

Aggressive Interventions: From prediabetes to diabetes - The role of Rosiglitazone

Abstract

In my presentation I plan to review studies related to early aggressive intervention in the prevention and treatment of diabetes. Prevention of progression of impaired glucose tolerance (IGT) to diabetes employed life-style interventions and antihyperglycemic agents. The DREAM study was the first diabetes prevention study to enrol people with impaired fasting glucose (IFG) and / or IGT. Rosiglitazone provided relative risk reduction of 60% compared to placebo.

Adoption of early combination therapy in patients with new onset diabetes and significant elevation in A1C resulted in better glycemic control and more patients reaching treatment targets. Studies 007 and 004 will be briefly reviewed.

A comparison between the durability of different oral antihyperglycemic agents in drug naive patients in the AFOPT study will be presented. Rosiglitazone was found to be more durable than metformin and glyburide.

1. Khan, S.E. et al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. *N Engl J Med* 2006; 355: 2427.
2. DREAM study ADOPT study. *Lancet* 2006; 368: 1096
3. Rosenstock, J et al. *Diabetes, Obesity and Metabolism* 2006; 8(6):650-660.
4. Rosenstock, J et al. *Diabetes, Obesity and Metabolism* 2006; 8(6):643-649.

Aggressive Interventions: from pre-diabetes to diabetes- The role of rosiglitazone

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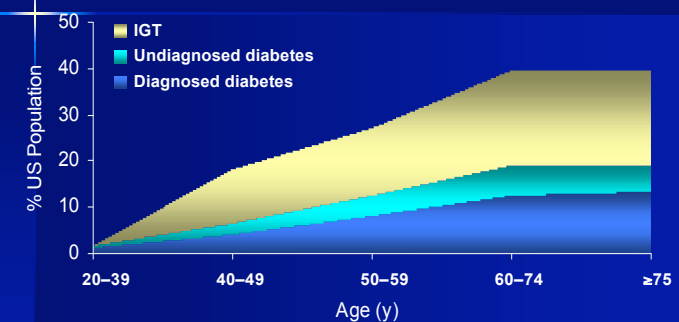
Duality of interest

- I received research grants, travel grants, consulting fees and speaking honoraria from GSK (makers of rosiglitazone) and several other pharmaceutical companies.

Outline

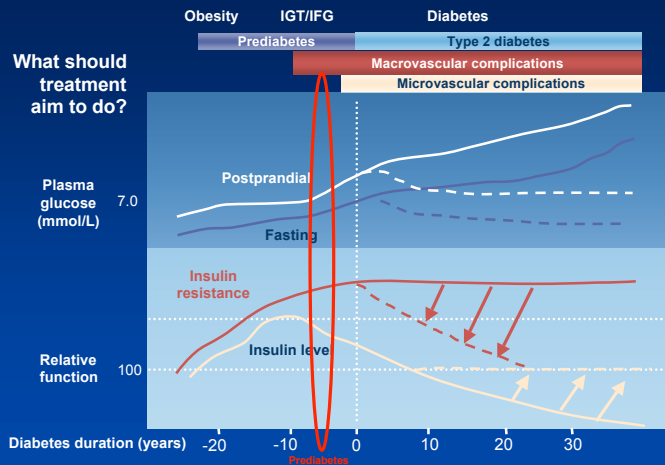
- Characteristics of rosiglitazone
- Interventions to prevent type 2 diabetes
- Durability of glycemic control with different oral antihyperglycemic agents

Prevalence of Diabetes and Impaired Glucose Tolerance (IGT)*



*IGT prevalence for 20- to 39-year olds was not reported and is shown here as 0; IGT prevalence for ≥75-year olds was not reported and is shown here as equal to that for 60- to 74-year olds. Data from Harris MI et al. *Diabetes Care*. 1998;21:518-524.

Clinical Rationale: Earlier Intervention



Adapted from Bergenstal RM et al. In: *Endocrinology*. 4th ed. 2001.

