

Glucagon-like Peptide-1 Receptor Agonists versus Sodium-Glucose Cotransporter Inhibitors for Treatment of T2DM

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Context. Cardiovascular outcome trials (CVOT) of glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) demonstrated reduction of major adverse cardiovascular events (MACE), cardiovascular deaths (CVD), and renal outcomes.

Objective. Assist in the prescribing decision regarding severity of illness and risk for adverse events.

Design. Meta-analysis of the major CVOT and previous meta-analyses.

Main Outcome Measures. Six trials of GLP-1 RA (51 762 subjects) and 4 trials of SGLT2i (33 457 subjects) showed both drug classes reduced MACE and CVD versus controls, with neither class preferred (comparison GLP1-RA vs SGLT2i: relative rate [rr] MACE 1.04, 95% confidence interval [CI] 0.94, 1.16, $P = \text{ns}$; rr CVD 1.04, 95% CI 0.87, 1.24, $P = \text{ns}$). Hospitalization for heart failure (HHF) improved with SGLT2i (rr 0.68, CI 0.61, 0.76, $P < 0.001$) but not with GLP-1 RA, (rr 0.93, CI 0.86, 1.03, $P = \text{ns}$). Meta-regression suggested benefits of the SGLT2i on CVD and HHF were accentuated with the underlying rate of MACE in the cohort (i.e., >10 events/1000pt*year). GLP-1 RA and SGLT2i showed reduction in renal outcomes (GLP-1 RA rr 0.83, CI 0.75, 0.91, $p \leq 0.001$, SGLT2i rr 0.67, CI 0.57, 0.79, $P < 0.001$) without a preferential difference (GLP-1 RA vs SGLT2i, rr 1.24, CI 0.95, 1.61, $P = \text{ns}$; relative difference (rd) 0.005, CI -0.011, 0.021, $P = \text{ns}$). Serious adverse events for SGLT2i were mycotic genital infections in women (number needed to harm [NNH] = 13 and diabetic ketoacidosis NNH = 595). Gastrointestinal intolerance was the serious adverse event in the GLP1-RA class (NNH = 35).

Conclusion. GLP-1 RA and SGLT2i classes showed similar reduction in MACE, CVD, and renal outcomes. SGLT2i have advantages over GLP-1 RA in reduction in HHF.

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Key Words: GLP1 receptor agonists, SGLT2 inhibitors, meta-analysis, type 2 diabetes mellitus

The American Diabetes Association and the European Association for the Study of Diabetes both recommend adjustment of pharmacological therapy of type 2 diabetes to include cardiovascular and chronic kidney disease as associated risks [1]. Recent cardiovascular outcome trials (CVOTs) have shown benefits associated with 2 classes of medications: glucagon-like

peptide-1 receptor agonists (GLP-1 RA) [2-7] and sodium-glucose cotransporter-2 inhibitors (SGLT2i) [8-11].

We reviewed the previous analyses to evaluate the relative benefit regarding underlying cardiovascular risks, underlying renal diseases, and the relative adverse event risk profile. The individual trials had differing inclusion criteria, different severity of cardiovascular and renal diseases, and different duration of follow-up of the populations. We re-evaluated the event rates regarding the underlying event rates in the control population to use these data to estimate the effectiveness of treatment strategies using existing cardiovascular risk engines and renal profiling.

1. Methods

We followed the review analysis of Bethel et al [12] of the 5 major GLP-1 RA CVOTs and of Zelniker et al [13,14] of the 4 major SGLT2i CVOTs. Data were abstracted from the primary publication, their supplements, and subsequent publications [15-18]. The primary efficacies were 3-point major adverse cardiovascular event (MACE; cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke) or 4-point MACE to include also hospitalizations for heart failure (HHF). Secondary endpoints included total mortality and hospitalization for heart failure. Prespecified renal outcomes varied among the trials. The majority evaluated renal outcomes as doubling of serum creatinine and decrease in estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m², progression to macroalbuminuria, initiation of renal replacement therapy, and death from renal disease. However, several trials used criteria of a decrease in eGFR of $>30\%$ from baseline. All studies monitored for serious adverse events.

Baseline statistical analyses were performed with the statistical program Statistica. Analyses of comparison of trials were performed as weighted means using nonpaired *t*-tests. Statistical significance was defined as a $P < 0.05$ by 2-tailed Student's *t*-test.

Meta-analyses were performed with the statistical program MIX 2.0 Professional software for meta-analysis in Excel, version 2.0.1.6 [19-21]. Heterogeneity of studies was calculated by I^2 (a statistic that indicates the variance in meta-analysis that is attributable to the study heterogeneity) where I^2 0% to 30% is considered low heterogeneity, and 30% to 60% may represent moderate heterogeneity [22]. Risk ratio (relative risk [rr]) and relative differences [rd] were performed using fixed effects model of Mantel-Haenszel for data considered to be of low and moderate heterogeneity. Data considered to have high degree of heterogeneity were evaluated by the random effects model of DerSimonian and Laird [23].

Analysis of continuous data was assessed as mean difference with a fixed mode model using an inverse variance method [21]. Subgroup interactions were calculated from *Q* statistics [22]. The study quality was considered according to the grade recommendations [24] and is included in Tables 1 and 2.

2. Results

A. Trial characteristics

There are 6 major cardiovascular trials of GLP-1 RA (LEADER Trial [2], SUSTAIN-6 Trial [3], ELIXA Trial [4], EXCEL Trial [5], REWIND Trial [6], PIONEER 6 Trial [7]) encompassing 51 762 subjects and 4 major cardiovascular trials of SGLT2i encompassing 33 457 subjects (EMPA-REG OUTCOME Trial [8], CANVAS Trial [9], DECLARE-TIMI 58 Trial [10], CREDENCE Trial [11]) (Table 1). The trials of both classes of drugs, GLP-1RA and SGLT2i, were similar in many baseline characteristics, including age at enrollment (63.6 ± 2.0 [standard deviation] vs 63.5 ± 0.4 , $P = \text{ns}$), the percentage of women ($39 \pm 5\%$ vs $35 \pm 3\%$, $P = \text{ns}$), and the percentage with cardiovascular disease entered ($68 \pm 25\%$ vs $50 \pm 16\%$, $P = 0.05$). The trials differed in the duration of the studies for GLP-1 RA versus SGLT2i (3.4 ± 1.2 years vs 3.7 ± 0.6 years, $P < 0.001$), baseline A1c (8.0 ± 0.5 vs 8.2 ± 0.1 , <0.001),

