

# RAPID APPRAISAL

**Name of Trial:** Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy (ADOPT – A Diabetes Outcome Progression Trial).

**Reference:** Kahn SE et al. *New England Journal of Medicine* 2006;355:2427-43

**Question:** Which oral antidiabetic drug provides the best long-term (4-year) glycaemic control when initiated in treatment naïve patients?

**Summary:** ADOPT provides insufficient evidence on which to recommend a change in current practice due to the established efficacy of metformin and glibenclamide and the greater cost of rosiglitazone. Therefore metformin should remain the first-choice antidiabetic drug for the majority of newly diagnosed type 2 diabetic patients with a sulphonylurea a suitable second-choice agent. ADOPT demonstrated significantly better glycaemic control with fewer patients progressing to a fasting glucose level > 10 mmol/L after 5 years with rosiglitazone monotherapy compared to metformin or glibenclamide alone. However the majority of patients did not reach this end-point regardless of treatment (66% with glibenclamide, 79% with metformin and 85% with rosiglitazone). Rosiglitazone was associated with greater LDL-cholesterol levels, use of lipid-lowering therapy, and weight gain; effects which are especially undesirable in diabetic patients.

## ***Did the study ask a clearly focussed question?***

**Yes.** The study evaluated glibenclamide (glyburide), metformin, and rosiglitazone as initial treatment for recently diagnosed ( $\leq 3$  years) type 2 diabetic patients.<sup>1</sup> Patients were eligible if their fasting plasma glucose level was between 7 and 13 mmol/L at screening and between 7 and 10 mmol/L at randomisation, with the only prior permitted intervention being lifestyle management.<sup>2,3</sup> There were some limited permitted exceptions (prior insulin use for gestational diabetes, short term ( $\leq 1$  month) insulin use during hospitalisation, and  $\leq 1$  month use of any antidiabetic drug  $\geq 2$  months prior to screening).<sup>3</sup> Patients were excluded if they had hepatic disease, renal impairment, a history of lactic acidosis, unstable or severe angina, congestive heart failure, or uncontrolled hypertension.<sup>1</sup> Patients were predominantly male (58%) and white (88%), with a mean age of 57 years (range 30–75). The mean body mass index was 32.2 and 15% were smokers. The mean glycosylated haemoglobin level (HbA<sub>1c</sub>) was 7.4%.<sup>2</sup>

Between 2000 and 2002, 4,360 patients were randomised at centres in North America and Europe to treatment with glibenclamide (n = 1,447), metformin (n = 1,455) or rosiglitazone (n = 1,458).<sup>1</sup> Patients were treated for a median of four years (maximum six).<sup>1</sup> The primary outcome measure was the time from randomisation to monotherapy treatment failure, defined as a fasting plasma glucose level > 10 mmol/L on consecutive testing after  $\geq 6$  weeks of treatment at the maximum permitted or tolerated dose.<sup>1</sup> Secondary outcome measures included the time from randomisation to a fasting plasma glucose level > 7.8 mmol/L (for patients entered into the study with a fasting plasma glucose  $\leq 7.8$  mmol/L),

levels of fasting plasma glucose for all patients, HbA<sub>1c</sub>, and body weight.<sup>1</sup>

## ***Was the study design appropriate?***

**Yes.** The study was a randomised, multi-centre, international, double-blind trial. The study was supported by GlaxoSmithKline, manufacturers of rosiglitazone (Avandia®).<sup>1,2,3</sup>

## ***Were participants appropriately allocated to intervention and control groups?***

**Yes.** Patients were randomly assigned to one of the three treatment groups with stratification for patient gender. The patient groups were well matched with respect to demographic and clinical parameters with no significant differences between groups.<sup>1</sup>

## ***Were participants, staff and study personnel 'blind' to participants study group?***

**Yes.** All study drugs were supplied in identical capsules with patients and investigators blinded to the actual treatment.<sup>1</sup> In patients for whom a confirmatory fasting plasma glucose test result was not available (e.g. absent test, patient withdrawal, or additional glucose-lowering drug treatment) an independent and treatment-blind adjudication committee determined whether the primary outcome had been reached. This committee determined treatment failure (i.e. the primary outcome measure) in 170 patients. Independent and treatment-blind cardiologists reviewed all serious adverse events including the emergence of congestive heart failure.<sup>1</sup>

