The cardiovascular benefits of GLP1-RAs are related to their positive effect on glycemic control: A meta-regression analysis

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Systematic Review

Keywords: Meta-regression analysis, GLP1-RAs, MACE, effect size variance, HbA1c

Posted Date: February 8th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1339432/v1

Version of Record: A version of this preprint was published at Diabetes Research and Clinical Practice on March 1st, 2022. See the published version at https://doi.org/10.1016/j.diabres.2022.109824.

Abstract

Backgrounds and Aims:

Glucagon-like-peptides 1 receptor analogues (GLP1-RAs) have gained primacy in the management of type 2 diabetes (T2D) as their use is associated with significant metabolic benefits as well as positive macrovascular outcomes, as evidenced by several cardiovascular outcomes trials (CVOT). However, in contrast to the CVOT conducted with sodium glucose cotransporter-2 inhibitors (SGLT-2i) and dipeptidyl peptidase-4 Inhibitor (DPP-IVi), there was a significant reduction in glycated haemoglobin (HbA1c) in some of the CVOT with GLP1RA. The aim of this analysis is to explore the possible association between cardiovascular outcome benefits with GLP1-RAs and HbA1c reduction

Methods:

With the use of the Cochrane library a web search was conducted using keywords and 9 citations were selected for analysis. The analysis was performed using the comprehensive meta-analysis (CMA) software version 3 (Biostat Inc., Englewood, NJ, USA). A meta-regression analysis was performed using HbA1c, weight, and systolic blood pressure reduction as moderators explaining the variance in true effects across the citations.

Result:

The meta-regression analysis was conducted on a pooled population of 64,236 patients. There was a significant heterogeneity associated with the MACE benefits (Q=16.88, I2: 52.59, df=7, p=0.03). Among the moderators selected to explain the variance in true effects, HbA1c reduction was significant (Q=7.00, P= <0.001, R2:1.0), with the regression model indicating a 21.86% reduction in MACE per 1% reduction in HbA1c. (Fig 1) Additional meta-regression analysis using 0.9% reduction of HbA1c from baseline indicated a significant association with MACE benefit (95% CI -0.23 to -0.02, P=0.01, R2: 0.98).

Conclusion:

The MACE benefits associated with GLP1-RAs are dependent on the reduction of HbA1c levels.

1. Introduction

The conventional management protocol for type 2 diabetes (T2D) included achieving glycemic and associated metabolic targets (weight, blood pressure, and lipids). (1) This strategy was supported by findings from the UKPDS study which documented an impressive reduction in microvascular complications. It was found that a 0.9% reduction in HbA1c from baseline could result in a 21% reduction in retinopathy, 33% reduction in albuminuria, and a 12% reduction in any diabetes related end points. (2) Though initially no macrovascular benefits were seen in this study, the 10-year follow up of the UKPDS cohort showed a significant 15% reduction in myocardial infarction (MI) and a 13% reduction in all-cause mortality with intensive therapy. (3) However, subsequent trials aiming at near physiological HbA1c targets did not achieve any macrovascular benefits. (4, 5, 6) In fact the ACCORD trial revealed an unexplained 22% increase in

mortality on targeting a HbA1c level below 6%. (4) As a result, individualization of glycemic targets became the new management strategy, a few years back.

However, the management of type 2 diabetes (T2D) underwent a paradigm shift after the publication of EMPA-REG outcomes trial wherein the SGLT-2 inhibitor empagliflozin, demonstrated impressive macrovascular as well as microvascular outcomes, compared to placebo, irrespective of metabolic control. (7) This trial was followed soon after by the publication of multiple studies documenting positive macro and microvascular outcomes with the usage of SGLT2i and glucagon-like-peptides 1 receptor analogues (GLP1-RAs). (8) As a result, the choice of drugs became as important as metabolic targets, if not more. The recent SIMPLE approach proposed the use of a combination of glucose lowering (GLA) and disease modifying agents (SGLT-2i and GLP1-RAs) in all T2D patients to achieve glycemic targets as well as prevent adverse outcomes. (9)

The initial cardiovascular outcomes trials (CVOTs) tried to accomplish glycemic equipoise to neutralise any positive impact of significant glucose lowering. (10) However, in the CVOTs investigating GLP1-RAs, glycemic equipoise was not maintained and significant HbA1c reduction was seen with GLP1-RA therapy compared to the placebo. In fact, in the SUSTAIN 6 study the HbA1c difference between the 1.0 mg semaglutide and placebo was 1.0%. (11) This naturally raises the question of whether the macrovascular benefits observed with GLP1-RAs group in CVOTs are a direct effect of the molecule per se or whether there is an additional contribution from significant glucose lowering, which would be in keeping with the findings of a meta-analysis by Turnbull et al which indicated a modest but significant impact of intensive glycemic control on macrovascular outcomes, driven primarily by a 15% reduction in MI; along with a HbA1c target range of 7.5–8.5% seemingly more favourable for macrovascular outcomes than targets below 7.5%.(12) Interestingly, the end-of-study HbA1c in the CVOTs with GLP1-RAs ranged between 7.1% and 7.8%, matching the benefit range suggested by Turnbull et al.

