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Cardiovascular risk reduction with glucagon-like peptide-1 receptor agonists is proportional to HbA1c lowering in type 2 diabetes: An updated meta-regression analysis incorporating FLOW and SOUL trials

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Abstract

Aims: To evaluate relationships of cardiovascular and kidney outcomes with glycemic or bodyweight reductions in randomised placebo-controlled trials of glucagon-like peptide-1 receptor agonists (GLP-1RAs), incorporating data from FLOW and SOUL trials.

Materials and Methods: PubMed and EMBASE were searched up to 22 August 2025 for placebo-controlled randomized trials of oral or bolus-type, subcutaneous GLP-1RAs reporting major adverse cardiovascular events (MACE; a composite of cardiovascular death, myocardial infarction, and stroke) in adults with type 2 diabetes. The primary outcome was MACE; secondary outcomes included heart failure (HF) and kidney outcomes. Random-effects meta-analyses were followed by meta-regression evaluating associations with HbA1c and bodyweight reduction.

Results: A total of 73 263 individuals were included from 10 trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL, Harmony Outcomes, PIONEER 6, REWIND, AMPLITUDE-O, FLOW, and SOUL). GLP-1RAs reduced MACE by 14% (hazard ratio: 0.86; 95% CI: 0.82 to 0.91; $p < 0.001$), as well as hospitalisation for HF and the composite kidney outcome (both $p < 0.001$). Meta-regression showed that every 1% extra reduction in HbA1c corresponded to a 27% lower HR for MACE ($p = 0.015$; $R^2 = 0.61$). While HbA1c reduction was not significantly associated with secondary outcomes, the directionality was consistent with MACE.

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Bodyweight change was not associated with any of the analysed endpoints, including MACE ($p = 0.13$; $R^2 = 0.21$).

Conclusions: HbA1c reduction, not bodyweight change, was significantly and proportionally associated with MACE risk reduction. HbA1c lowering may serve as a useful surrogate for the cardiovascular improvements associated with GLP-1RAs in type 2 diabetes.

KEYWORDS

cardiovascular disease, GLP-1 receptor agonists, meta-analysis, type 2 diabetes

1 | INTRODUCTION

People with type 2 diabetes are at elevated risk for developing cardiometabolic diseases, including myocardial infarction (MI), stroke, and heart failure (HF), as well as chronic kidney disease (CKD).^{1,2} A series of large randomised clinical trials (RCTs) has investigated the effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on these outcomes. Several of these trials have demonstrated significant reductions in major adverse cardiovascular events (MACE) and a slower decline in kidney function,³ resulting in guideline recommendations for the use of GLP-1RAs in individuals with type 2 diabetes who are at high risk for cardiovascular or kidney disease.⁴

Although GLP-1RAs improve glycemic and bodyweight control, the extent of these effects varies across trials, as do the cardiovascular and kidney outcomes.⁵ It remains unclear whether differences in glycemic or bodyweight reduction explain the variability in these clinical endpoints. Identifying whether reductions in blood glucose levels or bodyweight contribute to cardiovascular and kidney benefits can help determine which treatment effects of GLP-1RAs should be prioritised in clinical practice and guide personalised treatment.

In our previous meta-analysis and meta-regression of eight GLP-1RA trials published in 2022, we found that a reduction in glycated haemoglobin (HbA1c) levels, but not in bodyweight, was significantly associated with lower risks of MACE and kidney outcomes.⁶ Since then, two major RCTs have expanded the evidence base: FLOW, which primarily evaluated kidney outcomes with subcutaneous semaglutide, and SOUL, which investigated cardiovascular outcomes with oral semaglutide.^{7,8} Together, these trials contributed more than 13 000 additional participants, corresponding to an increase of over 20% compared with our 2022 analysis. They also included characteristics not present in earlier trials, specifically a CKD-focused population and an oral formulation of semaglutide, providing an updated dataset for analysis. Building on these new data, we conducted an updated meta-analysis and meta-regression of large-scale RCTs involving oral or bolus-type subcutaneous GLP-1RAs in type 2 diabetes. Our aim was to assess the effects of GLP-1RAs on cardiovascular, HF, and kidney outcomes, and to comprehensively examine whether reductions in HbA1c and bodyweight are associated with these outcomes in the currently available data.

2 | METHODS

2.1 | Search strategies and selection criteria

This study was conducted in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁹ and was prospectively registered with PROSPERO (registration number: CRD42022299075). Trials were considered eligible if they: (i) were RCTs enrolling a minimum of 1000 adults (age ≥ 18 years) with type 2 diabetes; (ii) compared an oral formulation or bolus-type, intermittent subcutaneous injection of GLP-1RAs against placebo; (iii) reported MACE as an endpoint; and (iv) had a follow-up duration of at least 1 year. We excluded trials employing implantable device-based, continuous-infusion systems because their pharmacokinetic profiles and delivery mechanisms differ fundamentally from those of oral or bolus-type subcutaneous GLP-1RAs.^{10,11}

We performed a comprehensive search of PubMed and EMBASE from inception to 22 August 2025 without language restrictions. The detailed search strategies for each database are provided in Figure S1, and the study selection procedure is summarised in the PRISMA flow diagram (Figure S2). Two investigators (MH and CYS) independently performed the literature search and study selection, and any discrepancies were resolved by discussion until consensus was achieved.

