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Cardiovascular Outcomes in the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) Study

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SUPPLEMENTAL APPENDIX ITEMS

GRADE Study Research Group Listing

Table S1. Baseline characteristics overall and by treatment group

Table S2. Treatment group differences across subgroups

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Abstract

Background: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The effects of glucose lowering medications on cardiovascular (CV) outcomes in individuals with T2DM and low CV risk are unclear. We investigated CV outcomes by treatment group in participants randomly assigned to insulin glargine, glimepiride, liraglutide, or sitagliptin, added to baseline metformin, in the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) Study.

Methods: 5047 participants with (mean ± standard deviation) age 57.2 (±10.0) years, T2DM duration 4.0 (±2.7) years, and low baseline prevalence of CVD (myocardial infarction [MI] 5.1%, cerebrovascular accident 2.0%) were followed for a median of 5 years. Pre-specified outcomes included between-group time-to-first event analyses of MACE-3 (CV death, MI, stroke), MACE-4 (MACE-3 + unstable angina requiring hospitalization/revascularization), MACE-5 (MACE-4 + coronary revascularization), MACE-6 (MACE-5 + hospitalization for heart failure [HHF]), and the individual components. MACE outcomes and HHF in the liraglutide-treated group were compared with the other groups combined using Cox proportional hazards models. MACE-6 was also analyzed as recurrent events using a proportional rate model to compare all treatment groups.

Results: We observed no statistically significant differences in the cumulative incidence of first MACE-3, −4, −5, or −6, or their individual components, by randomized treatment group. However, when compared to the other treatment groups combined, the liraglutide-treated group had significantly lower risk of MACE-5 (adjusted hazard ratio [HR_{adj}], 0.70 [95% CI, 0.54–0.91], p=0.021), MACE-6 (HR_{adj}, 0.70 [95% CI, 0.55–0.90], p=0.021), and HHF (HR_{adj}, 0.49 [95% CI, 0.28–0.86], p=0.022). Compared to the liraglutide group, significantly higher rates of recurrent MACE-6 events occurred in the groups treated with glimepiride (RR 1.61; [95% CI 1.13, 2.29]) or sitagliptin (RR 1.75; [95% CI 1.24, 2.48]).

Conclusions: This comparative effectiveness study of a contemporary cohort of adults with T2DM, largely without established CVD, suggests that liraglutide treatment may reduce the risk of CV events in relatively low risk patients compared to other commonly used glucose-lowering medications.

Clinical Trial Registration: http://www.clinicaltrials.gov. Unique identifier: NCT01794143.

Keywords

diabetes; cardiovascular; comparative effectiveness

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM)[1]. Traditional interventions to address cardiovascular

(CV) risk factors such as hypertension (HTN), dyslipidemia, and hyperglycemia in this population have been effective in reducing rates of certain CV events[2]. Unfortunately, even when these risk factors are managed, significant residual CV risk remains[3]. Over the past decade, certain medications in the glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) classes, originally indicated solely for glucose-lowering, have been shown to significantly reduce the risks of important CV and kidney complications in patients with T2DM[4,5]. However, these medications have primarily been studied in patients with T2DM and established or high risk for atherosclerotic CV disease (ASCVD), chronic kidney disease (CKD) or heart failure (HF). The impact of these interventions on CV outcomes in low risk individuals with T2DM remains unclear, as does the optimal approach to glucose-lowering in such patients.

The Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) Study provides a unique opportunity to assess the CV effects of randomized glycemic treatment assignment in a relatively low risk, contemporary cohort of individuals with T2DM[6,7]. In GRADE, participants with uncontrolled T2DM of relatively recent onset were randomly assigned to insulin glargine U-100, the sulfonylurea glimepiride, the GLP-1 receptor agonist liraglutide or the DPP-4 inhibitor sitagliptin, added to maximally tolerated metformin therapy. Although GRADE was not specifically designed or powered to assess the impact of treatment on CV outcomes, such events were systematically collected and adjudicated throughout the study. Previously published analyses from GRADE found that participants randomized to liraglutide had significantly lower risk of a broad, “any CVD” outcome (defined as the first of any major adverse cardiovascular event [MACE], unstable angina [UA] requiring hospitalization, revascularization in any arterial bed, or hospitalization for heart failure [HHF]) when compared to those in the other treatment groups combined (HR 0.71 [95% CI, 0.56 to 0.90])[8]. The present analyses expand these findings by assessing the relative effects of randomized, study-assigned glucose-lowering therapy on additional, prespecified secondary CV outcomes.

RESEARCH DESIGN AND METHODS

Data Availability

This article is based on follow-up data and outcome assessments for the 5047 participants enrolled into GRADE. This database will be available in the National Institutes of Diabetes and Digestive and Kidney Diseases Central Repository by 2024.

Study cohort and study medication

GRADE was a clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIDDK, NIH), which compared the impact of each of four randomly assigned glucose-lowering medications on glycemic outcomes in individuals with T2DM on metformin monotherapy. The study design, participant baseline characteristics, schedule of assessments, primary and key secondary results of GRADE have been published previously[6–9]. An external Data and Safety Monitoring Board oversaw the conduct of the study. The protocol was approved by the Institutional Review Board at each

participating study site, and all participants provided written informed consent prior to study enrollment.

In brief, the study enrolled 5047 adult participants with T2DM at 36 funded clinical centers including 9 additional sub-sites in the United States between July 2013 and August 2017. They were followed for a mean (and median) of 5 years. Eligible participants had T2DM of less than 10 years' duration, diagnosed at age ≥30 years or ≥20 years if American Indian/Alaska Native. At randomization, participants were required to have an HbA1c of 6.8–8.5% (50.8–69.4 mmol/mol) on maximally tolerated metformin at a dose of ≥1000 mg per day. Patients were excluded from participation if they had a major CV event in the year prior to randomization, HF with New York Heart Association (NYHA) functional class III-IV, an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2, or end-stage kidney disease (ESKD) requiring renal replacement therapy.

