

# Effect of early addition of rosiglitazone to sulphonylurea therapy in older type 2 diabetes patients (>60 years): the Rosiglitazone Early vs. SULphonylurea Titration (RESULT) study

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**Aim:** To compare the efficacy, safety and tolerability of adding rosiglitazone (RSG) vs. sulphonylurea (SU) dose escalation in older type 2 diabetes mellitus (T2DM) patients inadequately controlled on SU therapy.

**Methods:** A total of 227 T2DM patients from 48 centres in the USA and Canada, aged  $\geq 60$  years, were randomized to receive RSG (4 mg) or placebo once daily in combination with glipizide 10 mg twice daily for 2 years in a double-blind, parallel-group study. Previous SU monotherapy was  $\frac{1}{4}$  to  $\frac{1}{2}$  maximum recommended dose for  $\geq 2$  months prior to screening with fasting plasma glucose (FPG)  $\geq 7.0$  and  $\leq 13.9$  mmol/l. Treatment options were individualized, and escalation of study medication was specifically defined.

**Results:** Disease progression (time to reach confirmed FPG  $\geq 10$  mmol/l while on maximum doses of both glipizide and study medication or placebo) was reported in 28.7% of patients uptitrating SU plus placebo compared with only 2.0% taking RSG and SU combination ( $p < 0.0001$ ). RSG + SU significantly decreased HbA<sub>1c</sub>, FPG, insulin resistance, plasma free fatty acids and medical care utilization and improved treatment satisfaction compared with uptitrated SU.

**Conclusions:** Addition of RSG to SU in older T2DM patients significantly improved glycaemic control and reduced disease progression compared with uptitrated SU alone but without increasing hypoglycaemia. These benefits were associated with increased patient treatment satisfaction and reduced medical care utilization with regards to emergency room visits and length of hospitalization. Early addition of RSG is an effective treatment option for older T2DM patients inadequately controlled on submaximal SU monotherapy.

Keywords: early combination treatment, elderly subjects, glycaemic control, rosiglitazone, type 2 diabetes

Received 15 March 2005; returned for revision 2 June 2005; accepted 28 June 2005

## Introduction

Current guidelines emphasize the importance of achieving tight glycaemic targets in order to reduce the risk of complications. Unfortunately, conventional monotherapies such as sulphonylureas (SUs) and metformin are

generally unable to maintain glycaemic control in the long term [1]. The response to this continual loss of glycaemic control, which was associated with progressive loss of  $\beta$ -cell function in UK prospective diabetes study (UKPDS) [2], has often been to increase the dose of

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agent given in monotherapy. Despite studies demonstrating a flattening of the dose–response for SUs at half the maximal labelled dose [3] and that 50% of patients required polypharmacy after 3 years in UKPDS [1], high doses of monotherapy continue to be widely used in general clinical practice.

New approaches are required therefore in order to attain and maintain good glycaemic control over time and aggressive earlier introduction of combination therapy is being increasingly recommended over conventional stepwise strategies [4]. At the same time, management of elderly patients with type 2 diabetes mellitus (T2DM) involves special considerations, particularly with regard to the risk of drug-induced hypoglycaemia [5]. Here, we describe results from the Rosiglitazone Early vs. Sulphonylurea Titration (RESULT) Study. This is the longest (2 years), prospective, double-blind trial that challenges the conventional paradigm of dose escalation of SU monotherapy in older subjects with T2DM by comparing the addition of a thiazolidinedione rosiglitazone (RSG) to submaximal SU therapy.

## Methods

### Study Population

Male and female patients aged  $\geq 60$  years, with documented T2DM [6], who had been treated with submaximal SU monotherapy for  $\geq 3$  months prior to screening, were eligible for inclusion in the study. Patients must have been on one-quarter to one-half of the maximum-labelled SU dose for  $\geq 2$  months prior to screening with fasting plasma glucose (FPG)  $\geq 7.0$  and  $\leq 13.9$  mmol/l at randomization. Mean duration of diabetes was 6.8 years. Although patients with ischaemic heart disease (IHD) could be included in the study, those with severe or unstable angina, coronary insufficiency or congestive heart failure (NYHA class III/IV) were excluded.