2.2 | Data retrieval and quality evaluation

For each selected trial, we retrieved information on study characteristics, baseline participant demographics, the GLP-1RA used, average differences in HbA1c and bodyweight achieved between intervention and placebo arms, and outcome data including hazard ratios (HRs) with 95% confidence intervals (CIs). We collected data from original publications and their supplements, and, when necessary, extracted relevant information from secondary sources. Risk of bias was assessed using Version 2 of the Cochrane Risk of Bias Tool.¹² Data extraction and risk of bias assessment were independently conducted by two investigators (MH and CYS) and subsequently verified by a third reviewer (SY).

2.3 | Data integration and statistical analysis

We used the HRs for MACE as the primary endpoint. MACE was generally defined as a composite of cardiovascular death, non-fatal MI, or

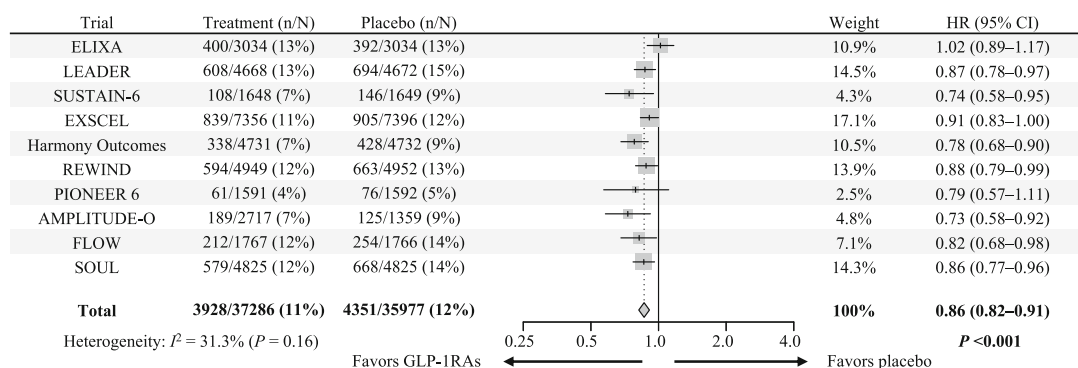
TABLE 1 Key characteristics of the included randomised controlled trials.

Trial	Year	Participants, n	Drug	Median follow-up, years	Age, years	Diabetes duration, years	Female, n (%)	eGFR, mL/min/1.73 m ²	Baseline CVD, n (%)	Baseline HF, n (%)	HbA1c, %	HbA1c reduction, %	BMI, kg/m ²	Bodyweight, kg	Bodyweight reduction, kg
ELIXA	2015	6068	Lixisenatide (SC) 20 µg/day	2.1	59.9 (9.7)	9.2 (8.2)	1861 (31%)	78 (21)	6068 (100%)	1358 (22%)	7.7 (1.3)	0.27 (0.89)	30.1 (5.6)	85.2 (19.4)	0.70 (3.97)
LEADER	2016	9340	Liraglutide (SC) 1.8 mg/day	3.8	64.2 (7.2)	12.8 (8.0)	3337 (36%)	80 (NR)	7598 (81%)	1667 (18%)	8.7 (1.6)	0.40 (1.36)	32.5 (6.3)	91.8 (21.0)	2.30 (6.16)
SUSTAIN-6	2016	3297	Semaglutide (SC) 0.5 or 1.0 mg/week	2.1	64.6 (7.4)	13.9 (8.1)	1295 (39%)	80 (61–92)	2735 (83%)	777 (24%)	8.7 (1.5)	0.85 (1.46)	32.8 (6.2)	92.1 (20.6)	3.61 (6.21)
EXSCEL	2017	14 752	Exenatide (SC) 2 mg/week	3.2	61.9 (9.4)	13.1 (8.3)	5603 (38%)	77 (61–92)	10 782 (73%)	2389 (16%)	8.1 (1.0)	0.53 (1.08)	32.7 (6.4)	93 (NR)	1.27 (4.18)
HARMONY Outcomes	2018	9463	Albiglutide (SC) 30 or 50 mg/week	1.5	64.1 (8.7)	14.2 (8.8)	2894 (31%)	79 (25)	9463 (100%)	1922 (20%)	8.7 (1.5)	0.52 (1.61)	32.3 (5.9)	92.5 (NR)	0.83 (5.71)
REWIND	2019	9901	Dulaglutide (SC) 1.5 mg/week	5.4	66.2 (6.5)	10.5 (7.2)	4589 (46%)	77 (23)	3114 (31%)	853 (9%)	7.3 (1.1)	0.61 (0.89)	32.3 (5.7)	NR	1.46 (5.33)
PIONEER 6	2019	3183	Oral semaglutide 14 mg/day	1.3	66.0 (7.0)	14.9 (8.5)	1007 (32%)	74 (21)	2695 (85%)	288 (12%)	8.2 (1.6)	0.70 (NR)	32.3 (6.5)	90.9 (21.2)	3.40 (NR)
AMPLITUDE-O	2021	4076	Efglenatide (SC) 4 or 6 mg/week	1.8	64.5 (8.2)	15.4 (8.8)	1344 (33%)	72 (22)	3650 (90%)	737 (18%)	8.9 (1.5)	1.24 (2.44)	32.7 (6.2)	NR	2.60 (9.78)
FLOW	2024	3533	Semaglutide (SC) 1.0 mg/week	3.4	66.6 (9.0)	17.4 (9.3)	1069 (30%)	47 (15)	1838 (52%)	678 (19%)	7.8 (1.3)	0.81 (2.73)	32.0 (6.3)	89.6 (20.5)	4.10 (13.8)
SOUL	2025	9650	Oral semaglutide 14 mg/day	4.1	66.1 (7.6)	15.4 (8.8)	2790 (29%)	74 (23)	8088 (84%)	2215 (23%)	8.0 (1.1)	0.56 (2.26)	31.1 (5.8)	87.9 (19.4)	2.65 (11.3)

