Reduction in Use of Healthcare Services With Combination Sulfonylurea and Rosiglitazone: Findings From the Rosiglitazone Early vs SULfonylurea Titration (RESULT) Study

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Objective: To assess and compare healthcare utilization and costs over a 2-year period in older patients (≥60 years) with type 2 diabetes receiving combination therapy with rosiglitazone plus a sulfonylurea (glipizide) or progressive up-titration of glipizide monotherapy.

Study Design: Two-year, randomized, double-blind, parallel-group clinical trial.

Patients and Methods: Older type 2 diabetic patients initially receiving submaximal doses of a sulfonylurea were randomized to receive rosiglitazone plus glipizide (n = 115) or up-titrated glipizide monotherapy (n = 110). Information on patient self-reported healthcare utilization (hospitalizations, emergency department [ED] visits, physician office visits) was collected prospectively for the duration of the trial. National average healthcare costs per unit were applied to calculate direct medical costs.

Results: Demographic characteristics of the 2 groups were similar. At the study's end, glycemic values were better in the rosiglitazone-plus-glipizide group. Compared with the glipizide group, patients receiving rosiglitazone plus glipizide had significantly fewer ED visits (P = .0006) and hospitalizations (P = .0263). Although the glipizide group had more unscheduled physician office visits, the difference was not statistically significant. Estimated treatment costs per patient per month were significantly lower for the rosiglitazone-plus-glipizide group than for the glipizide group ($480 vs $645; P < .05).

Conclusion: Addition of rosiglitazone to sulfonylurea therapy was associated with decreased use of medical resources, in particular hospitalizations and ED visits, compared with progressive sulfonylurea up-titration. Although causality could not be established, this therapeutic approach could improve clinical outcomes in patients with type 2 diabetes and reduce healthcare utilization and costs.

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Type 2 diabetes affects 18% to 20% of people more than 65 years of age in the United States.[1] The cost of diabetes increases with age.[2] In 2002, the total cost of diabetes in the United States was estimated to be $132 billion, with direct medical costs of $92 billion.[3] Direct medical costs of diabetes care, the chronic complications of diabetes, and the excess prevalence of general medical conditions in people with diabetes accounted for $23.2, $24.6, and $44.1 billion, respectively. Total per capita cost for patients with diabetes was estimated to be $13 243 (compared with $2560 for those without diabetes).[2] The increasing prevalence of diabetes,[4] the aging of the US population, and efforts at cost containment have raised concerns about the healthcare resource utilization and costs associated with type 2 diabetes.

Comprehensive information on the cost of treating diabetes, including the costs of treatments, side effects, and outcomes, would help decision makers to make more informed choices about how to manage the disease. A number of studies have analyzed costs associated with type 2 diabetes and its complications, using health insurance claims, patient medical records, and patient and provider surveys.[5-8] The annual direct medical costs for HMO patients with diet-controlled type 2 diabetes, a body mass index (BMI) of 30 kg/m^2, and no microvascular, neuropathic, or cardiovascular complications were $1700 and $2100 for white men and women, respectively. A 10-kg/m^2 increase in BMI, treatment with oral antidiabetic or antihypertensive agents, diabetic kidney disease, cerebrovascular disease, and peripheral vascular disease each were associated with a 10% to 30% increase in cost. Insulin treatment, angina, and myocardial infarction each were associated with a 60% to 90% increase in cost.[5] Compared with persons who have no complications or comorbidities, persons who have 2 or more complications or comorbidities used moderately more primary care services (1.3-1.9 times more) and markedly more specialty care servic-

