ORIGINAL ARTICLE

Effect of GLP-1 Mimetics on Blood Pressure and Relationship to Weight Loss and Glycemia Lowering: Results of a Systematic Meta-Analysis and Meta-Regression

Mohammad Katout,[1] Hong Zhu,[2] Jessica Rutsky,[1] Parthy Shah,[1] Robert D. Brook,[3] Jixin Zhong,[1] and Sanjay Rajagopalan[4]

BACKGROUND
Incretin therapies such as glucagon-like peptide 1 (GLP-1) agonists are commonly used for the treatment of type 2 diabetes mellitus. GLP-1 mimetics, besides improving glycemic control, have been shown to influence multiple pathways regulating blood pressure (BP). We investigated the GLP-1 analogs effects on BP from published randomized studies using a meta-analytic approach.

METHODS
Thirty-three trials (12,469 patients) that assessed the efficacy of GLP-1 analogs on glycemic control (HbA1C) over 12–56 weeks that met additional criteria, including the availability of standardized sitting BP assessment and weight parameters, were identified. Comparator therapy included oral antiglycemic drugs or placebo. The weighted mean difference (WMD) in systolic BP (SBP) change was calculated using a random-effects model after performing a test for heterogeneity.

RESULTS
Forty-one percent of patients were treated with liraglutide (0.3–3 mg once daily), whereas 59% were treated with exenatide (5–10 µg twice daily or 2 mg weekly). GLP-1 treatment achieved a greater SBP reduction than comparator therapy (WMD = 2.22 mm Hg; 95% confidence interval (CI) = −2.97 to −1.47). In the pooled analysis, GLP-1 had beneficial effects on weight loss (WMD = −2.56 kg; 95% CI = −3.12 to −2.00), HbA1c reduction (WMD = −0.41%; 95% CI = −0.78 to −0.04) but was associated with a heart rate increase (WMD = 1.30 bpm; 95% CI = 0.26–2.33). In a separate meta-regression analysis, the degree of SBP change was not related to baseline BP, weight loss, or improvement in HbA1C.

CONCLUSIONS
This meta-analysis provides evidence that GLP-1 analogs reduce sitting SBP. These findings may support potentially favorable long-term cardiovascular outcomes.

Keywords: blood pressure; exenatide; GLP-1; hypertension; liraglutide; meta-analysis.

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Glucagon-like peptide 1 (GLP-1) is a peptide hormone that stimulates insulin and inhibits glucagon secretion in a glucose-dependent manner.[1] GLP-1 exerts favorable effects on glycemic control additionally by binding to the GLP-1 receptor expressed in the gastrointestinal tract and central nervous system, exerting effects on gastric emptying and reductions in appetite. Recently it has been recognized that the GLP-1 receptor is widely expressed in the cardiovascular system in a number of different cell types, including endothelial and smooth muscle cells.[1] Several GLP-1 receptor (GLP-1R) agonists have been developed as therapeutic agents for the treatment of type 2 diabetes mellitus. GLP-1 agonists are effective in lowering weight and improving glycemic control, with recent meta-analysis suggesting an average lowering of weight by approximately 2 kg and reductions in HbA1C of 1.5%.[2] A variety of other pleiotropic effects have also been described, including improvements in endothelial function by activation of phosphoinositide 3 kinase, protein kinase B, and endothelial nitric oxide synthase, that may lead to lowering of blood pressure (BP).[1] Both short-term (with some including acute effects) and chronic studies and recent meta-analysis that have included both short-term and long-term studies have suggested that these agents may lower BP. In this meta-analysis, we pooled results from all published studies to date that have reported on BP as part of randomized controlled trials of GLP-1 agonists vs. placebo or non-GLP-1 comparator of at least 12-weeks duration and attempted to understand the relationship between BP lowering and improvements in weight and glycemia using a meta-regression approach.

Correspondence: Sanjay Rajagopalan (sraj@umm.edu).

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[1]Division of Cardiovascular Medicine, University of Maryland School of Medicine, Baltimore, Maryland; [2]Davis Heart and Lung Research Institute, The Ohio State University, Columbus, Ohio; [3]Division of Biostatistics Department of Clinical Sciences, UT Southwestern Medical Center, Dallas, Texas; [4]Division of Cardiovascular Medicine, University of Maryland, Baltimore, Maryland.

METHODS

Data sources and literature search

Pubmed, Scopus, Cochrane, and Clinicaltrials.gov trials databases were searched for English-language articles published from 1 January 2000 to 1 March 2013. Prespecified search terms were GLP-1, glucagon-like peptide 1, exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide, and BP. Titles and abstracts were searched. Studies included in our analyses were only blinded randomized controlled trials (RCTs) or open-labeled studies of 12- to 56-weeks duration.

