A Diabetes Outcome Progression Trial (ADOPT)

An international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes

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OBJECTIVE — Therapies with metformin, sulfonylureas, or insulin improve glycemic control in the short term but do not prevent progressive islet β-cell failure or long-term deterioration in glycemia. Our goal was to evaluate, in patients recently diagnosed with type 2 diabetes (<3 years), the long-term efficacy of monotherapy with rosiglitazone on glycemic control and on the progression of pathophysiological abnormalities associated with type 2 diabetes as compared with metformin or glyburide monotherapy.

RESEARCH DESIGN AND METHODS — A Diabetes Outcome Progression Trial (ADOPT) is a randomized, double-blind, parallel-group study consisting of a screening visit, a 4-week placebo run-in, a 4-year treatment period, and an observational follow-up of ~3,600 drug-naïve patients with type 2 diabetes diagnosed within the previous 3 years. After run-in, patients will be randomized to rosiglitazone, glyburide, or metformin titrated to the maximum effective daily doses (8 mg rosiglitazone, 15 mg glyburide, or 2 g metformin). The primary outcome is time to monotherapy failure, defined as the time following titration to the maximal effective or tolerated dose when fasting plasma glucose exceeds 180 mg/dl (10 mmol/l). Secondary outcomes include measures of islet β-cell function, insulin sensitivity, dyslipidemia, changes in urinary albumin excretion, plasminogen activator inhibitor-1 antigen, fibrinogen, and C-reactive protein. Safety and tolerability will also be evaluated. Patient-reported outcomes and resource utilization data will be collected and analyzed.

CONCLUSIONS — ADOPT will provide data on the effect of mechanistically differing treatment options on metabolic control, β-cell function, and markers of macrovascular disease risk in type 2 diabetes.

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Type 2 diabetes is a complex metabolic disorder characterized by chronic hyperglycemia resulting from target cell resistance to the actions of circulating insulin and a qualitative and quantitative deficiency in insulin secretion relative to what is necessary to achieve normal glycemic control (1). Additionally, type 2 diabetes is associated with increased prevalence of hypertension, disorders in lipid metabolism, fibrinolytic activity (2), and enhanced activity of markers of inflammation (3). All of these may contribute to an increased risk of early cardiovascular morbidity. The prevalence of diabetes worldwide has been estimated at 135 million people in 1995 and is projected to increase to 300 million by 2025 (4). This global trend not only has profound medical ramifications but also social and economic consequences due to the costs of managing diabetes and treating the secondary complications of the disease.

Currently, type 2 diabetes management involves a stepwise approach. First is the reduction of blood glucose concen-

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Abbreviations: ACR, albumin-to-creatinine ratio; ADA, American Diabetes Association; ADOPT, A Diabetes Outcome Progression Trial; AE, adverse event; CHD, coronary heart disease; CRP, C-reactive protein; DSC, Diabetes Symptoms Checklist; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FPG, fasting plasma glucose; HCG, human chorionic gonadotrophin; HOMA, homeostasis model assessment; HPI, intact human proinsulin; hsCRP, highly sensitive CRP; MRFIT, Multiple Risk Factor Intervention Trial; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor-1; PI/IRI, proinsulin-to-immunoreactive insulin ratio; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

