REVIEW

Annals of Internal Medicine

Benefits and Harms of Once-Weekly Glucagon-like Peptide-1 Receptor Agonist Treatments

A Systematic Review and Network Meta-analysis

Francesco Zaccardi, MD; Zin Zin Htike, MD; David R. Webb, PhD; Kamlesh Khunti, PhD; and Melanie J. Davies, MD

Background: Once-weekly glucagon-like peptide-1 receptor agonists (GLP-1RAs) are new drugs for the treatment of type 2 diabetes.

Purpose: To summarize evidence for the cardiometabolic efficacy and adverse effects of once-weekly GLP-1RAs in adults with type 2 diabetes.

Data Sources: Electronic databases (PubMed, Web of Science, Cochrane Central Register of Controlled Trials, U.S. Food and Drug Administration, European Medicines Agency, ClinicalTrials.gov) and congress abstracts from inception through 26 September 2015.

Study Selection: Randomized, controlled trials (≥24 weeks of follow-up) studying albiglutide, dulaglutide, once-weekly exenatide, semaglutide, and taspoglutide and reporting a cardiometabolic (primary outcome, hemoglobin A_{1c} [HbA_{1c}]) or safety outcome.

Data Extraction: Extraction was done in duplicate, and risk of bias was assessed. No language restriction was applied.

Data Synthesis: 34 trials (21 126 participants) were included. Compared with placebo, all once-weekly GLP-1RAs reduced HbA_{1c} and fasting plasma glucose; taspoglutide, 20 mg, once-weekly exenatide, and dulaglutide, 1.5 mg, reduced body weight. Among once-weekly GLP-1RAs, the greatest differences were found between dulaglutide, 1.5 mg, and taspoglutide, 10 mg, for HbA_{1c} (−0.4% [95% CI, −0.7% to −0.2%]), once-weekly exenatide and albiglutide for fasting plasma glucose (−0.7 mmol/L [CI, −1.1 to −0.2 mmol/L]; −12.6 mg/dL [CI, −19.8 to −3.6 mg/dL]), and taspoglutide, 20 mg, and dulaglutide, 0.75 mg, for body weight (−1.5 kg [CI, −2.2 to −0.8]). Clinically marginal or no differences were found for blood pressure, blood lipid levels, and C-reactive protein levels. Once-weekly exenatide increased heart rate compared with albiglutide and dulaglutide (1.4 to 3.2 beats/min). Among once-weekly GLP-1RAs, the risk for hypoglycemia was similar, whereas taspoglutide, 20 mg, had the greatest risk for nausea (odds ratios, 1.9 to 5.9).

Limitation: Data were unavailable for semaglutide, definitions of outcomes were heterogeneous, the last-observation-carried-forward imputation method was used in 73% of trials, and publication bias is possible.

Conclusion: Compared with other once-weekly GLP-1RAs, dulaglutide, 1.5 mg; once-weekly exenatide; and taspoglutide, 20 mg, showed a greater reduction of HbA_{1c}, fasting plasma glucose, and body weight. Taspoglutide, 20 mg, had the highest risk for nausea; risk for hypoglycemia among once-weekly GLP-1RAs was similar.

Primary Funding Source: Sanofi Aventis (grant to the University of Leicester).

Ann Intern Med. 2016;164:102-113. doi:10.7326/M15-1432 **www.annals.org**
For author affiliations, see end of text.
This article was published at www.annals.org on 8 December 2015.

Type 2 diabetes mellitus is a progressive metabolic disorder associated with an increased risk for vascular diseases and whose main and diagnostic characteristic is hyperglycemia (1–3). In the past decade, the number of available treatments for hyperglycemia has increased significantly (4). Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a relatively new class of drug that stimulate insulin and inhibit glucagon secretion, slow gastric emptying, and reduce food intake (5). In clinical studies, these drugs improve glucose control and reduce body weight, without an increased risk for hypoglycemia (6). The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend GLP-1RAs as a therapeutic option in patients receiving metformin with or without another glucose-lowering treatment if individualized metabolic targets are not achieved (7).

The first 2 approved GLP-1RAs are administered as subcutaneous daily injections (twice-daily exenatide and once-daily liraglutide). A direct comparison of these "daily" drugs has shown differences in terms of tolerability, efficacy, and pharmacokinetics (8). More recently, GLP-1RAs that are administered once weekly have emerged, reducing the number of injections and side effects and potentially improving patient compliance (6).

Several randomized, controlled trials (RCTs) have assessed the efficacy and safety of once-weekly GLP-1RAs compared with daily GLP-1RAs or other glucose-lowering therapies. However, to date, no direct comparisons between once-weekly GLP-1RAs have been available.

In the absence of direct evidence, network meta-analysis is an increasingly used statistical methodology that allows the estimation of the comparative effectiveness of multiple treatments (9, 10). In this context, we

See also:

Editorial comment 127

Web-Only
Supplement
CME quiz

conducted a systematic review and network meta-analysis to assess the comparative efficacy and safety of the once-weekly GLP-1RAs albiglutide, dulaglutide, exenatide, semaglutide, and taspoglutide.

METHODS

Data Sources and Searches

This study was done according to a prespecified protocol (Supplement 1, available at www.annals.org) and followed the standard guidelines for the conduct and reporting of systematic reviews and network meta-analysis (11–13). We searched the following databases from inception to 26 September 2015: PubMed, ISI Web of Science, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, U.S. Food and Drug Administration (www.fda.gov), European Medicines Agency (www.ema.europa.eu/ema), and the abstract databases of major diabetes conferences (ADA and EASD from 2012 onward). Reference lists of eligible studies, as well as systematic reviews and meta-analyses of GLP-1RAs, were manually scanned for additional relevant studies. No language restriction was applied. Detailed information on the search strategy is provided in Supplement 1.

Study Selection

Phase 3 RCTs in adults with type 2 diabetes that lasted 24 weeks or more were included. We included RCTs with at least 1 once-weekly GLP-1RA study group (albiglutide, dulaglutide, exenatide, semaglutide, and taspoglutide), regardless of the comparator (placebo or another glucose-lowering drug). We required that RCTs report data on cardiometabolic outcomes (primary outcome, HbA_{1c}; secondary outcomes, fasting plasma glucose; body weight; systolic and diastolic blood pressure; heart rate; C-reactive protein; and blood lipid values [total, low-density lipoprotein, and high-density lipoprotein cholesterol and triglycerides]) or safety outcomes (documented or symptomatic hypoglycemic events; severe hypoglycemic events; nausea and injection-site reaction events; fatal and nonfatal cardiovascular and cancer events; all-cause mortality). We excluded RCTs involving patients with chronic kidney disease. Although the clinical trial program of taspoglutide was stopped in 2010 and development has since been suspended, we included RCT data because they contribute to indirect estimations.

Data Extraction and Quality Assessment

Two authors independently performed the literature search and extracted study information by using standardized predefined forms. Extracted data included study characteristics and outcome measured (group-specific number of participants and mean difference and SE [or SD] for continuous outcomes; total number of participants and participants with event for dichotomous outcomes). Data were extracted on an intention-to-treat basis; that is, every participant who underwent randomization contributed to data according to their randomized treatment assignment. When published studies reported outcomes for different durations of follow-up, the longest was used. When it was not possible to extract relevant information for the primary outcome from published reports, we searched for trial results in ClinicalTrials.gov and contacted study authors.

Study-level quality was assessed by using the items reported in the Cochrane risk-of-bias tool (random-sequence generation, allocation concealment, blinding of participants and personnel and outcome assessment, and incomplete data and selective reporting) (14). If the 2 independent reviewers disagreed on the eligibility of an article, extracted information, or quality assessment, consensus was reached by reevaluation of the article and consultation with a third reviewer.

Data Synthesis and Analysis

Stata, version 14 (Stata Corp, College Station, Texas), was used for all analyses, and results are reported with 95% CIs. We performed pairwise random-effects meta-analyses by using the Knapp–Hartung method with the *metareg* command (15). We did network meta-analyses within a frequentist framework using the *network* suite (16). By using the *mvmeta* command (17), *network* performs network meta-analysis as multivariate random-effects meta-analysis and meta-regression, as recently proposed (18); the analysis assumes that all treatment contrasts have the same heterogeneity variance (18). We used the *network rank* option to estimate the ranking probabilities and the *netleague* command to report relative treatment effects for all pairwise comparisons estimated with the network meta-analysis (19).

Because our goal was to assess differences by comparing once-weekly GLP-1RAs with each other, we combined twice-daily exenatide and once-daily liraglutide treatments into one group of daily GLP-1RA therapies. We also combined insulin glargine and detemir (basal insulin) treatments. We defined a single group for albiglutide because the majority of RCTs were designed to titrate the drug to 50 mg if necessary, and dose-specific data were available only for 2 studies (20, 21); for these studies, we used data on the 50-mg dose.

We report the characteristics and summary data of included studies. For both pairwise and network meta-analyses, we used arm-specific mean differences from baseline and odds ratios (ORs) as effect measures for continuous and dichotomous data, respectively. We added 0.5 when studies reported no events in 1 treatment group (18). For the primary outcome, we reported a random-effect pairwise meta-analysis and estimated heterogeneity across studies by using the I^2 statistic. For each outcome, we summarized the evidence by using a network diagram (22). We present results against a common comparator (placebo) in forest plots and show comparisons across GLP-1RAs in forest plots and tables; we also display graphically the ranking probabilities (23). Within the networks, we assessed consistency between direct and indirect evidence by using the "design by treatment" interaction model (24).