Hence this meta-regression analysis was conducted to explore the degree of heterogeneity associated with the primary outcomes in the CVOTs with GLP1-RAs as the preferred intervention. The aim was to detect any variability in the true effect size across all the trials and focus on contributions made by the metabolic benefits afforded by GLP1-RAs, thus deducing whether the positive macrovascular outcomes associated with GLP1-RAs was a combined impact of the molecule and metabolic improvements, or solely a benefit related to the use of the molecule.

This meta-analysis was designed following the PICO question format (shown below):

P (patient population) = Patients diagnosed with T2D.

I (intervention) = Received drugs belonging to the GLP1-RAs group.

C (control group) = Compared to a control group that received a placebo.

O (outcome) = The primary aim was to analyse whether the primary outcome benefits seen in the included citations were dependent or independent of metabolic benefits.

2. Materials And Methods

This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (13). Our review protocol was prospectively registered with INPLASY (INPLASY202130077).

2.1 Search strategy and eligibility criteria:

An electronic database search was conducted using the Cochrane Library. Keywords included “Glucagon like peptide 1 receptor agonist”, “GLP 1RA”, “liraglutide”, “exenatide”, “lixisenatide”, “dulaglutide”, “semaglutide”, “albiglutide”, “efpeglenatide”, “MACE”, “major advance cardiovascular events”, “myocardial infarction” [MeSH], “AMI”, “Stroke” [MeSH], “CV death”, and “cardiovascular death”. The drug-related and outcome-related searches were combined using the Boolean “OR”, and both these entities combined using the Boolean “AND”. Additional filters used were RCT and date of selection between August 2008 (the publication of FDA guidance for the industry) without any restriction on the language of reporting. As an additional screening method, studies having placebo in the comparator arm as well as those having the standardized primary outcomes as the outcome of interest were included (Figure 1).

2.2 Data extraction and quality assessment of the included citations:

BS and SG conducted the web search independently and on different days. Having performed the original screening test screened data were assessed and filters were implemented based on consensus. Having identified the screened citations, further eligibility was assessed based on prespecified inclusion criteria.

The inclusion criteria were as follows:

- Randomized controlled trials.

- Type 2 diabetes patients aged 18-75 years.

- Placebo as the comparator arm.

- Primary outcomes including 3-point MACE and a clear definition of its individual components.

- Reporting of the metabolic components influenced by GLP1-RAS including HbA1c, weight, LDL-C, and systolic blood pressure.

Having identified the nine studies eligible for the meta-regression analysis, the raw data were entered by SG into a blank sheet provided by the CMA software. (11, 14-21) The accuracy of data entry was cross-checked by BS on another day. Any discrepancy was solved based on mutual consensus.

The quality of the individual studies was assessed using the Cochrane Risk of Bias algorithm (Supplementary figure 1).

2.3 Patient approval and ethical committee clearance:

The study was a systematic review and meta-regression analysis, so there was no direct patient handling. Since all the data used are in the public domain in the form of published articles and their associated supplementary materials, no ethical committee approval was sought.

2.4 Statistical analysis:

The planned analysis was divided into 4 stages:

Stage 1: The first stage involved documenting the effect size (hazard Ratio) related to the use of GLP1-RAs and the primary CV outcomes. We planned to perform a meta-analysis on major advance cardiac events (MACE) and its components using a random-effects model (since the baseline characteristics of these studies varied considerably and did not represent a single population of interest). Although the effect sizes of these 9 studies had already been reported, our main aim was to identify the variation in the effect size from one study to another and the degree of heterogeneity present in the effect size. With the help of Q statistics, we aimed to identify the sum of squared deviations (of observed effects from the mean) on a standardized scale. If it refuted the null hypothesis ($P<0.1$), it would indicate that the true effect size varies across studies. In addition, we aimed to look at I^2 statistics, which would indicate the relationship between the variance of the observed effect and the variance of true effect.

Step 2: Having identified significant variance (if any), a meta-regression analysis would be conducted using the metabolic parameters of interest (HbA1c, weight, and SBP) as the probable covariates explaining the variance in the true effect size across the studies. We planned to use all 3 moderators and to identify the model that best fits the outcomes of interest. Having identified the model, we would look at the proportion of variance explained by the model using R^2 statistics.

Step 3: Since the SUSTAIN-6, PIONEER-6 and FREEDOM trials were designed as noninferiority trials, and were underpowered to test for superiority, a subgroup analysis was planned to identify any difference in within-study variance in contrast to step 2. If there was concordance between the outcomes of step 2 and step 3, we would proceed to step 4.

Step 4: In the scenario of successfully identifying the covariates explaining the variance of true effects, a categorical evaluation was planned that would use a standardized cut off HbA1c value to explain the association in step 3.

