Triple Therapy in Type 2 Diabetes

Insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naïve patients

JULIO ROSENSTOCK, MD[1]
DANNY SUGIMOTO, MD[2]
POUL STRANGE, MD, PHD[3]
JOHN A. STEWART, MSC[4]

ERIKA SOLTES-RAK, PHD[3]
GEORGE DAILEY, MD[5]
ON BEHALF OF THE INSULIN GLARGINE 4014
STUDY INVESTIGATORS*

OBJECTIVE — To evaluate the efficacy and safety of add-on insulin glargine versus rosiglitazone in insulin-naïve patients with type 2 diabetes inadequately controlled on dual oral therapy with sulfonylurea plus metformin.

RESEARCH DESIGN AND METHODS — In this 24-week multicenter, randomized, open-label, parallel trial, 217 patients (HbA$_{1c}$ [A1C] 7.5–11%, BMI >25 kg/m^2) on ≥50% of maximal-dose sulfonylurea and metformin received add-on insulin glargine 10 units/day or rosiglitazone 4 mg/day. Insulin glargine was forced-titrated to target fasting plasma glucose (FPG) ≤5.5–6.7 mmol/l (≤100–120 mg/dl), and rosiglitazone was increased to 8 mg/day any time after 6 weeks if FPG was >5.5 mmol/l.

RESULTS — A1C improvements from baseline were similar in both groups (−1.7 vs. −1.5% for insulin glargine vs. rosiglitazone, respectively); however, when baseline A1C was >9.5%, the reduction of A1C with insulin glargine was greater than with rosiglitazone ($P < 0.05$). Insulin glargine yielded better FPG values than rosiglitazone (−3.6 ± 0.23 vs. −2.6 ± 0.22 mmol/l; $P = 0.001$). Insulin glargine final dose per day was 38 ± 26 IU vs. 7.1 ± 2 mg for rosiglitazone. Confirmed hypoglycemic events at plasma glucose <3.9 mmol/l (<70 mg/dl) were slightly greater for the insulin glargine group ($n = 57$) than for the rosiglitazone group ($n = 47$) ($P = 0.0528$). The calculated average rate per patient-year of a confirmed hypoglycemic event (<70 mg/dl), after adjusting for BMI, was 7.7 (95% CI 5.4–10.8) and 3.4 (2.3–5.0) for the insulin glargine and rosiglitazone groups, respectively ($P = 0.0073$). More patients in the insulin glargine group had confirmed nocturnal hypoglycemia of <3.9 mmol/l ($P = 0.02$) and <2.8 mmol/l ($P < 0.05$) than in the rosiglitazone group. Effects on total cholesterol, LDL cholesterol, and triglyceride levels from baseline to end point with insulin glargine (−4.4, −1.4, and −19.0%, respectively) contrasted with those of rosiglitazone (+10.1, +13.1, and +4.6%, respectively; $P < 0.002$). HDL cholesterol was unchanged with insulin glargine but increased with rosiglitazone by 4.4% ($P < 0.05$). Insulin glargine had less weight gain than rosiglitazone (1.6 ± 0.4 vs. 3.0 ± 0.4 kg; $P = 0.02$), fewer adverse events (7 vs. 29%; $P = 0.0001$), and no peripheral edema (0 vs. 12.5%). Insulin glargine saved $235/patient over 24 weeks compared with rosiglitazone.

CONCLUSIONS — Low-dose insulin glargine combined with a sulfonylurea and metformin resulted in similar A1C improvements except for greater reductions in A1C when baseline was ≥9.5% compared with add-on maximum-dose rosiglitazone. Further, insulin glargine was associated with more hypoglycemia but less weight gain, no edema, and salutary lipid changes at a lower cost of therapy.

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Over 60% of Americans with type 2 diabetes have HbA$_{1c}$ (A1C) levels >7% following stepwise treatments that fail to address the dual defects of insulin secretion and action responsible for the relentless disease course (1–3). Despite evidence that single-agent therapy for type 2 diabetes seldom maintains glycemic control >3 years (2), treatment inertia remains the norm in the U.S. In one managed care study (4), for example, patients received only monotherapy despite 14–20 months of exposure to A1C levels >8% until a second oral agent was added. Because the introduction of dual-agent therapy has the potential to lower A1C levels by only an additional 1.2–2%, use of a third agent, whether another oral drug or insulin, is invariably required in such patients with advancing type 2 diabetes (3,5).

