

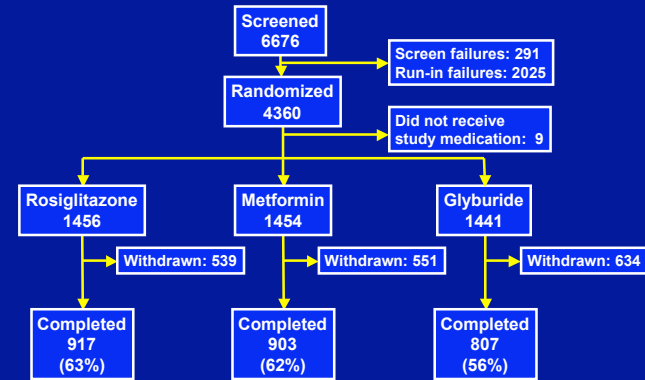
ADOPT

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)

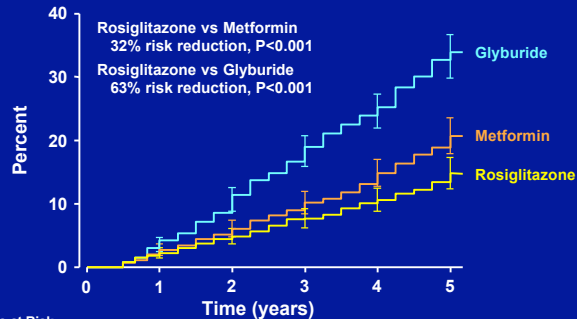
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Patient Disposition



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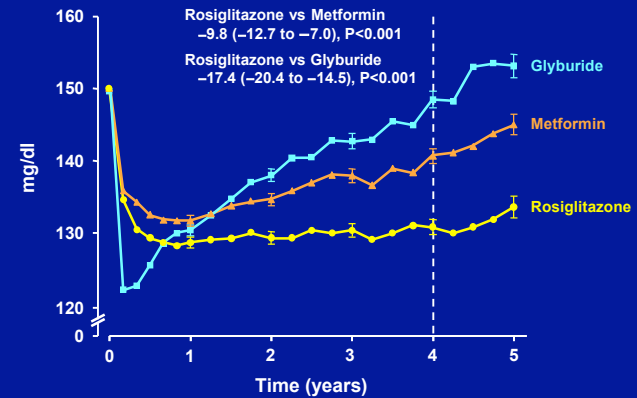
Cumulative Incidence of Monotherapy Failure (FPG >180 mg/dl)



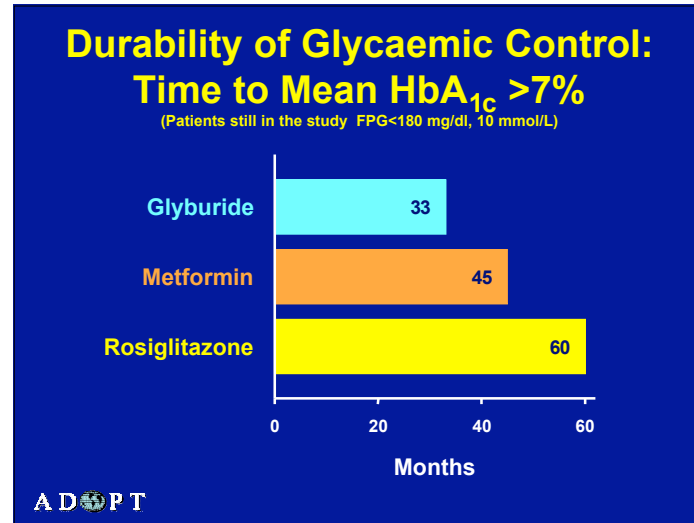
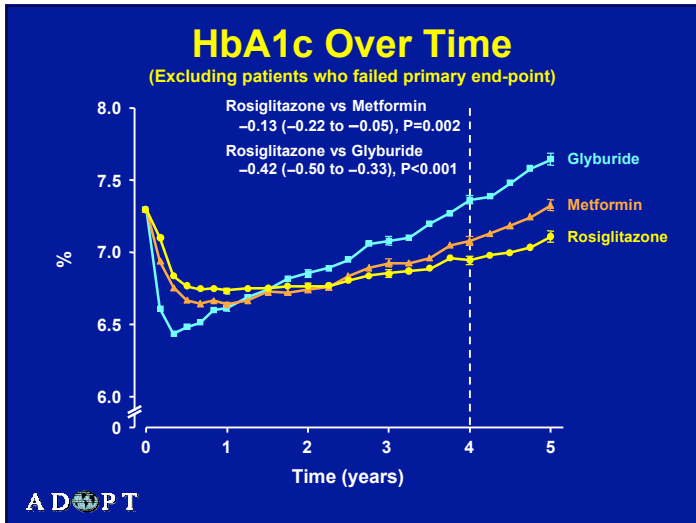
Patients at Risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