Table 1. Characteristics of major CVOTs of GLP-1RA and SGLT2i in type 2 diabetes mellitus

| Study | GLP-1RA | | | | | | SGLT2i | | | |
|---|---------------------------------|-------------------------|------------------------|-------------------------|-------------------------|-------------------------|------------------------|--------------------|---------------------------|---|
| | Marso (LEADER) 2016 Mann2017 | Pfeffer (ELIXA) 2015 | Marso (SUSTAIN-6) 2016 | Holman (EXSCEL) 2017 | Gerstein (REWIND) 2019 | Husain (Pioneer) 2019 | Zinman (EMPA-REG) 2015 | Neal (CANVAS) 2017 | Perkovic (CREDEENCE) 2019 | Wiviott (DECLARE-TIMI58) 2018/ Mosenzon 2019 |
| Subjects | 9340 | 6068 | 3297 | 14 752 | 9901 | 3183 | 7020 | 10 142 | 4401 | 17 160 |
| Drug | Liraglutide | Lixisenatide | Semaglutide | Exenatide | Dulaglutide | Oral Semaglutide | Empagliflozin | Canagliflozin | Canagliflozin | Dapagliflozin |
| Total drug | 4668 | 3034 | 1648 | 7356 | 4949 | 1591 | 4687 | 5795 | 2202 | 8582 |
| Total control | 4672 | 3034 | 1649 | 7396 | 4952 | 1592 | 2333 | 4347 | 2199 | 8578 |
| Duration, years | 3.8 | 2.08 | 2.1 | 3.2 | 5.4 | 1.325 | 3.1 | 3.62 | 2.62 | 4.2 |
| Age, years (SD) | 64.2 (7.2) | 59.9 (9.7) | 64.6 (7.4) | 62.0 (3.0) | 66.2 (6.5) | 66 (7) | 63.1 (8.6) | 63.3 (8.3) | 63.0 (9.2) | 63.9 (6.8) |
| | Drug, 64.4 (7.2) | Drug, 60.6 (9.6) | Drug, 64.4 (7.2) | Control, 64.4 (7.2) | Control, 66.2 (6.5) | Control, 66 (7) | Drug, 63.1 (8.6) | Drug, 63.3 (8.3) | Drug, 63.0 (9.2) | Drug, 63.9 (6.8) |
| Glycated hemoglobin %, mean (SD) | 8.7 (1.6) | 7.7 (1.3) | 8.7 (1.5) | 8.0 (0.4) | 7.2 (0.9) | 8.2 (1.6) | 8.1 (0.85) | 8.2 (0.9) | 8.3 (1.3) | 8.3 (1.2) |
| | Drug, 8.7 (1.6) | Control, 7.7 (1.3) | Drug, 8.7 (1.5) | Control, 8.0 (0.4) | Drug, 7.2 (0.9) | Control, 8.2 (1.6) | Control, 8.1 (0.85) | Control, 8.2 (0.9) | Control, 8.3 (1.3) | Control, 8.3 (1.2) |
| Women, % | 35.5 | 30.4 drug, 30.9 Control | 39.3 | 38 | 46.3 | 31.6 | 28.8 | 35.8 | 33.9 | 36.9 Drug, 37.9 Control |
| | Control, 35.5 | 30.4 drug, 30.9 Control | 39.3 | 38 | 46.3 | 31.6 | 28.8 | 35.8 | 33.9 | 36.9 Drug, 37.9 Control |
| Hypertension, % | 92 | 75.6 Drug, 77.1 Control | 92.8 | 90.5 (90.3) | 93.0 drug, 93.3 Control | 94.9 | 94.9 | 90 | 97 | 90 |
| | Control, 92 | 75.6 Drug, 77.1 Control | 92.8 | 90.5 (90.3) | 93.0 drug, 93.3 Control | 94.9 | 94.9 | 90 | 97 | 90 |
| Heart failure, % | 9.9 Drug, 10.2 Control | 22.5 Drug, 22.3 Control | 23.6 | 15.8 Drug, 16.6 Control | 8.5 drug, 8.7 Control | 11.8 Drug, 12.6 Control | 9.9 | 14.4 | 14.8 | 9.9 Drug, 10.2 Control |
| | 9.9 Drug, 10.2 Control | 22.5 Drug, 22.3 Control | 23.6 | 15.8 Drug, 16.6 Control | 8.5 drug, 8.7 Control | 11.8 Drug, 12.6 Control | 9.9 | 14.4 | 14.8 | 9.9 Drug, 10.2 Control |
| Cardiovascular disease, % | 32.9 drug, 33 Control | 100 | 60.5 | 73.3 Drug, 72.9 Control | 31.5 drug, 31.4 Control | 100 | 75.6 | 65.6 | 50.4 | 32.9 Drug, 33 Control |
| | 32.9 drug, 33 Control | 100 | 60.5 | 73.3 Drug, 72.9 Control | 31.5 drug, 31.4 Control | 100 | 75.6 | 65.6 | 50.4 | 32.9 Drug, 33 Control |
| Baseline eGFR | 80 (nr) | 76 (22) | 71 (nr) | 75 (15) | 76 (17) | 74 (21) | 74 (15) | 77 (21) | 56 (18) | 85 (8) |
| Change in glycolated hemoglobin, % drug vs. control | -0.40 (0.3) | -1.05 (0.07) | -1.05 (0.07) | -0.53 (0.01) | -0.61 (0.02) | -0.7 | -0.42 (0.03) | -0.58 (0.13) | -0.31 (0.4) | -0.42 (0.01) |

Table 1. Continued

| | GLP-1RA | | | | | | SGLT2i | | | |
|---|------------------------------|----------------------|------------------------|----------------------|------------------------|-----------------------|------------------------|--------------------|-----------------------------|--|
| | Marso (LEADER) 2016 Mann2017 | Pfeffer (ELIXA) 2015 | Marso (SUSTAIN-6) 2016 | Holman (EXSCEL) 2017 | Gerstein (REWIND) 2019 | Husain (Pioneer) 2019 | Zinman (EMPA-REG) 2015 | Neal (CANVAS) 2017 | Perkovic (CREDESCENCE) 2019 | Wiviott (DECLARE-TIMI58) 2018/ Mosenzon 2019 |
| Change in weight, Kg, drug vs. control | 2.3 (0.13) | -0.7 (0.10) | -4.35 (0.30) | -1.27 (nr) | -1.46 (0.11) | -3.4 | -1.98 (0.19) | -1.6 (0.05) | -0.8 (0.17) | -1.8 (0.08) |
| Primary cardiovascular end-point, number of subjects (drug/control) | 3-point MACE | 4-point MACE | 3-point MACE | 3-point MACE | 3-point MACE | 3-point MACE | 3-point MACE | 3-point MACE | 4-point MACE | 3-point MACE |
| Cardiovascular MACE drug/control (n/n) | 608/694 | 406/399 | 108/146 | 839/905 | 594/663 | 61/76 | 490/282 | 538/473 | 273/361 | 756/803 |
| Cardiovascular death drug / control (n/n) | 219/278 | 156/158 | 44/46 | 340/383 | 317/346 | 15/30 | 172/137 | 248/205 | 110/140 | 245/249 |
| Nonfatal myocardial infarction drug/control (n/n) | 292/339 | 261/270 | 47/64 | 483/493 | 223/231 | 37/31 | 223/126 | 228/193 | nr | 392/442 |
| Nonfatal stroke drug/control (n/n) | 159/177 | 54/49 | 27/44 | 169/193 | 135/175 | 12/16 | 150/60 | 149/132 | nr | 235/231 |
| Hospitalization for heart failure drug/control (n/n) | 218/248 | 122/127 | 59/54 | 219/231 | 213/226 | 21/24 | 126/95 | 111/132 | 89/141 | 212/286 |
| Grade criteria | A | A | A | A | A | A | A | A | A | A |

Abbreviation: nr, not reported.

