutide concentrations were at steady state. Consistent with these findings, a reduction in mean 24-hour pulse pressure was observed in patients treated with dulaglutide.

In a single-dose study in healthy subjects,3 dose-dependent increases in clinic DBP were reported at dulaglutide doses ranging from 3 to 12 mg, but no effects on clinic BP were observed in subsequent studies in patients with T2DM.6,11,12 Nevertheless, more recent analyses of phase 3 data from other GLP-1 receptor agonists suggest that these agents may lower clinic SBP. This ABPM trial using repeated 24-hour data may provide the most definitive evidence to date about the effects of a GLP-1 receptor agonist on BP, providing a full characterization of the diurnal and nocturnal effects in patients with T2DM and controlled blood pressure.

The mechanism(s) of action by which GLP-1 or GLP-1 receptor agonists may affect BP remain uncertain. In rodents, GLP-1–mediated increases in HR and BP seem to involve both central and peripheral nervous system pathways, require intact vagus nerve transmission, and may involve vasopressin release.13–15 GLP-1 and its degradation product GLP-1(9–36) may cause vasodilation through GLP-1 receptor-dependent and independent pathways.16,17 GLP-1 may act on the kidney and affect BP, based on diuretic and natriuretic effects observed in rats and humans.18–22 Recently, Kim et al23 showed that activation of GLP-1 receptors expressed in the cardiac atria of rodents promotes secretion of atrial natriuretic peptide, resulting in a reduction in blood pressure. In the present study, the potential modulation of BP effects through the renin–angiotensin–aldosterone system and neurohumoral mechanisms was investigated. No significant changes in serum aldosterone, plasma renin activity, plasma metanephrines and normetanephrines, or N-terminal pro–brain natriuretic peptide were observed, suggesting that these mechanisms are not involved although the frequency of these measures may not have been sufficiently sensitive. Weight reduction has been shown to lead to BP lowering.24,25 Although in the current study no significant correlations were found between weight loss and ambulatory BP, the effect of weight loss cannot be entirely dismissed as a potential mechanism.

Another key finding of this study is that dulaglutide is associated with small increases (2–4 bpm) in HR, as reported in previous studies and with other GLP-1 receptor agonists.2,5,6,11 These changes persisted throughout the 24 hours. Whether this small increase in HR is in response to the reduction in BP, or is the result of other mechanisms, remains to be investigated. These effects may be mediated by direct actions of GLP-1 receptor agonists on the heart, sympathetic mechanisms, or both.26 The clinical relevance of a small increase in HR in patients with T2DM, that remains within the normal accepted range, is not known.

Perspectives

In this study, we showed that dulaglutide 1.5 mg resulted in a 2 to 3 mm Hg reduction in SBP, and a 3 to 4 bpm increase in 24-hour HR in patients with T2DM. These findings were evident by 4 weeks and persisted throughout 26 weeks. No major AEs were reported that might be associated with the observed changes. Given the heightened concerns about the cardiac safety of new antidiabetic drugs, the effect of dulaglutide on blood pressure is in the desired direction. The clinical significance of the increase in HR remains unknown. The ongoing Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial27 is evaluating
the effects of dulaglutide 1.5 mg on the risk of major cardiovascular events.

Study Oversight

Eli Lilly and Company provided study drug and trial oversight. I3 Inventiv coordinated data management and performed statistical analysis under sponsor supervision (H.H.J.), with independent confirmation by Phase V (Marcia Testa; Ralph Turner; Max Su). M.J.G., K.E.R., R.B., and R.J.T. (sponsor) and K.C.F., D.A.C., and E.M.L. (investigators) wrote the protocol with approval by all study investigators. K.C.F., W.W., P.S., M.J.G., K.E.R., R.J.T., and S.S. wrote the article, with full access to the final data. All authors provided final review and approval. K.C.F., M.J.G., K.E.R., and H.H.J. assume responsibility for data integrity, accuracy, and completeness. All authors contributed to the study by acquisition of study data and its analysis and interpretation, and all attest that the study was performed in accordance with the protocol and the statistical analysis plan.

