The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 22, 2022 VOL. 387 NO. 12

Glycemia Reduction in Type 2 Diabetes — Glycemic Outcomes

The GRADE Study Research Group*

ABSTRACT

BACKGROUND

The comparative effectiveness of glucose-lowering medications for use with metformin to maintain target glycated hemoglobin levels in persons with type 2 diabetes is uncertain.

METHODS

In this trial involving participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%, we compared the effectiveness of four commonly used glucose-lowering medications. We randomly assigned participants to receive insulin glargine U-100 (hereafter, glargine), the sulfonylurea glimepiride, the glucagon-like peptide-1 receptor agonist liraglutide, or sitagliptin, a dipeptidyl peptidase 4 inhibitor. The primary metabolic outcome was a glycated hemoglobin level, measured quarterly, of 7.0% or higher that was subsequently confirmed, and the secondary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5%.

RESULTS

A total of 5047 participants (19.8% Black and 18.6% Hispanic or Latinx) who had received metformin for type 2 diabetes were followed for a mean of 5.0 years. The cumulative incidence of a glycated hemoglobin level of 7.0% or higher (the primary metabolic outcome) differed significantly among the four groups ($P<0.001$ for a global test of differences across groups); the rates with glargine (26.5 per 100 participant-years) and liraglutide (26.1) were similar and lower than those with glimepiride (30.4) and sitagliptin (38.1). The differences among the groups with respect to a glycated hemoglobin level greater than 7.5% (the secondary outcome) paralleled those of the primary outcome. There were no material differences with respect to the primary outcome across prespecified subgroups defined according to sex, age, or race or ethnic group; however, among participants with higher baseline glycated hemoglobin levels there appeared to be an even greater benefit with glargine, liraglutide, and glimepiride than with sitagliptin. Severe hypoglycemia was rare but significantly more frequent with glimepiride (in 2.2% of the participants) than with glargine (1.3%), liraglutide (1.0%), or sitagliptin (0.7%). Participants who received liraglutide reported more frequent gastrointestinal side effects and lost more weight than those in the other treatment groups.

CONCLUSIONS

All four medications, when added to metformin, decreased glycated hemoglobin levels. However, glargine and liraglutide were significantly, albeit modestly, more effective in achieving and maintaining target glycated hemoglobin levels. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; GRADE ClinicalTrials.gov number, NCT01794143.)

The members of the writing committee (David M. Nathan, M.D., John M. Lachin, Sc.D., Ashok Balasubramanyam, M.D., Henry B. Burch, M.D., John B. Buse, M.D., Nicole M. Butera, Ph.D., Robert M. Cohen, M.D., Jill P. Crandall, M.D., Steven E. Kahn, M.B., Ch.B., Heidi Krause-Steinrauf, M.S., Mary E. Larkin, R.N., Neda Rasouli, M.D., Margaret Tiktin, D.N.P., Deborah J. Wexler, M.D., and Naji Younes, Ph.D.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the writing committee are listed in the Appendix. Dr. Lachin can be contacted at grademail@bsc.gwu.edu or at the George Washington University Biostatistics Center–GRADE Coordinating Center, 6110 Executive Blvd., Ste. 750, Rockville, MD 20852.

*The members of the GRADE Study Research Group are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2022;387:1063-74.
DOI: 10.1056/NEJMoa2200433

A Quick Take is available at NEJM.org

Type 2 diabetes affects more than 30 million adults in the United States and more than 500 million worldwide, with an annual incidence in the United States of approximately 1.5 million cases.[1,2] Its major human and economic costs are caused primarily by the development of diabetes-specific complications, including retinopathy, nephropathy, and neuropathy, and a risk of cardiovascular disease that is two to five times as high as that among persons without diabetes.[3] The long-term diabetes-specific complications have been ameliorated by interventions that decrease chronic glycemia, as measured by glycated hemoglobin levels.[4,5] A target glycated hemoglobin level of less than 7.0% (<53.0 mmol per mole) has been established by consensus for most persons with type 2 diabetes, with the goal of decreasing morbidity.[6]

Virtually all recommendations for the management of glycemia in persons with type 2 diabetes have included metformin as the first medication to be used, with a second medication added when needed to achieve or maintain a glycated hemoglobin level of less than 7.0%.[7,8] Unfortunately, there are few long-term comparator studies to guide the choice of a second glucose-lowering medication. The purpose of the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) Study was to examine the relative effectiveness of agents from four of the most commonly used classes of glucose-lowering medications, when added to metformin, in achieving and maintaining target glycated hemoglobin levels in persons with recent-onset type 2 diabetes.[9] Here, we report the major glycemic outcomes of this trial. In our accompanying article in this issue of the *Journal*, we report the effects of the randomly assigned interventions on prespecified secondary outcomes (microvascular complications and cardiovascular events and their risk factors).[10]

Methods

Trial Design and Oversight

This multicenter, parallel-group, comparative-effectiveness clinical trial was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health and designed by a subgroup of the investigators with NIDDK participation.[9] Randomization was conducted with the use of a centralized Web-based system and stratified according to trial site. The participants and clinic staff were aware of the treatment assignments; however, the investigators at the laboratories and reading centers and the members of the adjudication committee were unaware of the treatment assignments and the identity of each participant.

