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ORIGINAL ARTICLE

Effects of exenatide long-acting release on cardiovascular events and mortality in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Aims Patients with type 2 diabetes (T2D) have an increased risk of cardiovascular disease. Recent cardiovascular outcome trials (CVOTs) with liraglutide, semaglutide, and albiglutide have shown significant reduction in major adverse cardiovascular events. Conversely, the CVOT with exenatide long-acting release (ELAR) confirmed cardiovascular safety of the drug, but did not reached superiority versus placebo. Herein, we systematically evaluated the effect of ELAR versus placebo or active comparators on cardiovascular events and mortality in patients with T2D.

Methods We screened the literature for randomized controlled trials reporting cardiovascular events and deaths in patients receiving ELAR versus those receiving placebo or any other glucose-lowering medications. Event rates were pooled and compared using the random-effects model.

Result We retrieved 16 trials comparing the occurrence of cardiovascular events and mortality in patients treated with ELAR versus placebo or active comparators. The pooled rate ratio for cardiovascular events was similar in the two groups (0.99; 95% CI 0.92–1.06). The rate ratio for all-cause mortality was significantly lower in exenatide group than in comparators (0.87; 95% CI 0.77–0.97). When results of the EXSCEL trial were omitted, the pooled rate ratio for cardiovascular events and mortality was 0.80 (95% CI 0.40–1.63) and 0.75 (95% CI 0.30–1.84), respectively.

Conclusions Treatment with ELAR does not increase the risk of cardiovascular events and may reduce all-cause mortality.

Keywords Cardiovascular outcome trials · Safety · Pharmacology

Introduction

Diabetic patients have a higher risk of cardiovascular disease compared with those without diabetes [1]. For patients with type 2 diabetes (T2D), cardiovascular diseases are the most common cause of morbidity and mortality [2]. Therefore, reducing cardiovascular risk is one of the main goals in the management of patients with T2D. In randomized controlled trials (RCTs), intensive glycaemic control has been shown to lead to a significant reduction in microvascular complications [3], but results on macrovascular complications are more controversial [4, 5]. Moreover, some glucose-lowering medications (GLMs) showed negative cardiovascular outcomes [6]. Therefore, since 2008, the US Food and Drug Administration (FDA) issued guidance for industry, requiring that all new GLMs entering the market display cardiovascular safety in dedicated cardiovascular outcome trials (CVOTs).

Glucagon-like peptide-1 receptor agonists (GLP-1RA) reduce blood glucose, body weight, and blood pressure and improve lipid levels [7]. Hence, cardiovascular benefit of these agents is plausible. To date, five CVOTs with different GLP-1RA have been published. Cardiovascular safety has been robustly confirmed for all GLP-1RA, but heterogeneity was observed in relation to protective effects. In the ELIXA trial, the use of lixisenatide in patients with T2D and with a recent acute coronary syndrome showed no significant

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difference in cardiovascular outcomes compared to placebo [8]. In contrast, treatment with liraglutide in LEADER trial, semaglutide in SUSTAIN-6 trial, and albiglutide in HARMONY trial was associated with a significant reduction in the risk of a 3-point major adverse cardiovascular event (MACE) compared to placebo [9–11]. The EXSCEL trial confirmed safety of exenatide long-acting release (ELAR), but superiority was not demonstrated for the primary endpoint of 3-point MACE: Although the incidence of the primary end point was nominally lower in the ELAR group than in placebo group, it did not achieve statistical significance ($p = 0.06$) [12].

The aim of the present meta-analysis was to evaluate the effects of ELAR compared to placebo or active comparators on cardiovascular events and overall mortality in patients with T2D.

Materials and methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [13] and registered in PROSPERO: International prospective register of systematic reviews (CRD42018087913).

Data sources, searches, and study selection

All RCTs on ELAR published in English up to December 2018 were retrieved from Medline/EMBASE and from www.clinicaltrial.gov website. The search string was [("exenatide AND ("QW" OR "weekly" OR "long-acting" OR "extended release") AND ("randomized controlled trial" OR "trial" OR "RCT" OR "diabetes")]. Systematic reviews and meta-analyses of GLP-1RA were examined for identifying further relevant studies. The meta-analysis was performed including all RCTs on adult patients with T2D, comparing ELAR with placebo or any other GLMs with duration of treatment of at least 24 weeks. A lower duration of treatment was deemed unlikely to show effects on cardiovascular event rates.