We performed sensitivity analyses to assess the robustness of our results. We considered separate daily

Table. Baseline Characteristics of the Included Studies

Study, Year (Reference)	Study Acronym	Background Therapy	Once-Weekly GLP-1	Comparator
Wysham et al, 2014 (51)	AWARD-1	MET + TZD	DUL 0.75/1.5 mg	PLA, exenatide twice daily
Giorgino et al, 2015 (52)	AWARD-2	MET ± OADs; SU ± OADs	DUL 0.75/1.5 mg	Insulin glargine
Umpierrez et al, 2014 (49)	AWARD-3	Diet + exercise	DUL 0.75/1.5 mg	MET
Blonde et al, 2015 (53)	AWARD-4	Insulin (basal/basal + prandial/premixed) ± OADs	DUL 0.75/1.5 mg§	Insulin glargine§
Weinstock et al, 2015 (41)	AWARD-5	MET	DUL 0.75/1.5 mg	Sitagliptin
Dungan et al, 2014 (34)	AWARD-6	MET	DUL 1.5 mg	Liraglutide once daily
Drucker et al, 2008 (33)	DURATION-1	MET, SU, TZD, or any two combination	EOW 2 mg	Exenatide twice daily
Bergenstal et al, 2010 (27)	DURATION-2	MET	EOW 2 mg	PIO, sitagliptin
Diamant et al, 2014 (31) and 2010 (32)‖	DURATION-3	MET ± SU	EOW 2 mg	Insulin glargine
Russell-Jones et al, 2012 (48)	DURATION-4	Diet + exercise	EOW 2 mg	PIO, sitagliptin, MET
Blevins et al, 2011 (28)	DURATION-5	MET, SU, TZD, or any combination	EOW 2 mg	Exenatide twice daily
Buse et al, 2013 (29)	DURATION-6	MET, SU, MET + SU, MET + PIO	EOW 2 mg	Liraglutide once daily
Reusch et al, 2014 (45)	HARMONY 1	PIO ± MET	ALB 30 mg	PLA
Nauck et al, 2013 (20)	HARMONY 2	Diet + exercise	ALB 30/50 mg¶	PLA
Ahrén et al, 2014 (25)	HARMONY 3	MET	ALB 30 to 50 mg	PLA, sitagliptin, glimepiride
Weissman et al, 2014 (50)	HARMONY 4	MET ± SU	ALB 30 to 50 mg	Insulin glargine
Home et al, 2015 (37)	HARMONY 5	MET + SU	ALB 30 to 50 mg	PLA, PIO
Rosenstock et al, 2014 (47)	HARMONY 6	Insulin glargine/detemir/NPH insulin ± OADs	ALB 30 to 50 mg	Insulin lispro
Pratley et al, 2014 (42)	HARMONY 7	MET, SU, TZD, or any combination	ALB 30 to 50 mg	Liraglutide once daily
Raz et al, 2012 (44)	T-emerge 1	Diet + exercise	TAS 10/20 mg	PLA
Rosenstock et al, 2013 (46)	T-emerge 2	MET, TZD, MET + TZD	TAS 10/20 mg	Exenatide twice daily
Henry et al, 2012 (35)	T-emerge 3	MET + PIO	TAS 10/20 mg	PLA
Bergenstal et al, 2012 (26)	T-emerge 4	MET	TAS 10/20 mg	PLA, sitagliptin
Nauck et al, 2013 (40)	T-emerge 5	MET + SU	TAS 10/20 mg	Insulin glargine
Pratley et al, 2013 (43)	T-emerge 6	SU ± MET	TAS 10/20 mg	PIO
Hollander et al, 2013 (36)	T-emerge 7	MET	TAS 20 mg	PLA
Miyagawa et al, 2015 (54)	–	Diet + exercise	DUL 0.75 mg	PLA, liraglutide once daily
Araki et al, 2015 (55)	–	SUs, BIGs, SUs + BIGs	DUL 0.75 mg	Insulin glargine
NCT01648582 (56)	–	MET, SU, MET + SU	DUL 0.75/1.5 mg	Insulin glargine
Wang et al, 2015 (57)	–	Diet + exercise ± OAD	DUL 0.75/1.5 mg	Glimepiride
Davies et al, 2013 (30)	–	MET ± SU	EOW 2 mg	Insulin detemir
Inagaki et al, 2012 (38)	–	BIG, BIG + TZD, BIG + SU, BIG + TZD + SU	EOW 2 mg	Insulin glargine
Ji et al, 2013 (39)	–	MET, SU, TZD, MET + SU, MET + TZD, SU + TZD	EOW 2 mg	Exenatide twice daily
NCT01733758 (21)	–	Diet + exercise, OAD	ALB 30/50 mg¶	PLA, liraglutide once daily

ALB = albiglutide; BIG = biguanide; DUL = dulaglutide; EOW = once-weekly exenatide; GLP-1 = glucagon-like peptide-1; MET = metformin; NPH = neutral protamine Hagedorn; OAD = oral antihyperglycemic drug; PIO = pioglitazone; PLA = placebo; SU = sulfonylurea; TAS = taspoglutide; TZD = thiazolidinedione.
* When not reported for the overall population, values have been estimated as weighted means.
† 26 wk for body weight, fasting plasma glucose, and side effects.
‡ 26 wk for body weight.
§ Both groups also added insulin lispro.
‖ Data from reference 31 (156 wk; year 2014) for continuous outcomes, nausea, and injection-site side effects; data from reference 32 (26 wk; year 2010) for hypoglycemic events.
¶ Data and analyses are reported for the higher dose (50 mg).
** 24 wk for fasting plasma glucose and body weight; 104 wk for side effects.
†† 156 wk for side effects.

GLP-1RA drugs and basal insulins and restricted the analyses for studies with similar duration of follow-up (24 to 26 weeks). For hypoglycemic events, we also excluded trials in which once-weekly GLP-1RAs were combined with either insulin or sulfonylurea.

Role of the Funding Source

Dr. Zaccardi is a Clinical Research Fellow funded by an unrestricted educational grant from Sanofi Aventis to the University of Leicester. The funding source had no role in the design, conduct, or analysis of the study or the decision to submit the manuscript for publication.

RESULTS

Study Characteristics and Quality

Of 1065 identified records, 35 reports (31 full-text articles [25–55], 2 studies in ClinicalTrials.gov [21, 56], and 2 abstracts [20, 57]) based on 34 unique RCTs fulfilled our inclusion criteria (**Appendix Figure 1**, available at www.annals.org). No RCT for semaglutide was found. Included RCTs were published between October 2008 and September 2015 and had a total of 21 126 participants with type 2 diabetes and study durations of 24 to 156 weeks (**Table**).

Overall, the risk of bias for the domains included in the Cochrane tool of risk assessment were judged to be low, high, and unclear in 51.0%, 24.5%, and 24.5% of the cases, respectively (**Supplement 2**, available at www.annals.org). In 24 of 34 RCTs (71%), risk of bias was high for incomplete outcome data and unclear for blinding of outcome assessment, whereas 21 RCTs (62%) had a high risk of bias in the domain of blinding of participants and personnel. Conversely, the risk of bias for random-sequence generation, allocation concealment, and selective reporting was considered low.

Table—Continued

Study Duration, *wk*	Sample Size, *n*	Women, %	Age, *y**	Duration of Diabetes, *y**	Hemoglobin A_{1c} Value, %*
52†	976	41.6	55.6	9.0	8.1
78	810	48.7	56.7	9.0	8.1
52‡	807	55.9	55.5	3.0	7.6
52	884	46.5	59.4	12.7	8.5
104	921	52.7	54.1	7.0	8.1
26	599	52.1	56.7	7.2	8.1
30	295	46.8	55.0	6.0	8.3
26	491	47.3	52.3	5.7	8.5
156	456	46.7	58.0	7.9	8.3
26	820	42.1	53.9	2.7	8.5
24	252	42.5	55.5	7.0	8.5
26	911	45.2	57.0	8.5	8.5
52	301	40.2	55.0	7.9	8.1
52	296	46.0	53.0	4.0	8.1
104	1012	53.5	54.4	6.0	8.1
52	745	43.9	55.4	8.7	8.3
52	663	46.8	55.2	8.9	8.2
26	563	52.9	55.5	11.0	8.5
32	812	49.6	55.6	8.3	8.2
24	368	60.3	55.0	2.4	7.6
52**	1149	47.4	56.9	6.7	8.3
24	313	46.7	54.2	7.7	8.1
52††	546	44.6	55.9	5.9	8.0
24	1028	48.3	57.7	9.5	8.3
24	740	50.4	56.4	8.8	8.3
24	292	59.2	53.5	5.1	7.5
26	487	18.7	57.4	6.6	8.1
26	361	28.5	56.8	8.8	8.0
52	770	45.4	54.9	-	-
26	807	46.1	52.8	3.7	7.9
26	216	33.8	58.5	7.5	8.4
26	427	32.1	56.8	9.0	8.5
26	678	45.9	55.5	8.1	8.7
24	330	25.1	57.8	-	8.1

The completion rate ranged from 60% to 97%, with 25 RCTs using the last-observation-carried-forward imputation for incomplete data outcome and 9 using a mixed-effects model for repeated measures (**Supplement 3**, available at www.annals.org). Thirteen RCTs used the last observation before hyperglycemia rescue, and data handling for rescued patients was not reported in 21 studies. Other characteristics of the included studies are reported in **Supplements 4** through **9** (available at www.annals.org).

