Review of Diabetes Therapies: Key Drivers of Disease Progression

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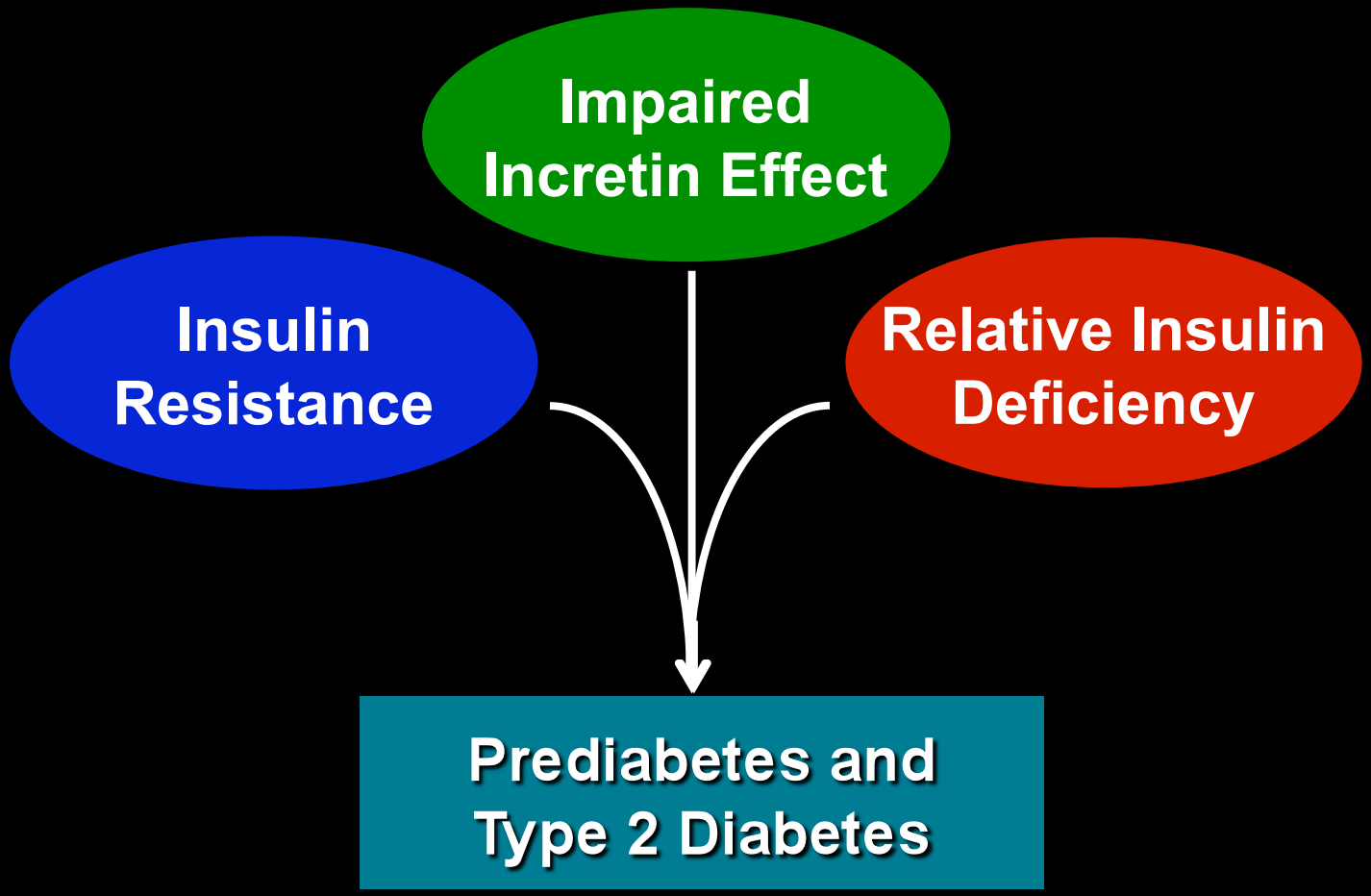
Diabetes Therapies and Disease Progression: Discussion Outline