Conventional barriers to insulin therapy, such as lingering concerns about hypoglycemia, complex regimens, and erratic absorption, have been substantially overcome with the advent of insulin analogues, but fear of hypoglycemia and injections remain a barrier to insulin therapy. As a result, triple oral therapy is a valid therapeutic step that is the most appealing for many patients. The advantages of adding a third oral agent, such as a thiazolidinedione, when two-drug therapy fails remain uncertain, however, especially since baseline A1C levels frequently exceed 9% and maximized triple oral therapy reduces A1C by 1.4–1.7% (6,7). For patients with poorly controlled glycemia, the additive risk of adverse events and higher cost of a third oral agent may not be justified unless the target A1C is achieved.

Recent studies have demonstrated the efficacy of basal insulin as add-on therapy in patients with type 2 diabetes inadequately controlled with oral agents. A comparison of twice-daily 70/30 insulin combined with metformin versus triple oral therapy (sulfonylurea, metformin, and a thiazolidinedione) showed equivalent A1C reduction (~1.7%), but only one-third of subjects in either group reached the target A1C of 7% (8). Of note, premixed insulin was associated with

more frequent hypoglycemia in ∼70% of the patients.

Alternatively, the Treat-to-Target Trial (9), featuring aggressive titration of once-daily NPH insulin or insulin glargine added to one or two oral agents, brought nearly 60% of patients to an A1C of ≤7%, with the glargine group exhibiting significantly lower risk of nocturnal hypoglycemia.

The current study, a 24-week multicenter, randomized, open-label, parallel trial, evaluated the efficacy and safety of insulin glargine or rosiglitazone as add-on therapy in patients with type 2 diabetes with chronic hyperglycemic control despite maximized combination therapy with metformin plus a sulfonylurea.

RESEARCH DESIGN AND METHODS

This was a randomized (1:1), parallel-group, two-arm, open-label study conducted in 42 U.S. centers. The study consisted of a screening/titration phase of up to 4 weeks and a 24-week treatment phase. Subjects >18 years of age with type 2 diabetes (A1C ≥7.5 and ≤11%) and a BMI of >25 kg/m² were included in the study. Continuous oral hypoglycemic treatment using stable daily doses of ≥50% of the maximally labeled dose of a sulfonylurea and at least 1,000 mg metformin was required for ≥3 months before the screening visit.

Subjects were excluded for any of the following criteria: stroke, myocardial infarction, angina pectoris, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within the previous 12 months; history of congestive heart failure; treatment with nonselective β-blockers; hypoglycemia unawareness; impaired renal function; active liver disease; substance or alcohol abuse; and malignancy and planned radiological examinations requiring administration of contrasting agents.

Study medications and treatments

During the screening/titration phase, patients not on the maximum metformin dose were titrated to 2,000 mg/day. Patients on 1,000 mg/day increased their dose to 1,500 mg/day immediately and to 2,000 mg/day 1 week later (or maximum tolerated dose), followed by a 2-week stabilization period. Patients on 1,500 mg/day increased their dose to 2,000 mg/day immediately followed by a 2-week stabilization period. Sulfonylurea and met-

Table 1—Forced insulin titration schedule

Titrated weekly according to fasting plasma glucose and monitored blood glucose meter levels for the previous 2 consecutive days and no severe hypoglycemia or blood glucose <72 mg/dl (<4 mmol/l)	Increase in insulin dose (IU)
≤100 mg/dl (≤5.5 mmol/l)	0*
≥100 and ≤120 mg/dl (≥5.5 and ≤6.7 mmol/l)	0*–2
≥120 and ≤140 mg/dl (≥6.7 and ≤7.8 mmol/l)	2
≥140 and ≤160 mg/dl (≥7.8 and ≤8.9 mmol/l)	4
≥160 and ≤180 mg/dl (≥8.9 and ≤10 mmol/l)	6
≥180 (≥10 mmol/l)	8

Insulin glargine was administered as a single subcutaneous injection once daily at bedtime (9:00–11:00 P.M.); the starting dose was 10 IU/day. *Often patients did not get insulin increments if FPG was 100–120 mg/dl.

formin doses remained unchanged during the treatment phase of the study.