Participants were randomly assigned to the addition of study-supplied insulin glargine, glimepiride, liraglutide, or sitagliptin to their baseline metformin therapy. Study site staff and participants were unmasked to treatment assignment; however, staff of the study laboratories, reading centers, and adjudication committees were masked to participant identity and treatment assignment. Study medications were started and adjusted consistent with contemporary FDA-approved labelling, with the goal of achieving and maintaining HbA1c <7% (53 mmol/mol) over an anticipated 4–7 year study period. Protocol-specified guidelines also required the addition of basal or mealtime insulin to the treatment of participants who reached a confirmed HbA1c > 7.5% (58 mmol/mol) while taking the maximum tolerated dose of their assigned study medication. Otherwise, all non-glycemic care and management was deferred to the participants' usual care providers. When national and international guidelines for the management of patients with T2DM and CVD or kidney disease changed during GRADE, recommendations for the addition of GLP-1 receptor agonists or SGLT2 inhibitors were communicated to relevant participants and their usual care providers for consideration and implementation[10,11]. Letters for participants with ASCVD were sent to usual care physicians in early 2019, with further updated letters for participants with ASCVD, heart failure, or CKD sent in mid-2020.

Study assessments and outcomes

Participants' medical history, medication use, weight and blood pressure (BP) were obtained at screening, baseline, and every 3 months during the study, and laboratory assessments were performed periodically. As previously published, the primary and secondary outcomes of GRADE were HbA1c levels indicating glycemic treatment failure[6,9]. CV events and procedures that occurred during the study period were reviewed and documented at each visit. The events and procedures specifically collected included the occurrence of myocardial infarction (MI), stroke (CVA), UA requiring hospitalization or revascularization, transient ischemic attack (TIA), HHF, interventional cardiology procedures (coronary artery stent placement and percutaneous coronary angioplasty), other vascular/peripheral vascular interventions, coronary artery bypass graft (CABG), and stent thrombosis. These events and all deaths were adjudicated and classified by an internal adjudication committee with an external expert cardiologist, all masked to treatment assignment, using definitions consistent

with those outlined in the 2017 Cardiovascular and Stroke Endpoints for Clinical Trials[12,13]. Two committee members independently reviewed each event; in the event of disagreement, a third member served as the tie-breaker.

The effects of randomized study treatment on the prespecified GRADE CV outcomes MACE-3 (a composite of non-fatal MI, non-fatal CVA and CV death) and "any CVD" have been previously published[8]. In the present analyses, we compare the incidence of a more expansive set of CV outcomes among the GRADE treatment groups. These outcomes include MACE-4 (MACE-3 + UA requiring hospitalization or revascularization), MACE-5 (MACE-4 + coronary revascularization), MACE-6 (MACE-5 + HHF), and the individual components of MACE-5 and HHF separately. The outcome of MACE-6 is also analyzed as a recurrent event (ALL MACE-6). In addition, we analyze the risks of HHF and the composite outcomes MACE-3 through MACE-6 in the liraglutide-treated group compared to the other 3 treatment groups combined. Finally, to assess for potential heterogeneity of study treatment effect, we determined the incidence of outcomes MACE-3 through MACE-6 in prespecified subgroups of particular clinical interest including sex; race (White, Black, Other) and ethnicity (Hispanic, Non-Hispanic); baseline tertile of age, body mass index (BMI), duration of diabetes, and HbA1c; baseline kidney function (eGFR <60 or ≥60 ml/min/1.73 m^2) and albuminuria category (moderately increased, [urine albumin:creatinine ratio (UACR) 30 to ≤300 mg/g] or severely increased, [UACR >300 mg/g]); smoking (current/past/never); hypertension (measured BP ≥130/80 mmHg or treatment with blood pressure-lowering agents); and dyslipidemia (fasting LDL-cholesterol ≥100 mg/dL [2.6 mmol/L], triglycerides ≥150 mg/dL [1.7 mmol/L], HDL-cholesterol <40 mg/dL [1.0 mmol/L] in men or <50 mg/dL [1.3 mmol/L] in women, or use of lipid-lowering medication).

Statistical analysis

All analyses were prespecified in the statistical analysis plan and were conducted under the intention-to-treat principle, including all randomized participants regardless of prior CVD history. Key baseline clinical characteristics were summarized by treatment group, with continuous values summarized as means (+/− standard deviation) or as the median (interquartile range). Categorical variables were summarized as counts and column percentages. The p-values are based on t-tests for continuous variables and chi-squared tests for binary and categorical variables.

Analyses of the outcomes (MACE-3 through MACE-6 and the components of MACE-6) were conducted using standard methods for the analysis of event-time (survival) data. For each outcome, Kaplan-Meier (KM) curves by treatment group were generated and unadjusted p-values from log-rank tests reported. The p-values (other than that for MACE-3, which was prespecified in the protocol) were then adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate procedure[14]. For each outcome for which the adjusted p-value was significant, Cox proportional hazards models were used with assigned treatment group as the only covariate to carry out the six pairwise comparisons of each treatment group against every other; these p-values were adjusted for multiple comparisons using the Holm procedure[15].

Informed by both the known CV benefits of liraglutide in higher risk patients[16] and the anticipated low number of CV events in GRADE, the CV effects of liraglutide were compared to those of the other three treatment groups combined, thereby increasing the power of this prespecified analysis to detect a difference. The same Cox proportional hazards models as above were used for each of the four MACE outcomes plus HHF with a binary treatment variable (liraglutide vs one of the other three treatments). The resulting five p-values for each outcome were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate procedure.