Table 2. Characteristics of secondary renal outcomes from major CVOTs of GLP-1RA and SGLT2i in type 2 diabetes mellitus

| | GLP-1RA | | | | | | SGLT2i | | | |
|---|-------------------------------|----------------------|------------------------|----------------------|------------------------|-----------------------|------------------------------------|--------------------|---------------------------|--|
| | Marso (LEADER) 2016 Mann 2017 | Pfeffer (ELIXA) 2015 | Marso (SUSTAIN-6) 2016 | Holman (EXSCEL) 2017 | Gerstein (REWIND) 2019 | Husain (Pioneer) 2019 | Zinman (EMPA-REG) 2015 Wanner 2016 | Neal (CANVAS) 2017 | Perkoviv (CRE-DENCE) 2019 | Wiviott (DECLARE-TIMI58) 2018/ Mosenzon 2019 |
| Subjects | 9340 | 6068 | 3297 | 14 752 | 9901 | 3183 | 7020 | 10 142 | 4401 | 17 160 |
| Drug | Liraglutide | Lixisenatide | Semaglutide | Exenatide | Dulaglutide | Oral semaglutide | Empagliflozin | Canagliflozin | Canagliflozin | Dapagliflozin |
| Duration, years | 3.8 | 2.08 | 2.1 | 3.2 | 5.4 | 1.325 | 3.1 | 3.62 | 2.62 | 4.2 |
| Baseline eGFR | 80 (nr) | 76(22) | 71 (nr) | 75 (15) | 76 (17) | 74 (21) | 74 (15) | 77 (21) | 56 (18) | 85 (8) |
| Renal outcomes | 4-point renal outcome | Not Prespecified | Not prespecified | Not prespecified | 2-point renal outcome | Not prespecified | Not prespecified | Not prespecified | 4-point renal outcome | 3-point renal outcome |
| Total subjects drug/control (n/n) | 4668/4672 | | 1648/1649 | 4949/4952 | 7344/7389 | | 4687/2333 | 5795/4347 | 2202/2199 | 8582/8578 |
| Renal outcome drug/control (n/n) | 268/337 | nr | 62/100 | 294/346 | 848/970 | | 525/388 | 115/141 | 245/340 | 127/238 |
| Macroalbuminuria, >300 mg/g creatinine drug/control (n/n) | 161/215 | | 44/81 | 154/196 | 441/561 | | 459/330 | | | |
| Doubling Serum Creatinine, eGFR < 45 mL/min/1.73m ² Drug/control (n/n) | 87/97 | | 18/14 | | | | 70/60 | | 118/188 | |
| 40% Reduction eGFR Drug/Control (n/n) | | | | 80/95 | 453/500 | | | 115/141 | | 120/221 |
| Renal replacement therapy drug/control (n/n) | 56/64 | | 11/12 | 55/65 | | | 13/14 | | 116/165 | 6/19 |
| Renal death drug/control (n/n) | 8/5 | | | 5/5 | | | | | 2/5 | 6/10 |
| Grade criteria | A | | B | B | A | | A | A | A | A |

Abbreviation: nr, not reported.

Table 3. Serious adverse events from CVOTs of GLP-1RA and SGLT2i in type 2 diabetes mellitus

| Adverse Event | Drug Class | Number Studied | RR | RD | NNH |
|-------------------------------|----------------|----------------|-----------------------------|-----------------------------------|------------|
| Genital infections in women | SGLT2i | 13 551 | 4.07 (3.41, 4.86)*** | 0.07 (0.06, 0.08)*** | 13 |
| Amputations | SGLT2i | 38 723 | 1.19 (0.92, 1.55) | 0.004 (0.001, 0.007) | 265 |
| Volume depletion | SGLT2i | 38 723 | 1.04 (0.96, 1.14) | 0.002 (-0.002, 0.007) | 472 |
| Fractures | SGLT2i | 38 723 | 1.01 (0.93, 1.11) | 0.0008 (-0.0035, 0.0051) | 1250 |
| Diabetic ketoacidosis | SGLT2i | 38 723 | 2.60 (1.54, 4.40)*** | 0.0017 (0.0008, 0.0026)*** | 595 |
| Urinary tract infections | SGLT2i | 38 723 | 1.00 (0.92, 1.10) | 0.000 (-0.004, 0.005) | N/A |
| GI intolerance | GLP-1RA | 46 451 | 2.65 (1.36, 5.14)** | 0.029 (0.011, 0.046)*** | 35 |
| Gallstone/gallbladder disease | GLP-1RA | 36 640 | 1.24 (1.02, 1.52)* | 0.005 (-0.001, 0.011) | 200 |
| Pancreatitis | GLP-1RA | 46 451 | 1.08 (0.79, 1.48) | 0.00026 (0.00079, 0.00132) | 3846 |

Data for rr and rd are presented as mean (95% CI) and mean (standard deviation), respectively. Bolded text highlights significant differences of drug versus placebo.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