Data extraction and quality assessment

Study selection and data extraction were performed independently by two of the authors (BMB and GPF), and any disagreement was resolved by a third investigator (AA). Results of trials were retrieved from the published articles and, if unavailable, from study results on www.clinicaltrials.gov. The following data were extracted from eligible studies: first author, year of publication, NCT number, study duration, sample size, patient characteristics including mean age, baseline measures (HbA1c, BMI), mean duration of diabetes, background GLMs, and safety/efficacy outcomes (cardiovascular events and deaths). When trials reported outcomes for different times of follow-up, the longest was used. Quality of trials was assessed using the Cochrane Collaboration's Tool for Assessing Risk of Bias in randomized controlled trials (random sequence generation, allocation concealment, blinding of participants and personnel, blinding outcome assessment, incomplete outcome data, and selective reporting) [14].

Data synthesis and analysis

The outcome of this analysis was the effect of ELAR on cardiovascular events and mortality in patients with T2D compared to placebo or other GLMs. Cardiovascular outcomes included myocardial infarction, acute coronary syndrome, unstable angina, heart failure, cardiac arrest, stroke, or brain stem infarction. For mortality, it was considered only all-cause mortality. For the EXSCEL study, we considered the following cardiovascular outcomes: fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospitalization for heart failure, hospitalization for acute coronary syndrome. When the study design included two arms with different dosages of a single drug or different comparator drugs, these were pooled.

Continuous data are expressed as mean and categorical data as percentages. Considering the different durations of follow-up of the studies, we assessed the person-time of follow-up and calculated the rate ratio as previously suggested [15]. Because of the differences across trials in terms of inclusion criteria and follow-up, the meta-analysis was performed using a random-effects model. Heterogeneity among studies was assessed by using I^2 statistics.

A sensitivity analysis was performed for all endpoints, excluding EXSCEL trial, the only CVOT retrieved. For all the principal endpoints, a sensitivity analysis was performed with continuity correction, in order to exclude publication bias.

MetaXL (EpiGear International) version 5.3 was used for the analysis.

Results

The search retrieved 462 articles, 446 of which were excluded for one or more of the following reasons: not investigating the LAR formulation of exenatide, not investigating the elected topic; being meta-analyses; being reviews; being observational studies; not involving humans; not involving T2D; lack of control group (Fig. 1). Details on the study populations, treatments, and trial durations of the studies included in the meta-analysis are presented in Table 1. Retrieved trials included a total of 22,003 patients: 10,801 treated with exenatide LAR and 11,202 treated with placebo

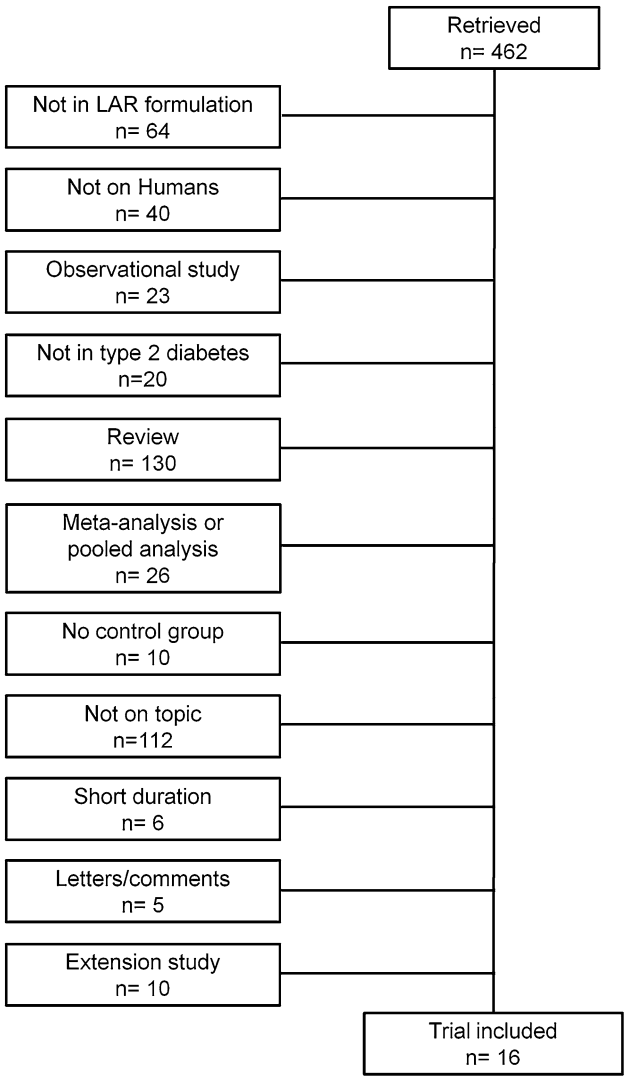

Fig. 1 Trial flow summary

or active comparator. The average follow-up was 134 weeks (2.5 years). The mean age, BMI, baseline HbA1c, and duration of diabetes of enrolled patients were 59 years, 31.8 kg/m^2, 8.2%, and 10.5 years, respectively.