Subjects were randomized on a 1:1 basis to receive either insulin glargine or rosiglitazone with continued sulfonylurea and metformin. All subjects randomized to insulin glargine (Lantus) received a single daily subcutaneous injection at bedtime at a starting dose of 10 IU/day for 7 days. Using the dose titration schedule shown in Table 1, the dose was titrated weekly according to self-monitored fasting plasma glucose levels (FPG), supervised centrally to ensure compliance, to meet target FPG <100–120 mg/dl (<5.5–6.7 mmol/l).

All subjects randomized to treatment with rosiglitazone (Avandia) received a starting oral dose of 4 mg once daily for 6 weeks. If the FPG value was >100 mg/dl (>5.5 mmol/l) after 6 weeks, rosiglitazone was increased to a maximum of 8 mg/day.

Outcome measures

The primary objective of this study was to compare glycemic control (measured by A1C) between insulin glargine and rosiglitazone as add-on therapy in patients receiving dual oral agent therapy consisting of a sulfonylurea and metformin. Secondary objectives included assessment of hypoglycemia profile; changes in FPG, body weight, and serum lipids; proportion of patients achieving A1C ≤7%; and cost of therapy.

Safety measures

Safety was assessed in the intent to treat (ITT) population through adverse events, hypoglycemia, body weight, physical examinations, vital signs, standard hematology, and blood chemistry. Serum glutamic-oxaloacetic transaminase and serum glutamate pyruvate transaminase were

performed at screening and weeks 6, 12, 18, and 24. Capillary blood glucose, hypoglycemic episodes, and adverse events were documented by the patient via diary cards or were recorded by the study investigator when mentioned by the patient. A physical examination to identify signs of peripheral edema was performed at baseline and final visit or at patient discontinuation.

Patients were instructed on proper self-monitoring technique using a glucose meter and had to demonstrate proper technique. They were also instructed to measure fasting blood glucose twice a day during the 1st week for 1 week after dose change and once a day at other times. At the time of a hypoglycemic episode, patients were instructed to measure glucose and document the date, start and end time, time of last meal, blood glucose level, and whether assistance was needed.

Confirmed symptomatic hypoglycemia was defined as an event with clinical symptoms consistent with hypoglycemia (confirmed with a meter reading). Nocturnal hypoglycemia was defined as symptomatic hypoglycemia occurring after the evening insulin injection and before getting up in the morning. Confirmed or documented hypoglycemia was defined as plasma glucose levels <70 mg/dl (<3.9 mmol/l), <50 mg/dl (<2.8 mmol/l), or <36 mg/dl (<2.0 mmol/l). Severe hypoglycemia was defined as that requiring assistance with either a plasma glucose level <36 mg/dl (<2.0 mmol/l) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

Statistical methods

Descriptive statistics, including means ± SE and median (range) for continuous variables and n (%) for categorical vari-

ables, were used to compare the study groups with respect to demographic and disease characteristics. The ITT population constituted all subjects who took at least one dose of the study medication and in whom a baseline measurement of A1C and one follow-up A1C measurement could be made. The safety evaluatable population included all subjects who took the study medication and those for whom follow-up safety data could be obtained.

ANCOVA was used to compare differences in the change from baseline for the continuous primary and secondary variables. This ANCOVA model included treatment and center (pooled) as fixed effects and the baseline value for the variable being analyzed as the covariate. Output included the mean difference between the changes from baseline for insulin glargine and rosiglitazone, the SE, and the 95% CI. A Cochran-Mantel-Haenszel procedure controlling for center (pooled) was used to compare event rates of categorical variables. For both sets of analyses, a two-side significance level of $\alpha = 0.05$ was used.

