Baseline Characteristics of Randomized Participants in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

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OBJECTIVE

GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study) is a 36-center unmasked, parallel treatment group, randomized controlled trial evaluating four diabetes medications added to metformin in people with type 2 diabetes (T2DM). We report baseline characteristics and compare GRADE participants to a National Health and Nutrition Examination Survey (NHANES) cohort.

RESEARCH DESIGN AND METHODS

Participants were age ≥30 years at the time of diagnosis, with duration of T2DM <10 years, HbA_{1c} 6.8–8.5% (51–69 mmol/mol), prescribed metformin monotherapy, and randomized to glimepiride, sitagliptin, liraglutide, or insulin glargine.

RESULTS

At baseline, GRADE's 5,047 randomized participants were 57.2 ± 10.0 years of age, 63.6% male, with racial/ethnic breakdown of 65.7% white, 19.8% African American, 3.6% Asian, 2.7% Native American, 7.6% other or unknown, and 18.4% Hispanic/Latino. Duration of diabetes was 4.2 ± 2.8 years, with mean HbA_{1c} of 7.5 ± 0.5% (58 ± 5.3 mmol/mol), BMI of 34.3 ± 6.8 kg/m^2, and metformin dose of 1,944 ± 204 mg/day. Among the cohort, 67% reported a history of hypertension, 72% a history of hyperlipidemia, and 6.5% a history of heart attack or stroke. Applying GRADE inclusion criteria to NHANES indicates enrollment of a representative cohort with T2DM on metformin monotherapy (NHANES cohort average age, 57.9 years; mean HbA_{1c}, 7.4% [57 mmol/mol]; BMI, 33.2 kg/m^2; duration, 4.2 ± 2.5 years; and 7.2% with a history of cardiovascular disease).

CONCLUSIONS

The GRADE cohort represents patients with T2DM treated with metformin requiring a second diabetes medication. GRADE will inform decisions about the clinical effectiveness of the addition of four classes of diabetes medications to metformin.

The optimal medication management of hyperglycemia in type 2 diabetes (T2DM) is not established. In addition to lifestyle intervention, metformin is the recommended initial medication in T2DM due to its glycemic effectiveness, lack of associated hypoglycemia or weight gain, low cost, and evidence of long-term benefit and safety

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**A complete list of the members of the GRADE Research Group can be found in the Supplementary Data online.*

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(1,2). Over time, most patients are unable to maintain glycemic control with metformin alone, with an estimated 20–50% incidence of metformin monotherapy failure within 5 years (3–6). The UK Prospective Diabetes Study (UKPDS) demonstrated that only 50% of patients with newly diagnosed diabetes could maintain glycemic goals with monotherapy after 3 years, declining to ~25% by 9 years (5). Hence, most patients with T2DM will require a second medication in addition to metformin for glycemic management.

Clinicians may choose among many medication classes and multiple options within each class, in addition to metformin, for the treatment of T2DM (7). In the absence of cardiovascular disease (CVD), current guidelines propose choosing from among individual medications or medication classes based on patient characteristics and treatment goals (8,9). Although patients take diabetes medications for many years, there has been a paucity of long-term head-to-head comparison trials, and, for the most part, only limited comparisons, usually involving two medications or classes, have been performed (1,10,11). The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) aims to fulfill a primary goal of comparative effectiveness research: testing commonly used medication combinations in randomly assigned treatment groups over time to aid in real-world clinical decision making (12). GRADE will compare four medications in combination with metformin over ~5 years.

This report describes the baseline characteristics of the 5,047 participants enrolled in GRADE, providing a novel description of a large randomized cohort with T2DM of <10 years' duration prescribed metformin monotherapy. In addition, we compare the GRADE cohort to a National Health and Nutrition Examination Survey (NHANES) cohort meeting GRADE inclusion criteria to assess the broader generalizability of GRADE.

RESEARCH DESIGN AND METHODS

General

GRADE is being conducted at 36 centers across the U.S. (Fig. 1). The full protocol is available at https://portal.bsc.gwu.edu/web/grade and in the Supplementary Data. The Institutional Review Board at each clinical center approved the protocol, and all participants gave written informed consent before any study procedures. The first patient was enrolled in July 2013, and enrollment concluded in August 2017. The trial is registered on ClinicalTrials.gov, identifier NCT01794143.

Participants

Eligibility requirements for GRADE at screening and randomization have been previously reported (1) and are updated in the Supplementary Data (Protocol 1.6.1, pages 13–15). Eligibility in the final protocol included patients with T2DM, with a diagnosis of diabetes <10 years prior (initially 5 years; Protocol v.1.3, released 15 January 2014, extended eligibility to 10 years), diagnosed at age ≥30 years in non-American Indian (AI)/Alaska Native (AN) patients or age ≥20 for AI/AN, taking metformin monotherapy (at least 1,000 mg/day), HbA_{1c} 6.8–8.5% (51–69 mmol/mol) at randomization, and willingness to take a second diabetes medication, including daily injections of insulin if required. Key exclusion criteria included evidence of type 1 or secondary forms of diabetes, use of other diabetes medications within the last 6 months, history of intolerance or allergy to any of the proposed study medications or sulfa drugs, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, major cardiovascular event within the previous year, history of pancreatitis, congestive heart failure (New York Heart Association Functional Classification ≥III), new diagnosis or treatment for any cancer (other than nonmelanoma skin cancer) within the previous 5 years, planned major surgery, or planned pregnancy for women of childbearing potential.