Risk of bias assessments is described in Fig. 2. In general, most of the domains for the sixteen studies were considered to have a low risk of bias. The most common source of bias was the absence of blinding in phase III RCTs with an open-label design.

Results of the meta-analysis showed that 1506 patients (13.9%) in ELAR group and 1539 patients (13.7%) in comparator group experienced a cardiovascular event (rate ratio 0.99; 95% CI 0.92–1.06) (Fig. 3). There was no significant difference between the two groups, suggesting that treatment with exenatide LAR was not associated with an increase in the risk of cardiovascular events. In detail, no significant differences were found in individual cardiovascular outcomes. No significant heterogeneity was found among the studies ($I^2 = 0\%$). The funnel plot analysis was symmetrical, suggesting no publication bias (Figure S1).

A small number of cardiovascular events occurred in RCTs excluding the EXSCEL study (Table 2). When results of the EXSCEL trial were omitted from the meta-analysis, the pooled rate ratio for cardiovascular events was (0.80; 95% CI 0.40–1.63), meaning that treatment with ELAR was associated with nominally lower numbers of events, but not significantly (Fig. 4).

As far as all-cause mortality is concerned, patients treated with ELAR had a significantly lower rate of death than those treated with placebo/active comparators (509 [4.7%] vs. 591 [5.2%]; rate ratio, 0.87; 95% CI 0.77–0.97) (Fig. 3). No significant heterogeneity was found among the studies ($I^2 = 0\%$). The funnel plot analysis suggested no substantial publication bias (Figure S1).

When results of the EXSCEL trial were omitted, two patients in the ELAR group and six patients in the control group died. No significant difference was found in the rate ratio for mortality in the two groups (0.75; 95% CI 0.30–1.84) (Fig. 4).

Discussion

This meta-analysis shows that ELAR has an optimal safety profile concerning cardiovascular risk in patients with T2D and is associated with a significant reduction in all-cause mortality, although this latter finding is driven mainly by results of the EXSCEL study.

In recent years, GLP-1RA have attracted great interest for potential protective cardiovascular effects [16]. Such expectations have been confirmed by results of CVOTs, showing that a treatment with liraglutide, semaglutide, or albiglutide was associated with a significant reduction in cardiovascular events compared with placebo in T2D patients with established CVD [9, 10, 17]. Conversely, lixisenatide was not associated with cardiovascular protection compared to placebo in T2D patients after a cardiovascular event [8]. Results concerning ELAR were controversial because, in the EXSCEL study, reduction in the 3-point MACE in patients randomized to ELAR versus those randomized to placebo was close to statistical significance [12]. A fragility analysis performed according to Walter [18] suggests that statistical significance for superiority of ELAR versus placebo in protecting against 3-point MACE was missed for just four patients experiencing a MACE in the ELAR group (removing four events in the ELAR group yields a p value < 0.05 for MACE in favor or ELAR). With such a small critical difference, we reasoned that pooling results of the EXSCEL study with those of other RCTs available in the literature

Table 1 Baseline characteristics of trials and populations included in the meta-analysis