Cost analysis

The economic costs of glycemic control were compared by combining selected measures of resource use with unit-cost estimates. Resource measures included study medication, other antihyperglycemic agents, syringes for insulin glargine, glucose testing supplies for both groups, and recommended liver function tests for the rosiglitazone group. Resource use was based on trial data over the 24-week period. Costs of medications, insulin syringes, test strips, and lancets were estimated using average wholesale prices expressed in 2002 U.S. dollars (10) and were based on the numbers actually dispensed. The cost of hepatic function panels was estimated using fee schedules under Medicare's Resource-Based Relative Value Scale (11). Economic costs were summarized using means and 95% CIs and calculated through techniques of bootstrapping. Results were not adjusted for differences between treatment groups in the duration of treatment.

RESULTS — A total of 341 patients were screened, 219 were randomized, and 217 received study medication (insulin glargine, $n = 105$; rosiglitazone, $n = 112$). Baseline characteristics are listed in Table 2. One patient in the insulin glargine group did not have an A1C level

**Table 2—Baseline characteristics of patients**

	RSG	Insulin glargine
n	112	104
Age (years)	55.3 ± 11.4	55.9 ± 10.5
Men/women	65/47 (58/42)	47/57 (45/55)
Diabetes duration (years)	8.1 ± 5.1	8.5 ± 5.8
BMI (kg/m²)	33.6 ± 6.3	34.6 ± 7.0
A1C (%)	8.7 ± 1.0	8.8 ± 1.0

Data are means ± SD and *n* (%). RSG, rosiglitazone.

at study entry and was excluded from the ITT population. A total of 18 patients withdrew during the treatment phase due to discontinuance (1 insulin glargine, 3 rosiglitazone), protocol violations (3 insulin glargine, 1 rosiglitazone), lost to follow-up (1 insulin glargine, 7 rosiglitazone), and other reasons (1 insulin glargine, 0 rosiglitazone). Mean duration of treatment was 190.4 and 180.0 days for patients receiving insulin glargine and rosiglitazone, respectively ($P = 0.0305$).

Glycemic control

Baseline mean A1C and FPG levels were comparable between the treatment groups (Table 2). At study end, A1C was reduced from baseline by 1.66% in the insulin glargine group and by 1.51% in the rosiglitazone group with no significant difference between the groups ($P = 0.1446$) (Fig. 1A). In patients with A1C <9.5% there was no significant difference between treatment groups ($P = 0.87$); however, glargine resulted in significantly greater A1C reduction compared with
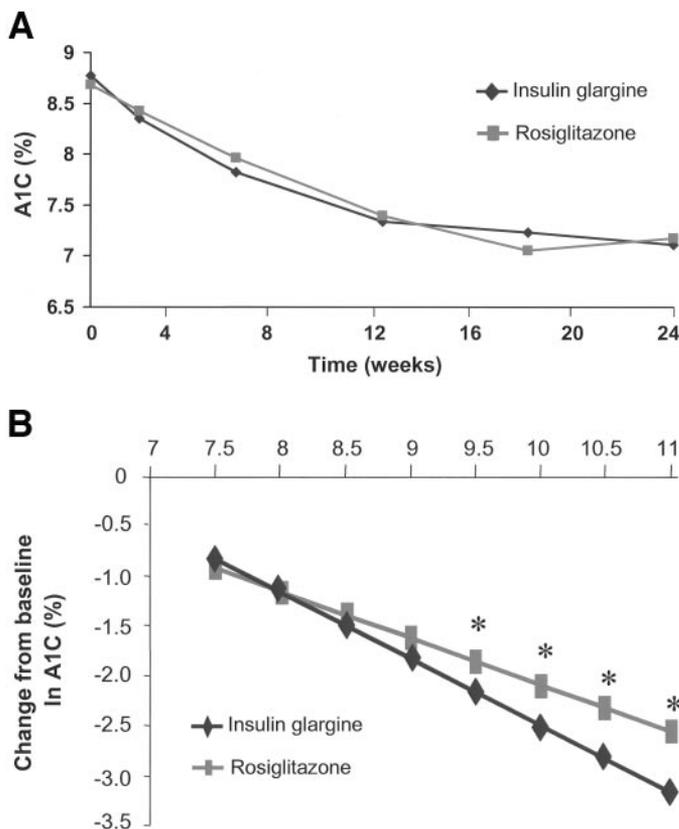
Figure 1—A: *Mean A1C levels from baseline to end point. Mean A1C levels showed a similar decrease for both insulin glargine (−1.66%) and rosiglitazone (−1.51%; P = 0.1446). B: Glycemic control by baseline A1C. Improvement was significantly greater for insulin glargine–treated patients versus rosiglitazone-treated patients who had a baseline A1C of ≥9.5% (*P < 0.05 by least square means for insulin glargine vs. rosiglitazone).*
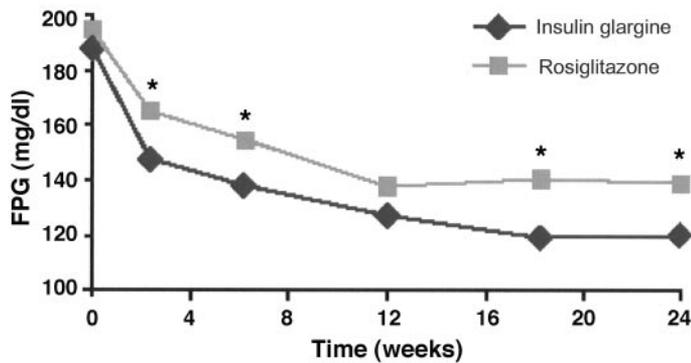
Figure 2— *Mean FPG levels from baseline to end point. FPG decreased significantly in both groups from baseline to end point, with a greater reduction seen with insulin glargine versus rosiglitazone (−64.9 mg/dl [−3.60 mmol/l] vs. −46.3 mg/dl [−2.57 mmol/l]; P = 0.001 for insulin glargine vs. rosiglitazone).*

