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Effects of Exenatide on Systolic Blood Pressure in Subjects With Type 2 Diabetes

Ted Okerson[1], Ping Yan[1], Anthony Stonehouse[1] and Robert Brodows[2]

BACKGROUND
The majority of patients with type 2 diabetes mellitus have blood pressure (BP) exceeding the recommended value of <130/80 mm Hg. Optimal control of hyperglycemia and hypertension has been shown to reduce the incidence of macrovascular and microvascular complications due to diabetes. Treatment with the GLP-1 receptor agonist exenatide, previously demonstrated to reduce hemoglobin A_{1C} and weight in subjects with type 2 diabetes, was associated with BP reduction in several studies.

METHODS
This analysis explored the effects of exenatide vs. placebo or insulin on BP measurements in pooled data from six trials including 2,171 subjects studied for at least 6 months.

RESULTS
Overall, 6 months of exenatide treatment was associated with a significantly greater reduction in systolic BP (SBP) compared with placebo (least squares mean (s.e.): difference of −2.8 mm Hg (0.75); $P = 0.0002$) or insulin (difference of −3.7 mm Hg (0.85); $P < 0.0001$). No significant intergroup differences in diastolic BP (DBP) were observed. The majority of the intergroup difference was observed in subjects with SBP ≥130 mm Hg (difference of −3.8 mm Hg (1.08) from placebo: $P = 0.0004$; difference of −4.0 mm Hg (1.01) from insulin; $P < 0.0001$). The largest intertreatment differences between exenatide and comparators were observed in subjects with SBP ≥150 mm Hg. Similar responses were observed in African-American subjects. A weak correlation between the amount of weight lost and reduction in SBP was found ($r = 0.09$, $P = 0.002$) for exenatide-treated subjects.

CONCLUSIONS
These results support the need for a prospective, randomized, controlled study of BP changes during exenatide treatment in patients with hypertension and type 2 diabetes.

Keywords: *African American; blood pressure; diabetes; exenatide; GLP-1; hypertension; insulin; placebo; weight loss*

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Approximately three out of four patients with type 2 diabetes also have hypertension,[1–3] which further increases their total risk of cardiovascular morbidity and mortality.[4] Blood pressure (BP) control in hypertensive patients with diabetes has been shown to significantly reduce their risk of myocardial infarction, stroke, microvascular disease, and death related to diabetes in the prospective observational United Kingdom Prospective Diabetes Study (UKPDS).[5,6] No threshold for the benefit of BP reduction was identified. Based on these and other data, a BP target of <130/80 mm Hg is recommended for hypertensive patients with diabetes by the American Diabetes Association and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[7,8] Achieving this BP goal in patients with both hypertension and diabetes often requires multiple antihypertensive agents with complementary modes of action. Although use of combination products reduces the pill burden in patients with hypertension and diabetes, therapies that treat both conditions might improve adherence and compliance.

Preclinical studies of GLP-1 receptor agonists, which were developed to treat hyperglycemia, indicated that cardiovascular function might also be affected by these agents. GLP-1 receptors have been identified in cardiac and vascular tissue as well as in the stomach, lung, brain, and kidneys.[9,10] In hypertension-prone salt-sensitive rats, GLP-1 administration increased natriuresis, improved endothelial function, and reduced renal and cardiac damage.[11] GLP-1 similarly induced natriuresis in both healthy and insulin-resistant obese men,[12] and appeared to modulate endothelial function and vasodilation.[13,14]

Based on the results of GLP-1 infusion studies, it was hypothesized that the injectable GLP-1 receptor agonist exenatide, which significantly decreased hemoglobin A_{1C} and body weight in clinical studies of subjects with poorly controlled type 2 diabetes,[15–20] might also modulate BP in humans. Initially, a marked reduction in systolic BP (SBP) from baseline (−9.2 mm Hg) was observed in obese subjects with type 2 diabetes treated with both exenatide and insulin: this reduction was independent of weight loss and associated with a reduction in C-reactive protein concentrations.[21] Subsequently, significant reductions in both SBP and diastolic BP (DBP) from baseline were observed in an exenatide-treated patient subgroup

