Rationale and Design of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

David M. Nathan, MD[1]
John B. Buse, MD[2]
Steven E. Kahn, MB[3]
Heidi Krause-Steinrauf, MS[4]
Mary E. Larkin, MS[1]
Myrlene Staten, MD[5]
Deborah Wexler, MD[1]
John M. Lachin, ScD[4]
the GRADE Study Research Group*

OBJECTIVE—The epidemic of type 2 diabetes (T2DM) threatens to become the major public health problem of this century. However, a comprehensive comparison of the long-term effects of medications to treat T2DM has not been conducted. GRADE, a pragmatic, unmasked clinical trial, aims to compare commonly used diabetes medications, when combined with metformin, on glycemia-lowering effectiveness and patient-centered outcomes.

RESEARCH DESIGN AND METHODS—GRADE was designed with support from a U34 planning grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The consensus protocol was approved by NIDDK and the GRADE Research Group. Eligibility criteria for the 5,000 metformin-treated subjects include <5 years' diabetes duration, ≥30 years of age at time of diagnosis, and baseline hemoglobin A_{1c} (A1C) of 6.8–8.5% (51–69 mmol/mol). Medications representing four classes (sulfonylureas, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists, and insulin) will be randomly assigned and added to metformin (minimum–maximum 1,000–2,000 mg/day). The primary metabolic outcome is the time to primary failure defined as an A1C ≥7% (53 mmol/mol), subsequently confirmed, over an anticipated mean observation period of 4.8 years (range 4–7 years). Other long-term metabolic outcomes include the need for the addition of basal insulin after a confirmed A1C >7.5% (58 mmol/mol) and, ultimately, the need to implement an intensive basal/bolus insulin regimen. The four drugs will also be compared with respect to selected microvascular complications, cardiovascular disease risk factors, adverse effects, tolerability, quality of life, and cost-effectiveness.

CONCLUSIONS—GRADE will compare the long-term effectiveness of major glycemia-lowering medications and provide guidance to clinicians about the most appropriate medications to treat T2DM. GRADE begins recruitment at 37 centers in the U.S. in 2013.

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The epidemic of type 2 diabetes (T2DM) that has affected the U.S. and other populations, is associated with the relentless increase in obesity, and threatens to become the major public health problem of this century, affecting up to one in three Americans if current trends continue (1). The most recent estimate of T2DM prevalence in the U.S. is >24 million people, with an incidence of 1.9 million new cases per year (1). Major human and economic costs associated with the epidemic are related to the development of long-term complications, including retinopathy, nephropathy, and neuropathy, that cause more cases of blindness, renal failure, and amputations than any other disease (2). Cardiovascular disease (CVD) is increased by two- to fivefold in diabetes and is the leading cause of death (3). The 2012 estimated annual cost of diabetes in the U.S. was $245 billion, with the greatest cost related to its chronic complications (4). In 2007, the annual expenditure for glucose-lowering drugs in the U.S. was $13 billion, almost doubling since 2001 (5). The estimate in 2012 was >$18 billion (4).

There are several reasons for guarded optimism in the setting of this ongoing epidemic. First, clinical trials have demonstrated effective means of delaying or preventing the development of diabetes (6–8). If these interventions were implemented successfully, they could decrease the annual incidence of diabetes substantially. Second, high-quality clinical trials have shown that lowering A1C to ~7% (53 mmol/mol), especially early after diagnosis, can substantially reduce the long-term complications that are characteristic of diabetes (9–11). Third, clinical studies have shown that antihypertensive and lipid-lowering medications can reduce CVD in T2DM as effectively as they do in the nondiabetic population (12) and that CVD risk in diabetes is decreasing (13). Finally, in the past two decades, the diabetes epidemic has spurred the development of eight new classes of glucose-lowering medications that may allow for more effective control of glycemia in T2DM and, thus, reduce complications (14).

One of the major challenges for practitioners is to choose from the considerable armamentarium of glucose-lowering medications the best means of maintaining an appropriate level of glycemic control over time. Consensus algorithms

From the [1]Diabetes Research Center, Massachusetts General Hospital and Harvard School of Medicine, Boston, Massachusetts; the [2]Division of Endocrinology, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina; the [3]Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, Washington; [4]The Biostatistics Center, The George Washington University, Rockville, Maryland; and the [5]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland.
Corresponding author: Heidi Krause-Steinrauf, heidi@bsc.gwu.edu.
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*A complete list of the GRADE Study Research Group investigators can be found in the Supplementary Data online.