Study Design

GRADE is a parallel treatment group, unmasked clinical trial. Eligible participants were randomly assigned to one of four diabetes medications (1:1:1:1) in combination with metformin, representing the four main treatment classes of diabetes medications that were approved by the U.S. Food and Drug Administration (FDA) in combination with metformin and in common use at the time the trial was designed: glimepiride (sulfonylurea), sitagliptin (dipeptidyl peptidase 4 [DPP-4] inhibitor), liraglutide (glucagon-like peptide 1 [GLP-1] receptor agonist), and glargine (basal insulin) (see Supplementary Data: Protocol Fig. 1). Medications were selected based on data regarding efficacy, safety profile, daily (rather than twice-daily) dosing, and availability of a donated supply by a subset of investigators without conflicts of interest and used in accordance with their labeling (1).

GRADE is an intention-to-treat study in which all participants are requested to continue quarterly follow-up for all study outcomes until the close of the study in April 2021. The planned follow-up period for participants ranges from 3.25 to 7.5 years, with an estimated mean duration of follow-up of 5.2 years, not accounting for losses to follow-up.

Clinical Centers

Clinical centers were chosen by peer review of applications received in response to a request for support announcement. Clinical centers were selected in part to ensure broad national representation, including representation of the overall racial and ethnic diversity of people with T2DM. As shown in Fig. 1, GRADE has 36 clinical centers varying in size, region, and practice environment (e.g., academic, community, closed-model HMOs, and Veterans Administration health care systems).

Recruitment

Participants were identified through Institutional Review Board-approved electronic health record queries and other local outreach methods. After an initial contact, participants attended a screening visit at which eligibility was assessed. Eligible participants then initiated a run-in period of 4–8 weeks during which the dose of metformin was escalated. Participants who were still eligible after the run-in attended the randomization visit.

Variables and Assessments

Assessments were completed during screening and run-in and at the baseline randomization visits. Participant race and ethnicity, medical history, current medications, alcohol intake, smoking status, and educational attainment were self-reported and obtained through interviews conducted by research staff. All assessments in this report were

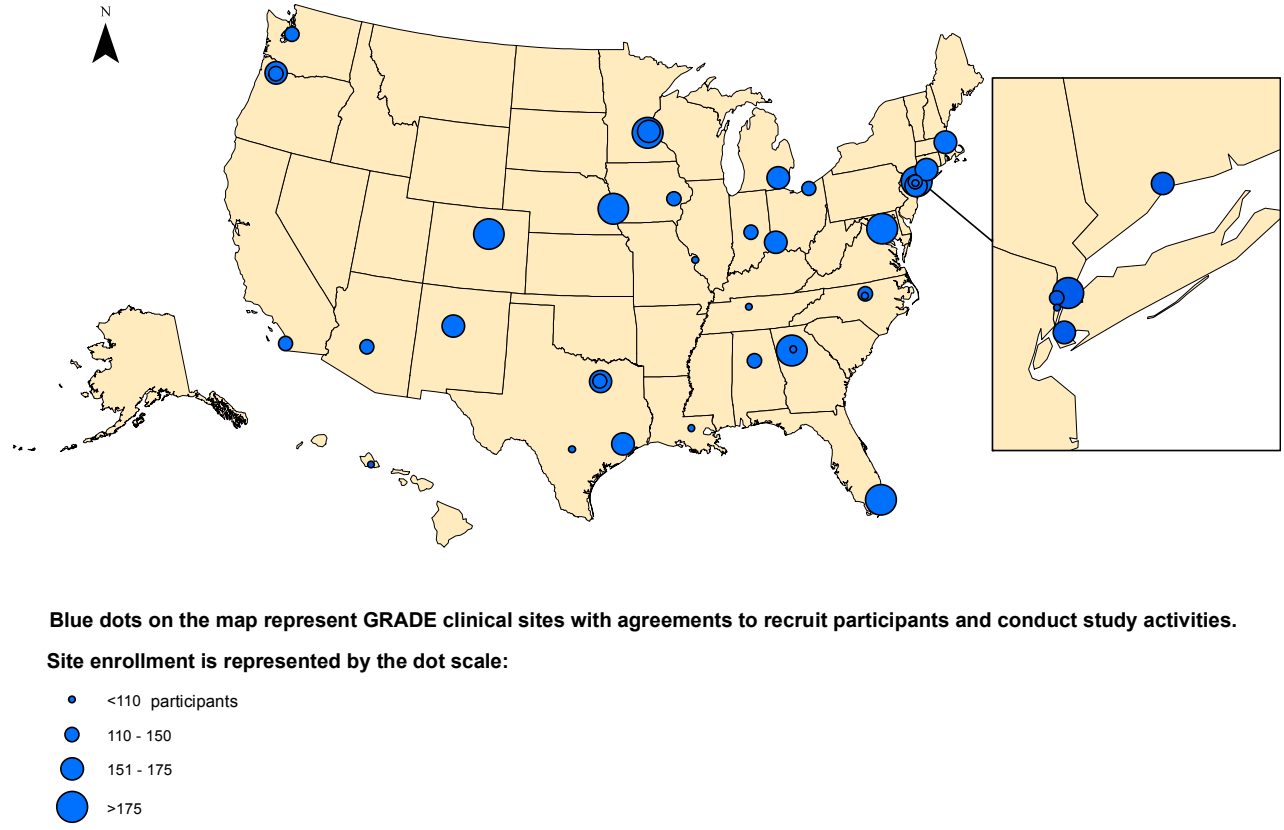

Figure 1—Map of GRADE clinical centers.