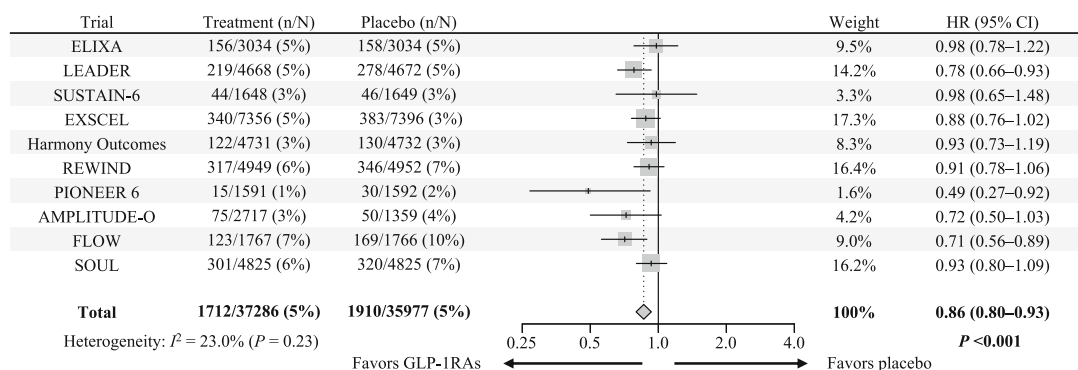
Note: All continuous variables, except for follow-up duration, are presented as mean (standard deviation [SD]). Categorical variables are reported as number (percentage). For SUSTAIN-6 and EXSCEL, eGFR is reported as median (interquartile range [IQR]).

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; NR, not reported; SC, subcutaneous.

