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The Time-Varying Cardiovascular Benefits of Glucagon-Like Peptide-1 Receptor Agonist Therapy in Patients with Type 2 Diabetes Mellitus: Evidence from Large Multinational Trials

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ORIGINAL ARTICLE

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The time-varying cardiovascular benefits of glucagon-like peptide-1 receptor agonist therapy in patients with type 2 diabetes mellitus: Evidence from large multinational trials

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Abstract

Aims: To evaluate the time-varying cardio-protective effect of glucagon-like peptide-1 receptor agonists (GLP-1RAs) using pooled data from eight contemporary cardiovascular outcome trials using the difference in the restricted mean survival time (ΔRMST) as the effect estimate.

Material and Methods: Data from eight multinational cardiovascular outcome randomized controlled trials of GLP-1RAs for type 2 diabetes mellitus were pooled. Flexible parametric survival models were fit from published Kaplan-Meier plots. The differences between arms in RMST (ΔRMST) were calculated at 12, 24, 36 and 48 months. ΔRMST values were pooled using an inverse variance-weighted random-effects model; heterogeneity was tested with Cochran's Q statistic. The endpoints studied were: three-point major adverse cardiovascular events (MACE), all-cause mortality, stroke, cardiovascular mortality and myocardial infarction.

Results: We included eight large (3183-14 752 participants, total = 60 080; median follow-up range: 1.5 to 5.4 years) GLP-1RA trials. Among GLP-1RA recipients, we observed an average delay in three-point MACE of 0.03, 0.15, 0.37 and 0.63 months at 12, 24, 36 and 48 months, respectively. At 48 months, while cardiovascular mortality was comparable in both arms (pooled ΔRMST 0.163 [−0.112, 0.437]; $P = 0.24$), overall survival was higher (ΔRMST = 0.261 [0.08-0.43] months) and stroke was delayed (ΔRMST 0.22 [0.15-0.33]) in patients receiving GLP-1RAs.

Conclusions: Glucagon-like peptide-1 receptor agonists may delay the occurrence of MACE by an average of 0.6 months at 48 months, with meaningfully larger gains in patients with cardiovascular disease. This metric may be easier for clinicians and patients to interpret than hazard ratios, which assume a knowledge of absolute risk in the absence of treatment.

KEYWORDS
cardiovascular outcomes trials, clinical trials, GLP receptor agonist, systematic review, type II diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health concern that leads to significant morbidity and mortality.[1] The global prevalence of T2DM in 2030 is projected to be 366 million.[2] In the United States, atherosclerotic cardiovascular disease (ASCVD) is present in approximately 50% of patients with T2DM and is, in fact, the leading cause of death in such patients.[3,4] Due to concern regarding the cardiovascular safety of rosiglitazone, since 2008, every new drug trial involving treatment for diabetes mellitus was required to undergo a cardiovascular safety evaluation.[5] Cardiovascular outcome trials (CVOTs) of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs), while designed to ensure cardiovascular safety, have reported a significant reduction in adverse cardiovascular events. To date, five trials (REWIND, LEADER, SUSTAIN-6, Harmony Outcomes, and Amplitude-O) of dulaglutide, liraglutide, semaglutide, albiglutide and efpeglenatide, respectively, have demonstrated positive cardiovascular results.[6-10] A recent meta-analysis pooled data from eight large randomized CVOTs.[11] On pooled analysis, these drugs were found to lead to relative reductions in major adverse cardiovascular event (MACE) rates, cardiovascular mortality and myocardial infarction of 14%, 12% and 11%, respectively. In fact, both the European and United States professional societies recommend that these agents be considered as first-line therapy for all T2DM patients with ASCVD or with significantly elevated risk of ASCVD.[12,13]

Trials in medicine often attempt to enumerate the treatment effect over an observed time period. Testing for, or assuming, proportional hazards and presenting the overall treatment effect as a hazard ratio (HR) is the traditional method for reporting results.[14] However, HRs are difficult to interpret[14] and are meaningless without knowledge of the absolute risk of events over a given period of follow-up in the absence of treatment. Moreover, if the treatment is beneficial and delays the endpoint, the proportional hazards assumption may be violated.[14] Restricted mean survival time (RMST) is the average survival time from the beginning to a specific time point during the follow-up (Figure S1).[15] Importantly, difference in RMST (ΔRMST) between treatment arms is an easy, reliable, and model-free estimate of the treatment benefit, expressed on a meaningful scale.[15] Depending on study design, it can also be presented in easily understood units of time (days, months, years). This measure has been routinely adopted to interpret and pool data from oncology trials.[16] Although a recent randomized trial on the use of direct oral anticoagulants after valve replacement used RMST for its primary prespecified analytical method,[17] this measure is rarely used for cardiovascular drug trials. We applied this method, therefore, to help interpret the results of large multinational randomized controlled trials evaluating the cardiovascular benefits of GLP-1RA therapy. We calculated the difference in RMST between treatment and control arms at specific time points and pooled trial estimates using a random-effect model. In doing so, we hoped to demonstrate the feasibility and utility of applying the RMST method for producing effect estimates, which are easier to understand and clinically interpret.