A Cox proportional hazards model containing treatment group, the subgroup variable, and a treatment by subgroup interaction was used to evaluate each of the 4 MACE outcomes in the 13 specified subgroups. The test of the interaction term in the model tested for treatment heterogeneity among the levels of the particular subgroup. For each outcome, the 13 p-values for subgroup heterogeneity were adjusted one outcome at a time using the Benjamini-Hochberg false discovery rate method. For any adjusted p-values which were significant at the 0.05 level, we further tested the six pairwise treatment group differences with no adjustment for multiple comparisons.

The analysis of the ALL MACE-6 outcome used a proportional rate model[15] with treatment group as the only covariate. Sensitivity analyses using negative binomial and quasi-Poisson models were conducted, with both models also using treatment group as the only covariate and an offset for the log of time at risk. Where the treatment effect was significant in the proportional rate model, the six pairwise comparisons of each treatment group against every other were conducted using contrasts from that model; the six pairwise p-values were adjusted for multiple comparisons using the Holm procedure. For the purposes of these analyses, multiple MACE-6 events that occurred on the same calendar day were counted as a single event. The mean number of events per participant was estimated using the mean cumulative function[17].

RESULTS

Baseline characteristics

Baseline characteristics of the overall study cohort and four treatment groups have been described previously[7] (Supplemental Table S1). In brief, the 5047 GRADE participants were 36.4% women, with mean age of 57.2 (± 10.0) years and duration of diabetes 4.0 (± 2.7) years. 65.7% of participants identified themselves as White, 19.8% Black or African-American, 4.2% Asian/Hawaiian/Pacific Islander, 2.7% American Indian/Alaska Native, and 7.6% Other/unknown, with 18.6% also self-identified as Hispanic. Mean BMI was 34.3 (± 6.8) kg/m^2, systolic BP 128.3 (± 14.7) mmHg, and diastolic BP 77.3 (± 9.9) mmHg.

Only 255 (5.1%) and 101 (2.0%) had a prior MI or CVA, respectively. However, CVD risk factors were common: 3339 (66.2%) had a history of HTN and 3321 (65.8%) were on lipid-lowering medication (3210 [63.6%] on statin therapy)[8]. Kidney disease was not common, with only 125 (2.5%) of participants having eGFR <60 mL/min/1.73 m^2 or moderate or severe albuminuria (716 [14.2%] and 84 [1.7%], respectively). 2933 (58.1%) of participants were treated with an ACE inhibitor or ARB, and 2288 (45.3%) were on aspirin.

Baseline characteristics were similar between treatment groups, with the exception of use of any lipid-lowering medication which was lowest (63.0%) in the liraglutide group and highest (68.3%) in the glimepiride group.

Comparisons of outcomes among randomized treatment groups

Incidence of CV outcomes among treatment groups—The cumulative incidence of the specified CV outcomes as assessed by time-to-first-event analysis did not differ significantly among treatment groups. Kaplan-Meier curves for each of the 10 specified outcomes are shown in Figure 1. The only significant differences among the treatment groups were for the MACE-6 composite outcome and coronary revascularization outcome; however, the adjusted p-values were no longer significant after adjusting for multiple comparisons. The numbers of participants with at least one CV outcome and the unadjusted and adjusted p-values for all 10 comparisons are shown in Table 1.

CV outcomes with liraglutide compared to the other treatment groups, combined—Results of the prespecified MACE and HHF comparisons of liraglutide treatment to the mean of the other three groups combined are shown in Table 2. The liraglutide treatment group had significantly lower risks of MACE-5, MACE-6, and HHF when compared to the other groups combined. The p-values for these comparisons remained significant after adjustment for multiple comparisons.

Recurrent events analysis of MACE-6—The treatment group effect for the models used in the recurrent events analysis were all significant, including the proportional rate model (p=0.0081) and the sensitivity analyses using negative binomial (p=0.0051) and quasi-Poisson models (0.0167). The pairwise comparisons based on contrasts from the proportional rate model are summarized in Figure 2. The glimepiride-treated and sitagliptin-treated groups had a significantly higher rate ratio (RR) of ALL MACE-6 events than the liraglutide group (RR 1.61; [95% CI 1.13, 2.29] and RR 1.75; [95% CI 1.24, 2.48], respectively). The higher risk with glargine treatment compared to liraglutide (RR 1.50; [1.08, 2.09]) was no longer significant after adjustment for the six pairwise treatment group comparisons using the Holm procedure (p=0.063). The remaining between-group pairwise comparisons were also not significant. The cumulative event rates [i.e. number of incident events per 100 person-years (py)] and 95% CIs for ALL MACE-6 events (first and recurrent) by treatment group are: 2.44 (2.05, 2.82); 2.63 (2.22, 3.03); 1.63 (1.31, 1.94); and 2.85 (2.44, 3.27) for glargine, glimepiride, liraglutide, and sitagliptin, respectively. We show the mean number of ALL MACE-6 events per participant by treatment group in Figure 3. Overall, sitagliptin had the highest number of ALL MACE-6 events (180), followed by glimepiride (164), glargine (153), and liraglutide (102), respectively.

CV outcomes in subgroups of interest—As shown in Supplemental Table S2, no significant treatment group differences were identified for each of the four MACE outcomes in the 13 subgroups of interest. Of note, the dyslipidemia subgroup models for MACE-3, MACE-4, and MACE-5 failed to converge due to the extremely small numbers of outcome events experienced by the 195 participants without dyslipidemia (a total of two MACE-3 events, three MACE-4 events, four MACE-5 events, and nine MACE-6 events). Among

the models that did converge, there were no significant treatment group differences across any subgroups. The smallest unadjusted p-value was 0.062 for sex, with a corresponding adjusted p-value of 0.569.