See accompanying commentary, p. 2146.

have been developed to help clinicians to select among the numerous medications and their combinations for achieving and maintaining a target A1C of <7% (53 mmol/mol) (15–17). Other published algorithms selected different glycemic goals and recommended different strategies to achieve them (18). Recent American College of Physicians guidelines suggest that metformin is the only drug supported by solid evidence and that data are insufficient to choose a second agent (19). The dearth of head-to-head comparator studies of glucose-lowering medications, either alone or in combinations, and of trials that have lasted >6–12 months to examine the durable effects of interventions on glycemic control (10,11,20,21) has hampered the development of all these algorithms.

Because T2DM is a progressive disease with worsening metabolic control over time, the long-term glycemia-lowering effects of interventions are particularly important. Safety, side effect profiles, tolerability, patient acceptance, burden of therapy, and cost are other important factors in the long-term treatment of this chronic, degenerative disease. Finally, recent position statements have emphasized individualization and patient-centered approaches to therapy (15), but few studies have examine which patients might do better or worse with specific therapies.

Comparative effectiveness research has been identified as a high national priority in the U.S. (22). Similarly, improved understanding of phenotypic and genotypic differences between patients that affect responses to medications has been identified as an important element in individualizing therapy for maximum effectiveness (23). Of note, most industry-sponsored studies have not addressed either long-term comparative effectiveness or interpatient differences that may affect responses to therapy. As a result, patients with T2DM are currently treated without taking into account individual characteristics that might direct the choice of more effective interventions.

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) is a pragmatic clinical trial that will make head-to-head comparisons of major drug classes currently used to treat T2DM, with the overarching goal of providing better guidance to practitioners in the choice of medications. Specifically, GRADE will compare a sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitor, glucagon-like peptide 1 (GLP-1) receptor agonist, and basal insulin in patients with recently diagnosed T2DM treated with metformin and will examine their effectiveness in maintaining the glycemic goal (A1C <7% [53 mmol/mol]) over time. Other outcomes will include relative effects on selected microvascular complications and cardiovascular risk factors; patient-centered outcomes, such as adverse effects, acceptability, and tolerability; and cost-effectiveness. Finally, GRADE will study the phenotypic characteristics that underlie the success, failure, and adverse effects of the different combinations to guide individualized treatment.

GRADE DESIGN AND METHODS

The concept of a comparative effectiveness study examining T2DM treatment was first presented to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health, by D.M.N. in 2008. With provisional enthusiasm expressed by NIDDK and financial support from the American Diabetes Association, clinical trialists D.M.N., J.B.B., Hertzel C. Gerstein, Rury R. Holman, Richard Kahn, S.E.K., J.M.L., and Bernard Zinman designed a preliminary proposal in early 2009. A U34 planning grant (to D.M.N., principal investigator) was funded in August 2010, and during the ensuing 2 years, the authors of this article developed a final protocol (available on the GRADE website at https://grade.bsc.gwu.edu and in Supplementary Data). A notice of opportunity was issued to solicit donations of medications within the four classes and other supplies, and the specific medications were selected by a subgroup with no dualities of interest. In addition, requests for applications were issued to clinical centers, central laboratories, and support units, which were subsequently selected by peer review. Additionally, study forms, model informed consents, and a manual of operations were developed.

GRADE was reviewed by an independent external evaluation committee in December 2011, reviewed and recommended for funding by an NIDDK study section in August 2012, and approved by the NIDDK Advisory Council in September 2012. Funding of the study began in October 2012 through a U01 grant (co-principal investigators D.M.N. and J.M.L.) to The George Washington University Biostatistics Center.

The data and safety monitoring board, an independent review group appointed by NIDDK, first convened on 1 February 2013. The GRADE steering committee, comprising the principal investigators of the clinical centers, representatives of the NIDDK, and selected members of the study group approved the final study protocol in March 2013. GRADE will begin recruitment at 37 centers in mid-2013.