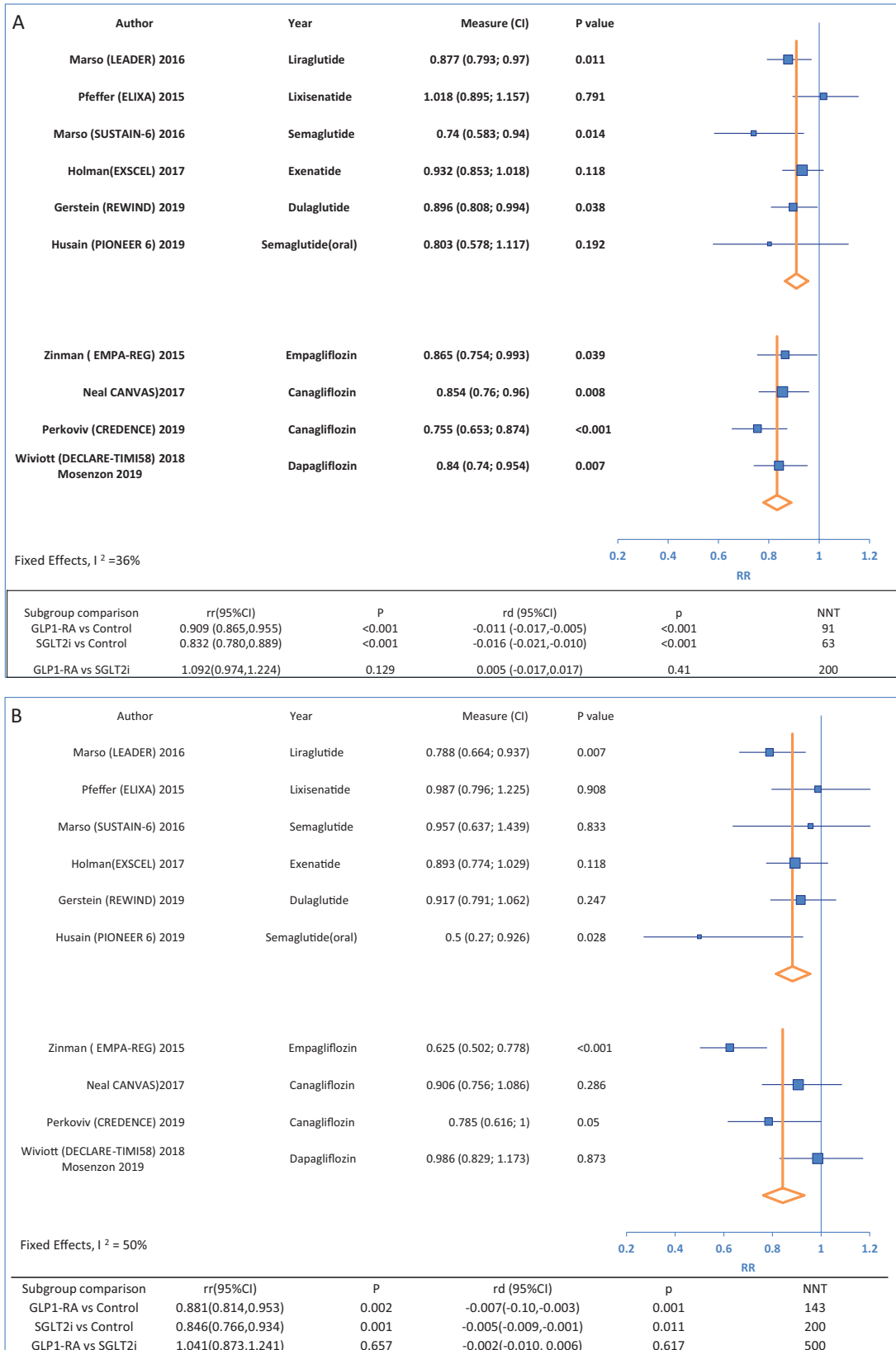


FIGURE 1. Meta-analysis of major CVOTs of GLP-1RA and SGLT2i in type2 diabetes mellitus. Comparisons of drug versus control for GLP-1RA versus SGLT2i. Outcomes $rr < 1.0$ denote better outcomes. (A) MACE. (B) Cardiovascular deaths. (C) Hospitalization for heart failure.

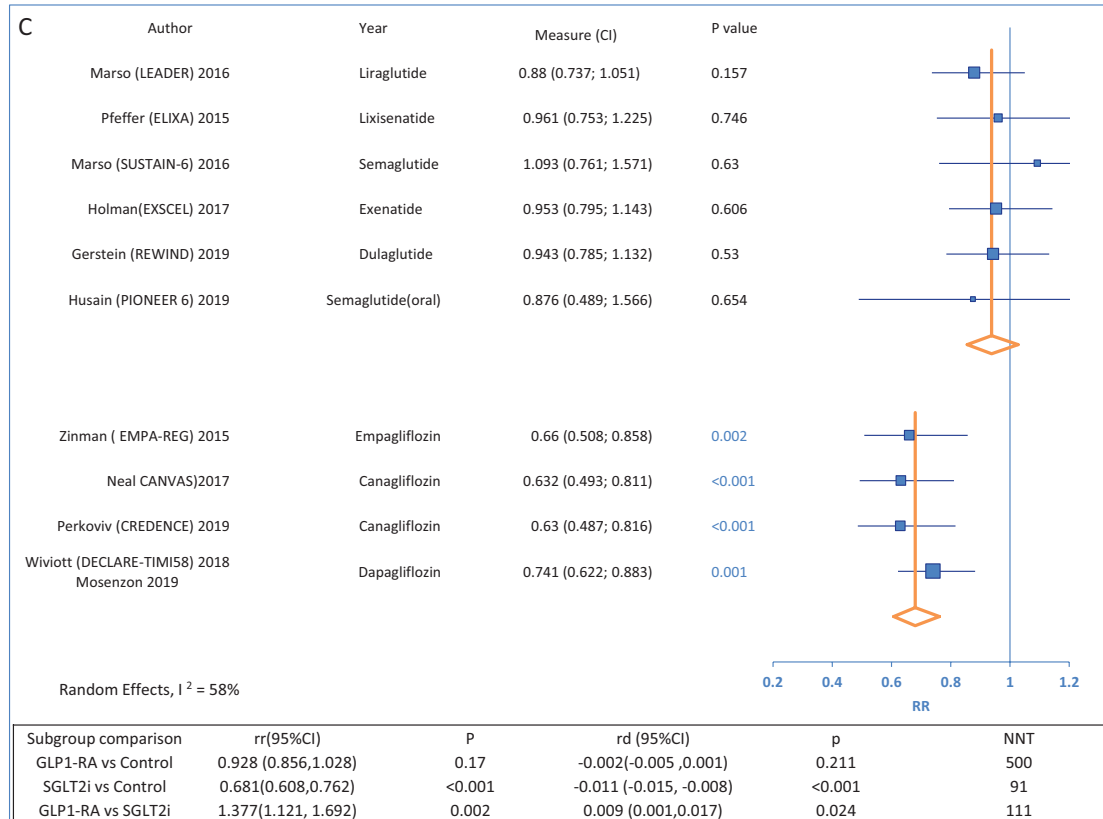


Figure 1. Continued.

percentage with hypertension ($86 \pm 6\%$ vs $92 \pm 3\%$, $P < 0.05$), percentage with heart failure ($16 \pm 5\%$ vs $12 \pm 2\%$, $P < 0.05$), and baseline eGFR (76 ± 2 vs 78 ± 9 mL/min/1.73 m², $P < 0.001$). The 2 classes of drug did not differ in the metabolic outcomes with regards to change in A1c (GLP1-RA vs SGLT2i, change in A1c -0.6 ± 0.1 vs -0.4 ± 0.2 , $P = \text{ns}$), or the change in weight (-2.2 ± 0.5 kg vs. -1.6 ± 0.2 kg, $P = \text{ns}$).

B. Cardiovascular outcomes

The predefined characteristics for clinical MACE were similar in both classes of drugs with the majority evaluating for 3-point MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and the ELIXA trial included a 4-point MACE (with the addition of hospitalizations for heart failure) (Table 1).

Both classes of drug were associated with improvements in MACE compared with controls for the GLP-1 RA (relative rate [rr] 0.91, 95% confidence interval [CI] 0.87, 0.96, $P < 0.001$) and for SGLT2i (rr 0.87, CI 0.82, 0.93, $P < 0.001$) (Fig. 1A). There was no difference in the rates of MACE between the GLP-1 RA and SGLT2i (rr comparison 1.04, CI 0.94, 1.16, $P = \text{ns}$) (Fig. 1A).

The rates of cardiovascular death as measured as secondary endpoints in these studies improved with the addition of the GLP-1 RA (rr 0.88, 95%CI 0.81, 0.95 $P = 0.002$) and with the addition of SGLT2i (rr 0.85, CI 0.77, 0.93, $P = 0.001$). There was no difference in the rates of cardiovascular deaths between the GLP-1 RA and SGLT2i (rr comparison 1.04, CI 0.87, 1.24, $P = \text{ns}$) (Fig. 1B).

The rates of HHF as another measure of secondary endpoints in these studies did not show improvement with the addition of the GLP-1 RA (rr 0.93, 95% CI; 0.86, 1.03, $P = \text{ns}$) but did show improvement and with the addition of SGLT2i (rr 0.68, 95% CI 0.61, 0.76,