DISCUSSION

GRADE offers an opportunity to compare CV outcomes across randomly assigned treatments, including insulin glargine, glimepiride, liraglutide, and sitagliptin, in a relatively low-risk contemporary cohort of patients with T2DM. In these prespecified secondary analyses, the pairwise comparisons of CV outcomes did not differ across treatment groups. However, in the time-to-first-event analysis, reduced risks of MACE-5, MACE-6, and HHF alone were found when liraglutide was compared to the other groups combined. Subgroup analyses suggest that the effects of treatment assignment on MACE outcomes did not vary based upon characteristics such as sex, age, or diabetes duration; however, some of these analyses were limited by small numbers of events. In the recurrent events analysis, the liraglutide-treated group also had significantly lower risk of the broad, HHF-inclusive MACE-6 outcome when compared to treatment with glimepiride or sitagliptin.

T2DM conveys an increased risk of CV complications that is not fully addressed with traditional risk-reduction strategies[18]. Decreasing rates of MI, CVA, ESKD, and amputation noted over recent decades are likely due to enhanced management of risk factors such as smoking, blood pressure, lipids, and glucose[2]. However, patients with diabetes are still at higher risk of these complications when compared to those without diabetes, and the numbers of such events are rising due to the increasing prevalence of T2DM[2]. HF has also been recognized as both a diabetes-related complication and a comorbidity indicative of poor outcomes, and is often the first presentation of CVD in people with diabetes[19,20]. An excess risk of HF persists in patients with diabetes even if they do not smoke and have optimal levels of HbA1c, LDL-cholesterol, and urinary albumin[3].

Opportunities to further mitigate CV risk in T2DM have expanded following the completion of recent CV outcomes trials of newer diabetes medications. These trials, intended to determine the CV safety of newer agents in high-risk patients with T2DM, have identified significant CV and/or kidney outcomes benefits with the use of several agents in the GLP-1RA and SGLT2i classes[4,5,21]. These benefits appear independent of the agents' glucose-lowering effects. Additionally, SGLT2i agents have now been found to improve cardio-renal outcomes in patients with HF or CKD, with or without diabetes[22–27]. Clinical care guidelines for the management of high-risk patients with T2DM have rapidly evolved to incorporate these findings, most now recommending preferential use of SGLT2i or GLP-1RA in patients with or at high risk of ASCVD, and SGLT2i for patients with HF or CKD, regardless of metformin use or the need for additional glucose lowering[28–30]. However, since the CV outcomes trials (CVOTs) to date have largely enrolled patients with or at high risk for ASCVD, CKD, or HF, the optimal pharmacologic treatment of lower risk patients with T2DM remains unclear. Current guidelines for the care of low risk patients with T2DM instead focus upon management of hyperglycemia, weight and CV risk factors to reduce the risks of diabetes-related complications and disease progression, rather than emphasizing use of specific medications to reduce the risk of CV events[28,31]. Although these

differences reflect the lack of outcomes data in lower risk populations, such dichotomy in guidelines may not be justifiable, given that, over a lifespan, diabetes will confer substantial CV risk.

The GRADE study cohort differs from those enrolled in recent CVOTs. Overall, GRADE participants were younger, healthier, and had shorter duration of T2DM than those enrolled in the CVOTs, and more were men. At baseline, just 6.4% had a prior MI or CVA and only 2.5% had an eGFR of less than 60 mL/min/1.73m^2 [8]. Nonetheless, the GRADE study cohort was on average obese and the majority had HTN and/or used lipid-lowering medication. All of the study-assigned treatments have been well-studied in prior CVOTs. Use of insulin glargine to intensively manage glucose in the ORIGIN trial (Outcome Reduction with Initial Glargine Intervention) did not significantly alter CV outcomes in patients with prediabetes or early T2DM compared to standard care[32]; the CV effects of glimepiride in patients with T2DM and high cardio-renal risk enrolled in the Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA) did not differ from those of the proven-neutral DPP-4 inhibitor linagliptin[33,34]; and CV outcomes with sitagliptin added to the care of patients with T2DM and established ASCVD in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) did not differ from placebo[35]. Liraglutide was the only study-assigned GRADE treatment with a demonstrated CV outcomes benefit, as the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial found significant reductions in the risk of MACE with liraglutide compared to placebo in patients with T2DM and high CV risk; however, it could not be assumed that such benefits would extend to a lower risk population[16]. In addition, the LEADER results were not known until several years after GRADE had been designed and begun enrollment.

It is important to note that although GRADE was not primarily designed to assess the CV effects of study medications, CV events were prospectively collected, recorded, and adjudicated throughout the study. During the study design, the projected rate of the “any CVD” outcome was expected to be 1% per year, which would have provided 72% power to detect a 50% difference. Initial concerns regarding the expected low rate of events, as well as the later LEADER trial results, prompted inclusion of the prespecified recurrent events analyses and the comparisons of liraglutide to the other treatment groups combined in this statistical analysis plan. These additional analyses, which were prespecified prior to the conclusion of the trial, were enacted in order to increase the statistical power to detect between-group differences. However, the overall numbers of CV events in GRADE were low, making the outcomes findings more hypothesis-generating than definitive of a benefit to liraglutide treatment in lower risk patients.