Meta-analyses

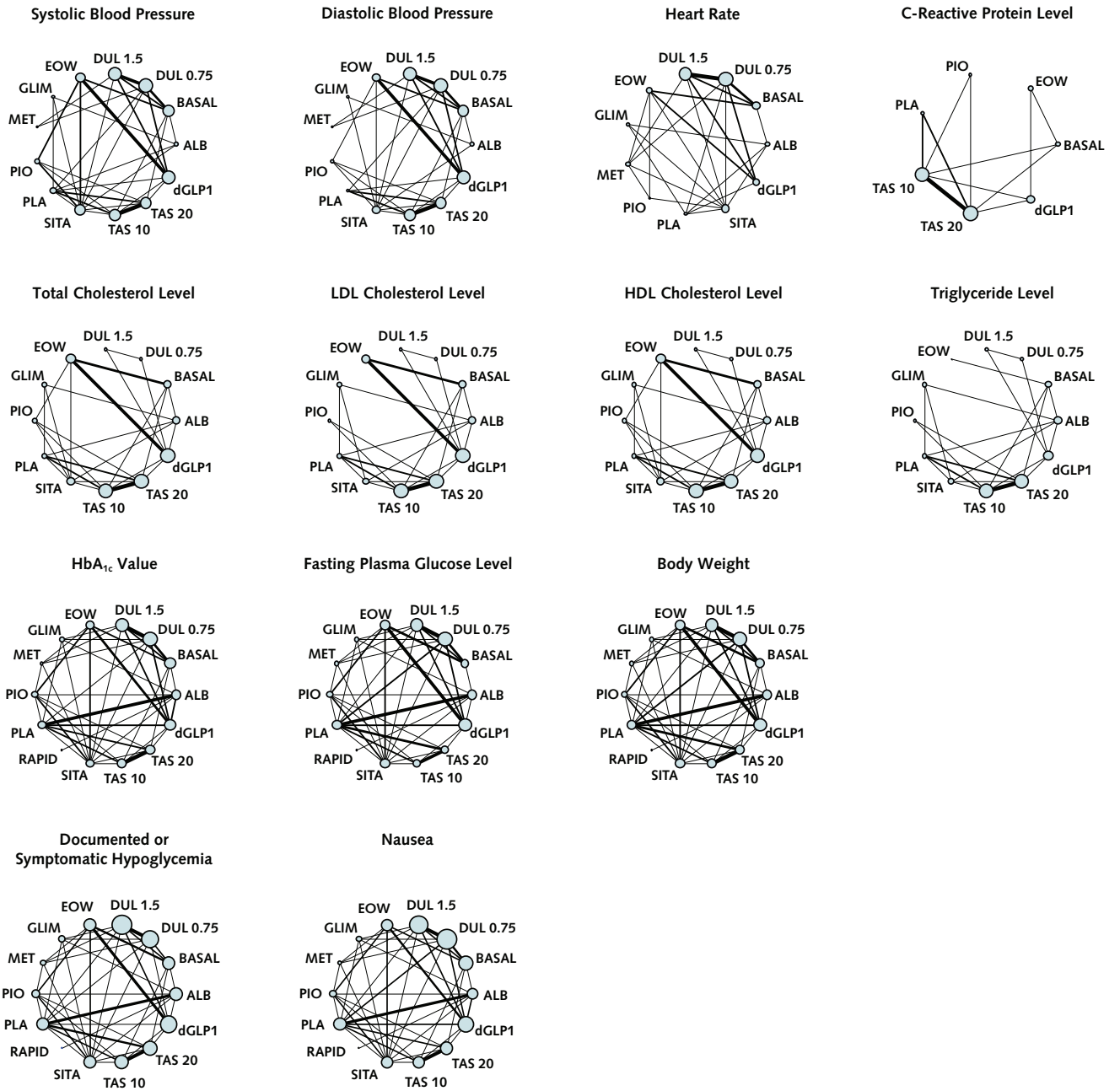
Details of available data are shown in **Supplements 4** through **6** for cardiometabolic outcomes and **Supplements 7** through **9** for safety outcomes; the results of network-specific inconsistency tests are presented in **Supplement 10** (available at www.annals.org). Networks of evidence are graphically displayed in **Figure 1**.

Primary Outcome: HbA_{1c}

Data on HbA_{1c} were available from all RCTs. Direct pairwise random-effects meta-analyses showed different effects of once-weekly GLP-1RAs compared with placebo or other glucose-lowering drugs, from a 1.6% reduction to a 0.3% increase in HbA_{1c} (**Appendix Figure 2**, available at www.annals.org). When direct and indirect evidence were combined, the network meta-analysis showed a mean reduction in HbA_{1c} values compared with placebo of –1.4% (95% CI, –1.6% to –1.2%) for dulaglutide, 1.5 mg; –1.3% (CI, –1.5% to –1.1%) for once-weekly exenatide; –1.2% (CI, –1.4% to –1.0%) for dulaglutide, 0.75 mg; –1.1% (CI, –1.3% to –0.9%) for taspoglutide, 20 mg; –1.0% (CI, –1.2% to –0.8%) for albiglutide; and –0.9% (CI, –1.2% to –0.8%) for taspoglutide, 10 mg (**Appendix Figure 3**, available at www.annals.org). Statistical inconsistency for the whole network was not significant. Comparisons across once-weekly GLP-1RAs showed a greater reduction in HbA_{1c} values with dulaglutide, 1.5 mg, compared with dulaglutide, 0.75 mg, albiglutide, and taspoglutide, 10 mg and 20 mg, whereas no difference was observed in comparison with once-weekly exenatide (**Figure 2** and **Supplement 11**, available at www.annals.org). The ranking probabilities and the mean rank for each drug included in the analysis are shown in **Appendix Figure 4** (available at www.annals.org) and **Supplement 12** (available at www.annals.org), respectively.

Sensitivity analyses considering separate daily GLP-1RAs (once-daily liraglutide and twice-daily exenatide) and basal insulins (detemir and glargine) showed results consistent with the main analysis (**Supplement 13**, available at www.annals.org). The estimates from stud-

Figure 1. Network maps for cardiometabolic and safety outcomes.



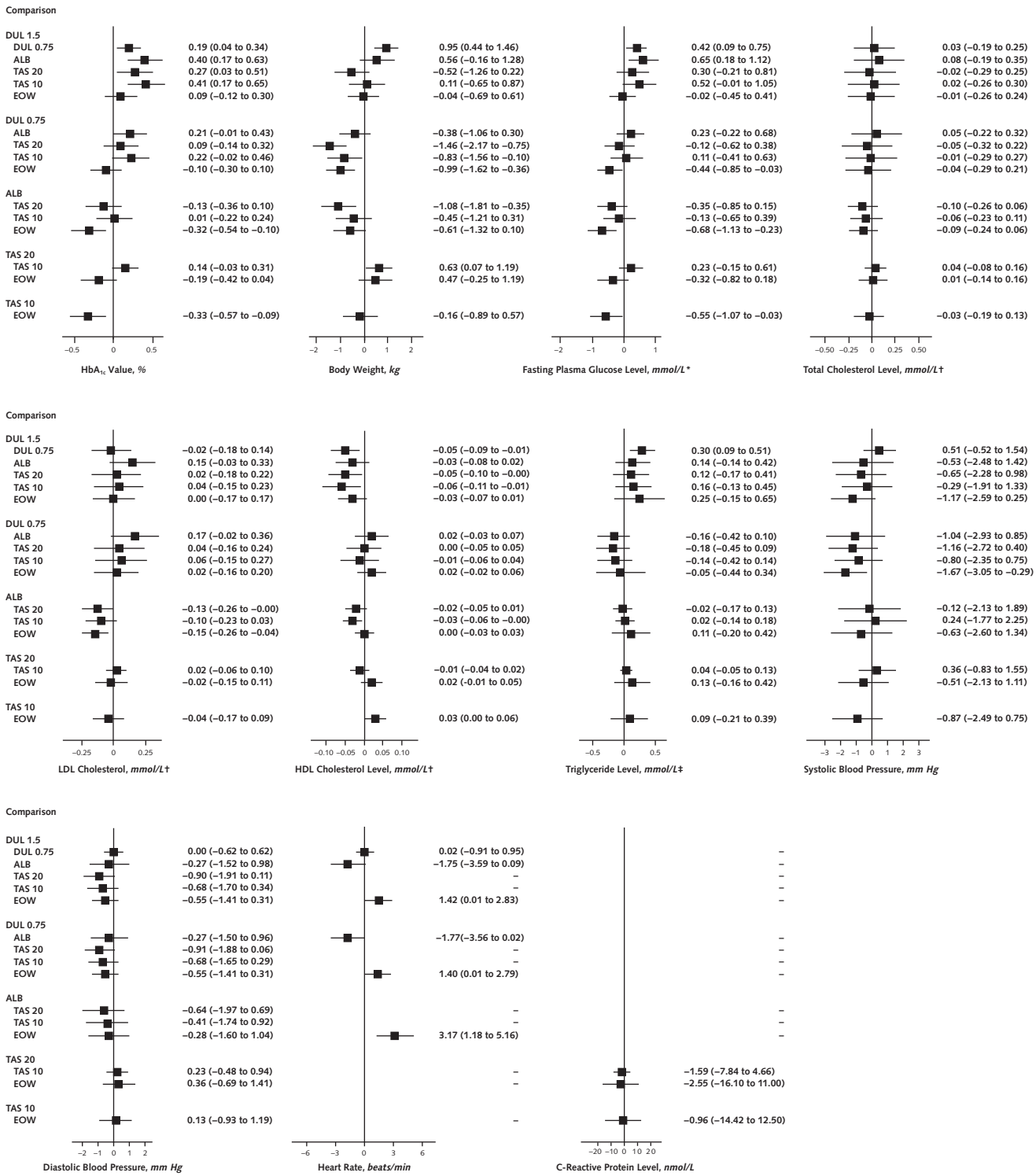
Nodes represent the treatments being compared; their size is proportional to the number of participants. Edges represent the available direct comparisons between pairs of treatments, and their width is proportional to the number of trials comparing every pair. ALB = albiglutide; BASAL = basal insulin; dGLP1 = daily glucagon-like peptide-1 receptor agonists; DUL 0.75 = dulaglutide, 0.75 mg; DUL 1.5 = dulaglutide, 1.5 mg; EOW = exenatide once-weekly; GLIM = glimepiride; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metformin; PIO = pioglitazone; PLA = placebo; RAPID = rapid insulin; SITA = sitagliptin; TAS 10 = taspoglutide, 10 mg; TAS 20 = taspoglutide, 20 mg.

ies with a follow-up duration of 24 to 26 weeks (28 RCTs) similarly showed a greater HbA_{1c} reduction with dulaglutide, 1.5 mg; no difference was found compared with albiglutide, possibly owing to the small number of albiglutide studies in this analysis compared with the main analysis (3 vs. 8) (**Supplement 14**, available at www.annals.org).

Secondary Cardiometabolic Outcomes

Data on fasting plasma glucose were available from 31 RCTs. Compared with placebo, once-weekly exenatide reduced fasting plasma glucose levels by −2.2 mmol/L (CI, −2.6 to −1.8 mmol/L) (−39.6 mg/dL [CI, −46.8 to −32.4 mg/dL]), followed by dulaglutide, 1.5 mg (−2.2 mmol/L [−2.6 to −1.7 mmol/L]; −39.6 mg/dL [CI,

Figure 2. Comparison of once-weekly glucagon-like peptide-1 receptor agonists for cardiometabolic outcomes.