Acknowledgments

We gratefully acknowledge the contributions of Fady T. Botros for assistance with protocol development; David Nelson, Nelson Concepcion, Kristina Grimes, and Christopher Watt for their assistance with ambulatory blood pressure monitoring validation, data transfer, and data management; and Susan A. Strobel and David E. Hartree for article preparation.

Sources of Funding

This study was funded by Eli Lilly and Company.

Disclosures

K.C. Ferdinand reports receiving speaker fees from Astra Zeneca, Takeda, and Novartis; grant and research support from Daiichi Sankyo, Forest, Novartis, and Lilly; and consulting fees from Roche Pharmaceuticals, Inc., Salix Pharmaceuticals, St Jude’s Medical, Shire Pharmaceuticals, and Teva Industries, and grant and research support from National Institutes of Health. E.M. Lonn has received research grant support from Astra Zeneca, Bayer, Novartis, and GlaxoSmithKline, and consulting or speaker fees from Agena Canada and Sevier Canada. H.H. Jiang, K.E. Robertson, and R.J. Threlkeld are employees of Lilly. M.J. Geiger, a former Lilly employee, is now at Regeneron. The other authors report no conflicts.

References


\begin{table}
\centering
\begin{tabular}{|l|}
\hline
\textbf{Novelty and Significance} \\
\hline
\hline
\textbf{What Is New?} \\
\hline
\bullet This was a large, randomized placebo-controlled ambulatory blood pressure monitoring study designed to assess the effects of dulaglutide, a glucagon-like peptide-1 receptor agonist, on blood pressure and heart rate. \\
\hline
\textbf{What Is Relevant?} \\
\hline
\bullet Both doses of dulaglutide were noninferior to placebo for changes in 24-hour systolic and diastolic blood pressure, and dulaglutide 1.5 mg significantly reduced systolic blood pressure ($P \leq 0.001$). The 0.75-mg dose was noninferior to placebo for 24-hour heart rate. Dulaglutide 1.5 mg was associated with a small increase in 24-hour heart rate. \\
\hline
\textbf{Summary} \\
\hline
Dulaglutide did not adversely affect blood pressure and may have some benefit. The relevance of a small increase in mean heart rate, while likely not detrimental, remains to be determined. \\
\hline
\end{tabular}
\end{table}
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Hypertension. published online June 30, 2014;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Running title: Effects of dulaglutide on ambulatory BP and HR

NCT01149421

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Study Oversight

The sponsor (Eli Lilly and Company) provided funding, study drug, study oversight, trial level safety reviews, and coordinated data management by I3 Inventiv. Statistical analysis was performed by I3 Inventiv under sponsor supervision (HHJ), with independent confirmation by Phase V Technologies (Marcia Testa; Ralph Turner; Max Su). The sponsor (MJG; KER; RB; RJT) and study investigators (KCF; DAC; EML) authored the protocol with approval by study investigators. The manuscript outline, first and subsequent drafts were written by KCF, WW, PS, MJG, KER, RJT, and S. Strobel, with full access to the final study data. All authors provided final review and approval of the final version for submission and publication. KCF, MJG, KER and HHT assume responsibility for data integrity, accuracy, and completeness. All authors contributed to the study by acquisition of study data and/or its analysis and interpretation, and all attest that the study was performed in accordance with the protocol and the statistical analysis plan.

The authors wish to thank the investigators who participated in the study.