rosiglitazone when baseline A1C levels were ≥9.5% (P < 0.05) (Fig. 1B). An A1C value of ≤7% was achieved by 48% of insulin glargine–treated patients and 49% of rosiglitazone-treated patients. Results for patients who completed the study were similar to those of the ITT population.

FPG decreased significantly from baseline to end point in both groups; however, greater reductions occurred in the insulin glargine group than in the rosiglitazone group (−3.60 ± 0.23 vs. −2.57 ± 0.22 mmol/l [−64.9 vs. −46.3 mg/dl]; P = 0.001). This difference was observed as early as week 2 of treatment (P = 0.0084) and continued throughout the 24-week study (Fig. 2).

Serum lipids
Contrasting lipid effects at end point, from baseline, were demonstrated between insulin glargine versus rosiglitazone for total cholesterol (196 to 186 mg/dl vs.196 to 215 mg/dl [−4.4 vs. +10.1%], respectively; P = 0.0001); LDL cholesterol (117 to 115 mg/dl vs. 106 to 120 mg/dl [−1.4 vs. +13.1%], respectively; P = 0.0004), and triglycerides (217 to 176 mg/dl vs. 241 to 252 mg/dl [−19.0 vs. +4.6%], respectively; P = 0.0011). HDL cholesterol was unchanged with insulin glargine but increased with rosiglitazone (+4.4%; P = 0.0407). Free fatty acids were similarly reduced by insulin glargine and rosiglitazone (−20.0 and −17.2%, respectively).

Adverse events, edema, and weight gain
Adverse events possibly related to the study medication occurred significantly more among patients on rosiglitazone than on insulin glargine (28.6 vs. 6.7%, respectively; P < 0.0001). Peripheral

edema occurred only in the rosiglitazone group, whereas no patient on insulin glargine reported edema (12.5 vs. 0%, respectively; P = 0.001). Rosiglitazone-treated patients gained more weight (3.0 ± 0.4 kg) than those on insulin glargine (1.7 ± 0.4 kg) (P = 0.02). Twenty-one subjects (18.8%) receiving rosiglitazone discontinued the study after beginning treatment versus eight (7.6%) receiving glargine (P = 0.0104). Two subjects (2%) in the insulin glargine group and nine (8%) in the rosiglitazone group withdrew due to adverse events. The adverse events in the insulin glargine group included hypoglycemia (related to the study medication) and gastrointestinal infection (unrelated to the study medication). In the rosiglitazone group, six of the nine adverse events, which included edema, nausea, hypoglycemia, elevated liver function tests, and weight gain, were apparently related to the study medication. Serious adverse events occurred in 4.8% (5 of 105) of insulin glargine–treated patients and 9.8% (11 of 112) of rosiglitazone-treated patients; of these, none in the insulin glargine group and 3 in the rosiglitazone group (hypoglycemia, overdose, and fibroid tumors and iron deficiency) were considered to be possibly related to the study medication.