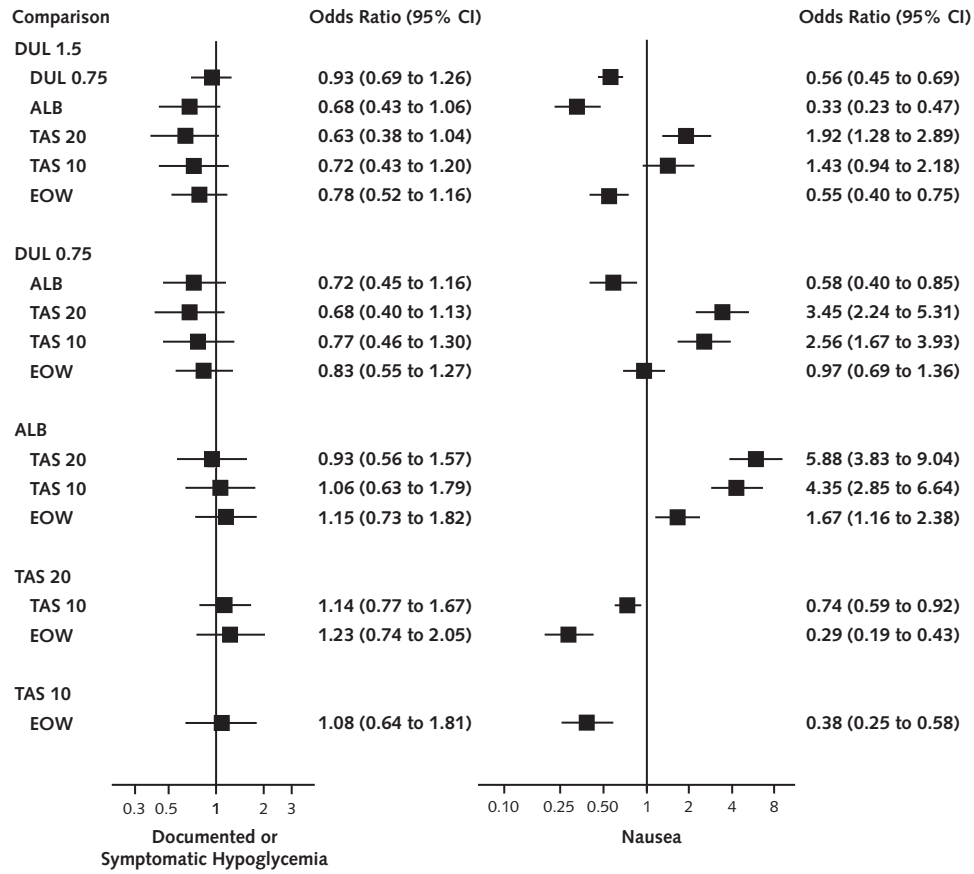
Data are reported as mean differences (95% CIs) and indicate differences versus the reference drug (for example, compared with dulaglutide, 1.5 mg, albiglutide increases HbA_{1c} by 0.40% [CI, 0.17% to 0.63%]). ALB = albiglutide; DUL 0.75 = dulaglutide, 0.75 mg; DUL 1.5 = dulaglutide, 1.5 mg; EOW = exenatide once-weekly; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TAS 10 = taspoglutide, 10 mg; TAS 20 = taspoglutide, 20 mg.

* To convert values to mg/dL, divide by 0.0555.

† To convert values to mg/dL, divide by 0.0259.

‡ To convert values to mg/dL, divide by 0.0113.

Figure 3. Comparison of once-weekly glucagon-like peptide-1 receptor agonists for safety outcomes.



Data are reported as odds ratios (95% CIs) and indicate differences versus the reference drug (for example, compared with dulaglutide, 1.5 mg, treatment with dulaglutide, 0.75 mg, is associated with an odds ratio for nausea of 0.56 [CI, 0.45 to 0.69]). ALB = albiglutide; DUL 0.75 = dulaglutide, 0.75 mg; DUL 1.5 = dulaglutide, 1.5 mg; EOW = exenatide once-weekly; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TAS 10 = taspoglutide, 10 mg; TAS 20 = taspoglutide, 20 mg.

–46.8 to –30.6 mg/dL]); taspoglutide, 20 mg (–1.9 mmol/L [CI, –2.3 to –1.5 mmol/L]; –34.2 mg/dL [CI, –41.4 to 27.0 mg/dL]); dulaglutide, 0.75 mg (–1.7 mmol/L [CI, –2.1 to –1.3 mmol/L]; –30.6 mg/dL [CI, –37.8 to 23.4 mg/dL]); taspoglutide, 10 mg (–1.6 mmol/L [CI, –2.1 to –1.2 mmol/L]; –28.8 mg/dL [CI, –37.8 to –21.6 mg/dL]); and albiglutide (–1.5 mmol/L [CI, –1.9 to –1.1 mmol/L]; –27.0 mg/dL [CI, –34.2 to –19.8 mg/dL]) (**Appendix Figure 3**). Statistical inconsistency for the network was not significant.

When once-weekly GLP-1RAs were compared, exenatide was associated with a greater fasting plasma glucose reduction than albiglutide, dulaglutide, 0.75 mg, and taspoglutide, 10 mg, and there were nonsignificant differences from taspoglutide, 20 mg, and dulaglutide, 1.5 mg (**Figure 2** and **Supplements 11** and **15**, available at www.annals.org).

Data on body weight were available from 32 RCTs. Network meta-analysis results showed a significant reduction of –1.3 kg (CI, –1.9 to –0.7 kg) for taspoglutide, 20 mg, compared with placebo, followed by once-weekly exenatide (–0.8 kg [CI, –1.5 to –0.1 kg]), dulaglutide, 1.5 mg (–0.8 kg [CI, –1.4 to –0.1 kg]), and taspoglutide, 10 mg (–0.6 kg [CI, –1.3 to –0.1 kg]), and no weight reduction for albiglutide (–0.2 kg [CI, –0.8, 0.4 kg]) and dulaglutide, 0.75 mg (0.2 kg [CI, –0.4 to 0.8 kg]) (**Appendix Figure 3**). Statistical inconsistency for the network was not significant.

Comparisons among once-weekly GLP-1RAs showed greater reduction in body weight with taspoglutide, 20 mg, compared with taspoglutide, 10 mg, albiglutide, and dulaglutide, 0.75 mg, and nonsignificant differences compared with dulaglutide, 1.5 mg, and once-weekly exenatide (**Figure 2** and **Supplements 11** and **12**).

Data availability for all other cardiometabolic outcomes ranged from 7 RCTs for C-reactive protein to 24 RCTs for systolic blood pressure. Comparisons among once-weekly GLP-1RAs were not significant for diastolic blood pressure, total cholesterol, or C-reactive protein (**Figure 2** and **Supplements 11** and **15**). Marginal differences were found for low-density lipoprotein cholesterol (maximum difference, 0.15 mmol/L [5.80 mg/dL]), high-density lipoprotein cholesterol (0.06 mmol/L [2.32 mg/dL]), triglycerides (0.30 mmol/L [26.57 mg/dL]), and systolic blood pressure (1.7 mm Hg). Once-weekly

exenatide increased heart rate compared with albiglutide (3.2 beats/min); dulaglutide, 0.75 mg (1.4 beats/min); and dulaglutide, 1.5 mg (1.4 beats/min). Network inconsistency was significant for heart rate (**Supplement 10**).

Documented or Symptomatic Hypoglycemia and Nausea

On the basis of 30 RCTs, network meta-analysis showed an increased risk for documented or symptomatic hypoglycemia for albiglutide (OR, 1.82 [CI, 1.05 to 3.15]), taspoglutide, 10 mg (OR, 1.94 [CI, 1.03 to 3.62]), once-weekly exenatide (OR, 2.08 [CI, 1.14 to 3.82]), dulaglutide, 0.75 mg (OR, 2.51 [CI, 1.39 to 4.54]), and dulaglutide, 1.5 mg (OR, 2.69 [CI to 1.51, 4.82]), but not for taspoglutide, 20 mg (OR, 1.69 [CI, 0.92 to 3.14]), compared with placebo (**Appendix Figure 5**, available at www.annals.org). No differences were found among once-weekly GLP-1RAs (**Figure 3** and **Supplement 16**, available at www.annals.org). Sensitivity analyses without grouping of basal insulins and daily GLP-1RAs that excluded studies with background therapy including sulfonylurea or insulin showed similar results (**Supplements 13** and **17**, respectively [available at www.annals.org]). Owing to the presence of a disconnected network (only HARMONY 6 reported data on albiglutide and rapid insulin), sensitivity analysis limited to studies with a follow-up duration of 24 to 26 weeks was not possible.

Data on nausea were available from all RCTs. Compared with placebo, risk for nausea was increased with albiglutide (OR, 1.43 [CI, 1.02 to 2.01]), once-weekly exenatide (OR, 2.38 [CI, 1.59 to 3.54]), dulaglutide, 0.75 mg (OR, 2.44 [CI, 1.62 to 3.66]), dulaglutide, 1.5 mg, (OR, 4.35 [CI, 2.93 to 6.47]), taspoglutide, 10 mg, (OR, 6.19 [CI, 4.20 to 9.11]), and taspoglutide, 20 mg (OR, 8.32 [CI, 5.74 to 12.07]) (**Appendix Figure 5**). Taspoglutide, 20 mg, showed the greatest risk compared with all other once-weekly GLP-1RAs, with odds ratios ranging from 1.92 (CI, 1.28 to 2.89) versus dulaglutide, 1.5 mg, to 5.88 (CI, 3.83 to 9.04) versus albiglutide (**Figure 3** and **Supplements 12** and **16**). A sensitivity analysis without grouping basal insulins and daily GLP-1RAs showed the same results (**Supplement 13**). Data from studies with durations of 24 to 26 weeks confirmed a higher risk for nausea for taspoglutide vs. once-weekly exenatide and dulaglutide, 0.75 mg, whereas no differences were found versus dulaglutide, 1.5 mg, and albiglutide, possibly owing to the small number of studies compared with the main analysis (4 vs. 8 for dulaglutide, 1.5 mg; 2 vs. 8 for albiglutide) (**Supplement 14**).

Other Safety Outcomes

Limited data for other safety outcomes were available, possibly because RCTs were designed to assess differences in HbA_{1c} (primary outcome) or outcomes were selectively reported (publication bias). Overall, there were 1668 heterogeneously defined cases of injection-site side effects, from 22 cases of "bruising" to 473 "reactions" (1.1% for dulaglutide, 1.5 mg; 1.9% for dulaglutide, 0.75 mg; 6.9% for taspoglutide, 10 mg; 7.1% for taspoglutide, 20 mg; 9.9% for albiglutide; and 18.3% for once-weekly exenatide). Similarly, few cases of severe hypoglycemia, fatal and nonfatal cardiovascular and cancer events, and all-cause mortality events were reported (**Supplements 7**, **18**, and **19**, available at www.annals.org).

