SLOWING DISEASE PROGRESSION IN TYPE 2 DIABETES: LATEST ADVANCES

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UKPDS: progressive hyperglycemia on monotherapy in type 2 diabetes

Adapted from UKPDS 34. *Lancet* 1998; 352:854–865.

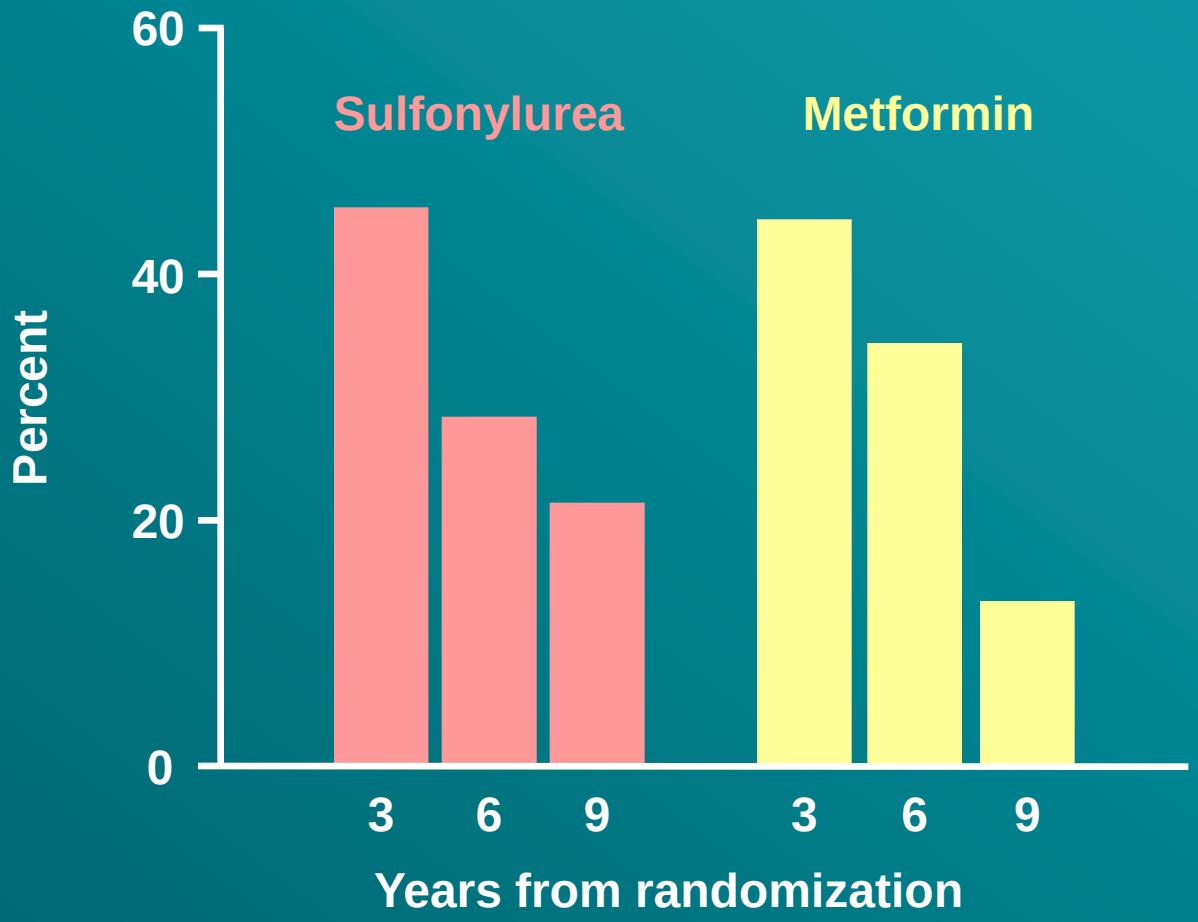
UKPDS: insulin sensitivity is decreased but stable

UKPDS 16. *Diabetes* 1995; 44:1249–1258.

UKPDS: β-cell function is decreased and declines progressively

UKPDS 16. *Diabetes* 1995; 44:1249–1258.

UKPDS: time-dependent reduction in percentage of patients achieving $HbA_{1c} < 7\%$



UKPDS 49. *JAMA* 1999; 281:2005–2012.

ADOPT: overview

Background:	Largest head-to-head, double-blind study of metformin, glyburide and rosiglitazone (N = 4,360)
Primary objective:	To compare the durability of glycemic control using rosiglitazone versus metformin or glyburide as initial monotherapy in patients with recently diagnosed type 2 diabetes
Design:	Double-blind, randomized, controlled trial
Inclusion criteria:	Type 2 diabetes ≤ 3 years, drug-naive, male and female, aged 30–75 years, FPG 126–180 mg/dl (7–10 mmol/l)
Exclusion criteria:	Previous use of glucose-lowering therapy, women of child-bearing potential, significant hepatic disease, renal impairment, unstable or severe angina, known CHF (NYHA Class I–IV), uncontrolled hypertension
Treatment duration:	Treatment period: 4 to 6 years Median duration of treatment: 4 years (rosiglitazone and metformin); 3.3 years (glyburide)
Interventions:	Rosiglitazone, metformin, glyburide

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.