attempted for all participants, with the exception of querying use of medications for depression or anxiety; this question was added after study initiation and was collected on 2,502 participants only. All physical and metabolic measurements were obtained by certified staff. Height, weight, and blood pressure were taken in duplicate by trained clinical research staff. Height was recorded to the nearest 0.1 cm and weight to the nearest 0.1 kg. Seated blood pressure was taken after resting for 5 min and repeated after 1 min; measurements were averaged.

History of hypertension, hyperlipidemia, heart attack or stroke, and retinopathy were obtained by self-report. Diabetic peripheral neuropathy was measured by combining the 15-item symptom questionnaire and the 4 physical examination components of the Michigan Neuropathy Screening Instrument (MNSI). A value of 3.2883 on the combined questionnaire and examination index correctly classifies 80% of diabetic peripheral neuropathy with a sensitivity of 48% and specificity of 93% (13).

All laboratory tests were performed by the Central Biochemistry Laboratory (Advanced Research and Diagnostic Laboratory, Department of Laboratory Medicine and Pathology, at the University of Minnesota) using standardized laboratory procedures. HbA_{1c} in GRADE, as for NHANES, is standardized per NGSP protocol. Baseline physical assessment and laboratory values are reported, with laboratory values obtained at the final run-in visit or at randomization.

Outcomes

Details of outcome ascertainment have been previously described (1). The primary outcome for GRADE is the time to primary failure of the randomly assigned treatment, defined as the time to an initial $HbA_{1c} \geq 7\%$ (≥ 53 mmol/mol), subsequently confirmed at the next visit, while being treated at maximum tolerable doses of both metformin and the second randomly assigned medication. Participants will be analyzed as part of their randomly assigned medication group according to intention-to-treat principles (14) regardless of adherence to the assigned medication.

Additional outcomes have been previously described (1), including metabolic outcomes, cardiovascular outcomes, microvascular outcomes, adverse effects, side-effect profiles, adherence, safety and tolerability, quality of life, and health-economic evaluation.

Statistical Analysis

For this baseline report, descriptive statistics are provided for all baseline characteristics presented. Data are presented as mean $\pm$ SD or median (interquartile range) for continuous variables and *n* (%) for categorical variables.

Comparisons to NHANES Cohort

We report baseline characteristics of GRADE participants compared with an NHANES subsample meeting GRADE eligibility criteria. NHANES is a set of stratified, multistage probability surveys conducted by the National Center for Health Statistics that are designed to represent the U.S. civilian noninstitutionalized population. NHANES uses standardized questionnaires and measurements, as previously described (15,16). We report characteristics of NHANES respondents in 2011–2014,

age ≥30 years with diabetes for <10 years, HbA_{1c} of 6.8–8.5% (51–69 mmol/mol), and taking metformin alone. We used the NHANES 2011–2014 cycle because it overlapped in time with the onset of GRADE recruitment and contained all relevant variables, including metformin use. NHANES analyses use weights provided by NHANES so that estimates are representative of the U.S. civilian noninstitutionalized population and to account for the complex survey design and survey nonresponse.

RESULTS

Enrollment

GRADE screened 11,259 patients in person (Fig. 2). Of these, 3,466 were immediately excluded, 58.8% because HbA_{1c} was too low at the time of screening or was deemed likely to fall below the inclusion criterion of 6.8% (51 mmol/mol) by the end of run-in. The final run-in visit was attended by 61.7% of screened participants, after which 1,903 were excluded, 41.6% because the HbA_{1c} was <6.8% (51 mmol/mol) and 33.7% because the HbA_{1c} was >8.5% (69 mmol/mol). Of those screened, 5,047 (44.8%) were randomly assigned to one of the four study treatment groups.

Demographic Characteristics

Baseline characteristics of participants are summarized in Table 1. Mean age is 57.2 ± 10.0 years, and 64% of the study participants are male. The racial composition of the cohort is 65.7% white, 19.8% African American, 3.6% Asian, 2.7% AI/AN, 0.6% Native Hawaiian or other Pacific Islander, 6.3% other or more than one race, and 1.3% unknown or not reported. Hispanic/Latino ethnicity was reported by 18.4% of participants.