DISCUSSION

Although many studies have investigated the efficacy and safety of once-weekly GLP-1RAs compared with other commonly used glucose-lowering drugs (including metformin, glimepiride, pioglitazone, sitagliptin, and insulin), to date no direct head-to-head comparison between GLP-1RAs has been reported. Using a network meta-analysis, we aimed to assess the comparative efficacy and safety of once-weekly GLP-1RAs across a wide range of cardiometabolic and safety outcomes. The results suggested similar effects of these drugs on several cardiometabolic outcomes, such as blood pressure, blood lipids, and C-reactive protein, and a modest increase in heart rate with once-weekly exenatide versus albiglutide (mean difference, 3 beats/min). Conversely, we found appreciable differences for HbA_{1c}, fasting plasma glucose, and body weight, with greater reductions for dulaglutide 1.5 mg, once-weekly exenatide, and taspoglutide, 20 mg, compared with albiglutide and other once-weekly GLP-1RAs at lower doses. We also found differences in the risk for nausea, which was highest for taspoglutide, 20 mg and 10 mg, and dulaglutide, 1.5 mg. Conversely, the risk for documented or symptomatic hypoglycemic did not differ among once-weekly GLP-1RAs.

Previous network meta-analyses (PubMed search, September 2015) have investigated the efficacy and safety of GLP-1RAs in patients with type 2 diabetes (58–67), with limited data on once-weekly GLP-1RAs. Moreover, single or few outcomes were reported, making it difficult to formulate a balanced overall assessment of GLP-1RA therapies. Our study included data from recent RCTs and compared once-weekly GLP-1RAs across a wide range of clinically relevant outcomes. Its aim is to assist decision makers in providing patient-centered care by balancing the potential risks and benefits of individual drugs within the class of once-weekly GLP-1RAs. Beyond HbA_{1c}, therapeutic decisions should be based on other outcomes, including body weight, risk for hypoglycemia, and gastrointestinal disorders. In this context, the results of our analyses could help clinicians to follow the ADA and EASD recommendations (7), because several outcomes have been assessed simultaneously.

Similar to other glucose-lowering agents (7), once-weekly GLP-1RAs reduced HbA_{1c} from 0.9% to 1.4% compared with placebo. Among once-weekly GLP-1RAs, the highest difference was found in favor of dulaglutide, 1.5 mg, versus taspoglutide, 10 mg (0.4%). All once-weekly GLP-1RAs significantly reduced fasting plasma glucose compared with placebo (reductions of 1.5 mmol/L to 2.2 mmol/L [27 mg/dL to 39.6 mg/dL]);

the greatest difference among once-weekly GLP-1RAs was 0.7 mmol/L (12.6 mg/dL) in favor of once-weekly exenatide versus albiglutide. With the exception of albiglutide and the lower doses of dulaglutide and taspoglutide, all other once-weekly GLP-1RAs significantly reduced body weight (maximum, 1.3 kg for taspoglutide, 20 mg; minimum, 0.7 kg for dulaglutide, 1.5 mg) compared with placebo; the greatest difference was 1.5 kg in favor of taspoglutide, 20 mg, vs. dulaglutide, 0.75 mg. Our results would therefore suggest clinically significant differences on 3 key indicators of metabolic control. Of note, comparisons among licensed drugs showed no differences between once-weekly exenatide and the maintenance dose of dulaglutide (1.5 mg) for all 3 metabolic outcomes, and both treatments reduced HbA_{1c} to a better extent than albiglutide.

The results also evidenced differences in the risk for nausea. Compared with placebo, all once-weekly GLP-1RAs increased significantly the risk for nausea, from 1.4-fold for albiglutide to 8.3-fold for taspoglutide, 20 mg. Comparisons among once-weekly GLP-1RAs showed a 1.9-fold to 5.9-fold greater risk with taspoglutide, 20 mg, versus all other once-weekly GLP-1RAs. Discrepancies in the risk for nausea could be related to outcome definition, study design, a true pharmacologic difference among drugs, or a combination of these factors. In contrast to HbA_{1c}, fasting plasma glucose, and body weight, comparison of once-weekly exenatide and dulaglutide, 1.5 mg, showed a significant difference in the risk for nausea (1.8-fold higher for dulaglutide).

Our study has limitations. First, we performed a study-level meta-analysis based only on available articles, abstracts, and Web documents. These are more likely than unpublished reports to report positive findings. This risk should be low for RCTs and, for the primary outcome and nausea (the most important side effect), data were available from all trials.

Second, the magnitude of HbA_{1c} reduction could depend on the baseline HbA_{1c} value, because higher reductions are typically associated with higher baseline HbA_{1c} values (68). Most of the studies, however, reported baseline-adjusted HbA_{1c} differences, and each once-weekly GLP-1RA has been evaluated in a wide range of patients and HbA_{1c} values.

Third, we selected the longest study duration for the main analysis to better reflect "real-world" conditions, where these drugs are used for month to years. We performed sensitivity analyses to assess the effect of study duration, although the limited number of RCTs for albiglutide made it difficult to derive definitive conclusions. The effects of albiglutide on HbA_{1c}, fasting plasma glucose, body weight, and nausea were consistent and, along with available direct evidence, would suggest a lower efficacy of this drug. This is in line with the pharmacologic properties of albiglutide, whose large molecular weight (about 73 kDa) reduces crossing of the blood–brain barrier and speculatively modulates central nervous system effects (37).

Fourth, the small number of events and heterogeneous definitions did not allow analyses for severe hypoglycemic and injection-site side effects. The different formulations of once-weekly GLP-1RAs (as injectable microspheres [33], in combination with human albumin [45], bound to modified human immunoglobulin G_4 [51], or with a modified amino acid sequence [69]) has implications in terms of preparation for injection and results in a different risk for and nature of injection site reactions.

Fifth, the fewer injections with once-weekly versus daily GLP-1RAs should increase quality of life, patient satisfaction, and possibly adherence to therapy. However, we did not collect data to explore this hypothesis.

Sixth, the absence of significant differences for several cardiometabolic risk factors does not necessarily mean the absence of a difference for "hard" cardiovascular outcomes. We collected data on cardiovascular, cancer, and all-cause mortality events, although the small numbers prevented any analysis. Published individual-level meta-analysis (PubMed search, September 2015) (**Supplement 20**, available at www.annals.org) suggested a neutral profile of once-weekly GLP-1RAs drugs on hard cardiovascular end points. Ongoing RCTs will further elucidate the comparative effects of these drugs on cardiovascular risk factors and their long-term cardiovascular safety (**Supplement 21**, available at www.annals.org).

Seventh, 73% of RCTs used the last-observation-carried-forward imputation method for handling missing data. This can result in biased estimations, because it assumes the last measure as the final measure regardless of the "true" direction (increase or decrease of the outcome value) (70).

Eighth, in 3 studies with zero events in one group, we added the standard 0.5 continuity correction. Although the influence of this correction on summary estimates has been investigated in the context of pairwise meta-analysis (71), little is known about the degree to which zero-event groups and the 0.5 correction affect network meta-analysis estimates. Results should therefore be interpreted with caution, and further research is needed in this area.

Finally, RCTs are not independent because they "cluster" within the same sponsoring company; that is, RCTs sponsored or conducted by the same pharmaceutical company are more similar than are RCTs from 2 different companies in terms of follow-up duration, definition and assessment of outcomes, design of hyperglycemia rescue, data analysis and reporting, and sharing of results. Although it is difficult to avoid this limitation, it should be considered while interpreting combined data from RCTs.

To our knowledge, our study is the first attempt to summarize available data on once-weekly GLP-1RAs for a wide range of outcomes. Given the small number of safety end points in some studies, we also added detailed data on study, drug, and outcome-specific number of participants to help the reader interpret the results.

In conclusion, available data suggest differences in cardiometabolic outcomes and safety among once-weekly GLP-1RAs. Further RCTs with direct comparisons of once-weekly GLP-1RAs can help better clarify their comparative tolerability and efficacy and inform the choice among these newly available glucose-lowering agents.

From the Diabetes Research Centre, University of Leicester, Leicester, United Kingdom.

Disclaimer: The views expressed are those of the authors and do not necessarily reflect those of the United Kingdom's National Health Service, National Institute for Health Research, or Department of Health.

Acknowledgment: The authors thank the National Institute for Health Research, Collaboration for Leadership in Applied Health Research and Care–East Midlands and Diet, Lifestyle & Physical Activity Biomedical Research Unit, based at the University Hospitals of Leicester and Loughborough University, United Kingdom, for their support of this work. They also thank Sarah Sutton (University of Leicester, United Kingdom) for her assistance with the literature search and Dimitris Mavridis (University of Ioannina, Greece) for his valuable suggestions.

Grant Support: From Sanofi Aventis to the University of Leicester.

Disclosures: Dr. Khunti reports having acted as a consultant, speaker, and advisory board member for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen Pharmaceuticals, and Boehringer Ingelheim; grants from AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, Merck Sharp & Dohme, and Roche. Dr. Davies reports having acted as a consultant, an advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen Pharmaceuticals and as a speaker for the Mitsubishi Tanabe Pharma Corporation, as well as grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, and Lilly, outside the submitted work. Authors not named here have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-1432.

Reproducible Research Statement: *Study protocol:* Available as **Supplement 1** at www.annals.org. *Statistical code and data set:* Available from Dr. Zaccardi (e-mail, fz43@le.ac.uk).