[1]Amylin Pharmaceuticals, San Diego, California, USA; [2]Lilly Research Laboratories, Indianapolis, Indiana, USA. Correspondence: Ping Yan (ping.yan@amylin.com)

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on oral therapies followed for ≥3 years (−3.5 and −3.3 mm Hg, respectively);[22] in a retrospective database study of exenatide-treated subjects (±metformin) with metabolic syndrome (−2.6 and −1.2 mm Hg, respectively)[23]; and in a 24-week prospective placebo-controlled study of exenatide monotherapy (−3.7 and −2.3 mm Hg, respectively).[20]

Because BP measurements were prospectively collected in all clinical studies of exenatide, it was possible to pool these data and explore the effects of exenatide and its comparators on BP in a large patient population. The objective of this *post hoc* analysis was to characterize the effects of exenatide vs. placebo or insulin on BP in pooled data from 2,171 subjects who participated in clinical trials for at least 6 months.[15–20] The effect of exenatide on BP in African-American subjects, a subgroup with higher prevalence, earlier onset, greater severity, and generally poorer control of hypertension,[24,25] were also examined.

METHODS

Study population. The database studied included clinical data from six randomized, placebo- or insulin-controlled trials lasting 24–52 weeks that were performed by Amylin Pharmaceuticals and Eli Lilly. Study designs, entry criteria, and primary efficacy and safety outcomes for these clinical trials have been reported previously.[15–20] Four of the trials were placebo controlled,[15–17,20] and the remaining two trials compared the efficacy of exenatide bid with insulin (biphasic insulin aspart or insulin glargine).[18,19] All trials followed protocols approved by local institutional review or ethics boards, and were conducted in accordance with the principles described in the Declaration of Helsinki (1997).[26] The subjects enrolled in these studies were ≥18 years of age, and had hemoglobin A_{1C} ≥6.5 and ≤11.0%, BMI ≥25 and ≤45 kg/m^2, and stable body weight. Enrolled subjects continued existing oral glucose-lowering, antihypertensive, and lipid-lowering therapies; all subjects in the insulin-comparator studies also received metformin and a sulfonylurea. Subjects randomly assigned to the exenatide groups received exenatide subcutaneously twice daily: 5 μg for 4 weeks followed by 10 μg for the remainder of the trial. Subjects treated only with 5 μg exenatide twice daily were not included in the analysis, as the purpose of the study was to evaluate the BP treatment effects derived from 10 μg exenatide twice daily, the recommended therapeutic dose of exenatide.

BP measurements. BP and pulse pressure (PP) was measured according to standard clinical practices in the investigators' offices. Instructions to the investigators requested BP measurement after ≥2 min rest with the patient in a seated position. The equipment to be used was not specified.

Statistical methodology. Data from trials comparing exenatide and placebo[15–17,20] were analyzed separately from data obtained during trials comparing exenatide with insulin.[18,19] The analyses included data points collected after ~6 months of therapy (weeks 24, 26, 28, and 30 for studies lasting 24, 26, 52, and 30 weeks, respectively).[15–20] Missing postbaseline data were imputed using the last-observation-carried-forward method in all studies.

Change-from-baseline values of SBP, DBP, and PP (PP = SBP − DBP) were compared between treatment groups using the analysis of covariance model including treatment, study, and baseline value of the dependent variable as covariates to account for variability. Subjects were initially stratified according to abnormal or normal baseline BP values (i.e., SBP <130 mm Hg; DBP <80 mm Hg).[7] In subjects with abnormal SBP or DBP values, the data were further stratified into three categories of SBP (130–139, 140–149, and ≥150 mm Hg) or two categories of DBP (80–89 mm Hg, and ≥90 mm Hg). The proportions of subjects shifting from an abnormal to normal BP classification at the study end point (6 months) were compared between the treatment groups using the Cochran–Mantel–Haenszel test, where the study served as the stratification factor.

A subgroup analysis of BP changes in subjects of African-American descent was performed. Due to limited numbers of African-American subjects in the trials, data from all six studies were pooled and patients treated with either insulin or placebo were categorized as nonexenatide subjects. A Pearson correlation coefficient for the potential relationship between weight loss and improvement in BP for all exenatide-treated subjects was also calculated. Inferential statistical tests were performed using two-sided test and at a significance level of 0.05. Change-from-baseline values are presented as least squares mean change ± s.e. Statistical analyses were performed using SAS 8.02 (SAS, Cary, NC).