All the data were collected and analyzed by the trial research group. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the Supplementary Appendix with the full text of this article at NEJM.org. The authors wrote the manuscript and made the decision to submit it for publication. No confidentiality restrictions were imposed by the sponsors.

The manufacturers contributed the trial medications under clinical-trial agreements with the NIDDK but had no role in the design, conduct, or analysis of the trial. An independent data and safety monitoring board appointed by the NIDDK oversaw the conduct of the trial. All participating centers obtained approval from local institutional review boards.

Participants

Participants with type 2 diabetes were recruited at 36 clinical centers (Section S1 in the Supplementary Appendix) with the goal of composing a cohort that was broadly representative of the population with type 2 diabetes in the United States according to race and ethnic group. Eligible participants had type 2 diabetes that had been diagnosed at or after the age of 30 years, with the exception of American Indians or Alaska Natives, in whom the age at diagnosis was at least 20 years.[9] At initial screening, the known duration of diabetes was less than 10 years, and the participants had received at least 500 mg of metformin per day without the use of other glucose-lowering medications for the previous 6 months and were willing to use injection therapy. During a run-in period of 6 to 14 weeks before randomization, the metformin dose was increased to at least 1000 mg per day, with a target maximal dose (one that could be taken without unacceptable side effects) of 2000 mg per day. Eligible participants had a glycated hemoglobin level of 6.8 to 8.5% (50.8 to 69.4 mmol per mole) at the end of the run-in period.

TREATMENTS

The four medications selected for the current trial had to be approved by the Food and Drug Administration (FDA) and had to be in common use in combination with metformin at the time of the trial launch in 2013. Immediate-release or extended-release formulations of metformin (Bristol Myers Squibb) were supplied to all the participants. The randomly assigned treatment doses were adjusted on the basis of their labeling.

The treatments included the following: insulin glargine U-100 (hereafter, glargine) (Sanofi), administered daily at an initial dose of up to 20 U and adjusted according to glucose levels monitored by the participant and to avoid hypoglycemia; the sulfonylurea glimepiride (Sanofi), increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses and adjusted according to glucose levels monitored by the participant and to avoid hypoglycemia; the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide (Novo Nordisk) initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects; and the dipeptidyl peptidase 4 inhibitor sitagliptin (Merck) at a dose of 100 mg, with the dose adjusted according to kidney function.

The assigned treatment was continued until the participant had a confirmed glycated hemoglobin level greater than 7.5% (>58.5 mmol per mole) (the secondary metabolic outcome) (Fig. S1 in the Supplementary Appendix). At that time, glargine was added to the three assigned noninsulin treatments. In participants assigned to receive glargine who had a secondary outcome event and those in the other three treatment groups who had a tertiary outcome event, described below, treatment was intensified by adding prandial rapid-acting insulin aspart to the glargine regimen, and the randomly assigned medications, with the exception of glargine, were discontinued.

Thiazolidinediones were not included in the trial because of safety concerns present at the time of trial planning; these concerns included bone loss, fluid retention, and a risk of bladder cancer with pioglitazone.[11] Sodium–glucose cotransporter 2 (SGLT2) inhibitors were not included because they had not been approved by the FDA in the United States during the planning and launch of this trial, and there was no clinical experience with them.

During the trial, consensus recommendations on the preferential use of GLP-1 receptor agonists and SGLT2 inhibitors in persons with prevalent cardiovascular disease or kidney disease were issued by the American Diabetes Association and the European Association for the Study of Diabetes.[12,13] These recommendations were communicated to participants with cardiovascular disease or kidney disease and to their health care providers. Any glucose-lowering medications other than those included as part of the trial were prescribed by the participants' own health care providers.