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es (5.8-6.3 times more), emergency department (ED) visits (3.3-5.5 times more), and hospital stays (3.3-11.9 times more).[9] The costs of managing diabetes complications were estimated to be $47 240 per patient over the period of 30 years.[10] Intensive glycemic control, although more expensive, was reported to significantly reduce the risk of microvascular complications (eg, retinopathy, nephropathy, neuropathy) in patients with type 2 diabetes. The greater costs of intensive therapy were largely offset by the cost savings associated with fewer complications.[11] Although type 2 diabetes and its complications have been recognized as important healthcare cost drivers, no clinical trial other than the United Kingdom Prospective Diabetes Study has focused on the long-term healthcare resource use and costs associated with treatment and complications.[12]

The objective of this study was to analyze resource utilization and cost of care in the Rosiglitazone Early vs. SULfonylurea Titration (RESULT) study, a 2-year clinical trial involving older patients (≥60 years) with type 2 diabetes randomized to receive combination treatment with rosiglitazone plus a sulfonylurea (glipizide) or up-titration of glipizide monotherapy.

METHODS

Study Design

The RESULT study was a 2-year, double-blind, randomized, parallel-group clinical trial. It has been described in detail elsewhere (J. Rosenstock, MD, B. J. Goldstein, MD, PhD, A. I. Vinik, MD, PhD, et al., unpublished data, 2004). In brief, after screening, eligible patients ≥60 years of age received 4 weeks of treatment consisting of diet/exercise reinforcement and the prescribed half-maximum dose of glipizide (10 mg twice daily). Patients whose diabetes remained insufficiently controlled were randomized in equal numbers to 1 of 2 treatment groups: rosiglitazone plus glipizide and rosiglitazone-matched placebo plus glipizide. During the 2-year study period, physicians individualized each patient's treatment using a systematic, stepwise titration schedule and were encouraged to titrate medication to attain targets recommended by the American Diabetes Association (ADA).[13] Although study medications could be adjusted at the discretion of the study physicians, up-titration to the maximum labeled dosages (glipizide 40 mg/day, rosiglitazone 8 mg/day) was required if the fasting plasma glucose level was ≥180 mg/dL (10 mmol/L) and was recommended if the fasting plasma glucose level was >140 mg/dL (7.8 mmol/L).

Patients

Eligible patients were men and women at least 60 years of age who had a diagnosis of type 2 diabetes mellitus and who had been treated with sulfonylurea monotherapy for at least 3 months before screening, at ¼ to ½ of the maximum recommended dose of the sulfonylurea for a minimum of 2 of those 3 months. In addition, patients were required to have fasting plasma glucose levels between 126 mg/dL and 250 mg/dL at the first study visit, and between 126 mg/dL and 179 mg/dL by the third study visit, during the 4-week run-in period with diet and exercise reinforcement and monotherapy with glipizide 10 mg twice daily.

Resource Utilization and Costs

Resource utilization data were collected prospectively for all nonprotocol-related events requiring a healthcare system encounter. Resource utilization included hospitalizations, ED visits, and unscheduled outpatient visits to the study physician or other healthcare providers. Dates of hospitalizations, ED visits, and physician office visits were collected. These assessments were made at baseline (the point of randomization) and at all subsequent study visits. Patients were asked to self-report any nonprotocol-related healthcare utilization since the last scheduled visit. In addition, patients were asked to self-report the number of bed days (days spent in bed at home for half a day or more) and restricted-activity days (days patients reduced their usual activities, such as work, housework, and shopping) in the 7 days before the clinic visit. Patient-reported utilization data were supplemented with data on protocol-mandated outpatient visits, use of medications (both related and unrelated to the study), laboratory tests, and self-monitoring of blood glucose to estimate the total cost of care in both study groups. Use of study medications was recorded in the clinical trial, and use of nonstudy medications was self-reported. Nonstudy medication was defined as any concomitant medication taken by the patient during the period of study participation that was not diabetes specific. Assumptions about types and frequency of the laboratory tests were based on ADA recommendations.[13] The latter also served as a basis for estimates about the frequency of self-monitoring of blood glucose.