Review methods and selection criteria

The reference lists of relevant papers were reviewed manually by one reviewer, with 1,156 articles included for initial screening. We included trials of adult patients with or without type 2 diabetes mellitus with a GLP-1R agonist treatment arm. Studies were included only if they had a non-GLP-1 comparator (includes placebo and active comparator trials) with sample size mentioned for each comparator group and reported systolic BP (SBP) measurements before and after active treatment with SD or confidence interval (CI). DPP-4 as comparator drugs were allowed, provided there was a nonincretin treatment group and/or placebo arm. All studies had to include a minimum duration of 12 weeks of drug exposure. The control groups were thus either placebo or active comparator arms that included oral antidiabetic drugs, DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin, alogliptin, and vildagliptin) PPARγ agonist, pioglitazone, sulfonylureas, orlistat, and insulin. We also assessed whether the trials included standardized diet/exercise regimens. If trials included >1 medication strength or >1 study duration, we took the higher titration dose and/or the longer duration group for weight and HbA1c and combined all the strengths in the meta-analysis for SBP effects. The applied exclusion criteria excluded acute dosing studies, duplicate trials, trials with incomplete data, or those without BP measurements. The following article types were excluded: reviews, letters, opinions, or treatment guidelines; abstracts published before January 2000 or duplicate abstracts; experimental nonhuman studies; studies in type 1 diabetes; studies in obesity in the absence of diabetes; and studies of drug mechanism of action, pharmacokinetics, or pharmacodynamics properties. Studies were further eliminated if BP data were not included, if a nonapproved administration method or dose was studied, if the protocol was unclear, or if data were missing. Publications that provided comparison with placebo were analyzed separately and compared with the treatment effect in active comparator trials. Liraglutide was used in nondiabetic, obese patient who had body mass index of either ≥30 kg/m^2 or body mass index of 27–30 kg/m^2 with presence of comorbidities such as hypertension or dyslipidaemia. Eight percent of patients did not have diabetes.

Data extraction

Mean baseline characteristics and demographic data collected included duration of therapy, duration of diabetes, age, HbA1c, body weight, and baseline BP. In addition, mean and/or least-squares (LS) mean (95% CI) changes from baseline to study endpoint for HbA1c, weight, and BP were extracted from each treatment arm but were not imputed if data were missing. Data entered into the statistical model were checked for accuracy against the original references by 2 individuals (M.K. and Z.H).

Statistical analysis

We used random-effect models for primary analyses because we expected clinical heterogeneity between studies caused by different criteria for patient inclusion and different intervention regimens. Results of the meta-analyses were presented as weighted mean difference (WMD) between the treatment group and the control group for continuous outcomes, with 95% CIs. Heterogeneity between studies was measured as I^2, which describes the percentage of variability in effect estimates that is attributed to variability in the true treatment effect, rather than sampling variation. The P value of heterogeneity χ^2 test was provided. A value of $I^2 > 50\%$ was considered to indicate substantial heterogeneity, and a P value < 0.05 was considered to suggest significant heterogeneity. We also repeated the meta-analyses using fixed-effect models to test the robustness of the results after attributing less weight to small trials, and we report the results of the fixed-effect meta-analyses only if they differed from those of the random effects models. We also performed a subgroup analysis of the primary endpoint to examine treatment effects in studies with a restricted duration of therapy (≤26 weeks). The random-effect meta-regression analyses were conducted to assess whether baseline body weight, baseline HbA1c, baseline SBP, weight loss, HbA1c lowering, heart rate change, and study duration could predict the size of the estimated treatment effects. Regression analysis of funnel plot asymmetry was used to assess any evidence of publication bias and small study effects (Egger's test). All analyses were performed with Stata version 11 (Stata Corp, College Station, TX).

RESULTS

After the initial database search, 139 potentially relevant publications were identified, of which 52 publications were screened for initial consideration. Of these, 33 met full eligibility criteria (Figure 1). Figure 2 depicts the comparator arms. Exenatide studies exceeded liraglutide studies, and of the exenatide studies, roughly 21% were with the long-acting formulation. Active comparator drugs exceeded placebo (62% vs. 38%). The drug doses included in the current meta-analysis included 5 and 10 μg of exenatide twice daily, 2 mg of exenatide every week, and 0.6, 0.9, 1.2, and 1.8 mg of liraglutide once daily. No studies reporting BP effect with the newer agents, taspoglutide or albiglutide, were available at the time of this analysis. The majority of studies in these analyses were conducted during phase III development, and all studies were published in 2004 or later. Thirty-three percent of the studies were 12–24 weeks in duration, 67% were >6 months in duration, and 82% included ≥90 patients