Argentina: Dr. Pedro Calella, Dr. Nélida Laura Espeche, Dr. Fabio Massari, Dr. Adrian Proietti, Dr. Georgina Sposetti; Brazil: Dr. Antonio Chacra, Dr. Luis Russo; Canada: Dr. Suzan Abdel-Salam, Dr. Ronnie Aronson, Dr. Gordon Bailey, Dr. Richard Dumas, Dr. Tom Elliott, Dr. Carol Joyce, Dr. Stuart Ross, Dr. Nouhad Saliba, Dr. David Twum-Barima, Dr. Lucretia van den Berg, Dr. Vincent Woo; Czech Republic: Dr. Petra Horanska, Dr. Jiri Kuchar, Dr. Alena Vachova; Denmark: Dr. Peter Alexandersen, Dr. Hans-Christian Hoeck, Dr. Christence Teglbjaerg; India: Dr. Ramanathan Balamurugan, Dr. Dugal Gupta, Dr. Sunil M Jain, Dr. Parag Shah, Dr. Parminder Singh; United States: Dr. Philip Behn, Dr. Bradley Block, Dr. Paul Bristol, Dr. Christopher Case, Dr. Luis Rivera Colon, Dr. Matthew Davis, Dr. Michael DeMicco, Dr. Anthony Dulgeroff, Dr. Mitchell Efros, Dr. David Fitz-Patrick, Dr. Edward Hubach, Dr. Richard Kastelic, Dr. Bobby Khan, Dr. Leslie Klaff, Dr. Andrew Lewin, Dr. Robert Lipetz, Dr. Michael McCartney, Dr. Brock McConnehey, Dr. Christopher Miller, Dr. Derek Muse, Dr. John Nicasio, Dr. Christina Orr, Dr. Grisell Ortiz-Lasanta, Dr. Jeffrey Rosen, Dr. Lance Rudolph, Dr. Luis R Ruiz-Rivera, Dr. William Saway, Dr. Larry Severa, Dr. Randall Severance, Dr. Shalizeh Shokooh, Dr. Timothy Smith, Dr. Cacia Soares-Welch, Dr. David Stricklin, Dr. Alain Taylon, Dr. Phillip Toth, Dr. Agnes Ubani, Dr. Carl Vance, Dr. Daniel Van Hamersveld, Dr. Gildred Colon Vega, Dr. Philip Waller, Dr. Robert Weiss, Dr. David Williams, Dr. John Willis, Dr. David Winslow, Dr. Jonathan Wise.
Table S1. Baseline Demographics and Characteristics

<table>
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<tr>
<th>Baseline Characteristics</th>
<th>Dulaglutide 1.5 mg n=251</th>
<th>Dulaglutide 0.75 mg n=254</th>
<th>Placebo n=250</th>
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<td>Age, y</td>
<td>56.0±10.1</td>
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<td>Diabetes duration*, y</td>
<td>7.6±5.3</td>
<td>9.0±6.4</td>
<td>8.4±5.8</td>
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<td>68.1</td>
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<td>Dyslipidemia, %</td>
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<td>120.3±42.3</td>
<td>117.9±37.5</td>
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<td>Creatinine clearance (according to CKD-EPI equation), mL/min</td>
<td>89.4±18.2</td>
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<td>3rd Visit</td>
<td>4th Visit</td>
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<tr>
<td>SBP, mm Hg</td>
<td>126.7±12.4</td>
<td>127.4±12.8</td>
<td>126.8±13.7</td>
<td>127.0±13.0</td>
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<tr>
<td>DBP, mm Hg</td>
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<td>75.8±8.8</td>
<td>76.1±9.2</td>
<td>76.0±10.3</td>
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<tr>
<td>HR, bpm</td>
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<td>73.7±9.3</td>
<td>74.9±10.6</td>
<td>74.4±10.3</td>
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<td>Antihypertensive agents, %‡</td>
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<tr>
<td>ACE inhibitors</td>
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<td>61.8</td>
<td>61.6</td>
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<td>ARBs</td>
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<td>38.1</td>
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<td>19.7</td>
<td>21.0</td>
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<td>19.3</td>
<td>19.1</td>
<td>20.2</td>
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<tr>
<td>Other§</td>
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<td>2.2</td>
<td>3.9</td>
<td>3.4</td>
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<tr>
<td>Antihypertensive Class, %‡</td>
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<tr>
<td>1 Class</td>
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<td>49.7</td>
<td>55.1</td>
<td>50.9</td>
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<td>29.8</td>
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<td>20.4</td>
<td>13.5</td>
<td>16.9</td>
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<td>Oral antihyperglycemic medications, %</td>
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<td>Metforin</td>
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<td>93.7</td>
<td>93.2</td>
<td>92.7</td>
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<td>Sulfonylureas or glinides</td>
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<td>2.0</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Aspirin, %</td>
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<td>31.5</td>
<td>31.2</td>
<td>30.1</td>
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<td>Lipid-lowering agents§, %</td>
<td>51.8</td>
<td>48.8</td>
<td>56.0</td>
<td>52.2</td>
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</table>
All data are mean ± SD unless otherwise noted; ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; BMI = body mass index; bpm = beats per minute; CVD = cardiovascular disease; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin; HR = heart rate; N/A = not available; SBP = systolic blood pressure; y=years.