Requests for Single Reprints: Francesco Zaccardi, MD, Diabetes Research Centre, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, United Kingdom; e-mail, fz43@le.ac.uk.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Inzucchi SE.** Diagnosis of diabetes [Letter]. N Engl J Med. 2013; 368:193. [PMID: 23301749]
2. **Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al; Emerging Risk Factors Collaboration.** Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011;364:829-41. [PMID: 21366474]
3. **Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al; Emerging Risk Factors Collaboration.** Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375:2215-22. [PMID: 20609967]
4. **Majumdar SK, Inzucchi SE.** Investigational anti-hyperglycemic agents: the future of type 2 diabetes therapy? Endocrine. 2013;44: 47-58. [PMID: 23354728]
5. **Holst JJ, Knop FK, Vilsbøll T, Krarup T, Madsbad S.** Loss of incretin effect is a specific, important, and early characteristic of type 2 diabetes. Diabetes Care. 2011;34 Suppl 2:S251-7. [PMID: 21525464]
6. **Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB.** Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. Diabetes Care. 2010;33:428-33. [PMID: 20103558]
7. **Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al.** Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015;58:429-42. [PMID: 25583541]
8. **Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al; LEAD-6 Study Group.** Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009; 374:39-47. [PMID: 19515413]
9. **Sutton A, Ades AE, Cooper N, Abrams K.** Use of indirect and mixed treatment comparisons for technology assessment. Pharmacoeconomics. 2008;26:753-67. [PMID: 18767896]
10. **Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, et al.** Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17:157-73. [PMID: 24636374]
11. **Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group.** Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62:1006-12. [PMID: 19631508]
12. **Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, et al.** Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health. 2011;14:429-37. [PMID: 21669367]
13. **Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al.** The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162: 777-84. [PMID: 26030634]
14. **Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al; Cochrane Bias Methods Group.** The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928. [PMID: 22008217]
15. **Harbord RM, Higgins JP.** Meta-regression in Stata. Stata J. 2008; 8:493-519.
16. **Medical Research Council Biostatistics Unit.** Ian White's Stata software list. 2015. Accessed at www.mrc-bsu.cam.ac.uk/software/stata-software on 1 October 2015.
17. **White IR.** Multivariate random-effects meta-regression: updates to mvmeta. Stata J. 2011;11:255-70.
18. **White IR, Barrett JK, Jackson D, Higgins JP.** Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods. 2012;3:111-25. [PMID: 26062085]

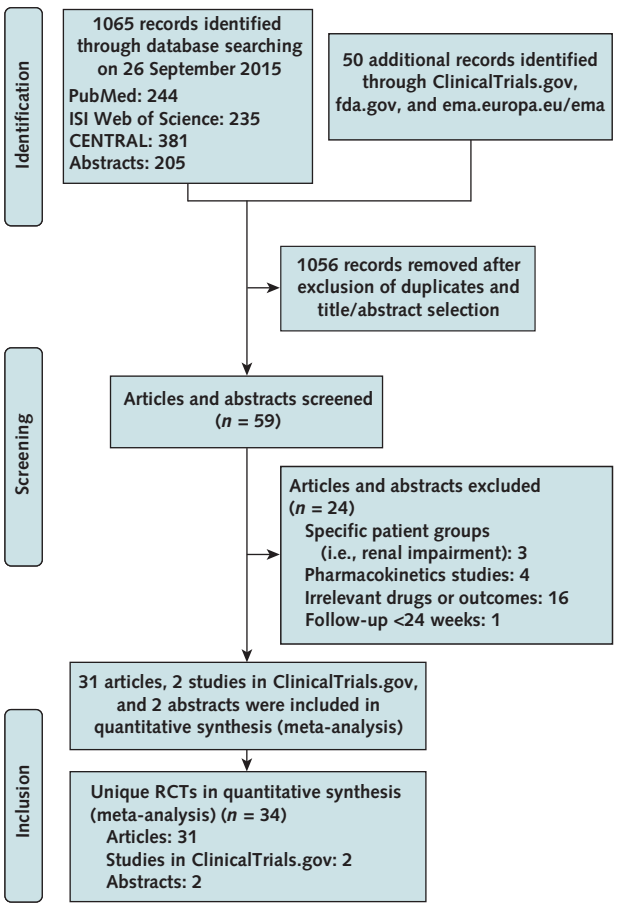
19. **Multiple-Treatments Meta-Analysis. 2015.** Using STATA for network meta-analysis. Accessed at www.mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis on 1 October 2015.
20. **Nauck M, Stewart M, Perkins C, Jones-Leone A, Yang F, Perry C, et al.** HARMONY 2 wk 52 results: albiglutide monotherapy in drug naïve patients with type 2 diabetes mellitus [Abstract]. Presented at American Diabetes Association 73rd Scientific Session, Chicago, Illinois, 21–25 June 2013. Abstract no. 55-LB.
21. A monotherapy study to evaluate the efficacy and safety of 2 dose levels of albiglutide in Japanese subjects with type 2 diabetes mellitus (T2DM). ClinicalTrials.gov: NCT01733758. Accessed at https://clinicaltrials.gov/ct2/show/NCT01733758 on 26 September 2015.
22. **Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G.** Graphical tools for network meta-analysis in STATA. PLoS One. 2013;8:e76654. [PMID: 24098547]
23. **Salanti G, Ades AE, Ioannidis JP.** Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64:163-71. [PMID: 20688472]
24. **Jackson D, Barrett JK, Rice S, White IR, Higgins JP.** A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. Stat Med. 2014;33:3639-54. [PMID: 24777711]
25. **Ahrén B, Johnson SL, Stewart M, Cirkel DT, Yang F, Perry C, et al; HARMONY 3 Study Group.** HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care. 2014;37:2141-8. [PMID: 24898304]
26. **Bergenstal RM, Forti A, Chiasson JL, Woloschak M, Boldrin M, Balena R.** Efficacy and safety of taspoglutide versus sitagliptin for type 2 diabetes mellitus (T-emerge 4 trial). Diabetes Ther. 2012;3:13. [PMID: 23138449]
27. **Bergenstal RM, Wysham C, Macconell L, Malloy J, Walsh B, Yan P, et al; DURATION-2 Study Group.** Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010;376:431-9. [PMID: 20580422]
28. **Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, et al.** DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96:1301-10. [PMID: 21307137]
29. **Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al.** Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013;381:117-24. [PMID: 23141817]
30. **Davies M, Heller S, Sreenan S, Sapin H, Adetunji O, Tahbaz A, et al.** Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. Diabetes Care. 2013;36:1368-76. [PMID: 23275363]
31. **Diamant M, Van Gaal L, Guerci B, Stranks S, Han J, Malloy J, et al.** Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. Lancet Diabetes Endocrinol. 2014;2:464-73. [PMID: 24731672]
32. **Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, et al.** Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet. 2010;375:2234-43. [PMID: 20609969]
33. **Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, et al; DURATION-1 Study Group.** Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet. 2008;372:1240-50. [PMID: 18782641]
34. **Dungan KM, Povedano ST, Forst T, González JG, Atisso C, Sealls W, et al.** Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014;384:1349-57. [PMID: 25018121]
35. **Henry RR, Mudaliar S, Kanitra L, Woloschak M, Balena R; T-emerge 3 Study Group.** Efficacy and safety of taspoglutide in patients with type 2 diabetes inadequately controlled with metformin plus pioglitazone over 24 weeks: T-emerge 3 trial. J Clin Endocrinol Metab. 2012;97:2370-9. [PMID: 22539590]
36. **Hollander P, Lasko B, Barnett AH, Bengus M, Kanitra L, Pi-Sunyer FX, et al.** Effects of taspoglutide on glycemic control and body weight in obese patients with type 2 diabetes (T-emerge 7 study). Obesity (Silver Spring). 2013;21:238-47. [PMID: 23404788]
37. **Home PD, Shamanna P, Stewart M, Yang F, Miller M, Perry C, et al.** Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. Diabetes Obes Metab. 2015;17:179-87. [PMID: 25406730]
38. **Inagaki N, Atsumi Y, Oura T, Saito H, Imaoka T.** Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. Clin Ther. 2012;34:1892-908. [PMID: 22884767]
39. **Ji L, Onishi Y, Ahn CW, Agarwal P, Chou CW, Haber H, et al.** Efficacy and safety of exenatide once-weekly vs. exenatide twice-daily in Asian patients with type 2 diabetes mellitus. J Diabetes Investig. 2013;4:53-61. [PMID: 24843631]
40. **Nauck M, Horton E, Andjelkovic M, Ampudia-Blasco FJ, Parusel CT, Boldrin M, et al; T-emerge 5 Study Group.** Taspoglutide, a once-weekly glucagon-like peptide 1 analogue, vs. insulin glargine titrated to target in patients with type 2 diabetes: an open-label randomized trial. Diabet Med. 2013;30:109-13. [PMID: 22937895]
41. **Weinstock RS, Guerci B, Umpierrez G, Nauck MA, Skrivanek Z, Milicevic Z.** Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes Obes Metab. 2015;17:849-58. [PMID: 25912221]
42. **Pratley RE, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, et al; HARMONY 7 study group.** Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol. 2014;2:289-97. [PMID: 24703047]
43. **Pratley RE, Urosevic D, Boldrin M, Balena R; T-emerge 6 Study Group.** Efficacy and tolerability of taspoglutide versus pioglitazone in subjects with type 2 diabetes uncontrolled with sulphonylurea or sulphonylurea-metformin therapy: a randomized, double-blind study (T-emerge 6). Diabetes Obes Metab. 2013;15:234-40. [PMID: 22958426]
44. **Raz I, Fonseca V, Kipnes M, Durrwell L, Hoekstra J, Boldrin M, et al.** Efficacy and safety of taspoglutide monotherapy in drug-naive type 2 diabetic patients after 24 weeks of treatment: results of a randomized, double-blind, placebo-controlled phase 3 study (T-emerge 1). Diabetes Care. 2012;35:485-7. [PMID: 22301126]
45. **Reusch J, Stewart MW, Perkins CM, Cirkel DT, Ye J, Perry CR, et al.** Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. Diabetes Obes Metab. 2014;16:1257-64. [PMID: 25155146]
46. **Rosenstock J, Balas B, Charbonnel B, Bolli GB, Boldrin M, Ratner R, et al; T-emerge 2 Study Group.** The fate of taspoglutide, a weekly GLP-1 receptor agonist, versus twice-daily exenatide for type 2 diabetes: the T-emerge 2 trial. Diabetes Care. 2013;36:498-504. [PMID: 23139373]
47. **Rosenstock J, Fonseca VA, Gross JL, Ratner RE, Ahrén B, Chow FC, et al; HARMONY 6 Study Group.** Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a

weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. Diabetes Care. 2014;37:2317-25. [PMID: 24898300]
48. **Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, González JG, Chan M, et al; DURATION-4 Study Group.** Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care. 2012; 35:252-8. [PMID: 22210563]
49. **Umpierrez G, Tofé Povedano S, Pérez Manghi F, Shurzinske L, Pechtner V.** Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care. 2014;37:2168-76. [PMID: 24842985]
50. **Weissman PN, Carr MC, Ye J, Cirkel DT, Stewart M, Perry C, et al.** HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. Diabetologia. 2014;57:2475-84. [PMID: 25208756]
51. **Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, et al.** Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care. 2014;37:2159-67. [PMID: 24879836]
52. **Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V.** Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). Diabetes Care. 2015. [PMID: 26089386]
53. **Blonde L, Jendle J, Gross J, Woo V, Jiang H, Fahrbach JL, et al.** Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. Lancet. 2015;385:2057-66. [PMID: 26009229]
54. **Miyagawa J, Odawara M, Takamura T, Iwamoto N, Takita Y, Imaoka T.** Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. Diabetes Obes Metab. 2015;17:974-83. [PMID: 26179187]
55. **Araki E, Inagaki N, Tanizawa Y, Oura T, Takeuchi M, Imaoka T.** Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. Diabetes Obes Metab. 2015;17:994-1002. [PMID: 26179754]
56. A study comparing the effects and safety of dulaglutide with insulin glargine in type 2 diabetes mellitus. ClinicalTrials.gov: NCT01648582. Accessed at https://clinicaltrials.gov/ct2/show/NCT01648582 on 26 September 2015.
57. **Wang W, Huang CN, Young MC, Li P, Gu L, Yang J.** The efficacy and safety of once-weekly, subcutaneous dulaglutide monotherapy compared to glimepiride in Asian patients with type 2 diabetes mellitus. Presented at 51st EASD Meeting, Stockholm, Sweden, 15–18 September 2015. Abstract no. 778. Accessed at www.easdvirtual meeting.org/resources/the-efficacy-and-safety-of-once-weekly-subcutaneous-dulaglutide-monotherapy-compared-to-glimepiride-in-asian-patients-with-type-2-diabetes-mellitus-2 on 26 September 2015.
58. **Sun F, Chai S, Li L, Yu K, Yang Z, Wu S, et al.** Effects of glucagon-like peptide-1 receptor agonists on weight loss in patients with type 2 diabetes: a systematic review and network meta-analysis. J Diabetes Res. 2015;2015:157201. [PMID: 25688373]
59. **Sun F, Chai S, Yu K, Quan X, Yang Z, Wu S, et al.** Gastrointestinal adverse events of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetes Technol Ther. 2015;17:35-42. [PMID: 25375397]
60. **Sun F, Wu S, Guo S, Yu K, Yang Z, Li L, et al.** Effect of GLP-1 receptor agonists on waist circumference among type 2 diabetes patients: a systematic review and network meta-analysis. Endocrine. 2015;48:794-803. [PMID: 25115635]
61. **Sun F, Wu S, Wang J, Guo S, Chai S, Yang Z, et al.** Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis. Clin Ther. 2015;37:225-241. [PMID: 25554560]
62. **Sun F, Yu K, Wu S, Zhang Y, Yang Z, Shi L, et al.** Cardiovascular safety and glycemic control of glucagon-like peptide-1 receptor agonists for type 2 diabetes mellitus: a pairwise and network meta-analysis. Diabetes Res Clin Pract. 2012;98:386-95. [PMID: 23020934]
63. **Sun F, Yu K, Yang Z, Wu S, Zhang Y, Shi L, et al.** Impact of GLP-1 receptor agonists on major gastrointestinal disorders for type 2 diabetes mellitus: a mixed treatment comparison meta-analysis. Exp Diabetes Res. 2012;2012:230624. [PMID: 23365557]
64. **Sun F, Wu S, Guo S, Yu K, Yang Z, Li L, et al.** Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetes Res Clin Pract. 2015;110:26-37. [PMID: 26358202]
65. **Zhong X, Zhang T, Liu Y, Wei X, Zhang X, Qin Y, et al.** Effects of three injectable antidiabetic agents on glycaemic control, weight change and drop-out in type 2 diabetes suboptimally controlled with metformin and/or a sulfonylurea: a network meta-analysis. Diabetes Res Clin Pract. 2015;109:451-60. [PMID: 26233934]
66. **Zintzaras E, Miligkos M, Ziakas P, Balk EM, Mademtzoglou D, Doxani C, et al.** Assessment of the relative effectiveness and tolerability of treatments of type 2 diabetes mellitus: a network meta-analysis. Clin Ther. 2014;36:1443-53. [PMID: 25109773]
67. **Scott DA, Boye KS, Timlin L, Clark JF, Best JH.** A network meta-analysis to compare glycaemic control in patients with type 2 diabetes treated with exenatide once weekly or liraglutide once daily in comparison with insulin glargine, exenatide twice daily or placebo. Diabetes Obes Metab. 2013;15:213-23. [PMID: 22958381]
68. **DeFronzo RA, Stonehouse AH, Han J, Wintle ME.** Relationship of baseline HbA_{1c} and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. Diabet Med. 2010;27: 309-17. [PMID: 20536494]
69. **Kapitza C, Heise T, Birman P, Jallet K, Ramis J, Balena R.** Pharmacokinetic and pharmacodynamic properties of taspoglutide, a once-weekly, human GLP-1 analogue, after single-dose administration in patients with type 2 diabetes. Diabet Med. 2009;26:1156-64. [PMID: 19929995]
70. **Stack CB, Localio AR, Griswold ME, Goodman SN, Mulrow CD.** Handling of rescue and missing data affects synthesis and interpretation of evidence: the sodium-glucose cotransporter 2 inhibitor example. Ann Intern Med. 2013;159:285-8. [PMID: 24026261]
71. **Sweeting MJ, Sutton AJ, Lambert PC.** What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23:1351-75. [PMID: 15116347]

Current Author Addresses: Drs. Zaccardi, Htike, Webb, Khunti, and Davies: Diabetes Research Centre, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, United Kingdom.

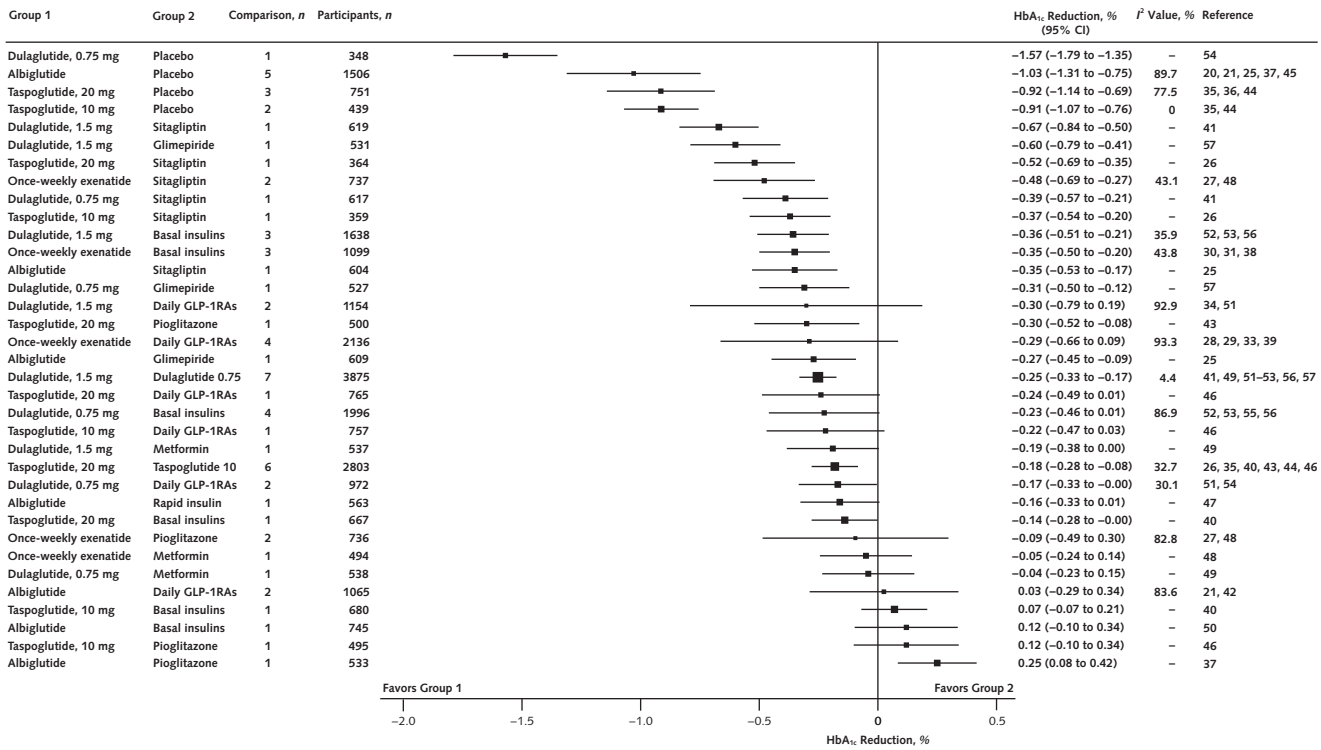
Author Contributions: Conception and design: F. Zaccardi, Z.Z. Htike, D.R. Webb, M.J. Davies.
Analysis and interpretation of the data: F. Zaccardi, D.R. Webb.
Drafting of the article: F. Zaccardi, Z.Z. Htike, D.R. Webb, M.J. Davies.
Critical revision of the article for important intellectual content: F. Zaccardi, Z.Z. Htike, D.R. Webb, M.J. Davies.
Final approval of the article: F. Zaccardi, Z.Z. Htike, D.R. Webb, K. Khunti, M.J. Davies.
Statistical expertise: F. Zaccardi.
Obtaining of funding: D.R. Webb.
Collection and assembly of data: F. Zaccardi, Z.Z. Htike, K. Khunti.

Appendix Figure 1. Summary of evidence search and selection.