The analysis was conducted using the comprehensive meta-analysis (CMA) software version 3 (Biostat Inc., Englewood, NJ, USA).

3. Results

3.1 Baseline characteristics of the included citations:

The meta-analysis was conducted on a pooled population of 64,236 patients with 32,769 patients in the GLP1-RAS arm and 31,467 participants in the placebo arm. The mean age of participants across these studies ranged from 60 years to 66.2 years. The duration of follow up ranged from 1.3 years to 5.4 years, with the REWIND trial having the longest follow-up duration. All the studies had placebo as comparator. The mean baseline HbA1c ranged from 7.2% to 8.9%, with the REWIND representing the former and the AMPLITUDE-O trial representing the latter. The mean baseline weight and SBP ranged from 84.6 kg to 92.9 kg and 129 mm of Hg to 137.5 mm of Hg respectively. Two studies (AMPLITUDE-O and FREEDOM) did not report the baseline

weight of participants, although the weight difference was mentioned. The FREEDOM trial did not report the mean difference in patients' SBP.

There was no significant risk of bias identified in any of the 9 studies according to the Cochrane risk-of -bias algorithm. There was no significant publication bias as assessed visually with funnel plots and quantitatively with Egger's regression intercept (2 tailed p value = 0.64) (Supplementary figure 2).

The baseline characteristics of the studies are detailed in table 1.

Study [Year]	GLP1-RAS	Mean age (years)	GLP1-RAS Group/Placebo group (n)	Duration of follow up	Baseline HbA1c (%)	Baseline Weight (kg)	Baseline SPM (mm of Hg)
ELIXA [2015][14]	Lixisenatide	60	3034/3034	2.1	7.7	84.6	129
LEADER [2016][15]	Liraglutide	64.3	4668/4672	3.8	8.7	91.9	135.9
SUSTAIN-6 [2016][11]	Semaglutide OW	64.6	1648/1649	3.1	8.7	92.9	135.8
EXSCEL [2017][16]	Exenatide OW	62	7356/7396	3.2	8.0	92*	136
HARMONY [2018][17]	Albiglutide	64	4731/4732	1.6	8.7	92*	134.8
REWIND [2019][18]	Dulaglutide OW	66.2	4949/4952	5.4	7.2	88.4*	137.1
PIONEER-6 [2019][19]	Semaglutide (Oral)	66	1591/1592	1.3	8.2	91	135
AMPLITUDE-O [2021][20]	Efpeglenatide	64.5	2717/1359	1.8	8.9	NR#	134.9
FREEDOM [2021][21]	Exenatide (ITCA 650)	63	2075/2081	1.4	8.0	94	137.5

Table 1: Baseline characteristics of the studies included in the analysis. OW: Once weekly; * extrapolated from figures (an approximation of the exact value); #NR: Not reported.

3.2 Step 1: Results of the meta-analysis related to within-study variance:

The Q statistics (12.62) and associated p value (<0.01) indicated that the effect size of MACE varied significantly across the studies. Regarding the individual components of MACE, although there was no significant heterogeneity or publication bias detected, they were taken up for the meta-regression analysis in view of gross variability in the baseline characteristics of the studies.

Meta-analyses parameters	MACE	CV Death	NFMI	NFS
HR	0.87	0.88	0.91	0.85
95% CI	0.81-0.94	0.80-0.95	0.84-1.00	0.76-0.93
P Value	<0.01	<0.01	0.06	<0.01
Tests of heterogeneity				
Q	16.88	9.44	11.76	5.94
df	8	8	8	8
I^2	52.56	15.23	32.00	0.00
P Value	0.03	0.31	0.16	0.65

Table 2: Primary outcome (MACE) with its individual components: effect size and variance. (MACE: major cardiac events; CV: cardiovascular; NFMI: nonfatal myocardial infarction; NFS: nonfatal stroke).

3.3 Step 2: Covariates and their probable association with MACE:

We used three covariates for the meta-regression analysis (HbA1c, weight, and SBP). The initial screening demonstrated a significant association between MACE and the moderators. Since the individual components of MACE could not explain the variability in the true effect size, they were excluded from this analysis. In addition, the FREEDOM trial was excluded from the meta-regression analysis since a change in SBP was not reported.

A model was created using HbA1c, weight, and SBP as the moderators and MACE as the outcomes of interest. Keeping HbA1c and SBP fixed, reduction of body weight (-coefficient 0.02; 95% CI -0.09 to 0.04, p=0.43) did not explain the variation in the true effect size for MACE. A reduction in SBP keeping HbA1c and weight fixed, was unable to account for the variation in the true effect size (coefficient 0.07, 95% CI 0.06 to -0.06, p=0.27). (Figure 2) However, HbA1c reduction, keeping weight and SBP fixed, correlated with the variance in MACE benefit (p=0.03) (Table 2).