Major specific aims

The relative effects of four commonly used glucose-lowering medications with different mechanisms of action when added to metformin will be compared for the following:

- Maintenance of metabolic control, defined as time to primary failure with an A1C ≥7.0% (53 mmol/mol), confirmed, while receiving maximally tolerated doses of both metformin up to 2,000 mg/day and the assigned medication;
- The time to secondary metabolic failure with an A1C >7.5% (58 mmol/mol), confirmed, requiring the addition of basal insulin for oral agent-treated subjects and intensification of insulin therapy for those assigned to basal insulin at baseline;
- The time to tertiary metabolic failure with an A1C >7.5% (58 mmol/mol), confirmed, requiring implementation of intensive insulin therapy with basal plus rapid-acting insulin, while treated with metformin, the assigned study medication, and basal insulin among those not originally assigned to basal insulin;
- Cumulative incidence of diabetes complications, such as microalbuminuria; and
- Other metabolic outcomes, adverse effects, and effects on CVD risk factors, quality of life, tolerability, and cost-effectiveness.

In addition, we will determine the phenotypic characteristics associated with response to and failure of the four different medication combinations and identify factors that determine the success and/or failure of specific regimens over time, including longitudinal mechanistic investigations of β-cell function.

Design

GRADE will be a pragmatic, parallel-group, clinical trial that compares as objectively as possible the effects of four different glucose-lowering medications in metformin-treated patients with relatively recently diagnosed T2DM. Subjects will adjust

metformin during the run-in phase to achieve maximum tolerated doses of 2,000 mg/day with at least 1,000 mg/day required for eligibility (Fig. 1). The trial is unmasked for practical reasons because it will compare oral agents and injectable medications.

Eligible subjects will be randomly assigned to one of the four medications shown in Fig. 1. The principal comparisons among these medications will start from the time of randomization. The trial will be conducted under an intention-to-treat design. All randomized subjects will continue follow-up and complete all outcome assessments until the planned conclusion of the study (planned follow-up of 4–7 years, depending on the time of entry), including those who reach the primary outcome. Otherwise, analyses of all other outcomes would be susceptible to a healthy survivor effect because the only subjects evaluated in the out years would be those who had not yet experienced primary failure of the assigned regimen. To encourage retention in the study over time and ensure a longer exposure to the study medications for the purposes of analyses of other outcomes, assigned study medications will be continued until the need for intensification of insulin therapy with basal plus rapid-acting insulin (Fig. 2).

GRADE was designed entirely by the planning group (the authors) with input from an NIDDK-appointed external evaluation committee and the investigators. No pharmaceutical manufacturers contributed to the planning or design or will participate in the conduct of GRADE. Medication and supply manufacturers were approached to donate product after the medications and supplies had been selected by members of the planning group without any dualities of interest.

Study population and recruitment

GRADE will compare the relative effects of the four interventions in relatively recently diagnosed T2DM subjects treated with metformin, with the recognition that earlier treatment is more likely to maintain endogenous insulin secretion and promote advantageous levels of glycemia over time (24). Eligibility criteria enumerated in the protocol (Supplementary Data) and summarized in Table 1 reflect a balance between the stringent requirements usually applied in recruiting a clinical trial population and the desire to create a pragmatic and easily translatable study.

To be eligible, potential subjects must have an A1C of 6.8–8.5% (51–69 mmol/mol), as measured in the central laboratory, after metformin therapy has been maximized, as tolerated, during the run-in period. The study cohort (Fig. 1) of 5,000 subjects will include patients with <5 years' diabetes duration who are treated with metformin but no other glucose-lowering medications. The majority of potential subjects will be identified on the basis of a prior diagnosis of diabetes detected through reviews of medical histories and self-reports and aided by the use of electronic medical records and other databases.

GRADE will aim to recruit as much representation as possible from racial and ethnic minority groups that are disproportionately affected by T2DM and a substantial fraction (>20%) who are ≥60 years of age. Recruitment and implementation of the GRADE protocol will take place at 37 clinical centers, which were selected by peer review through an open competition process. The GRADE clinical centers (Supplementary Data) are distributed throughout the U.S. (Supplementary Data) and were selected in part because of their ability to recruit a diverse population of research subjects, including patients >60 years of age. Each clinical center will enroll 150 eligible subjects to reach the study-wide total enrollment of 5,000 subjects over a period of ~3 years.