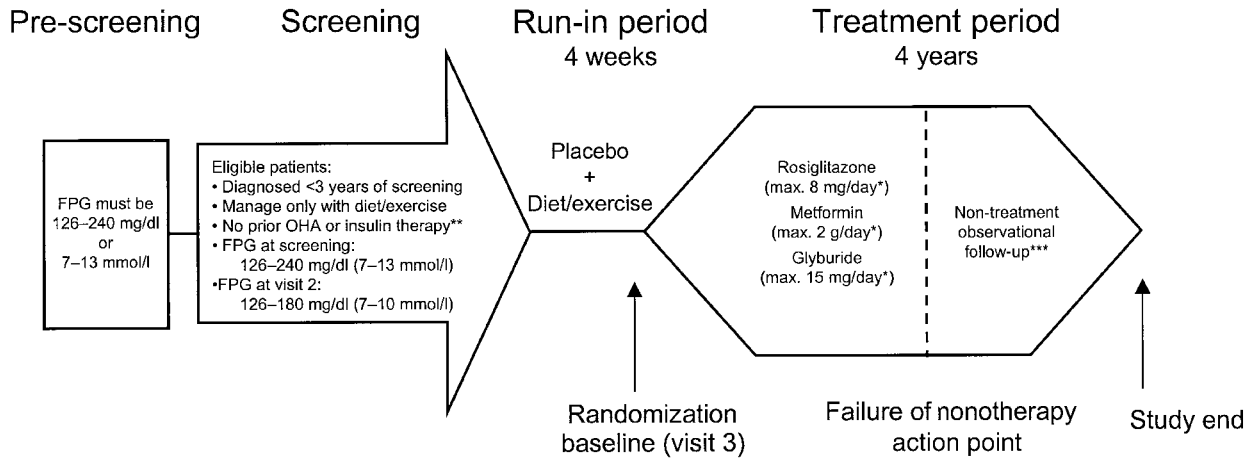

Figure 1—*ADOPT study design. *All study medication will be titrated to optimal effect using protocol-defined steps. **Exceptions: insulin use during gestational diabetes, short-term (≤1 month) insulin use, or ≤1 month of oral hypoglycemic agent (OHA) treatment 2 months before screening. ***Patients who withdraw from treatment for any reason will continue to be followed in nontreatment observational follow-up.*

trations through diet and exercise and weight reduction. However, only 8% of newly diagnosed patients are able to maintain glycemic control, i.e., fasting plasma glucose (FPG) <140 mg/dl (7.8 mmol/l), with dietary intervention alone. Furthermore, despite the initial efficacy seen with traditional agents such as sulfonylureas, metformin, or insulin, normoglycemia is frequently not obtained and progressive loss of glycemic control has been shown to correlate with declining β-cell function (5).

Recently, a new class of compounds, the thiazolidinediones, has been developed for the treatment of type 2 diabetes. These agents act by reducing insulin resistance, one of the key underlying defects in the disease pathophysiology, thereby sensitizing the liver, muscle, and adipose tissue to the actions of circulating insulin (6). They are believed to exert their insulin-sensitizing effects by binding to and activating the nuclear peroxisome proliferator–activated receptor-γ as well as by modifying transcription factors involved in the regulation of insulin action. In addition, preliminary data suggest that thiazolidinediones may have the potential to prevent or delay β-cell decline (7).

This article describes the rationale for a study to determine whether rosiglitazone, metformin, or glyburide (as monotherapy) might alter disease progression, through direct or indirect actions, in drug-naïve patients with recently diagnosed (<3 years) type 2 diabetes.

RESEARCH DESIGN AND METHODS

Approximately 500 centers in North America, Canada, and Europe are participating in the study. The protocol has been approved by the Ethics Review Committee/Institutional Review Board affiliated with each center. The study is being conducted in accordance with Good Clinical Practice, Declaration of Helsinki, and VS21 Code of Federal Regulation parts 50 and 56. All participants will provide written informed consent. An external data safety monitoring board will monitor safety throughout the study.

Study design

The study is a randomized, double-blind, parallel-group trial consisting of a screening visit, a 4-week placebo run-in period, and a 4-year treatment period. Patients who are withdrawn from study medication before completion of 4 years of treatment will enter an observational follow-up (Fig. 1). Patients deemed eligible at screening will enter a single-blind placebo run-in period, reinforced by diet and exercise recommendations, to obtain entry plasma glucose concentrations between 126 and 180 mg/dl (7 and 10 mmol/l).

Study population

Patients aged 30–75 years who have been diagnosed with type 2 diabetes within 3 years from study screening and who have been previously managed with diet/exercise only will be included in the study, with the following exceptions: prior insulin use for management of gestational diabetes; short-term (≤1 month) insulin use to maintain glycemic control for hospitalization, medical procedure, or intervention; and ≤1 month use of any oral hypoglycemic agent at least 2 months before screening. Other entry criteria include FPG concentration ranging from 126 to 240 mg/dl (7–13 mmol/l) at screening and from 126 to 180 mg/dl (7–10 mmol/l) at randomization.