Main results for Model 1, Random effects (MM), Z-Distribution, Log hazard ratio						
Covariate	Coefficient	Standard Error	95% CI (Lower)	95% CI (Upper)	Z value	2-sided p value
Intercept	-0.02	0.09	-0.19	0.16	-0.24	0.81
HbA1c difference	-0.31	0.14	-0.59	-0.02	-2.08	0.03
Weight difference	-0.02	0.04	-0.09	0.04	-0.78	0.43
SBP difference	0.07	0.07	-0.06	0.21	1.10	0.27
Statistics for Model 1						
Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero						
Q = 8.51, df = 3, p = 0.0366						
Goodness of fit: Test that the unexplained variance is zero						
Tau² = 0.0001, Tau = 0.0073, I² = 1.05%, Q = 4.04, df = 4, p = 0.4003						
Comparison of Model 1 with the null model						
Total between-study variance (intercept only)						
Tau² = 0.0042, Tau = 0.0647, I² = 44.56%, Q = 12.63, df = 7, p = 0.0818						
Proportion of total between-study variance explained by Model 1						
R² analog = 0.99						

Table 3: Covariates explaining the within-study variance of the true effect (MACE)

The regression model indicated a significant association between one of the moderators (HbA1c) and the variation in effect size (Table 3).

Since HbA1c emerged as the covariant of importance, we performed a meta-regression analysis using HbA1c as the sole moderator (Figure 3).

There was a correlation between an HbA1c reduction and a variance in the MACE benefits ruling out any sampling error (Table 4). The model (Y=0.0329-0.3115*HbA1c difference) indicated a 21.86% reduction in MACE per 1% mean difference in HbA1c from the placebo arm.

Main results for Model 1, Random effects (MM), Z-Distribution, Log hazard ratio						
Covariate	Coefficient	Standard Error	95% CI (Lower)	95% CI (Upper)	Z value	2-sided p value
Intercept	0.03	0.06	-0.10	0.17	0.49	0.63
HbA1c difference	-0.31	0.12	-0.54	-0.08	-2.65	<0.01
Statistics for Model 1						
Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero						
Q = 7.00, df = 1, p = 0.0082						
Goodness of fit: Test that the unexplained variance is zero						
Tau² = 0.0000, Tau = 0.0000, I² = 0.00%, Q = 5.63, df = 6, p = 0.4663						
Comparison of Model 1 with the null model						
Total between-study variance (intercept only)						
Tau² = 0.0042, Tau = 0.0647, I² = 44.56%, Q = 12.63, df = 7, p = 0.0818						
Proportion of total between-study variance explained by Model 1						
R² analog = 1.00						

Table 4: HbA1c as the sole moderator explaining the within-study variance of the true effect size (MACE)

3.3 Step 3: Subgroup analysis excluding underpowered studies:

The meta-analysis performed by excluding the SUSTAIN-6 and PIONEER-6 trials did not influence the effect size of MACE (HR: 0.87, 95% CI 0.81-0.94, p<0.01) or the within-study variance (Q=10.37, df=5, I^2=51.78, p=0.06). No significant within-study variance was detected in any of the individual components of MACE.

3.4 Step 4: Assessing the proportion of variance in the effect size (MACE) explained by achieving a HbA1c reduction ≥0.9%:

Two categorical groups were formed based on whether the GLP1-RAs in question in the CVOT could reduce HbA1c by ≥0.9% (Y) or not (N). With the N group acting as the intercept, we performed a meta-regression to determine the degree of association with the Y group (Figure 4).

There was a strong correlation between an HbA1c reduction ≥0.9% and the variance in MACE benefits (p<0.01) (Supplementary table 1). We could possibly infer that the lower HR for MACE in the GLP1-RA group was complemented by an HbA1c reduction of ≥0.9%.

4. Discussion

4.1 Background

An absolute difference in HbA1c of 0.8% in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial resulted in a 16% significant reduction in the key secondary endpoints (composite of all-cause mortality, non-fatal stroke (NFS), and non-fatal myocardial infarction (NFMI). (22) In addition, to the meta-analysis by Turnbull et al (which has been previously described) a recent meta-analysis including 15 RCTs revealed a significant 36% reduction in non-fatal stroke and a 22% reduction in all-cause mortality with intensive glycemic control achieving a HbA1c between 7.0%-7.7% when compared with conventional control. (23)

In view of this anticipated beneficial impact of mitigation of hyperglycaemia on reduction in macrovascular complications, the initial CVOTs post 2008 attempted to achieve glycemic equipoise to illustrate the inherent cardiovascular safety and efficacy of the newer anti hyperglycemics. (10) In the CVOTs conducted using SGLT-2i and DPP-IVi as the intervention the HbA1c difference with the standard of care ranged between 0.25% to 0.58%. (7,24,25,26,27) This difference was not significant enough to influence micro- and macrovascular benefits.