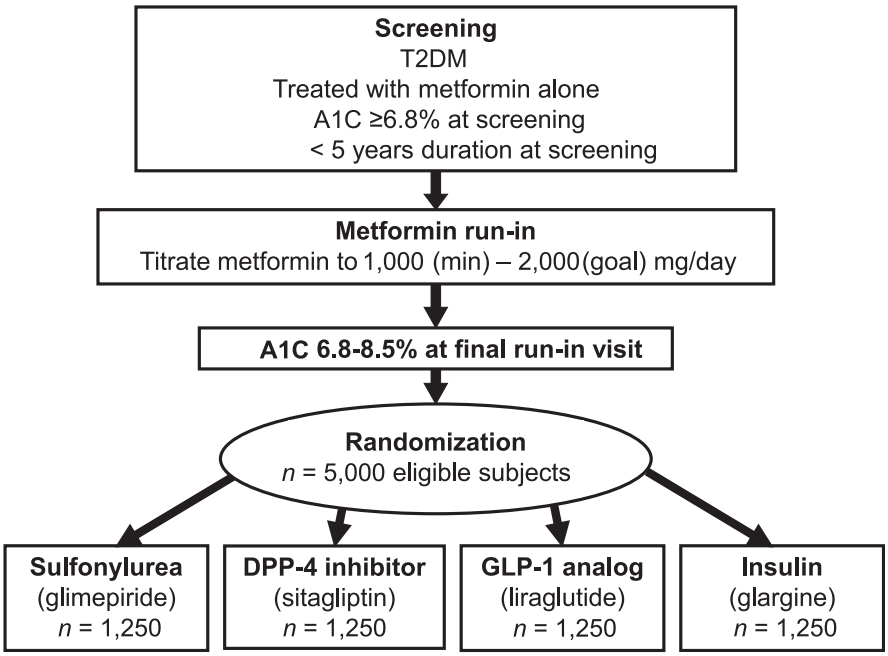

Figure 1—*Study design.*

Interventions

Rationale. Metformin was selected as the foundation therapy according to the same rationale used in most of the recently developed consensus algorithms (15–18), namely, its long-term clinical experience, effectiveness in lowering glycemia over a wide range of A1C levels without causing hypoglycemia, weight-neutral or weight-loss effect, putative cardiovascular risk reduction (10,11,25), safety and side effect profiles, high level of patient tolerance, and low cost. Recent surveys have shown that a large majority of patients with recent-onset T2DM are treated with metformin (26), making this choice both practical and clinically relevant.

The selection of the other study medications from the ten classes of available agents to add to metformin was predicated on the most commonly used approved combinations and the availability of preliminary data to support their glycemia-lowering effectiveness, safety, and tolerability. Increasing concern about the future of pioglitazone, owing to the putative increased risk for bladder cancer (27) superimposed on previously established safety concerns regarding volume retention and bone loss, contributed to its elimination from the study design. The potential adverse impact on recruitment of including a drug that is receiving increasing and highly visible negative