Patients will be excluded from the study for any of the following reasons during screening: presence of clinically significant hepatic disease or serum alanine aminotransferase level ≥2.5 times the upper limit of the normal reference range; renal impairment indicated by serum creatinine concentration >1.3 mg/dl (114 μmol/l) for men and >1.2 mg/dl (106 μmol/l) for women; anemia, defined as a hemoglobin concentration <11 g/dl for men and <10 g/dl for women; a history of lactic acidosis, unstable or severe angina, congestive heart failure (New York Heart Association class I–IV), uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg), any chronic disease requiring continuous intermittent treatment with corticosteroids, any associated condition that could preclude completion of the study; and active drug or alcohol abuse within the last 6 months. Patients with a variation in body weight ≥5% during the run-in period will also be excluded.

Table 1—*Outline of study assessments*

	Time (relative to baseline)																		
	Weeks				Months														
Assessment	0	8	16	24	8	10	12	15	18	21	24	27	30	33	36	39	42	45	48
FPG	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
HbA_{1c}	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Liver function tests	√	√	√	√	√	√	√		√		√		√		√		√		√
GAD antibodies, brain natriuretic peptide	√																		
C-peptide, immunoreactive insulin, proinsulin, PAI-1, fibrinogen, CRP	√			√			√		√		√		√		√		√		√
OGTT	√			√			√		√		√		√		√		√		√
Routine fasting chemistry, lipids, hematology, serum HCG and urine specimens	√			√			√				√				√				√
AEs	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Quality-of-life questionnaires	√						√				√				√				√
Medical care utilization questions	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Treatment

Patients will be randomized to receive double-blinded rosiglitazone, glyburide, or metformin. As required to attain current American Diabetes Association (ADA) glycemic control guidelines, patients will be titrated to the maximum effective daily doses, i.e., 8 mg rosiglitazone, 15 mg glyburide, or 2 g metformin. Uptitration is required for any patient with FPG concentration ≥140 mg/dl (≥7.8 mmol/l) at each scheduled visit. Dosages can be titrated down if poorly tolerated. All study medication will be supplied in capsules of identical size and color, and all patients will take the same number of capsules each day. Initiation and dose adjustments of antihypertensive and lipid-lowering agents can be made as medically appropriate.

Methods of evaluation

An outline of the study assessments at clinic visits is shown in Table 1. Patients will be fasted from the evening before each clinic visit. In brief, patients will undergo a standard 75-g oral glucose tolerance test (OGTT) every 6 months. At each OGTT, glucose and insulin samples will be collected at 0 and 30 min. Fasting C-peptide, immunoreactive insulin, proinsulin, plasminogen activator inhibitor-1 (PAI-1) antigen, fibrinogen, and C-reactive protein (CRP) plasma levels will also be assessed at 6-month intervals. Liver enzymes will be checked at each visit for the first year and at 6-month intervals thereafter. Routine fasting plasma chemistry, lipid profile, hematology, serum β-human chorionic gonadotrophin (HCG) (in women), and urine samples will be assessed at baseline, 6 months, 1 year, and annually thereafter. FPG, HbA_{1c}, and blood pressure will be measured at each visit. Details of all adverse events (AEs) will be documented throughout the study and followed-up through resolution.

Health status and patient-reported outcomes will be assessed (using Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36], the Diabetes Treatment Satisfaction Questionnaire [DTSQ], and the Diabetes Symptoms Checklist [DSC]) at the baseline visit and annually thereafter (or at the time of withdrawal from the study). Medical care utilization data for non–protocol-related events requiring a health care professional or medical intervention will be collected by self-report at each clinic visit.