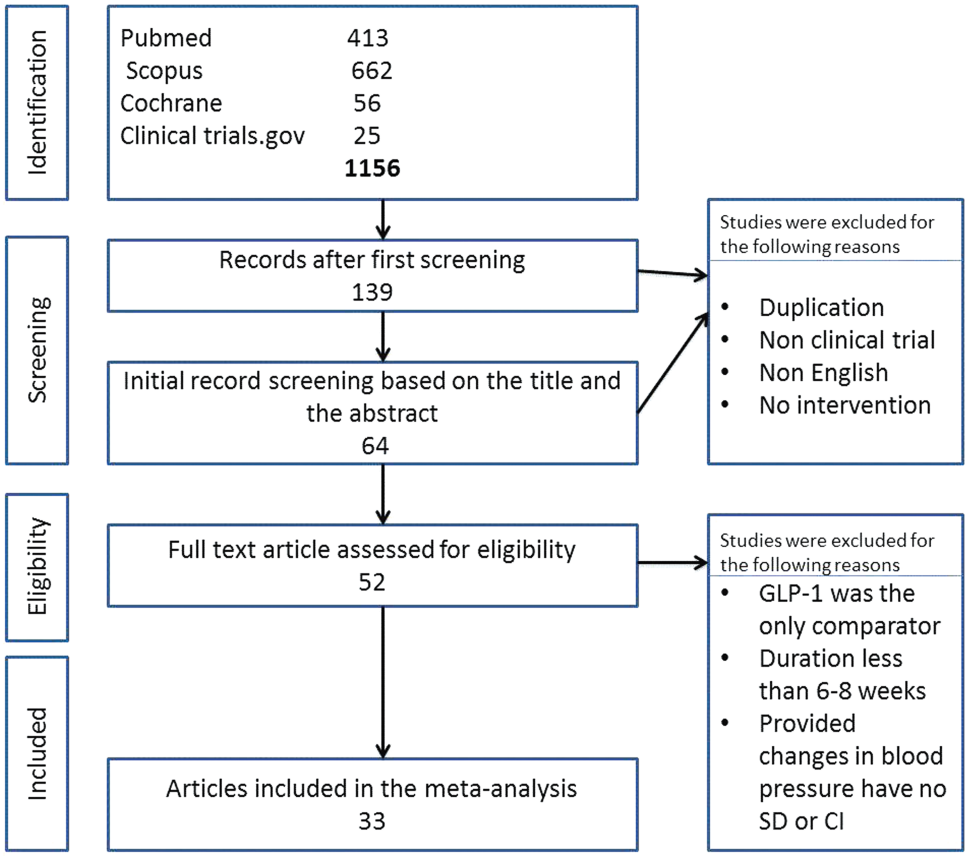

Figure 1. Study flow that details strategy for inclusion of articles in meta-analysis.

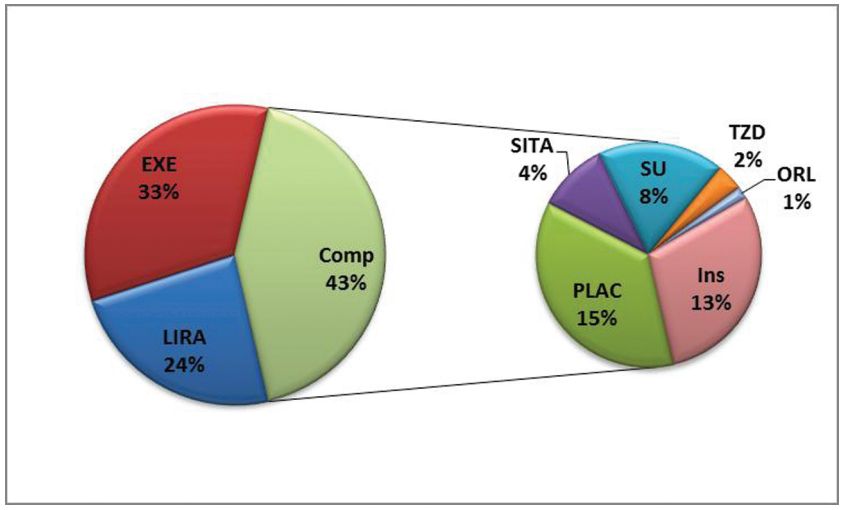

Figure 2. Study drugs used in trials included in meta-analysis. Abbreviations: COMP, comparator; EXE, exenatide; INS, Insulin; LIRA, liraglutide; ORL, orlistat; PLAC, placebo; SITA, sitagliptin; SU, sulfonylurea (glimepiride); TZD, thiazolidinedione (pioglitazone).

per arm. Mean age of the population was 65 ± 12 years. The mean baseline HbA1c values were 8.6 ± 1% mmol/mol (Table 1). Key differences among the clinical trial programs included number of patients per trial, number of doses tested, duration of diabetes, comparator arms, proportion of double-blinded trials, and proportion of trials preceded by discontinuation of prior oral glucose-lowering therapies (run-in vs. add-on design) (Table 1). Some studies did not report baseline BP or diastolic BP data but only reported differences after treatment. Of the 16 studies that did