### Study Design

Patients were recruited into this 2-year, randomized, double-blind, parallel group study from 48 North American centres. All subjects were converted to glipizide [10 mg BID (twice daily)] at study entry, then entered a 4-week run-in period (placebo and glipizide 10 mg BID). Thereafter, subjects were randomized to RSG 4 mg once daily (OD) in combination with glipizide 10 mg BID (RSG + SU) or RSG-matched placebo OD in combination with glipizide 10 mg BID (uptitrated SU). During the study period, physicians individualized

each patient's treatment using a systematic, stepwise titration schedule (fig. 1) and were encouraged to titrate medication to attain American Diabetes Association (ADA)-recommended targets.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, as amended in the Republic of South Africa (1996). The protocol and informed consent were approved by an Ethics Committee at each participating centre prior to study initiation. Each patient gave their written, informed consent prior to enrolment.

### Efficacy and Safety Measurements

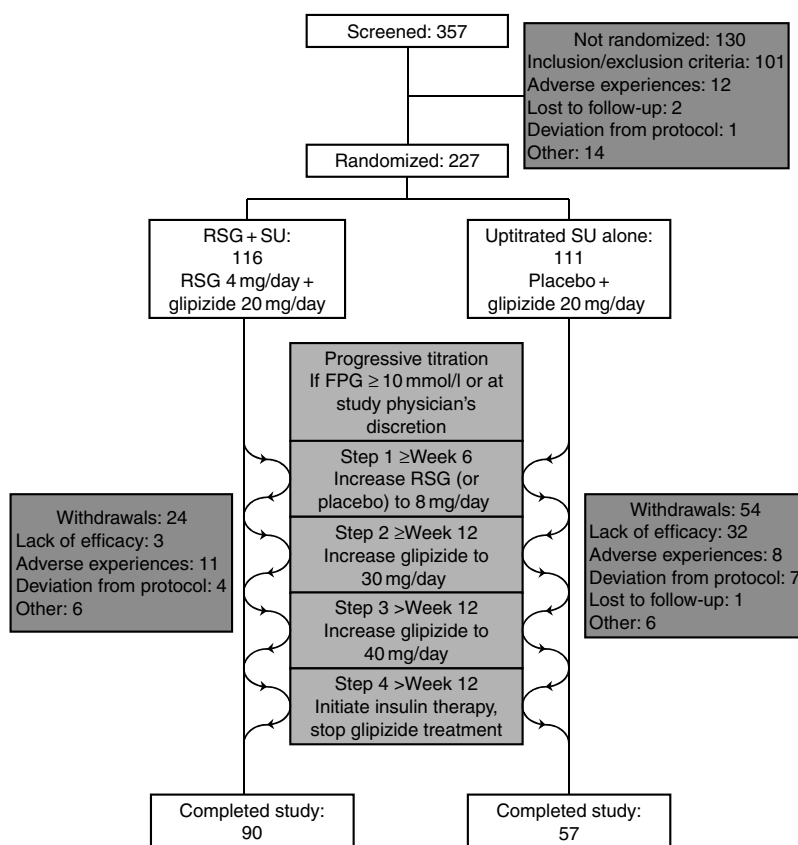
The primary endpoint was disease progression, defined as the time at which FPG rose to  $\geq 10$  mmol/l, confirmed by a second FPG test within 3 days, for a patient who had been titrated to maximum doses of SU and study medication (RSG or placebo).

Secondary endpoints included time to titration of maximum SU dose and changes from baseline to 24 months in FPG, HbA<sub>1c</sub> and free fatty acids (FFAs). Percentage change from baseline at 24 months in insulin resistance (for patients who did not begin insulin therapy) was estimated using the homeostasis model assessment (HOMA) [7]. Changes in responses from patient self-administered instruments [the Diabetes Treatment Satisfaction Questionnaire (DTSQ), the Short Form 36 (SF-36) and the Diabetes Symptom Checklist (DSC)] [8–11] were assessed from baseline to the end of the study. Self-reported medical care utilization [emergency room (ER) visits and hospitalizations] was prospectively collected at each study visit.