Hypoglycemia
Confirmed hypoglycemic events at plasma glucose <3.9 mmol/l (<70 mg/dl) were slightly greater with insulin glargine (n = 57) (rosiglitazone, n = 47; P = 0.0528). Confirmed events <2.0 mmol/l (<36 mg/dl) were similar between groups (insulin glargine, n = 1; rosiglitazone, n = 3; P = 0.3514), whereas confirmed symptomatic hypoglycemic events at plasma glucose <2.8

mmol/l (<50 mg/dl) were greater in the insulin glargine–treated group (insulin glargine, n = 26; rosiglitizone, n = 14; P < 0.0165). More patients in the insulin glargine group had confirmed nocturnal hypoglycemia of <3.9 mmol/l (insulin glargine, n = 29; rosiglitazone, n = 12; P = 0.02) and <2.8 mmol/l (insulin glargine, n = 10; rosiglitazone, n = 3; P < 0.05) than in the rosiglitazone group. The calculated average rate per patient-year of a confirmed hypoglycemic event (defined as <70 mg/dl), after adjusting for BMI, was 7.7 (95% CI 5.4–10.8) and 3.4 (2.3–5.0) events for insulin glargine and rosiglitazone, respectively (P = 0.0073). Severe hypoglycemic events occurred in six rosiglitazone- and three insulin glargine–treated patients.

Treatment dose and costs
Starting daily doses were 10 IU insulin glargine and 4 mg rosiglitazone. At study end point, the mean daily dose of insulin glargine was 38.5 ± 26.5 IU and of rosiglitazone 7.1 ± 1.7 mg. The total cost of glycemic control was $1,368 ($1,301–1,433) in the insulin glargine group (insulin glargine $216 [$192–243], metformin $461 [$422–479], sulfonylurea $302 [$271–334], syringes $58 ($54–61), and monitoring supplies for blood glucose $331 [$309–353]) and $1,603 ($1,514–1,683) in the rosiglitazone group (rosiglitazone $564 [$527–598], metformin $448 [$422–471], sulfonylurea $272 [$241–303], monitoring supplies for blood glucose $291 [$268–315], and hepatic function panel $29 [$28–30]). The mean numbers of dispensed test strips and lancets was higher in the insulin glargine group than in the rosiglitazone group (419.4 ± 141.9 vs. 368.0 ± 168.1). Patients were assumed to receive the same number of lancets as test strips, since the number of lancets dispensed was not available. The mean cost of study therapy was $348 lower among subjects receiving insulin glargine ($216) versus rosiglitazone ($564). However, the cost of other antihyperglycemic medications and resources was slightly higher in the insulin glargine group ($1,152) than in the rosiglitazone group ($1,040). The cost of monitoring liver function (now optional) was $29. Overall, the estimated mean total cost of glycemic control over 24 weeks was $235 lower among subjects treated with insulin glargine ($1,368) compared with rosiglitazone ($1,603), despite

longer duration of treatment with glargine.

CONCLUSIONS — The choice of add-on thiazolidinedione or insulin therapy when two oral agents are insufficient to control glycemia in patients with type 2 diabetes necessitates balancing the risks and benefits of each drug beyond their antidiabetic action (12,13). For example, recent studies have shown that adding a thiazolidinedione may be beneficial if baseline A1C is mildly elevated (7) and weight gain is of little concern (14). Other trials demonstrate a cost advantage with add-on insulin (8), as well as the potential for superior glycemic control (9) only limited by hypoglycemia. However, common barriers to insulin therapy such as misconceptions about the potential but unsubstantiated association with atherogenesis and, more realistically, hypoglycemia, weight gain, and the patient's fear of injection have delayed its use in the past (15).