Diagnosis of prediabetes & Diabetes

- Who to screen?
 - Age >40 or earlier in high-risk patient
- How to screen?
 - FPG: If <5.6 re-screen in 1 yr
 - FPG: >7 mmol/L (X2): diagnose diabetes
 - FPG 5.6-6.9: do 2-h OGTT

Glucose Tolerance Categories

FPG		2-h PG in a 75-g OGTT	
Diabetes Mellitus*		Diabetes Mellitus*	
Impaired Fasting Glucose (IFG)	7.0 mmol/L	Impaired Glucose Tolerance (IGT)	11.1 mmol/L
Normal	6.1 mmol/L**	Normal	7.8 mmol/L

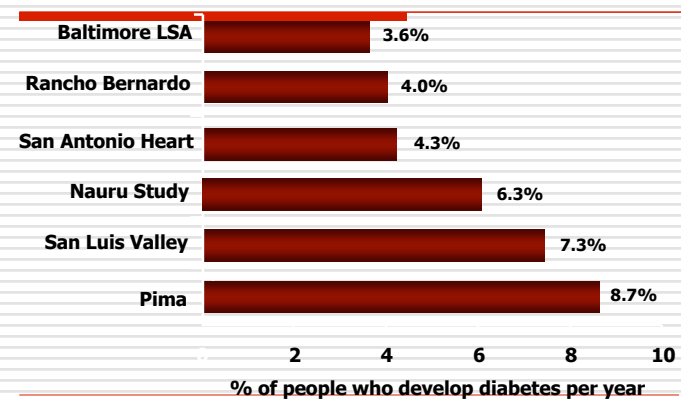
*For the diagnosis of diabetes, a confirmatory laboratory glucose test (a FPG, casual PG, or a 2-hour PG in a 75-g OGTT) must be done in all cases on another day in the absence of unequivocal metabolic decompensation

**ADA defines IFG as FPG 5.6–6.9 mmol/L

PG: plasma glucose; OGTT: oral glucose tolerance test

CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2003; 27(Suppl 2):S1-S152. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003; 26:3160-67.

Rate of Conversion per Year to Type 2 Diabetes in Persons With IGT (F/U 2-27 years, n=177-693)



Edelstein SL et al. *Diabetes* 1997;46:701-710.

Interventions to reduce insulin resistance & enhance islet –cell function

- Decrease insulin resistance:
 - Weight loss
 - Physical activity
 - Insulin sensitizers
- Enhance islet-cell function (decrease islet –cell death):
 - Insulin sensitizers
 - Incretins
 - Decrease FFA and glucose levels
 - Interleukin-1 inhibitors
 - Insulin treatment?

Intervention Studies for Diabetes Prevention: Risk Reduction and Number Needed To Treat

Study	Intervention	RRR (%)	NNT	NNT for 3y
Da Qing ¹ (n = 577)	Diet	31	4 for 6 y	8
	Physical exercise	46	4 for 6 y	8
	Diet and exercise	42	5 for 6 y	10
Finnish DPS ² (n = 522)	Diet and exercise	58	8 for 4 y	10
DPP ³ (n = 3,234)	Lifestyle intervention	58	7 for 3 y	7
	Metformin	31	14 for 3 y	14
	Troglitazone	75	15 for 0.9 y	5
TRIPOD ⁴ (n = 236)	Troglitazone	55	6 for 2.5 y	5
STOP-NIDDM ⁵ (n = 1,429)	Acarbose	25	10 for 3.3 y	11

TRIPOD: Troglitazone in Prevention of Diabetes; STOP-NIDDM: Study to Prevent Non-insulin Dependent Diabetes Mellitus; RRR: relative risk reduction; NNT: number needed to treat