Table 1. Baseline and study characteristics

Author	Intervention	Age, y	Treatment arm, no.	Control arm, no.	Study Duration (weeks)	HbAlc (%)	Duration of DM, years
Buse *et al.*[3]	Exenatide (5–10 μg BID)	56 ± 11	254	123	30	8.5 ± 0.1	6.45 ± 5.9
	Placebo	55 ± 11	183	89	30	8.7 ± 0.1	5.7 ± 4.7
Defronzo *et al.*[4]	Exenatide (5–10 μg BID)	53 ± 11	282	267	2	8.25 ± 1	5.55 ± 5.3
	Placebo	54 ± 9	486	247	3	8.2 ± 1	6.6 ± 6.1
Heine *et al.*[5]	Exenatide (5–10 μg BID)	60 ± 9	121	112	1	8.2 ± 1.0	9.9 ± 6.0
	Insulin glargine	58 ± 10	136	127	16	8.3 ± 1.0	9.2 ± 5.7
Kendall *et al.*[6]	Exenatide (5–10 μg BID)	55 ± 10	31	12	15	NA	8.7 ± 6.15
	Placebo	56 ± 10	253	248	52	NA	9.4 ± 6.2
Zinman *et al.*[7]	Exenatide (10 μg BID)	56 ± 11	155	77	24	7.9 ± 0.9	7.3 ± 4.9
	Placebo	57 ± 10	135	141	56	7.9 ± 0.8	8.2 ± 5.8
Kim *et al.*[8]	Exenatide (0.8–2.0 mg/wk)	53 ± 11	498	248	52	8.45 ± 1.1	4.5 ± 4
	Placebo	55 ± 9	234	232	16	8.6± 1.4	4 ± 4
Barnett *et al.*[9]	Exenatide 10 μg BID	5 ± 1	113	40	12	NA	NA
	Insulin glargine QD	55 ± 1	232	349	26	NA	NA
Nauck *et al.*[10]	Exenatide (5–10 μg BID)	59 ± 9	720	121	26	8.6 ± 1.0	9.8 ± 6.3
	Biphasic insulin aspart	58 ± 9	36	33	52	8.6 ± 1.1	10.0 ± 6.2
Moretto *et al.*[11]	Exenatide (5–10 μg BID)	55 ± 10	118	116	26	7.8 ± 1.0	2 ± 3
	Placebo	53 ± 9	355	177	26	7.8 ± 0.9	1 ± 2
Garber *et al.*[12]	Liraglutide (1.2–1.8 mg/d)	52 ± 11	371	193	20	8.3 ± 1.1	5 ± 5
	Glimepiride (8 mg/d)	53 ± 11	96	50	26	8.4 ± 1.2	6 ± 5
NCT00781937 2008	Liraglutide (3 mg/d)	46 ± 12	45	45	20	NA	NA
	Placebo	47 ± 11	233	223	26	NA	NA
Kadowaki *et al.*[13]	Exenatide (2.5 –10 μg BID)	60 ± 9	446	219	26	7.9 ± 0.8	11.9 ± 7.76
	Placebo	61 ± 10	96	98	24	8.1 ± 0.7	11.9 ± 6
Gao *et al.*[14]	Exenatide (5–10 μg BID)	55 ± 9	28	26	12	8.3 ± 1.0	8 ± 6
	Placebo	54 ± 9	160	331	26	8.3 ± 1.0	8 ± 5
Nauck *et al.*[15]	Liraglutide (0.6,1.2,1.8 mg)	57 ± 10	284	219	52	8.35 ± 1.0	7.4 ± 5
	Placebo	56 ± 9	196	66	16	Placebo: 8.4 ± 1.1	Placebo: 8 ± 6
	Glimepiride (4 mg/d)	57 ± 9				Glimepiride: 8.4 ± 1.0	Glimepiride: 8 ± 5
Russell-Jones *et al.*[16]	Liraglutide (1.8 mg/d)	58 ± 10	135	137	26 weeks	8.3 ± 0.9	9.2 ± 5.8
	Placebo	58 ± 10	137	122	30 weeks	Placebo: 8.3 ± 0.9	Placebo: 9 ± 6
	Insulin glargine	58 ± 11				Insulin glargine: 8.2 ± 0.9	Insulin glargine: 10 ± 5