Safety and tolerability were assessed, including changes in physical examination, vital signs, body weight, clinical laboratory tests, adverse events (AEs) and electrocardiograms. Symptomatic hypoglycaemia data were collected through patient report of suspected symptoms and did not require confirmation or documentation of glucose levels.

### Assays and Calculations

All assays were performed at a central laboratory. FPG was measured using a hexokinase method (Olympus America Inc., Melville, NY, USA), and HbA<sub>1c</sub> was determined using the Bio-Rad Variant HbA<sub>1c</sub> assay (Hercules, CA, USA). Serum immunoreactive insulin was quantified using a double-antibody radioimmunoassay (Linco, St. Louis, MO, USA). Cholesterol was measured by an enzymatic method that hydrolyses cholesterol esterase to cholesterol and FFAs. High-density lipoprotein (HDL)



**Fig. 1** Study profile and titration regimen for patients randomized to receive rosiglitazone or placebo in combination with sulphonylurea. Although study medications could be adjusted at the discretion of the study physicians, step-wise uptitration to maximum approved doses of glipizide (40 mg/day) and rosiglitazone (8 mg/day, as divided doses) was required if fasting glucose (FPG)  $\geq 180$  mg/dl (10 mmol/l) and recommended if FPG exceeded 140 mg/dl (7.8 mmol/l). Patients who experienced disease progression could initiate insulin therapy and remain in the study. Eleven patients required insulin therapy (all from the uptitrated SU group) and of these, four withdrew early from the study. No patient in the rosiglitazone (RSG) + sulphonylurea (SU) group required insulin intervention.

cholesterol was measured using the direct HDL cholesterol methodology. Triglycerides were measured using an enzymatic method that hydrolyses the sample by lipase to FFAs and glycerol and measures colour formation. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedwald equation when triglyceride levels were  $<400$  mg/dl.

### Statistical Analysis

The primary efficacy population was the intent-to-treat (ITT) population, including all patients randomized to receive study medication who had at least one on-therapy value for an efficacy parameter. On-therapy data consisted of observations after baseline, and up to and including 1 day after the last dose of randomized study medication,

but not including data points collected more than 1 day after initiation of insulin therapy. The safety population comprised randomized patients who were dispensed study medication.

The 'time to event' endpoints were compared between treatment groups using a proportional hazard regression, with baseline HbA<sub>1c</sub> as a covariate. For the assessment of differences between treatment groups with regard to continuous variables, a repeated measures analysis incorporating on-therapy values at all time points and including the baseline value as a covariate was employed. Insulin resistance data were log-transformed prior to analysis. Hospitalizations and ER visits were assessed using a Poisson regression model, which included terms for treatment and baseline HbA<sub>1c</sub> and accounted for the duration of therapy. This trial was not

powered for the statistical analysis of safety data, which were analysed descriptively.

### Results

A total of 357 patients were screened for eligibility, with 227 patients randomized to double-blind medication, of whom 225 had at least one on therapy efficacy measurement and formed the ITT population (fig. 1).

Baseline demographics were similar between the groups (table 1). Mean baseline HbA<sub>1c</sub>, FPG and time since T2DM diagnosis were well matched between groups. Concomitant illnesses at baseline were typical of those in older T2DM patients and were similar in both treatment groups. Commonly reported concomitant conditions included hypertension (57% of randomized patients), dyslipidaemia (47%), IHD (16%), angina pectoris (9%) and oedema (10%). Nearly all patients (99%) were taking at least one concomitant medication, most commonly statins, thiazide diuretics, calcium channel blockers, nitrates and digoxin.

### Disease Progression

Twenty-seven of 110 SU-up-titrated patients (28.7%, adjusted for early withdrawals) compared with only

two of 115 patients in the RSG + SU group (2.0%, adjusted for early withdrawals) reached the primary endpoint of disease progression ( $p < 0.0001$ ; fig. 2). RSG + SU reduced the risk of losing glycaemic control by approximately 95% relative to up-titrated SU alone (hazard ratio 0.048,  $p < 0.0001$ ). An additional five patients in the up-titrated SU group and one patient in the RSG + SU group withdrew due to 'lack of efficacy'.