- Disease progression in Type 2 diabetes
  - The role of beta cell function and insulin resistance
  - Clinical consequences of disease progression
    - Glycemic control and treatment “failure”
- Specific therapies – effect on diabetes progression
  - Diabetes prevention vs. disease progression
- A Glimpse of the Future – Implications for Treatment
  - Early intervention and diabetes treatment response
  - Impact on the risk of complications

The Pathophysiology of Type 2 Diabetes



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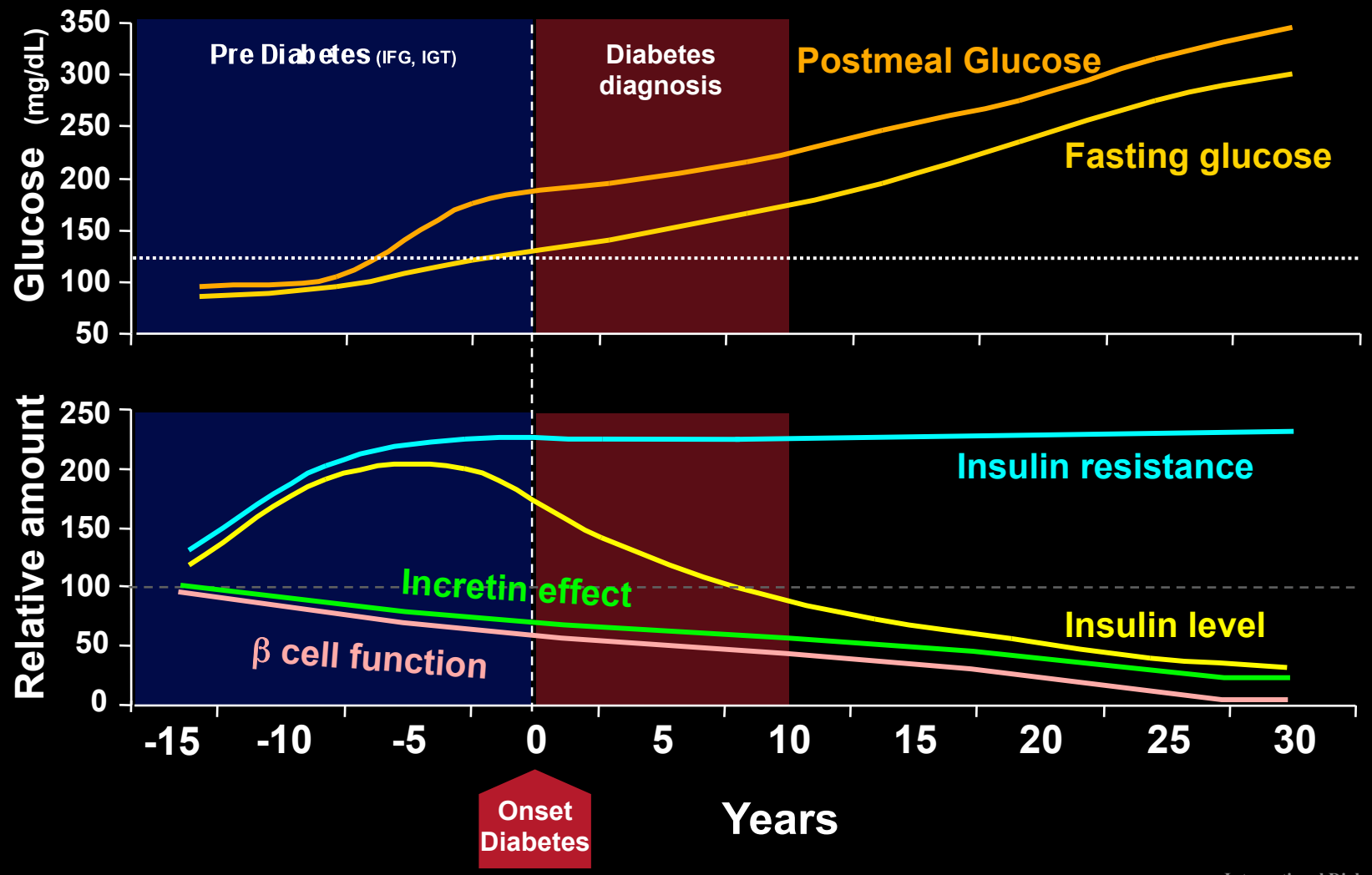
Natural History of Type 2 Diabetes