*Duration of diabetes was significantly different across treatment groups (P=0.029). †History of CVD was defined as having at least one of the following: myocardial infarction, coronary revascularization, hospitalization for unstable angina or heart failure, stroke or transient ischemic attack, peripheral arterial disease, lower extremity or carotid artery revascularization, or documented coronary artery disease; ‡ Percentage based on patients receiving antihypertensive therapy, dulaglutide 1.5 mg/wk (n=175), dulaglutide 0.75 mg/wk (n=181), placebo (n=178), total (n=534); §Other antihypertensive medications included antiadrenergic agents and direct renin inhibitors; ‖ Other oral antihyperglycemic medications included alpha-glucosidase inhibitors and DPP-IV inhibitors; #Lipid-lowering agents included HMG-CoA reductase inhibitors, fibrates, niacin, bile acid sequestrants, and cholesterol absorption inhibitors.
Table S2. Baseline Demographics and Characteristics of Non-Completers and Completers

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Non-Completers</th>
<th>Completers</th>
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<tbody>
<tr>
<td></td>
<td>Dula 1.5 mg n=52</td>
<td>Dula 0.75 mg n=29</td>
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<td>Age, y</td>
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<td>Female, %</td>
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<tr>
<td>Race, % white</td>
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<td>72.4</td>
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<td>Ethnicity, % Hispanic</td>
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<tr>
<td>BMI, kg/m²</td>
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<td>32.0</td>
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<tr>
<td>HbA1c, %</td>
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<td>7.8</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>7.8</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Seated clinic measurements at baseline

| SBP, mm Hg               | 128.4          | 128.7       | 128.9      | 128.6      | 126.3          | 127.3         | 126.4      | 126.7      |
| DBP, mm Hg               | 77.4           | 76.4        | 78.6       | 77.6       | 75.6           | 75.7          | 75.6       | 75.6       |
| HR, bpm                  | 76.1           | 75.2        | 74.9       | 75.5       | 74.1           | 73.5          | 74.9       | 74.2       |

Mean 24-hr ABPM measurements at baseline

| Mean 24-hr SBP, mm Hg    | 133.0          | 130.5       | 133.9      | 132.7      | 130.3          | 132.3         | 130.5      | 131.1      |
| Mean 24-hr DBP, mm Hg   | 77.7           | 76.2        | 78.6       | 77.7       | 75.9           | 76.7          | 75.4       | 76.0       |
| Mean 24-hr HR, bpm      | 81.7           | 79.4        | 80.5       | 80.7       | 79.4           | 79.0          | 79.8       | 79.4       |

ABPM = ambulatory blood pressure monitoring; BMI = body mass index; bpm = beats per minute; DBP = diastolic blood pressure; Dula = dulaglutide HbA1c = glycosylated hemoglobin; HR = heart rate; SBP = systolic blood pressure; y=years.
**Figure S1.** Patient disposition. AE = adverse event.