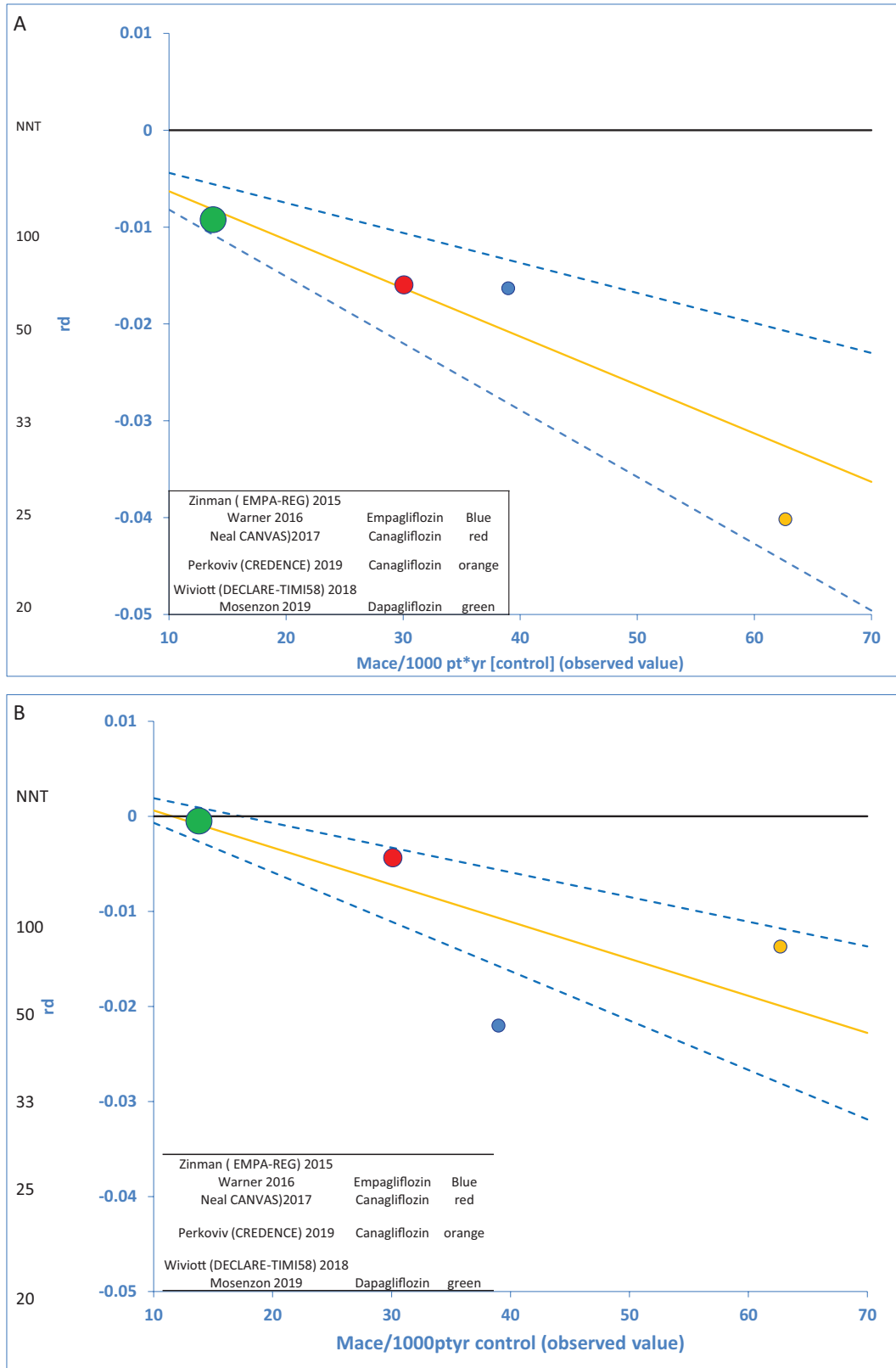


Figure 2. Meta-regression of major CVOTs of SGLT2i. Comparison of rd of events with severity of underlying cardiovascular disease as manifested by the observed MACE in the matched control population. Shown are the weighted linear regression and standard error of the means of confidence intervals. The size of the circles is proportionate to the number of subjects in the trial. (A) MACE. (B) Cardiovascular deaths. (C) Hospitalization for heart failure.

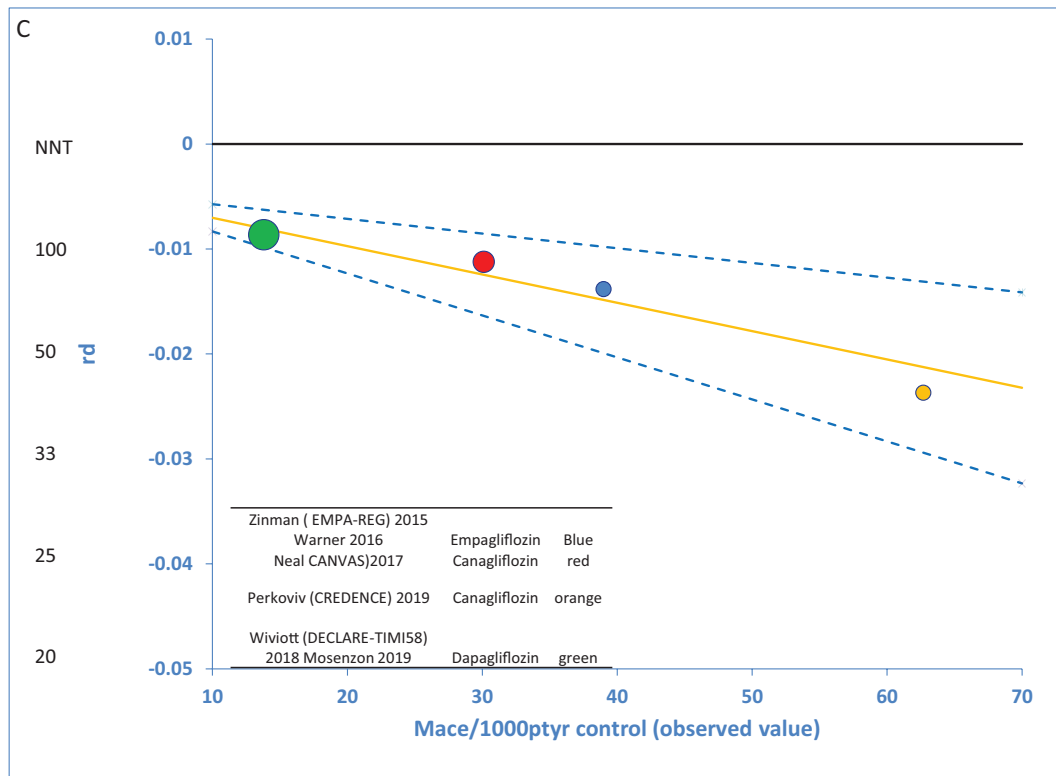


Figure 2. Continued.

$P < 0.001$). There was a difference in the rate of HHF between the GLP-1 RA and SGLT2i (rr comparison 1.38, 95% CI; 1.12, 1.69, $P < 0.01$) (Fig. 1C) and rd of the comparison between the 2 classes (rd 0.009, 95%CI 0.001, 0.017, $P < 0.05$). Thus, the benefit of SGLT2i over GLP-1 RA in HHF equated to a number needed to treat (NNT, $1/\text{rd}$) of 111 (Fig. 1C).

The trials included patients with and without cardiovascular diseases. We estimated the effectiveness of the treatment regimens (as dependent factors) with regards to the underlying prevalence of cardiovascular disease as measured by the underlying rate of MACE in the control populations (independent variables) by meta-regression. The benefits of the SGLT2i were accentuated with the severity of the underlying disease in the cohort, for MACE, cardiovascular death, and hospitalization for heart failure Figs. 2A-2C. The improvement in cardiovascular death rate was predominantly seen in patients in which the control population had a cardiovascular MACE event rate greater than 10 events/1000 patient*year (i.e., estimated cardiovascular MACE risk of >10% per 10 years). For treatment with GLP-1 RA, there were no differential rd of clinical events over a range of MACE events in the control population (Figs. 3A-3C).