RESULTS

Pooled baseline patient demographics and BP characteristics from six clinical trials (N = 2,171) in subjects with type 2 diabetes are presented in **Table 1**. Baseline demographics and BP characteristics were well matched between the exenatide and placebo groups and between the exenatide and insulin groups. In the overall study population, analyses showed that by the end of the 6-month trial period, treatment with exenatide was associated with a statistically significant greater reduction in SBP compared to placebo (least squares mean (s.e.), −2.2 mm Hg (0.56) vs. +0.6 mm Hg (0.56), difference of −2.8 mm Hg (0.75), P = 0.0002) or insulin (−4.5 mm Hg (0.60) vs. −0.9 mm Hg (0.60), difference of −3.7 mm Hg (0.85), P < 0.0001). In contrast, DBP in the overall study population was minimally decreased relative to baseline and not significantly different between the exenatide and placebo groups (−0.7 mm Hg (0.33) vs. −0.2 mm Hg (0.33); P = 0.21) or the exenatide and insulin groups (−1.6 mm Hg (0.35) vs. −0.8 mm Hg (0.36); P = 0.16). Although change in use of hypertensive medications was not a prespecified end point in the studies, no differences in the percentage of subjects altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatment groups (data not shown).

Subjects with abnormal SBP at baseline showed the greatest SBP reductions with exenatide therapy, which were significantly greater than treatment with either comparator

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Table 1 | Baseline demographics and blood pressure profiles of intention-to-treat patients

	Exenatide vs. placebo group[a] (*N* = 1,121)		Exenatide vs. insulin group[a] (*N* = 1,050)	
Demographics	**Exenatide (*N* = 561)**	**Placebo (*N* = 560)**	**Exenatide (*N* = 535)**	**Insulin (*N* = 515)**
Age (years)	55 ± 10	55 ± 10	59 ± 9	58 ± 9
Sex, female/male (%)	41/59	42/58	46/54	47/53
Race (%)				
Caucasian	68	69	87	87
Black	11	11	1	1
Hispanic	14	14	8	8
Other	7	6	4	4
Weight (kg)	96 ± 20	97 ± 19	87 ± 16	86 ± 17
BMI (kg/m^2)	33 ± 6	34 ± 5	31 ± 4	31 ± 4
HbA_{1C} (%)	8.4 ± 1.1	8.4 ± 1.0	8.4 ± 1.0	8.5 ± 1.0
Fasting serum glucose (mg/dl)	176 ± 46	181 ± 50	190 ± 48	196 ± 51
Duration of diabetes (years)	6.6 ± 6.2	6.9 ± 6.1	10 ± 6	10 ± 6
Concomitant OAD (% of points)				
MET	19.6	18.9	0.0	0.0
SFU	22.6	21.6	0.0	0.0
MET + SFU	43.9	44.6	100.0	100.0
None	13.9	13.8	0.0	0.0
Overall blood pressure				
Systolic (mm Hg)	128.9 ± 14.2	130.0 ± 14.6	137.8 ± 16.7	136.3 ± 16.2
Diastolic (mm Hg)	78.4 ± 8.4	78.9 ± 8.7	80.3 ± 9.3	80.3 ± 9.0
Pulse pressure	50.5 ± 12.1	51.1 ± 12.8	57.4 ± 14.2	56.0 ± 13.6
Abnormal blood pressure (% of points)[b]				
Abnormal systolic (overall)	50.8%	54.5%	73.1%	71.3%
130–139 mm Hg	26.4%	27.1%	21.9%	25.0%
140–149 mm Hg	16.0%	19.5%	27.3%	23.9%
≥150mm Hg	8.4%	7.9%	23.9%	22.3%
Abnormal diastolic (overall)	53.8%	54.6%	64.7%	68.7%
80–89 mm Hg	44.7%	41.1%	43.6%	50.3%
≥90 mm Hg	9.1%	13.6%	21.1%	18.4%
Concomitant AHD (% of points)	63%	54%	70%	67%