OUTCOMES AND ASSESSMENTS

The participants were evaluated quarterly. The primary outcome was primary metabolic failure of the randomly assigned treatment, defined as confirmation (usually at the next quarterly visit) of a glycated hemoglobin level of 7.0% or higher.[9] A participant could first have a primary-outcome event at 6 months, with confirmation at 9 months, unless the glycated hemoglobin level was greater than 9.0% (>74.9 mmol per mole), in which case the outcome event could occur at 3 months with confirmation at 3 to 6 weeks thereafter. The secondary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5% after the primary outcome. The protocol stipulated initiation of glargine in the three noninsulin treatment groups and intensification of insulin therapy in the original glargine treatment group after a secondary-outcome event.[9] The tertiary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5% after the secondary outcome, regardless of whether glargine was initiated in the three noninsulin treatment groups and insulin therapy was intensified in the original glargine treatment group. All laboratory measurements were performed in the GRADE Central Biochemical Laboratory (Section S3).

In the comparisons of the four treatments, other important trial outcomes included the following: serious adverse events; targeted adverse events (severe hypoglycemia warranting treatment, as well as pancreatitis and pancreatic and other cancers, with the exception of nonmelanoma skin cancer) adjudicated by committee[9]; and effects on microvascular complications and cardiovascular disease and risk factors for these conditions.

STATISTICAL ANALYSIS

The analyses were conducted in accordance with the intention-to-treat principle. We estimated that a sample of 5000 participants, with an assumed hazard rate of 0.0875 per year for the primary outcome, would provide the trial with 90% power, corrected for six pairwise tests at the 0.05 level, to detect a 25% reduction in the risk of treatment failure among the groups. Kaplan–Meier plots were used to capture the cumulative incidence of outcomes according to the time from randomization to the visit at which an event was first reported and subsequently confirmed. We used a Cox proportional-hazards model to assess differences among the treatment groups, and the results are described with hazard ratios and robust confidence limits.[14] Differences in the outcomes were also reported as the restricted mean survival time,[15] or time to event, over 4 years of follow-up (when 85.8% of the trial cohort was followed). Additional analyses compared each treatment group with the other three combined with the use of hazard ratios and confidence intervals.[16]

For the primary outcome, a global log-rank test was used to test for any differences among the four groups, and additional tests were used to assess pairwise differences between groups. The closed-testing procedure provided protected P values for the six pairwise comparisons[17] and for the comparison of each treatment group with the other three combined.[16] The results of all other analyses were expressed as hazard ratios, estimates of effects (risk reductions), or mean values, all with accompanying 95% confidence intervals, or as simple percentages. The widths of the confidence intervals have not been adjusted for multiple testing, and any inferences drawn may not be reproducible; therefore, P values are not reported.

Prespecified subgroup analyses included baseline factors as categories (age <45, 45 to 59, and ≥60 years; sex; and race or ethnic group) or strata in thirds (body-mass index [BMI; the weight in kilograms divided by the square of the height in meters], duration of diabetes, and glycated hemoglobin levels). Sensitivity analyses were conducted to assess the effect of coronavirus disease 2019 (Covid-19) and adherence to trial medications ("per-protocol analysis"). Details are provided in Figures S2 and S3.

RESULTS

BASELINE CHARACTERISTICS OF THE PARTICIPANTS

The first participant underwent randomization in July 2013, and the last participant underwent randomization in August 2017 (Fig. S4). The baseline characteristics of the 5047 participants, which were reported previously[18] and are shown in Table S1, included a mean (±SD) age of 57.2±10.0 years. A total of 63.6% were men, which reflected the inclusion of 10 Veterans Affairs medical centers as trial sites, and 41.5% of the participants were at least 60 years of age. A total of 65.7% of the participants identified as White, 19.8% as Black, and 3.6% as Asian. Ethnic group was also reported by the participants: 18.6% identified as Hispanic or Latinx, 2.7% as American Indian or Alaska Native, and 0.6% as Native Hawaiian or Pacific Islander.

The mean duration of diabetes as reported by the participants was 4.2±2.7 years. The daily metformin dose was 1576±525 mg at initial screening and 1944±205 mg at randomization, and 92.3% of the participants received 2000 mg per day. The mean BMI was 34.3±6.8, and the mean glycated hemoglobin level was 7.5±0.5% (58.3±5.3 mmol per mole). There were no substantial differences in any baseline demographic characteristic or findings on physical examinations or laboratory measurements among the four treatment groups. The baseline characteristics of the recruited cohort resembled those in the U.S. population who had type 2 diabetes that was being treated with metformin, who were of a similar age, and who had a similar duration of diabetes and a similar glycated hemoglobin range (Table S2).