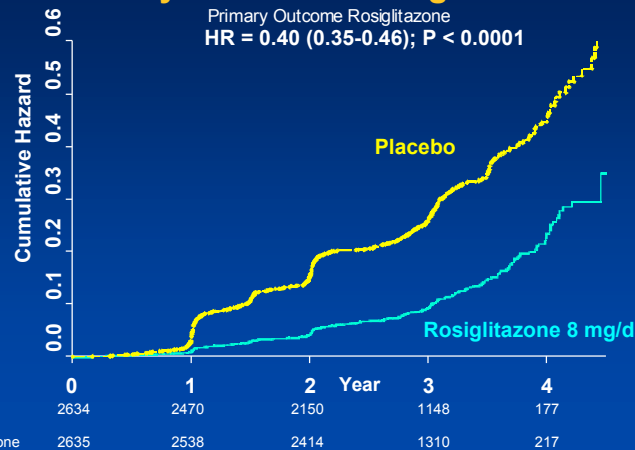
1. Pan XR, et al. *Diabetes Care* 1997; 20:537-44. 2. Tuomilehto J, et al. *N Engl J Med* 2001; 344:1340-50. 3. Knowler WC, et al. *N Engl J Med* 2002; 346:393-403. 4. Buchanan TA, et al. *Diabetes* 2002; 51:2796-803. 5. Chiasson JL, et al. *Lancet* 2002; 359:2072-7.

DREAM

(Diabetes REduction Assessment with ramipril and rosiglitazone Medication)

Primary Outcome: Rosiglitazone

Primary Outcome Rosiglitazone
HR = 0.40 (0.35-0.46); P < 0.0001

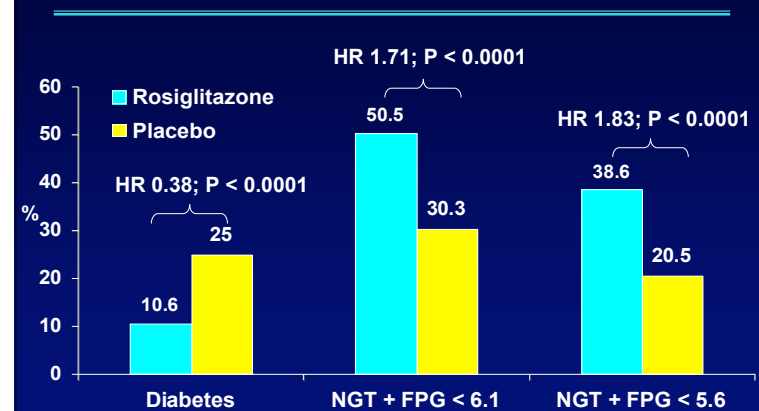


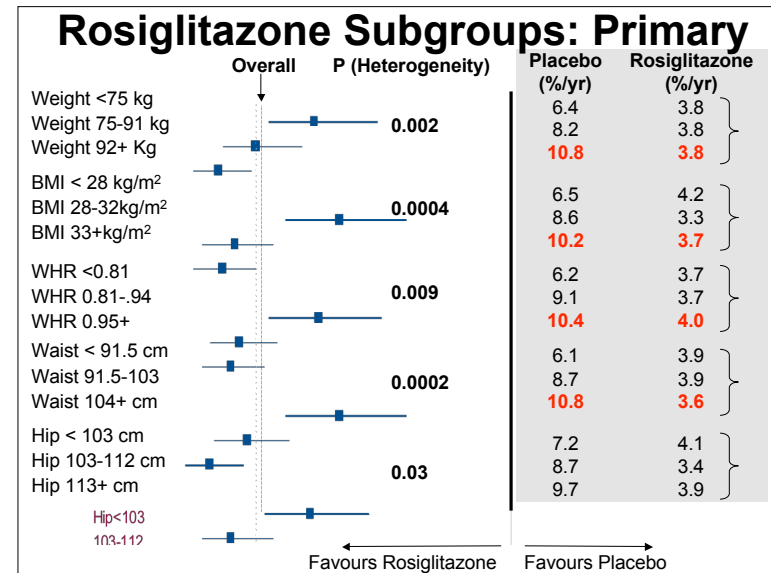
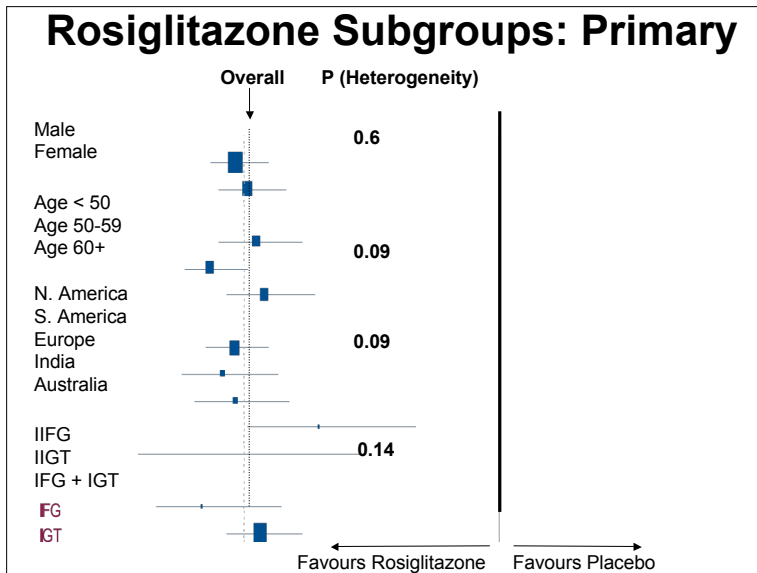
The DREAM Trial Investigators. *Lancet* 2006; 368:1096-105.