ADOPT: study endpoints

Primary outcome: monotherapy failure

- FPG > 180 mg/dl (> 10 mmol/l)
  - After at least 6 weeks of treatment at maximum tolerated dose, confirmed on repeat testing

OR

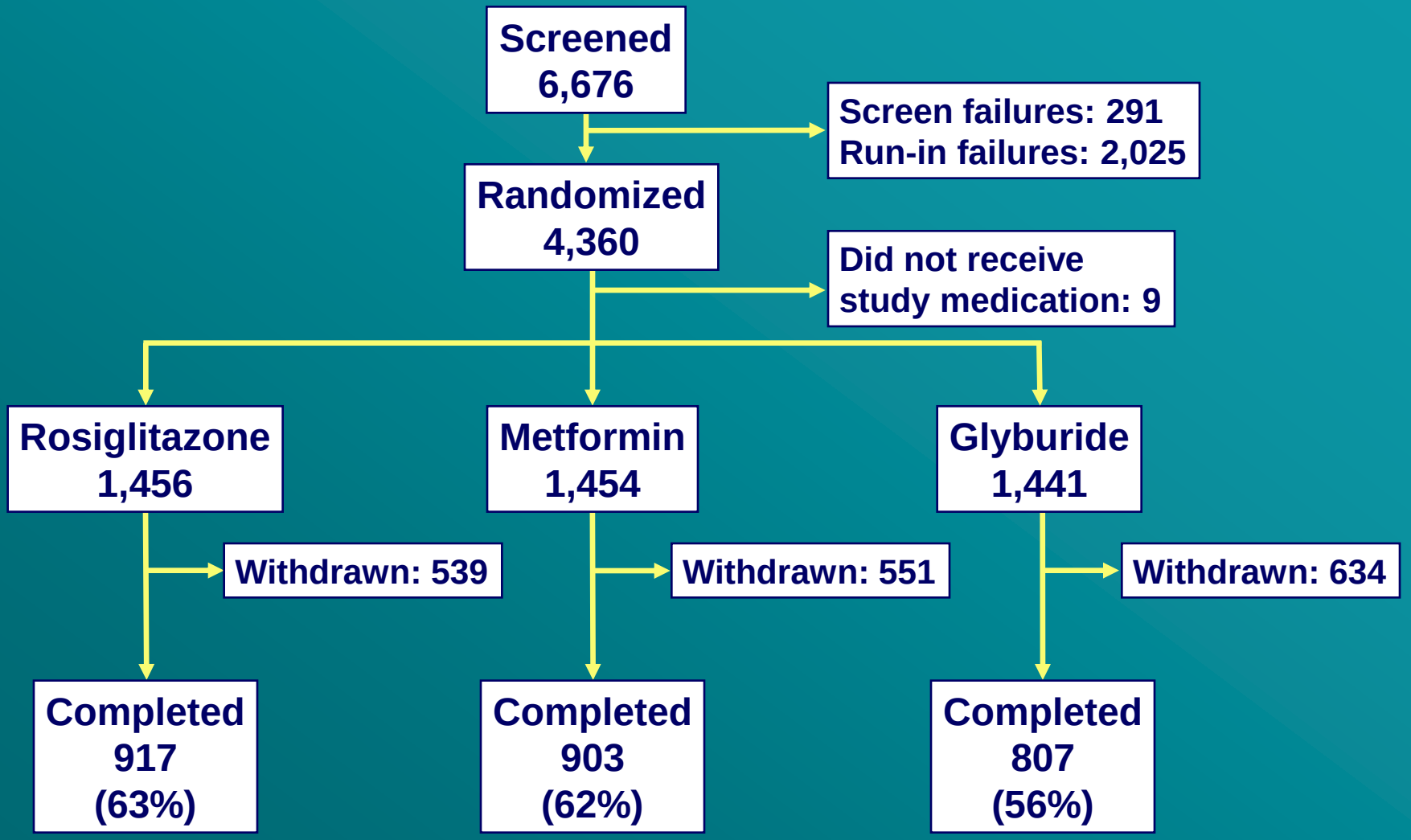
- Independent, masked adjudication for subjects with:
  - No repeat testing, withdrawal due to insufficient therapeutic effect, initiation of non-study glucose-lowering therapy

Secondary outcomes:

- Confirmed FPG > 140 mg/dl (> 7.8 mmol/l)
- Remaining on monotherapy with HbA_{1c} < 7%
- Longitudinal collection of glycemic measures, anthropometrics, insulin sensitivity and β-cell function

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: patient disposition



Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
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ADOPT: baseline characteristics

	Rosiglitazone (N = 1,456)	Metformin (N = 1,454)	Glyburide (N = 1,441)
Age, years	56.3 ± 10.0	57.9 ± 9.9	56.4 ± 10.2
Male	56%	59%	58%
Caucasian	87%	89%	89%
North America	52%	52%	53%
Europe	48%	48%	47%
Time since diabetes diagnosis			
< 1 year	45%	46%	44%
1–2 years	52%	50%	52%
> 2–3 years	3%	4%	4%

P > 0.05 for all comparisons

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
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ADOPT: baseline characteristics (cont'd)

	Rosiglitazone (N = 1,456)	Metformin (N = 1,454)	Glyburide (N = 1,441)
Hypertension treatment	51%	51%	52%
Lipid-lowering treatment	26%	26%	26%
History of CVD	16%	19%	17%
BMI (kg/m^2)	32.2 ± 6.7	32.1 ± 6.1	32.2 ± 6.3
FPG (mg/dl)	152 ± 26	151 ± 26	152 ± 27
HbA_{1c} (%)	7.4 ± 0.9	7.4 ± 0.9	7.4 ± 0.9