Clinical Characteristics

At baseline, HbA_{1c} was 7.5 ± 0.5% (58 ± 5.3 mmol/mol), fasting glucose was 151 ± 31 mg/dL (8.4 ± 1.7 mmol/L), and duration of diabetes was 4.2 ± 2.8 years. BMI was 34.3 ± 6.8 kg/m^2. The prevalence of hypertension and dyslipidemia was 66.6% and 72.2%, respectively. Self-reported history of heart attack or stroke was 6.5%. History of self-reported eye disease due to diabetes was 1.0%. Baseline neuropathy prevalence was 21.5% by combined MNSI index. Nondiabetes medication use and metabolic parameters are listed in Table 1. Among the cohort, 69% were treated with antihypertensive medications, with mean blood pressure for the entire cohort of 128 ± 15/77 ± 10 mmHg. Mean total cholesterol was 164 ± 38 mg/dL (4.24 ± 0.98 mmol/L) and mean LDL was 91 ± 32 mg/dL (2.3 ± 0.8 mmol/L), with 64% of all participants reporting statin use. Approximately one-fifth reported taking antidepressant or anxiolytic medications (see Table 1, second footnote).

Comparison of GRADE to NHANES Respondents Meeting GRADE Inclusion Criteria

For this report, we applied GRADE inclusion but not exclusion criteria to unpublished data available from NHANES respondents ≥18 years with diabetes in the 2011–2014 surveys (Table 2). The number of respondents with diabetes was 1,432. After applying GRADE inclusion criteria, 201 NHANES respondents with diabetes met criteria of age ≥30 years, diabetes duration of <10 years, and HbA_{1c} of 6.8–8.5% (51–69 mmol/mol). Of these, 120 were taking metformin alone, representing 2,000,987 of the 21,686,032 Americans with diabetes, a weighted percentage of 9.1% (95% CI 7.4–11.2) of American adults with diabetes. The NHANES cohort had a mean age of 57.9 ± 12.0 years, with a mean HbA_{1c} of 7.4 ± 0.56% (57 ± 6.6 mmol/mol) and BMI of 33.2 ± 8.2 kg/m^2, and 7.2% had a history of CVD (Table 2).

CONCLUSIONS

GRADE has met its first goal of enrolling a national cohort of people with T2DM treated with metformin alone who require a second diabetes medication. Although GRADE is not a population-based study, it is informative to compare the GRADE cohort to the general population of Americans with diabetes. The Centers for Disease Control and Prevention reported in 2017 that 84.4% of adults with diabetes had HbA_{1c} of ≤9% (75 mmol/mol) (17). In a published report of the 2005–2010 NHANES cohort, 57.8% of Americans with diagnosed diabetes were on oral antihyperglycemics only, and 13.4% took no diabetes medication. Among those taking medication, 77.6% had an HbA_{1c} of <8% (64 mmol/mol) (18). In GRADE, all participants were treated with metformin and had a mean HbA_{1c} of 7.5 ± 0.5% (58 ± 5.3 mmol/mol).

Focusing on the analysis performed for this report of NHANES respondents meeting GRADE inclusion criteria, it is apparent that GRADE participants are similar with respect to mean age, BMI (with 4-kg difference in body weight with broad CIs), HbA_{1c}, current smoking, and self-reported history of CVD (Table 2) despite the small actual number of NHANES respondents from which these data are derived.

There are, however, notable differences. GRADE enrolled a higher proportion of men, and GRADE participants had higher educational attainment than NHANES respondents. In addition, GRADE selected centers specifically to ensure enrollment of populations disproportionately affected by diabetes and as such was more racially and ethnically diverse than the NHANES population: GRADE participants are 19.8% African American and 18.4% Hispanic compared with 15.1% African American and 12.1% Hispanic in the NHANES subset meeting GRADE inclusion criteria (Table 2). It is important to note that inclusion criteria for a clinical trial narrow the eligible population substantially: applying GRADE inclusion criteria to the NHANES yielded 9.1% of the original sample. Expanding the eligibility for duration of diabetes early on during recruitment likely yielded a slightly longer duration of diabetes than would otherwise have been seen but likely did not affect other characteristics because the overall sample is similar to the NHANES-eligible cohort.

GRADE in the Context of Other Major Diabetes Studies

GRADE fits into a spectrum of large trials of patients with T2DM evaluating durability of glycemic therapy (Table 2). The UKPDS enrolled patients with newly diagnosed diabetes starting in 1977 (19,20). This study, which reported initial results in 1998, nonetheless provides the basis of our knowledge of T2DM treatment over a prolonged period. GRADE participants have a longer duration of diabetes and higher baseline HbA_{1c} than those who participated in UKPDS. A Diabetes Outcome Progression Trial (ADOPT), conducted in the U.S. between 2000 and 2006, was a trial of initial glucose-lowering therapy in which