### Requirement for Titration of Maximum Permitted Doses

Among the RSG + SU patients, 51.3% (59/115) remained on RSG 4 mg/day plus the initial SU dose over the 2 years of the study. Only 11.3% (13/115) of the RSG + SU group required titration to the maximum SU dose compared with 48.1% (53/110) with up-titrated SU alone.

### Glycaemic Effects

FPG was reduced by a mean of 1.32 mmol/l ( $p < 0.0001$ ) from a baseline of 8.71 mmol/l over 104 weeks with RSG + SU. This compares with a significant increase of 0.78 mmol/l ( $p = 0.0010$ ) from baseline (8.84 mmol/l) with up-titrated SU alone. The difference between treatment groups was statistically significant ( $-2.09$  mmol/l,  $p < 0.0001$ ).

RSG + SU significantly decreased HbA<sub>1c</sub> by a mean of 0.65% from a baseline of 7.72% over 104 weeks ( $p < 0.0001$ ), whereas up-titrated SU alone produced no significant improvement from baseline ( $\Delta = +0.13\%$ , baseline = 7.65%,  $p = 0.1871$ ). The HbA<sub>1c</sub> reduction with RSG + SU was significantly different from up-titrated SU alone ( $-0.79\%$ ,  $p < 0.0001$ ). RSG + SU produced maximal improvements in HbA<sub>1c</sub> by 24 weeks that were sustained over the 2 years of the study, with a mean HbA<sub>1c</sub> of <7% at study end (fig. 3). Specifically, 50 and 32% of patients in the RSG + SU group achieved target HbA<sub>1c</sub> < 7% and  $\leq 6.5\%$ , respectively, compared with only 22 and 9% with up-titrated SU alone (fig. 3A).

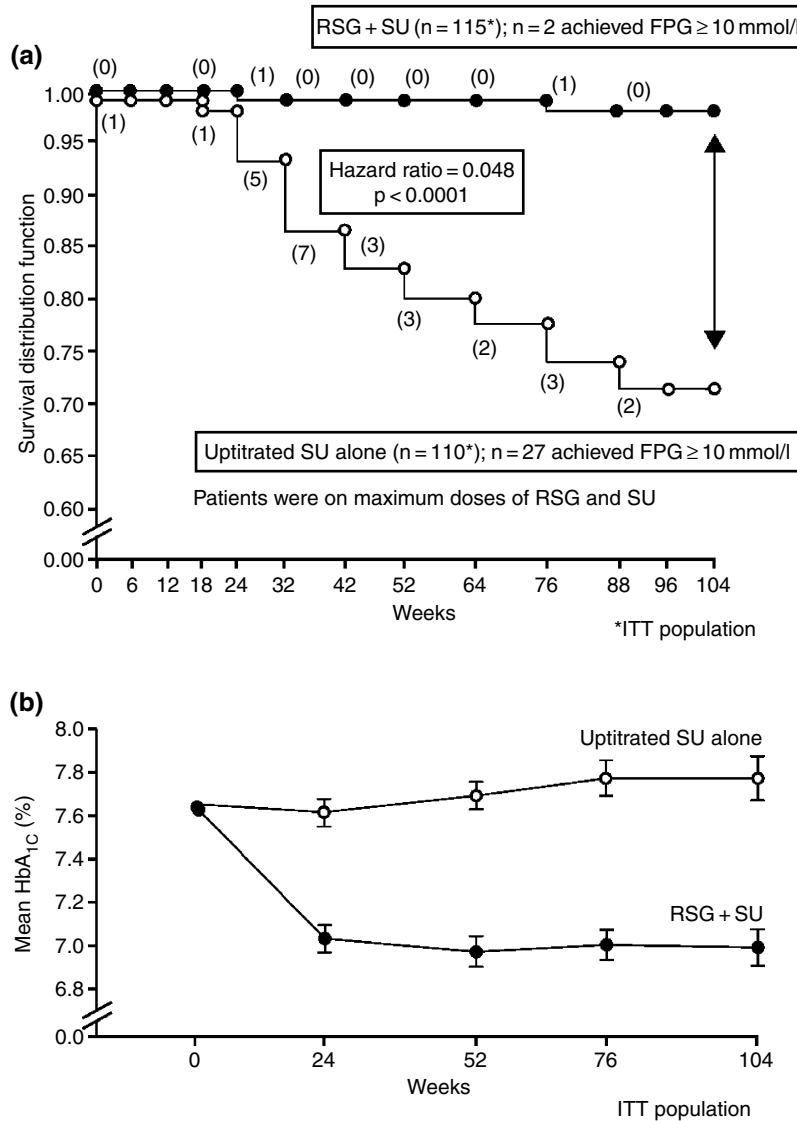
### Effects on Estimates of Insulin Resistance