P > 0.05 for all comparisons

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
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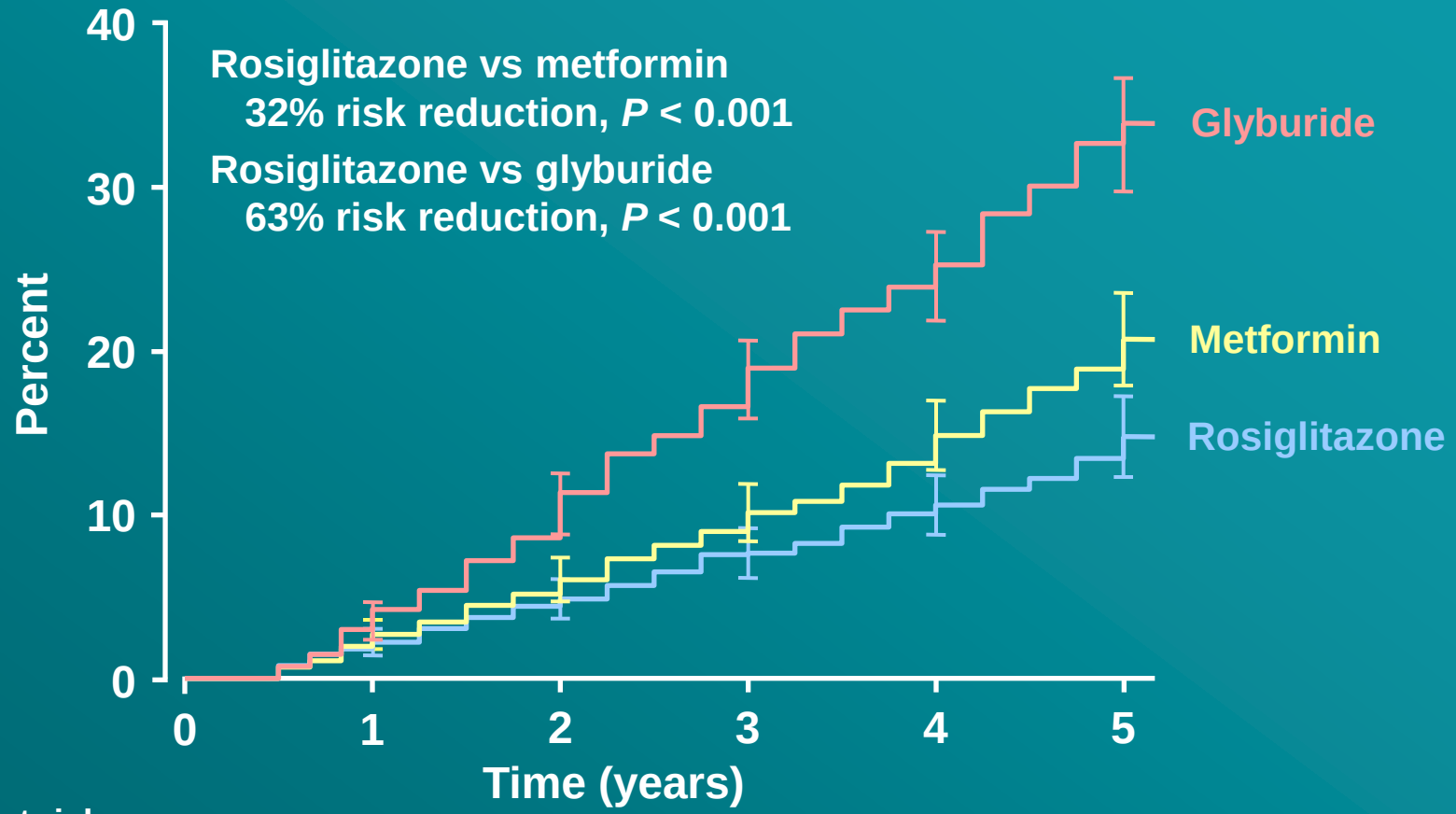
ADOPT: cumulative incidence of monotherapy failure (FPG > 180 mg/dl)



Patients at risk

Rosiglitazone	1,393	1,207	1,078	957	844	324
Metformin	1,397	1,205	1,076	950	818	311
Glyburide	1,337	1,114	958	781	617	218

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
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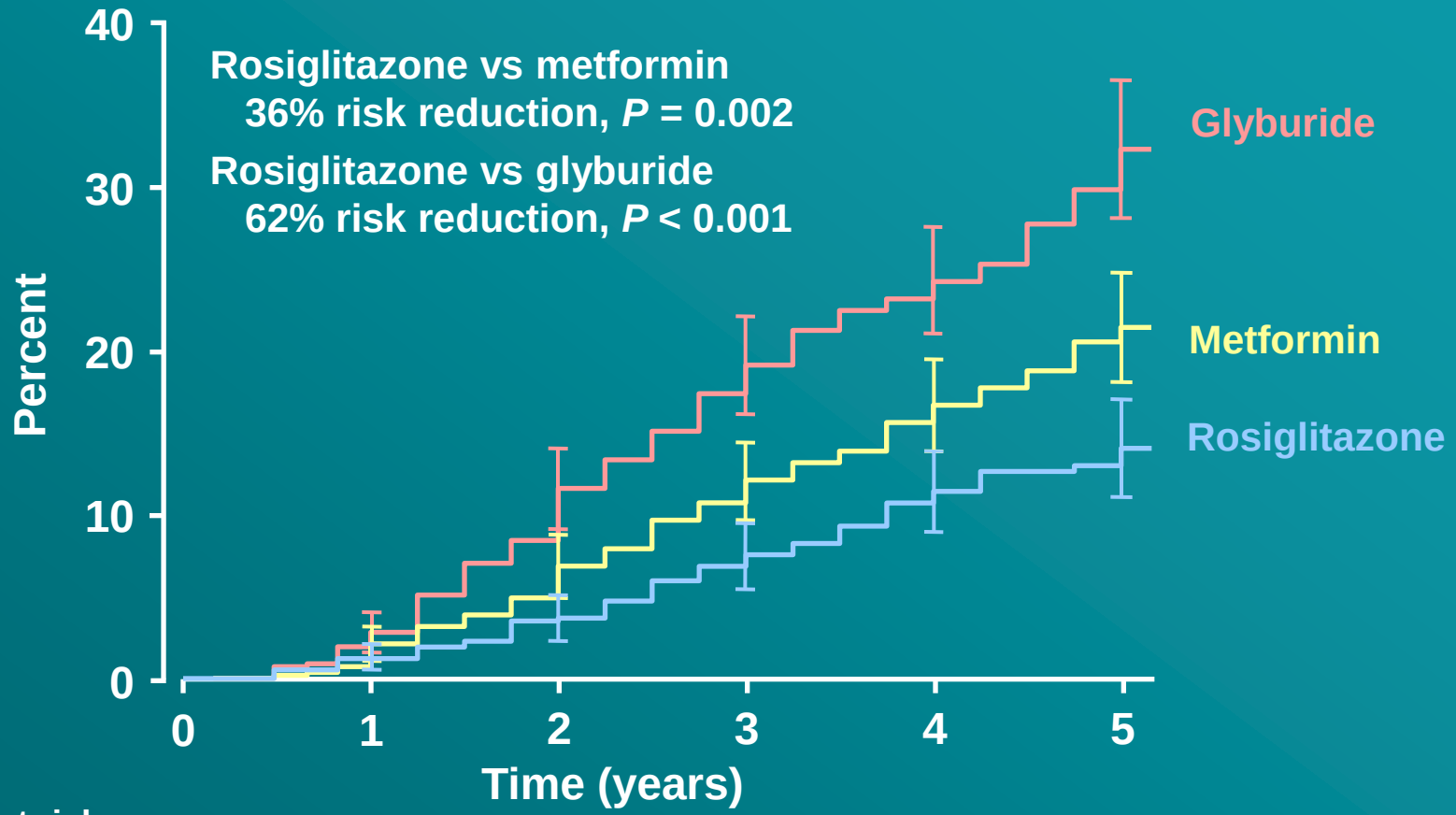
ADOPT: cumulative incidence of FPG > 140 mg/dl among patients with baseline FPG ≤ 140 mg/dl