References	NCT number	Comparator drugs	Background therapy	Trial duration (weeks)	Number of patients	Mean HbA1c (%)	Mean Age (year)	Mean duration of diabetes (year)	Mean BMI (kg/m^2)
Drucker [29]	NCT00308139	Exenatide BID	OAD	30	295	8.3	55	6.7	35
Bergenstal [30]	NCT00637273	Sita, Pio	Met	26	491	8.5	52	6	32
Diamant [31]	NCT00641056	Glargine	OAD	84	456	8.3	58	7.9	32
Russel-Jones [32]	NCT00676338	Met, Pio, Sita	Diet	26	820	8.5	54	2.7	31.2
Blevins [33]	NCT00877890	Exenatide BID	Diet, Met, SU, TZD	24	252	8.4	55	7	33.3
Buse [26]	NCT01029886	Liragutide	Diet, Met, SU, TZD	26	911	8.5	57	8.5	32.3
Guja [34]	NCT02229383	PLB	Glargine ± Met	28	463	8.5	58	11.3	33.7
Jabbour [27]	NCT02229396	Dapagliflozin	Met	52	457	9.3	55	7.3	33
Wysham [35]	NCT01652716	Exenatide BID	Diet, Met, SU, TZD	28	375	8.5	56	8.6	33
Gadde [36]	NCT01652729	Sita, PLB	Met	28	364	8.4	54	8.3	31.8
Davies [37]	NCT01003184	Detemir	Met ± SU	26	216	8.4	58	NA	33.7
Inagaki [38]	NCT00935532	Glargine	Met ± TZD	26	427	8.5	57	9	26.2
Ji [39]	NCT00917267	Exenatide BID	Met, SU, TZD	26	678	8.7	56	8.2	26.6
Abdul-Ghani [40]	NCT02887625	Basal ± bolus insulin	Met + SU	52	231	10	52	10.7	30.8
Ahmann [28]	NCT01885208	Semaglutide	Met, SU, TZD	56	809	8.3	56	9.2	33.8
Holman [12]	NCT01144338	PLB	OAD, insulin	180	14,752	8	62	12	31.8

BID bis in die, *OAD* oral anti-diabetic drugs, *Sita* sitagliptin, *Pio* piglitazone, *Met* metformin, *SU* sulphonylureas, *TZD* thiazolidinedione, *PLB* placebo, *NA* not available

would help moving the risk estimate toward significance or definitely away from it.

In the present study, we confirm results of EXSCEL trial for what concerns cardiovascular safety of ELAR, but without showing any trend toward reduction in cardiovascular events. The reason why the trend toward cardiovascular protection was not confirmed for ELAR is that we herein considered a broader outcome compared to the 3-point MACE, also including other types of cardiovascular events, usually recorded for safety reasons in phase III RCTs.

Heterogeneity in the results of CVOTs investigating different GLP-1RA may be due to different reasons. First, GLP-1RA differ in their pharmacokinetic properties: Lixisenatide is considered "short acting" because of his short duration of action. Unlike "long-acting" GLP-1RA, lixisenatide is not supposed to allow circulating drug concentrations within the therapeutic range throughout 24 h [19]. It has been also postulated that structural similarities to human GLP-1 could play a role in the different cardiovascular results observed of CVOTs investigating GLP-1RA. Exenatide and lixisenatide have only 50% of sequence homology with human GLP-1. Conversely, liraglutide and semaglutide reach more than 90% sequence homology [20]. Moreover, differences in the population included in the studies could be a relevant factor. In EXSCEL, only 73% of patients had established CVD at baseline. In contrast, in LEADER, SUSTAIN-6, and HARMONY, 81%, 83%, and 100% of the population, respectively, were in secondary prevention [9–12]. For ELAR, one of the reasons of failure to reach statistical significance may be the high rate of treatment discontinuation (44%). Despite such a limited drug exposure, the nearly significant 9% reduction in MACE may be noteworthy. Whether cardiovascular protection by GLP-1RA is a class effect is still under debate, and ongoing CVOTs investigating other GLP-1RA (PIONEER, FREEDOM-CVO) [21–23] are expected to provide further information about this issue. Headlines on the anticipated results of the REWIND study suggest further evidence that the class effect may extend to dulaglutide [24].

EXSCEL and LEADER showed a reduction in overall mortality in patients treated with ELAR or liraglutide, respectively, versus placebo. Conversely, SUSTAIN-6 and HARMONY did not show a reduction in mortality in patients treated with semaglutide or albiglutide, respectively. This meta-analysis confirmed a reduction in all-cause mortality in patients treated with ELAR. It should, however, be noted that this finding was mostly driven by results of the EXSCEL study. After removing EXCEL from the meta-analysis, the difference in the pooled rate ratio between ELAR and comparators was no longer significant.