Data are presented as mean ± s.d.
AHD, antihypertensive drugs; BMI, body mass index; MET, metformin; OAD, oral antidiabetic drugs; SFU, sulfonylurea.
[a]Pooled data from studies comparing exenatide vs. placebo or insulin. Concomitant OAD and AHD medications were also administered in many of the studies. [b]Abnormal values for systolic and diastolic blood pressures are defined in accordance with ADA standards.[7]

(exenatide vs. placebo: −8.3 mm Hg (0.79) vs. −4.5 mm Hg (0.79), difference of −3.8 mm Hg (1.08), $P = 0.0004$; exenatide vs. insulin: −8.3 mm Hg (0.70) vs. −4.2 mm Hg (0.72), difference of −4.0 mm Hg (1.01), $P < 0.0001$). Furthermore, when treatment effects were evaluated by BP strata, BP reductions were associated with the degree of SBP elevation observed at baseline. The largest between-group differences were observed at baseline SBP ≥150 mm Hg (exenatide vs. placebo: −22.4 mm Hg (2.35) vs. −14.2 mm Hg (2.39), difference of −8.2 mm Hg (3.12), $P = 0.01$; exenatide vs. insulin: −16.0 mm Hg (1.36) vs. −11.5 mm Hg (1.42), difference of −4.6 mm Hg (1.97), $P = 0.02$; Figures 1 and 2). In subjects with normal BP at baseline, no differences in change of SBP or DBP from baseline were observed between exenatide and either comparator. PP effects trended similarly to SBP effects, with the most pronounced reduction occurring in exenatide-treated subjects with baseline PPs ≥40 mm Hg. In this subgroup, the reduction in PP was significantly greater with exenatide than with either placebo (−3.5 mm Hg (0.52) vs. −0.5 mm Hg (0.52), difference of −2.9 mm Hg (0.71), $P < 0.0001$) or insulin (−4.0 mm Hg (0.52) vs. −0.9 mm Hg (0.54), difference of −3.0 mm Hg (0.75), $P < 0.0001$).

By the end of the 6-month treatment period, a higher proportion of exenatide-treated subjects with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetes compared to insulin-treated subjects (19%; treatment difference,

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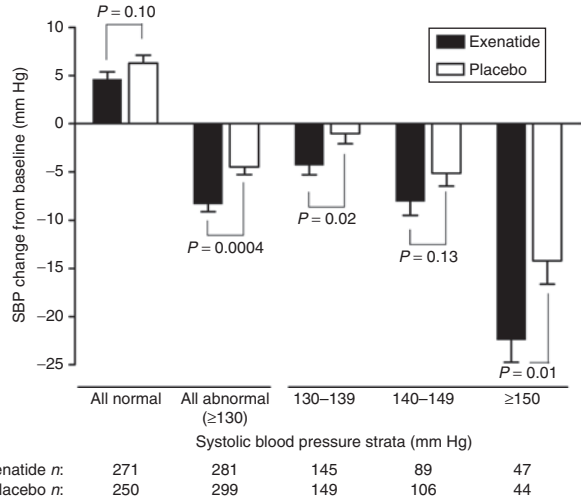

Figure 1 | Summary of changes in systolic blood pressure (SBP) at the 6-month study end point in subjects with type 2 diabetes treated with exenatide vs. placebo. Data are presented as baseline-to-end point differences in the least squares mean ± s.e.

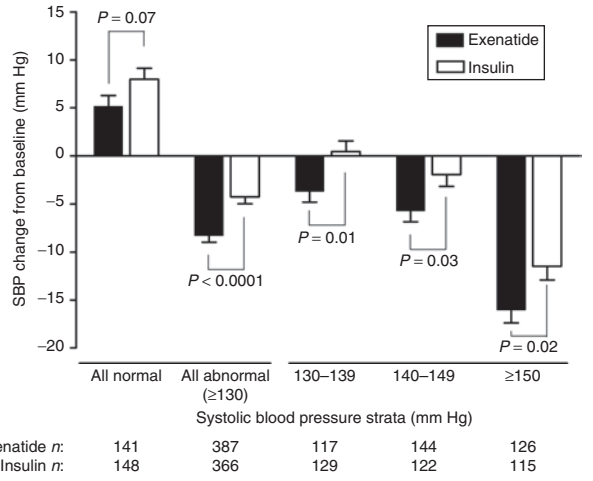

Figure 2 | Summary of changes in systolic blood pressure (SBP) at the 6-month study end point in subjects with type 2 diabetes treated with exenatide vs. insulin. Data are presented as baseline-to-end point differences in the least squares mean ± s.e.