Patients at risk

Rosiglitazone	511	445	393	351	295	107
Metformin	520	456	403	348	296	112
Glyburide	480	412	343	264	200	63

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
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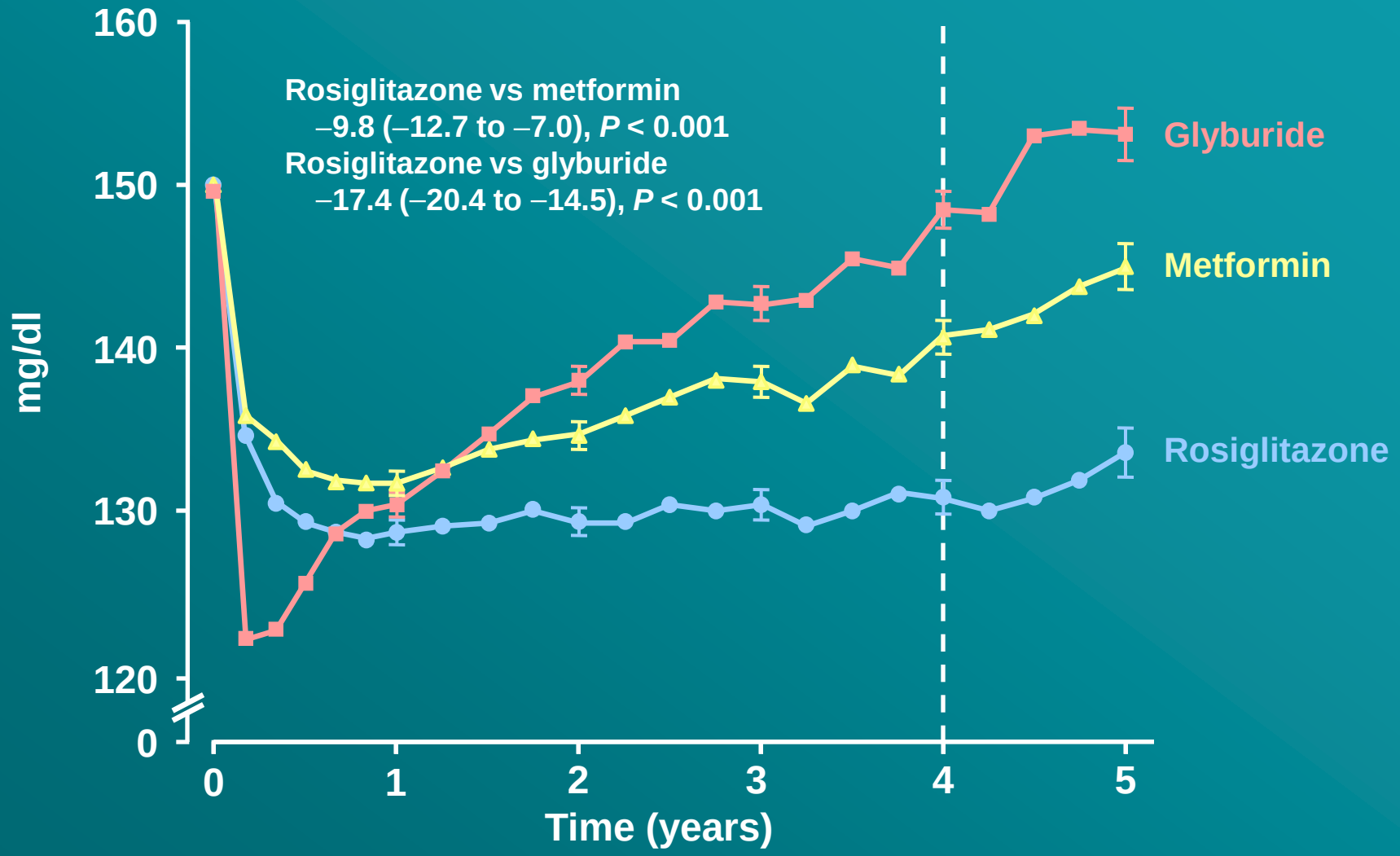
ADOPT: FPG over time