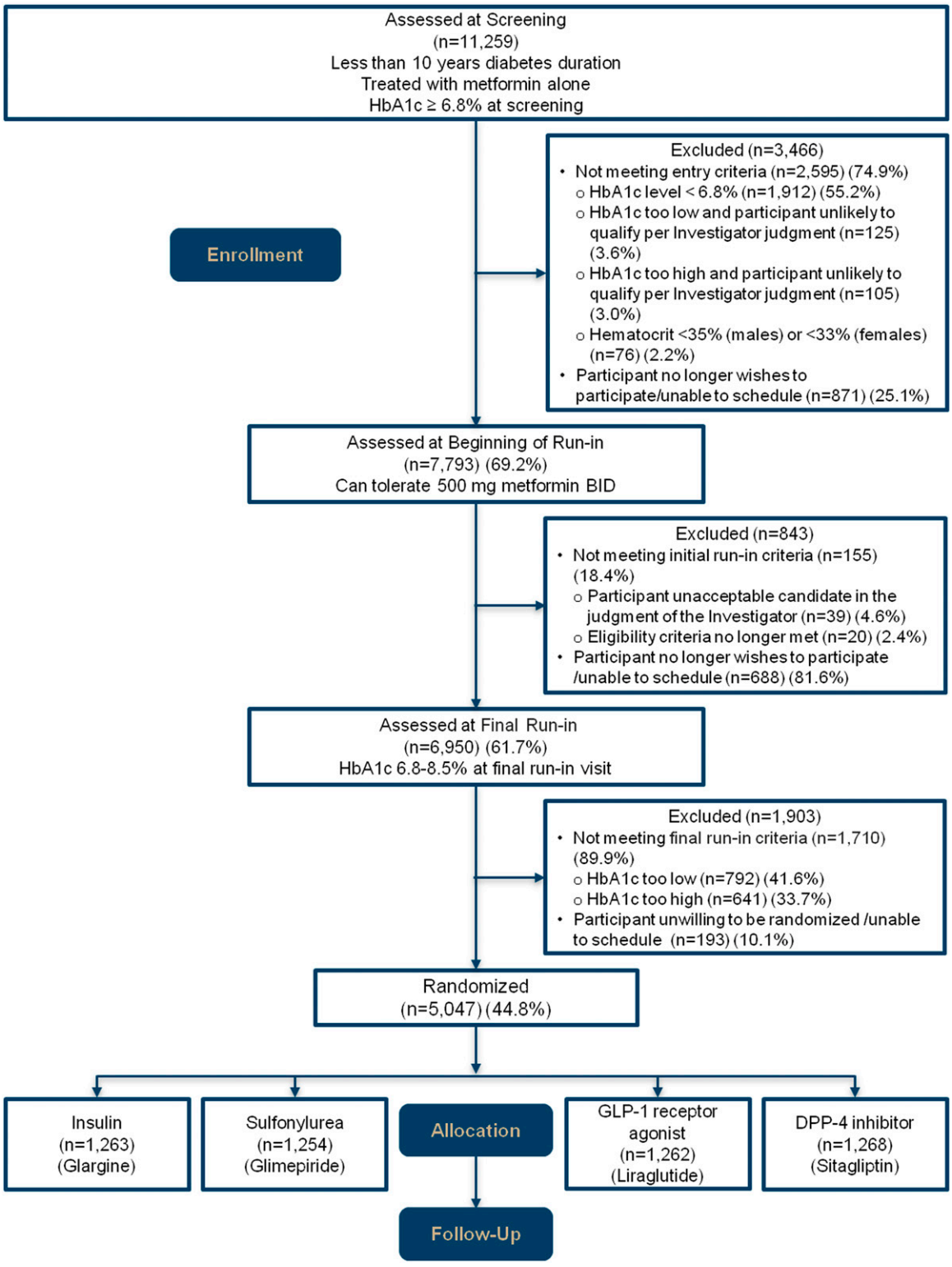

Figure 2—Consolidated Standards of Reporting Trials diagram.

96% of participants had been diagnosed with diabetes for ≤3 years (21). Participants in GRADE are similar in age but more racially and ethnically diverse than those in ADOPT. These major diabetes trials disproportionately enrolled men (61% in UKPDS and 58% in ADOPT), and GRADE is similar in this respect.

GRADE is different from the major diabetes clinical trials of the last decade that tested the hypothesis that intensive glycemic control would reduce CVD outcomes in T2DM. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) (22), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (23), and Veterans Affairs Diabetes Trial