Our findings suggest that when compared to the alternative therapies studied, treatment with liraglutide may decrease the total CV event burden (MACE and HF) in relatively low risk patients with T2DM. The present analyses cannot identify the mechanisms or mediators of protective benefit potentially conveyed by liraglutide treatment in GRADE. However, others have suggested that the outcomes benefits are in part attributable to improvements in multiple CV risk factors commonly associated with GLP-1RA use[36]. In GRADE, participants in the treatment groups assigned to glargine and liraglutide were more

likely to achieve and sustain HbA1c <7% (53 mmol/mol) than those receiving sitagliptin or glimepiride; however, these glycemic differences were quite modest (mean HbA1c 7.1% in the liraglutide and glargine groups, 7.2% in the sitagliptin group and 7.3% in the glimepiride group at 4 years) and thus unlikely to explain the between-group differences found in CV outcomes[9]. All treatment groups experienced a decrease in weight, but with mean weight loss at 4 years being greater in the liraglutide and sitagliptin groups (3.5 and 2.0 kg, respectively) than in the glimepiride and glargine groups (0.73 and 0.61 kg, respectively)[9]. Small differences in SBP over time were also present, being highest in the glargine and glimepiride groups (129.1 mmHg and 128.7 mmHg, respectively), lower in the sitagliptin group (128.1 mmHg) and lowest in the liraglutide group (126.9 mmHg)[9]. Although these differences are notable, it is unlikely that these small improvements in traditional CV risk factors fully explain the differences identified in CV outcomes. Interestingly, despite the divergence in these known risk factors for both micro- and macrovascular complications, there were no important between-group differences in the rates of microvascular complications which occurred during the study[9].

Many aspects of the GRADE study strengthen our analyses and conclusions, including the enrollment of a large, highly diverse patient population followed long-term and with minimal dropout. Randomized treatments included commonly prescribed glucose-lowering medications, and the care provided by GRADE was embedded in otherwise usual care. Previously reported use of non-study SGLT2i or GLP-1RA by GRADE participants was low and was less frequent in the group assigned to liraglutide treatment[9]. The present analyses do not include or adjust for the use of these non-study medications. However, the most likely effect of this drop-in treatment would be to minimize the differences in CV outcomes between liraglutide and the other treatment groups. Given the small proportion of participants with prior MI or CVA, the present analyses also do not include assessment of outcomes in subgroups with or without ASCVD at baseline. Higher rates of CV events in the GRADE participants with prior CVD have been previously reported, but nominally lower rates of CV events with liraglutide treatment in patients with and without established CVD were also noted[8].

Limitations beyond those previously mentioned include the selection of Steering Committee (SC) members and institutions based upon their expertise in clinical trials and ability to recruit a representative population of individuals with T2DM, rather than taking an approach designed to ensure diversity of SC members themselves. There is also an absence of complete HF-related data at baseline. Although patients with HF and NYHA class III-IV functional status were excluded, it is possible that participants with less severe manifestations of HF were enrolled. These data were not captured at baseline; however, as seen with the other baseline characteristics, randomization was highly effective and it is unlikely that the prevalence of this complication would have differed significantly among treatment groups. In addition, although HHF events were adjudicated, there was not a systematic capture of data such as ejection fraction for the incident HF events. Importantly, SGLT2i were not included in GRADE as the study was designed before the approval of the first SGLT2 inhibitor. Thus, the absence of an SGLT2i treatment group limits our ability to fully translate the GRADE findings into contemporary management of T2DM. Further studies are warranted to more fully evaluate the CV effects of glucose-lowering medications,

including SGLT2i, in relatively low risk patients with T2DM. However, the GRADE results suggest that GLP-1RA treatment may play a beneficial role in reducing CV risk in patients with T2DM at relatively low risk for CV events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms:

T2DM	Type 2 diabetes mellitus
HTN	Hypertension
GLP-1RA	Glucagon-like peptide-1 receptor agonist
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
GRADE	The Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness Study

NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NYHA	New York Heart Association
ESKD	End-stage kidney disease
FDA	Food and Drug Administration
UA	Unstable angina
HHF	Hospitalization for heart failure
MACE-3	composite outcome comprised of non-fatal MI, non-fatal CVA and CV death
MACE-4	composite outcome comprised of MACE-3 + UA requiring hospitalization or revascularization
MACE-5	composite outcome comprised of MACE-4 + coronary revascularization
MACE-6	composite outcome comprised of MACE-5 + HHF
ALL MACE-6	The outcome of MACE-6, analyzed as a recurrent event
UACR	Urine albumin:creatinine ratio
KM curve	Kaplan-Meier curve
RR	Rate ratio
PY	Person-years
CVOTs	Cardiovascular outcomes trials
ORIGIN trial	Outcome Reduction with Initial Glargine Intervention
CAROLINA study	Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes
TECOS trial	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
LEADER trial	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

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Clinical Perspective

What Is New?

- The GRADE comparative effectiveness study of four randomized medications (sitagliptin, glimepiride, insulin glargine, or liraglutide) added to metformin in patients with type 2 diabetes, permits comparison of cardiovascular (CV) outcomes by treatment group in a cohort largely without CV disease.
- CV event rates did not differ by individual treatment group; however, when compared to the other groups combined, the liraglutide-treated group had significantly lower risk of a CV composite (myocardial infarction, stroke, CV death, unstable angina and coronary revascularization) with and without heart failure hospitalization.
- Recurrent CV events were more common with glimepiride and sitagliptin treatment compared to liraglutide.

What Are the Clinical Implications?

- Based upon CV outcomes trials enrolling patients with or at high risk for atherosclerotic CV disease, contemporary diabetes care guidelines recommend use of specific medications, including liraglutide, to reduce CV outcomes in high risk patients with type 2 diabetes.
- The GRADE CV outcomes data suggest that liraglutide may also reduce the risk of CV events in relatively low-risk patients with diabetes, compared to treatment with other commonly used glucose-lowering medications.
- Given the substantial lifetime CV risk associated with diabetes, the current dichotomy in the care of high vs. lower CV risk patients with type 2 diabetes may not be justifiable.