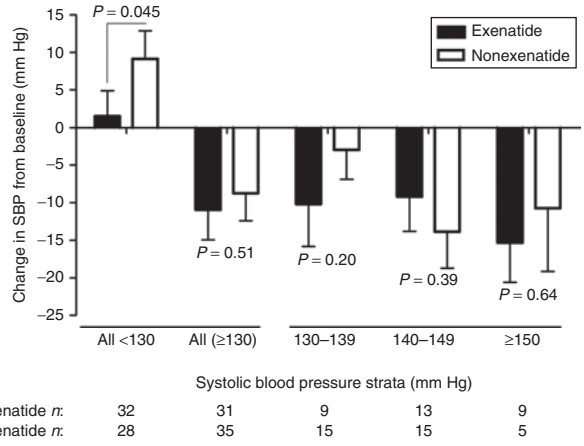

Figure 3 | Summary of changes in systolic blood pressure (SBP) at the 6-month study end point in African-American subjects with type 2 diabetes treated with exenatide or a comparator (nonexenatide: placebo or insulin). Data are presented as baseline to end point differences in the least squares mean ± s.e.

P = 0.03); however, no significant treatment effect on DBP was observed. In contrast, although no significant exenatide-treatment-related shifts were observed in SBP classifications, a higher proportion of subjects treated with exenatide were favorably shifted from a baseline classification of "abnormal DBP" to "normal DBP" compared to subjects treated with placebo (41.4% vs. 32.4%; treatment difference, P = 0.02).

Subgroup analysis of the effect of exenatide vs. nonexenatide therapy on subjects of African-American descent demonstrated baseline-to-end point reductions in stratified SBP and DBP consistent with the changes seen in the overall study population (**Figure 3**). These subjects were younger than the study population as a whole and more were female, but there were no notable demographic differences between exenatide and nonexenatide-treated patients (**Table 2**).

To explore a possible mechanism for the overall reduction in SBP observed in subjects with hypertension, the relationship between weight loss and reductions in BP was investigated. This analysis showed that, although the majority of exenatide-treated subjects lost weight (consistent with earlier reports in the same population), weight loss was only weakly correlated with BP changes in all exenatide-treated subjects (r = 0.09, P = 0.002).

DISCUSSION

In this exploratory *post hoc* analysis of pooled clinical data from 2,171 subjects with type 2 diabetes mellitus, administration of fixed-dosed exenatide therapy (10 µg subcutaneously, b.i.d.) to subjects who were also hypertensive was associated with statistically significant greater reductions in SBP compared with administration of placebo or insulin (P = 0.0004 and P < 0.0001, respectively). In the overall population, these significantly larger reductions were observed across a spectrum of abnormal BP strata, but not in subjects with normal BP (P = 0.10 and P = 0.07 vs. placebo and insulin, respectively). Subjects in the highest SBP stratum at baseline (≥150 mm Hg) experienced the greatest BP reduction by the end of the study. In the subgroup of African-American subjects included in the studies, whose hypertension might be more difficult to control,[24,25] the results were similar to results in the overall population but conclusions are limited by the low number of subjects studied.

Interestingly, the beneficial BP lowering effects associated with exenatide administration were observed despite no significant changes in the use of antihypertensive drugs, and correlated only weakly with weight loss, suggesting that these BP reductions might be mediated by an alternative mechanism.