DREAM

(Rosiglitazone 8 mg/day Vs. placebo for 3 years)

Effect on Glucose Category





DREAM

Summary & Conclusions: Rosiglitazone

- Slight increase in the risk of CHF
- For every 1000 people treated with rosiglitazone for ~ 3 years, 144 cases of DM will be prevented with an excess of ~ 4 cases of CHF**

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DREAM ^{6,7} (n = 5,269)	Rosiglitazone	62	7 for 3 y	7
	Ramipril	9 (NS)	NS	NS

1. Pan XR, et al. *Diabetes Care* 1997; 20:537-44. 2. Tuomilehto J, et al. *N Engl J Med* 2001; 344:1340-50. 3. Knowler WC, et al. *N Engl J Med* 2002; 346:393-403. 4. Buchanan TA, et al. *Diabetes* 2002; 51:2796-803. 5. Chiasson JL, et al. *Lancet* 2002; 359:2072-7. 6. The DREAM Trial Investigators. *Lancet* 2006; 368:1096-105. 7. The DREAM Trial Investigators. *N Engl J Med* 2006; 355.

Glycemic Targets

	A1C (%)	Fasting / Premeal (mmol/L)	2-h PPG (mmol/L)
Target (for most patients)	≤ 7	4–7	5–10
Normal range (if achievable safely)	≤ 6	4–6	5–8

Treatment goals and strategies must be tailored to the patient, with consideration given to individual risk factors

Timely adjustments to and/or additions of oral antihyperglycemic agents and/or insulin should be made to attain target A1C within 6 to 12 months

CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2003; 27(Suppl 2):S1-S152.

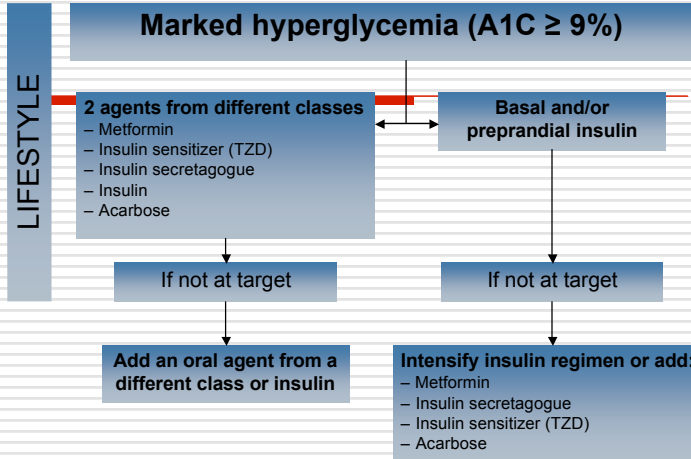
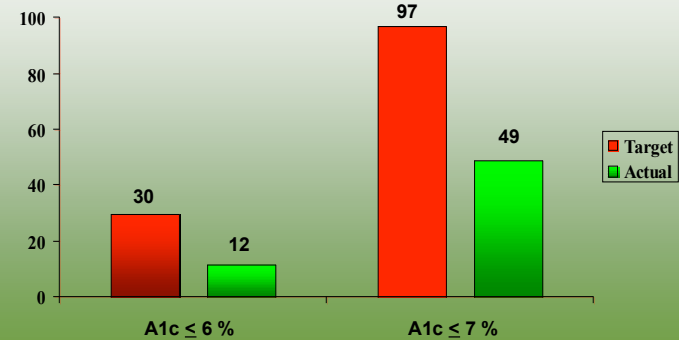