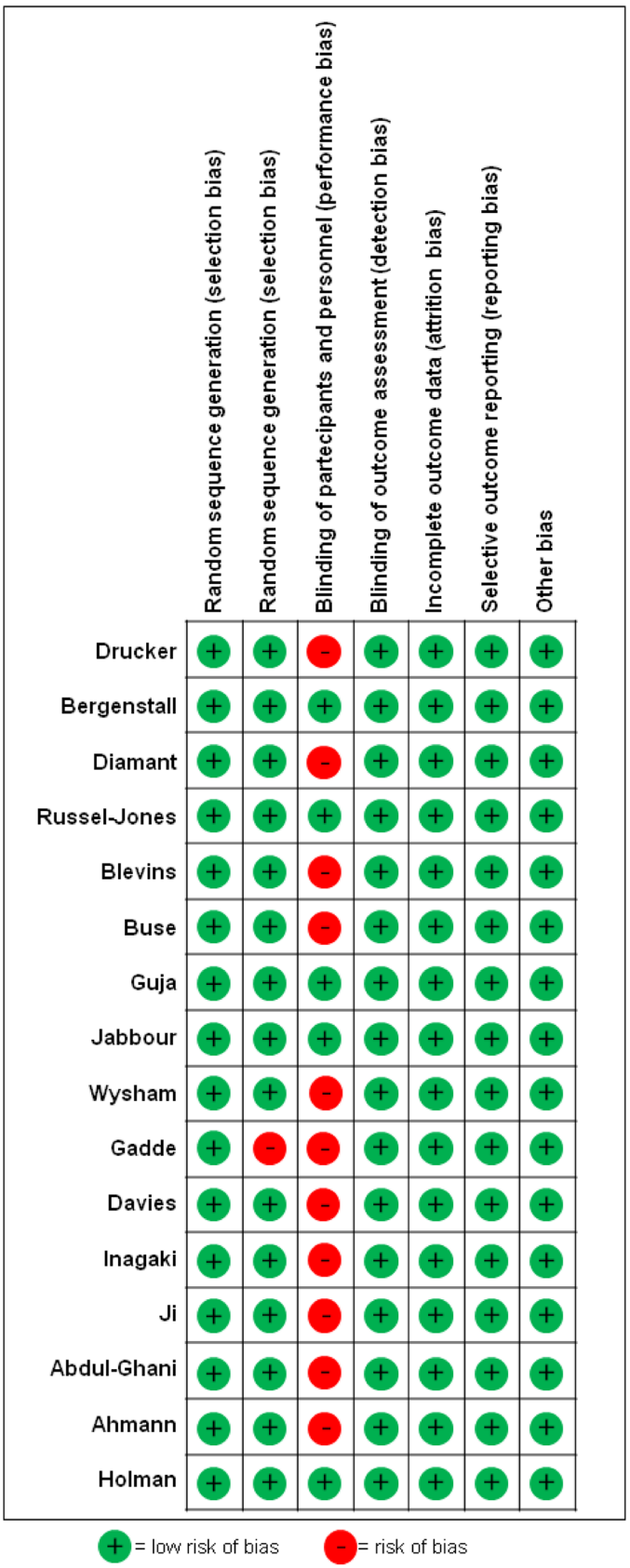

Fig. 2 Quality assessment of trials included in the meta-analysis. Randomized controlled trials (RCTs) included in the meta-analysis were evaluated for the risk of bias using the Cochrane risk of bias tool. Most of the included studies were found to be at low risk of bias, except for performance bias; in fact, some of the studies were open label