C. Renal outcomes

The studies on renal effects had adjudicated outcomes in GLP-1 RA trials [2,25,26] and the four SGLT2i trials [9,11,27,28] and in the others renal events were considered as adverse events [3,5]. The criteria for projected renal events varied among the studies and included new onset macroalbuminuria, doubling of serum creatinine (with resulting eGFR $<45\text{mL}/\text{min}/1.73\text{m}^2$), requirements for renal replacement therapy (dialysis or transplantation) and death from renal causes (Table 2). However, other studies used other surrogate endpoints such as either a decrease in eGFR to $<30\text{mL}/\text{min}/1.73\text{m}^2$ [5] or a decrease in eGFR of 30% [26] or 40% [9,10]. The studies in the SGLT2i cohorts varied in duration and starting eGFR both of which factors may contribute to an endpoint of doubling of eGFR, which may be time

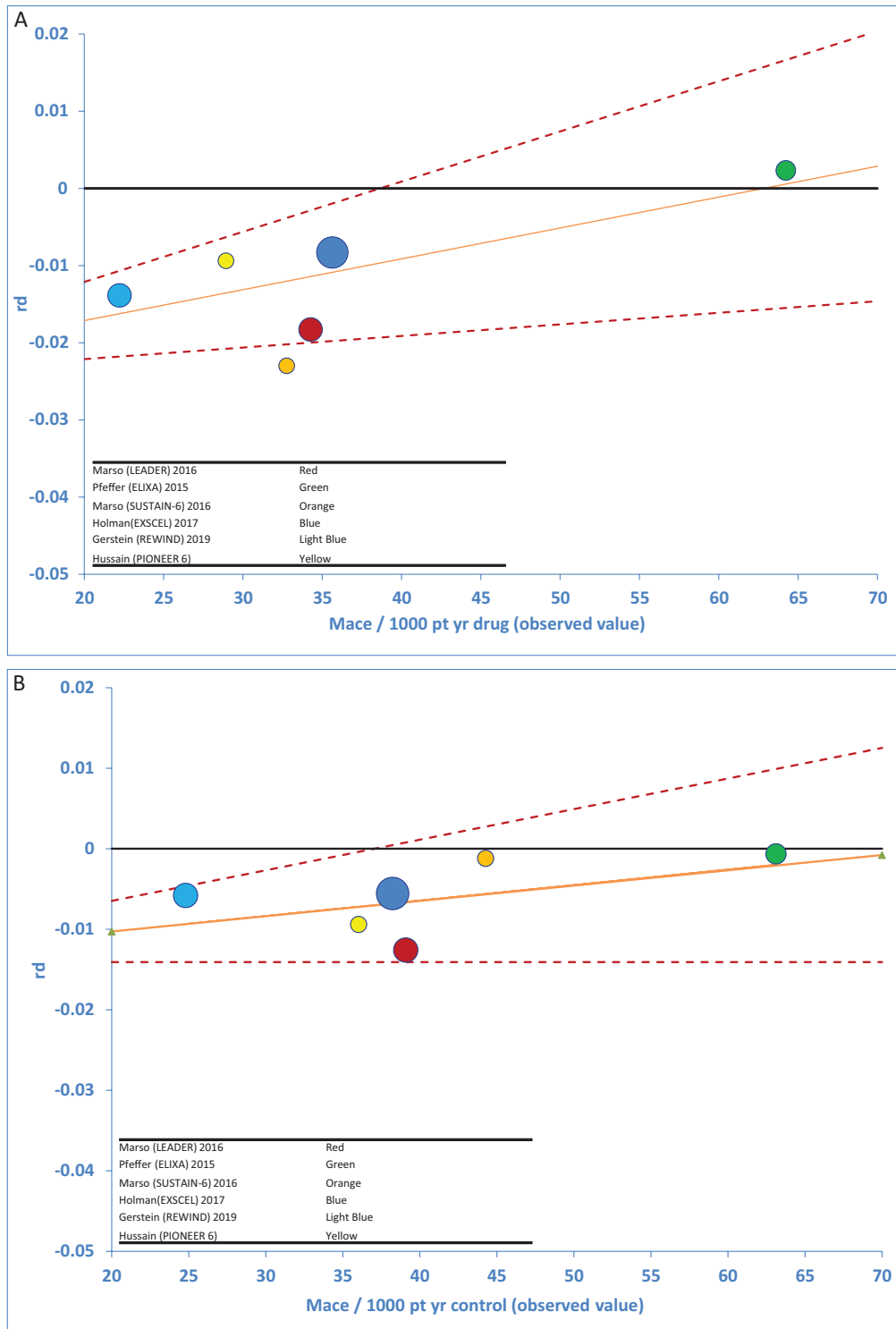


Figure 3. Meta-regression of major CVOTs of GLP1-RA. Comparison of rd of events with severity of underlying cardiovascular disease as manifested by the observed MACE in the matched control population. Shown are the weighted linear regression and standard error of the means of confidence intervals. The size of the circles is proportionate to the number of subjects in the trial. (A) MACE. (B) Cardiovascular deaths. (C) Hospitalization for heart failure.

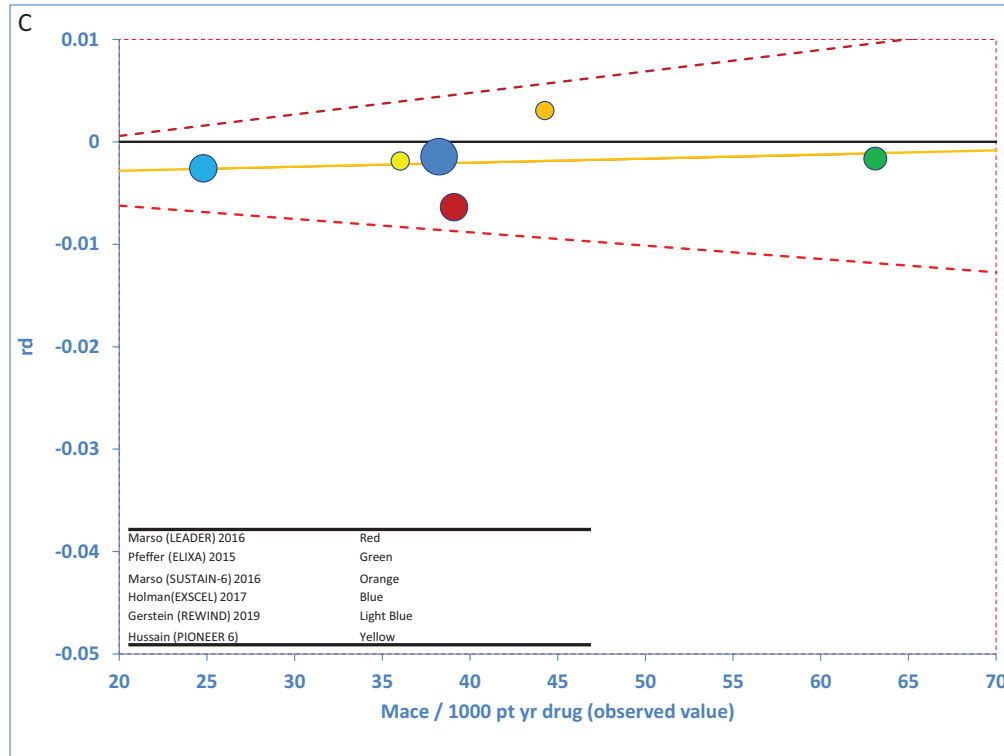


Figure 3. Continued.

dependent. Both classes of medicines improved the outcome for renal major adverse events compared with controls (GLP-1RA, rr 0.83, CI 0.75, 0.91, $P < 0.001$, SGLT2i, rr 0.67, CI 0.57, 0.79, $P < 0.001$) (Fig. 4). There was no difference however between the renal outcomes between the classes (GLP-1RA vs SGLT2i, rr 1.24, CI 0.95, 1.61, $P = ns$) nor a statistical difference in the number to treat to prevent an adverse renal outcome (NNT GLP-1 vs SGLT2i 67 vs 50).