Chart Review

A1c Perceived Target Vs Actual



% of Patients

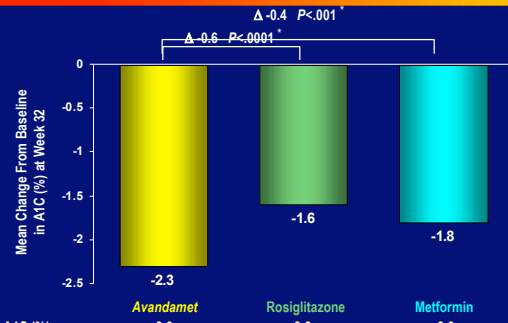


CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2003; 27(Suppl 2):S1-S152.

Evidence that Early Combination Therapy results in Better Glucose Control (Compared to monotherapy)

- Avandamet studies 007 & 004
- Combination of Metformin & SU

Avandamet Provided Superior Reductions in A1C (007)

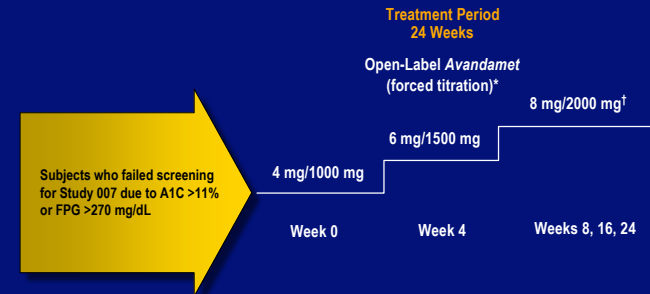


Baseline A1C (%)	8.9	8.8	8.8
n=	152	155	150

Intent to treat with LOCF.
* P value reflects difference from model-adjusted change based on ANCOVA.

Rosenstock J et al. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. *Diabetes, Obesity and Metabolism* 2006; 8(6):650-660.

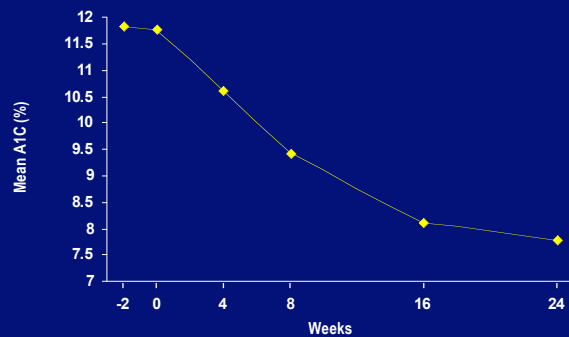
Overview of Study Design: Open-Label Study



* Unless tolerability issues arose, subjects were up-titrated in 2 mg/500 mg increments at 4 week intervals up to a maximum daily dose of 8 mg/2000 mg.
† Subjects were withdrawn for insufficient therapeutic effect if they had been on Avandamet 8 mg/2000 mg for at least 4 weeks and had a FPG >240 mg/dL.

Rosenstock J et al. Improvement in glycaemic control with rosiglitazone/metformin fixed-dose combination therapy in patients with type 2 diabetes with very poor glycaemic control. *Diabetes, Obesity and Metabolism* 2006; 8(6):643-649.

