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Original Article

Effects of once-weekly glucagon-like Peptide-1 receptor agonists on cardiovascular risks and rare events: a meta-analysis of randomized clinical trials

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Abstract: Objective: Exenatide, albiglutide, dulaglutide, and semaglutide are once-weekly glucagon-like peptide receptor agonists (GLP-1 RAs), approved to treat type 2 diabetes mellitus (T2DM). However, there is limited evidence concerning safety levels of once-weekly GLP-1 RAs, including cardiovascular risks and rare events. The current meta-analysis was conducted to pool all relevant evidence regarding safety levels of once-weekly GLP-1 RAs. Methods: The current meta-analysis was conducted using PubMed, Embase, Cochrane Library, and the Website www.clinicaltrials.gov, aiming to identify all available trials with a duration of at least 24 weeks. For dichotomous variables, Mantel-Haenszel odds ratios (MH-OR) for incidence of major cardiovascular events (MACE), such as all-cause and cardiovascular mortality, pancreatic cancer, prostate cancer, and papillary thyroid cancer, were calculated. Cardiovascular risks were estimated according to mean differences in changes in HbA1c, body weights, blood pressure, heart rates, and lipid profiles. Results: Of the 41 included trials, 39 studies provided at least one event on MACE. Incidence of MACE was significantly reduced by once-weekly GLP-1 RAs, compared with the comparators group. Subgroup analyses suggested that a significant reduction was obtained, comparing once-weekly GLP-1 RAs and placebos ($P < 0.001$). Furthermore, a significant reduction was noted in all-cause mortality rates. Non-significant differences were observed in cardiovascular mortality rates, as well as incidence rates of pancreatic cancer, papillary thyroid cancer, and prostate cancer. Conclusion: Cardiovascular safety levels of once-weekly GLP-1 RAs were determined for patients with type 2 diabetes mellitus.

Keywords: GLP-1 analogue, cardiovascular disease, mortality, meta-analyses, type 2 diabetes mellitus

Introduction

Progressive β-cell failure and insulin resistance are main clinical features of type 2 diabetes mellitus, leading to time-consuming treatments. Hence, exogenous insulin therapy has gradually become the most common replacement therapy, helping people receive the glycemic goal [1]. In a previous study [2], however, GLP-1 RAs showed superior effects, compared to other oral antidiabetic drugs, concerning reduction of glycated hemoglobin (HbA1c, %). They significantly reduced the risk of hypoglycemia in patients. GLP-1 acts on islet β-cells in a glucose-dependent manner. It promotes the transcription of insulin genes and increases the biosynthesis and secretion of insulin. Moreover, it can stimulate the proliferation and differentiation of β-cells and inhibit the apoptosis of β-cells, thereby increasing the numbers of islet β-cells. This suppresses the secretion of glucagon, appetite, and ingestion, delaying gastric emptying [3-5]. These pharmacological actions help to reduce postprandial blood glucose, maintaining it at a constant level without hypoglycemia. Clinical trials have demonstrated that GLP-1 RAs can control glycemia, reducing risks of hypoglycemia and improving weight loss.

Data from several sources have identified a significantly better adherence in once-weekly GLP-1 RAs-treated patients diagnosed with type 2 diabetes mellitus, compared with once-daily GLP-1 RAs-treated patients [6]. The appearance of once-weekly injections has offered a great convenience to patients with type 2 diabetes mellitus. Once-weekly GLP-1 RAs include exenatide, albiglutide, dulaglutide, and semaglutide. In January 2012, an exenatide susta-

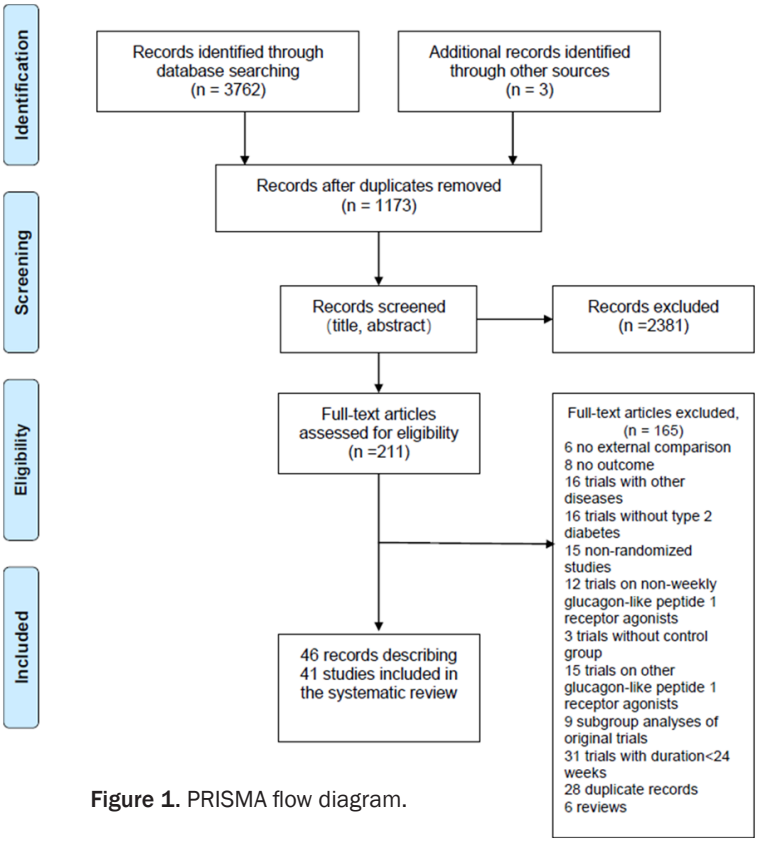

Figure 1. PRISMA flow diagram.

ined-release microsphere formulation was approved by the Food and Drug Administration (FDA). It is the first long-acting GLP-1 formulation with only one injection per week, aiming to greatly improve the quality of lives of diabetic patients [7]. Dulaglutide is the third once-weekly GLP-1 RAs after exenatide and albiglutide. Semaglutide was approved by the FDA in December 2017, as the newest GLP-1 RA [8].

Evidence has demonstrated that uncontrolled diabetes increases risks of cardiovascular diseases (CVD). A large-scale and long-term randomized trial showed that GLP-1 RAs reduced occurrence rates of major adverse cardiovascular events (MACE) [9]. However, cardiovascular safety data of once-weekly GLP-1 RAs is lacking. Therefore, in the current study, MACEs of once-weekly GLP-1 RAs were analyzed, aiming to assess the cardiovascular safety from available trials and short-term clinical trials with a meta-analysis. One area of concern with GLP-1 Ras is pancreatic safety [10]. Rare events seldom supported by evidence before, such as papillary thyroid cancer and prostate cancer, were also assessed. Cardiovascular and rare events safety of once-weekly GLP-1 Ras, including exenatide, albiglutide, dulaglutide, and semaglutide, in randomized controlled trials (RCTs) were assessed. They were compared with placebos or other active drugs in patients diagnosed with type 2 diabetes mellitus.

Materials and methods

The current meta-analysis was based on the criteria of PRISMA statement [11] and was registered on PROSPERO. The registration number is CRD-42019121315.

Search method and study selection

Relevant studies were drawn from PubMed, Embase, and the Cochrane Library using the search terms ‘exenatide’ OR ‘dulaglutide’ OR ‘albiglutide’ OR ‘semaglutide’. Studies using these terms were collected from inception up to December 2018. In addition, some completed but unpublished studies were reviewed from the www.clinicaltrials.gov register.

A meta-analysis was performed, collecting all randomized clinical trials mainly comparing cardiovascular risks with once-weekly GLP-1 RAs treatment with placebos or other active drugs (oral antidiabetic drugs and/or insulin). All screened trials lasted at least 24 weeks and all patients enrolled were diagnosed with type 2 diabetes mellitus. Two reviewers, independently, screened the titles and abstracts of the remaining studies after removing duplicates. They then investigated eligible studies by viewing full texts. Trials enrolling non-diabetic, non-weekly GLP-1 RAs, other diseases, and GLP-1RAs were excluded. No reviews were published elsewhere. After these exclusions, 46 records remained, describing 41 studies. These were included in the current meta-analysis (**Figure 1**).