2 | METHODS

There has already been a recent meta-analysis in which a thorough systematic review of the available literature was performed.[11] Trials included in that review were selected for analysis in our study. We further evaluated the full text of these trials to ensure that results were presented graphically as Kaplan-Meier (KM) plots and not simply as HRs.

Post hoc analyses of trials may not be adequately powered to evaluate secondary outcomes; such trials were therefore excluded, even if they reported cardiovascular outcomes as their endpoints. The protocol for our meta-analysis was prospectively registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (ID - INPLASY202170097; doi: 10.37766/inplasy2021.7.0097). The study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

2.1 | Study quality assessment

Study quality and bias were independently evaluated by two authors (S.M., S.V.D.) using the Cochrane risk-of-bias tool and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria, respectively. The PRECIS-2 (Pragmatic Explanatory Continuum Indicator summary) tool, a set of nine questions pertaining to study design, each scored on a five-point scale, was used to evaluate whether the trial was more explanatory or more pragmatic in nature (Figure S2).[18]

2.2 | Selection of endpoints

The primary endpoint evaluated in seven trials was three-point major adverse cardiovascular events (MACE), defined as a composite of cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke. The ELIXA trial reported a four-point MACE endpoint (unstable angina, cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke). Secondary endpoints evaluated in our study were cardiovascular mortality, all-cause mortality, stroke and myocardial infarction. The survival curves for the selected endpoints were collected from each eligible trial publication. The total number of patients randomized to each arm of the study, the number of patients at risk at specific time periods during the observation period and the total number of events in each arm were abstracted from the information provided in each of the included studies.

2.3 | Statistical Analysis

The published survival curves were individually imported as large images into ScanIt, a digitizing software.[19] The survival lines for each arm were then traced and the corresponding coordinate data were abstracted. From this information, the survival curves were then reconstructed using the method described by Guyot et al.[20] Among tools available to obtain information from published KM curves, the Guyot method has been

TABLE 1 Brief overview of included trials with information regarding follow-up times, primary endpoint event rates and the completeness of follow-up

	EXCSEL (n = 14 752)	ELIXA (n = 6068)	LEADER (n = 9340)	Sustain-6 (n = 3297)	REWIND (n = 9901)	Harmony outcomes (n = 9463)	Pioneer 6 (n = 3183)	AMPLITUDE-O (n = 4076)
Year study published	2017	2015	2016	2016	2019	2018	2019	2021
Drug studied	Exenatide	Lixisenatide	Liraglutide	Semaglutide	Dulaglutide	Abiglutide	Semaglutide (oral)	Efpeglenatide
Pharmacology	Exendin-4 analogue	Exendin-4 analogue	GLP-1 homologue	GLP-1 homologue	GLP-1 homologue	GLP-1 homologue	GLP-1 homologue	Exendin-4 analogue
Median/Total follow-up time	3.2 (2.2-4.4) years/5 years	25 months/38 months	3.5 years /54 months	2.1 years /109 weeks	5.4 (5.1-5.9) years /6 years	1.5 years /28 months	15.9 (0.4-20) months /83 weeks	1.81 (1.69-1.98) years /24 months
Established ASCVD	73%	100%	81%	83%	31%	100%	85%	89.6%
Endpoints included in our analysis	3-part MACE, CV mortality, All-cause mortality	4-part MACE	3-part MACE, CV mortality, All-cause mortality, Myocardial infarction	3-part MACE, CV mortality, Myocardial infarction	3-part MACE, CV mortality, Myocardial infarction	3-part MACE,CV mortality, Myocardial infarction	3-part MACE	3-part MACE
Event rate for primary outcome (per 100 patient-years) (SC/CC)	3.7/4	6.4/6.3	3.4/3.9	3.24/4.4	2.35/2.66	4.57/5.87	2.9/3.7	3.1/5.9
Completeness of follow-up	98.8%	98.9%	99.7%	99.6%	97.1%	99.3%	100%	99.9%
Participants that completed the trial	96.2 %	96.2%	96.8%	–	–	–	99.7%	–

Abbreviations: CC, control cohort; CV, cardiovascular; SC, study cohort; MACE, major adverse cardiovascular event.