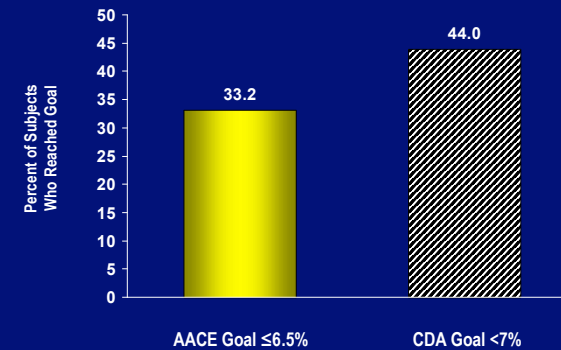
Avandamet Provided a Substantial Reduction in A1C Over 24 Weeks



All enrolled subjects with LOCF.

Rosenstock J et al. Improvement in glycaemic control with rosiglitazone/metformin fixed-dose combination therapy in patients with type 2 diabetes with very poor glycaemic control. *Diabetes, Obesity and Metabolism* 2006; 8(6):643-649.

44% of Subjects Achieved an A1C of <7%



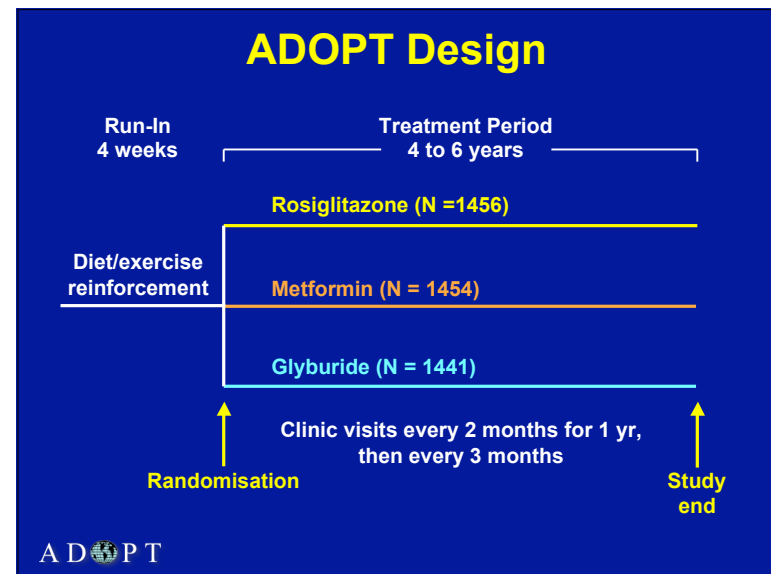
All enrolled subjects with LOCF (n=184).

Rosenstock J et al. Improvement in glycaemic control with rosiglitazone/metformin fixed-dose combination therapy in patients with type 2 diabetes with very poor glycaemic control. *Diabetes, Obesity and Metabolism* 2006; 8(6):643-649.

ADOPT

A Diabetes Outcome Progression Trial

Which oral agent will control glycemia the longest?