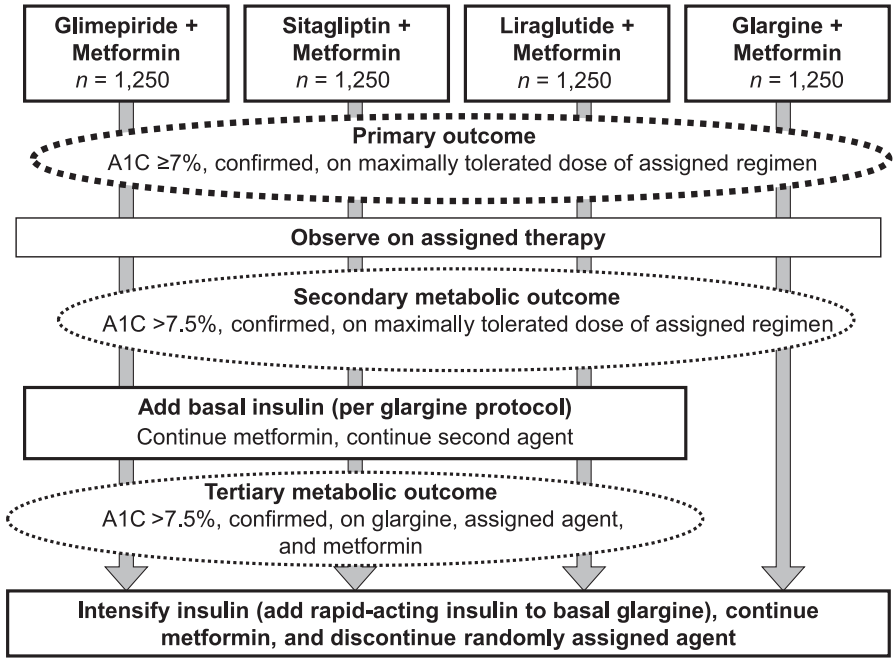

Figure 2—*Metabolic outcomes and subsequent therapy.*

attention was an additional consideration. Because the four medication classes proposed capture the majority of glucose-lowering medications prescribed, and all four combinations have been approved by the Food and Drug Administration and its European and Canadian counterparts, the study will be clinically relevant and generalizable, and its results immediately and widely translatable to practice.

Medications. We selected specific agents within the four classes as dictated by their specific attributes. All have been studied (28–31) and are approved by the Food and Drug Administration in their proposed initial combinations. The criteria by which specific agents were chosen within classes by members of the planning group without any dualities of interest included differences between the agents in the following: lowering glycemia, published side effect profiles, effects on CVD risk factors, clinical experience, ease of administration, and acceptability. In cases where there were no appreciable or substantive differences between agents within the classes, consideration was given to those agents that are used most frequently and were made available by the manufacturers. At the time of randomization, all subjects will be assigned to one of the following medications in each of the named classes: sulfonylurea (glimepiride), DPP-4 inhibitor (sitagliptin), GLP-1 receptor agonist (liraglutide), or insulin (glargine) (Fig. 2).

The number of medications selected in GRADE was predicated on resource availability. The other classes of glucose-lowering medications, aside from pioglitazone (discussed previously), that were considered but not chosen were the α-glucosidase inhibitors, nonsulfonylurea sulfonylurea receptor agonists, rapid-acting insulins, bile acid sequestrant colesevelam, and dopamine agonist bromocriptine. They were not selected for a number of reasons, including potential safety concerns, limited clinical use and experience in recent-onset T2DM, and relatively low efficacy, poor tolerability, and frequent side effects. No agents in the most recent class of glucose-lowering medications, the SGLT-2 inhibitors, had been approved during the planning phase of GRADE. Moreover, none of them had sufficient clinical use or experience to be acceptable in the study.

Diabetes management strategy. All the medications will be used according to their labeling and/or usual practice (32). Adjustments of glimepiride or insulin will be based on self-monitoring of blood glucose, aiming for fasting glucose levels between 70 and 130 mg/dL without symptomatic hypoglycemia. Additionally, medications will be titrated to achieve A1C values <7.0% (53 mmol/mol) up to the maximally tolerated dose (Table 2).

GRADE staff at each clinical center will assume responsibility for glycemic management of subjects according to the GRADE protocol and will communicate this arrangement with the primary-care providers. Of note, GRADE staff will not be responsible for routine surveillance for diabetes complications or for the treatment of other cardiovascular risk factors; however, the results of clinically relevant physical examination and laboratory results will be communicated to subjects' care providers to aid clinical management.

The randomly assigned medication and metformin will be continued until the secondary metabolic outcome (see OUTCOMES) has been reached (Fig. 2), at which time basal insulin (glargine) will be added for the three groups that were not originally assigned to insulin, using the same algorithm as in the original glargine-assigned treatment group. The rationale for the continued combination therapy is to maximize the time while receiving the assigned treatment and to enable further study of which combinations may delay further metabolic worsening to the need for insulin intensification—the tertiary metabolic outcome. Moreover, the use of three agents has become increasingly popular in routine clinical practice.

For the group that was originally assigned to glargine, insulin intensification with rapid-acting (aspart) insulin will be started and adjusted by GRADE clinic staff according to the study protocol after the secondary metabolic outcome has been reached (Fig. 2). In the three groups originally assigned to treatment other than glargine, intensification of insulin therapy with rapid-acting insulin will be implemented when the tertiary metabolic outcome is reached. Their randomly assigned medication will be stopped at that time.