observed to be the most reliable.[21] For each available trial endpoint, a flexible Royston and Parmar parametric model with three cubic spline terms and a time-varying covariate (treatment arm) was fitted. Rather than using a fixed mathematical distribution such as the exponential, Weibull or log-normal models, using spline segments lends flexibility and allows for a more reliable fit to data, especially in the presence of non-proportional hazards. For each trial, the model fit was evaluated by graphing the fitted parametric curve and the non-parametric KM curve together. Model fits using the flexible parametric model were excellent, as shown in Figure S4. This was also observed at the tails of the distribution; therefore, we were able to reliably extrapolate trial effects beyond their original duration. In studies where data were not directly available, these flexible parametric models were used to obtain the ΔRMST. This mathematical modelling was performed with the assumption that the observed treatment effect was constant during the extended follow-up (until 48 months). Using information generated from the fitted models, ΔRMST values for all trials were obtained at 12-, 24-, 36- and 48-month follow-ups for three-/four-point MACE and at 24- and 48-month follow-ups for the other endpoints. To obtain summary estimates, the ΔRMST values derived from each trial were pooled using the DerSimonian and Laird random-effects method and inverse variance weighting.[22] Inter-study heterogeneity was assessed using the I^2 index and Cochran´s Q test. I^2 index values ≤25%, 26% to 50% and >50% indicated low, moderate and high degrees of heterogeneity, respectively, and Cochran´s Q statistic $P< 0.05$ suggested significant heterogeneity. Statistical analyses were performed in R 4.0.2 (R Foundation for Statistical Computing). Packages used in analyses were: metafor (version 3.0-2),[23] metaRMST (version 1.1.0)[24] and rstpm2 (version 1.5.2).[25]

2.4 | Sensitivity analysis

A sensitivity analysis was performed using various methods. Firstly, ΔRMST values were also calculated from the KM estimates (KM model) at the same timepoints and were pooled using the same random-effects method. These two estimates (from the parametric and KM models) were then graphed (red and blue squares in all presented forest plots) and visually compared for overlap, an indicator that both values were not statistically different from each other.

Secondly, our primary endpoint (three-point MACE) was also re-analysed by excluding results of the ELIXA trial. Unlike the other trials pooled, ELIXA included only patients with acute coronary syndrome, used lixisenatide, a very short-acting exendin-4 analogue, and reported a slightly different composite endpoint. The analysis for three-/four-point MACE was also repeated, selecting studies which primarily included participants with established stable ASCVD (>85% at enrolment). Thirdly, to evaluate the consistency between the absolute and relative effect estimates, semi-parametric Cox proportional hazards models were fit for the data of each trial at 24 and 48 months. From these models, the HR for the treatment arm versus control arm was calculated. The log transformed HRs from each trial were then pooled using the DerSimonian and Laird random-effects model with inverse variance weighting.

Lastly, for each trial and each studied endpoint, we calculated the ratio of the restricted mean time lost (RMTL) for the GLP-1RA versus the control group, and abstracted the corresponding reported HR. These RMTL ratios (explained further in Appendix S1) and HRs were separately pooled using a random-effects inverse variance-weighted model. Our observation (Figure S3) that these two summary estimates are numerically quite similar further supports the validity of our ΔRMST method.

3 | RESULTS

3.1 | Overview of included trials

In our study, the ΔRMST for included endpoints was calculated from graphs published in eight trials (totalling 60 080 participants).[6-10,26-28] Study participation ranged from 3183 (semaglutide; Pioneer-6) to

TABLE 2 Results obtained using the parametric and the Kaplan-Meier method for each studied endpoint

Endpoint studied	Time point, months	Parametric method	*P* value	Heterogeneity, I^2	Trials pooled (KM method)	KM method (sensitivity analysis)	*P* value
Three-point MACE	12	0.035 (0.014, 0.056)	0.001	0% ($P = 0.63$)	8	0.034 (0.012, 0.057)	0.002
	24	0.158 (0.083, 0.233)	<0.001	25% ($P = 0.22$)	6	0.154 (0.081, 0.227)	<0.001
	36	0.368 (0.178, 0.558)	<0.001	54% ($P = 0.03$)	3	0.188 (0.007, 0.368)	0.04
	48	0.627 (0.27, 0.984)	<0.001	60% ($P = 0.01$)	2	0.381 (0.089, 0.673)	0.01
Stroke	24	0.052 (0.020, 0.085)	0.001	0% ($P = 0.82$)	4	0.065 (0.029, 0.101)	<0.001
	48	0.204 (0.100, 0.308)	<0.001	0% ($P = 0.80$)	2	0.222 (0.105, 0.338)	<0.001
All-cause mortality	24	0.055 (0.003, 0.107)	0.03	0% ($P = 0.73$)	2	0.054 (0, 0.108)	0.04
	48	0.261 (0.085, 0.437)	<0.01	0% ($P = 0.95$)	2	0.266 (0.087, 0.443)	<0.001
Cardiovascular mortality	24	0.04 (−0.03, 0.12)	0.30	59% ($P = 0.02$)	3	0.02 (−0.01, 0.06)	0.30
	48	0.163 (−0.112, 0.437)	0.24	56% ($P = 0.04$)	2	0.142 (−0.08, 0.442)	0.35
Myocardial infarction	24	0.08 (0.018, 0.143)	0.01	0% ($P = 0.5$)	3	0.081 (0.017, 0.144)	0.01
	48	0.416 (−0.021, 0.853)	0.06	74% ($P = 0.01$)	2	0.197 (−0.003, 0.397)	0.05

Abbreviations: KM, Kaplan-Meier; MACE, major adverse cardiovascular event.