Data extraction

For each eligible study, relevant data were extracted, including trial design, details of inter-

Table 1. Details of included trials in this meta-analyses

Study	Clinical trials	Trial duration	Intervention	Comparator	Patients (ID/C)		Background therapy	Total HbA1c	Total BMI
Wysham 2014 [15]	AWARD-1/NCT01064687	52	Dulaglutide 1.5 mg	Exenatide BID	245	237	Metformin (1500-3000 mg) and pioglitazone (30-45 mg)	8.1	33
			Dulaglutide 0.75 mg		254				
GIORGINO 2014 [16]	AWARD-2/NCT01075282	78	Dulaglutide 1.5 mg	Insulin glargine titrated once daily	273	262	Metformin + glimepiride	8.1	33
			Dulaglutide 0.75 mg		272				
Umpierrez 2014 [17]	AWARD-3/NCT01126580	52	Dulaglutide 1.5 mg	Metformin 1500~2000 mg daily	220	213	Up to one oral antidiabetic drug (background treatment was discontinued after enrollment)	7.6	33
			Dulaglutide 0.75 mg		218				
JENDLE 2014 [18]	AWARD-4/NCT01191268	52	Dulaglutide 1.5 mg	Glargine	295	296	Prandial lispro (± metformin)	8.5	32.5
			Dulaglutide 0.75 mg		293				
Nauck 2014 [19], Weinstock 2015	AWARD-5/NCT00734474	52 + 104	Dulaglutide 1.5 mg	Sitagliptin 100 mg	304	315	Metformin ≥ 1500 mg daily	8.1	31
			Dulaglutide 0.75 mg		302				
Dungan 2014 [20]	AWARD-6/NCT01624259	26	Dulaglutide 1.5 mg	Liraglutide 1.8 mg	299	300	Metformin	8.1	33.6
Dungan 2016 [21]	AWARD-8/NCT01769378	26	Dulaglutide 1.5 mg	Placebo	240	60	Sulfonylurea	8.4	31.6
Pozzilli 2017 [22]	AWARD-9/NCT02152371	28	Dulaglutide 1.5 mg	Placebo	150	150	Insulin glargine ± metformin	8.4	32.7
Ludvik 2018 [23]	AWARD-10/NCT02597049	24	Dulaglutide 1.5 mg	Placebo	142	140	SGLT2 inhibitor ± metformin	8.04	32.68
			Dulaglutide 0.75 mg		142				
Araki 2015 [24]	NCT01584232	26	Dulaglutide 0.75 mg	Once-daily glargine	181	180	Sulfonylurea only, biguanides only, or sulfonylurea and biguanide	8.0	26.0
Miyagawa 2015 [25]	NCT01558271	26	Dulaglutide 0.75 mg	Liraglutide	281	141	Oral antidiabetic drugs	8.14	25.5
				Placebo		70			
Drucker 2008 [26], Taylor 2011 [27], Wysham 2015 [28], Henry 2016 [29]	DURATION-1/NCT00308139	30 + 104 + 5 years + 6 years	Exenatide once a week	Exenatide twice a day	148	147	With or without metformin ± sulfonylurea ± thiazolidinedione	8.3	35
Bergenstal 2010 [30]	DURATION-2/NCT00637273	26	Exenatide once a week	Sitagliptin once daily	160	166	Metformin	8.5	32
				Pioglitazone once daily		165			
Diamant 2010 [31], DIAMANT 2012 [32], Diamant 2014 [33]	DURATION-3/NCT00641056	26 + 84 + 156	Exenatide once a week	Once daily insulin glargine	233	223	Metformin ± sulfonylurea	8.3	32
RUSSELL-JONES 2012 [34]	DURATION-4/NCT00676338	26	Exenatide once a week	Metformin	248	246	None	8.5	31.2
				Pioglitazone		163			
				Sitagliptin		163			
Blevins 2011 [35]	DURATION-5/NCT00877890	24	Exenatide once a week	Exenatide twice a day	129	123	With or without metformin ± sulfonylurea ± thiazolidinedione	8.4	33.3
Buse 2013 [36]	DURATION-6/NCT01029886	26	Exenatide once a week	Liraglutide	461	450	Metformin ± sulfonylurea ± pioglitazone	8.4	32.3
Guja 2018 [37]	DURATION-7/NCT02229383	28	Exenatide once a week	Placebo	233	231	IG ± metformin	8.53	33.7
Gadde 2017 [38]	DURATION-NEO-2/NCT01652729	28	Exenatide 2.0 mg QWS-AI	Sitagliptin 100 mg	181	122	Metformin	8.5	31.7
				Placebo		61			

Holman 2017 [39]	EXSCEL/NCT01144338	7.5 years	Exenatide once a week	Placebo	7356	7396	None	8.0	32
Ferdinand 2014 [40]	NCT01149421	26	Dulaglutide 1.5 mg	Placebo	251	250	With or without metformin ± sulfonylurea ± thiazolidinedione	7.9	33.0
			Dulaglutide 0.75 mg		254				
Ji 2013 [41]	NCT00917267	26	Exenatide once a week	Exenatide twice a day	340	338	With or without other OAMs	8.7	26.6
Inagaki 2012 [42]	NCT00935532	26	Exenatide once a week	Once daily insulin glargine	215	212	Biguanide + sulfonylurea (± thiazolidine derivative)	8.5	26.15
Reusch 2014 [43], Perkins 2014 [44]	HARMONY-1/NCT00849056	52 + 156	Albiglutide 30 mg once weekly	Placebo	150	151	Pioglitazone ≥ 30 mg ± metformin ≥ 1500 mg daily	8.0	34.1
Nauck 2016 [45]	HARMONY-2/NCT00849017	52	Albiglutide 30 mg weekly	Placebo	101	101	None	8.1	33.5
			Albiglutide 50 mg weekly		99				
Ahren 2014 [46]	HARMONY-3/NCT00838903	104	Albiglutide 30-50 mg weekly	Glimepiride	302	307	Metformin ≥ 1500 mg daily	8.1	32.6
				Sitagliptin		302			
				Placebo		101			
Weissman 2014 [47]	HARMONY-4/NCT00838916	52	Albiglutide 30 mg once weekly	Insulin glargine	504	241	Metformin ≥ 1500 mg daily ± sulfonylurea	8.31	33.1
Home 2015 [48]	HARMONY-5/NCT00839527	52	Albiglutide 30-50 mg	Pioglitazone 30-45 mg	281	288	Metformin ≥ 1500 mg daily + sulfonylurea dose equivalent to ≥ 4 mg daily of glimepiride	8.24	32.2
				Placebo		116			
Rosenstock 2014 [49]	HARMONY-6/NCT00976391	52	Albiglutide 30-50 mg once weekly	Insulin lispro titrated thrice weekly	285	281	Insulin glargine ± oral antidiabetic drugs	8.4	-
Pratley 2014 [50]	HARMONY-7/NCT01128894	32	Albiglutide 50 mg once weekly	Liraglutide 1.8 mg once daily	404	408	Insulin glargine ± oral antidiabetic drugs	8.16	32.8
Leiter 2014 [51]	HARMONY-8/NCT01098539	52	Albiglutide 30-50 mg once weekly	Sitagliptin 25-100 mg once daily	249	246	Oral antidiabetic drugs	8.18	30.39
Leiter 2017 [52]	NCT00976391	52	Albiglutide 30-50 mg once weekly	Thrice-daily lispro	285	281	Insulin glargine ± oral antidiabetic drugs	7.25	-
Chen 2018 [53]	NCT01644500	26	Dulaglutide 1.5 mg	Daily glimepiride (1-3 mg/d).	239	242	Oral antidiabetic drugs	8.0	25.9
			Dulaglutide 0.75 mg		239				
Nino 2017 [54]	NCT01733758	52	Albiglutide 30 mg once weekly	Liraglutide	160	103	Oral antidiabetic drugs	8.11	25.8
			Albiglutide 50 mg once weekly	Placebo	150	77			
Davies 2013 [55]	NCT01003184	30	Exenatide once a week	Once- or twice-daily insulin detemir	111	105	Metformin ± sulfonylurea	8.36	33.7
Sorli 2017 [56]	SUSTAIN1/NCT02054897	30	Semaglutide 0.5 mg weekly	Placebo	128	129	Metformin	8.05	32.93
			Semaglutide 1.0 mg weekly		130				
Ahren 2017 [57]	SUSTAIN2/NCT01930188	56	Semaglutide 0.5 mg weekly	Sitagliptin 100 mg once daily	409	407	Metformin ± thiazolidinediones	8.1	32.5
			Semaglutide 1.0 mg weekly		409				

Aroda 2017 [58]	SUSTAIN4/NCT02128932	30	Semaglutide 0.5 mg weekly	Insulin glargine	362	360	Metformin ± sulfonylurea	8.2	33.0
			Semaglutide 1.0 mg weekly		360				
Rodbard 2018 [59]	SUSTAIN5/NCT02305381	30	Semaglutide 0.5 mg weekly	Placebo	132	133	Oral antidiabetic drugs	8.4	32.2
			Semaglutide 1.0 mg weekly		131				
Marso 2016 [60]	SUSTAIN6/NCT01720446	104	Semaglutide 0.5 mg weekly	Placebo 0.5 mg	826	824	Oral antidiabetic drugs ± basal or premixed insulin	8.7	-
			Semaglutide 1.0 mg weekly	Placebo 1.0 mg	822	825			
Hernandez 2018 *[61]*	*NCT02465515*	3 years	Albiglutide 30-50 mg once weekly	Placebo	4731	4732	None	-	32.3

vention and control treatment, participant baseline characteristics, and prespecified outcomes on rare events.

