

ADOPT: Are all hypoglycemic agents the same?

Abstract

In the United Kingdom Prospective Diabetes Study(UKPDS), patients with type 2 diabetes assigned to metformin, sulfonylureas or insulin treatment showed a progressive loss of glycemic control over the study period of over 10 years (1). This was attributed in part to beta-cell dysfunction and to the lack of aggressive use of combination therapy with oral agents and/or insulin. Beta-cell function at diagnosis of diabetes in the UKPDS was already <50% at the time of diagnosis (2), and none of the treatments used in the study were able to prevent or delay the progressive deterioration of beta-cell function (3). On average, beta-cell function declines by 1% per year with normal aging compared to 4% per year in diabetes.

Thiazolidinediones have previously been shown to preserve beta-cell mass in experimental animals and to be associated with improved beta-cell function in humans as measured by the homeostasis model assessment (HOMA).

ADOPT is an international, long-term, double-masked, randomized clinical trial to evaluate whether the thiazolidinedione rosiglitazone provides more durable and safe glycemic control than metformin or glyburide (4).

The primary study end-point is time from randomization to monotherapy failure, defined as fasting plasma glucose greater than 10 mmol/L following a minimum 6 weeks' treatment at the maximum tolerated dose of study medication.

Monotherapy failure at 5 years was 15% with rosiglitazone, 21% with metformin and 34% with glyburide. This represents a relative risk reduction of 32% for rosiglitazone compared to metformin and 63% compared to glyburide (P<0.001).

Glyburide was associated with lower risk of cardiovascular events including CHF compared to rosiglitazone (P<0.05), and the risk associated with metformin was similar to that with rosiglitazone.

Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide but with fewer GI events than metformin and with less hypoglycemia than glyburide (P<0.001 for all comparisons).

References:

1. Turner, RC et al. UKPDS 49. JAMA 1999; 281: 2005
2. Holman, RR. Diabetes Res Clin Pract 1998; 4 (Suppl): S21-5
3. UKPDS (16). Diabetes 1995; 44:1249
4. Khan, S.E. et al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. N Engl J Med 2006; 355: 2427.

ADOPT: Are all hypoglycemic agents the same?

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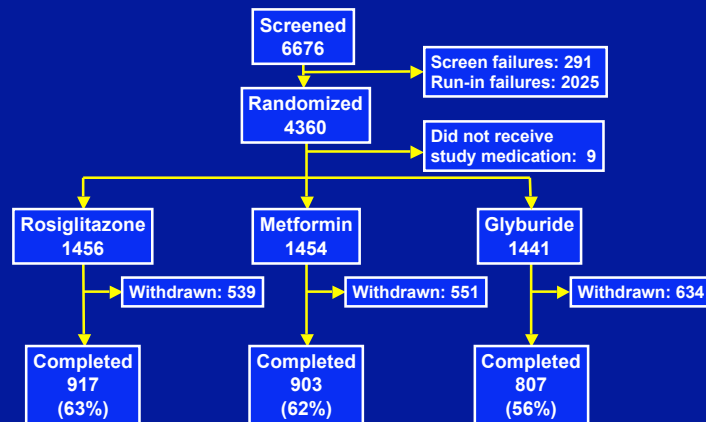
ADOPT

A Diabetes Outcomes Progression Trial

An international, long-term, double-masked, randomised clinical trial to evaluate whether the thiazolidinedione rosiglitazone provides more durable and safe glycaemic control than the biguanide metformin or the sulphonylurea glyburide (glibenclamide)

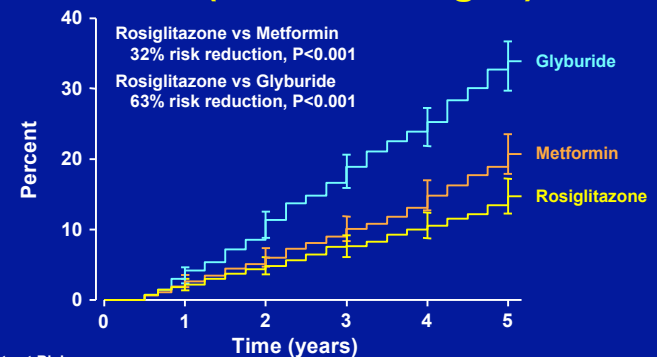
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Patient Disposition



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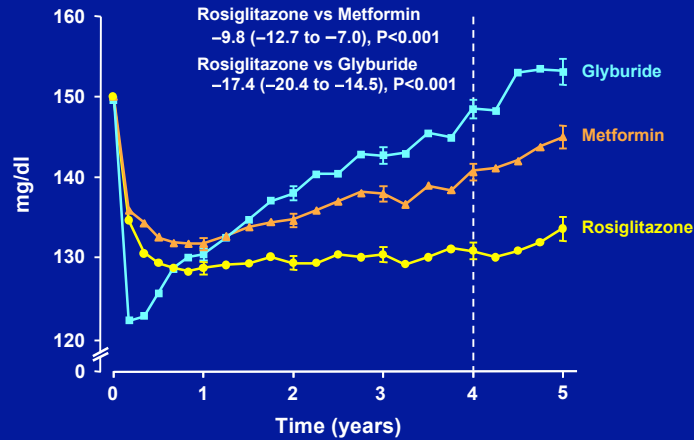
Cumulative Incidence of Monotherapy Failure (FPG >180 mg/dl)



| Patients at Risk | 0 | 1 | 2 | 3 | 4 | 5 |
|------------------|------|------|------|-----|-----|-----|
| Rosiglitazone | 1393 | 1207 | 1078 | 957 | 844 | 324 |
| Metformin | 1397 | 1205 | 1076 | 950 | 818 | 311 |
| Glyburide | 1337 | 1114 | 958 | 781 | 617 | 218 |