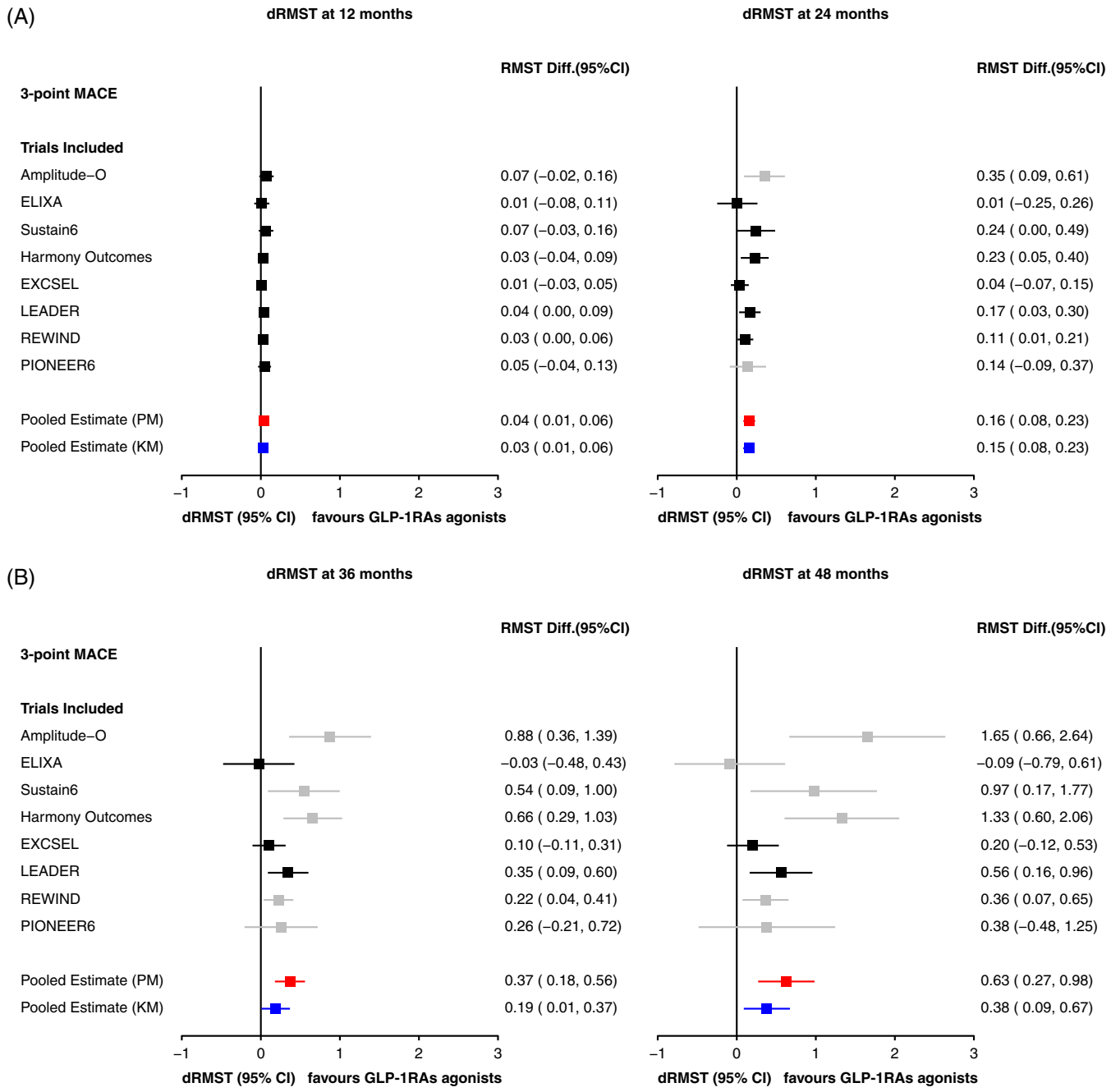

FIGURE 1 Endpoint studied: three-/four-point major adverse cardiovascular events (MACE). This panel of forest plots presents the difference in restricted mean survival time (ΔRMST) obtained for each trial and the pooled estimate obtained using the parametric method (red) and Kaplan-Meier method (blue). Grey = ΔRMST calculated from the extrapolated parametric model data; black = ΔRMST calculated directly from the trial data

14 752 (exenatide; EXCSEL). The prevalence of ASCVD was lowest in the REWIND trial (31%), while a large proportion of patients enrolled in all other studies had established stable ASCVD (ranging from 73% in the EXCSEL trial to 100% in Harmony Outcomes, Amplitude-O). Unlike other trials, ELIXA only enrolled patients with acute coronary syndrome.[26] The REWIND trial (dulaglutide)[10] and the Harmony Outcomes trial (albiglutide)[8] had the longest (5.4 years) and shortest (1.5 years) median follow-ups. Completeness of follow-up in all trials was excellent (ranging from 97% to 100%). All trials were of high quality and free from significant bias (Figure S5). The eligible trials were also reasonably pragmatic in their study design. Using the PRECIS-2 tool, the pooled median score observed was 33.5/45. Every trial scored highly (4 or 5) for the following criteria: trial setting; primary analysis; and primary outcome (Table S1). At enrolment, most patients were already receiving angiotensin receptor blockers/angiotensin-converting enzyme antagonists, statins, and appropriate antihypertensive agents. In the Amplitude-O and Pioneer 6 trials, 15% and 10% of patients also concomitantly received SGLT2 inhibitors.