MACE was the principal outcome, including cardiovascular deaths, strokes and acute myocardial infarction, and serious cardiovascular events (heart failure, angina pectoris, coronary artery disease, sinus bradycardia). Secondary outcomes included all-cause and cardiovascular mortality. This study also collected cardiovascular risk factors, including changes in HbA1c, changes in body weights, data on endpoint totals and HDL cholesterol and triglycerides, as well as systolic and diastolic blood pressure levels, as secondary outcomes. In addition, occurrence rates of pancreatic cancer, papillary thyroid cancer, and prostate cancer, as rare adverse events, were assessed.

Risk of bias assessment

Cochrane's collaboration risk of bias tool [12] was used to determine risk of selection bias (random sequence generation), selection bias (allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting), as well as other biases.

Data synthesis and analyses

Assessing occurrence of MACE, all-cause and cardiovascular mortality, pancreatic cancer, prostate cancer, papillary thyroid cancer, and relative cardiovascular risk factors, the current study pooled estimates across all trials, comparing once-weekly GLP-1 RAs with placebos or other active drugs. Subgroup analyses were condcuted for different types of comparators or individual once-weekly GLP-1 RAs.

For dichotomous variables, such as incidence of MACE and all-cause cardiovascular mortality, as well as prevalence of pancreatic cancer, prostate cancer, and papillary thyroid cancer, the number of events and totals of the treatment group and control group were collected, respectively. Mantel-Haenszel odds ratios (MH-OR) with 95% confidence intervals were calculated by the software directly. Zero events were excluded. A fixed-effects model was applied because of low heterogeneity. For continuous variables, such as cardiovascular risk factors, the mean and standard deviation of the treatment group and control group were collected, respectively. The inverse variance method was used to calculate mean differences (MDs) with 95% confidence intervals and a random-effects model was applied. Heterogeneity was assessed via I^2 statistics, with values < 50% accredited [13]. Funnel plots and Begg's adjusted rank correlation tests were used to estimate publication bias [14]. A 0.05 significance level was performed in all analyses. Study results were combined using RevMan 5.3 and STATA 12.0.

Results

Study characteristics

The study selection process is shown in **Figure 1**. A total of 3,765 studies were searched, with 1,173 duplicates removed. The remaining 2,592 reports were screened across titles and abstracts. The broad search identified 211 potentially eligible papers, with 165 excluded. There were 31 with a shorter duration. MACE, which was the principal outcome variable, could not be yielded by these papers. A total of 46 records, describing 41 studies, were eligible for the current meta-analysis. Of these, 13, 12, 11, and 5 reported information on once weekly dulaglutide, exenatide, albiglutide, and semaglutide, respectively. In total, there were 49,902 patients included in all eligible studies, with 26,322 in once-weekly GLP-1 RA groups and 23,580 in comparator groups. Once-weekly GLP-1 RAs were compared against placebos (17 studies), insulin (10 studies), metformin (2 studies), sitagliptin (7 studies), glimepiride (2 studies), other daily GLP-1 RAs (9 studies), and pioglitazone (3 studies). GLP-1 RAs in each study were compared with two or more medications and placebos. Characteristics of these included studies are shown in **Table 1** [15-61]. The duration of trials ranged from 24 weeks to 7.5 years. Mean trial duration, baseline HbA1c, and body mass indexes (BMI) of enrolled patients were 4.6 years, 8.0%, and 30.75 kg/m^2, respectively.

Risk of bias

Assessment of risk of bias is shown in **Figure 2**. Selection bias was reported in almost all published studies adequately. Only conference abstracts or parts of full texts were not described. A total of 15 studies were open trails with at

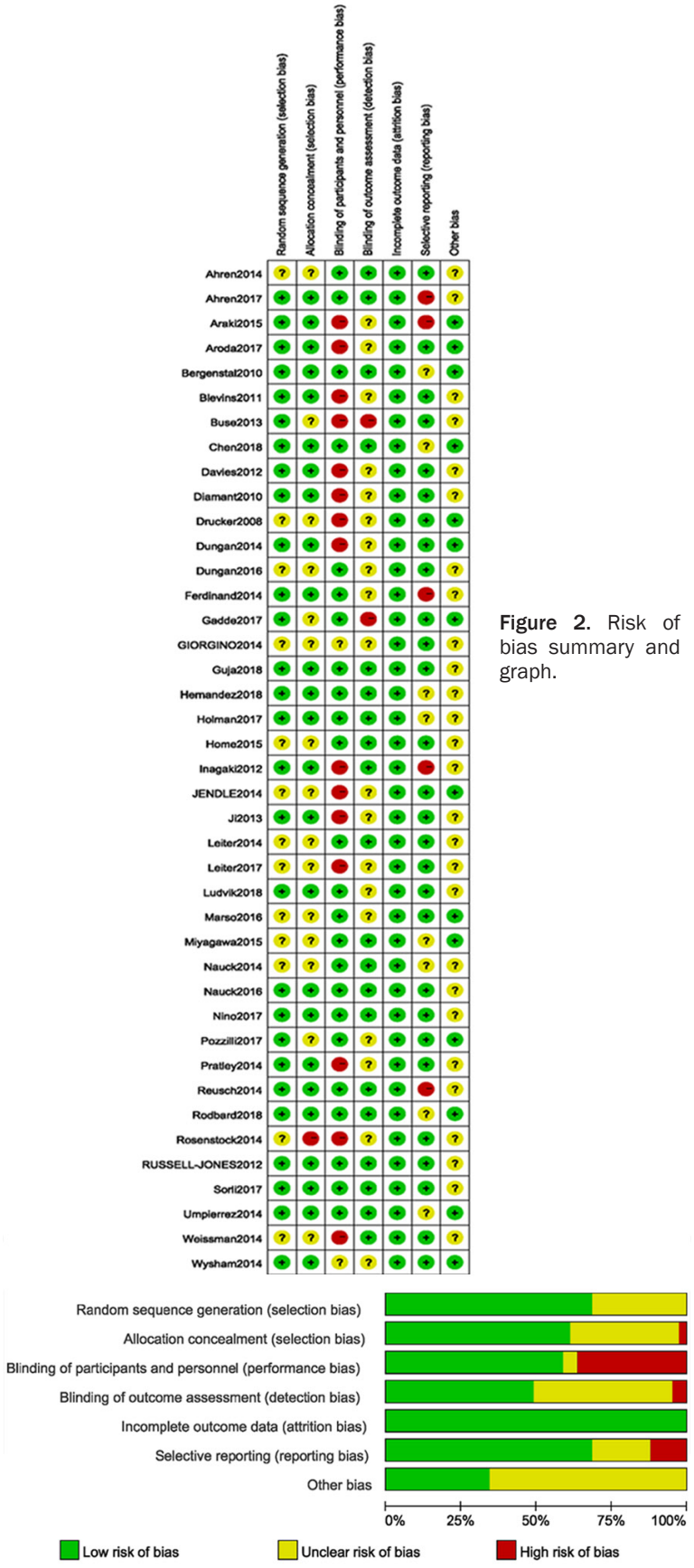

Figure 2. Risk of bias summary and graph.

least one arm, while others were double-blind trails. In all studies, there was low risk of bias associated with incomplete outcome data. Funnel plots and Egger's tests showed no evidence of publication bias ($P = 0.828$).

MACE

Of the 41 studies, 39 studies provided at least one MACE. Cases of albiglutide (NCT01733758) [54] and semaglutide (NCT01930188) [57] were excluded because of the absence of MACE. Overall, once-weekly GLP-1 RAs showed a significant reduction in MACE, with an odds ratio of 0.87 (0.82 to 0.94, $P < 0.001$) versus comparators (**Figure 3**). It also showed low heterogeneity levels, with a value of $I^2 < 50\%$. The funnel plot (**Figure 4**) showed no significant publication bias.

According to subgroup analyses, once-weekly GLP-1 RAs were associated with a non-significant trend towards a reduction in the rate of MACE, compared to insulin and pioglitazone. The number of trials was 10 and 3 ($P = 0.08$ and 0.07). A significant reduction was performed between once-weekly GLP-1 RAs and placebos ($P < 0.001$). Details are shown in **Figure 5**. In placebo-controlled trials, only albiglutide produced a significant reduction, compared to placebos [MH-OR 0.80 (0.70-0.92), $P < 0.01$].