Self-monitoring of blood glucose. Subjects assigned to insulin or sulfonylurea for safety reasons (to prevent hypoglycemia) will self-monitor blood glucose levels on a specified schedule and adjust doses to achieve glucose goals according to usual care recommendations (32). Self-monitoring of blood glucose levels will also be recommended for safety reasons for all subjects with symptoms suggestive of hypoglycemia or hyperglycemia or during intercurrent illness likely to affect glucose control.

Outcomes

Metabolic outcomes. The primary outcome is the time to primary metabolic failure of the randomly assigned treatment, which is defined as the time to an initial A1C ≥7% (53 mmol/mol), subsequently confirmed at the next quarterly visit, while

Table 1—*Summary of major eligibility criteria

Inclusion criteria
1. Men or women ≥30 years of age at time of diabetes diagnosis; for American Indians, ≥20 years of age at time of diagnosis
2. Duration of diagnosed diabetes <5 years determined as accurately as possible on the basis of available records at screening
3. A1C criteria (at final run-in visit, ~2 weeks before randomization): 6.8–8.5% (51–69 mmol/mol)
4. Taking a daily dose of ≥1,000 mg metformin for a minimum of 8 weeks at final run-in
5. Willingness to administer daily subcutaneous injections, take a second diabetes drug after randomization, potentially initiate insulin, intensify insulin therapy if study metabolic goals are not met, and perform self-monitoring of blood glucose
6. A negative pregnancy test for all women of childbearing potential (i.e., premenopausal, not surgically sterile)
7. Provision of signed and dated informed consent before any study procedures
Exclusion criteria
1. Suspected type 1 diabetes (lean with polyuria, polydipsia, and weight loss with little response to metformin) or secondary diabetes resulting from specific causes (e.g., previously diagnosed monogenic syndromes, pancreatic surgery, pancreatitis)
2. Current or previous (within past 6 months) treatment with any diabetes drug or glucose-lowering medication other than metformin, including short-term insulin use during hospitalization
3. More than 5 years of treatment with metformin at time of randomization
4. History of intolerance, allergy, or other contraindications to any of the proposed study medications
5. A life-threatening event within 30 days before screening or currently planned major surgery
6. Any major cardiovascular event in previous year, including history of myocardial infarction, stroke, or vascular procedure, such as coronary artery or peripheral bypass grafting, stent placement (peripheral or coronary), or angioplasty
7. Plans for pregnancy during the course of the study for women of childbearing potential
8. History of or planning for bariatric surgery, including banding procedures or surgical gastric and/or intestinal bypass
9. History of congestive heart failure (New York Heart Association class III or IV)
10. History of conditions that are specific contraindications to any of the study medications
11. Serum creatinine level ≥1.4 mg/dL in women and ≥1.5 mg/dL in men or end-stage renal disease requiring renal replacement therapy
12. History of cancer, other than nonmelanoma skin cancer, that required therapy in the 5 years before randomization
13. Treatment with oral or systemic glucocorticoids (other than short-term treatment, e.g., for poison ivy) or disease likely to require periodic or regular glucocorticoid therapy (inhaled steroids allowed)
14. Treatment with atypical antipsychotics
15. Clinically or medically unstable with expected survival <1 year

*A complete list of the eligibility criteria is included in the protocol (Supplementary Data).

being treated at maximum tolerable doses of both metformin and the second randomly assigned medication. If the second (confirmatory) A1C is <7% (53 mmol/mol), then the primary outcome is not yet reached.

If the initially observed A1C is >9% (75 mmol/mol), then confirmation will be performed within 3–6 weeks. Taking into account the need for confirmation, the earliest time that the primary end point can be confirmed is at 6 months after randomization for subjects whose A1C at 3 months is ≥7% and at 4 months if the 3-month A1C is >9%. All A1C results will be measured in the study central laboratory.

The secondary outcome is the time to the observation of an A1C >7.5% (58 mmol/mol), subsequently confirmed, while treated with originally assigned medications and metformin. For the three groups originally assigned to medications other than insulin, the tertiary outcome is the time to an A1C >7.5% (58 mmol/mol), confirmed as previously described, while receiving metformin, the originally assigned medication, and basal insulin. Each of the three metabolic outcomes will be counted regardless of adherence to assigned medications, according to the principles of intention-to-treat analysis.