D. Adverse events

The major serious adverse effects are shown in Table 3. Presumably associated with the increased glycosuria, there was a major increase in the rate of genital mycotic infections in women on SGLT2i (rr 4.07, CI 3.41, 4.86, $P < 0.0001$; rd 0.07, CI 0.06, 0.08, $P < 0.001$, NNH = 13). Diabetic ketoacidosis occurred in those on SGLT2i, (rr 2.60, CI 1.54, 4.40, $P < 0.001$; rd 0.01, CI 0.008, 0.026, $P < 0.001$, NNH = 595). Despite the concern that glycosuria might be associated with urinary tract infections, this adverse event was not confirmed in the analysis. Other observations from a single trial (CANVAS) [9], of volume depletion, bone fractures and amputations were also not confirmed in the meta-analysis (Table 3).

Major serious adverse events, causing drug discontinuation, in the GLP-1 RA trials were due to gastrointestinal disorders (rr 2.65, CI 1.36, 5.14, $P < 0.01$; rd 0.029, CI 0.011, 0.046, $P = 0.001$, NNH = 35) (Table 3). Gallstones were a serious adverse event in the liraglutide trial [29] and suggestive in the overall analysis (rr 1.24, CI 1.02, 1.52, $P < 0.05$; rd 0.005, CI -0.001, 0.011, $P = ns$, NNH = 200). Pancreatitis, which had been a theoretical consideration, was also not observed. It should be noted that there was a direct correlation of weight loss with the rate difference of serious adverse gastrointestinal event ($P < 0.001$), with both oral

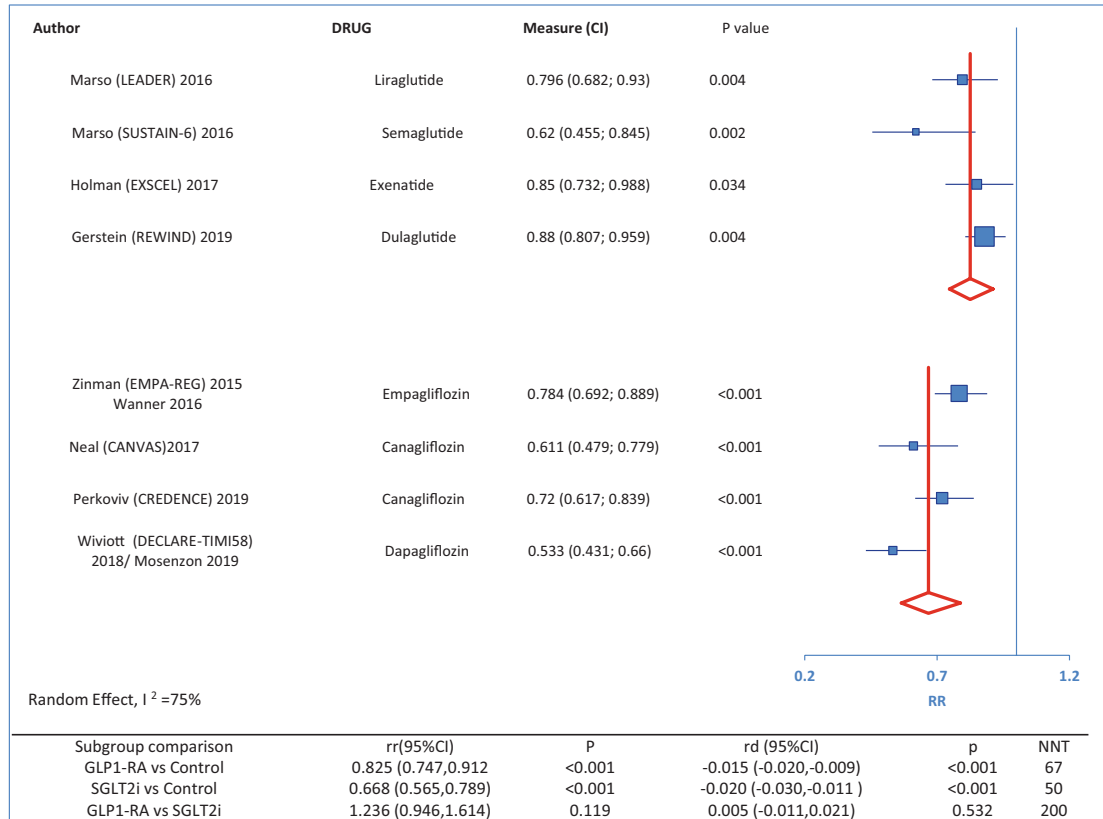


Figure 4. Meta-analysis of secondary renal outcome events from major CVOTs of GLP-1RA and SGLT2i in type2 diabetes mellitus. Comparisons of drug versus control for GLP-1RA versus SGLT2i. Outcomes $rr < 1.0$ denote better outcomes.

and subcutaneous semaglutide having both the greatest weight loss and highest rate difference of gastrointestinal side effects (Fig. 5).

3. Discussion

Per our analysis, both GLP-1 RA and SGLT2i reduced MACE and cardiovascular deaths, with neither class superior to the other. However, there was a clear benefit for SGLT2i in reduction in HHF compared to GLP-1 RA in which there was no direct benefit. When data were stratified according to the severity of the cardiac disease, subjects treated with the SGLT2i class benefited more in terms of reduction of MACE, CV death, and reduction in HHF in those patients with greater severity of illness of illness as determined by the major adverse cardiovascular event rate in the control population. When examining renal benefit, both classes were associated with improvements in outcomes, and whether SGLT2i are superior to GLP-1RA is unclear.

These results supplement existing meta-analyses. Bethel et al [12] evaluated the 4 earlier GLP-1RA trials (LEADER[2], ELIXA[4], SUSTAIN-6[3], EXCEL[5]) and found improvements in MACE when compared to controls. Kristensen et al [30] added analyses of the HARMONY [31] (although the drug albiglutide is no longer available), Rewind [6], and Pioneer-6 [7] trials. They confirmed the benefits of the GLP1-RA class of drug with regards to MACE and cardiovascular deaths. They proposed that although GLP-1RA reduced the risk of worsening renal failure, this class was inferior to comparable results of the SGLT2i class, although no formal comparison was given. Zelniker et al [13] reviewed the SGLT2i class of EMPA-REG [8], CANVAS [9], and DECLARE [10] trials and confirmed these drugs reduced MACE and HHF, but the data on the CREDESCENCE trial [11], which lead to the formal Food