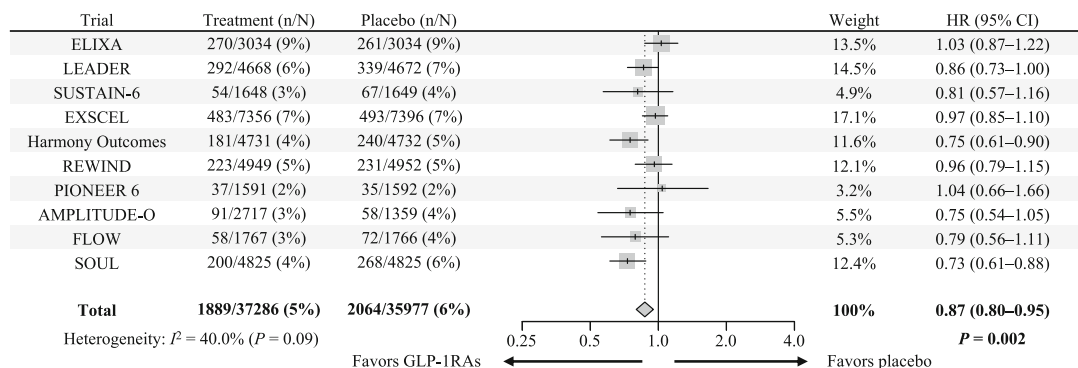
(A) MACE



(B) Cardiovascular death



(C) Myocardial infarction



(D) Stroke

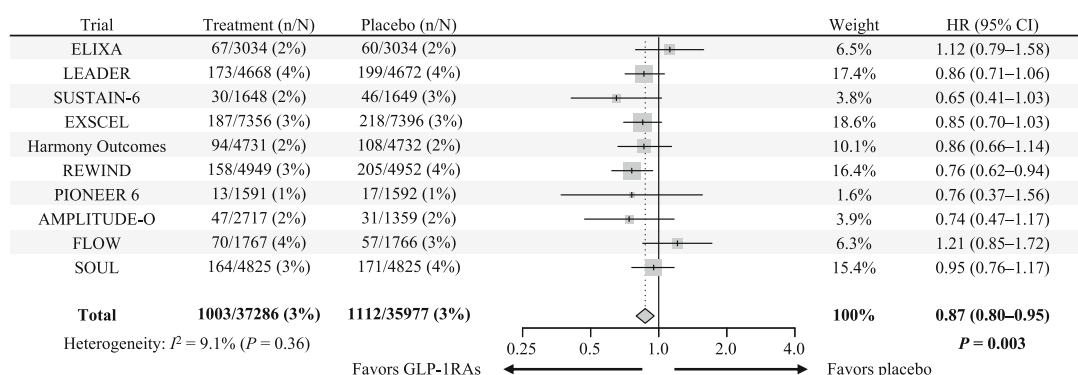


FIGURE 1 Legend on next page.

FIGURE 1 Effects of GLP-1RAs on (A) MACE, (B) cardiovascular death, (C) myocardial infarction, and (D) stroke. CI, confidence interval; GLP-1RAs, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; MACE, major adverse cardiovascular events.

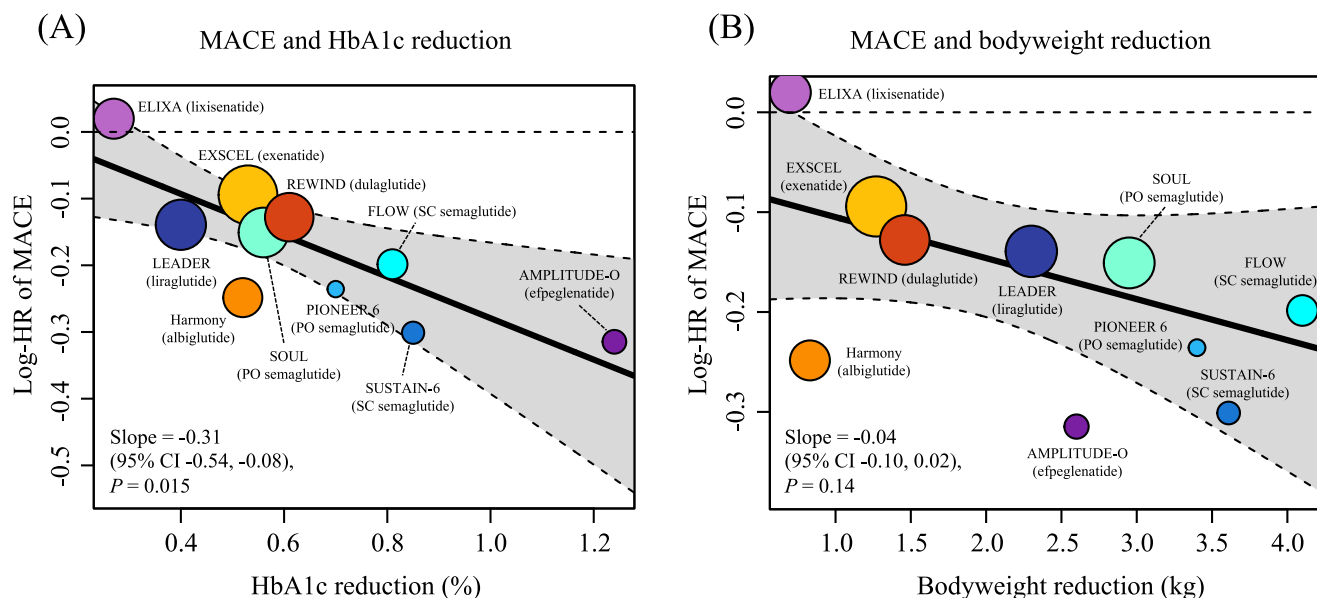


FIGURE 2 Association between the risk of MACE and reductions in (A) HbA1c or (B) bodyweight. The thicker line represents the meta-regression line, with the shaded area indicating the 95% CI. Circle size reflects the precision of the HR estimate in each trial, with greater precision (i.e., lower variance) shown as larger circles. CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; log-HR, estimated log hazard ratio; PO, oral; SC, subcutaneous.

(HR: 0.84; 95% CI: 0.76–0.91; $p < 0.001$; $I^2 = 13.7\%$), and worsening kidney function (HR: 0.79; 95% CI: 0.70–0.90; $p < 0.001$; $I^2 = 33.4\%$) (Figure S6).