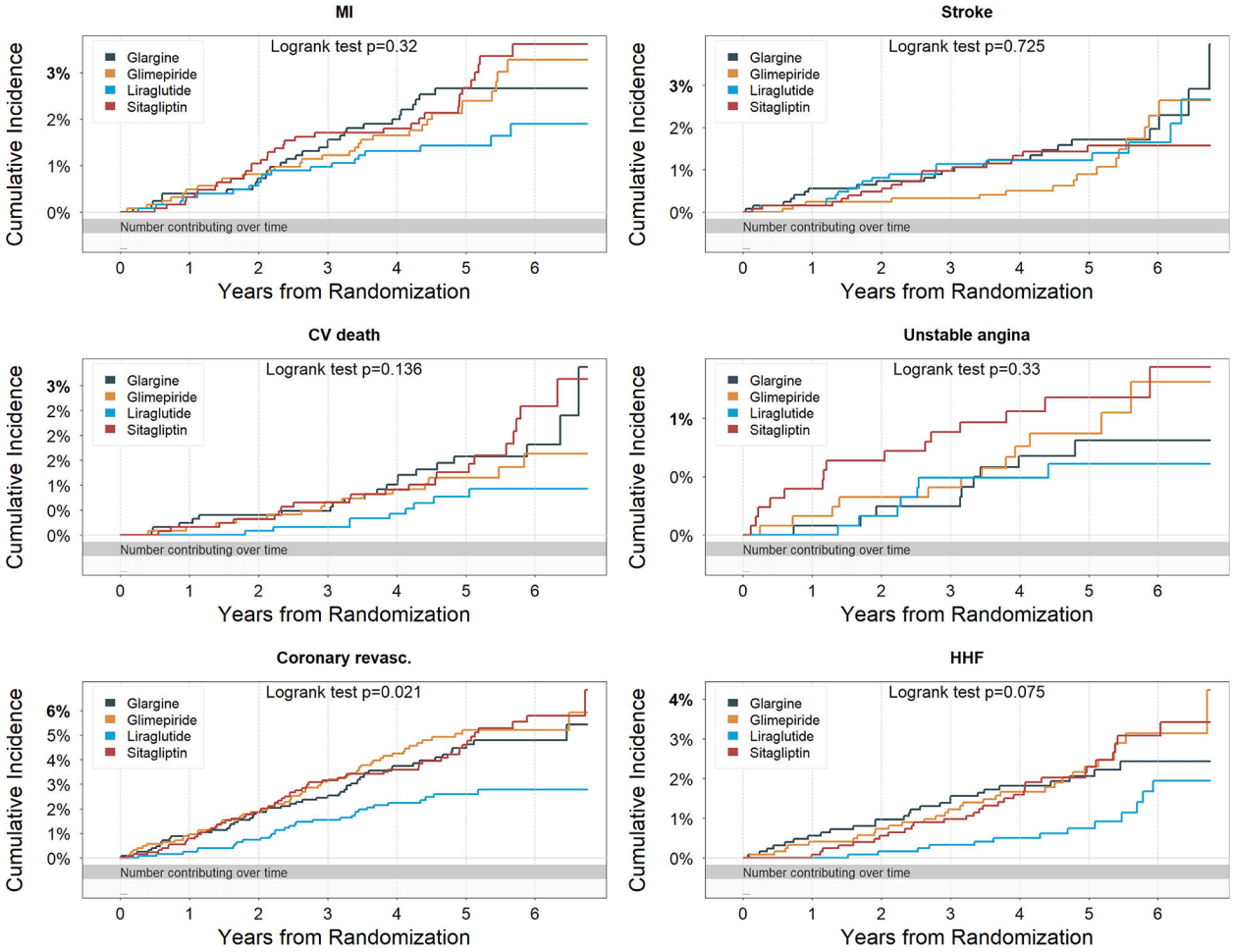

Figure 1. Kaplan-Meier curves for each of the CV outcomes among the GRADE treatment groups.

Cumulative incidence of composite cardiovascular outcomes (panel A) and of their components (panel B). The shaded bar along the x-axis of each figure indicates the number of participants available for analyses. The p-values are from the log-rank tests with no adjustment for multiple comparisons. MI = myocardial infarction; CV = cardiovascular; Revasc = revascularization; HHF = hospitalization for heart failure; UA = unstable angina; MACE = major adverse cardiovascular events; MACE-3 = a composite of MI, stroke (CVA), and CV death. P-values are not adjusted for multiple comparisons