## ***Were all of the participants who entered into the trial accounted for at its conclusion?***

**No.** Efficacy analysis excluded nine randomised patients who did not receive study medication and 224 who withdrew before the first scheduled

efficacy evaluation (in total, 110 assigned to glibenclamide, 58 to metformin, and 65 to rosiglitazone). Efficacy was therefore based upon 1,337 assigned to glibenclamide, 1,397 to metformin, and 1,393 to rosiglitazone. Although analysis was not conducted on a strictly intention-to-treat basis, the post-randomisation withdrawal rate is low enough (5.3%) to be unlikely to affect the results. After a median follow-up of four years the withdrawal rates for each group were 44%, 38%, and 37% respectively. The most common reason for withdrawal from all groups was adverse events. Safety analysis was based upon 1,441, 1,454, and 1,456 patients respectively.<sup>1</sup>

***Were the participants in all groups followed up and data collected in the same way?***

**Yes.** There were no differences in the follow-up of each group. Patients were initiated on either glibenclamide 2.5 mg, metformin 500 mg, or rosiglitazone 4 mg, once daily. The dose was increased at each visit if the fasting plasma glucose was  $\geq 7.8$  mmol/L to a maximum daily dose of glibenclamide 15 mg (7.5 mg twice daily), metformin 2 g (1 g twice daily), or rosiglitazone 8 mg (4 mg twice daily).<sup>1</sup> Fasting plasma glucose and HbA<sub>1c</sub> were measured about every two months in the first year and thereafter every three months.<sup>3</sup>

***Was the study large enough?***

**Yes.** The study originally planned to recruit 3,600 patients to provide 90% power to detect a 30% relative risk reduction of treatment failure for rosiglitazone compared to metformin or glibenclamide at a significance level of  $p = 0.05$ . Because of the greater than expected withdrawal rate and a lower than expected number of primary outcomes, the protocol was amended to increase patient numbers to 4,182 and extend follow-up to four years with a revised power estimate of 83%.<sup>1</sup>

***How are the results presented and what is the main result?***

The results are presented as a Kaplan-Meier estimate of the cumulative incidence of monotherapy failure (defined as a fasting plasma glucose level  $> 10$  mmol/L on consecutive testing after  $\geq 6$  weeks of treatment at the maximum permitted or tolerated dose) at five years, as well as the actual results obtained with associated risk-reductions and 95% confidence intervals (95% CI). Actual treatment failure is expressed as a rate per 100 patient-years.<sup>1</sup>

Monotherapy failed in 311 patients treated with glibenclamide (7.5 per 100 patient-years), 207 treated with metformin (4.3 per 100 patient-years) and 143 treated with rosiglitazone (2.9 per 100 patient-years). The Kaplan-Meier cumulative incidences of treatment failure at five years were 34%, 21% and 15% respectively. The relative risk reduction of treatment failure with rosiglitazone compared to glibenclamide was 63% (95% CI 55 to 70), and compared to metformin was 32% (95% CI 15 to 45),  $p < 0.001$  for both comparisons.<sup>1</sup>

With respect to secondary outcomes, the rate of progression to a fasting plasma glucose level  $> 7.8$  mmol/L closely matched the overall results with a relative risk reduction of treatment failure with rosiglitazone compared with glibenclamide of 62% ( $p < 0.001$ ), and with metformin of 34% ( $p = 0.002$ ). The glibenclamide group experienced annual increases of 0.31 mmol/L in the fasting plasma glucose level and 0.24% in the HbA<sub>1c</sub> level ( $p < 0.001$  compared to rosiglitazone for both outcomes). The same outcomes for metformin were 0.15 mmol/L and 0.14% respectively ( $p < 0.001$  compared to rosiglitazone for both outcomes), and those for rosiglitazone were 0.04 mmol/L and 0.07% respectively. At the four-year evaluation, 40% of 1,456 rosiglitazone patients had a HbA<sub>1c</sub>  $< 7\%$  compared with 36% of 1,454 metformin patients ( $p = 0.03$ ) and 26% of 1,441 glibenclamide patients ( $p < 0.001$ ). After five years, patient mean weight changed from baseline by 1.6 kg in the glibenclamide group (95% CI 1.0 to 2.2), -2.9 kg in the metformin group (95% CI -3.4 to -2.3), and 4.8 kg in the rosiglitazone group (95% CI 4.3 to 5.3).<sup>1</sup>