A central laboratory will be used during the study. Samples will be collected and transferred under appropriate conditions to the central laboratory. Routine chemistry analyses, including FPG and automated complete blood count, and routine urinalyses will be performed. FPG concentration will be measured using an enzymatic method and read biochromatically. HbA_{1c} will be measured using the Biorad Variant Hemoglobin A_{1c} assay. HCG will be measured using the Total HCG assay (Tarrytown, NY). Highly sensitive CRP (hsCRP) will be analyzed by fixed time nephelometry. Serum immunoreactive insulin (Linco kit) will be analyzed by a double-antibody radioimmunoassay. The assay is specific for insulin only and has negligible cross-reactivity with proinsulin and its conversion intermediates (intact human proinsulin [HPI] <0.2%; des 31, 32 HPI <0.2%; des 64, 65 HPI 76%). Proinsulin will be measured using serum samples that are immunoprecipitated with highly specific C-peptide antibody. After immunoprecipitation, the supernatant will be discarded, the precipitated immunocomplex will be washed, and the resulting supernatant will be discarded. Therefore, the potential for insulin interference will be removed. The assay recognizes proinsulin; large doses of C-peptide or insulin have little effect on the assay. Fibrinogen will be measured using photo-optical clot detection/MLA Electra 1000cc (Medical Laboratory Automation). Urinary albumin-to-creatinine ratio (ACR) will be measured by rate nephelometry. Brain natriuretic peptide will be obtained at baseline as a qualitative measure of preexisting congestive heart failure and measured by an extraction method with partial purification of brain natriuretic peptide. GAD

antibodies will be measured using a radiobinding assay. PAI-1 antigen will be quantitated using a Biopool TintElize (Ventura, CA) enzyme immunoassay kit. PAI-1 activity will be measured using a Chromolize PAI-1 immunoactivity kit (Ventura, CA).

Observational follow-up study

In accordance with the intent-to-treat principle, the observational part of the study will be to attempt to follow-up all patients for secondary outcomes from the time of treatment withdrawal until 48 months have elapsed from their date of randomization. Patients withdrawn from randomly assigned double-blind therapy, or who reach the primary outcome, will enter an observational follow-up study. This is intended to provide information regarding the glycemic status of all study participants at 4 years as well as their other outcomes and indexes of disease progression after early treatment of diabetes. There are no restrictions on medical care or diabetes therapy. Laboratory tests, vital signs, and information on micro- and macrovascular events, medication use, and quality of life will be collected.

Efficacy outcomes

Primary outcome

The primary efficacy outcome is the time from randomization to the time of monotherapy failure. Monotherapy failure is defined as the point at which the patient attains a reconfirmed FPG >180 mg/dl (>10 mmol/l) after at least 6 weeks of treatment at the maximum efficacious or tolerated dose of study medication. The confirmatory FPG >180 mg/dl will be performed within 3 days of receipt of the laboratory result.

Secondary outcomes

Glycemic control. The change in HbA_{1c} and FPG from baseline value to 48 months will be calculated. In addition, change in FPG and HbA_{1c} from baseline to on-therapy average will be assessed.

Insulin sensitivity. The percentage change in insulin sensitivity from baseline to 48 months will be estimated using the homeostasis model assessment (HOMA) (8).

β-cell function. β-cell function will be determined by the insulinogenic index [$\Delta I/\Delta G_{(0-30)}$] expressed as the ratio of the incremental (0–30 min) insulin and glucose responses after commencement of oral glucose intake during the OGTT. Consequently, the rate of change in β-cell function, as measured by $\Delta I/\Delta G$, will be determined. Information on the rate of change in β-cell function will also be ascertained using HOMA as well as by evaluation of the proinsulin-to-immunoreactive insulin ratio (PI/IRI). Because initial treatment is expected to transiently improve β-cell function, the slope of the curve that is being used to assess β-cell function will be computed starting with the first follow-up evaluation at month 6 in order to measure the rate of decline (unconfounded by the initial improvement). The baseline level of the measure will be used as an adjusting covariate. This allows for the acute effect of treatment on these measures during the immediate introduction of therapy followed by a systemic rate of change thereafter (9).

The change from baseline to 48 months in proinsulin, immunoreactive insulin, and C-peptide as well as on-therapy average for immunoreactive insulin and C-peptide will be assessed.

Cardiovascular risk markers

The percentage change in serum lipids (total cholesterol, HDL cholesterol, LDL cholesterol, free fatty acids, and triglycerides), ratios between lipid parameters, and systolic and diastolic blood pressure will be assessed. Change from baseline in levels of CRP and fibrinolytic variables will be assessed at selected centers.