Table 1—Baseline characteristics of participants in GRADE

	Overall (n = 5,047)*	Normal range for laboratory tests
Age at baseline visit (years)	57.2 ± 10.0	
Age group (years)		
<45	619 (12.3)	
45–59	2,327 (46.1)	
≥60	2,101 (41.6)	
Male sex	3,210 (63.6)	
Race		
White	3,314 (65.7)	
African American or black	1,000 (19.8)	
Asian	182 (3.6)	
AI/AN	137 (2.7)	
Native Hawaiian or other Pacific Islander	28 (0.6)	
Other or more than one race	319 (6.3)	
Unknown or not reported	67 (1.3)	
Ethnicity		
Hispanic/Latino	929 (18.4)	
Not Hispanic/Latino	4,077 (80.8)	
Unknown/not reported	41 (0.8)	
Education completed		
<High school	364 (7.2)	
High school graduate	1,039 (20.6)	
Some college	1,463 (29.0)	
≥College degree	2,180 (43.2)	
Duration of diabetes (years)	4.2 ± 2.8	
Duration of diabetes (years), median (IQR)	3.8 (1.9, 6.4)	
Screening metformin dose (mg/day)	1,575.5 ± 525.2	
Baseline metformin dose (mg/day)	1,944.2 ± 204.5	
Family history of any first-degree relatives with diabetes	3,522 (69.8)	
Medical history		
Heart attack/stroke	330 (6.5)	
Retinopathy	49 (1.0)	
Neuropathy	1,083 (21.5)	
Hypertension	3,360 (66.6)	
Elevated blood lipids	3,646 (72.2)	
Current medications		
Blood pressure medications	3,495 (69.2)	
Lipid-lowering medications	3,317 (65.7)	
Statin	3,209 (63.6)	
Aspirin	2,288 (45.3)	
Depression/anxiety medication(s)†	472/2,502 (18.9)†	
Smoking status		
Current smoker	695 (13.8)	
Former smoker	1,617 (32.0)	
Never smoked	2,735 (54.2)	
Physical measurements		
Weight (kg)	100.0 ± 22.3	
BMI (kg/m^2)	34.3 ± 6.8	
Blood pressure		
Systolic (mmHg)	128.3 ± 14.7	
Diastolic (mmHg)	77.3 ± 9.9	
Blood pressure <140/90 mmHg	3,802 (75.3)	
Blood pressure <130/80 mmHg	2,172 (43.0)	
Laboratory tests*		
HbA_{1c} (%)	7.5 ± 0.5	≥6.5% or 48 mmol/mol may indicate diabetes
HbA_{1c} (mmol/L)	58 ± 5.3	
HbA_{1c} <7%	725 (14.4)	
Cholesterol (mg/dL)	163.8 ± 37.8	<200 mg/dL
Cholesterol (mmol/L)	4.2 ± 0.98	5.172 mmol/L
Triglycerides (mg/dL)	154.0 ± 121.6	0–100 mg/dL
Triglycerides (mmol/L)	1.7 ± 1.4	0–1.7 mmol/L

Continued on p. 2104

Table 1—Continued

	Overall (n = 5,047)*	Normal range for laboratory tests
HDL (mg/dL)	43.4 ± 10.6	Female >50 mg/dL; male >40 mg/dL
HDL (mmol/L)	1.1 ± 0.3	Female >1.3 mmol/L; male >1.0 mmol/L
LDL (mg/dL)	90.5 ± 31.7	<129 mg/dL
LDL (mmol/L)	2.3 ± 0.8	<3.4 mmol/L
LDL <100 mg/dL	3,348 (66.3)	
UACR (mg/g)	6.4 (3.1, 16.9)	<30 mg albumin/g creatinine
UACR <30 mg/g creatinine	4,241 (84.1)	
Fasting glucose (mg/dL)	151.5 ± 30.9	60–99 mg/dL
Fasting glucose (mmol/L)	8.4 ± 1.7	3.3–5.5 mmol/L
eGFR (mL/min/1.73 m^2)	95.3 ± 16.9	≥60 mL/min/1.73 m^2
eGFR <60 mL/min/1.73 m^2	121 (2.4)	
Serum creatinine (mg/dL)	0.83 ± 0.2	Female 0.4–1.1 mg/dL; male 0.5–1.2 mg/dL
Fasting C-peptide (nmol/L)	1.34 ± 0.6	0.37–1.47 nmol/L
Fasting insulin (pmol/L)	129.4 ± 95.4	12–150 pmol/L
Fasting insulin (mU/L)	21.6 ± 15.9	2–25 mU/L

Continuous data are presented as the mean ± SD or as the median (interquartile range), and categorical data are presented as n (%). UACR, urinary albumin-to-creatinine ratio. *N was 5,047 except for depression/anxiety medication question (see next note). †This question was added after the study started and was answered by 2,498 participants at baseline. Of these, 472 participants answered "yes" and 2,032 participants answered "no": 472/2,502 = 0.19.

(VADT) (24) trials enrolled patients with established CVD or at high cardiovascular risk. The intervention treatment groups of ACCORD and ADVANCE aimed for and achieved lower glycemic targets than were then or are currently recommended. All three trials used complex diabetes medication regimens to achieve glycemic targets. Moreover, the choice of diabetes medication was not protocolized. By contrast, GRADE aims to achieve a uniform glycemic target (<7%) using medications representative of four major diabetes medication classes while allowing investigator discretion to adjust individual participant glycemic targets over time for changes in clinical status.

GRADE is also unlike the major cardiovascular outcomes trials (CVOT) reported over the last half-decade. CVOT trials, mandated by the FDA starting in 2008 to demonstrate the cardiovascular safety of new diabetes drugs, have enrolled participants with T2DM who have established CVD or are at very high cardiovascular risk to accrue a sufficient number of outcomes to evaluate cardiovascular safety during relatively brief follow-up periods. The prevalence of established CVD in ACCORD, ADVANCE, and VADT was 30–40% and was even higher in CVOT trials of sodium–glucose cotransporter 2 (SGLT2) inhibitors and GLP-1 receptor agonists (usually ≥70%) (25). The prevalence of CVD in GRADE at baseline is much lower, with only 6.5% reporting a history of myocardial infarction or stroke at study entry. Determining the overall prevalence of CVD in patients with T2DM can be difficult, but one large U.S. electronic medical record database reported CVD prevalence of 21% among 1,389,016 patients with T2DM (26). This is consistent with an NHANES report showing 18.3% prevalence of CVD among adults with diabetes in 2012 (27). Although the prevalence of CVD in GRADE is lower than in the general U.S. population with diabetes, it is representative of the age-similar NHANES population meeting GRADE eligibility criteria (7.2%) (Table 2).