Table 1. Continued

Author	Intervention	Age, y	Treatment arm, no.	Control arm, no.	Study Duration (weeks)	HbAlc (%)	Duration of DM, years
Bunck *et al.*[17]	Exenatide (5–10 μg BID)	88 ± 1	490	487	42 months	NA	5.7 ± 0.8
	Insulin glargine	58 ± 1	248	572	26 weeks	NA	4.0 ± 0.6
Zinman *et al.*[18]	Liraglutide (1.2–1.8 mg/d)	55 ± 11	Number of subjects in treatment arm	Number of subjects in control arm	Study duration	8.6 ± 1.2	9 ± 6
	Placebo	55 ± 10	254	123	30 weeks	8.4 ± 1.2	9 ± 6
Davies *et al.*[19]	Exenatide (10μg BID)	57 ± 10	183	89	30 weeks	8.65 ± 0.68	9 ± 5
	Insulin glargine	56 ± 8	282	267	26 weeks	8.5 ± 0.7	8 ± 4
Astrup *et al.*[20]	Liraglutide (1.2–3.0 mg/d)	46 ± 11	486	247	30 weeks	NA	NA
	Placebo, Orlistat	46 ± 10	121	112	16 weeks	NA	NA
Liutkus *et al.*[21]	Exenatide (5–10 μg BID)	55 ± 8	136	127	16 weeks	8.2 ± 0.9	6.3 ± 4.2
	Placebo	54 ± 9	31	12	15 `	8.3 ± 0.9	6.4 ± 4.6
Defronzo *et al.*[22]	Exenatide (10 μg BID)	57 ± 10	253	248	52	7.8 ± 0.1	6.5 ± 0.7
	Rosiglitazone (4 mg BID)	56 ± 11	155	77	24	7.9 ± 0.1	8.2 ± 0.8
Diamant *et al.*[23]	Exenatide 2 mg/wk	58 ± 10	135	141	56	8.3 ± 1.1	8·0 ± 6·0
	Insulin glargine	58 ± 9	498	248	52	8.3 ± 1.0	7·8 ± 6·0
Pratley *et al.*[24]	Liraglutide (1.2–1.8 mg/d)	55 ± 9	234	232	16	8.4 ± 0.7	6 ± 5
	Sitagliptin	55 ± 9	113	40	12	8.5 ± 0.7	6 ± 5
Gill *et al.*[25]	Exenatide (5–10 μg BID)	57 ± 11	232	349	26	7.5 ± 0.9	7 ± 4
	Placebo	54 ± 10	720	121	26	7.1 ± 0.7	6 ± 4
Apovian *et al.*[26]	Exenatide (5 μg BID)	55 ± 10	36	33	52	7.7 ± 0.9	6 ± 6
	Placebo	55 ± 9	118	116	26	7.5 ± 0.8	5 ± 5
Bergenstal *et al.*[27]	Exenatide (2 mg/w)	52 ± 10	355	177	26	8.6 ± 1.2	6 ± 5
	Sitagliptin (100 mg/d)	52 ± 11	371	193	20	8.5 ± 1.2	5 ± 4
	Pioglitazone (45 mg/d)	53 ± 10	96	50	26	8.5 ± 1.1	6 ± 5
Umpierrez *et al.*[28]	LY2189265 (0.5–2.0 mg/w)	54 ± 11	45	45	20	8.43 ± 1.0	9 ± 7
	Placebo	56 ± 12	233	223	26	8.1 ± 0.8	8 ± 5
Gallwitz *et al.*[29]	Exenatide (5–10 μg BID)	57 ± 10	446	219	26	7.9 ± 0.8	5 ± 4
	Insulin aspart (70/30 BID)	57 ± 10	96	98	24	7.9 ± 0.9	5 ± 5
Pratley *et al.*[30]	Liraglutide (1.2–1.8 mg/d)	56 ± 9	28	26	12	8.4 ± 0.7	6.2 ± 5
	Sitagliptin	55 ± 9	160	331	26	8.5 ± 0.7	6.3 ± 5.4
Buse *et al.*[31]	Exenatide (10 μg BID)	59 ± 9	284	219	52	8.32 ± 0.9	12 ± 7
	Placebo	59 ± 10	196	66	16	8.5 ± 1.0	12 ± 7

Table 1. Continued

Author	Intervention	Age, y	Treatment arm, no.	Control arm, no.	Study Duration (weeks)	HbAlc (%)	Duration of DM, years
Russell-Jones *et al.*[32]	Exenatide (2 mg/wk)	54 ± 11	135	137	26	NA	2.7 ± 3.2
	Metformin (2 g/d)	53 ± 11	137	122	30	NA	2.6 ± 3.6
	Sitagliptin (100 mg/d)						
	Pioglitazone (45 mg/d)						
Gallwitz *et al.*[33]	Exenatide (5–10 µg BID)	56 ± 10	490	487	42	7.5(58) ± 0.7	5·8 ± 4·8
	Glimepiride once daily	56 ± 9	248	572	26	7.4(57) ± 0.7	5·5 ± 4·3
Inagaki *et al.*[34]	Exenatide 2 mg/w	57 ± 10	254	123	30	8.51(69) ± 0.8	9 ± 6
	Insulin glargine	56 ± 11				8.5(69) ± 0.8	9 ± 6

Abbreviations: BID, twice daily; DM, Diabetes Mellitus; QD, every day; NA, not applicable.

report baseline BP, the mean SBP was 130 ± 31 mm Hg. We found evidence of significant heterogeneity between studies (I^2 = 99.5%; $P < 0.001$), suggesting that a random-effects model would accurately describe the data. The regression analysis did not show any clear evidence of publication bias or small study effects (Egger's test, $P > 0.1$ for all analyses). Cochrane bias table (Supplementary Table S1) shows results of risk of bias assessment, summarizing mostly low-risk selection bias, performance bias, and reporting bias. Funnel plot (Supplementary Figure 6) was broadly symmetrical, with no evidence of publication bias.

BP effects

On analysis of the pooled data, GLP-1 therapy was associated with a WMD in SBP reduction of −2.22 mm Hg (95% CI = −2.97 to −1.47) using a random-effect model; n = 7,540 active treatment and n = 5,759 in comparator arms) (Figure 3). Using a fixed-effect model, the results were more modest (WMD= −2.16 mm Hg; 95% CI = −2.72 to −2.60), which confirmed the primary meta-analysis. GLP-1 therapy was associated with a WMD in DBP of −0.47 mm Hg (95% CI = −1.20 to 0.25; n = 5,902 active treatment and n = 4,684 in comparator arms) using a random-effects model (Figure 4).The effect was more modest using fixed-effects model (WMD = −0.28 mm Hg; 95% CI = −0.33 to −0.24). In a subgroup analysis involving studies ≤26 weeks (n = 23 studies), the effect was no different than that of the main analysis (WMD = −2.03 mm Hg; 95% CI = −2.99 to −1.07) (Supplementary Figure S1). Examining the treatment effect in 14 placebo controlled studies separately, GLP-1 therapy was associated with a WMD in SBP reduction of −1.56 mm Hg (95% CI = −2.78 to −0.35) using a random-effect model and a WMD of −3.42 mm Hg (95% CI = −3.54 to −3.31) using a fixed-effect model.