All-cause and cardiovascular mortality

A total of 22 studies provided data concerning all-cause mortality. Of the 14 studies included in the meta-analysis,

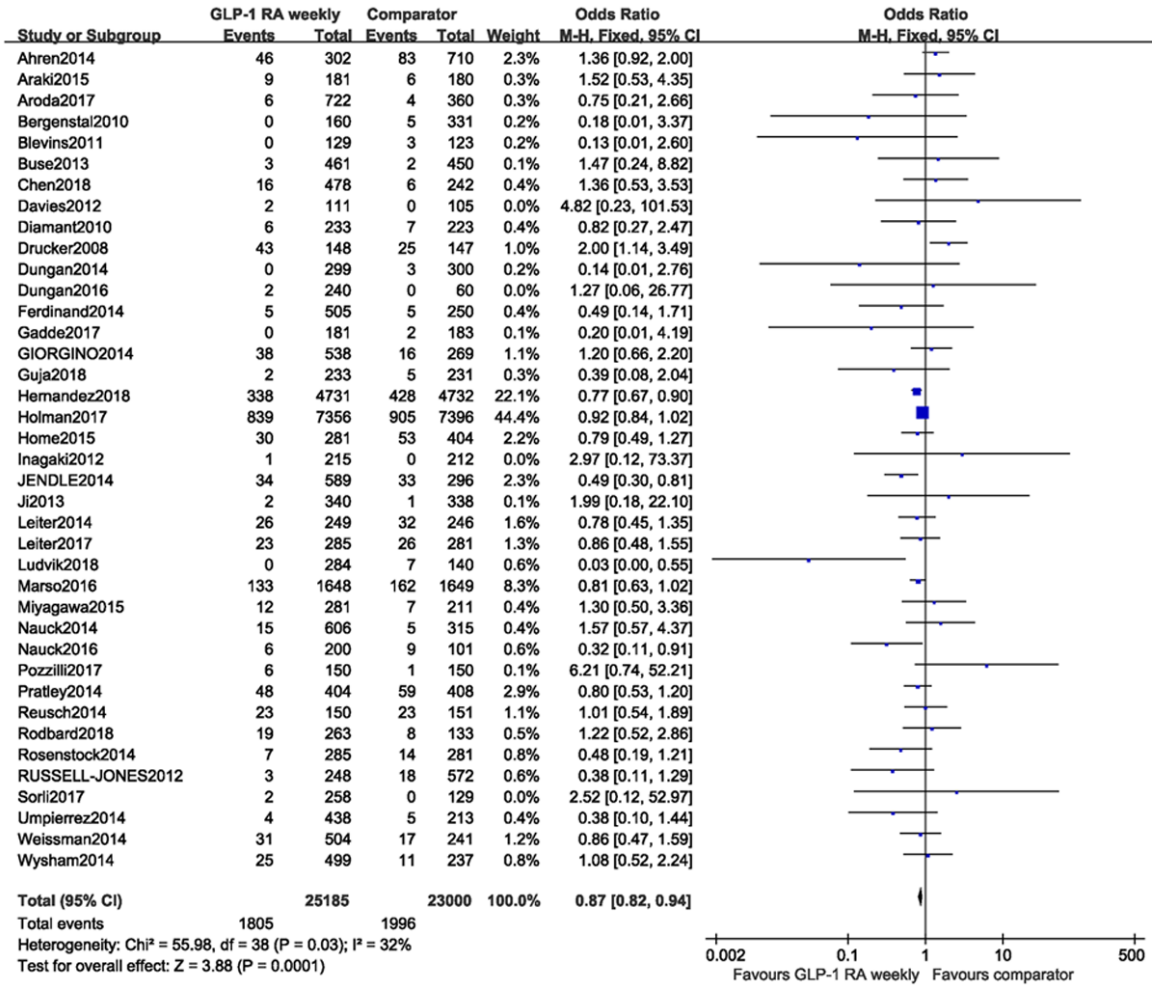

Figure 3. Forest plot showing incidence rates of major cardiovascular events for each individual trial with at least once event.

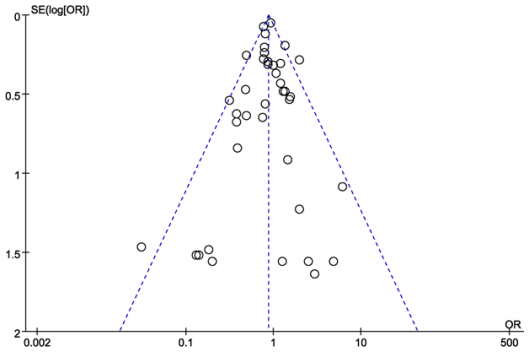

Figure 4. Funnel plot for major cardiovascular events for eanch individual trial with at least one event.

each study described at least one death. Compared with comparators, once-weekly GLP-1 RAs produced significant changes in all-cause mortality [MH-OR 0.90 (0.81-0.99), p = 0.03] (**Figure 6**). Furthermore, subgroup analyses showed significant changes, compared to placebos (7 trials). However, non-significant changes were shown, compared to sitagliptin (2 trials), insulin (2 trials), other daily GLP-1 RAs (3 trials), and metformin (1 trial) (values of OR (95% CI) 0.59 (0.18-1.92), 0.68 (0.12-3.71), 1.36 (0.33-5.62), and 0.33 (0.01-8.12) and P = 0.38, 0.65, 0.67, and 0.50, respectively).

A total of 19 studies provided cardiovascular mortality data. Of the 6 studies included in the meta-analysis, each study described at least one death. No significant differences between once-weekly GLP-1 RAs and comparators were demonstrated [MH-OR 0.91 (0.80-1.03), P = 0.13].

Cardiovascular risk factors

HbA1c: Most included trials provided data concerning changes in HbA1c. Values they used as

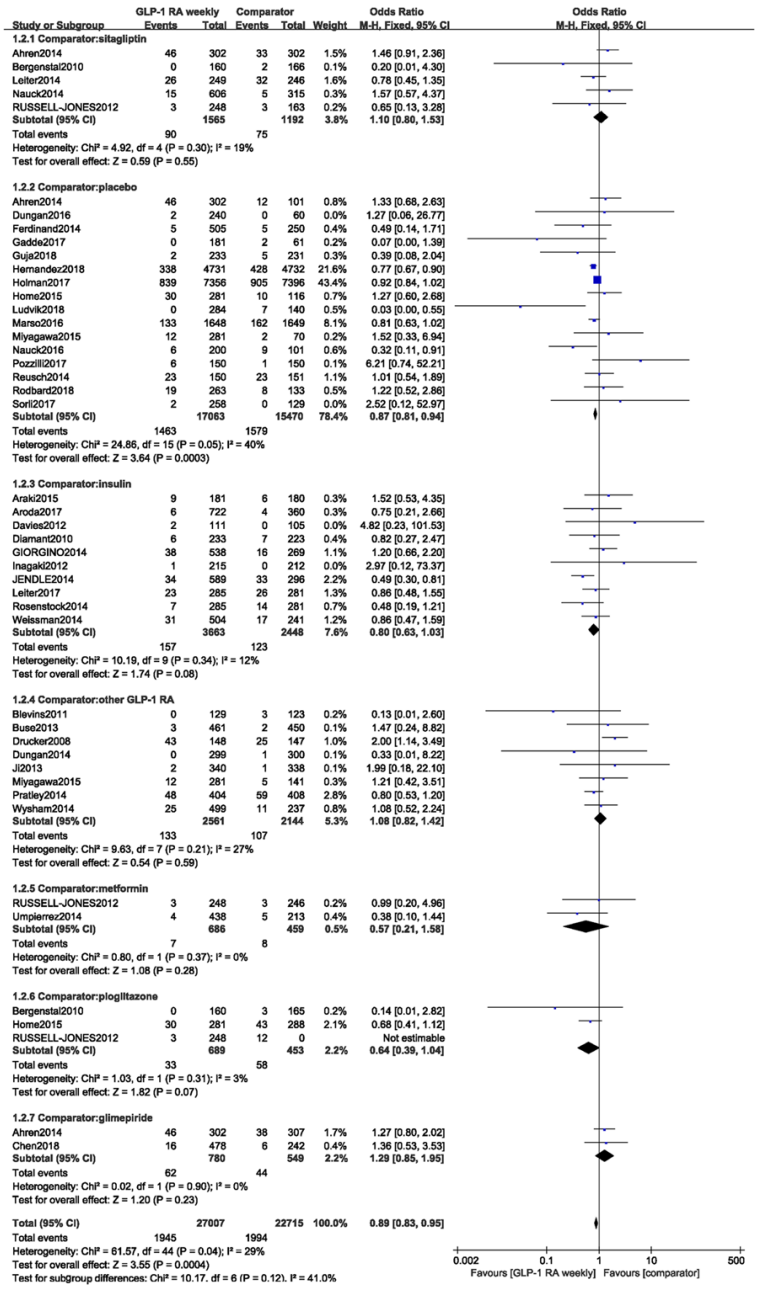

Figure 5. Subgroup analyses for incidence rates of major cardiovascular events for each individual trial with at least once event, comparing once-weekly GLP-1 RAs with different comparator groups.

primary outcomes were performed in the current analysis. Pooled analyses showed a significant reduction in HbA1c between once-weekly GLP-1 RAs and comparators ($P < 0.001$). Once-weekly GLP-1 RAs produced a significant reduction, compared to placebos, insulin, sitagliptin, and glimepiride. Mean differences of changes in HbA1c were -1.04% (-1.21 to -0.88), -0.28% (-0.43 to -0.13), -0.51% (-0.73 to -0.29), and -0.36% (-0.54 to -0.19), respectively. *P*-values were all less than 0.001 (**Table 2**). Conversely, no significant differences were produced, compared to metformin and pioglitazone. Compared with other daily GLP-1 RAs, a trend towards a reduction was shown in changes in HbA1c with once-weekly GLP-1 RAs ($P = 0.08$).