Healthcare utilization was expressed as a rate per 1000 patient-days. A Poisson regression model (PROC GENMOD) was used to estimate the event rate per 1000 patient-days and to test for treatment differences for each end point separately. Each model used the number of events as the dependent variable; independent variables included terms for treatment (rosiglitazone plus glipize versus glipizide) and baseline glycosylated hemo-

globin (HbA_{1c}), and accounted for the duration of therapy. SAS statistical software, version 8 (SAS Institute Inc, Cary, NC), was used in all analyses.

A standard unit-cost method was used to calculate direct medical costs. Hospitalizations, ED visits, and physician office visits reported by patients were assigned monetary values based on published US national average unit costs.[14] US national average unit costs were inflated using the consumer price index for medical care and all costs were expressed in 2002 US dollars. Cost of study medication was based on wholesale acquisition cost, and the dose and frequency used in each study arm. Cost of nonstudy medication was based on the reported national average annual cost of prescription medications.[14] Laboratory costs were derived from the published Medicaid fee schedule.[15] Cost of self-monitoring was based on the current market price of monitoring devices and test strips.[16] Per patient per month (PPPM) costs were calculated for hospitalizations, ED visits, physician visits, medications, laboratory tests, and self-monitoring separately, and total costs were calculated for both study groups. All costs were adjusted for the duration of therapy, which varied among members in both groups.

To assess the economic impact of each therapy, costs were reported and analyzed as cost of hospitalizations, ED visits, physician visits, medication, laboratory tests, self-monitoring, cost per study group participant, and total cost. For comparison purposes, the costs were expressed as cost PPPM.

Sensitivity Analysis

The distribution of cost data tends to be skewed due to the presence of outliers. To estimate the impact of outliers, sensitivity analysis was conducted by identifying outliers and excluding them from the analyses.

RESULTS

Patients

The 2 treatment groups were comparable with respect to age, sex, race, BMI, and smoking status. The majority of patients were male (73%) and white (91%), with a mean BMI of 30.4 ± 4.7 kg/m^2. The mean age of the patients was 68.4 ± 6.2 years, with approximately 43% of patients older than 70 years of age. **Table 1** summarizes the demographic characteristics of the study population.

Efficacy

The primary clinical outcome was time from randomization to a final action point, defined as a fasting plasma glucose level of ≥180 mg/dL (upon confirmatory testing) for a patient who was titrated to maximum doses of glipizide and study medication. Only 2 of 115 patients reached the final action point in the rosiglitazone-plus-glipizide group (2.0%) compared with 27 of 110 patients in the glipizide monotherapy group (24.5%), a difference that was significant ($P < .0001$). The average duration of therapy was 20.1 months for all selected subjects, with mean exposure of 21.5 and 18.8 months in the rosiglitazone-plus-glipizide and glipizide groups, respectively.

Resource Utilization

Compared with patients in the glipizide group, patients in the rosiglitazone-plus-glipizide group had significantly fewer hospitalizations ($P = .0263$), self-reported bed days ($P = .0002$), and ED visits ($P = .0006$). In addition, patients in the rosiglitazone-plus-glipizide group had a significantly shorter mean length of stay per hospitalization than those in the glipizide group (4.5 days vs 7.4 days; $P < .001$). Although numerically greater in the glipizide group, there were no significant differences between the 2 treatment groups in unscheduled visits to study physician offices or restricted activity days (**Table 2**).

Cost of Treatment

Based on the national average, the cost of 1 hospital day is $2577.[14] Total hospitalization costs were $311 684 and $744 655 in the rosiglitazone-plus-glipizide and glipizide groups, respectively. In the group receiving rosiglitazone plus glipizide, the average hospitalization cost per study group member was $2710, and the exposure-adjusted hospitalization cost PPPM was $126; comparable figures for the group receiving glipizide monotherapy were $6770; and $361.