Weight loss, HBA1C, and heart rate effects

Pooled analysis using a random-effects model revealed that GLP-1 therapy was associated with a WMD in weight of −2.56 kg (95% CI = −3.12 to −2.00; n = 7,258 active treatment and n = 5,492 in comparator) (Supplementary Figure S2). The effect was a little larger using a fixed-effects model (WMD = −3.34 kg; 95% CI = 3.36 to −3.33). GLP-1 therapy was associated with a WMD of −0.41% in HbA1c lowering (95% CI = −0.78 to −0.04; n = 7,540 active treatment and n = 5,759 in comparator arms) Supplementary Figure S3). A repeat meta-analysis with a fixed-effect model showed more modest effects (WMD = −0.08%; 95% CI = 0.08 to −0.07). Meta-analysis using a random-effect model showed that GLP-1 therapy was associated with a heart rate increase of 1.30 bpm (95% CI = 0.26–2.33; n = 4,372 active treatment and n = 3,582 in comparator arms) (Supplementary Figure S4). The effect was a little larger using a fixed-effects model (WMD = 1.89 bpm; 95% CI = 1.77–2.00).

Random-effect meta-regression of the primary meta-analysis on SBP found that baseline body weight ($P = 0.32$), baseline HbA1c ($P = 0.84$), baseline SBP ($P = 0.79$), study

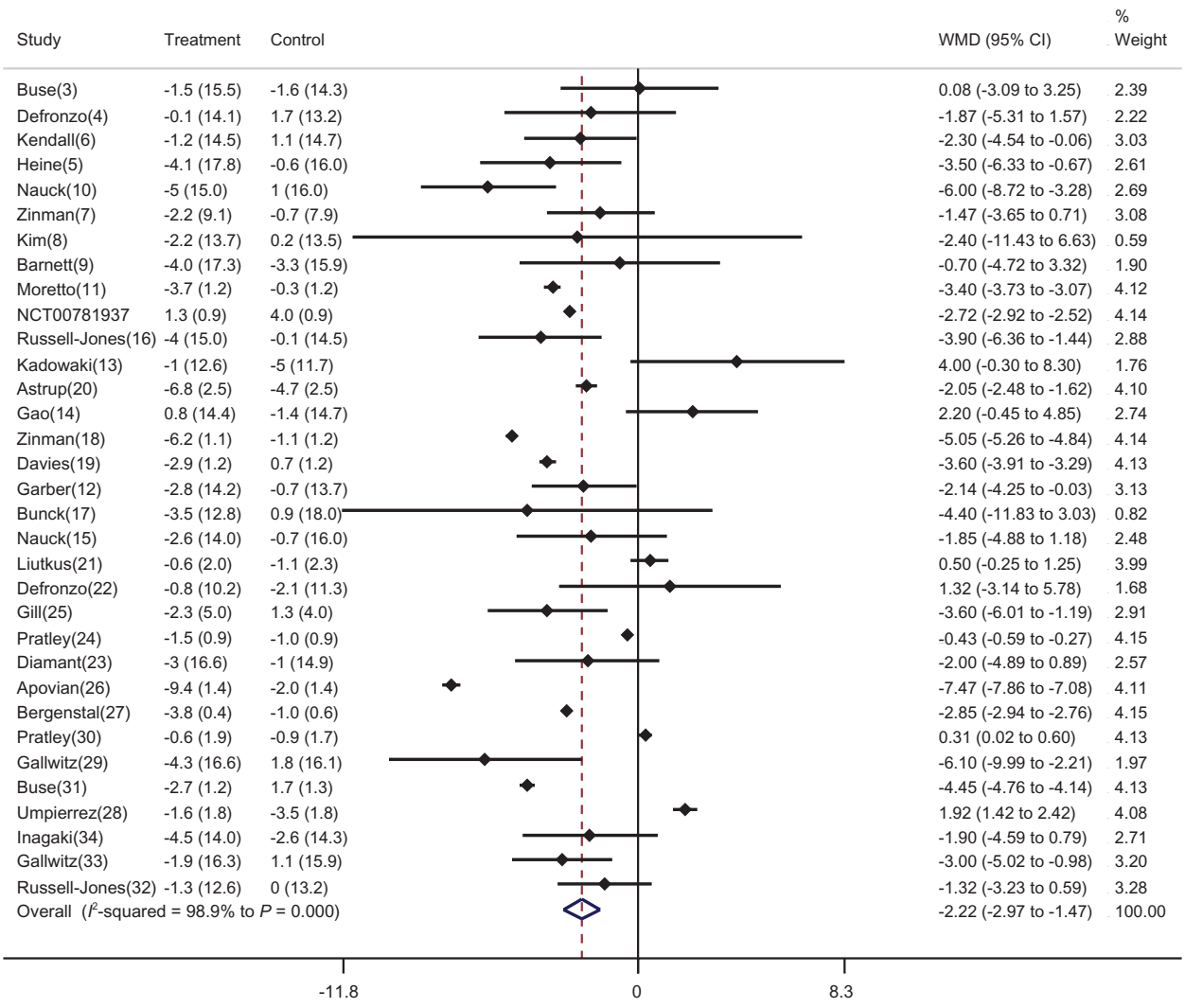

Figure 3. Meta-analysis of difference in systolic blood pressure (SBP) lowering in included studies between treatment and control, using random-effects model. Values for treatment and control are mean (SD). Weights are from random-effects analysis. Abbreviation: WMD, weighted mean difference in SBP (mm Hg).