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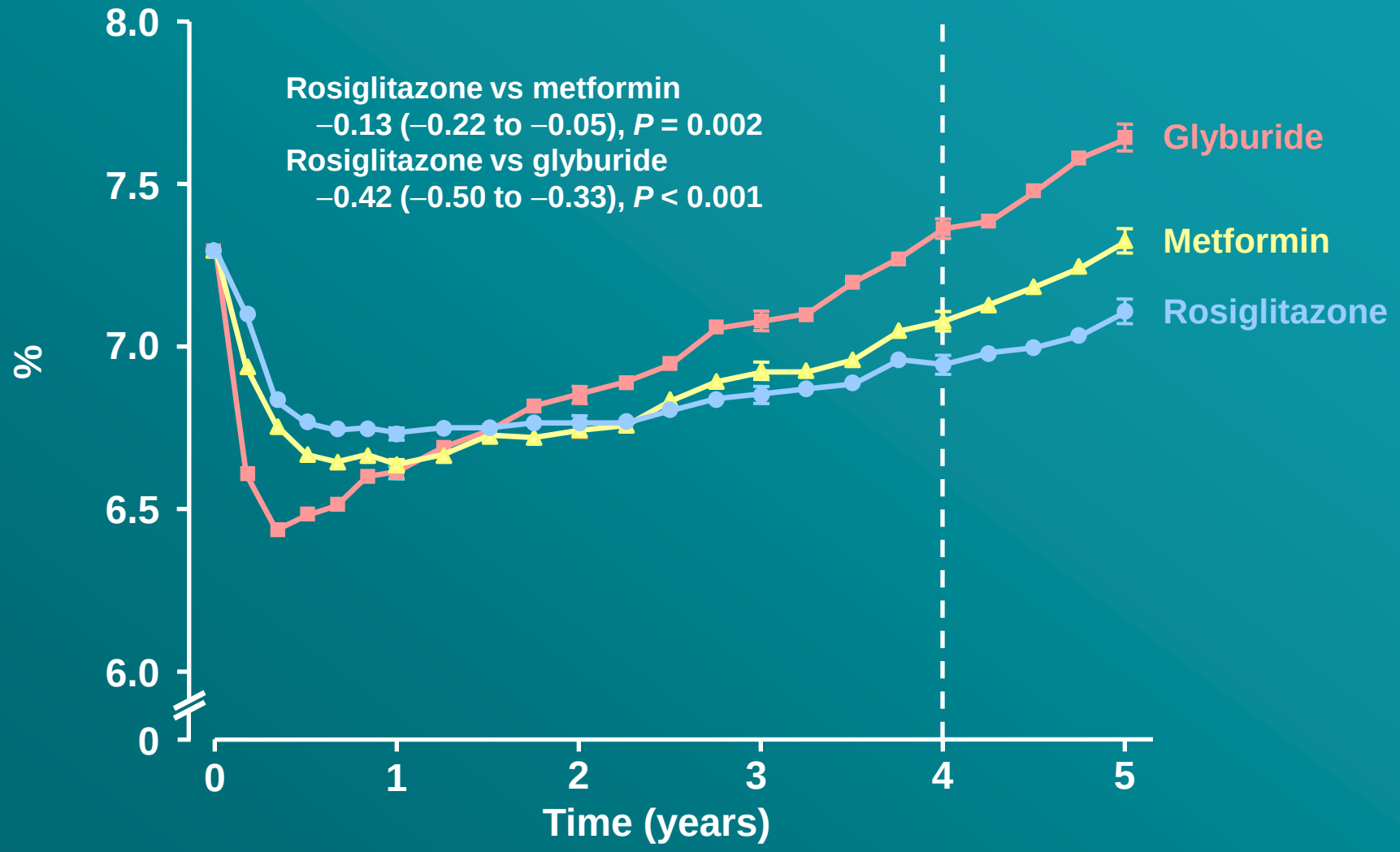
ADOPT: HbA_{1c} over time