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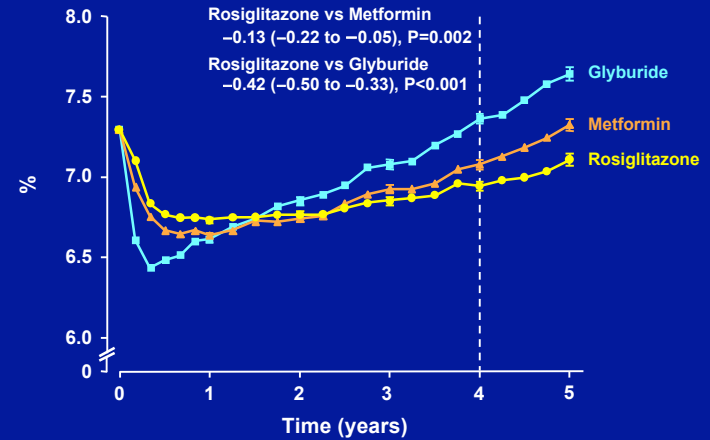
Fasting Plasma Glucose Over Time



ADAPT

HbA1c Over Time

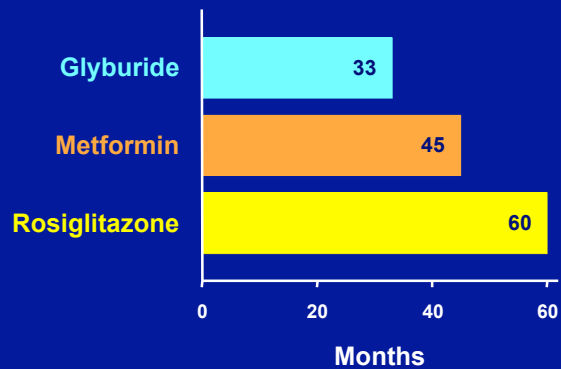
(Excluding patients who failed primary end-point)



ADAPT

Durability of Glycaemic Control: Time to Mean HbA_{1c} >7%

(Patients still in the study FPG<180 mg/dl, 10 mmol/L)



ADAPT

Congestive Heart Failure

| | Rosiglitazone (N = 1456) | Metformin (N = 1454) | Glyburide (N = 1441) |
|-------------------------------|-----------------------------|-------------------------|-------------------------|
| Adverse events, n (%) | 22 (1.5%) | 19 (1.3%) | 9 (0.6%) |
| Serious adverse events, n (%) | 12 (0.8%) | 12 (0.8%) | 3 (0.2%) |
| Cardiologist review, n (%) | 9 (0.6%) | 8 (0.6%) | 4 (0.3%) |

P<0.05 vs. rosiglitazone

ADAPT

Other Adverse Events

(While on monotherapy i.e. before failing the 1ry end-point)

| | Rosiglitazone (N = 1456) | Metformin (N = 1454) | Glyburide (N = 1441) |
|--|-----------------------------|-------------------------|-------------------------|
| Gastrointestinal, n (%) | 335 (23%) | 557 (38%) | 316 (22%) |
| Weight gain, n (%) <small>(complaint by patient)</small> | 100 (7%) | 18 (1%) | 47 (3%) |
| Hypoglycaemia, n (%) <small>(patient reported) (severe hypoglycemia was not captured)</small> | 142 (10%) | 168 (12%) | 557 (39%) |
| Oedema, n (%) | 205 (14%) | 104 (7%) | 123 (9%) |

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P<0.05 vs. rosiglitazone

Answer from ADOPT

Does initial monotherapy with the thiazolidinedione rosiglitazone slow the progression of hyperglycaemia compared to the biguanide metformin or the sulphonylurea glyburide?

✓ Yes

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Rosiglitazone vs. Metformin

Overall, rosiglitazone was more effective than metformin (32% risk reduction of monotherapy failure)

Sub-group analysis showed that this effect was more pronounced in:

- Older patients (≥ 50 years)
- More obese patients (waist circumference > 110 cm)

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Rosiglitazone vs. Glyburide

Overall, rosiglitazone was more effective than glyburide (63% risk reduction of monotherapy failure)

Sub-group analysis showed that this effect was more pronounced in:

- Older patients (≥ 50 years)
- Women
- More obese patients (BMI ≥ 30 kg/m²)

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Adverse Events

- Rosiglitazone was associated with weight gain and oedema, and in women, fractures
- Metformin was associated with adverse gastrointestinal events
- Glyburide was associated with hypoglycaemia and weight gain
- Rosiglitazone and metformin had a similar risk of cardiovascular events. Glyburide had a lower risk of cardiovascular events than rosiglitazone

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Limitation

- The proportion of patients who withdrew from the study was high
 - Rosiglitazone 37%
 - Metformin 38%
 - Glyburide 44%
- But
 - The characteristics of patients who withdrew were similar among groups
 - Sensitivity analyses showed that withdrawals did not appear to bias efficacy results

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Clinical Implications

- The progressive hyperglycaemia of type 2 diabetes can be slowed
- Rosiglitazone was most effective, probably due to its positive effects on both insulin sensitivity and beta-cell function
- Use of rosiglitazone early in the course of the disease is preferable to the use of glyburide
- Use of rosiglitazone as initial monotherapy in type 2 diabetes requires a full appreciation of its efficacy, adverse event profile and cost

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