Previous studies have demonstrated clinical benefit from BP reductions in hypertensive subjects with type 2 diabetes.[5,6,27,28] In a UKPDS investigation of BP control in subjects with both conditions, each 10 mm Hg reduction in SBP was associated with a 15% decrease in risk of death due to diabetes

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Table 2 | Demographics and baseline measurements for the subgroup of African-American (AA) subjects treated with exenatide or a comparator

Demographics	All AA subjects treated with exenatide (*N* = 65)	All AA subjects treated with nonexenatide (placebo or insulin) (*N* = 64)
Age (years)	52 ± 10	52 ± 10
Sex, female/male (%)	58/42	69/31
Weight (kg)	97 ± 21	97 ± 16
BMI (kg/m^2)	34 ± 6	35 ± 6
HbA_{1C} (%)	8.5 ± 1.3	8.5 ± 1.2
Fasting serum glucose (mg/dl)	160 ± 52	169 ± 41
Duration of diabetes (years)	7.5 ± 6.8	7.8 ± 5.3
Concomitant OAD (% of points)		
MET	15	20
SFU	32	16
MET + SFU	48	59
None	5	5
Baseline blood pressure (mm Hg)		
Systolic	131 ± 16	131 ± 15
Diastolic	81 ± 8	81 ± 9
Pulse pressure	50 ± 14	50 ± 15
Abnormal blood pressure (%)		
Abnormal systolic (overall)	51	56
Abnormal diastolic (overall)	66	69

Data are presented as mean ± s.d.
BMI, body mass index; HbA_{1C}, hemoglobin A_{1c}; MET, metformin; OHA, oral antidiabetic drugs; SFU, sulfonylurea.

($P < 0.0001$).[6] Because SBP is continuously and positively associated with vascular risk, lesser BP reductions may also confer benefit in diabetic subjects with hypertension.[27] In the Heart Outcomes Prevention Evaluation study, which compared the efficacy of ramipril and placebo, 2.5 mm Hg reductions in SBP and 1 mm Hg reductions in DBP in subjects with diabetes were associated with a 25% reduction in the risk of myocardial infarction, stroke, or cardiovascular death over 4.5 years.[28] However, mechanisms other than BP reduction may have been responsible for the observed improvement in clinical end points.[28]

The correlation between SBP and weight loss in this study was weak, and does not convincingly support the hypothesis that weight loss alone causes SBP reduction associated with exenatide. Other hypotheses have been proposed based on the effects of GLP-1 infusion in humans, namely that increased excretion of sodium or improved arterial vasodilatation, or both, may mediate reductions in BP.[12–14] Additional studies are needed to establish the precise mechanism(s) of the observed reductions in SBP during GLP-1 receptor agonist therapy. The current data suggest that GLP-1 receptor agonists improve BP via different mechanisms than current antihypertensive therapies, and their effects may be complementary.

Although both GLP-1 receptor agonists and dipeptidyl peptidase-4 inhibitors control hyperglycemia by stimulating the GLP-1 receptor, GLP-1 receptor agonists may affect vascular function via different mechanisms than dipeptidyl peptidase-4 inhibitors. Dipeptidyl peptidase-4 inhibitors prevent native GLP-1 degradation and also inhibit degradation (and thereby increase the concentration) of numerous other peptides, including the vasoconstrictors neuropeptide Y and peptide YY.[29,30] As a result, they stimulate plasma GLP-1 activity to a lesser extent than GLP-1R agonist addition[31] and may affect additional signaling pathways, which may result in different clinical effects on BP.[32]

Limitations of the current study include nonstandardized methods for measuring BP and some adjustments in use of antihypertensive medications during the study. However, statistically significant intergroup differences in SBP were observed despite any variability introduced by nonstandard BP measurement techniques, and there were no significant differences in change in antihypertensive medications between the exenatide-treated group and the placebo or insulin-comparator groups. Significant decreases in SBP from baseline were observed in the nonexenatide-treated comparator groups, which may indicate that the diabetes education and support received during the trial also affected SBP. The magnitude of decrease observed in the comparator groups is consistent with that observed with lifestyle intervention in the LOOK AHEAD study.[33]

The results of this study support the need for a prospective, randomized, controlled study of BP changes in patients with type 2 diabetes and hypertension treated with exenatide as well as studies to determine mechanisms by which GLP-1 receptor agonists may reduce BP. It is important that a large subpopulation of African-American patients be enrolled to determine the effects of exenatide on BP in this high-risk population. Twenty-four hour ambulatory BP monitoring to determine the effects of exenatide on nocturnal dipping may also be of interest as impaired circadian BP variation in patients with type 2 diabetes is associated with increased cardiovascular mortality.[34,35] If the antihypertensive effects of exenatide are confirmed, these data may have long-term clinical implications on therapeutic choices for patients with both type 2 diabetes and hypertension.

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