In contrast the CVOTs conducted with GLP1-RAS were associated with a larger HbA1c difference between intervention and standard of care ranging between 0.4% to 1.24%. (11,14-21) In addition, GLP1-RAs are known to produce a greater impact on metabolic parameters (HbA1c, SBP, and weight reduction) in contrast to SGLT-2i.

As a result, it is worth speculating whether the macrovascular benefits associated with GLP1-RAs in CVOTs are exclusively due to the molecules themselves or are due to the improvement in metabolic parameters. This meta-regression analysis was undertaken to address this important question.

4.2 Findings from our study

We found a significant heterogeneity in the MACE effect size in the pooled meta-analysis of nine studies using the random effects model (Q:12.62; df:8, $p<0.01$), indicating that there were covariates apart from the use of GLP1-RAs which could explain the MACE benefit. There was no significant effect size variance seen with the individual components of MACE (CV death, NFMI, and NFS). A subgroup analysis excluding the underpowered studies (SUSTAIN-6 and PIONEER-6) did not impact the MACE effect size variance. The meta-regression analysis using three clinical moderators of interest (HbA1c, SBP, and weight) of interest indicated that the variance between the observed effect size and the true effect size could be explained by the model (Q: 8.51, df: 3, $p = 0.03$). However, an HbA1c reduction keeping weight and SBP reduction fixed drove the model to significance. Using an HbA1c reduction as the sole moderator, the model was found to be significant (Q :7.00, df :1, $p<0.01$), with 100% of the variance explained by the HbA1c reduction; this indicated the absence of any sample errors. The model indicates a 28.6% reduction in MACE for every 1.0% difference in HbA1c between the GLP1-RAs and placebo. Achieving a HbA1c reduction of $\geq$0.9% from baseline complimented the GLP1-RAs in achieving MACE benefits ($p<0.01$).

4.3 Limitations and strengths:

One of the limitations of the study was inclusion of a the nonuniform definitions for NFMI and NFS. Two studies (EXSCEL and HARMONY) used fatal or nonfatal MI and stroke as the individual components of MACE,

in contrast to the other six trials that included NFMI or NFS. This could have skewed the results, including those related to MACE, which was our primary focus of analysis. However, removing these two studies did not significantly impact either MACE or the within-study variability. Another limitation was inclusion of calculated effect size and not those from individual-level pooled data.

The main strengths of this analysis are a large sample size along with data from randomised controlled trials which all had preadjudicated and prespecified analytical designs. In addition, there were no significant bias associated with the included citations. In addition, since we identified the citations from a literature search the random effects model was used throughout to identify the variations in the true effect size in contrast to the observed one. This exposed the outcomes of interest through a stringent scrutiny making the conclusion robust and generalizable to a wider population.

5. Conclusion

In addition to adding GLP1-RAS to T2DM patients with established CV disease or high CV risk, we believe achieving glycemic targets are equally important. This analysis reinstates and reiterates the huge importance of achieving metabolic targets. We conclude therefore, that though the choice of antihyperglycemic agents with cardiovascular benefits are a priority in the management of T2D, control of HbA1c should also share equal importance.

Declarations

Data availability statement:

The original contributions presented in this study are included in the article and in the supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement:

We analyzed published data; hence, ethical approval was not required.

Author contributions:

The study was conceptualized by SG. An electronic database search was conducted independently by BS and SG and the selected studies were identified based on consensus. The meta-analysis was conducted by SG. The manuscript was written by BS with contributions by SG in the methodology section. All authors contributed to the article and approved the submitted version.

Conflict of interest:

The authors do not have any conflicts of interest to declare.