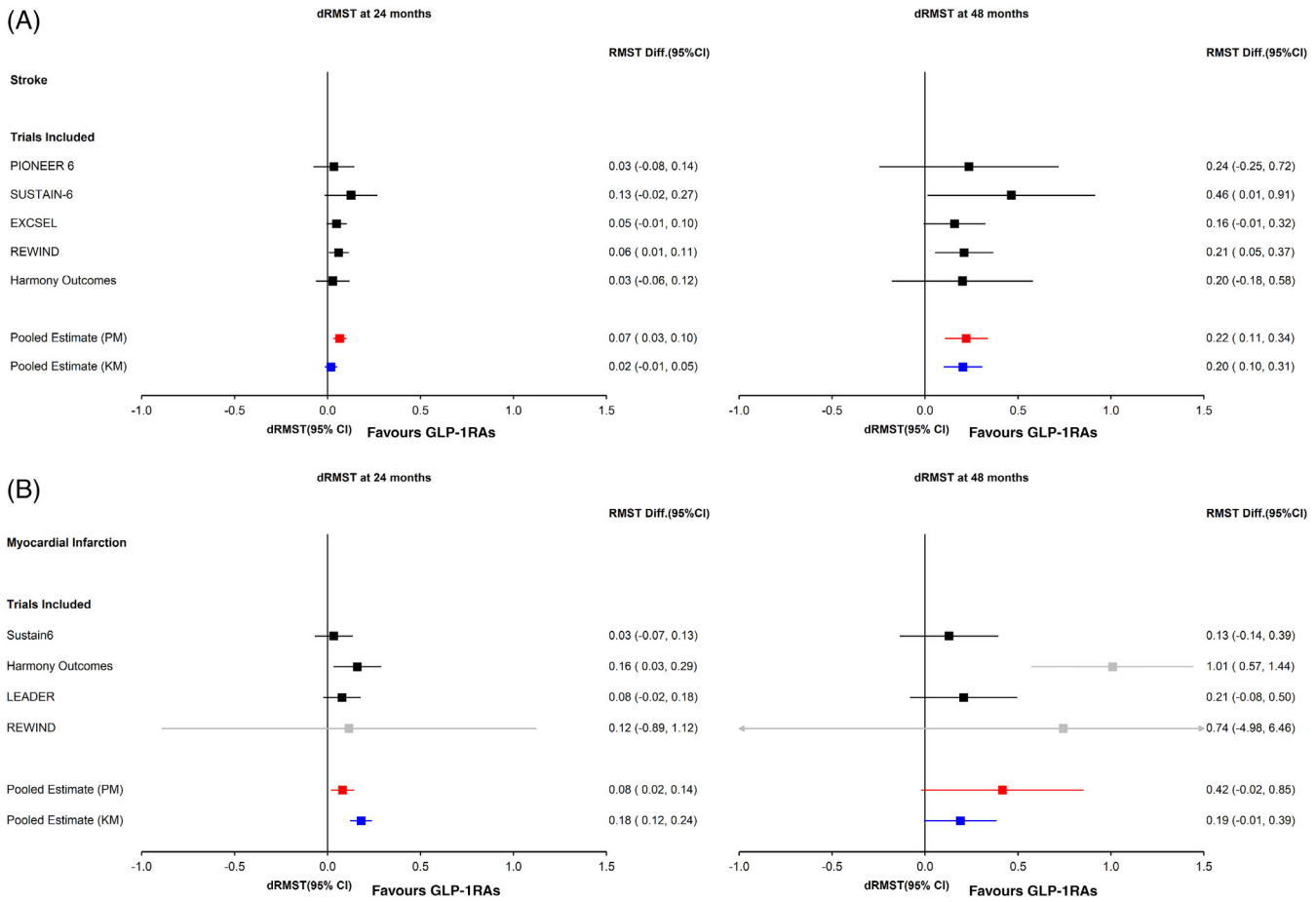

FIGURE 2 Endpoint studied: (A) stroke and (B) myocardial infarction. This panel of forest plots presents the difference in restricted mean survival time (ΔRMST) obtained for each trial and the pooled estimate obtained using the parametric method (red) and Kaplan-Meier method (blue). Grey = ΔRMST calculated from the extrapolated parametric model data; black = ΔRMST calculated from the trial data.