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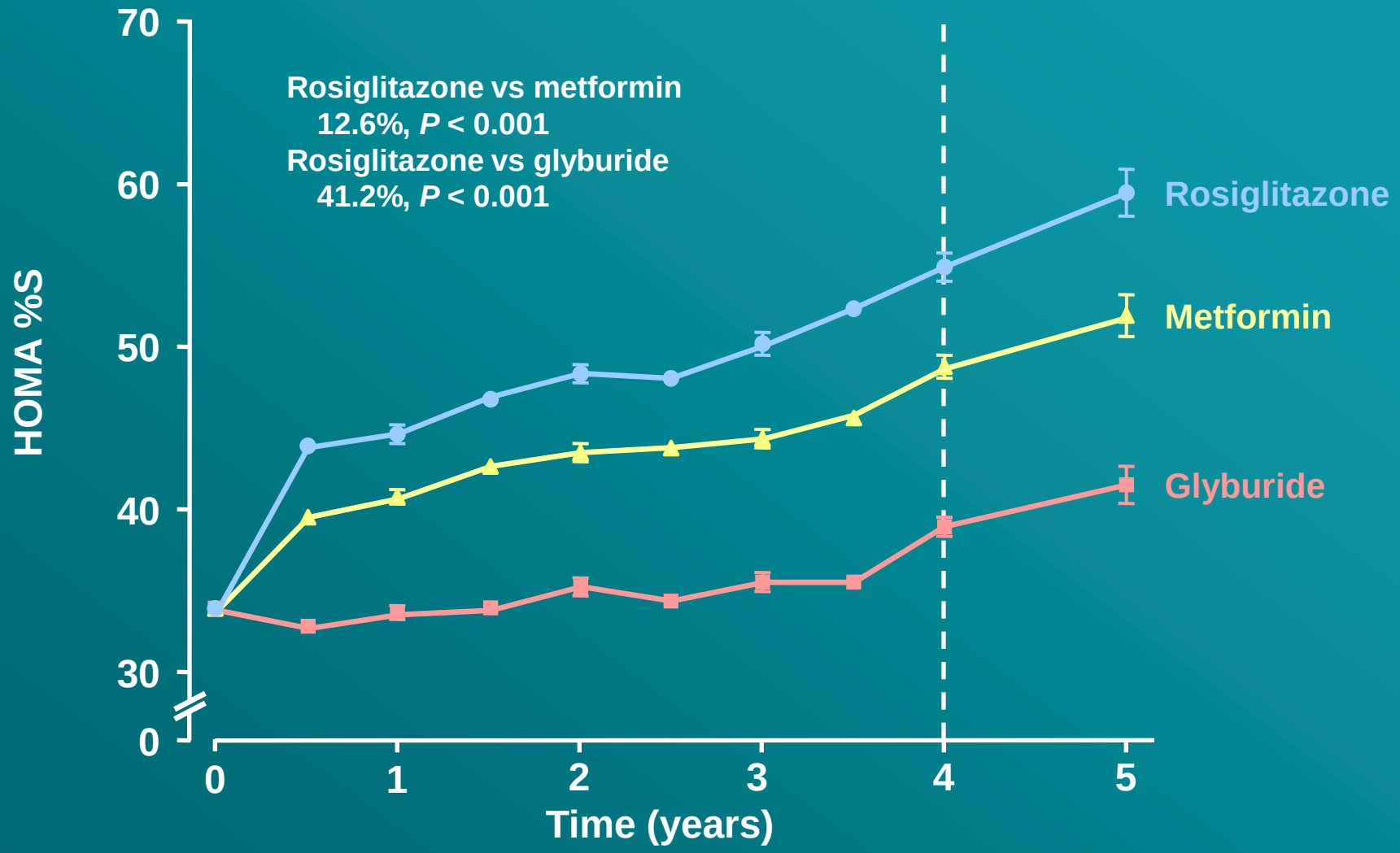
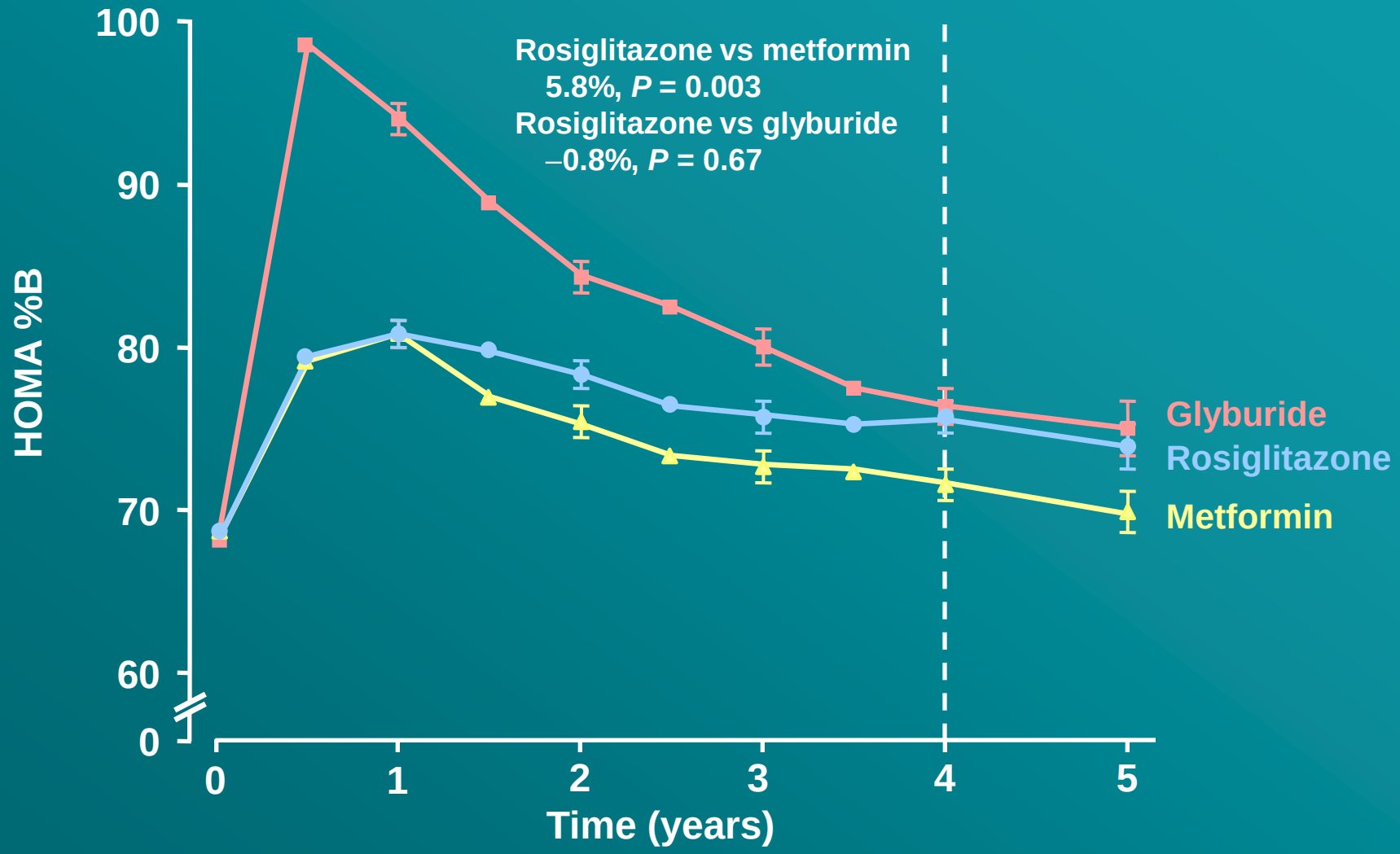
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: insulin sensitivity over time