The national average Medicare reimbursement rate for ED visits is $183.[14] In the rosiglitazone-plus-glipizide and glipizide groups, ED visit costs totaled $8595 and $16 093, or $75 and $146 per patient, respectively. The respective exposure-adjusted ED costs PPPM were $4 and $8.

The national average Medicare outpatient visit reimbursement rate is $56.[14] This figure was applied to all the protocol-related and patient-reported physician visits in the rosiglitazone-plus-glipizide and glipizide groups. The total cost of physician visits was $92 878 and $84 277 ($807.60 and $766.20 per patient) in the rosiglitazone-plus-glipizide and glipizide groups, respectively. Exposure-adjusted PPPM costs for physician visits were $38 and $41 in the 2 groups, respectively.

Based on the wholesale acquisition cost, the duration of treatment, and the final dosage for study medication,

Table 1. Summary of Demographic Characteristics*

Characteristic	Treatment Group: Glipizide (n = 110)	Treatment Group: Rosiglitazone + Glipizide (n = 115)	*P*	Total (N = 225)
Age ≥ 65 y	71 (65%)	74 (64%)	.998	145 (64%)
Mean (SD) age, y	68.2 (6.3)	68.7 (6.2)	.1256	68.4 (6.2)
Male	79 (72%)	86 (75%)	.6152	165 (73%)
BMI ≥ 27 kg/m^2	80 (73%)	92 (80%)	.2122	172 (76%)
Mean (SD) BMI, kg/m^2	30.5 (4.9)	30.2 (4.5)	.5903	30.4 (4.7)
Nonsmoker	100 (90.9%)	106 (92.2%)	.5256	206 (91.6%)

*BMI indicates body mass index.

study medication costs during the clinical trial totaled $243 550 and $22 689 in the rosiglitazone-plus-glipizide and glipizide groups, respectively. The respective costs of study medication per participant were $2118 and $206, and the exposure-adjusted costs of study medication were $99 and $11 PPPM.

Nonstudy medication was assessed by using the reported national average annual prescription drug cost of $446 per medication.[14] Based on study data, nonstudy medications cost a total of $449 876 and $402 698 in the rosiglitazone-plus-glipizide and glipizide groups, respectively. The respective costs of nonstudy medication per participant were $3912 and $3661, and the exposure-adjusted costs PPPM were $182 and $195.

The types of laboratory tests performed and their frequency were based on ADA recommendations. They included a HbA_{1c} measurement every 3 months, and a lipid panel and urine albumin assessment once per year. A liver enzyme test was performed every 2 months for the first year of therapy for the rosiglitazone-plus-glipizide group, as was recommended for thiazolidinediones at the time this study was performed. (Subsequent to this study, liver enzyme testing was required only prior to the initiation of therapy with rosiglitazone and periodically thereafter per the clinical judgment of the healthcare professional.) The cost of laboratory tests for both study groups was calculated using appropriate procedure codes and their rates as quoted in the Medicaid fee schedule.[15] Lab test unit costs were $13.42, $18.50, $8.00, and $11.29 for HbA_{1c}, the lipid panel, the urine albumin/creatinine ratio, and the hepatic enzyme panel, respectively. Based on these data, total lab costs were $23 827 and $13 792 for the rosiglitazone-plus-glipizide and glipizide groups, respectively. The respective costs of lab tests per study group member totaled $207 and $125, with exposure-adjusted costs of $10 and $7 PPPM.

Following ADA recommendations,[13] all patients were encouraged to self-monitor their blood glucose. It was expected that, on average, patients would perform self-monitoring once a day. The cost of self-monitoring was assumed to be $0.75 per day based on average retail price of the meter and test strips.[16] The total cost of self-monitoring was $55 582 and $46 455 in the rosiglitazone-plus-glipizide and glipizide groups, respectively, or $483 and $422 per study group member. The exposure-adjusted cost was $23 PPPM for both groups.