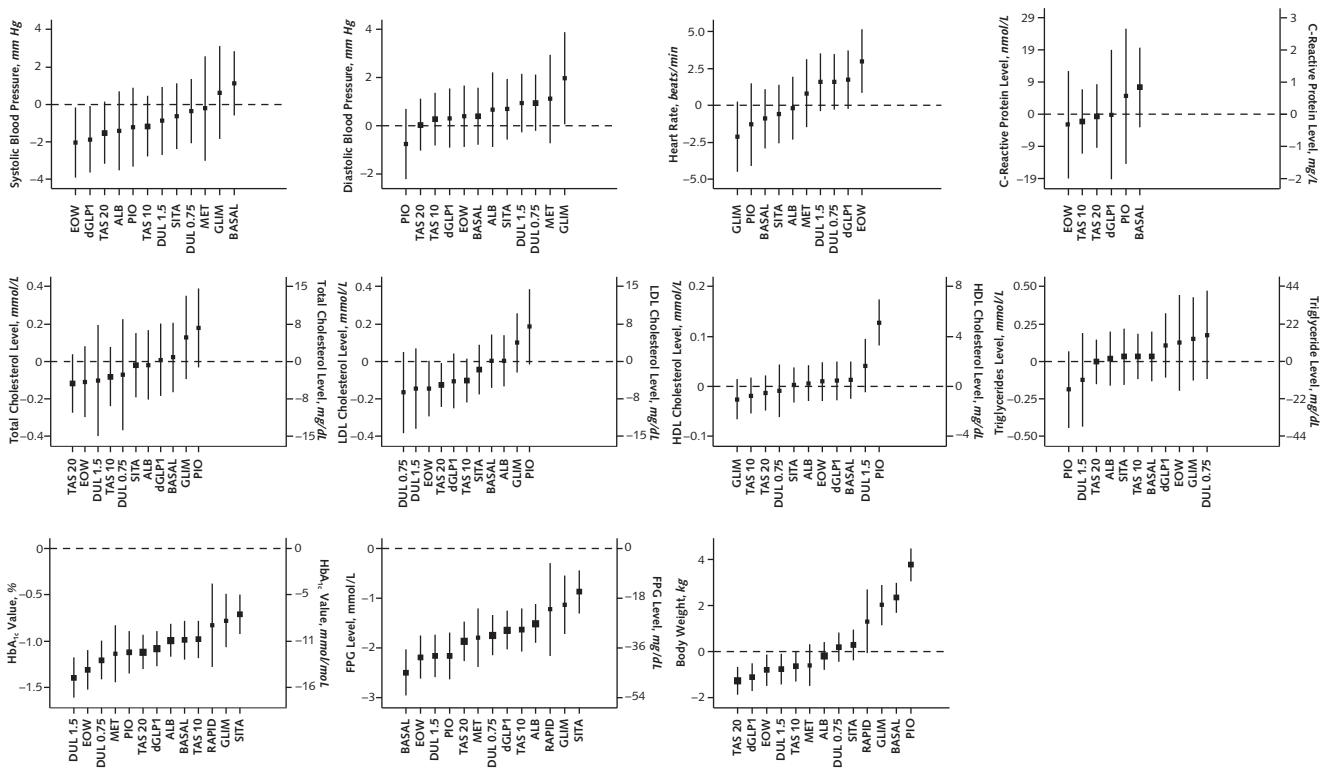
For PubMed, the search was "Exenatide" OR "Taspoglutide" OR "Albiglutide" OR "Dulaglutide" OR "Semaglutide"; limits: Humans and Randomized Controlled Trial. The search strategy was specifically translated for other databases. RCT = randomized, controlled trial.

Appendix Figure 2. Pairwise random-effects meta-analysis for the primary outcome (HbA_{1c}).



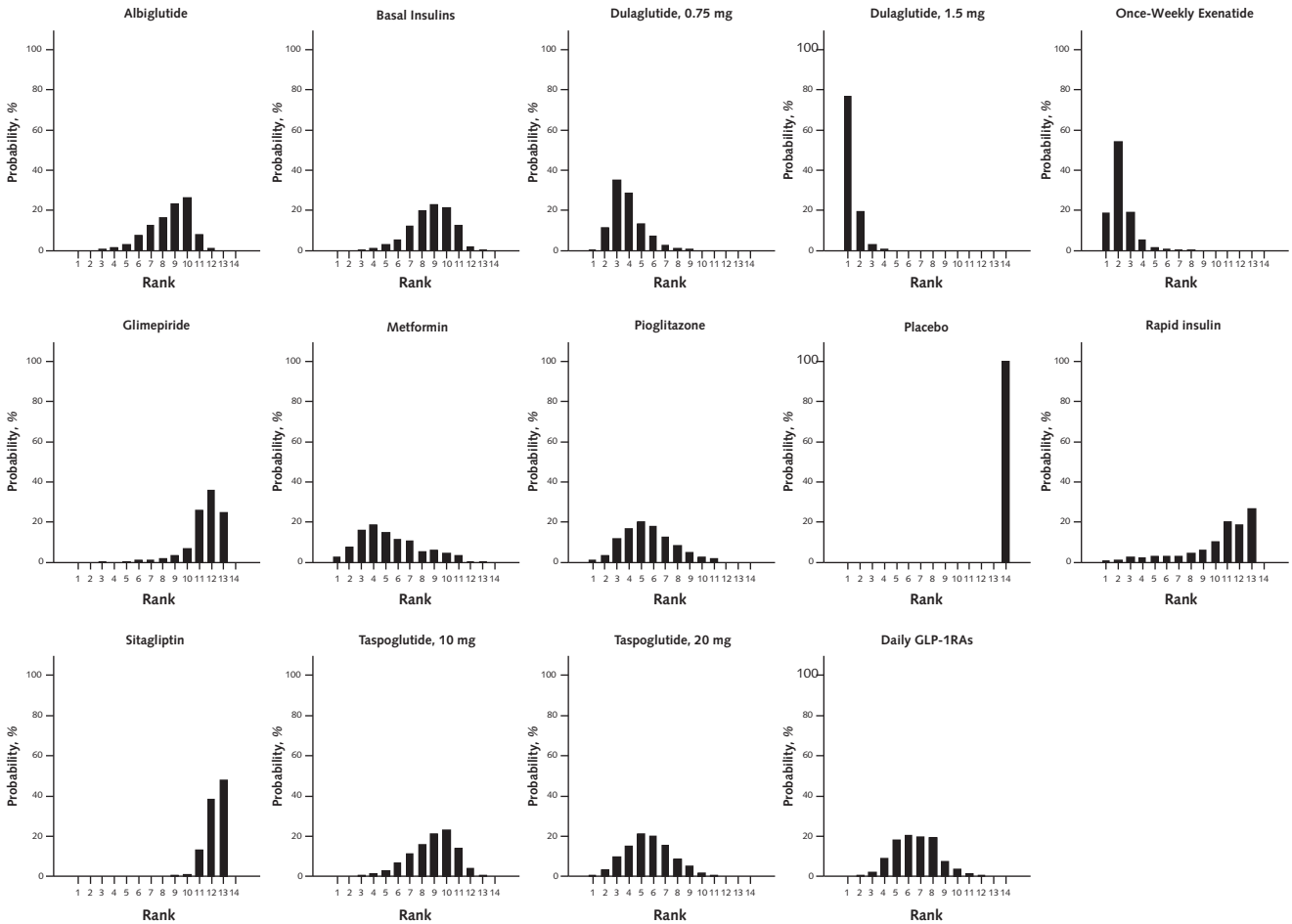
Mean differences are reported for comparisons with at least 1 once-weekly GLP-1RA group. GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA_{1c} = hemoglobin A_{1c}.

Appendix Figure 3. Differences versus placebo (*dashed line*) for cardiometabolic outcomes.



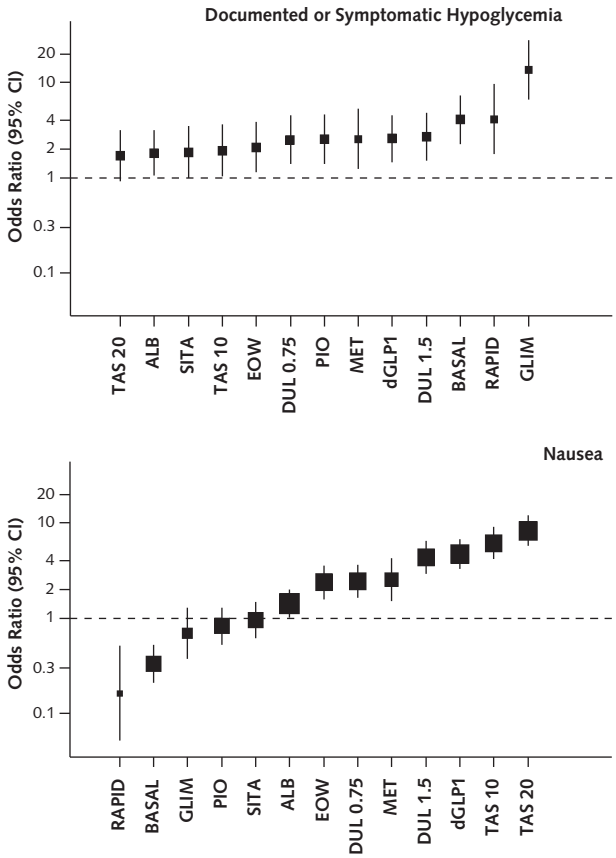
ALB = albiglutide; BASAL = basal insulin; dGLP1 = daily glucagon-like peptide-1 receptor agonists; DUL 0.75 = dulaglutide, 0.75 mg; DUL 1.5 = dulaglutide, 1.5 mg; EOW = exenatide once-weekly; FPG = fasting plasma glucose; GLIM = glimepiride; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metformin; PIO = pioglitazone; PLA = placebo; RAPID = rapid insulin; SITA = sitagliptin; TAS 10 = taspoglutide, 10 mg; TAS 20 = taspoglutide, 20 mg.

Appendix Figure 4. Rank probabilities for the primary outcome (hemoglobin A_{1c}).



GLP-1RA = glucagon-like peptide-1 receptor agonist.

Appendix Figure 5. Differences versus placebo (*dashed line*) for safety outcomes.



ALB = albiglutide; BASAL = basal insulin; dGLP1 = daily glucagon-like peptide-1 receptor agonists; DUL 0.75 = dulaglutide, 0.75 mg; DUL 1.5 = dulaglutide, 1.5 mg; EOW = exenatide once-weekly; GLIM = glimepiride; MET = metformin; PIO = pioglitazone; PLA = placebo; RAPID = rapid insulin; SITA = sitagliptin; TAS 10 = taspoglutide, 10 mg; TAS 20 = taspoglutide, 20 mg.