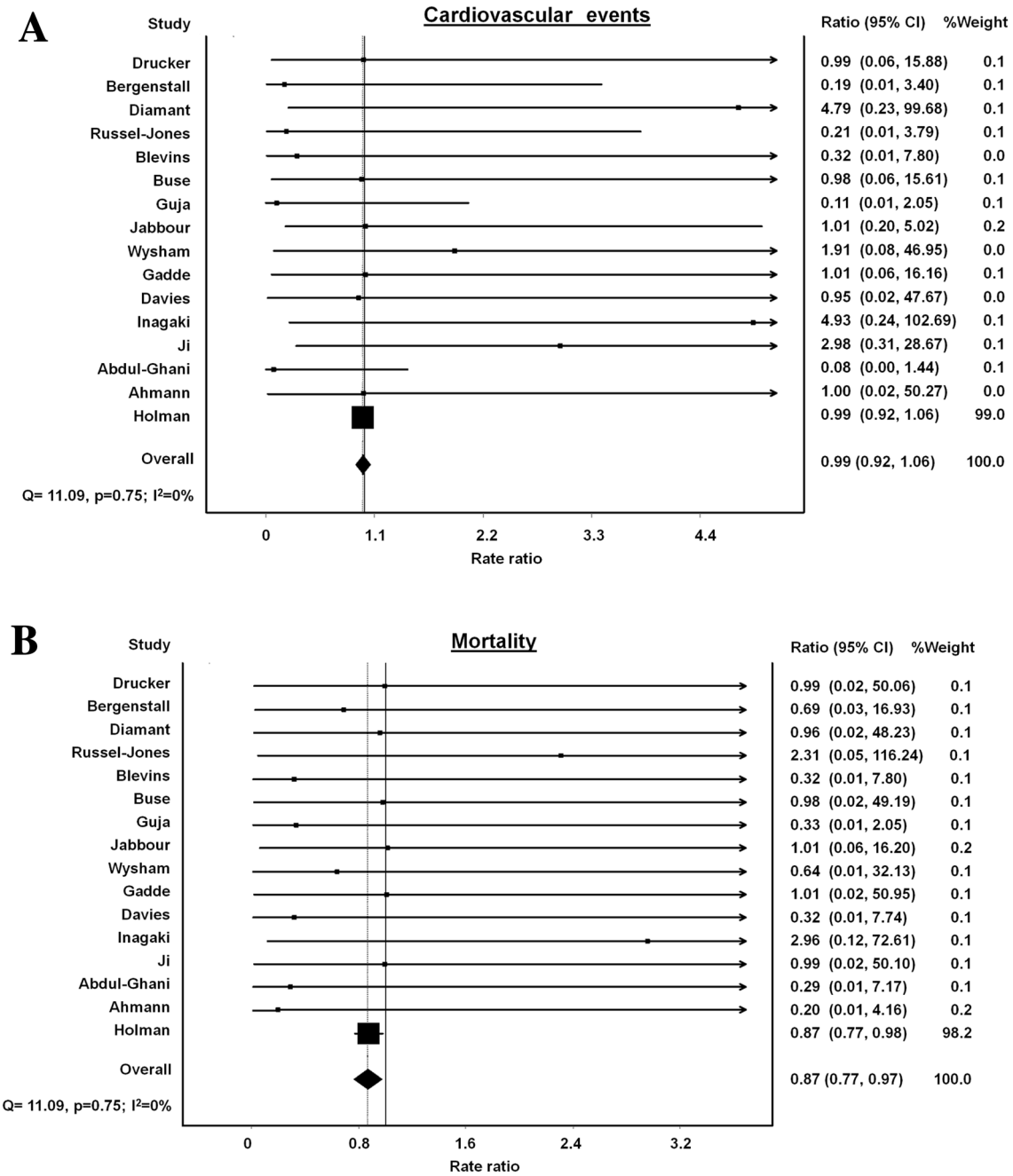

Fig. 3 Forest plots of the primary analysis. Rate ratio with 95% confidence intervals for cardiovascular events (**a**) and all-cause mortality (**b**) in each study and in the pooled estimate is given in the tables on the right. Random-effects model has been used

In EXSCEL, deaths were classified as cardiovascular, non-cardiovascular, or unknown. Cardiovascular deaths included sudden cardiac death or death due to acute myocardial infarction, heart failure or cardiogenic shock, cerebrovascular event (intracranial hemorrhage or non-hemorrhagic stroke), or other cardiovascular causes (e.g., dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Unknown deaths were those that could not be classified as either cardiovascular or non-cardiovascular by the Clinical Events Classification Committee. A large number of deaths due to unknown cause (110 [21.7%] in the ELAR group and 142 [24.3%] in placebo group) were considered of cardiovascular origin in all analyses assessing cardiovascular deaths. This concern about reliability of adjudication of the causes of death should be carefully taken into consideration when assessing the reasons why no significant effect was noted for ELAR on cardiovascular mortality.

Table 2 Description of cardiovascular and mortality outcomes considered in the meta-analysis