***How safe were the regimens?***

About 92% of patients in each treatment group reported an adverse event and about 21 to 24% of these were classified as serious. Compared to metformin, rosiglitazone was associated with significantly less gastrointestinal adverse events (38% vs. 23%,  $p \leq 0.01$ ) but more weight gain (7% vs. 1%,  $p \leq 0.01$ ) and greater oedema (14% vs. 7%,  $p \leq 0.01$ ). Compared to glibenclamide, rosiglitazone was associated with significantly less hypoglycaemia (39% vs. 10%,  $p \leq 0.01$ ) but more weight gain (7% vs. 3%,  $p \leq 0.01$ ) and more oedema (14% vs. 9%,  $p \leq 0.01$ ). Rosiglitazone was associated with non-significant increases in the incidence of investigator-reported congestive heart failure, with 22 cases in the rosiglitazone group, 19 with metformin and 9 with glibenclamide (for rosiglitazone compared to metformin  $p = 0.52$ , and compared to glibenclamide  $p = 0.05$ ). The independent cardiologists adjudged nine cases of true congestive heart failure in the rosiglitazone group, eight with metformin and four with glibenclamide (for rosiglitazone compared to glibenclamide,  $p = 0.26$ ). Rosiglitazone was also associated with a significant decrease in the haematocrit with a level of 40.6% compared to 42.7% with glibenclamide and 41.6% with metformin ( $p \leq 0.01$  for both comparisons). Rosiglitazone was associated with significantly higher levels of low-density lipoprotein cholesterol than either metformin ( $p < 0.001$ ) or glibenclamide ( $p = 0.008$ ), and consequently a greater use of lipid-lowering therapy (actual values were not published). An addendum to the published study identified a higher risk of fractures in female patients receiving rosiglitazone ( $p \leq 0.01$ ).<sup>1</sup>

### **How precise are the results?**

The study was well designed and robust. It is unfortunate that since its inception HbA<sub>1c</sub> has overtaken the fasting plasma glucose level as the preferred measure of glycaemic control for diabetic patients, thus detracting importance from the primary outcome measure. Nonetheless, with such large patient numbers and an adequate length of follow-up, meaningful results have been produced. The results can be considered precise however caution is recommended in interpreting HbA<sub>1c</sub> levels as the study was not powered to detect differences in this outcome.

### **Can the results be applied to the local population?**

**Yes.** Although about half of the trial population was recruited from North America and half from Europe with patients from North America being significantly younger, more obese, more likely to be female, and a greater proportion from non-white ethnic groups.<sup>2</sup> These factors are themselves associated with different profiles in type 2 diabetes.

### **Which oral antidiabetic drug provides the best long-term (4-year) glycaemic control when initiated in treatment naïve patients?**

The results of the ADOPT study indicate that rosiglitazone monotherapy can result in prolonged glycaemic control compared to metformin or glibenclamide alone, but only at a 6% absolute benefit over metformin in the time to a fasting plasma glucose level > 10 mmol/L and 0.1% in terms of HbA<sub>1c</sub>. After five years in the metformin group 79% of patients maintained glycaemic control according to the study definition, 66% did do so with glibenclamide, and 85% with rosiglitazone. The number needed to treat (NNT) with rosiglitazone in preference to metformin to prevent one patient progressing to a fasting plasma glucose level of > 10 mmol/L after five years is 17. At the maximum doses used in the study, the cost associated with this NNT is £51,700 at current prices.<sup>4</sup>

Given the greater cost of rosiglitazone compared to metformin and glibenclamide ADOPT provides insufficient evidence on which to recommend a change in current practice and therefore metformin should remain the first-choice antidiabetic drug for newly diagnosed type 2 diabetic patients with a sulphonylurea as a suitable second-choice agent.<sup>5</sup>

## **REFERENCES**

1. Kahn SE et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *New England Journal of Medicine* 2006;355:2427-43 (RCT)
2. Viberti G et al. A diabetes outcome progression trial (ADOPT): baseline characteristics of type 2 diabetic patients in North America and Europe. *Diabetic Medicine* 2006;23:1289-94
3. Viberti G et al. A diabetes outcome progression trial (ADOPT). *Diabetes Care* 2002;25:1737-43

4. NHS dictionary of medicines and devices. <http://dmd.medicines.org.uk/DesktopDefault.aspx?tabid=3> (accessed on 13/12/2006)
5. National Institute for Health and Clinical Excellence. Management of type 2 diabetes: management of blood glucose. September 2002. (G)

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