Other outcomes. A full list of the GRADE outcomes is included in the protocol (Supplementary Data). They can be considered in the following categories: metabolic, such as mean A1C and fasting plasma glucose levels, frequency of hypoglycemia, and measures of insulin secretion and sensitivity; cardiovascular, including risk factors and major events; microvascular, such as albuminuria, estimated glomerular filtration rate (eGFR), and peripheral neuropathy; adverse events specific to the medications under study; adverse effects; adherence and tolerability to metformin and the assigned medications and treatment satisfaction; health economics; and other outcomes, including mortality, hospital admissions, cognitive function, and cancer.

Baseline and follow-up measurements of phenotypic variables (demographic, physiologic, and genetic) will facilitate the study of patient factors that may mediate responsiveness to different therapies. Oral glucose tolerance testing, performed annually, will contribute to our understanding of the mechanisms of medication success and failure. From these assessments, a number of different outcome measurements will be obtained with the goal of assessing the differential metabolic effects of each drug combination on β-cell function and insulin sensitivity over time. These measurements, combined with the phenotypic measures, will be used to determine patient-specific characteristics that are associated with responsiveness or failure to respond to specific agents and will facilitate an understanding of how to individualize therapy.

Statistical analyses and power calculations

All analyses will compare the randomly assigned treatment groups under the intention-to-treat principle with use of the treatment as assigned to each subject and all available data from all subjects.

Primary outcome. The cumulative incidence of the primary outcome within each treatment group will be estimated with a modified, discrete-time Kaplan-Meier estimate, allowing for periodic outcome assessments (33). Differences between groups will be tested and relative risk estimates obtained from a Cox proportional hazards model for discrete time observations adjusted for the baseline A1C (33). A single overall omnibus test at the 0.05 significance level will be conducted as well

Table 2—*Initiation and adjustment of assigned study medications*

Medication	Initial dose	Adjustment
Glimepiride	A1C ≤8% 1 mg, >8% 2 mg	Weekly adjustment based on self-monitoring of blood glucose level to a maximum of 4 mg twice daily
Sitagliptin	100 mg/day	Reduce to 50 mg if eGFR <45 mL/min
		Reduce to 25 mg if eGFR <30 mL/min
Liraglutide	0.6 mg/day	Advance to 1.2 mg and then 1.8 mg, as tolerated
Glargine	10 units	Increase or decrease dose according to self-monitoring of blood glucose level and hypoglycemia

as significance tests and relative risk (hazard ratio) estimates for each of the six pairwise drug group comparisons, with *P* values adjusted with the Holm closed sequential multiple testing procedure (34). If tests of the proportional hazards assumption do not apply, inferences (CIs and *P* values) will be obtained from robust information sandwich estimates of SEs (35).

Other outcomes. Similar analyses will be applied to other secondary discrete time-to-event outcomes, such as the time to secondary metabolic failure or to microalbuminuria based on 6-monthly albumin: creatinine ratio measurements. For time-to event outcomes measured nearly continuously, such as the number of days to a cardiovascular event, this strategy will use the corresponding methods for continuous time observations.

For longitudinal analyses of binary outcomes over time, such as the proportion of subjects (prevalence) at each visit who are still maintaining an A1C <7% while receiving the originally assigned therapy, the odds will be compared between groups with use of a repeated-measures logistic model fit through generalized estimating equations with a robust estimate of the covariance structure (34). Longitudinal analyses of quantitative outcomes over time (e.g., A1C) will use a longitudinal normal errors repeated-measures model for the estimation of group mean levels over time (36). For longitudinal assessments of the rate of change of an outcome over time, such as the slope of the decline in eGFR, a random-effects (random coefficient) model will be used to estimate the mean slope within each treatment group, allowing for random variation of slopes among subjects (36). Comparison of rates of events (e.g., hypoglycemia) will use Poisson regression models with the robust information sandwich variance estimates (33).