Renal function

The percentage change from baseline to 48 months in urinary ACR in patients with microalbuminuria, as well as the progression of albuminuria, will be reported. Categories will be defined as normoalbuminuria (ACR <30 μg/mg), microalbuminuria (ACR ≥ 30 and <300 μg/mg), and macroalbuminuria (ACR ≥300 μg/mg).

Patient-reported outcomes and resource utilization

Patient-reported outcomes will be assessed using SF-36, the DTSQ, and the DSC. Direct health care costs will be assessed as the number of emergency room visits, number of unscheduled visits to the study physician's office, number of hospitalizations, and length of stay. Furthermore, indirect economic costs associated with bed days (days when patients stay in bed for half a day or more) and restricted-activity days (days when patients reduce their usual activities, such as housework or shopping) will be evaluated. These data will be collected from the patient at baseline and at all subsequent visits. Patients will be asked to self-report the number of bed days and restricted-activity days they have had in the 7 days before the clinic visit. Health care use will be reported and analyzed as a rate per 1,000 person days. Previously described standard methods for evaluation of the economic impact of the treatment groups will be conducted as part of the trial (10).

Safety parameters

Clinically significant changes in physical examination, vital signs, clinical laboratory tests, AEs, and electrocardiogram will be reported. In accordance with the ADA guidelines for the management of hypertension, the study recommends that investigators aim to control patient blood pressure at <130/85 mmHg, although no formal guidelines are given for the introduction of antihypertensive agents. If alanine aminotransferase levels increase more than three times the upper limit of the reference range levels, then they will be rechecked. Patients will be discontinued from the study if levels remain more than three times the upper limit. Cases of clinically determined hypoglycemia (per World Health Organization definition of hypoglycemia grades I–IV) ranging from mild to moderate symptoms requiring minor intervention (e.g., a sugary drink) to severe symptoms requiring medical intervention (e.g., glucose injection or glucagon) will be recorded as AEs. Patients who become pregnant during the study will be discontinued from the study and followed-up to term.

Statistical methods

Sample size estimates (11) provide 90% power to detect a hazard ratio of 0.70 (i.e., a 30% risk reduction) for the rosiglitazone group relative to the metformin or glyburide groups in the incidence of monotherapy failure using a two-group log-rank test at $P = 0.05$ (two-sided test, adjusted for two comparisons). Based on the U.K. Prospective Diabetes Study (UKPDS), we assume that 18.2% in the rosiglitazone group will reach monotherapy failure compared with 25% in the metformin or glyburide groups over the 4 years of treatment. The sample size also

allows for 20% loss to follow-up over a 4-year period. As there is the potential that GAD antibody–positive patients could influence disease progression (12), the sample size was also increased to allow for a lack of treatment effect in the 7% of patients assumed to be GAD antibody positive (11). In addition to analyses including all patients, separate analyses of the primary end point, insulin sensitivity, β-cell function, and glycemic parameters will be performed for subgroups of patients as defined by GAD antibody classification (positive or negative). Approximately 3,600 patients (1,200 patients per arm) will be randomized from ~500 centers in North America, Canada, and Europe.

The intent-to-treat analysis will be based on all patients randomized and use all available data collected during either the double-blind treatment study or the observational follow-up study. All patients who complete 4 years of double-blind treatment, including assessments and procedures, will be considered "study completers." All patients who withdraw from double-blind treatment but who continue to be followed in observational follow-up and complete all annual visits through 4 years from their randomization date will be considered "observational follow-up completers."

Treatment comparisons will be performed at an overall significance level of $P = 0.05$, based on two-sided tests, using Hochberg's modification of the Bonferroni adjustment for multiple (two) comparisons.

The modified Kaplan-Meier estimate of the cumulative incidence of the primary outcome, allowing for periodic assessments, will be computed and the incidence rates compared between treatment regimens via proportional hazard regression with baseline HbA_{1c}, country, and sex as covariates (13).

For the assessment of differences between the treatment groups with regard to quantitative variables (i.e., change from baseline over 4 years in FPG, HbA_{1c}, measures of insulin sensitivity, and β-cell function based on insulin, proinsulin and C-peptide measurements, hsCRP, fibrinolytic variables, and ACR), a multivariate linear model analysis (9) incorporating on-therapy values at all time points will be used.