3.3 | Meta-regression analyses

Meta-regression conducted across the 10 trials showed that greater reductions in HbA1c were correlated with a significantly lower log-HR of MACE (slope: -0.31 ; 95% CI: -0.54 to -0.08 ; $p = 0.015$; $R^2 = 0.61$) (Figure 2A). This corresponded to a 27% relative reduction in the HR for MACE per 1% greater HbA1c reduction (95% CI: 7% to 42%). Across the individual MACE components, although they did not reach statistical significance, directionally consistent relationships were observed: cardiovascular death (slope = -0.26 ; 95% CI: -0.72 to 0.19 ; $p = 0.22$), MI (slope = -0.26 ; 95% CI: -0.69 to 0.17 ; $p = 0.20$), and stroke (slope = -0.22 ; 95% CI: -0.80 to 0.36 ; $p = 0.40$) (Figure 3A–C). On the other hand, bodyweight reduction did not demonstrate a significant relationship with MACE log-HR (slope: -0.04 ; 95% CI: -0.10 to 0.02 ; $p = 0.14$; $R^2 = 0.21$) (Figure 2B), nor with its individual components: cardiovascular death (slope = -0.06 ; 95% CI: -0.14 to 0.02 ; $p = 0.12$), MI (slope = -0.06 ; 95% CI: -0.15 to 0.03 ; $p = 0.14$), and stroke (slope = 0.03 ; 95% CI: -0.09 to 0.14 ; $p = 0.63$) (Figure 3D–F).

For the other secondary outcomes, neither HbA1c nor bodyweight reduction was significantly associated with any individual

endpoint. Most outcomes showed negative slopes, consistent with the primary MACE findings, except for the composite kidney outcome, which showed positive slopes for both HbA1c and bodyweight reduction (Figure 4). Full meta-regression results are provided in Table S6.

4 | DISCUSSION

This meta-analysis and meta-regression incorporated data from 73 263 individuals with type 2 diabetes across 10 RCTs of GLP-1RAs, including the most recent results from the FLOW and SOUL trials. The pooled analyses demonstrated that GLP-1RAs significantly reduced the risks of MACE, its individual components, all-cause mortality, hospitalisation for HF, composite kidney outcomes, and worsening kidney function, with pooled HRs ranging from 0.79 to 0.87. In meta-regression analyses, reductions in HbA1c were significantly associated with decreases in the log-HR for MACE; specifically, each 1% additional decrease in HbA1c corresponded to a 27% relative reduction in MACE risk. These findings reinforce the role of HbA1c reduction as a surrogate indicator of cardiovascular benefit in individuals receiving GLP-1RA therapy. In contrast, reductions in bodyweight were not associated with any of the outcomes examined, including MACE. To our knowledge, our study is the most comprehensive and up-to-date meta-regression to evaluate how reductions in HbA1c and bodyweight relate to cardiovascular, HF, and kidney outcomes.