duration (P = 0.20), weight loss (P = 0.422), HbA1c reduction (P = 0.776), and heart rate change (P = 0.64) did not predict the size of the estimated treatment effect or explain heterogeneity between studies. The degree of HbA1c reduction or degree of weight loss did not predict BP lowering. We did not find any evidence of publication bias or small study effects in regression analyses (Egger's test: SBP: P = 0.79; weight: P = 0.26; Hba1c: P = 0.44; heart rate: P = 0.59).

DISCUSSION

In this meta-analysis we investigated data from randomized trials of GLP-1 receptor agonists to discern an effect on BP lowering. The main findings are that GLP-1R agonists induce a small but significant change in SBP that appeared to be independent of baseline characteristics known to influence BP as well the degree of glycemia lowering and weight loss. This was accompanied by a small but significant increase in heart rate of 1.3 bpm. Our results add to the growing body of evidence suggesting that GLP-1 agonists may have weight loss–independent cardiovascular effects that may lead to favorable modulation of cardiovascular events.

The strengths of our meta-analysis are related to the incorporation of direct evidence from both unpublished and published trials of glycemic efficacy of GLP-1 agonists that have also included BP data with a nonincretin control group and exclusion of short-term studies of <12 weeks duration. Additional strengths include the use of meta-regression to examine the contribution of participants' baseline characteristics, extent of glycemia lowering, weight loss, and heart rate increase to the effect estimate of the primary outcome measure; the investigation of plausible clauses of heterogeneity by sensitivity analyses; and calculation of prediction intervals for the primary outcome of the change in BP. Nevertheless, multiple limitations should also be recognized. We did not conduct separate analyses for each GLP-1 agonist because of the small number of relevant trials. Second, concomitant therapy with antihypertensive agents or changes