RSG + SU decreased HOMA estimates of insulin resistance by 14% vs. baseline ( $p = 0.001$ ) compared with an increase of 18% with up-titrated SU alone ( $p = 0.0028$ ). The difference between the two treatment groups was statistically significant ( $p < 0.0001$ ). RSG + SU significantly decreased mean FFA by 2.037 mg/dl from baseline to week 104 (13.2% reduction from baseline;  $p = 0.0021$ ) compared with no significant change with

**Table 1** Baseline characteristics

| Parameter                                    | Treatment group<br>(all randomized population)  |                       |
|--|---|-----------------------|
|  | Up-titrated SU<br>alone (n = 111)               | RSG + SU<br>(n = 116) |
| Age (years)                                  |   |                       |
| $\geq 65$                                    | 64.5%   | 64.3%                 |
| $\geq 75$                                    | 29.1%   | 27.5%                 |
| Mean $\pm$ SD                                | 68.2 $\pm$ 6.3                                  | 68.7 $\pm$ 6.1        |
| Sex  |   |                       |
| Male   | 71.8%   | 74.8%                 |
| Body mass index (kg/m <sup>2</sup> )         |   |                       |
| $\geq 27$                                    | 72.7%   | 80.0%                 |
| Mean $\pm$ SD                                | 30.5 $\pm$ 4.9                                  | 30.2 $\pm$ 4.5        |
| Duration of diabetes (years since diagnosis) |   |                       |
| Mean $\pm$ SD                                | 6.8 $\pm$ 6.4                                   | 6.8 $\pm$ 5.3         |
| Parameter                                    | Treatment group<br>(intent-to-treat population) |                       |
|  | Up-titrated SU<br>alone (n = 110)               | RSG + SU<br>(n = 115) |
| HbA <sub>1c</sub> (%)                        |   |                       |
| Mean $\pm$ SD                                | 7.65 $\pm$ 0.99                                 | 7.72 $\pm$ 1.03       |
| FPG (mmol/l)                                 |   |                       |
| Mean $\pm$ SD                                | 8.84 $\pm$ 1.59                                 | 8.71 $\pm$ 1.19       |

RSG, rosiglitazone; SU, sulphonylurea



Estimated means and standard errors from a repeated measures analysis adjusted to a common baseline and incorporating on-therapy values at all time points

**Fig. 2** Effect of rosiglitazone added to sulphonylurea on (a) disease progression and (b) HbA<sub>1c</sub>. RSG, rosiglitazone; SU, sulphonylurea.