Body weights: Compared with comparators, pooled analyses showed a significant reduction in changes in body weights with once-weekly GLP-1 RAs. ($P < 0.001$). Weights changed by -1.36 kg (-2.09 to -0.63), compared to placebos, -2.53 kg (-3.58 to -1.48), compared to insulin, -1.19 kg (-2.03 to -0.35), compared to sitagliptin, -2.13 kg (-2.50 to -1.75), compared to glimepiride, and by -4.45 kg (-5.39 to -3.52), compared to pioglitazone. Only when compared to other daily GLP-1 Ras did mean differences of changes in body weights increase by 0.39 kg (-0.21 to 0.99). There were no significant changes in body weights, compared to metformin (**Table 2**).

Blood pressure: A total of 30 trials included in this analysis measured blood pressure changes. Mean differences of changes in blood pressure were analyzed between once-weekly GLP-1 RAs and placebos (11 trials), insulin (7 trials), metformin (2 trials), sitagliptin (6 trials), glimepiride (2 trials), other daily GLP-1 RAs (7 trials), and pioglitazone (2 trials), respectively. Significant changes in endpoint systolic (SBP) and diastolic blood pressure (DBP) were noted (**Table 3**). Once-weekly GLP-1 RAs significantly reduced systolic blood pressure by -1.85 mmHg (-2.72 to -0.99), compared to placebos, and by -2.29 mmHg (-3.13 to -1.44), compared to insulin. When compared with other daily GLP-1 Ras, mean differences of changes in SBP increased by 0.45 mmHg (-0.60 to 1.50).

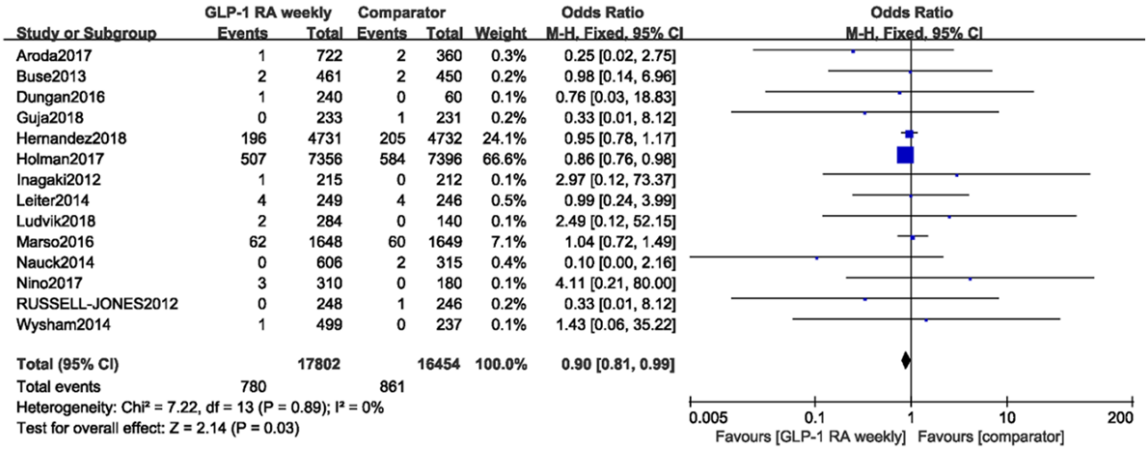

Figure 6. Frost plot showing all-cause mortality for each individual trial with at least one event.

Reduction in diastolic blood pressure levels was on the margin of statistical significance (P = 0.05). Only when compared with pioglitazone were significant changes noted.

Heart rate: Only 19 trials measured heart rate changes. Overall, once-weekly GLP-1 RAs produced significant increases, according to pooled analyses (P < 0.001). In these subgroups, there were no significant differences in the effects of metformin and other daily doses of GLP-1 RAs on heart rates in patients.

Lipid profiles: A total of 18 studies provided total cholesterol, HDL cholesterol, and triglycerides data. Data from included trials demonstrated significant changes in total and HDL cholesterol between once-weekly GLP-1 RAs and comparators. Changes in HDL cholesterol levels were on the edge of statistical significance (P = 0.05). Conversely, no significant changes in triglycerides were noted between once-weekly GLP-1 RAs and comparators (**Table 4**). Total cholesterol was significantly reduced, comparing placebos and sitagliptin. HDL cholesterol was significantly reduced, compared with metformin. Triglycerides were reduced significantly in pioglitazone only.

Pancreatic cancer, papillary thyroid cancer, and prostate cancer

Across all studies, 22 studies reported pancreatic cancer. Of the 16 studies included in the current meta-analysis, each study described at least one death. In these trials, 36 patients experienced pancreatic cancer in once-weekly GLP-1 RA groups, compared with 28 patients in comparator groups, showing non-significant differences between the two groups [MH-OR 1.20 (0.76-1.89, p = 0.44)] (**Figure 7**).

Only 7 studies reported papillary thyroid cancer. Of the 5 studies included in the meta-analysis, each described at least one death. Moreover, only 2 patients evolved into papillary thyroid cancer in the once-weekly GLP-1 RA groups, compared with 4 patients in the comparator groups. No significant differences were noted between the two groups [MH-OR 0.84 (0.23-3.10), P = 0.79] (**Figure 8**).

Prostate cancer was reported in 3 trials. Only 3 patients evolved into prostate cancer while receiving once-weekly GLP-1 Ras. No patients evolved into prostate cancer in the comparator group. Non-significant differences were noted between the two groups [MH-OR 2.39 (0.38-15.21), P = 0.36] (**Figure 9**).

Discussion

Clinical efficiency levels of once-weekly GLP-1 Ras, compared to placebos or other active antidiabetic agents, have been reported in many meta-analyses [62-65]. Once-weekly GLP-1 RAs have shown better effects on HbA1c, lowering and controlling glucose, compared to other antidiabetic agents. Most importantly, good patient adherence has been reported. However, cardiovascular and rare events are important areas that require concern. Prior studies [66, 67] have noted the importance of cardiovascular and rare events but did not report details. The current meta-analysis pooled most available trials showing the safety of

Table 2. Mean differences in changes in HbA1C and body weights as the primary endpoint between once-weekly GLP-1 RA and placebo/active comparators in trials included in the meta-analyses

	Placebo	Insulin	Metformin	Sitagliptin	Glimepiride	Other GLP-1 RA	Pioglitazone	Overall
HbA1c (%)								
N trials	15	10	2	7	2	9	3	39
Effect estimate (95% CI)	-1.04 [-1.21; -0.88]**	-0.28 [-0.43; -0.13]**	-0.09 [-0.21; 0.04]	-0.51 [-0.73; -0.29]**	-0.36 [-0.54; -0.19]**	-0.16 [-0.34; 0.02]	0.03 [-0.26, 0.33]	-0.50 [-0.63; -0.37]**
Body weight (kg)								
N trials	15	10	2	7	2	9	3	39
Effect estimate (95% CI)	-1.36 [-2.09; -0.63]**	-2.53 [-3.58; -1.48]**	0.19 [-0.21; 0.59]	-1.19 [-2.03; -0.35]*	-2.13 [-2.50; -1.75]**	0.39 [-0.21; 0.99]	-4.45 [-5.39; -3.52]**	-1.42 [-1.93; -0.92]**

*$p < 0.05$, **$p < 0.001$.