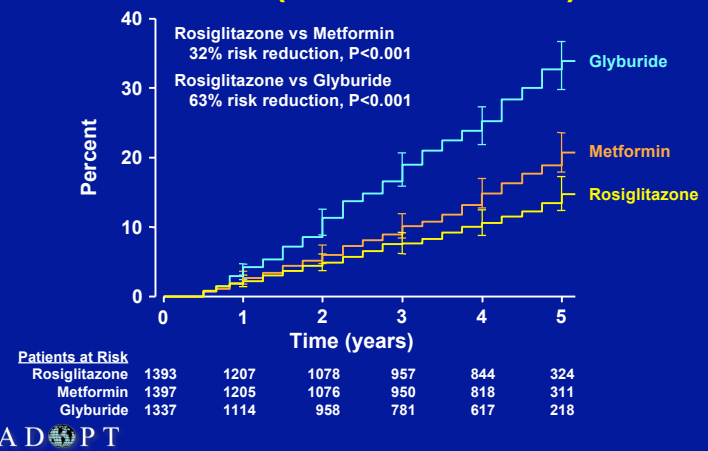


Rationale for more durability of glycemic control with rosiglitazone

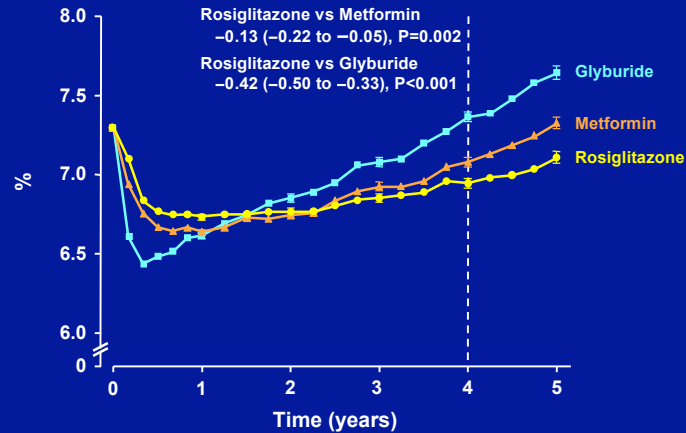
- Less insulin resistance decreases demand on Beta-cell insulin secretion
- Decreased FFA decreases lipotoxicity of Beta-cells
- Decreased apoptosis of Beta-cells seen in animal studies
- Previous shorter studies showing more durability of glycemic control

ADOPT

Cumulative Incidence of Monotherapy Failure (FPG >10 mol/L)

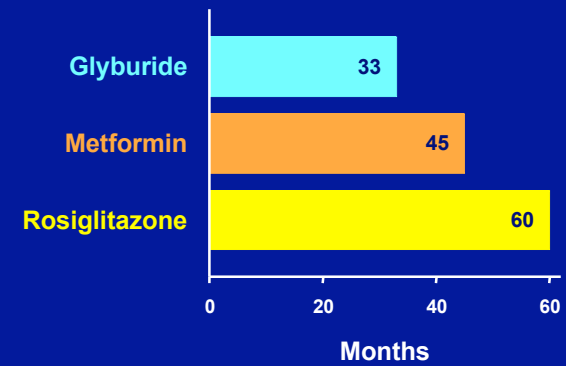


HbA1c Over Time



A D O P T

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



A D O P T

Vascular Serious Adverse Events: Investigator Reported

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Cardiovascular disease, n (%)	49 (3.4%)	46 (3.2%)	26 (1.8%)
Myocardial infarction			
Fatal, n (%)	2 (0.1%)	2 (0.1%)	3 (0.2%)
Non-fatal, n (%)	22 (1.5%)	18 (1.2%)	11 (0.8%)
CHF, n (%)	12 (0.8%)	12 (0.8%)	3 (0.2%)
Stroke, n (%)	13 (0.9%)	17 (1.2%)	12 (0.8%)
Peripheral vascular disease, n (%)	7 (0.5%)	6 (0.4%)	4 (0.3%)

P<0.05 vs. rosiglitazone

A D O P T

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

A D O P T

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%)

ADOPT

P<0.05 vs. rosiglitazone

Fractures

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Men , n (%)	32 (4.0%)	29 (3.4%)	28 (3.4%)
Women , n (%)	60 (9.3%)	30 (5.1%)	21 (3.5%)
Upper limb, n (%)	22 (3.4%)	10 (1.7%)	9 (1.5%)
Lower limb , n (%)	36 (5.6%)	18 (3.1%)	8 (1.3%)
Hip, n (%)	2 (0.3%)	2 (0.3%)	0 (0.0%)
Spine, n (%)	1 (0.2%)	1 (0.2%)	1 (0.2%)

ADOPT

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

ADOPT

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

ADOPT

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

A D  P T

Conclusions

▼ Early intervention at the pre-diabetes stage:

- Can be accomplished by lifestyle intervention or medications
- Rosiglitazone decreases the risk of progression from IFG &/ or IGT to DM by 60%, more than any other medication
- Decreases the burden of diabetes
- Will possibly decrease diabetes complications

▼ Early aggressive glycemic control in type 2 diabetes (together with treatment of other risk factors):

- Results in attaining treatment targets in more patients
- Rosiglitazone monotherapy resulted in more durable glycemic control