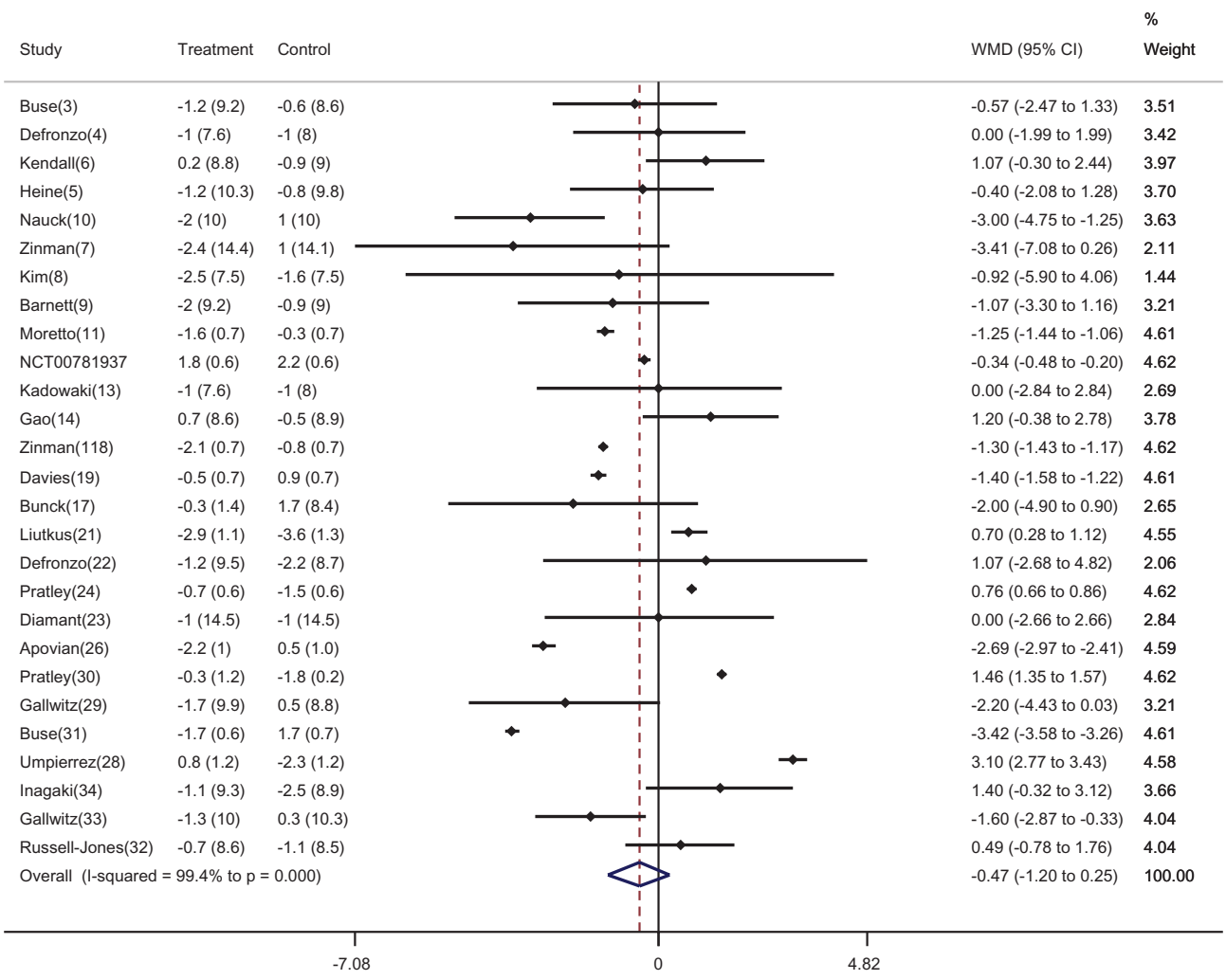

Figure 4. Meta-analysis of difference in diastolic blood pressure (DBP) lowering between GLP-1 treatment and control groups, using random-effects model. Values for treatment and control are mean (SD). Weights are from random-effects analysis. Abbreviation: WMD, weighted mean difference in DBP (mm Hg).

in medications before enrollment and/or during the course of the study were not adequately reported by many of the studies, making assessment of the results more complicated. Third, a number of the studies were open label, rendering potential biases in interpretation of BP data more likely. Finally, none of the included studies were designed to assess the comparative effect of GLP-1agonists on BP lowering, and thus the results in this analysis must be viewed as hypothesis generating and any conclusions should be considered with caution.

How may GLP-1 agonism modulate BP? Both GLP-1 and exendin 4 induce dose-dependent and time-reversible endothelial-dependent relaxation of systemic and pulmonary arteries.[35] GLP-1R agonists, including exenatide and liraglutide, increase eNOS phosphorylation/nitric oxide production through PKA-PI3K/Akt–dependent pathways.[36] GLP-1 agonists also reduce endothelial inflammation through inhibition of nuclear factor kappa B via 5′-AMP–activated protein kinase–dependent mechanisms.[37] The effects in improving endothelial function appear, however, to involve both nitric oxide–dependent and –independent pathways.[38] Although in acute administration in rodents, GLP-1 receptor activation has been noted to raise BP and heart rate due to sympathetic activation, this mechanism does not appear operational in humans, at least with acute administration, where GLP-1 (7–36) amide was shown to increase muscle sympathetic activity but not to have any effects on cardiac sympathetic or parasympathetic activity. In this analysis, we examined 2 different GLP-1 agonists that differ in structure and pharmacokinetics and potentially in efficacy. Liraglutide, for instance, resembles human GLP-1, with a fatty acid moiety to improve *in vivo* stability, whereas exenatide shares 53% amino acid sequence identity with human GLP-1. The half-lives of GLP-1RAs range from 2.4 hours (exenatide) to 13 hours (liraglutide). The once-weekly formulation of exenatide achieved by embedding exenatide in biodegradable microspheres releases exenatide over 10 weeks. These differences in GLP-1 may affect not only glycemic control efficacy but also, potentially, antihypertensive and heart rate effects. A review of trial data from 5 long-acting

GLP-1 agonists (exenatide once weekly, taspoglutide, albiglutide, LY2189265, and CJC-1134-PC) concluded that they were more likely than shorter-acting formulations to raise the heart rate.[39] A study of the GLP-1 agent PF-04603629 (a long-acting GLP-1) reported a substantial rise in the heart rate (a mean increase of 23 bpm at 24 hours after injection of the higher dose studied), together with a rise in the diastolic BP.[40] These differences suggest that there could be important variation between the long-acting and shorter-acting GLP-1 analogs, and this may merit independent study. Studies from rodent models seem to suggest sympathetic mechanisms but whether these may be applicable to humans is unclear.[1]

Prior prospective randomized trials as well as prospective epidemiologic studies have demonstrated that even small changes translate into reductions in major adverse cardiovascular events, with a 2 mm Hg reduction in SBP resulting in a 4% reduction in coronary heart disease (CHD) events and a 6% reduction in strokes.[37] Thus if our findings can be confirmed in well-designed prospective studies, they have implications for cardiovascular risk reduction.

There are several limitations of this study. For all the studies, measurement of BP and heart rate was not a primary or even a key secondary endpoint. Many studies did not list pre- and post-trial BP and the percentage of patients on antihypertensive treatment. Concomitant therapy with other antihypertensives or changes in medications (glycemia-lowering or lipid-lowering drugs) during the course of the study was not adequately reported by many of the studies. Thus, our findings would need careful confirmation in well-performed randomized studies where BP is a primary or key secondary variable. Future trials with ambulatory BP lowering may help address the issue of BP lowering with GLP-1 agonist with certainty.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

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