References	Myocardial infarction/ acute coronary syndrome		Unstable angina		Cardiac arrest		Heart failure		Stroke/brain stem infarction		All-cause death	
	Exe LAR	Comparator	Exe LAR	Comparator	Exe LAR	Comparator	Exe LAR	Comparator	Exe LAR	Comparator	Exe LAR	Comparator
Drucker [29]	1	0	0	0	0	1	0	0	0	0	0	0
Bergenstal [30]	0	2	0	1	0	0	0	0	0	2	0	1
Diamant [31]	2	0	0	0	1	0	0	0	1	0	0	0
Russel-Jones [32]	0	2	0	1	0	0	0	1	0	1	0	0
Blevins [33]	0	1	0	0	0	0	0	0	0	0	0	1
Buse [26]	1	0	0	0	0	0	0	0	0	1	0	0
Guja [34]	0	1	0	1	0	0	0	2	0	0	0	1
Jabbour [27]	2	2	1	0	0	0	0	0	0	1	1	1
Wysham [35]	1	0	0	0	0	0	0	0	0	0	0	0
Gadde [36]	0	1	0	0	0	0	0	0	1	0	0	0
Davies [37]	0	0	0	0	0	0	0	0	0	0	0	0
Inagaki [38]	0	0	0	0	0	0	1	0	1	0	1	0
Ji [39]	1	1	0	0	0	0	0	0	2	0	0	0
Abdul-Ghani [40]	0	4	0	0	0	0	0	0	0	1	0	1
Ahmann [28]	0	0	0	0	0	0	0	0	0	0	0	0
Holman [12]	1085	1063	NA	NA	NA	NA	219	231	187	218	507	584