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Figures

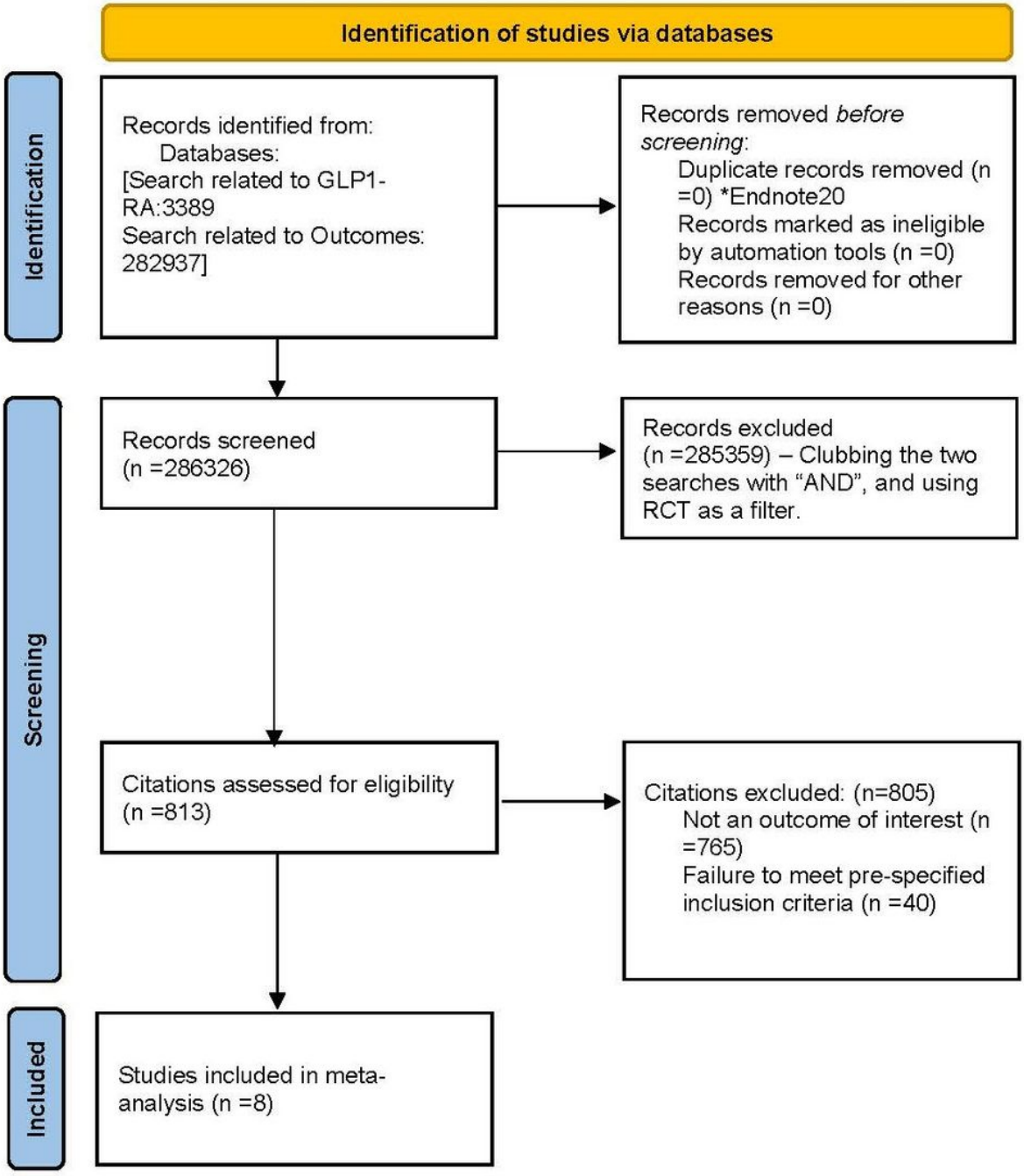

Figure 1

Study selection process

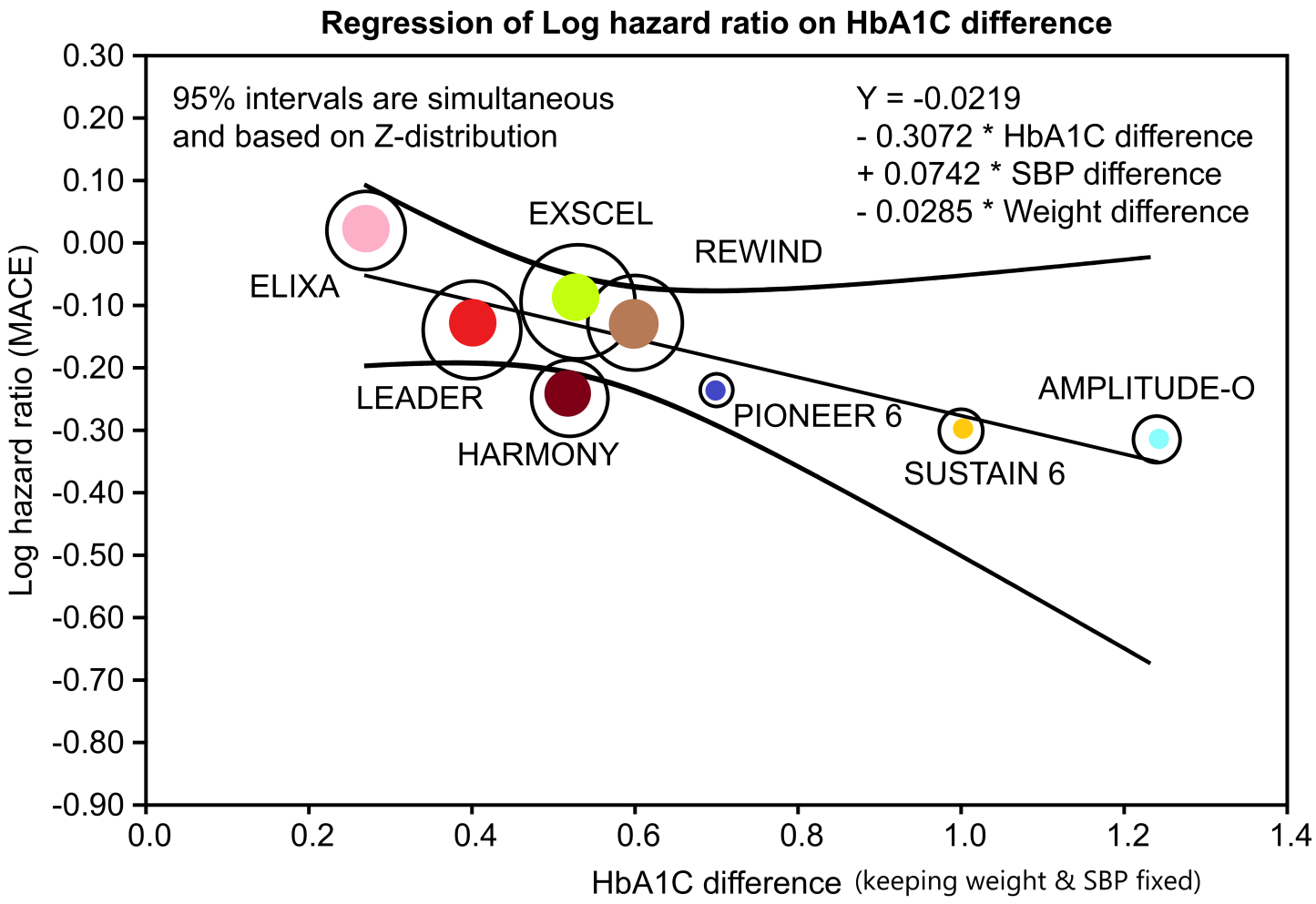

Figure 2

Regression of Log Hazard Ratio (MACE) on HbA1c lowering of ≥0.9%. (N: HbA1c <0.9%; Y: HbA1c ≥0.9%)