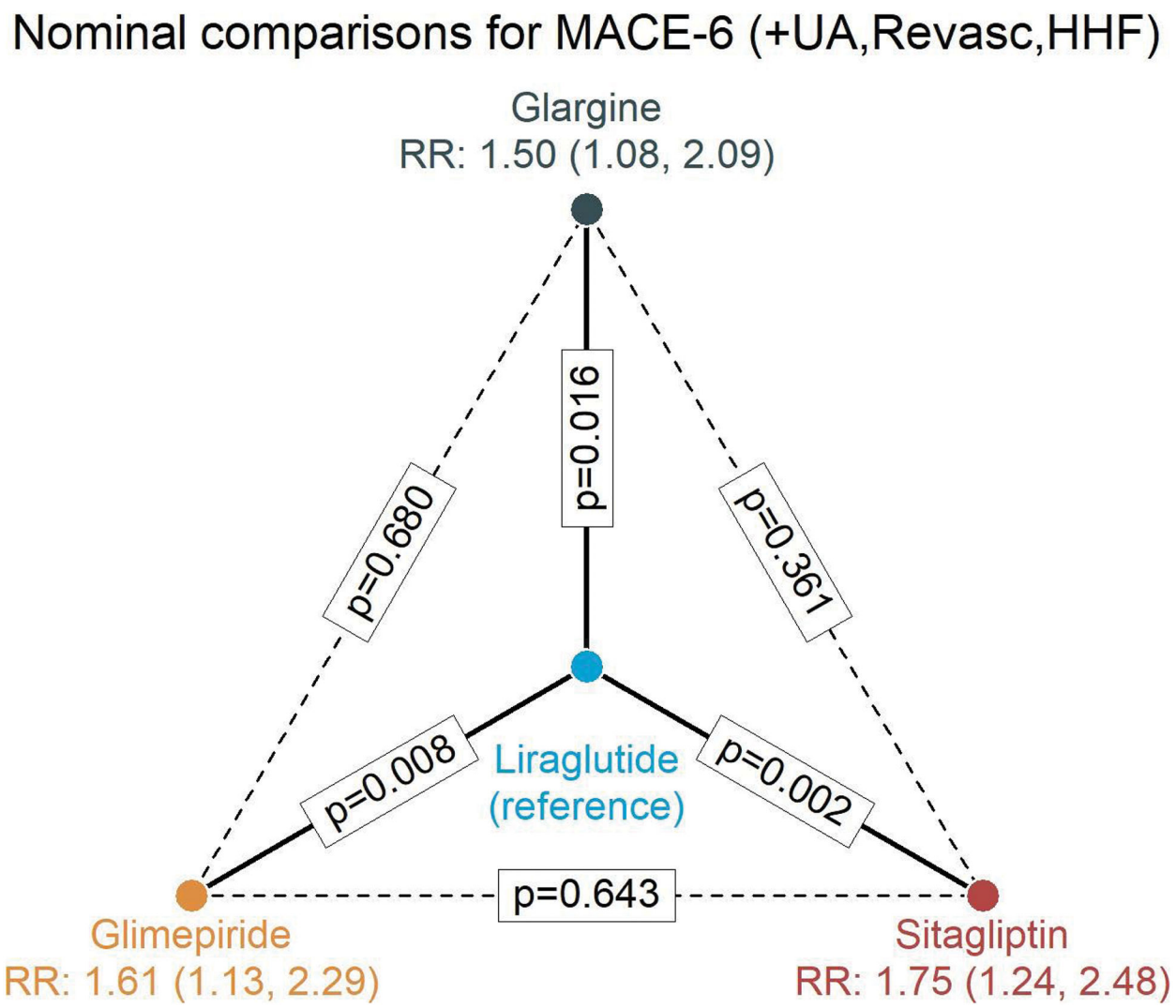

Figure 2. Pairwise comparison of MACE-6 recurrent event analysis.

This figure summarizes the 6 pairwise comparisons among the 4 treatment groups (glargine, glimepiride, liraglutide, and sitagliptin) for ALL MACE-6 events using solid and dashed lines to denote significance. A solid line between any 2 treatment groups means that the 2 groups have significantly different event rates for ALL MACE-6 events: a dashed line between any 2 treatment groups means that the 2 groups do not differ significantly in their total MACE-6 event rates. The p-value for each pairwise comparison is provided in the center of the solid or dashed line between the 2 relevant treatment groups. Of note, after adjustment for multiple comparisons using the Holm procedure for the 4 treatment groups (6 pairwise comparisons), liraglutide has a lower risk than either glimepiride (HR: 1.63) or sitagliptin (HR: 1.77); however, liraglutide's lower risk estimate compared to glargine (HR: 1.51) is no longer significant (p-value = 0.063). The remaining pairwise comparisons are not significant. The rate ratios (RR) denote the event rate of ALL MACE-6 events in the glargine, glimepiride, and sitagliptin groups, respectively, relative to liraglutide (the reference group) and arise from the proportional rate model as described in the text. MACE = major adverse cardiovascular events; MACE-6 = a composite of myocardial infarction,

stroke, CV death, unstable angina requiring hospitalization, coronary revascularization and hospitalization for heart failure; ALL MACE-6 = all first and recurrent MACE-6.