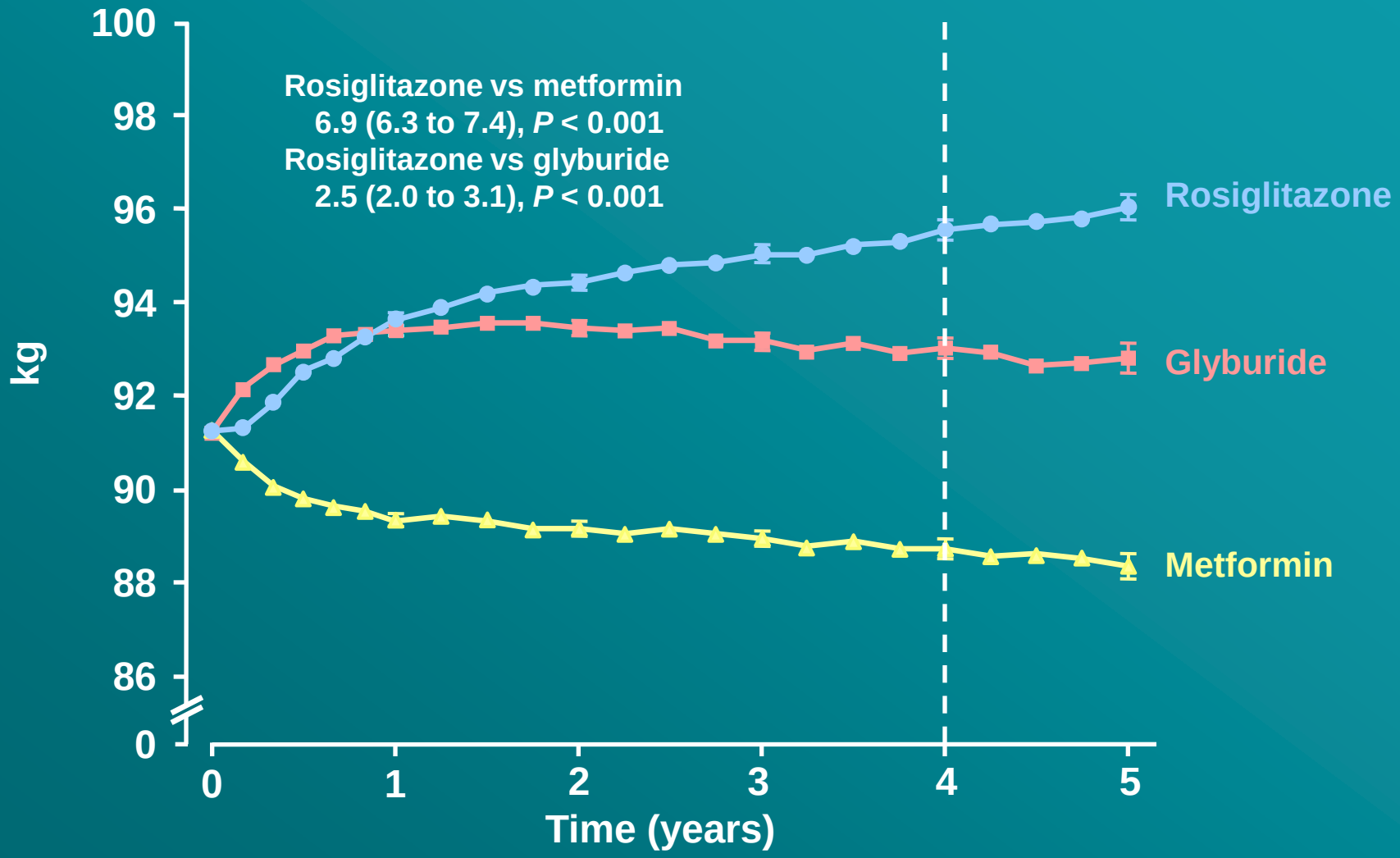
Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: β-cell function over time



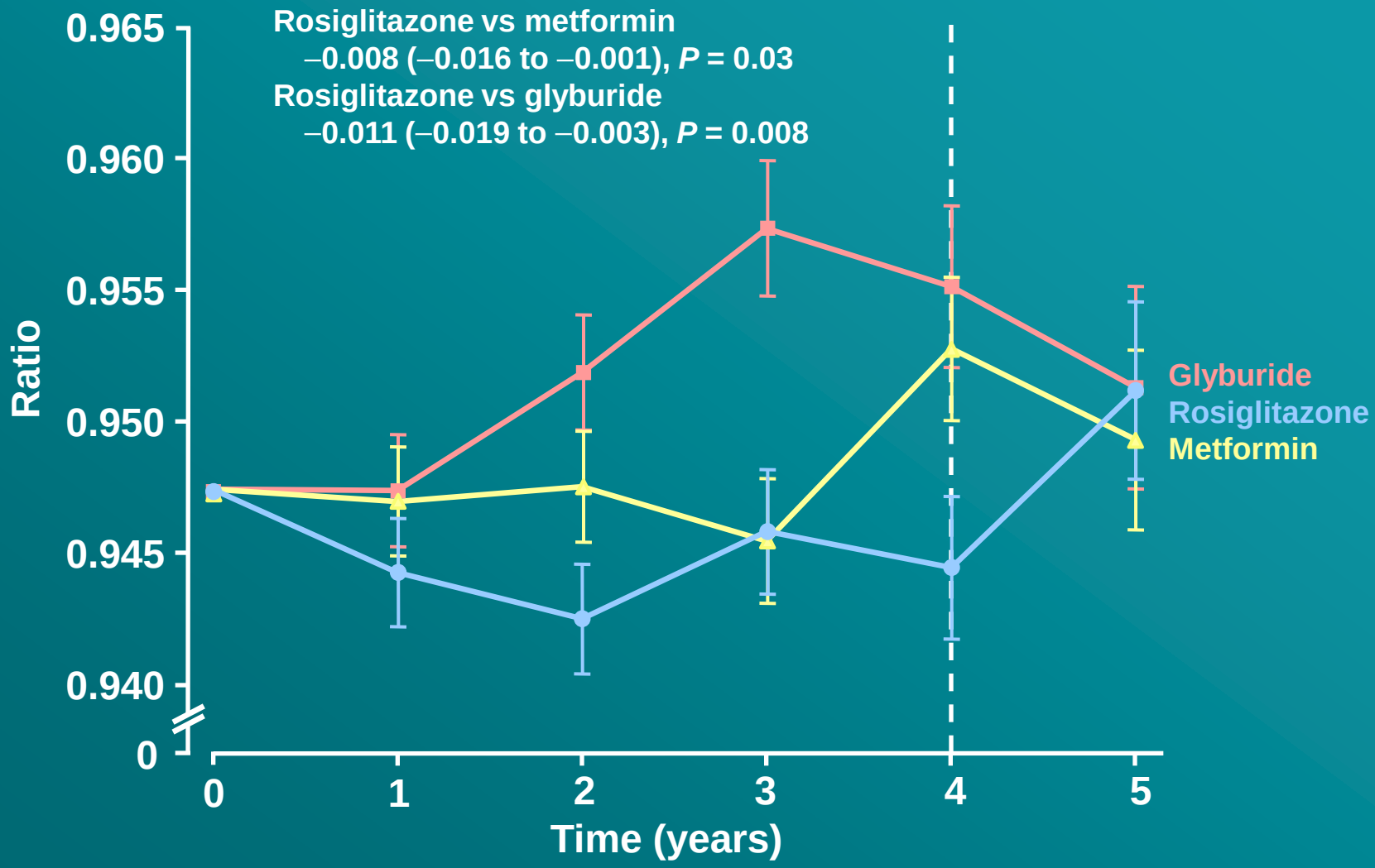
Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: weight over time



Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: waist-hip ratio over time



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ADOPT: lipids

	Rosiglitazone (N = 1,456)	Metformin (N = 1,454)	Glyburide (N = 1,441)
LDL cholesterol, mg/dl (95% CI)	104 (102–106)	97 (94–99)	99 (97–102)
HDL cholesterol, mg/dl (95% CI)	52 (51–52)	51 (50–51)	49 (48–50)
Triglycerides, mg/dl (95% CI)	164 (159–168)	167 (162–171)	172 (167–177)

P < 0.05 vs rosiglitazone

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: laboratory measures

	Rosiglitazone (N = 1,456)	Metformin (N = 1,454)	Glyburide (N = 1,441)
ALT (IU/l) (95% CI)	21.4 (20.6–22.2)	24.9 (24.1–25.8)	27.2 (26.3–28.1)
ALT > 3x ULN, n (%)	14 (1.0%)	16 (1.1%)	11 (0.8%)
Hematocrit, % (95% CI)	40.6 (40.4–40.8)	41.6 (41.4–41.8)	42.7 (42.5–42.9)
Hematocrit ≥ 5% below ref. range, n (%)	41 (2.8%)	22 (1.5%)	14 (1.0%)

P< 0.05 vs rosiglitazone

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
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ADOPT: adverse events, hospitalizations and deaths

	Rosiglitazone (N = 1,456) n (%)	Metformin (N = 1,454) n (%)	Glyburide (N = 1,441) n (%)
Patients with event(s)	1,338 (92)	1,341 (92)	1,321 (92)
Hospitalization from any cause			
Patients	169 (12)	172 (12)	150 (10)
Events	251	267	203
Death from any cause	34 (2.3)	31 (2.1)	31 (2.2)

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
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ADOPT: vascular serious adverse events, investigator reported

	Rosiglitazone (N = 1,456) n (%)	Metformin (N = 1,454) n (%)	Glyburide (N = 1,441) n (%)
Cardiovascular disease	49 (3.4)	46 (3.2)	26 (1.8)
Myocardial infarction			
Fatal	2 (0.1)	2 (0.1)	3 (0.2)
Non-fatal	22 (1.5)	18 (1.2)	11 (0.8)
Congestive heart failure	12 (0.8)	12 (0.8)	3 (0.2)
Stroke	13 (0.9)	17 (1.2)	12 (0.8)
Peripheral vascular disease	7 (0.5)	6 (0.4)	4 (0.3)

P < 0.05 vs rosiglitazone

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: congestive heart failure

	Rosiglitazone (N = 1,456) n (%)	Metformin (N = 1,454) n (%)	Glyburide (N = 1,441) n (%)
Adverse events	22 (1.5)	19 (1.3)	9 (0.6)
Serious adverse events	12 (0.8)	12 (0.8)	3 (0.2)
Cardiologist review	9 (0.6)	8 (0.6)	4 (0.3)

P < 0.05 vs rosiglitazone

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: other adverse events

	Rosiglitazone (N = 1,456) n (%)	Metformin (N = 1,454) n (%)	Glyburide (N = 1,441) n (%)
Gastrointestinal	335 (23)	557 (38)	316 (22)
Weight gain	100 (7)	18 (1)	47 (3)
Hypoglycemia	142 (10)	168 (12)	557 (39)
Edema	205 (14)	104 (7)	123 (9)

P < 0.05 vs rosiglitazone

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: fractures

	Rosiglitazone (N = 1,456) n (%)	Metformin (N = 1,454) n (%)	Glyburide (N = 1,441) n (%)
Men	32 (4.0)	29 (3.4)	28 (3.4)
Women	60 (9.3)	30 (5.1)	21 (3.5)
Upper limb	22 (3.4)	10 (1.7)	9 (1.5)
Lower limb	36 (5.6)	18 (3.1)	8 (1.3)
Hip	2 (0.3)	2 (0.3)	0 (0.0)
Spine	1 (0.2)	1 (0.2)	1 (0.2)

P < 0.05 vs rosiglitazone

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: summary of findings

- Initial treatment of type 2 diabetes with rosiglitazone slowed progression of hyperglycemia compared to metformin or glyburide as assessed by FPG > 180 mg/dl and > 140 mg/dl
- 32% risk reduction of monotherapy failure vs metformin ($P < 0.001$) (FPG > 180 mg/dl)
  - Effect was more pronounced in older patients (≥ 50 years) and more obese patients (waist circumference > 110 cm)
- 63% risk reduction of monotherapy failure vs glyburide ($P < 0.001$) (FPG > 180 mg/dl)
  - Effect was more pronounced in older patients (≥ 50 years), women and more obese patients (BMI ≥ 30 kg/m^2)
- Rosiglitazone was associated with significant improvements in insulin sensitivity and a reduced rate of loss of β-cell function vs metformin and glyburide

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
http://www.adopt-study.org/slides.php. Accessed December 2006.

ADOPT: summary of findings (cont'd)

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

Kahn SE, *et al. N Engl J Med* 2006; 355:2427–2443.
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CHALLENGE OF DISTINGUISHING TYPE 2 FROM TYPE 1

	Type 1A	Type 1B	LADA	Type 2
Clinical Type 1	25 (41.7%)	33 (55%)	0 (0)	2 (3.3%)
Clinical TZDM < 25	4 (6.7%)	13 (21.6%)	4 (6.7%)	39 (65%)
> 25	0 (0%)	2 (3.00%)	3 (4.70%)	59 (92.0%)

Sensitivity 71% specificity 95%

GOOD DIABETES CONTROL

MAKES SENSE

SAVES CENTS

THANK YOU