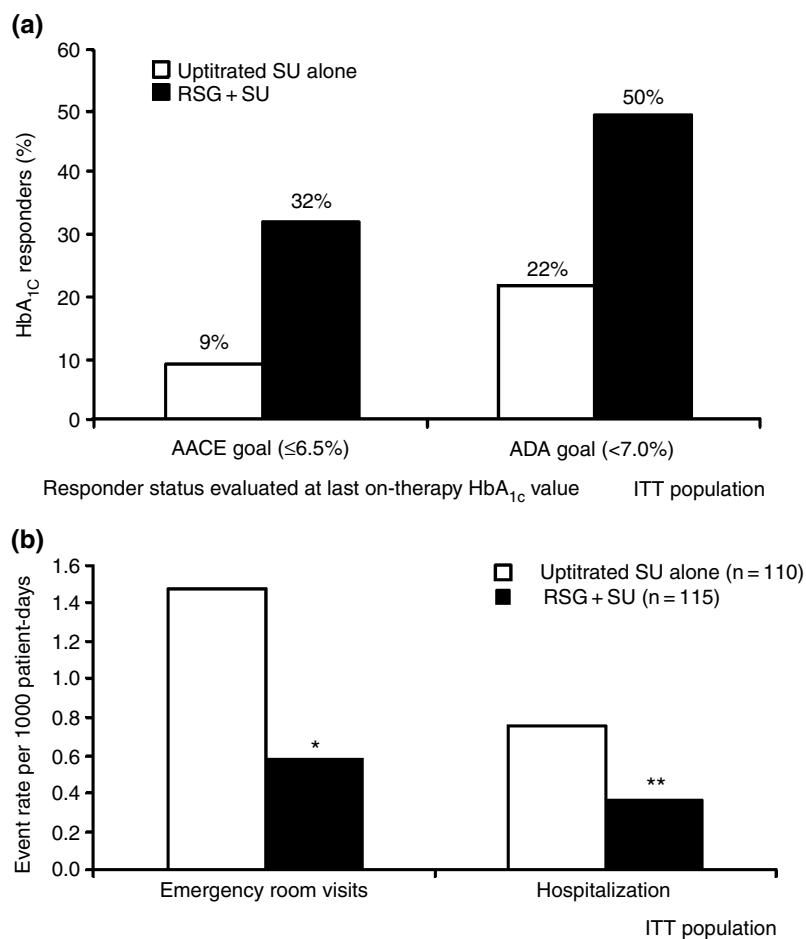
uptitrated SU alone (0.077 mg/dl,  $p = 0.9232$ ). The reduction with RSG + SU represented a significant decrease of 2.114 mg/dl ( $p = 0.0416$ ) compared with uptitrated SU alone.

**Safety and Tolerability**

Withdrawal due to deterioration of glycaemic control occurred more frequently with uptitrated SU alone, resulting in a different mean duration of exposure to medication in the two groups (644 days with

RSG + SU compared with 560 days with uptitrated SU alone). Despite this, the overall incidence of AEs was comparable between the groups. Only two on-therapy deaths were reported, both in the uptitrated SU alone group and of cardiovascular origin. The incidence of on-therapy AEs leading to withdrawal was similar in both groups: 11 (9.5%) with RSG + SU and 8 (7.2%) with uptitrated SU alone.

The incidence of symptomatic hypoglycaemia was similar in the two treatment groups (32% for RSG + SU, 27% for uptitrated SU alone). Mean body



**Fig. 3** Effect of rosiglitazone added to sulphonylurea on (a) percentage of HbA<sub>1c</sub> responders and (b) emergency room visits and hospitalizations. \**p* < 0.001 for number of emergency room visits; \*\**p* < 0.05 for number of hospitalizations. RSG, rosiglitazone; SU, sulphonylurea.

weight increased by 4.3 kg over 104 weeks with RSG + SU compared with a slight decrease (−1.2 kg) with uptitrated SU alone. Oedema was more frequent with RSG + SU (23 vs. 9%), but all cases were mild-to-moderate, and only two patients withdrew due to oedema-related AEs. There was no difference in the incidence of congestive heart failure between groups (RSG + SU 4/116 patients; uptitrated SU alone 3/111 patients).

Mean changes in HDL-cholesterol and LDL-cholesterol at week 104 compared with baseline were small and broadly comparable between treatment groups (HDL-cholesterol +2.7 and +1.6%, LDL-cholesterol +3.3 and −1.3% for RSG + SU and uptitrated SU alone, respectively). Total cholesterol was slightly reduced with uptitrated SU alone (−1.7%) but increased with RSG + SU (+6.2%). However, the total cholesterol : HDL and LDL : HDL cholesterol ratios

were unchanged in both treatment groups. Triglycerides increased with RSG + SU (+9.5%) but were reduced with uptitrated SU alone (−5.4%).