Table 3. Mean differences in changes in systolic and diastolic blood pressure and heart rates at the endpoint between GLP-1 RA and placebo/active comparators

	N trials	Mean differences (95% CI)	*P*
Systolic blood pressure (mmHg)			
Placebo	11	-1.85 [-2,72; -0.99]	< 0.001
Insulin	7	-2.29 [-3.13; -1.44]	< 0.001
Metformin	2	-0.88 [-2.39; 0.64]	0.26
Sitagliptin	6	-1.14 [-2.72; 0.44]	0.16
Glimepiride	2	-1.38 [-3.41; 0.65]	0.18
Other GLP-1 RAs	7	0.45 [-0.60; 1.50]	0.40
Pioglitazone	2	-0.70 [-3.14; 1.74]	0.57
Diastolic blood pressure (mmHg)			
Placebo	11	0.15 [-0.28; 0.58]	0.50
Insulin	7	0.31 [-0.21; 0.83]	0.24
Metformin	2	0.11 [-0.89;1.12]	0.82
Sitagliptin	6	0.17 [-0.56; 0.90]	0.65
Glimepiride	2	-0.90 [-2.31; 0.50]	0.21
Other GLP-1 RA	7	0.33 [-0.19; 0.84]	0.21
Pioglitazone	2	1.54 [0.43; 2.66]	0.007
Heart rate (bpm)			
Placebo	7	1.36 [0.29; 2.43]	0.01
Insulin	5	2.49 [1.29; 3.69]	< 0.001
Metformin	2	0.83 [-0.24; 1.90]	0.13
Sitagliptin	5	1.68 [0.56; 2.79]	0.003
Glimepiride	1	1.80 [0.22; 3.38]	0.03
Other GLP-1 RAs	4	0.12 [-1.36; 1.59]	0.87
Pioglitazone	1	3.20 [1.37; 5.03]	< 0.001

cardiovascular and rare events of once-weekly GLP-1 RAs on patients diagnosed with type 2 diabetes mellitus. Results indicated that once-weekly GLP-1 RAs showed superior cardiovascular safety, compared with several antidiabetic agents. A significant reduction of MACE incidence was demonstrated, compared to placebos. Compared with insulin and pioglitazone, once-weekly GLP-1 RAs showed a trend towards a reduction of MACE incidence. Differences between various weekly GLP-1 RAs were performed. In placebo-controlled trials, albiglutide was associated with a greater reduction of incidence of MACE. In placebo-controlled trials of dulaglutide, heterogeneity was reduced to less than 50% when removing a single trial (AWARD-10) [23]. Heterogeneity of exenatide trials was reduced from 49% to 2% if one trial was removed (EXSCEL) [39]. A major cause of death of type 2 diabetes mellitus, MACE was not shown to play an important role in cardiovascular mortality between the two groups. Drawing conclusions from the above results, once-weekly GLP-RAs have better cardiovascular safety for treatment of type 2 diabetes mellitus.

Significant reductions in HbA1c levels [68], blood pressure, lipid profiles, and body weights of these agents demonstrated that once-weekly GLP-1 RAs had prominent efficiency in reducing cardiovascular risks, compared to placebos, insulin, and sitagliptin. It is conceivable that adiposity is a cause of MACE and lower weight and systolic blood pressure levels can reduce cardiovascular risks [69]. However, increments of heart rates would be a contrast to others, as it might increase the risk of MACE and death. Thus, to some extent, once-weekly GLP-1 RAs provides effects, facilitating the reduction of cardiovascular risks. Rare events (pancreatic cancer, papillary thyroid cancer, and prostate cancer) were also analyzed for the two groups. There were no distinct differences between weekly and daily GLP-1 RAs, except for better adherence and tolerance for weekly GLP-1 RAs.

Effects and safety levels of once-weekly GLP-1 RAs have been assessed in previous studies. However, these studies mainly paid attention to blood glucose control and major adverse reactions. Only a limited number of trials included assessment of exenatide, albiglutide, and dulaglutide. Hence, to the best of our knowledge, the current meta-analysis is the first to collect evidence from trials supporting all once-weekly GLP-1 RAs approved by the FDA, including the newest agent semaglutide. Additionally, this is the first analysis to focus on cardiovascular risks and rare events. This study also included three published large-scale clinical trials with MACE as the principal outcome (EXSCEL, SUSTAIN-6 [60] and Harmony Outcomes [61]), enlarging the sample size and increasing the credibility of results.

Table 4. Mean differences in changes in total and HDL-cholesterol and triglycerides between GLP-1 RA and placebo/active comparators

	N trials	Mean differences (95% CI)	*P*
Total cholesterol			
Placebo	5	-0.03 [-0.05; -0.00]	0.04
Insulin	4	-0.16 [-0.54; 0.21]	0.40
Metformin	2	0.99 [-1.43; 3.41]	0.42
Sitagliptin	4	-0.23 [-0.43; -0.04]	0.02
Glimepiride	1	-0.14 [-2.63; 2.35]	0.91
Other GLP-1 RAs	6	-0.09 [-0.36; 0.18]	0.51
Pioglitazone	2	-2.61 [-8.67; 3.45]	0.40
HDL cholesterol			
Placebo	5	0.01 [-0.01; 0.03]	0.42
Insulin	4	-0.01 [-0.04; 0.01]	0.26
Metformin	2	-0.06 [-0.09; -0.03]	< 0.001
Sitagliptin	4	-0.03 [-0.07; 0.01]	0.17
Glimepiride	1	0.04 [-0.52; 0.59]	0.90
Other GLP-1 RAs	6	-0.00 [-0.02; 0.02]	1.00
Pioglitazone	2	-2.09 [-6.05; 1.86]	0.30
Triglycerides			
Placebo	5	-0.02 [-0.07; 0.04]	0.52
Insulin	4	0.07 [-0.01; 0.15]	0.08
Metformin	2	-1.37 [-5.46; 2.72]	0.51
Sitagliptin	4	0.01 [-0.04; 0.06]	0.69
Glimepiride	1	-0.19 [-4.70; 4.32]	0.93
Other GLP-1 RAs	6	-0.01 [-0.07; 0.06]	0.87
Pioglitazone	2	0.12 [0.06; 0.17]	< 0.001

One major drawback to the current study was that most of the trials only published positive data. The paucity of negative results may lead to a higher heterogeneity and publication bias. The lack of relevant data could also lead to additional bias. Two included trials did not report incidence of MACE. Only half of the trials reported mortality. Furthermore, few trials assessed rare events. Low incidence leads to less credibility. Only one trial did not assess cardiovascular risk factors. Moreover, analyses of cardiovascular risk factors had a higher heterogeneity due to different treatment backgrounds, additive doses of agents, criteria of outcomes, inclusion and exclusion standards, and trial duration. Due to data deficiencies, sensitivity-analyses could not be conducted in most cases.

Another limitation of the current study was that most of the trials were short-term clinical trials. Although a limitation was set, demanding that the duration of intervention could not be less than 24 weeks, typical cardiovascular outcome studies require longer duration times. Furthermore, most studies did not use cardiovascular outcomes as their principal outcome measure. Thus, existing data was incomplete. More importantly, patients with type 2 diabetes mellitus analyses were associated with low cardiovascular risks. Some of them had no history of cardiovascular disease. Patients included in typical cardiovascular outcome studies are mostly high-risk patients. To create a more credible meta-analysis, more large-scale and long-term clinical trials, assessing cardiovascular outcomes, are necessary. The current study performed comparisons concerning different types of active oral antidiabetic agents, such as DPP-4 inhibitors, biguanides, sulfonylureas, thiazolidinediones (TZDs), and daily GLP-1 RAs. However, in this study, assessing efficacy and safety differences from weekly GLP-1 RAs, only one representative drug was selected for each type of oral hypoglycemic agent. Only liraglutide and exenatide BID were selected for GLP-1 RAs administered daily. Therefore, more medicines from different active oral agents are necessary, aiming to expand the scope of application of results.

In conclusion, once-weekly GLP-1 RAs may reduce cardiovascular risks for patients with type 2 diabetes mellitus, to some extent. In this study, cardiovascular safety levels of this method were confirmed, compared with placebos or active antidiabetic agents. Furthermore, incidence rates of rare events were confirmed to be similar between once-weekly GLP-1RAs and comparators. Aiming to achieve more credible results, more large-scale and long-term trials should be implemented.