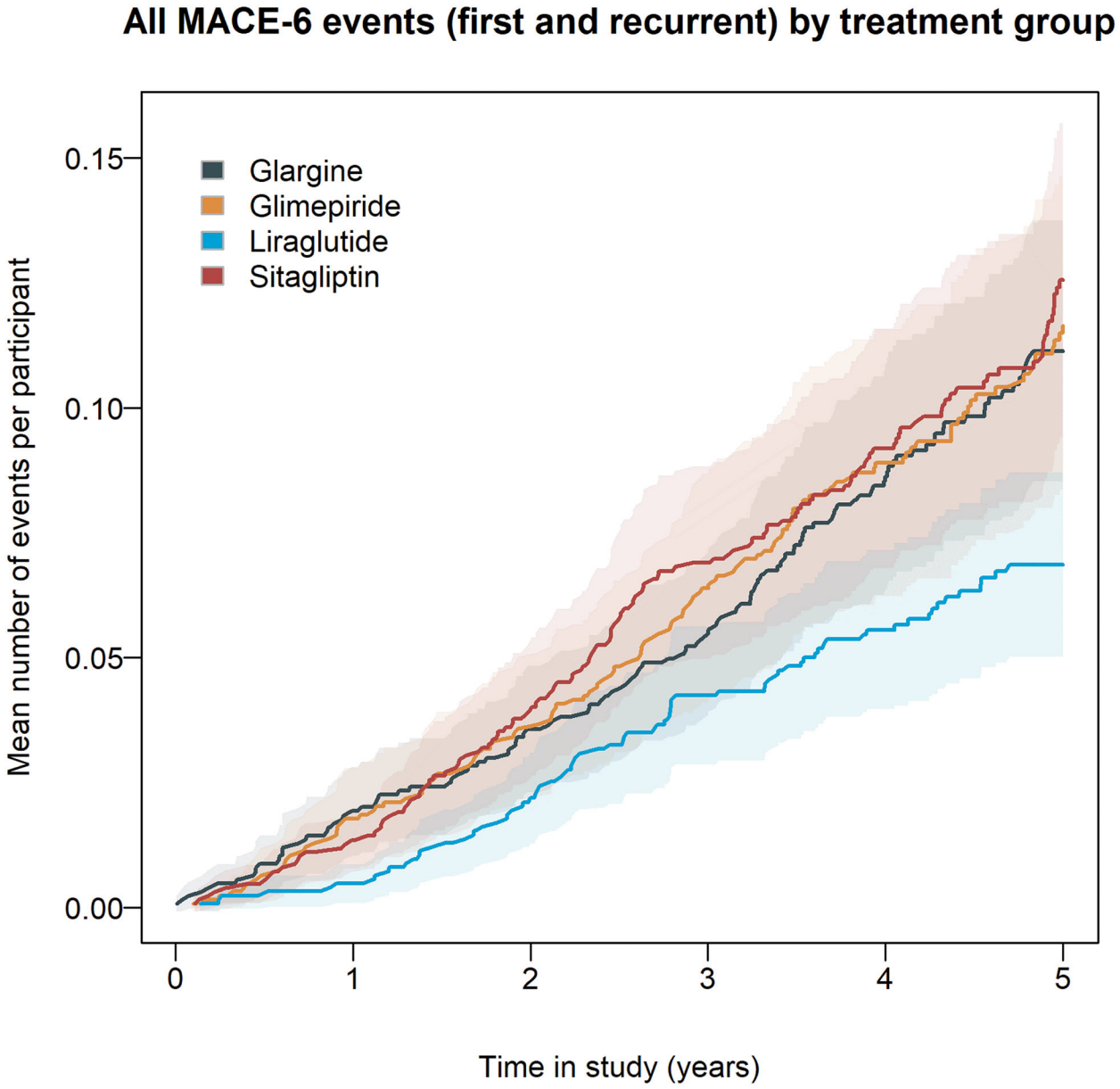

Figure 3. Mean number of all MACE-6 events (first and recurrent) per participant, by treatment group.

Mean number of ALL MACE-6 events (first and recurrent) by treatment group up to 5 years post-randomization. The liraglutide treatment group had the lowest mean number of ALL MACE-6 events per participant throughout the 5 years. The shaded areas represent 95% confidence bands for mean participant event estimates by treatment group.

Table 1.

CV outcomes and treatment group comparisons for time-to-first-event analyses

CV Outcome	All	Treatment Group				P-value	
		Glargine	Glimepiride	Liraglutide	Sitagliptin	Unadjusted*	Adjusted†
MI	116 (2.3%)	30 (2.4%)	30 (2.4%)	21 (1.7%)	35 (2.8%)	0.320	0.371
Stroke	76 (1.5%)	23 (1.8%)	16 (1.3%)	19 (1.5%)	18 (1.4%)	0.725	0.725
CV death	67 (1.3%)	21 (1.7%)	16 (1.3%)	9 (0.7%)	21 (1.7%)	0.136	0.245
Unstable angina	43 (0.9%)	9 (0.7%)	12 (1.0%)	7 (0.6%)	15 (1.2%)	0.330	0.371
Coronary revascularization	206 (4.1%)	54 (4.3%)	60 (4.8%)	33 (2.6%)	59 (4.7%)	0.021	0.164
HHF	100 (2.0%)	26 (2.1%)	30 (2.4%)	14 (1.1%)	30 (2.4%)	0.075	0.168
MACE-3	241 (4.8%)	65 (5.1%)	59 (4.7%)	48 (3.8%)	69 (5.4%)	0.255	-
MACE-4	270 (5.3%)	71 (5.6%)	67 (5.3%)	54 (4.3%)	78 (6.2%)	0.211	0.316
MACE-5	352 (7.0%)	93 (7.4%)	91 (7.3%)	67 (5.3%)	101 (8.0%)	0.055	0.164
MACE-6	407 (8.1%)	108 (8.6%)	106 (8.5%)	78 (6.2%)	115 (9.1%)	0.041	0.164

*Unadjusted (nominal) p-values from the log-rank test comparing all four treatment groups for each CV outcome.

†P-values adjusted for nine comparisons using a Benjamini-Hochberg false discovery rate adjustment. MACE-3 was pre-specified in the protocol and is therefore unadjusted.

Table 2.

MACE and HHF outcomes for liraglutide compared to the other three treatments groups, combined

Outcome	HR	95% CI	p value (unadj)	p value (adj)
MACE-3	0.75	(0.54, 1.03)	0.071	0.071
MACE-4 (+UA)	0.75	(0.56, 1.01)	0.058	0.071
MACE-5 (+UA,Revasc)	0.70	(0.54, 0.91)	0.008	0.021
MACE-6 (+UA,Revasc,HHF)	0.70	(0.55, 0.90)	0.005	0.021
HHF	0.49	(0.28, 0.86)	0.013	0.022

The table shows the hazard ratio (HR) for the time to first event analyses of liraglutide vs the mean of the other three treatment groups (HR <1 indicates a lower risk in the liraglutide group compared to the average of the other three) along with its 95% asymptotic confidence interval (CI). Unadjusted p-values testing that the hazard ratio is 1 as well as the p-values adjusted for five comparisons are shown.