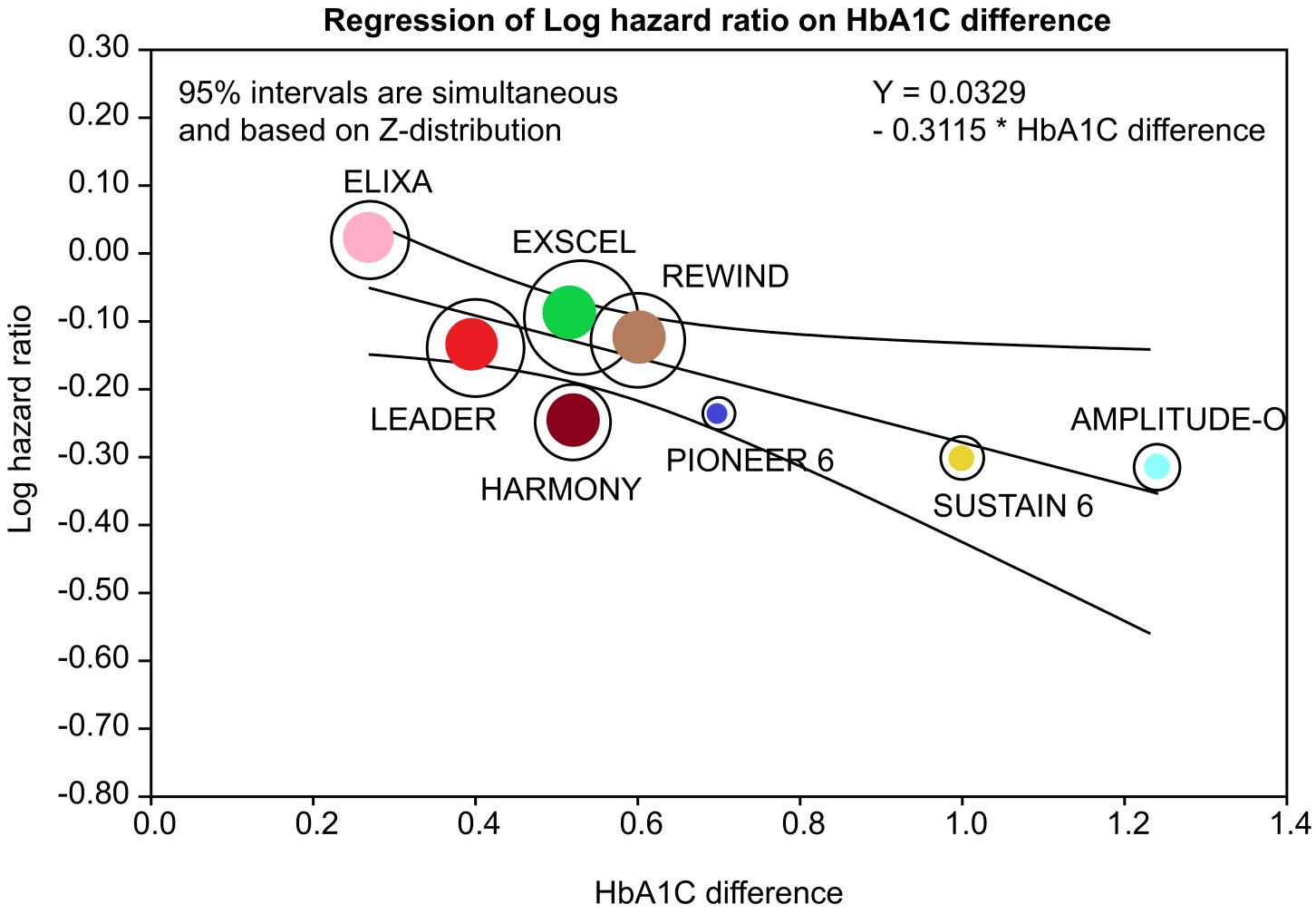

Figure 3

Regression of hazard Ratio (MACE) on HbA1c difference (keeping weight and SBP fixed)

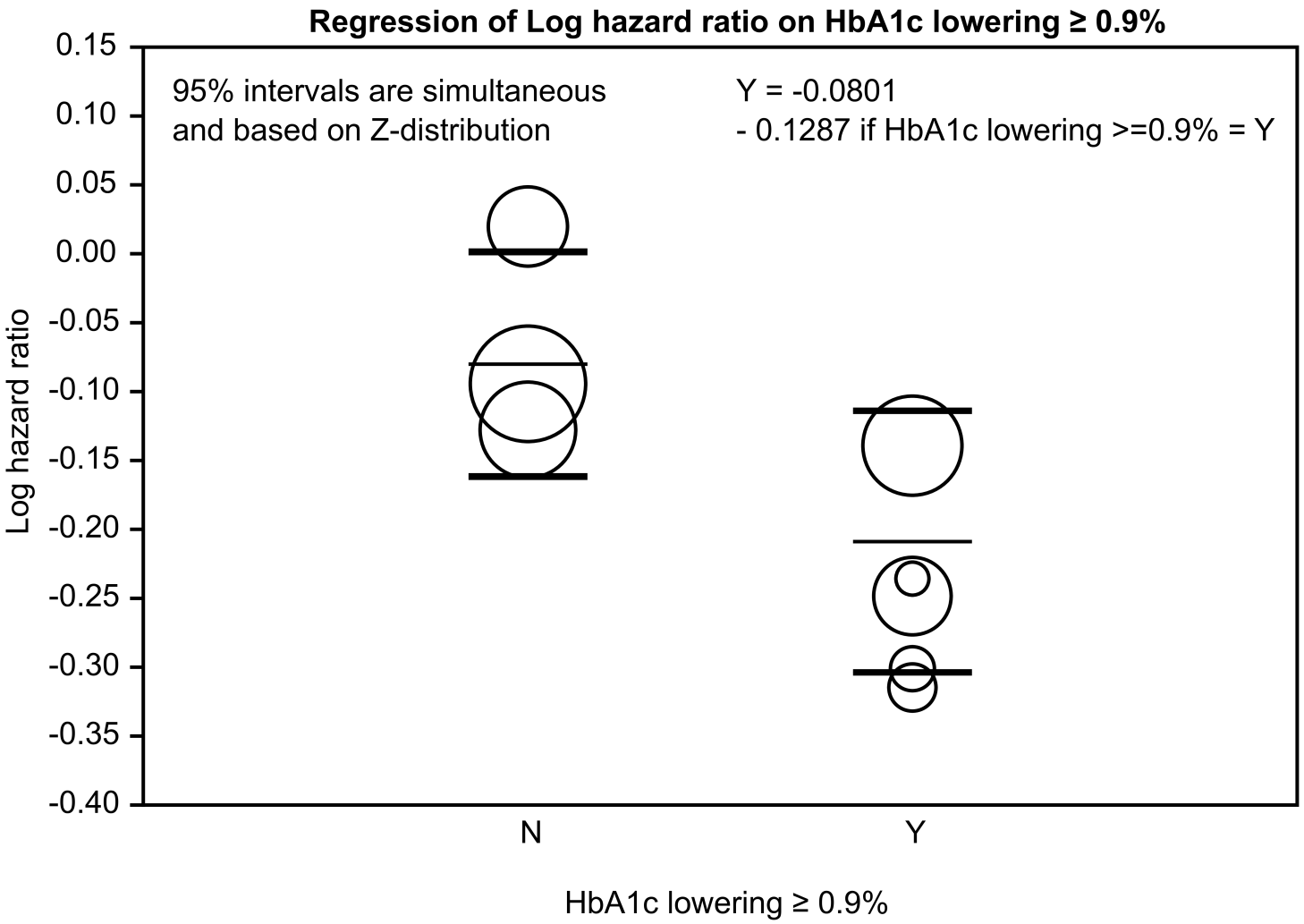

Figure 4

Regression of Log Hazard Ratio (MACE) on HbA1c difference (single moderator)

Supplementary Files

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- Supplementaryfigure1.jpg
- Supplementaryfigure2.jpg
- Supplementarytable1.docx