PARTICIPANT RETENTION AND ADHERENCE TO TRIAL VISITS AND ASSIGNED MEDICATIONS

At the end of the trial in April 2021, the mean duration of follow-up was 5.0 years (range, 0 to 7.6), and 85.8% of the participants had been followed for at least 4 years. Retention and adherence were high; 94% of the participants completed a final visit, and they adhered to a mean of 92% of their expected trial visits (Table 1). A total of 27 of 5047 participants (0.5%) were lost to follow-up, and 153 died during the trial. During the Covid-19 pandemic, which overlapped with the trial closeout period, many visits were conducted by telephone and data on the glycated

Table 1. Protocol Completion and Adherence in the Treatment Groups during the Trial.

Variable	Glargine (N=1263)	Glimepiride (N=1254)	Liraglutide (N=1262)	Sitagliptin (N=1268)
Retention — no./total no. (%)*	1138/1221 (93.2)	1142/1211 (94.3)	1156/1235 (93.6)	1144/1227 (93.2)
Overall adherence to trial visits — %†	91.4	92.9	92.3	92.8
Mean follow-up — yr‡§	4.9±1.4	5.0±1.3	5.0±1.3	5.0±1.3
Discontinuation of metformin — no. (%)	105 (8.3)	98 (7.8)	88 (7.0)	97 (7.6)
Use of nontrial, glucose-lowering medications outside the protocol, discontinuation of assigned trial treatment outside the protocol, or both — no. (%)¶	332 (26.3)	426 (34.0)	368 (29.2)	347 (27.4)
<1 yr after randomization	65 (5.1)	61 (4.9)	150 (11.9)	60 (4.7)
1 to <2 yr after randomization	51 (4.0)	65 (5.2)	51 (4.0)	60 (4.7)
≥2 yr after randomization	216 (17.1)	300 (23.9)	167 (13.2)	227 (17.9)
Duration of assigned trial treatment in accordance with the protocol — yr§¶‖	4.3±1.8	4.2±1.7	4.1±2.0	4.3±1.7
Percentage of trial time during which participant received originally assigned treatment in accordance with the protocol §¶‖**	83.7±28.9	82.0±28.7	79.1±34.6	84.0±27.7
Discontinuation of assigned trial treatment outside the protocol — no. (%)¶	172 (13.6)	294 (23.4)	289 (22.9)	236 (18.6)
Maximum dose of assigned treatment received††‡‡	51.4±39.7 U	5.4±2.8 mg	1.6±0.5 mg	98.4±12.2 mg
Use of nontrial glucose-lowering medication outside the protocol — no. (%)	176 (13.9)	208 (16.6)	136 (10.8)	193 (15.2)

* Retention was defined as completion of the trial closeout visit. The denominators in this row sum to 4894 (i.e., participants who were not known to have died before the end of the trial).
† Visit adherence was calculated for each participant as 100% multiplied by the number of trial visits attended, divided by the maximum number of trial visits according to either the expected closeout trial visit date in participants who survived to the end of the trial or the date of death.
‡ The duration of follow-up was calculated as the date of last trial contact minus the date of randomization.
§ Plus–minus values are means ±SE.
¶ Participants were considered to have received assigned treatment if treatment was discontinued in accordance with the trial protocol (e.g., the randomized medication was discontinued because the participant had a tertiary outcome event, as stated in the protocol).
‖ The duration shown is the time from randomization to the date of first discontinuation of trial treatment, use of nontrial glucose-lowering medication, or both in participants who discontinued trial treatment, used nontrial glucose-lowering medication during the trial, or both, or the time from randomization to the date of the last trial contact in those who did not discontinue trial treatment, did not use nontrial glucose-lowering medication during the trial, or both.
** The denominator for this percentage is the time from randomization to expected closeout visit date in participants who survived to the end of the trial, or the time from randomization to death, calculated for each participant.
†† Shown is the mean maximum dose of randomly assigned medication taken at any time during the trial.
‡‡ Plus–minus values are means ±SD.

hemoglobin level were collected with the use of a validated mail-in kit.[19] As a result, 89% of all expected visits were completed during the final year of the trial (May 1, 2020, through April 30, 2021).

No differences were observed across the four treatment groups with respect to the retention of participants or adherence to trial visits (Table 1). Slight differences were observed with respect to metformin use, with 8% of the participants overall discontinuing metformin during study follow-up. There were differences in adherence to randomly assigned medications, with a higher frequency of discontinuation in the glimepiride and liraglutide groups (23% of the participants in each group) than in the sitagliptin (19%) and glargine (14%) groups. In the liraglutide and sitagliptin groups, most participants received the maximum doses of their assigned treatment; the mean daily maximum doses in the glimepiride and glargine groups were 5.4 mg and 51.4 U, respectively (Table 1 and Table S3). The percent-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.