Compared with UKPDS, which enrolled patients with newly diagnosed T2DM, and with ACCORD, ADVANCE, and VADT and the more recent CVOTs that focused on participants with T2DM of longer duration and established CVD, GRADE represents an intermediate stage of treatment of T2DM. Immediately after diabetes diagnosis, as was seen in UKPDS and ADOPT, lifestyle change and initial single-agent pharmacotherapy are effective for a period of time, usually followed by deterioration in glycemic control. At the other end of the spectrum, long-standing diabetes may require insulin treatment if β-cell deficiency is advanced.

Although there are data from CVOTs that certain medications reduce the risk of heart failure and renal outcomes, or, in the case of one long-term GLP-1 receptor agonist trial, major adverse cardiac events, even in those without established CVD (28–30), the subgroups without established atherosclerotic CVD in these studies had two or more cardiovascular risk factors and longer duration of diabetes than participants in GRADE. The evidence remains inconclusive regarding which medication to choose for individuals with diabetes who have had deterioration in glycemic control despite initial management with metformin and lifestyle intervention but who are younger, have fewer cardiovascular risk factors, and do not yet have significant complications. This has been highlighted in the American Diabetes Association's and numerous other position statements (9,31). As a large-scale, longitudinal trial of patients with T2DM conducted in the current treatment era, characterized by more aggressive blood pressure and statin treatment, GRADE will allow comparative assessment of different diabetes medication classes with regard to efficacy and durability of achieving a target HbA_{1c} of <7% (53 mmol/mol) and patient-centered outcomes, including the safety of treatment.

The major limitation of GRADE is the lack of an SGLT2 inhibitor treatment group. SGLT2 inhibitors were not approved at the time the study was designed in 2012 and were in limited use at the time of study launch (32). As a comparative effectiveness study, GRADE selected commonly used, FDA-approved medication combinations (1). An inherent pitfall of long-term trials is that evidence and practice patterns may change within the time frame of the study. It is notable that despite the emergence of new evidence supporting use of GLP-1 receptor agonists and SGLT2 inhibitors in patients with T2DM and established CVD or high CVD risk, the best medication choice in the population enrolled in GRADE remains unclear. Similarly, pioglitazone was considered as a fifth

Table 2—Comparison of GRADE study to UKPDS, ADOPT, and GRADE-eligible NHANES cohort

	GRADE (1)	UKPDS (20)	ADOPT (3,21)	NHANES (16)
Primary study aim	Glycemic durability of second diabetes medication after metformin	Diabetes outcomes of intensive vs. conventional control after initial diagnosis of T2DM	Glycemic durability of initial diabetes medication	Subsample of NHANES participants meeting similar criteria (below) as GRADE (n = 120 [unweighted])
Study characteristics				
Key eligibility criteria	• Age ≥30 years • T2DM <10 years • HbA_{1c} 6.8–8.5% (51–69 mmol/mol) taking metformin monotherapy	• Age 25–65 years • Newly diagnosed with T2DM • Mean FPG 110–270 mg/dL (6.1–15.0 mmol/L) after 3 months' diet treatment	• Age 30–75 years • T2DM ≤3 years • FPG 126–180 mg/dL (7–10 mmol/L) with lifestyle management alone	• Age ≥30 years • T2DM <10 years • HbA_{1c} 6.8–8.5% (51–69 mmol/mol) taking metformin monotherapy
Randomized intervention	Medications representing four classes: Sulfonylurea (glimepiride), DPP-4 inhibitor (sitagliptin), GLP-1 analog (liraglutide), or insulin (glargine)	Intensive glycemic control with sulfonylurea or insulin or metformin (aim FPG <108 mg/dL (6 mmol/L), or conventional control with diet	Rosiglitazone, metformin, or glyburide	NA
Primary outcome	Time to primary failure, defined as HbA_{1c} ≥7% (53 mmol/mol), confirmed	Any diabetes-related end point,* diabetes-related death, all-cause mortality	Time to monotherapy failure (FPG >180 mg/dL [10 mmol/L], confirmed) for rosiglitazone, compared with metformin or glyburide	NA
Years of study conduct	2013–2021 (planned)	1977–1997	2000–2006	2011–2014
Follow-up (years)	5.2 (planned)	10.0 (median)	4.0 (median)	NA
Baseline characteristics of randomized cohort				
Demographic				
N	5,047	3,867	4,360	120 (representing population n = 2,000,987)
Age (years)	57.2 ± 10.0	53.2 ± 8.6	57 ± 10	57.9 ± 12.0
Sex (% male)	63.6	61.0	57.7	55.9
Race/ethnicity				
Caucasian	65.7	81	88.4	62.1†
African Ancestry	19.8	8	4.0	15.1†
Hispanic	18.4	—	4.4	12.1
Asian	3.6	10 (Indian Asian)	2.4	8.5†
AI	2.7 (AI/AN)	—	—	—
Clinical				
Duration of diabetes (years)	4.2 ± 2.8	New-onset	96% <2 years	4.2 ± 2.5
Weight (kg)	100.0 ± 22.3	77.5 ± 15.5	91.7 ± 19.5	95.8 ± 27.2
BMI (kg/m^2)	34.3 ± 6.8	27.5 ± 5.2	32.2 ± 6.4	33.2 ± 8.2
Systolic BP (mmHg)	128.3 ± 14.7	135 ± 20	133 ± 15.3	132.2 ± 18.2
Diastolic BP (mmHg)	77.3 ± 9.9	82 ± 10	79.7 ± 9.0	74.1 ± 11.4
Current smoker	13.8	31	15	14.2
History of CVD	6.5	NA	NA	7.2
Education				
<High school	7.2			16.8
High school graduate	20.6			24.9
Some college	29.0			30.8
≥College degree	43.2			27.5
Biochemical				
Glycemia				
Fasting plasma glucose				
mg/dL	151.5 ± 30.9	144 (128, 175)**‡	151.7 ± 26.2	161.7 ± 35.0
mmol/L	8.41 ± 1.72	8.0 (7.1, 9.7)**‡	8.42 ± 1.45	9.0 ± 1.9