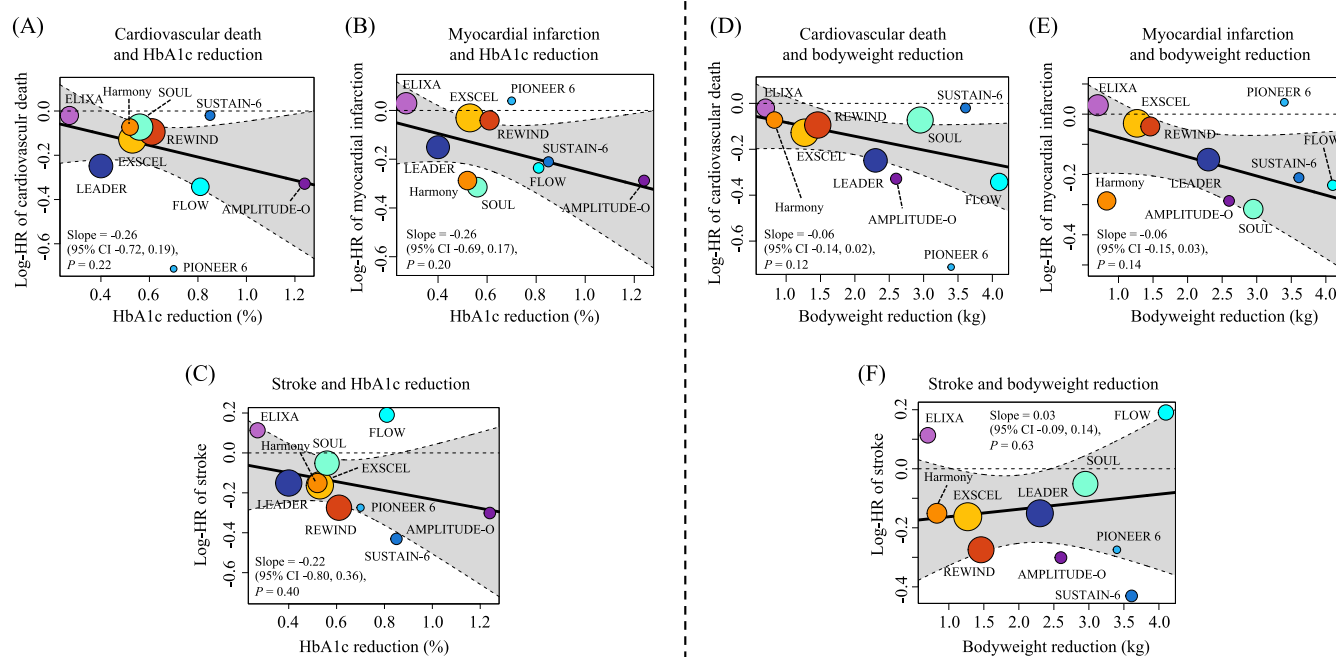


FIGURE 3 Association between the risks of cardiovascular death, myocardial infarction, and stroke and reductions in HbA1c (A)–(C) or bodyweight (D)–(F). The thicker line represents the meta-regression line, with the shaded area indicating the 95% CI. Circle size reflects the precision of the HR estimate in each trial, with greater precision (i.e., lower variance) shown as larger circles. CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; log-HR, estimated log hazard ratio.

Our updated meta-analysis confirms that GLP-1RAs consistently reduce the risks of cardiovascular, HF, and kidney outcomes in subjects with type 2 diabetes. These findings are consistent with previous meta-analyses and reinforce current clinical guidelines recommending GLP-1RAs for people with established or high-risk cardiovascular or kidney disease.^{3–6} The inclusion of the two most recent large-scale trials, FLOW and SOUL, added more than 13 000 participants and contributed data from a CKD-focused population and from oral semaglutide.^{7,8} This allowed for more precise estimates and enabled the most comprehensive evaluation of GLP-1RAs efficacy across clinically relevant outcomes in type 2 diabetes, incorporating populations and formulations not represented in earlier trials.

The FREEDOM-CVO trial, which evaluated continuous-subcutaneous infusion of exenatide via the implantable ITCA 650 device, was not included in this analysis because its mode of delivery is fundamentally different from the oral and subcutaneous regimens assessed in the other trials and did not meet the eligibility criteria (Table S5).²⁵ Although exenatide has demonstrated a favourable safety profile in previous injection-based trials,²⁰ ITCA 650 provides long-term continuous drug exposure via a subdermal osmotic pump, resulting in distinct pharmacokinetics and device-related considerations.¹⁰ In addition, the trial raised safety concerns, including a possible increase in acute kidney injury, and did not demonstrate a consistent cardioprotective effect. As a result, the device was ultimately not approved by the US Food and Drug Administration.³³ Its

exclusion, therefore, ensured a more homogeneous analysis of GLP-1RA treatments relevant to current clinical practice.

In the current study, greater reductions in HbA1c were significantly associated with larger decreases in MACE risk among individuals with type 2 diabetes. This finding is consistent with our previous meta-regression of GLP-1RA cardiovascular outcome trials,⁶ our broader analysis involving all types of glucose-lowering therapies,⁵ and post hoc analyses from the LEADER and REWIND trials, which identified HbA1c as a major mediator of cardiovascular benefit.^{34,35} It is also supported by the UK Prospective Diabetes Study, which showed that each 1% lower updated mean HbA1c was associated with a 14% lower risk of MI and a 21% lower risk of diabetes-related death, indicating a proportional glycemic contribution to cardiovascular risk reduction in type 2 diabetes management.³⁶ We acknowledge, however, that glycemic control alone does not fully account for the cardioprotective effects of GLP-1RAs; the SELECT trial demonstrated that high-dose semaglutide reduced MACE risk in individuals with obesity but without diabetes, suggesting glucose-independent mechanisms.³⁷ Still, the consistent association between HbA1c reduction and cardiovascular outcomes implies that glycemic improvement is linearly associated with the cardiometabolic benefits of GLP-1RA therapy in individuals with type 2 diabetes. As HbA1c lowering is frequently accompanied by improvements in blood pressure, inflammatory markers, and other metabolic parameters, it may serve as a pragmatic indicator of the overall benefits conferred by GLP-1RA therapy.^{38–40}