3.2 | Three-/four-point MACE

All studies provided information regarding three-/four-point MACE (Table 1 and 2). On pooling data from these trials, using the parametric model method, we observed that, compared to the control arm, in participants receiving GLP-1RAs, this endpoint was delayed by 0.03 (95%CI: 0.01 - 0.05), 0.15 (95%CI: 0.08 - 0.23), 0.36 (95% CI: 0.18 - 0.56) and 0.62 (95%CI: 0.27 - 0.98) months at 12, 24, 36 and 48 months, respectively (Figure 1). While we observed minimal heterogeneity over short follow-up periods (12 and 24 months), significant inter-study heterogeneity was observed at 36- ($P = 0.03$) and 48-month ($P = 0.01$) follow-ups.

After excluding the ELIXA trial, at 48 months, the pooled ΔRMST further increased to 0.72 (95% CI 0.34-1.1) months ($P < 0.001$), favouring GLP-1RAs. Individually, among trials, ΔRMST was largest in the Amplitude-O (efpeglenatide) trial (1.65 months), followed by the Harmony Outcomes (albiglutide) trial (1.33 months). On limiting the analysis to studies that enrolled ≥85% patients with established ASCVD (Harmony Outcomes, PIONEER 6, AMPLITUDE-O), we observed an even greater benefit in the cohort receiving GLP-1RAs (pooled ΔRMST = 1.1 [95% CI 0.39-1.82]; $P = 0.002$ at 48 months; Table S2). These results were supported by findings observed using direct KM integration (Figure 1). We also observed a nonlinear increase in the benefit of GLP-1RAs over time. While ΔRMST was 0.03 (95% CI 0.01-0.056) after 12 months of GLP-1RA therapy, this increased to 0.368 (95% CI 0.1780.558) and 0.627 (95% CI 0.2700.984) at 36 and 48 months, respectively. (Figure S6).

3.3 | Stroke

Cumulative stroke rates were pooled from five studies (PIONEER 6, SUSTAIN-6, EXCSEL, REWIND and Harmony Outcomes). At 48 months, time to stroke was delayed in patients treated with GLP-1RAs (pooled ΔRMST 0.22 [95% CI 0.15-0.33]; $P < 0.001$ [Figure 2A]).

3.4 | Myocardial infarction

Data regarding myocardial infarction were pooled from four trials (Sustain-6, REWIND, Harmony Outcomes, LEADER). At 48-month follow-up, we observed a small delay in the occurrence of myocardial infarction in patients treated with GLP-1RAs (0.42 [95% CI −0.02,