A "completers" analysis using the 48-month "completers" population will also be performed using ANCOVA, with terms in the model for baseline, country, treatment, and sex (14). For assessment of resource utilization data, a Poisson regression model will be used to estimate the event rate per 1,000 patient-days and to test for treatment difference for each outcome separately. The analysis will include all on-therapy data, and the model will include terms for treatment and baseline HbA_{1c} and account for the duration of therapy. For secondary outcomes, the multivariate linear model analysis will be considered primary. However, results from each analysis will be compared to assess possible biases in the various methods.

All patients who received at least one dose of double-blind study medication will be assessed for clinical safety and tolerability.

CONCLUSIONS — There are few prospective clinical trials in patients with type 2 diabetes that have directly compared the impact of alternative therapies on metabolic and clinical outcomes. The best known and longest prospective trial is the UKPDS, which accumulated almost 20 years' worth of data. The UKPDS observed a progressive failure of the glucose-lowering therapies used (metformin, sulfonylureas, and insulin) to maintain glycemic control. The stepwise addition of antihyperglycemic agents to achieve glycemic goals resulted in substantial therapeutic overlap between the groups, making it difficult to analyze the effects of individual therapies. Finally, pharmacotherapeutics directly targeting insulin resistance were restricted to metformin. Thiazolidinediones, the only agents to directly increase insulin sensitivity of target peripheral tissues, were only introduced within the past few years, and their effects have not been reported from any long-term, blinded, controlled, outcome-based trials.

A Diabetes Outcome Progression Trial (ADOPT) is a blinded, prospective, randomized controlled trial that was developed to compare three mechanistically distinct antidiabetic agents currently available for the first-line pharmacological treatment of type 2 diabetes, in terms of their effects on glycemic control, β-cell function, and cardiovascular risk factors. The study started in March 2000 and recruitment is currently ongoing. Rosiglitazone is a thiazolidinedione that increases the sensitivity of target tissues to insulin, thereby improving glycemic control (15). Metformin is a biguanide whose primary mechanism is to reduce hepatic glucose output (16). Glyburide, a sulfonylurea, binds to the sulfonylurea receptor on the cell membrane, thereby depolarizing the cell membrane and closing the ATP-sensitive K^+ channel. Rosiglitazone improves insulin resistance and glucose control in patients with type 2 diabetes (15); has potential beneficial effects on β-cell function, blood pressure, urinary albumin excretion, postprandial glycemic excursions, and markers of fibrinolysis; and decreases free fatty acid levels, improves vascular reactivity, and improves markers of inflammation (17–23). Concomitant with improving glycemic control in type 2 diabetes, metformin has also been shown to stabilize or reduce weight gain, lower plasma triglyceride levels, and may have beneficial effects on blood pressure and the fibrinolytic system (24). There have been few reports of the secondary effects of glyburide treatment, but it may have antioxidant activity in a rat model of diabetes (25) as well as positive effects on reducing markers of reactive oxygen species in diabetic patients (18). This study will assess treatment effects in terms of attainment of sustained glycemic control, delayed monotherapy failure, and prevention of β-cell deterioration and effects on risk factors for the vascular complications of type 2 diabetes. The attempted follow-up of patients after withdrawal from diabetic monotherapy will provide information regarding the outcome and disease progression after early treatment of diabetes.

Glycemic control

The benefits of lowering blood glucose to normal or near-normal levels in patients with type 2 diabetes were demonstrated by the UKPDS. Epidemiological analysis of the UKPDS data showed there was a continuous relationship between risk of microvascular complications and glycemia. For every percentage point decrease in HbA_{1c}, there was an associated 37% reduction in risk of microvascular complications (26). The ADA guidelines for glycemic control recommend a target level of $HbA_{1c} < 7\%$ to reduce the risk of micro- and macrovascular complications.

Insulin sensitivity

The gold standard for measuring insulin resistance is the euglycemic-hyperinsu-

linemic clamp. However, this method cannot be easily used in large, multicentered, population-based studies. Insulin resistance, as estimated by HOMA, has been strongly correlated with the insulin resistance index, assessed by the euglycemic-hyperinsulinemic clamp, and is a useful method of assessment of insulin secretion in population-based studies in which only fasting samples are available.