Because the addition of a third oral agent is unlikely to decrease A1C levels by >1.5–1.7%, insulin is often the only means of lowering A1C to target levels when the baseline is >8.5–9.0%. Newer insulin analogues that allow more physiologic insulin replacement with less risk of hypoglycemia (9) have prompted a move toward earlier introduction of insulin to achieve glycemic targets and forestall diabetes complications.

In the present study, both triple therapy regimens showed substantial and comparable improvement in A1C levels, with almost half of the patients in each group achieving the target of ≤7%. The benefit of add-on insulin glargine was greater when baseline A1C was ≥9.5% and with respect to FPG. Presumably, the improved FPG levels had a greater impact in those with higher A1C, but the effects on postprandial glucose levels, not measured in this study, might have been important to explain the otherwise similar outcome A1C levels in both groups. Given the progressive nature of type 2 diabetes, however, introducing either triple-agent combination at lower baseline A1C levels (i.e., earlier in the disease course) could potentially increase the percentage of patients attaining A1C ≤7%. In addition, longer-term studies beyond 24 weeks may demonstrate that more patients can attain and, most importantly, sustain these glycemic targets.

The average daily dose of rosiglitazone approached the maximum dosage of 8 mg, thereby precluding further glycemic improvement. In contrast, the average dose of insulin glargine by the end of the study was only 39 IU as compared with 47 IU in the Treat-to-Target Trial (9), presumably owing to less aggressive insulin titration (Table 1). Given that the more actively titrated regimen of add-on glargine in the Treat-to-Target Trial achieved the A1C target of ≤7% in almost 60% of patients with appreciably less nocturnal hypoglycemia than NPH, it is possible to extrapolate that higher doses of glargine in this study could have yielded greater glycemic benefit. This highlights the importance of adequate titration of insulin to achieve target glycemic control.

A higher incidence of confirmed overall and nocturnal hypoglycemic events occurred in the insulin glargine group. However, compared with rosiglitazone, insulin glargine was associated with fewer adverse events, less weight gain, and no edema, whereas 12.5% of patients receiving rosiglitazone reported edema, a common side effect associated with these agents (16). Although insulin therapy typically produces modest weight gain, rosiglitazone led to twice as much weight gain (3.0 kg) as insulin glargine (1.6 kg). As previously demonstrated with insulin treatment (17–20), patients treated with insulin glargine resulted in a significantly improved serum lipid profile compared with those treated with rosiglitazone

The cost of improved glycemic control was substantially lower among patients receiving insulin glargine, despite a significantly longer duration of treatment. Specifically, the estimated mean cost per 1% A1C reduction was $824 with insulin glargine versus $1,062 with rosiglitazone, an important difference given that improved medical resource utilization resulting from better glycemic control may yield ultimate cost savings (21–23).

In summary, both low-dose insulin glargine and maximum-dose rosiglitazone effectively lowered A1C levels in triple therapy regimens, with glargine conferring lower FPG levels overall and greater improvement in patients with higher baseline A1C levels. Compared with rosiglitazone, insulin glargine was associated with more hypoglycemia but fewer adverse reactions, no edema, less weight gain, and salutary lipid changes at a lower cost of therapy. These results provide solid clinical evidence for the decision-making process needed to select a third antidiabetic agent when dual therapy is deemed inadequate in the complex setting of worsening type 2 diabetes.

APPENDIX

Investigators in the Insulin Glargine 4014 Study Group
Arnold G, Brady SS, Bray ES, Bruschetta HR, Byars WD, Coats TL, Cohen AJ, Collins GV, Cronyn M, Daisley SJ, Dalili C, DeGarmo RG, Entrup MH, First B, Forbes R, Gaddam SP, Gamel W, Gillie E, Hagedorn J, Harrison BJ, Ishak SG, Kaye WA, Khan M, Klein TD, LaFata J, LaSalle JR, Levy P, Lunde NM, McCluskey DC, Montenegro-Rodas F, Nadeau DA, Nguyen T, Rattray CF, Riddle MC, Riff DR, Rosenstock J, Salmon JS, Schwartz SL, Seger WM, Seyler LE, Shear MJ, Sugimoto DH, Taggart PR, and Waser G.

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