Continued on p. 2106

Table 2—Continued

	GRADE (1)	UKPDS (20)	ADOPT (3,21)	NHANES (16)
HbA_{1c}				
%	7.5 ± 0.5	7.1 ± 1.51	7.4 ± 0.93	7.4 ± 0.6
mmol/mol	58 ± 5.3	54 ± 16.5	57 ± 10.2	57 ± 6.6
Fasting insulin				
pmol/L	129.4 ± 95.4	92 (52, 160)§	150.7 ± 111	122.17 ± 96.36
mU/L	21.57 ± 15.9	15 (8.7, 27)§	25.12 ± 18.5	20.362 ± 16.06
Lipids				
Total cholesterol				
mmol/L	4.236 ± 0.976	5.4 ± 1.1	5.276 (4.58, 5.98)‡	4.74 ± 1.51
mg/dL	163.8 ± 37.8	209 ± 43	203.7 (177, 231)‡	183.19 ± 58.46
LDL cholesterol				
mmol/L	2.3 ± 0.8	3.5 ± 1.0	3.1 (2.5, 3.73)‡	NA
mg/dL	90.5 ± 31.7	135 ± 39	120 (97, 144)‡	
HDL cholesterol				
mmol/L	1.12 ± 0.27	1.07 ± 0.24	1.21 (1.02, 1.42)‡	1.12 ± 0.2
mg/dL	43.4 ± 10.6	41.4 ± 9.3	46.9 (39.2, 55.0)‡	43.3 ± 10.9
Triglycerides				
mmol/L	1.740 ± 1.374	2.35 (0.84–6.55)§	1.823 (1.28, 2.58)‡	2.8 ± 5.9
mg/dL	154.0 ± 121.6	208 (74–580)§	161.3 (113, 228)‡	246.5 ± 518.7

Continuous data are reported as the mean ± SD or as indicated and categorical data as the percentage. FPG, fasting plasma glucose; NA, not available. *Defined as sudden death, hyper- or hypoglycemia-related death, myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy requiring photocoagulation, and blindness. **Fasting serum glucose reported (not plasma). †Non-Hispanic. ‡Median (interquartile range) reported. §Geometric mean, 1 SD reported.

treatment group of the study but was not included based on budgetary concerns, safety concerns, and declining use at the time the study was designed. Another limitation is that each medication is but one representative of a class and may have different properties than others in that class. Nonetheless, the four medications studied in this trial have long safety records, with each representing classes with distinct pathophysiologic approaches to the treatment of T2DM. Finally, the primary focus of GRADE is glycemic outcomes, and although some microvascular outcomes are included, the trial is not adequately powered to determine the myriad effects of individual treatment assignments on other outcomes of interest in patients with diabetes.

These limitations are balanced by other strengths. GRADE is a prospective randomized trial with a large number of participants recruited from 36 U.S. clinical centers. Participants were recruited not only from academic centers but also from community practices, Veterans Affairs medical centers, and closed-model HMOs. Finally, it is notable that GRADE's racial and ethnic composition, although similar to other large, National Institutes of Health–funded trials, such as the Diabetes Prevention Program (33) and ACCORD, is more diverse than often seen in diabetes clinical development programs (34,35). Also, GRADE is a comparative effectiveness trial in which each medication is used according to its product label to maximal effect over a sustained period of time. The current state of knowledge of the comparative effectiveness of diabetes medications stems largely from observational trials, which are limited by allocation and time-related biases (36). As a randomized controlled trial that will monitor participants for a planned mean follow-up of >5 years, GRADE will provide valid comparisons unhindered by allocation and time-related bias. Results from GRADE, expected in late 2021, will inform the choice of the most durable diabetes medication added to metformin.

In conclusion, GRADE's 5,047 participants are broadly representative of U.S. patients with T2DM who require a second diabetes medication after metformin to achieve and maintain HbA_{1c} ≤7% (53 mmol/mol). Results of the GRADE study will inform decisions about clinical effectiveness of the addition of four commonly used classes of diabetes medications to metformin.

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