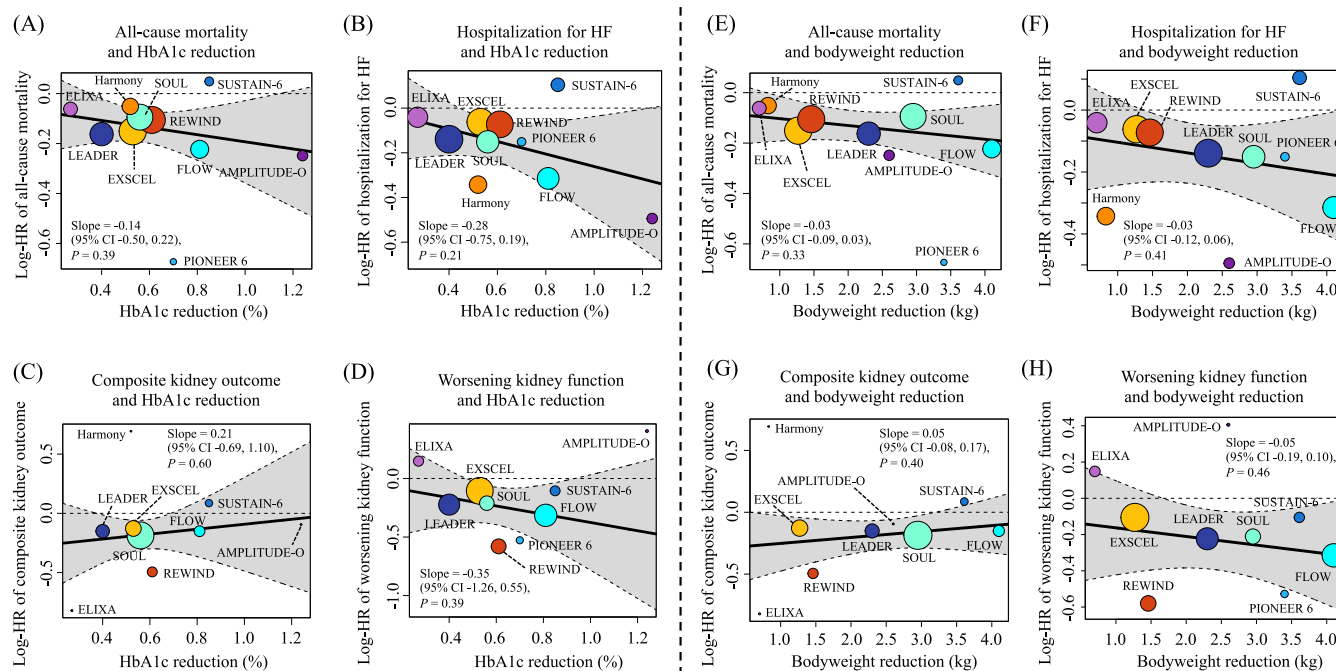


FIGURE 4 Association between the risks of all-cause mortality, hospitalisation for HF, composite kidney outcome, and worsening kidney function and reduction in HbA1c (A)–(D) or bodyweight (E)–(H). The thicker line represents the meta-regression line, with the shaded area indicating the 95% CI. Circle size reflects the precision of the HR estimate in each trial, with greater precision (i.e., lower variance) shown as larger circles. For the composite kidney outcome and worsening kidney function, risk ratios were used for EXSCEL, as HRs were not reported. CI, confidence interval; HbA1c, glycated haemoglobin; HF, heart failure; HR, hazard ratio; log-HR, estimated log hazard ratio.

In contrast to HbA1c, reductions in bodyweight were not significantly associated with MACE, although the direction of effect was consistent with a lower risk. This finding aligns with our previous meta-regression analyses.^{5,6} One plausible explanation is that overall bodyweight may not adequately reflect the specific fat depots most relevant to cardiovascular risk.⁴¹ In the placebo arm of the REWIND trial, waist-to-hip ratio and waist circumference were associated with MACE and cardiovascular mortality, whereas body mass index (BMI) was not.⁴² Separately, imaging studies have shown that GLP-1RAs preferentially reduce visceral rather than subcutaneous fat, even at comparable levels of bodyweight loss.^{43,44} These observations suggest that incorporating measures of central adiposity, rather than general body size, may improve the evaluation of cardiometabolic effects associated with GLP-1RA therapy.

Regarding the secondary outcomes, our meta-regression analyses did not reveal any statistically significant associations with either HbA1c or bodyweight reduction, although the estimated slopes were generally negative. This lack of significance may in part reflect the limited number of events, as most included trials were designed and powered to evaluate MACE rather than individual secondary endpoints. Among these outcomes, HF and kidney outcomes merit further discussion given their clinical relevance and contrasting patterns observed across prior studies as follows.