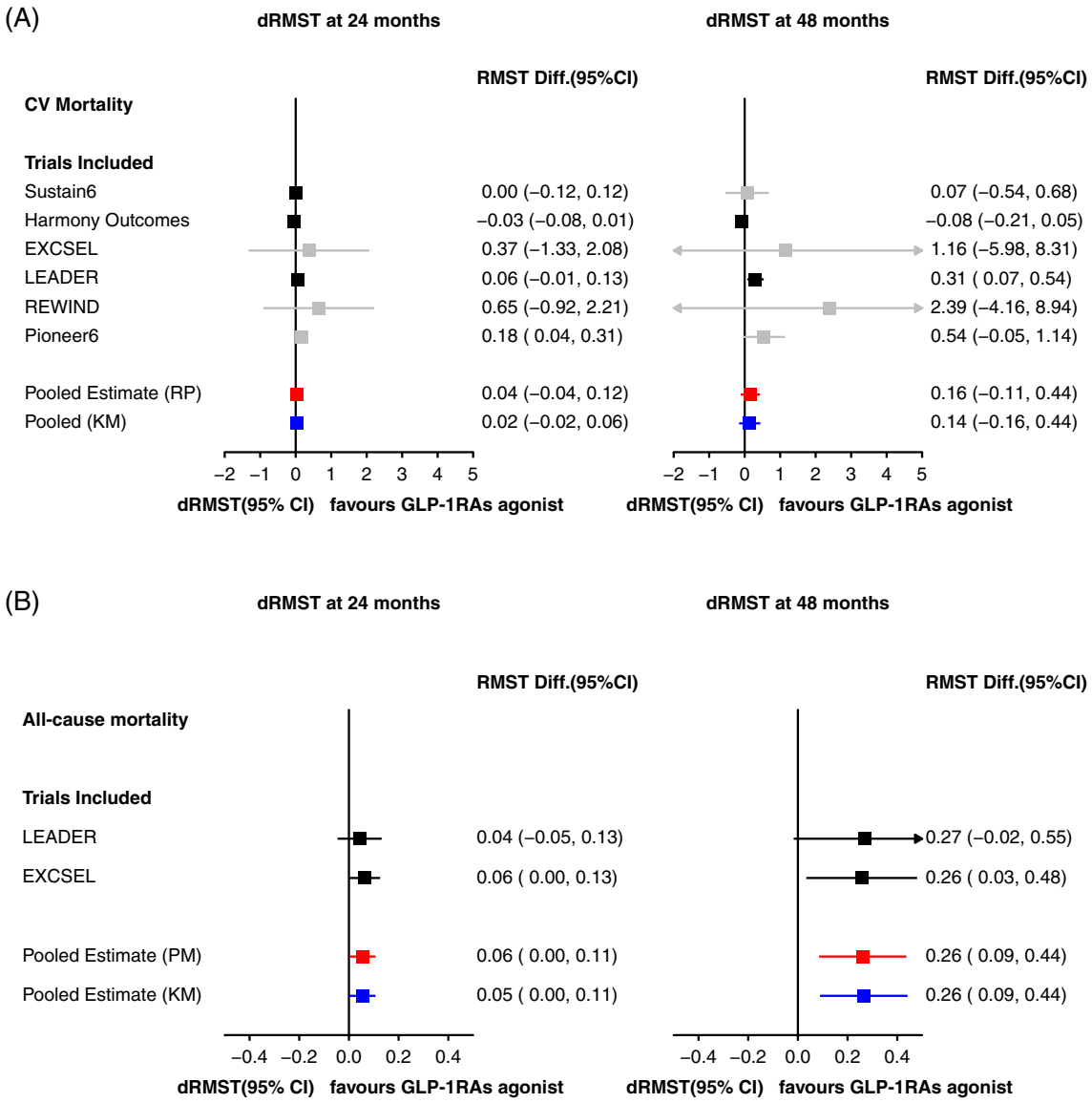

FIGURE 3 Endpoint studied: (A) Cardiovascular mortality and (B) all-cause mortality. This panel of forest plots presents the difference in restricted mean survival time (ΔRMST) obtained for each trial and the pooled estimate obtained using the parametric method (red) and Kaplan-Meier method (blue). Grey = ΔRMST calculated from the extrapolated parametric model data; black = ΔRMST calculated directly from the trial data

0.85]; $P = 0.06$); however, we also observed substantial heterogeneity in our model ($I^2 = 75\%$; $P = 0.01$ [Figure 2B]).

3.5 | Cardiovascular mortality

Cardiovascular mortality was reported in six trials (Sustain 6, Harmony Outcomes, EXSCEL, LEADER, REWIND, Pioneer-6). At 48-month follow-up, cardiovascular mortality was not significantly different in the two arms (pooled ΔRMST 0.163 [95% CI −0.112, 0.437]; $P = 0.24$ [Figure 3A]). This was corroborated by the sensitivity analysis. We observed moderate between-study variation ($I^2 = 59\%$ at 24 months, $P = 0.01$; $I^2 = 56\%$ at 48 months, $P = 0.04$) for our pooled model.

3.6 | All-cause mortality

All-cause mortality estimates were pooled from two trials (LEADER, EXCSEL). On pooled analysis, at 48 months, we observed increased survival in patients receiving GLP-1RAs (pooled ΔRMST = 0.261 [95% CI 0.08-0.43] months; $P < 0.001$ [Figure 3B]).

3.7 | Sensitivity analyses

On graphically comparing the parametric and KM model results for each endpoint, we observed that they demonstrated substantial overlap. Pooled HR and RMTL ratios for each endpoint were also quite similar (Figure S3), further supporting our primary observations.

4 | DISCUSSION

We used a novel application of an existing method to analyse and pool time-to-event data from large multinational cardiovascular outcome trials of GLP-1RAs in patients with T2DM. Using published KM graphs, we fit parametric models to each trial, calculated the differences in RMST between study arms (ΔRMST) and pooled them using the DerSimonian and Laird inverse-weighting random-effects model. We determined that, at 48-month follow-up, there was a significant delay in the occurrence of three-point MACE among GLP-1RA-treated patients, which was equivalent, on average, to an additional 0.6-month freedom from three-point MACE. Among GLP-1RA-treated patients, we also observed a delay in the occurrence of stroke (based on pooling five trials), and possibly, all-cause mortality (based on pooling two trials). In GLP-1RA-treated patients, we also report a 15% relative risk reduction in the occurrence of three-point MACE at 12 months post randomization, an observation, that remained consistent during the 48 months of follow-up.

Prior meta-analyses have reported the beneficial cardiovascular effects of GLP-1RAs in patients with T2DM based on HRs.[29,30] Sattar et al recently pooled the HRs of these eight multinational large trials and reported a 14% relative risk reduction for three-part MACE. However, interpretation of this result is difficult without knowing the absolute risk of MACE in controls and how this varies over time. Therefore, knowledge regarding the relative risk reduction may be of limited utility in reaching an informed decision in the context of a clinical consultation. In contrast, an average gain of 0.6 months over 4 years is easy for patients and clinicians to understand and discuss, especially as the absolute benefit appears to increase in a nonlinear fashion over time. A recent study of 15 heart failure trials that used RMST also reports similar small positive effects.[31] In the Dapagliflozin in heart failure (DAPA-HF) trial, Perego et al report a 10-day (0.3-month) benefit over the 2-year study period.[31] However, like us, they observed a nonlinear benefit over time; this therefore supports continued therapy. We observed an 80% increase in ΔRMST from 36 to 48 months. Hence, the continued use of GLP-1RAs may lead, over time, to larger increases in event-free survival. According to a recent study, but using differing methods, treatment with GLP-1RAs is projected to result in an average gain of 1.7 life-years, with a larger benefit (2.0) observed in patients with established cardiovascular disease.[32]