All hepatic enzyme parameters (AST, ALT, total bilirubin and alkaline phosphatase) were reduced with RSG + SU at week 104 compared with baseline. There were no hepatic enzymes greater than three times the upper limit of normal at any visit in either treatment group. The incidence of anaemia was low and comparable between treatments, and there were no withdrawals due to anaemia.

#### Health Care Utilization and Quality of Life

Compared with uptitrated SU alone, RSG + SU was associated with significantly fewer ER visits (*p* = 0.0006) and hospitalizations (*p* = 0.0263; fig. 3b). Mean length of stay per hospitalization was

significantly lower with RSG + SU compared with uptitrated SU alone (4.48 days vs. 7.41 days,  $p < 0.001$ ).

Approximately half of the hospitalizations in each treatment group (RSG + SU 10/19 patients; uptitrated SU alone 12/25 patients) were due to cardiac-related events. Five patients in the uptitrated SU alone group experienced chest pain that resulted in hospitalization but were not classified as cardiac-related events. One patient in the RSG + SU group was admitted to the hospital due to hypoglycaemia and one due to oedema. One patient in the RSG + SU group and two patients in the uptitrated SU alone group were hospitalized due to congestive heart failure. Proportionately fewer patients had ER visits due to cardiac-related events with RSG + SU as compared with uptitrated SU alone.

### Effect on Quality of Life

At study completion, patients in the RSG + SU group had a significantly higher DTSQ satisfaction score than at baseline (1.15 point increase;  $p < 0.05$ ), while treatment satisfaction decreased by 1.61 points in the uptitrated SU alone group ( $p < 0.01$ ). The difference between treatments was statistically significant ( $p < 0.001$ ).

While there were no statistically significant differences between the two groups, SF-36 component scores in the uptitrated SU alone group were significantly lower in the physical health (-2.43 points) and mental health (-1.71 points) components at study end than in the self-reported scores at the start of the study, suggesting a deterioration in health. There were no significant changes in SF-36 scores in the RSG + SU group or DSC scores in either group.

### Discussion

This study was designed to evaluate in older patients with T2DM the efficacy, durability, safety and tolerability of early combination of RSG with glipizide compared with glipizide monotherapy while allowing the conventional dose escalation of glipizide in both treatment groups.

The difference between the two treatment groups in terms of disease progression (see fig. 2) indicates that glycaemic control was more durable with RSG + SU. Furthermore, with RSG + SU, only 3 patients withdrew from the study due to lack of efficacy compared with 32 patients with uptitrated SU alone. Improvements in FPG with RSG + SU and the 0.8% difference in HbA<sub>1c</sub> between treatment groups were both clinically and statistically significant and were durable for the 2-year

study duration. ADA HbA<sub>1c</sub> goals were achieved and sustained in significantly more patients with RSG + SU compared with uptitrated SU alone.

The data demonstrating a dose-response relationship for SUs are limited [12]. Indeed, while the recommended maximum total daily dose of glipizide is 40 mg, increasing the glipizide dose above 10 mg/day has been found to provide little or no additional improvement in glycaemic control [3]. This study provides further rationale for the early introduction of combination therapy rather than up titration of the SU dose. The early addition of RSG was also SU-sparing. Importantly, and indicative of the efficacy of their treatment with combination therapy at 2 years, the majority of patients in the RSG + SU group remained on the starting dose (4 mg) of RSG and did not require further titration of either RSG or glipizide.

Insulin resistance and endogenous hyperinsulinaemia have been associated with increased risk of cardiovascular disease [13]. A significant and sustained decrease in insulin resistance, as assessed using HOMA, was noted in the RSG + SU group compared with the uptitrated SU alone group providing additional evidence of the potential benefits of this combination treatment. In addition, analyses have shown that RSG + SU significantly improved  $\beta$ -cell function [14]. These changes may be related to the significant reductions in FFAs seen in the RSG + SU group because elevated FFA levels are associated with insulin resistance and impaired insulin secretion [15,16].