Concerning HF, our present findings are consistent with our previous GLP-1RA-specific meta-regression showing no significant association between bodyweight reduction and HF events.⁶ However,

these null findings require cautious interpretation, as the included trials mainly enrolled people with type 2 diabetes at high atherosclerotic risk, in whom HF was less common and GLP-1RA-induced bodyweight loss modest. Recently, the STEP-HFpEF DM trial demonstrated that a potent GLP-1RA produced substantial bodyweight reduction (−6.4 kg at 52 weeks compared with placebo) in patients with HF with preserved ejection fraction, type 2 diabetes, and marked obesity (median BMI: 36.9 kg/m²), accompanied by improved HF outcomes (HR: 0.40; 95% CI: 0.15–0.92).⁴⁵ These findings suggest that the relationship between GLP-1RA-induced bodyweight loss and HF may need to be considered in the context of patient characteristics, especially when a potent agent is used to achieve substantial bodyweight loss. Nevertheless, at the same time, GLP-1RAs may influence HF outcomes through mechanisms beyond bodyweight loss, such as natriuresis, vascular modulation, or anti-inflammatory effects.^{39,46–48} One example highlighting the relevance of alternative markers is our previous meta-regression of sodium-glucose co-transporter-2 inhibitor trials, which found no association between bodyweight change and HF outcomes but identified a significant relationship with changes in eGFR slope.⁴⁹

On the other hand, for the composite kidney outcome, the regression slopes were close to zero or slightly positive for both HbA1c and bodyweight reduction, differing from our previous findings of GLP-1RA trials that identified a significant association with glycemic improvement.⁶ A key difference is that previous analyses included new-onset macroalbuminuria, a more frequent and

glycemia-sensitive outcome,⁵⁰ as part of the composite kidney outcome.⁶ The present study excluded macroalbuminuria and focused exclusively on more definitive kidney outcomes, such as sustained $\geq 50\%$ decline in eGFR and kidney failure, which occur less frequently and may be less responsive to short-term metabolic improvements. In advanced stages of CKD, progression is more likely to be driven by haemodynamic and inflammatory factors than by glycemic exposure, potentially diminishing observable associations with traditional metabolic markers.⁵¹

This study has several strengths. First, it represents the most up-to-date meta-analysis and meta-regression of GLP-1RA cardiovascular outcome trials in individuals with type 2 diabetes, incorporating recently published trials such as FLOW and SOUL. These additions increased the sample size by approximately 20% and diversified the study populations including individuals with type 2 diabetes and CKD, as well as those treated with oral semaglutide. Notably, even with broader study populations, the results showed consistent results, broadening the applicability of the findings. Second, the findings highlight HbA1c reduction as a valuable indicator of lowered MACE risk, reinforcing the robustness of this association and offering clinically meaningful insights into the cardiometabolic effects of GLP-1RA therapy.

However, the study also has some limitations. First, it relied on trial-level summary data, which precluded more granular analyses of individual-level relationships between specific metabolic parameters and clinical outcomes. Second, this limitation also prevented us from examining whether HbA1c reduction functions as a similarly valid surrogate across clinically distinct subgroups, such as those defined by ancestry or obesity status. Because subgroup-specific changes in HbA1c, bodyweight, or inflammation-related markers are generally not publicly available, these questions remain unanswered. Future analyses using individual participant-level data will be essential to determine in which populations HbA1c serves best as a surrogate marker and to identify alternative or complementary markers of cardiometabolic risk. Third, as noted previously, most of the included trials, except for FLOW, were primarily designed to assess MACE as the primary outcome; therefore, meta-regressions focusing on secondary endpoints may have been underpowered. Fourth, the majority of trial participants were White and had obesity, warranting caution in extrapolating the results to other populations.

In summary, GLP-1RAs lower the incidence of MACE, its component events, hospitalisation for HF, all-cause mortality, composite kidney outcomes, and worsening kidney function. Meta-regression analyses showed a proportional association between greater HbA1c reductions and lower MACE risk, whereas no significant relationship was observed for bodyweight reduction. These findings highlight HbA1c lowering as a pragmatic surrogate marker for the cardiovascular benefits of GLP-1RA therapy in individuals with type 2 diabetes.

AUTHOR CONTRIBUTIONS

MH and SY conceived and designed the study, performed analyses, and interpreted the data. MH and CYS conducted the literature review, collected the data, and drafted the initial manuscript. YK, HM, DY, NI, and SY critically revised the manuscript and provided

intellectual input. SY supervised the study. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

DY received clinically commissioned or joint research grants from Novo Nordisk, Ono Pharmaceutical, Taisho Pharmaceutical, Terumo, and Arklay. DY also received consulting or speaker fees from Sumitomo Dainippon Pharma, Boehringer Ingelheim, Astellas Pharma, MSD, Novo Nordisk, Ono Pharmaceutical, Eli Lilly, and Takeda Pharmaceutical. NI received joint research grants from Asken Inc.; speaker honoraria from Novo Nordisk Pharma Ltd., Eli Lilly Japan K.K., Sumitomo Pharma Co., Ltd., Sanofi K.K., and Mitsubishi Tanabe Pharma Corporation; and scholarship grants from Mitsubishi Tanabe Pharma Corporation, Sumitomo Pharma Co., Ltd., and Nippon Boehringer Ingelheim Co., Ltd. SY serves as an Analytical Consultant for the Broad Institute of MIT and Harvard under contract with Precision Global Consulting. All other authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70121>.

DATA AVAILABILITY STATEMENT

All data were extracted from publicly available sources and are included in this published article and its supplementary file.

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