Substantial heterogeneity was observed in some pooled analyses. This may be attributable to several factors. Firstly, it is still unclear, at present, if all GLP-1RAs provide similar cardiovascular benefits. Among randomized trials, to date, a positive cardiovascular benefit has been observed in the trials using albiglutide, dulaglutide, semaglutide, liraglutide and efpeglenatide. All these agents, apart from efpeglenatide, are GLP-1RA human homologues. Amplitude-O (efpeglenatide) is, in fact, the first trial, wherein an exendin-4 analogue has demonstrated a positive cardiovascular effect. Kristensen et al argue that earlier trials with exendin-4 agents (EXCSEL, ELIXA) failed to demonstrate CV benefits due to pharmacological differences (short-acting nature of exenatide) or poor drug adherence (40% permanent treatment discontinuation with lixisenatide).[29] Secondly, this heterogeneity may be attributable to differences in participant characteristics among trials, specifically the varying proportion of patients with established cardiovascular disease.

Traditionally, meta-analyses of time-to-event outcomes are performed by pooling reported HRs from included studies. While this method is valid for dichotomous events, trials often have variable study durations. Participants are also observed for differing time periods. Therefore, although simple, this method does not consider the possibility of a time-varying relationship between study and control arms. The reliability of HR as a measure also depends on fulfilling the proportional hazards assumption, which is more challenging when multiple studies with variable time periods are combined. ΔRMST, being an absolute measure, is not dependent on the proportional hazards assumption and can be calculated for any time point within the study duration. Recent data suggest that using RMST rather than HR may lead to improved study design with a possible reduction in study sample size.[33]

In this study, we present results using an absolute summary estimate (ΔRMST) and have demonstrated the validity of our primary result with numerous sensitivity analyses. Absolute and relative measures provide complementary information for understanding data.[34] Relative risk measures do not incorporate the baseline hazard; hence, relative risks often appear artificially inflated when compared to the absolute summary estimates calculated from the same data. Absolute measures, on the other hand, adjust for the baseline hazard in the study population and provide a clearer understanding of the treatment effect. Another measurement often presented is the number needed to treat. While number needed to treat is derived from the absolute risk reduction and is therefore also an absolute measure, this measure may be unclear to many patients.[35]

We have followed guidelines provided by the National Institute of Health and Care Excellence regarding study extrapolation.[36] Furthermore, by adopting a flexible parametric modelling approach, we have successfully captured the true observed effects in each trial (Figures S1 and S2). The maximum extrapolated duration (24 months) was utilized for data in the Amplitude-O trial, while for all other trials, it was largely less than 12 months. While this method has often been used to assess the economic benefit and quality-adjusted life-years gained in the study of cancers, it has rarely been implemented in the study of cardiovascular trials.[31] As Perego et al discuss,[31] cost, practical complexities and need for rapid evidence generation often lead to limitations in our ability to extend trials beyond a certain period. Therefore, correctly applied, these methods can be used to obtain reliable, model-free estimates of the delay in adverse events observed in studies. We, and others, have also demonstrated that RMST/RMTL ratios are consistent with conventional HRs[37,31] A recent study reported the use of RMST to evaluate the lifetime benefit of dapagliflozin in the treatment of patients with heart failure.[38] Increased reporting of the ΔRMST (along with other conventional measures) may allow clinicians to better understand study results, which, in turn, will promote informed decision making and increased treatment adherence among patients.

This study has some limitations. In the absence of access to individual trial data, we abstracted information from published KM curves. However, we used a well-validated, highly sensitive method to do so. Our choice to use ΔRMST to pool studies lends temporal flexibility and provides easy-to-understand results. Extrapolation of trial data by fitting parametric models may either under- or overestimate treatment effects; however, flexible parametric models often capture the varying trajectory of each study arm better than fixed mathematical functions. Our multiple sensitivity analyses further support our primary findings. Although we were able to report most of the important CV endpoints, we were not able to examine subgroup analyses in greater detail because not all trial results were reported as KM curves and we did not have access to individual trial data.

In conclusion, our pooled meta-analysis of eight large randomized CVOTs on GLP-1RAs corroborates previous findings that, as a class, these agents have significant cardiovascular benefits. Furthermore, we determined that, on average, treatment with GLP-1RAs may delay the occurrence of MACE by an average of 0.6 months over a 4-year period, and potentially longer in trials where all participants had existing ASCVD. Whether such gains increase linearly or perhaps accelerate with longer use of GLP-1RAs remains to be established.

CONFLICT OF INTEREST

Salil Deo, Shayan Marsia, David McAllister, Yakov Elgudin and Jill Pell have no conflict of interest to declare. Naveed Sattar has consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer and Sanofi, and received grant support from Boehringer Ingelheim outside the submitted work.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

All datasets (data zip file) containing the information extracted from the published KM curves for each trial and all R code (rscript zip file) are avaialble from the corresponding author on reasonable request. They are also available for direct download from the corresponding authors github page - https://github.com/svd09/RMST_glp1a.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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