An overall total treatment cost was calculated for each study group subject. The overall cost was $480 and $645 PPPM for the rosiglitazone-plus-glipizide and glipizide groups, respectively. A summary of total healthcare

Table 2. Healthcare Utilization Event Rates

Event	Mean (SD) Rate of Occurrence*: Glipizide (N = 110)	Mean (SD) Rate of Occurrence*: Rosiglitazone + Glipizide (N = 115)	*P*
Hospitalization	0.76 (1.82)	0.37 (1.07)	.0263
Emergency department visit	1.47 (3.91)	0.59 (1.32)	.0006
Unscheduled physician office visit	7.94 (11.28)	5.95 (7.42)	.2144
Self-reported bed days	3.03 (20.80)	0.85 (4.80)	.0002
Self-reported restricted activity days	22.82 (71.76)	16.48 (49.11)	.3522

*Event rates are per 1000 patient days and are cumulative to the study's end.

costs by resource category, expressed as cost PPPM, is provided in **Table 3.**

Table 3. Treatment Costs

Event	Cost Per Patient Per Month, $		
	Glipizide	Rosiglitazone + Glipizide	Difference
Hospitalization	360.7	126.1	234.6
Emergency department visit	7.8	3.5	4.3
Physician visit	40.8	37.6	3.2
Prescription, study medication	11.0	98.6	(87.6)
Prescription, nonstudy medication	195.0	182.1	12.9
Lab tests	6.7	9.7	(3.0)
Supplies/self-monitoring	22.5	22.5	0
Total	645	480	164

Sensitivity Analysis

The distribution of cost estimates was skewed in the rosiglitazone-plus-glipizide and glipizide groups. To evaluate the impact of skewedness on cost estimates, a sensitivity analysis was performed by excluding patients with costs more than 2 standard deviations above or below the mean. A total of 10 outliers were identified: 6 in the rosiglitazone-plus-glipizide group (PPPM cost range $1294 to $3297) and 4 in the glipizide group (PPPM cost range $3734 to $9850). PPPM costs generated after the exclusion of outliers were $418 and $588 for the rosiglitazone-plus-glipizide and glipizide groups, respectively, resulting in PPPM cost savings of $170 in the combination-therapy group. The difference in cost PPPM between the 2 study groups before excluding the outliers was $165 [AU: 645 – 480 = 165] ($480 vs $645 cost PPPM in the rosiglitazone-plus-glipizide and glipizide groups, respectively). This indicates that the presence of outliers, while increasing PPPM values, did not have a significant impact on relative cost estimates and distribution.

DISCUSSION

Prospectively collected economic data demonstrating the effects of improved glycemic control are limited. This analysis of economic outcomes in the clinical-trial setting establishes a direction of effect and contributes to the ongoing efforts to show economic benefits of improved glycemic control.

The RESULT study is the first trial to prospectively assess resource utilization and estimate cost of care in older patients with type 2 diabetes treated with a thiazolidinedione, the newest and most expensive class of antidiabetic agents. Specifically, early addition of rosiglitazone to a sulfonylurea was compared with maximal dose titration of an inexpensive sulfonylurea. Patients were systematically and prospectively assessed for hospitalizations, ED visits, and physician office visits, as well as bed days and restricted activity days. A standard unit-cost method, which had been previously applied to estimate costs associated with prevention and treatment of type 2 diabetes,[14] was used to compare budget implications of each therapy. The method provides a common metric to sum the value of different categories of resources using approximate unit costs.

The results of the study indicate that despite greater medication costs, rosiglitazone-plus-glipizide therapy provided better clinical efficacy and reduced total healthcare resource utilization. The differences in favor of the rosiglitazone-plus-glipizide combination therapy appeared to be driven by decreased resource utilization in terms of hospitalizations and ED visits.