β-cell function

Reduced β-cell function is associated with normal aging and type 2 diabetes. In this study, we will assess changes in β-cell function over time using the ratio of the incremental excursions in insulin to glucose during the first 30 min after an oral glucose tolerance load [$\Delta I/\Delta G_{(0-30)}$]. The PI/IRI will also be assessed to evaluate the quality of insulin secretion. The increased PI/IRI observed in diabetic patients has been shown to correlate inversely with a reduced maximal β-cell secretory capacity in patients with type 2 diabetes (27). Furthermore, ongoing deterioration of β-cell function (assessed by HOMA modeling) closely mirrored the progressive rise in FPG in a 10-year prospective study of newly diagnosed type 2 diabetic patients under intensive dietary management (28).

Macro- and microvascular complications

Type 2 diabetes is associated with a two- to fourfold increased risk of coronary heart disease (CHD), and patients with diabetes are often found to have increased cardiovascular risk factors, including dyslipidemia and hypertension. The simultaneous presence of high fasting glucose and complex dyslipidemia increases the risk of CHD events threefold. Glycemic control alone is unlikely to completely eliminate the risk of CHD in patients with type 2 diabetes; therefore, a multifactorial approach to the prevention of CHD appears necessary.

The association of microvascular complications such as retinopathy and nephropathy with type 2 diabetes is well known, and the Multiple Risk Factor Intervention Trial (MRFIT) verified diabetes to be a strong independent risk factor of end-stage renal disease (29). Urinary albumin levels have been suggested to be markers of both diabetic retinopathy and nephropathy. By examining levels of this marker and the ACR, the present study will determine how treatment targeting insulin resistance and impaired β-cell function might impact microvascular disease progression. Microalbuminuria (urinary albumin excretion rate between 30 and 300 mg/24 h) is not only a marker of renal and cardiovascular disease risk but also increases the risk of all-cause mortality (30).

Markers of systemic inflammation have been identified linking CHD and type 2 diabetes. CRP, a sensitive inflammatory marker, has been linked with CHD mortality, most notably in the MRFIT (31) and the U.S. Physicians' Health Study (32). Hypercoagulability and impaired fibrinolysis are possible candidates linking hyperinsulinism with atherosclerotic disease. Decreased insulin sensitivity has recently been associated with both elevated PAI-1 and fibrinogen levels, and increased levels of both insulin and proinsulin were associated with elevated PAI-1 (33). An association among CRP, fibrinogen, and microalbuminuria has also been described in type 2 diabetes (34).

In the UKPDS obese patient substudy, it is interesting to note that metformin, which some consider a weak and indirect insulin sensitizer of peripheral tissues, was the only agent to positively impact on mortality and cardiovascular complications. Rates of major cardiovascular events are expected to be low, and ADOPT is not expected to have the statistical power to detect differences across treatment groups. However, it is expected that comparisons of the effects of treatments on numerous traditional and nontraditional markers of cardiovascular risk will be performed. Effects of concomitant antihypertensive and lipid-lowering treatment on cardiovascular outcomes will only be ascertained through AE reporting, because event rates in this patient population are unlikely to be high enough to ascertain treatment differences.

Health outcomes

As the worldwide prevalence of diabetes increases (4), the economic, social, and medical costs will be daunting. There is some evidence from the UKPDS that the long-term costs due to complications of type 2 diabetes could be offset by an increase in initial costs to achieve optimal glycemic control. Therefore, ADOPT will also assess the effect of different diabetes monotherapy regimens on resource use and patient-reported outcomes. It has already been suggested that improvements in glycemic control are of benefit to the quality of life for type 2 diabetic patients (35).

SUMMARY — ADOPT is poised to provide data that will expand our understanding of the effect of mechanistically differing treatment options on metabolic control, β-cell function, cardiovascular risk factors, and factors related to progression in type 2 diabetes. Because the patients are recently diagnosed, it is unlikely that outcomes such as death, blindness, amputation, stroke, or myocardial infarction will occur in substantial numbers. However, this study will use well-characterized surrogate outcomes to investigate the effectiveness of the three main classes of oral antidiabetic agents in treating type 2 diabetes and their influence on the progression of risk factors associated with long-term complications.

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