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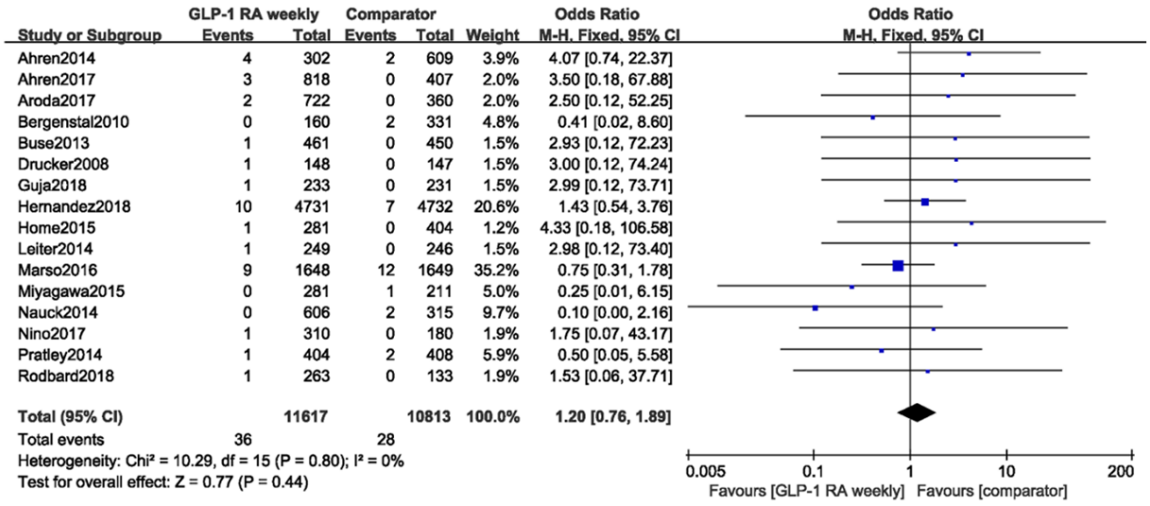

Figure 7. Forest plot showing prevalence of pancreatic cancer for each individual trial with at least once event.

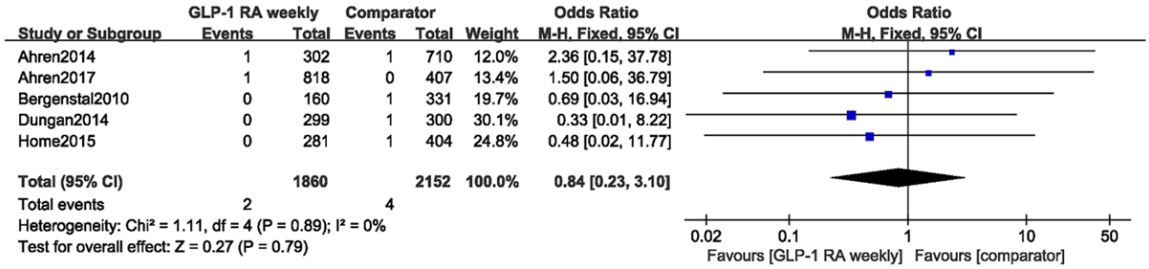

Figure 8. Forest plot showing prevalence of papillary thyroid cancer for each individual trial with at least once event.

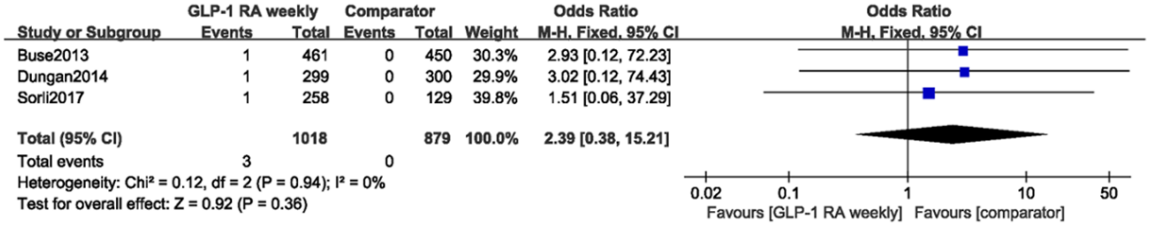

Figure 9. Forest plot showing prevalence of prostate cancer for each individual trial with at least once event.

Disclosure of conflict of interest

None.

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References

[1] Kahn SE, Cooper ME and Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet 2014; 383: 1068-1083.

[2] Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, Søndergaard RE and Davies M. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 2010; 375: 1447-1456.

[3] Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012; 8: 728.

[4] Meloni AR, DeYoung MB, Lowe C and Parkes DG. GLP-1 receptor activated insulin secretion from pancreatic β-cells: mechanism and glucose dependence. Diabetes Obes Metab 2012; 15: 15-27.
[5] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R and Matthews DR. 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: 429-442.
[6] Krass I, Schieback P and Dhippayom T. Adherence to diabetes medication: a systematic review. Diabet Med 2014; 32: 725-737.
[7] Murphy CE. Review of the safety and efficacy of exenatide once weekly for the treatment of type 2 diabetes mellitus. Ann Pharmacother 2012; 46: 812-821.
[8] Tuchscherer RM TA, Trujillo JM. Semaglutide: the newest once-weekly GLP-1 RA for type 2 diabetes. Ann Pharmacother 2018; 52: 1224-1232.
[9] Abdul-Ghani M DR, Del Prato S, Chilton R, Singh R, Ryder REJ. Cardiovascular disease and type 2 diabetes: has the dawn of a new era arrived? Diabetes Care 2017; 40: 813-820.
[10] Nauck MA, Frossard JL, Barkin JS, Anglin G, Hensley IE, Harper KD and Milicevic Z. Assessment of pancreas safety in the development program of once weekly glp-1 receptor agonist dulaglutide. Diabetes Care 2017; 40: 647-654.
[11] Moher D, Liberati A, Tetzlaff J, Altman DG, and the PG. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. Ann Intern Med 2009; 151: 264-9.
[12] Higgins JPT, Altman DG and Sterne JAC. Cochrane Statistical Methods Group, Cochrane Bias Methods Group. Chapter 8: assessing risk of bias in included studies. In: Cochrane handbook for systematic reviews of interventions. Version 5.1.0. The Cochrane Collaboration 2011.
[13] Deeks JJ, Higgins JPT and Altman DG. Cochrane statistical methods group. Chapter 9.5.2 identifying and measuring heterogeneity. In: Cochrane handbook for systematic reviews of interventions. Version 5.1.0. The Cochrane Collaboration 2011.
[14] Sterne JA, Egger M. Funnel plots for detecting bias in meta-analyses: guidelines on choice of axis. J Clin Epidemiol 2001; 54: 1046-55.
[15] Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, Kuhstoss D, Scism-Bacon J and Lakshmanan M. Efficacy and safety of dulaglutide versus placebo and exenatide in type 2 diabetes (award-1). Diabetes Care 2014; 37: 2159-67.
[16] Giorgino F, Benroubi M, Sun JH, Zimmermann AG and Pechtner V. Efficacy and safety of once weekly dulaglutide vs. insulin glargine in combination with metformin and glimepiride in type 2 diabetes patients (AWARD-2). Canadian Journal of Diabetes 2014; 38: S4.
[17] Umpierrez G, Povedano ST, Manghi FP, Shurzinske L and 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.
[18] Jendle J, Rosenstock J, Blonde L, Woo V, Gross J, Jiang H and Milicevic Z. Better glycemic control and less weight gain with once weekly dulaglutide vs. once daily insulin glargine, both combined with Pre-Meal Insulin Lispro, in type 2 diabetes Patients (AWARD-4). Canadian Journal of Diabetes 2014; 38: S50.
[19] Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z and Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care 2014; 37: 2149-2158.
[20] Dungan KM, Povedano ST, Forst T, Gonzalez JG, Atisso C, Sealls W and Fahrbach JL. 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: 1349-1357.
[21] Dungan KM, Weitgasser R, Perez Manghi F, Pintilei E, Fahrbach JL, Jiang HH, Shell J and Robertson KE. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). Diabetes Obes Metab 2016; 18: 475-482.
[22] Pozzilli P and Norwood P, Jódar E, Davies MJ, Ivanyi T, Jiang H, Woodward DB, Milicevic Z. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). Diabetes Obes Metab 2017; 19: 1024-1031.
[23] Ludvik B, Frías JP, Tinahones FJ, Wainstein J, Jiang H, Robertson KE, García-Pérez LE, Woodward DB, Milicevic Z. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2018; 6: 370-381.
[24] Araki E, Inagaki N, Tanizawa Y, Oura T, Takeuchi M and 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.

[25] Miyagawa J, Odawara M, Takamura T, Iwamoto N, Takita Y and 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: 974-983.

[26] Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D and Porter L. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008; 372: 1240-1250.

[27] Taylor K, Gurney K, Han J, Pencek R, Walsh B and Trautmann M. Exenatide once weekly treatment maintained improvements in glycemic control and weight loss over 2 years. BMC Endocr Disord 2011; 11: 9.

[28] Wysham CH, MacConell LA, Maggs DG, Zhou M, Griffin PS and Trautmann ME. Five-year efficacy and safety data of exenatide once weekly: long-term results from the DURATION-1 randomized clinical trial. Mayo Clin Proc 2015; 90: 356-365.

[29] Henry RR, Klein EJ, Han J and Iqbal N. Efficacy and tolerability of exenatide once weekly over 6 years in patients with type 2 diabetes: an uncontrolled open-label extension of the DURATION-1 Study. Diabetes Technol Ther 2016; 18: 677-686.

[30] Bergenstal RM, Wysham C, Macconell L, Malloy J, Walsh B, Yan P, Wilhelm K, Malone J and Porter LE. 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: 431-439.