The lower utilization patterns for healthcare resources in the rosiglitazone-plus-glipizide group reflect significant economic benefits of the combination therapy. Rates of hospitalization and ED visits per 1000 patient days in the rosiglitazone-plus-glipizide group (0.37 ± 1.074 vs 0.59 ± 1.324, respectively), compared with those in the glipizide group (0.76 ± 1.816 vs 1.47 ± 3.905, respectively), clearly support the hypothesis that the combination therapy is associated with less intensive use of healthcare resources. In addition to the lower hospitalization rate in rosiglitazone-plus-glipizide group, the average length of stay per hospitalization in that group was significantly shorter than that in the progressive up-titrated glipizide group.

With clear indications of less intensive resource use in the rosiglitazone-plus-glipizide group, service costs were identified and assigned to the unique events within the trial to determine budgetary implications and compare the economic outcomes of both therapies. The favorable budget impact of rosiglitazone-plus-glipizide therapy due to lower resource utilization also was supported by the lower cost of services used in rosiglita-

zone-plus-glipizide group compared with the group receiving glipizide monotherapy. Hospitalization, ED, and physician office visit costs per person in rosiglitazone-plus-glipizide and glipizide groups ($2710 vs $6770, $75 vs $146, and $808 vs $766, respectively) suggest that the cost of healthcare services utilized was lower in the combination-therapy cohort, resulting in tangible savings for healthcare decision makers and payers, while ensuring quality and efficacious care for patients with diabetes. Adjusted for duration of therapy, lower PPPM hospitalization costs, ED visit costs, and physician office visit costs in the rosiglitazone-plus-glipizide, compared with the glipizide group, indicate decrease in the level of consumption of healthcare resources in the combination-therapy group. From the perspective of a healthcare decision maker, these differences demonstrate potential cost savings resulting from reduced healthcare utilization and support the early addition of a thiazolidinedione to sulfonylurea therapy.

It is worth noting that, although the focus of this analysis was the total direct treatment costs, combination therapy with rosiglitazone and a sulfonylurea may be associated with improvements in productivity, based on the significant differences in self-reported bed days (0.85 vs 3.03 per 1000 patient days; $P = .0002$). Applying a published rate for time lost from doing usual activity due to morbidity or mortality,[14] the estimated per-patient cost of bed days was $65 and $202 in the rosiglitazone-plus-glipizide and glipizide groups, respectively. The total indirect-cost estimates based on patient-reported bed days and restricted activity days were $1321 and $1722 per patient or $62 and $92 PPPM in the rosiglitazone-plus-glipizide and glipizide groups, respectively. Therefore, the combination therapy may be able to decrease not only the direct costs, but also the indirect costs associated with type 2 diabetes.

Although the differences in healthcare resource utilization cannot be directly attributed to the experimental treatments, the trial results demonstrate a strong association between rosiglitazone-plus-glipizide therapy and lower healthcare utilization. Lower use of healthcare services and decreased cost of care have been reported to be associated with improved glycemic control,[17,18] which was achieved by the rosiglitazone-plus-glipizide therapy. The early intervention with rosiglitazone to optimize long-term glycemic control was associated with substantial clinical and economic benefits and may present a more efficient alternative to the traditional dose escalation of a sulfonylurea.

The study limitations derive from the nature of self-reported healthcare utilization data. These data are subject to recall bias and were not independently reconciled with medical-record data because no subjects' medical records were available to verify the reasons for hospital admissions, ED visits, or physician office visits in either of the study arms.

CONCLUSION

This 2-year prospective study in older patients with type 2 diabetes demonstrated that treatment with a combination of rosiglitazone and a sulfonylurea may provide a health economic benefit through use of fewer healthcare resources compared with progressive dose titration of sulfonylurea monotherapy, even after accounting for the increase in treatment costs. In clinical practice, the earlier addition of rosiglitazone to a sulfonylurea in a patient with type 2 diabetes may substantially reduce the costs associated with managing the disease, in addition to providing improved glycemic control. Economic evaluations of therapeutic approaches and health policy should consider costs and side effects of treatment, and changes in health outcomes resulting from therapy.

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