Treatment with RSG + SU had a favourable safety profile and was generally well tolerated. Comparable numbers of patients reported AEs in the two treatment groups despite the exposure to medication being significantly greater with RSG + SU. Intensive glycaemic control has been found to increase the risk of hypoglycaemia especially with SUs [17]. Despite tighter glycaemic control with RSG + SU treatment, the incidence of hypoglycaemia was not increased. This is likely to be due to the mechanism by which thiazolidinediones improve glycaemic control, that is, by reducing insulin resistance [18,19].

Weight gain is a known class effect of thiazolidinediones and is due in part to improved glycaemic control. Importantly, it is associated with an increase in subcutaneous adipose deposits rather than abdominal fat deposits [20]. Oedema is a class effect of the thiazolidinediones and occurred more frequently with RSG + SU than uptitrated SU alone. All cases were mild to moderate and only two patients withdrew due to oedema in the RSG + SU group. Importantly, the rates of congestive heart failure and other cardiac events were

similar between the treatment groups. This suggests that the oedema observed did not increase cardiac risk in this predominantly older patient cohort over a 2-year period.

The RESULT study was the first study with a thiazolidinedione in which information and data on medical care utilization was prospectively obtained, as described by Herman *et al.* [21]. Treatment with RSG + SU was associated with significantly fewer ER visits and hospitalizations compared with uptitrated SU alone. The explanation for these consistent observations is not clear. It could represent a non-specific effect of improved glucose control or potential benefits owing to the action of RSG to improve insulin sensitivity with its associated conditions and risks. However, it could also represent potential negative consequences of SU dose escalation.

### Conclusions

This 2-year prospective study, the longest double-blind, placebo-controlled study in T2DM, demonstrated clearly that the early addition of RSG to a submaximal dose of SU was significantly more effective at improving and sustaining glycaemic control in individuals with T2DM than dose escalation of SU alone. In clinical practice, the addition of RSG to a submaximal dose of a conventionally used SU is expected to provide excellent control of hyperglycaemia with a predictable safety profile.

### Acknowledgements

The following are the RESULT Investigators. **Canada:** Ronnie Aronson, MD; Gordon Bailey, MD; Makram Boctor, MD; Philip Hardin, MD; Carol Joyce, MD; Andre Nadeau, MD; Wilson Rodger, MD; Hugh Tildesley, MD; Vincent Woo, MD; Jean Francois Yale, MD. **United States:** Lawrence Alwine, DO; Alan Braun, MD; Geoffrey Burgess, MD; Harold Kennedy Cathcart, DO; George Chao, MD; Andrian Dobs, MD; Bruce Clayton Douglas, MD; (formerly Beverly Phillipson, MD); Paul Edgar, MD; Charles Eil, MD; J. Gary Evans, MD; Joseph Fallon, MD; John Gilbert Jr., MD; Barry Goldstein, MD; George Groch, MD; Burritt Haag, MD; Michael Harris, MD; Scott Heatley, MD; Priscilla Hollander, MD; Eric Horst, MD; Sean Hurley, MD; Andrian James, MD; Harvey Katzeff, MD; William Kaye, MD; Danny Keiller, MD; Thomas Knecht, MD; Daniel Lorber, MD; Kathryn Jean Lucas, MD; Jennifer Marks, MD; Umesh Masharani, MRCP (UK); Mark McClanahan, MD; James McKenney, PharmD; Bernard

Michlin, MD; David Miller, DO; Joel Neutel, MD; Fernando Ovalle, MD; Xavier Pi-Sunyer, MD; Nicholas Mezitis, MD; Mark Radbill, DO; Sid Rosenblatt, MD; Julio Rosenstock, MD; Graham Scott, MD; John Seibel, MD; William Smith, MD; James Snyder, MD; Alan Steckel, MD; (formerly Stasia Miaszkiewicz), MD; Roger Steinbrenner, MD; Charles Stotler, MD; Allen Sussman, MD; Barbara Troupin, MD; (formerly Stuart Weiss, MD); Jacob Vadakekalam, MD; Aaron Vinik, MD; Peter Winkle, MD; Jose Yanez, MD; (formerly Michael Doyle, MD); Franklin Zieve, MD.

We thank Leanne Strow and Dahong Yu at GlaxoSmithKline for assistance with data analysis.

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