[31] Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K and Trautmann M. 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: 2234-2243.

[32] Diamant M, Van Gaal L, Stranks S, Guerci B, MacConell L, Haber H, Scism-Bacon J and Trautmann M. Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. Diabetes Care 2012; 35: 683-689.

[33] Diamant M, Van Gaal L, Guerci B, Stranks S, Han J, Malloy J, Boardman MK and Trautmann ME. 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: 464-473.

[34] Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzalez JG, Chan M, Wolka AM and Boardman MK. 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: 252-258.

[35] Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, Trautmann M and Porter L. 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: 1301-1310.

[36] Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, Hoogwerf BJ, Gao A, Boardman MK, Fineman M, Porter L and Schernthaner G. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013; 381: 117-124.

[37] Guja C. Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: the DURATION-7 randomized study. PLoS One 2018; 20: 1602-1614.

[38] Gadde KM, Vetter ML, Iqbal N, Hardy E and Ohman P. Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: the DURATION-NEO-2 randomized clinical study. Diabetes Obes Metab 2017; 19: 979-988.

[39] Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in Type 2 Diabetes. N Engl J Med 2017; 377: 1228-1239.

[40] Ferdinand KC, White WB, Calhoun DA, Lonn EM, Sager PT, Brunelle R, Jiang HH, Threlkeld RJ, Robertson KE, Geiger MJ. Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with Type 2 diabetes mellitus. Hypertension 2014; 64: 731-737.

[41] Ji L, Onishi Y, Ahn CW, Agarwal P, Chou CW, Haber H, Guerrettaz K and Boardman MK. 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.

[42] Inagaki N, Atsumi Y, Oura T, Saito H and 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: 1892-1908.

[43] Reusch J, Stewart MW, Perkins CM, Cirkel DT, Ye J, Perry CR, Reinhardt RR and Bode BW. 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: 1257-1264.

[44] Perkins CM, Bode BW, Stewart MW, Cirkel DT, Yang F, Perry CR and Ambery PD. Harmony 1 year 3 Results: albiglutide vs placebo in patients with type 2 diabetes mellitus not controlled on pioglitazone (pio) +/- metformin (met). Diabetologia 2014; 57: S23.

[45] Nauck MA, Stewart MW, Perkins C, Jones-Leone A, Yang F, Perry C, Reinhardt RR and Rendell M. Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 2): 52 week primary endpoint results from a randomised, placebo-controlled trial in patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetologia 2016; 59: 266-274.

[46] Ahrén B, Matthews JE, Ye J, Carr MC and Stewart MW. Harmony 3 year 3 results: Albiglutide vs. Sitagliptin and glimepiride in patients with T2DM on metformin. Diabetes 2014; 63: A86-A87.

[47] Weissman PN, Carr MC, Ye J, Cirkel DT, Stewart M, Perry C and Pratley R. 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: 2475-2484.

[48] Home PD, Shamanna P, Stewart M, Yang F, Miller M, Perry C and Carr MC. 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: 179-187.

[49] Rosenstock J, Fonseca VA, Gross JL, Ratner RE, Ahren B, Chow FC, Yang F, Miller D, Johnson SL, Stewart MW and Leiter LA. 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: 2317-2325.

[50] Pratley RE, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, Ye J, Scott R, Johnson S, Stewart M and Rosenstock J; 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: 289-297.

[51] Leiter LA, Carr MC, Stewart M, Jones-Leone A, Scott R, Yang F and Handelsman Y. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. Diabetes Care 2014; 37: 2723-2730.

[52] Leiter LA, Gross JL, Chow F, Miller D, Johnson S and Ahren B. Once weekly glucagon-like peptide-1 receptor agonist albiglutide vs. prandial insulin added to basal insulin in patients with type 2 diabetes mellitus: results over 52 weeks. J Diabetes Complications 2017; 31: 1283-1285.

[53] Chen YH, Huang CN, Cho YM, Li P, Gu L, Wang F and Yang J. Efficacy and safety of dulaglutide monotherapy compared with glimepiride in East-Asian patients with type 2 diabetes in a multicentre, double-blind, randomized, parallel-arm, active comparator, phase III trial. Andrologia 2018; 20: 2121-2130.

[54] Nino A, Okuda I, Wilson TH, Yue L, Nakajima H, Tsuboi M, Carr MC and Seino Y. Weekly glucagon-like peptide-1 receptor agonist albiglutide as monotherapy improves glycemic parameters in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study. J Diabetes Investig 2017; 9: 558-566.

[55] Davies M, Heller S, Sreenan S, Sapin H, Adetunji O, Tahbaz A and Vora J. 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: 1368-1376.

[56] Sorli C, Harashima S-i, Tsoukas GM, Unger J, Karsbøl JD, Hansen T and Bain SC. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group,

multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol 2017; 5: 251-260.
[57] Ahren B, Masmiquel L, Kumar H, Sargin M, Karsbol JD, Jacobsen SH and Chow F. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol 2017; 5: 341-354.
[58] Aroda VR, Bain SC, Cariou B, Piletic M, Rose L, Axelsen M, Rowe E and DeVries JH. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol 2017; 5: 355-366.
[59] Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, Araki E, Chu PL, Wijayasinghe N and Norwood P. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. J Clin Endocrinol Metab 2018; 103: 2291-2301.
[60] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J and Vilsboll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016; 375: 1834-1844.
[61] Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, Thorpe KM, McMurray JJV, Del Prato S. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018; 392: 1519-1529.
[62] Scott DA, Boye KS, Timlin L, Clark JF and Best JH. A network meta-analyses 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: 213-223.
[63] Karagiannis T, Liakos A, Bekiari E, Athanasiadou E, Paschos P, Vasilakou D, Mainou M, Rika M, Boura P, Matthews DR and Tsapas A. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonists for the management of type 2 diabetes: a systematic review and meta-analyses of randomized controlled trials. Diabetes Obes Metab 2015; 17: 1065-1074.
[64] Shi FH, Li H, Cui M, Zhang ZL, Gu ZC and Liu XY. Efficacy and safety of once-weekly semaglutide for the treatment of type 2 diabetes: protocol for a systematic review and meta-analyses. Medicine (Baltimore) 2018; 97: e0420.
[65] Fahrbach JL, Fu H, Shurzinske L, Skrivanek Z and Martin S. Network meta-analyses accurately predicted the outcome of a subsequent randomised trial comparing once weekly dulaglutide 1.5 mg and once daily liraglutide 1.8 mg. Int J Clin Pract 2016; 70: 218-221.
[66] Monami M, Dicembrini I, Nardini C, Fiordelli I and Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analyses of randomized clinical trials. Diabetes Obes Metab 2013; 16: 38-47.
[67] Wang Q, Liu L, Gao L and Li Q. Cardiovascular safety of GLP-1 receptor agonists for diabetes patients with high cardiovascular risk: a meta-analyses of cardiovascular outcomes trials. Diabetes Res Clin Pract 2018; 143: 34-42.
[68] Elley CR, Kenealy T, Robinson E and Drury PL. Glycated haemoglobin and cardiovascular outcomes in people with type 2 diabetes: a large prospective cohort study. Diabetic Medicine 2008; 25: 1295-1301.
[69] Fall T, Hägg S, Ploner A, Mägi R, Fischer K, Draisma HH,Sarin AP, Benyamin B, Ladenvall C, Åkerlund M, Kals M, Esko T, Nelson CP, Kaakinen M, Huikari V, Mangino M, Meirhaeghe A, Kristiansson K, Nuotio ML, Kobl M, Grallert H, Dehghan A, Kuningas M, de Vries PS, de Bruijn RF, Willems SM, Heikkilä K, Silventoinen K, Pietiläinen KH, Legry V, Giedraitis V, Goumidi L, Syvänen AC, Strauch K, Koenig W, Lichtner P, Herder C, Palotie A, Menni C, Uitterlinden AG, Kuulasmaa K, Havulinna AS, Moreno LA, Gonzalez-Gross M, Evans A, Tregouet DA, Yarnell JWG, Virtamo J, Ferrières J, Veronesi G, Perola M, Arveiler D, Brambilla P, Lind L, Kaprio J, Hofman A, Stricker BH, van Duijn CM, Ikram MA, Franco OH, Cottel D, Dallongeville J, Hall AS, Jula A, Tobin MD, Penninx BW, Peters A, Gieger C, Samani NJ, Montgomery GW, Whitfield JB, Martin NG, Groop L, Spector TD, Magnusson PK, Amouyel P, Boomsma DI, Nilsson PM, Järvelin MR, Lyssenko V, Metspalu A, Strachan DP, Salomaa V, Ripatti S, Pedersen NL, Prokopenko I, McCarthy MI, Ingelsson E; ENGAGE Consortium. Age- and sex-specific causal effects of adiposity on cardiovascular risk factors. Diabetes 2015; 64: 1841-52.