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Fasting Plasma Glucose Over Time



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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

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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 (%) (complaint by patient)	100 (7%)	18 (1%)	47 (3%)
Hypoglycaemia, n (%) (patient reported) (severe hypoglycemia was not captured)	142 (10%)	168 (12%)	557 (39%)
Oedema, n (%)	205 (14%)	104 (7%)	123 (9%)

P<0.05 vs. rosiglitazone

ADAPT

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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BOTTOM LINE

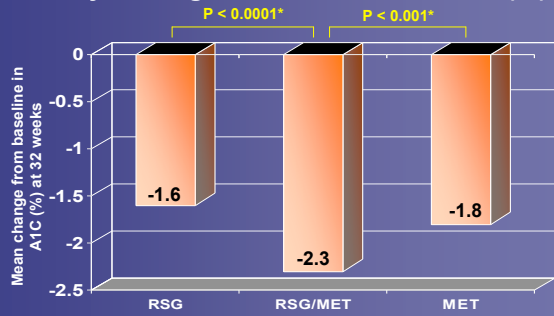
- Some drugs ARE better than others in achieving longer-term glucose control
- Some drugs are safer especially when assessing hypoglycemia risks
- Earlier use of combination therapies may be required
- We can reach established glucose targets
- **JUST DO IT**

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The ADOPT study raises interesting clinical questions:

- Should rosiglitazone now be considered as initial monotherapy as part of the algorithm for treating Type 2 diabetes?
- Should rosiglitazone be given at the time of diagnosis of Type 2 diabetes?
- Does the ADOPT data provide greater emphasis to the 007 diabetes study that suggests early combination therapy may provide added advantages in achieving glucose targets and reducing the risks of vascular complications?

Combination Metformin/TZD Therapy 007 Study: Change from Baseline in A1C (%)

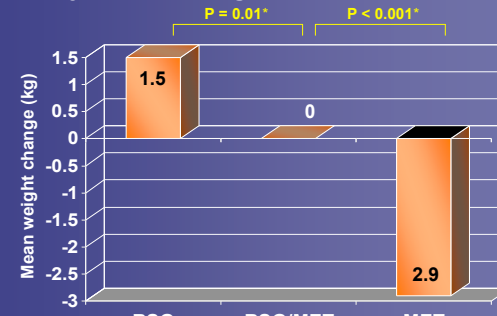


ITT with LOCF

Baseline: n=155 8.8% n=152 8.9% n=150 8.8%

*P-value reflects difference from model-adjusted change based on ANCOVA: Change = baseline + sex + country + treatment
Rosenstock J, et al. *Diabetes Obes Metab* 2006;8:650-60.

Combination Metformin/TZD Therapy 007 Study: Mean Change from Baseline in Weight



ITT with LOCF

Baseline: n = 136 92.3 kg n = 136 93.3 kg n = 123 91.5 kg

*P-value reflects difference from model-adjusted change based on ANCOVA: Change = baseline + sex + country + treatment

Rosenstock J, et al. *Diabetes Obes Metab* 2006;8:650-60.