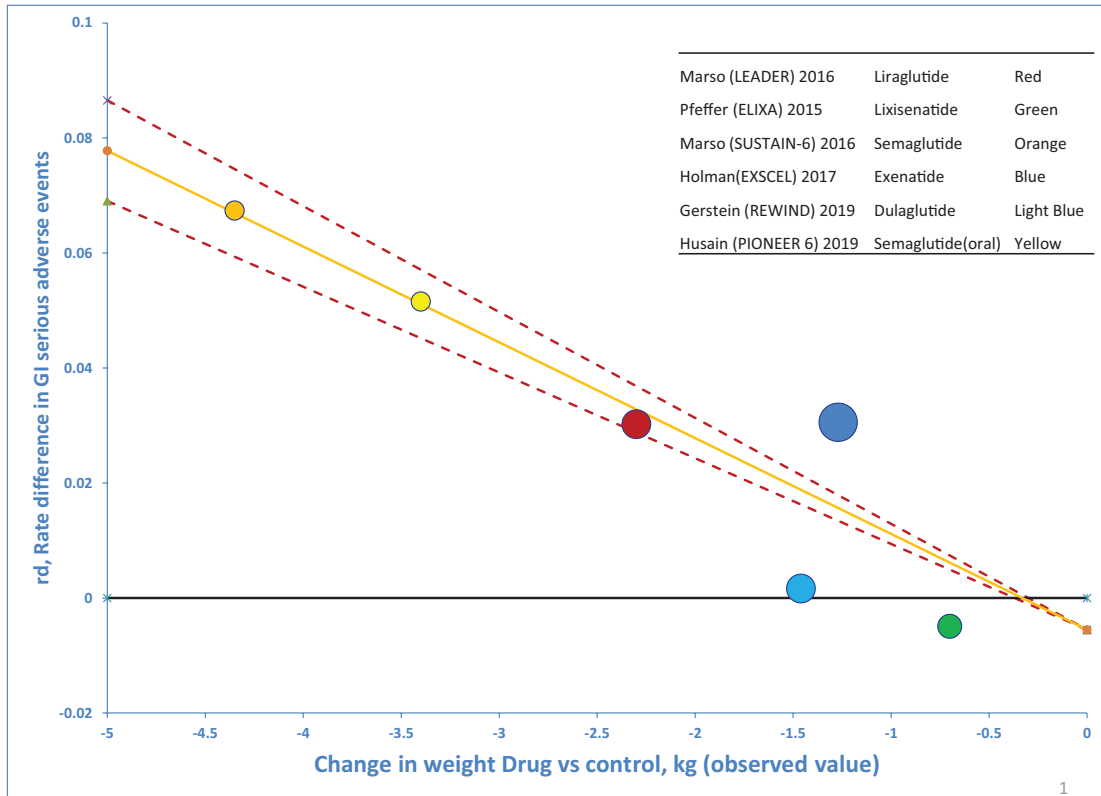


Figure 5. Meta-regression of serious adverse gastrointestinal events from major CVOTs of GLP-1RA. Comparison of rd of gastrointestinal events with the change in weight loss with drug versus control population. Shown are the weighted linear regression and standard error of the means of confidence intervals. The size of the circles is proportionate to the number of subjects in the trial.

and Drug Administration (FDA) approval of canagliflozin for renal protection, were not yet available. The later Zelniker et al [14] meta-analysis of the comparison of GLP-1 RA and SGLT2i included in the GLP-1RA evaluation the HARMONY [31] but not the REWIND [6] or PIONEER-6 [7] trials, nor did it include in the SGLT2i analysis the CREDENCE [11] trial, and found only the SGLT2i class reduced the progression of renal disease. The current analysis performed here confirms the cardiovascular benefits of both classes of drugs regarding MACE and cardiovascular death and further suggests that the benefit of the SGLT2i class are more pronounced with patients with more severe of heart failure. It has also been shown that the benefit of the SGLT2i can be demonstrated in those with heart failure due to reduced ejection fraction even in those without diabetes and presumably without major effects of glycemic control or A1c [32]. It is unknown from these trials whether the improvement in HHF were also found in patients with preserved ejection fraction.

The current analysis also suggests that both classes of drug improve renal outcomes compared with controls. It is unclear whether there is a preferential benefit to the SGLT2i class over that of the GLP-1 RA class. In this analysis, there was no statistical benefit in renal protection of the SGLT2i class over the GLP-1 RA class. Canagliflozin is FDA approved for the indication of preservation of renal function due to highly significant delayed renal deterioration in patients with a lower baseline eGFR ($56 \text{ mL/min/1.73 m}^2$) with macroalbuminuria. In this analysis, although the GLP-1RA and SGLT2i groups had similar baseline mean eGFR, there were significant difference in the variance of the starting eGFR and differences in the criteria for adverse renal outcomes. It is possible that the original data from the respective CVOTs may be re-analyzed regarding consistent endpoints and life table analyses of effects over time.

The most common adverse event in the SGLT2i group was genital mycotic infections in women and potentially the most serious was development of diabetic ketoacidosis. The risks of amputation and fractures were only found in 1 trial (CANVAS) [9] as also reviewed by Zekner [13]. With regard to the GLP-1RA, gastrointestinal intolerance was a major serious adverse event leading to discontinuation of drug (NNH = 35). However, it should be noted that both the subcutaneous and oral semaglutides had the highest frequency of gastrointestinal serious adverse events and the greatest degree of weight loss. It may be that providers must be required to titrate the deleterious gastrointestinal side effect versus the beneficial effects of weight loss in an obese population. Also, within the GLP-1RA class, there was also the possibility of increased biliary symptoms (in liraglutide, as shown previously [29]) but this was weakly confirmed here over the entire GLP-1RA class.

Our study has limitations including the use of secondary data and that outcomes were not compared at individual subject level data. The duration of follow up was similar across both classes GLP-1 RA and SGLT2i, but there were differences in the duration of individual trials. The trial duration would be especially important in comparing the renal outcomes, in which the longer the duration of the trial, the more the possibility of observing a doubling or creatinine. Both classes of drugs evaluated patients with a cardiovascular risk estimate (i.e., the MACE rate in the control population) of greater than 10%, so that the implications of benefit of these classes of drugs may not be present in patients with lower degrees of cardiovascular risk.

Our findings would suggest modifying the current ADA recommendations (Figure 9.1 in [1]) to guide clinicians toward the use of either GLP-1RA or SGLT2i for patients with type 2 diabetes and cardiovascular risk, but preferentially encourage use of SGLT2i for those with heart failure and more advanced cardiovascular disease. The SGLT2i have theoretical benefits of renal protection, as demonstrated prospectively in the CREDENCE trial [11], which provided sufficient evidence for FDA approval of an indication for renal protection. Only the LEADER (liraglutide) [2,25] and REWIND (dulaglutide) [26] trials prospectively adjudicated renal events. Although there was no preferential benefit of the SGLT2i class compared to the GLP-1RA class for renal protection, the 2 classes of drugs need to be analyzed either in head-to-head trials or, retrospectively, through the primary source documents using a common definition of adverse renal events.

4. Conclusion

In conclusion, we confirm previous reports that both GLP-1 RA and SGLT2i reduce MACE and CV deaths, and neither class was superior to the other. However, when severity of cardiovascular illness (hospitalization for heart failure or rate of MACE > 10%/10 years) illness was accounted for, subjects on SGLT2i showed greater overall benefit. SGLT2i are also more beneficial in reducing HFrEF compared to GLP-1 RA. In terms of renal outcomes, there is a need for standardized criteria for defining such outcomes. Despite the variations in the definition of renal outcomes by trial, this analysis shows that both classes of medications, GLP-1 RA and SGLT2i, demonstrate renal benefit. Adverse effects are extremely common as mycotic infections in women on SGLT2i and should be anticipated if the drug is to be continued. Diabetic ketoacidosis is a less common but more severe event. The GLP-1RA have a high incidence of gastrointestinal intolerance, which may be titrated against the possible beneficial effect to weight loss.

Additional Information

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