Composite outcomes. A multivariate one-sided (or one-directional) test of stochastic ordering will be conducted to compare differences between groups for multiple outcomes simultaneously, such as A1C, weight, and hypoglycemia. The O'Brien mean rank score test (37) will be applied to an analysis of multiple quantitative (or ordinal) components at a single point in time. The Wei-Lachin test of stochastic ordering will be used to test other components, including proportions, rates, and event times (38). In addition, a single composite outcome can be defined from the components, such as the prevalence of subjects at 4 years who are still able to maintain an A1C <7% without having experienced severe hypoglycemia or gained weight. A longitudinal analysis of the proportions meeting this criterion at each visit over time and a survival analysis of such outcomes will also be conducted. Proportional hazards and parametric regression models will be used to assess the ability of multiple variables simultaneously to predict the time to primary or to secondary failure.

Subgroup and stratified analyses. Analyses will also assess the differences in study outcomes within subgroups defined by baseline characteristics, including race/ethnicity, sex, age, diabetes duration, weight, body mass index, A1C, and measures of insulin sensitivity, insulin secretion, and the glucose disposal index. For each factor, the treatment groups will be compared separately within each subgroup (e.g., males, females) with a test of homogeneity between strata. For a quantitative variable (e.g., age), an additional analysis will be conducted with use of the quantitative covariate rather than simply of the discrete strata.

Sample size and power

With recruitment over 3 years and total study duration of 7 years, continued follow-up of all subjects to study end would provide 4–7 years of follow-up. To be conservative, sample size and power for the primary analysis were computed assuming a lag in recruitment, with 40% of subjects recruited in the first half of the 3-year recruitment period (39). Assuming that 4% will be lost to follow-up before reaching the primary outcome, the average follow-up time would be 4.8 years, with 15% of subjects lost to follow-up.

Primary outcome. On the basis of the ADOPT (A Diabetes Outcomes Progression Trial) (20), we conservatively estimated a hazard rate of 0.0875 per year for the primary outcome. With the aforementioned assumptions, a sample size of 1,242 per group (rounded to 1,250) provides 90% power to detect a 25% risk difference at a significance level of 0.00833, adjusting for six pairwise tests.

Secondary outcomes—microalbuminuria and clinical CVD. The hazard rate of onset of microalbuminuria is projected to be ~0.04 per year in whichever group has a higher event rate (40). The 5,000 subjects provide 88% power with a hazard rate of 0.04 per year, or 92% with 0.045 per year, to detect a 33% difference in risk for microalbuminuria between any pair of groups.

In the ADOPT study (20), the incidence of major atherosclerotic cardiovascular events was 0.76% per year and of major atherosclerotic cardiovascular events plus congestive heart failure, 1.14% per year. Assuming an incidence rate of 1% per year, GRADE will provide 80% power to detect a 50% difference in the risk of CVD between any pair of drug groups, adjusted for six pairwise comparisons.

CONCLUSIONS—GRADE is a comparative effectiveness study that aims to compare four major classes of glucose-lowering medications in relatively recently diagnosed T2DM patients treated with metformin. The study is unique in comparing as many major diabetes treatments as possible, given available study resources, over a clinically relevant period. GRADE is also unique because it will study the totality of the effects of the medications, including an emphasis on patient-centered outcomes in addition to metabolic outcomes. Finally, its focus on individual demographic, clinical, and other factors that may influence a differential response to medications will add to our understanding of therapy for T2DM. GRADE results should not only help practitioners to choose the medications

that are the most appropriate with regard to metabolic control and patient-oriented outcomes, but should also provide insights to allow individualization of treatment.

The major aims of GRADE, which focus on a comparison of the effectiveness and other clinically important attributes of glucose-lowering medications, have major health economic implications in addition to their obvious public health impact. The cost of glucose-lowering medications accounts for a disproportionate share of medication costs, doubling from 6.3% of all prescribed drug spending in the U.S. in 2001 to 12.2% in 2007 (5).

The planning process for GRADE differed from that for most large, multicenter trials sponsored by NIDDK. The U34 planning grant was used to allow a relatively small group of investigators to plan, design, and develop the study to the point of implementation. This process contrasts with the usual design of multicenter trials by a large group of investigators who have been selected on the basis of their response to a request for application.

GRADE investigators will leverage the core study to amplify the range of scientific inquiry by actively promoting ancillary studies. These independently funded projects will take advantage of the study design and cohort. Some, such as genetics studies, will require minimal subject participation, whereas others may involve additional study procedures; however, all ancillary proposals will be judged on the basis of clinical and scientific value and burden to the subjects and centers.

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