NA not available

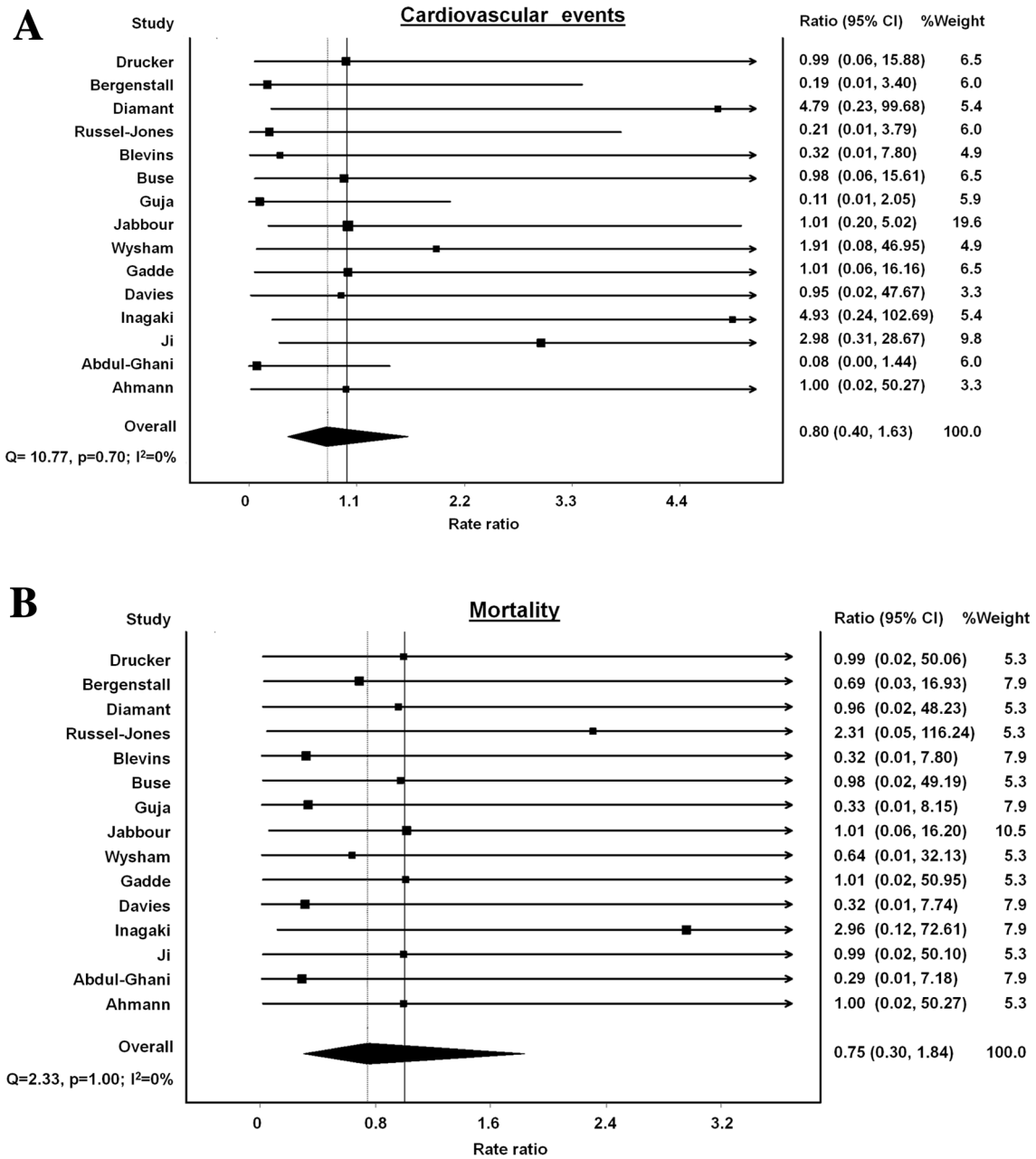

Fig. 4 Forest plots of the secondary analysis without EXSCEL. Rate ratio with 95% confidence intervals for cardiovascular events (**a**) and all-cause mortality (**b**) in each study, excluding EXSCEL, and in the pooled estimate is given in the tables on the right. Random-effects model has been used

There are some limitations of this meta-analysis that we wish to acknowledge. The short follow-up duration of some studies likely reduced the probability of yielding reliable estimates of cardiovascular protection. In fact, most of the non-cardiovascular phase III RCTs had a follow-up of 24–26 weeks. It is also possible that baseline characteristics of participants may have influenced the assessment of the cardiovascular efficacy. Patients enrolled in CVOTs were older, with a longer duration of diabetes, and more comorbidities with respect to patients enrolled in other studies included in this meta-analysis. This translated into a low rate of cardiovascular events observed in the non-cardiovascular phase III RCTs that, consequently, had a low weight in the meta-analysis. Most patients enrolled in these studies were likely to be at low cardiovascular risk because exclusion criteria typically list recent cardiac disease or abnormal ECG, renal disease (eGFR < 60 ml/min or ACR > 300 mg/g creatinine). Hence, these studies were likely underpowered

for the assessment of cardiovascular safety or efficacy. On the other hand, they are quite representative of patients with diabetes referred to outpatient clinic, which have cardiovascular diseases in about 20% of cases [25]. A further limitation of this meta-analysis is the lack of independent adjudication of cardiovascular events in many of the smaller studies, which can lead to the possibility of misdiagnosis. Finally, in some studies, the active comparator was a drug that has shown a cardiovascular benefit [26–28] and this may have interfered with the results. In DURATION-6 [26], where the treatment with ELAR was compared to liraglutide, the number of cardiovascular events and deaths was the same in the two groups. Similar results were found in SUSTAIN-3 [28] sand DURATION-8 [27]. In the former, patients with T2D were randomized to receive semaglutide or ELAR: No patients experienced cardiovascular events. In the latter, no differences in terms of cardiovascular events were found in the ELAR group as compared to the dapagliflozin group. An analysis of ELAR phase III trials yielded a point estimate for cardiovascular events < 1.0 with a 95% upper confidence limit comprised between 1.3 and 1.8, thereby advocating the need for a dedicated CVOT. The major strength of this meta-analysis is that it is the first that analyzed all RCTs with ELAR, including EXSCEL, yielding a large number of patients. Another strength is the inclusion of a broad population that is representative of the general T2D population, which is often not considered in CVOTs. Despite that statistical significance for cardiovascular events in the EXSCEL trial was missed for just four events, adding data from smaller RCTs did not yield a pooled risk estimate in favor of ELAR. Nor the signal for a protective effect of ELAR against all-cause mortality rates was confirmed in smaller RCTs, despite a nonsignificant trend. Therefore, this meta-analysis helps putting results of EXCEL in the perspective of other available literature on cardiovascular effects of ELAR. In conclusion, the present data suggest that treatment of patients with T2D with exenatide LAR for up to 134 weeks does not increase the risk of cardiovascular events. Though based on the results of the EXSCEL trial, ELAR may reduce all-cause mortality, and this cannot be concluded on the basis of the trial hierarchical outcome testing.

Compliance with ethical standards

Conflict of interest GPF received grant support, lecture, or advisory board fees from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Novo-Nordisk, Sanofi, Genzyme, Abbott, Novartis, Merck Sharp & Dohme. BMB received lecture or advisory board fees from Novartis, Eli Lilly, AstraZeneca, and Boehringer-Ingelheim. AA received research grants, lecture, or advisory board fees from Merck Sharp & Dome, AstraZeneca, Novartis, Boehringher-Ingelheim, Sanofi, Mediolanum, Janssen, NovoNordisk.

Ethical approval Not applicable.

Informed consent Not applicable.

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