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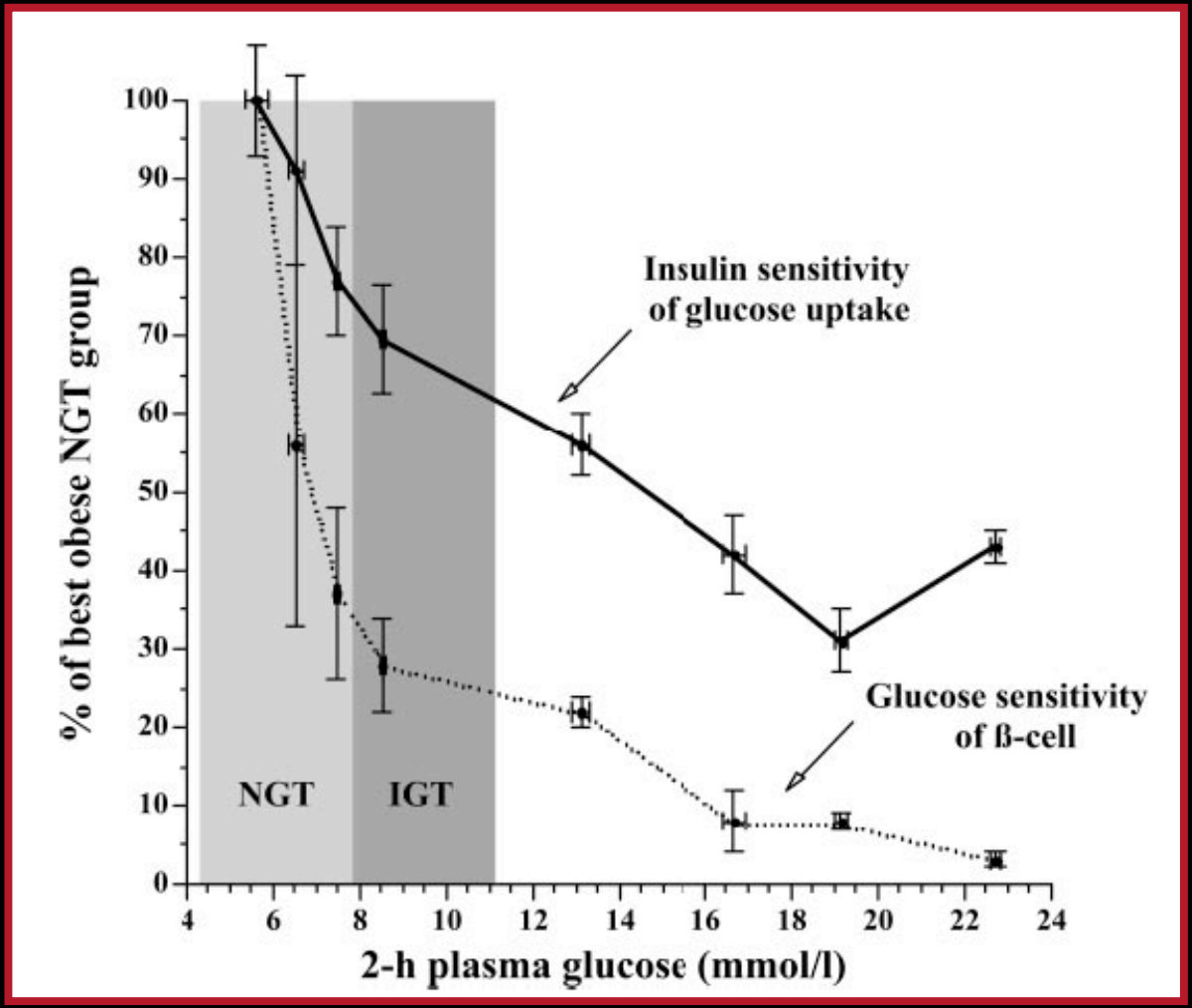
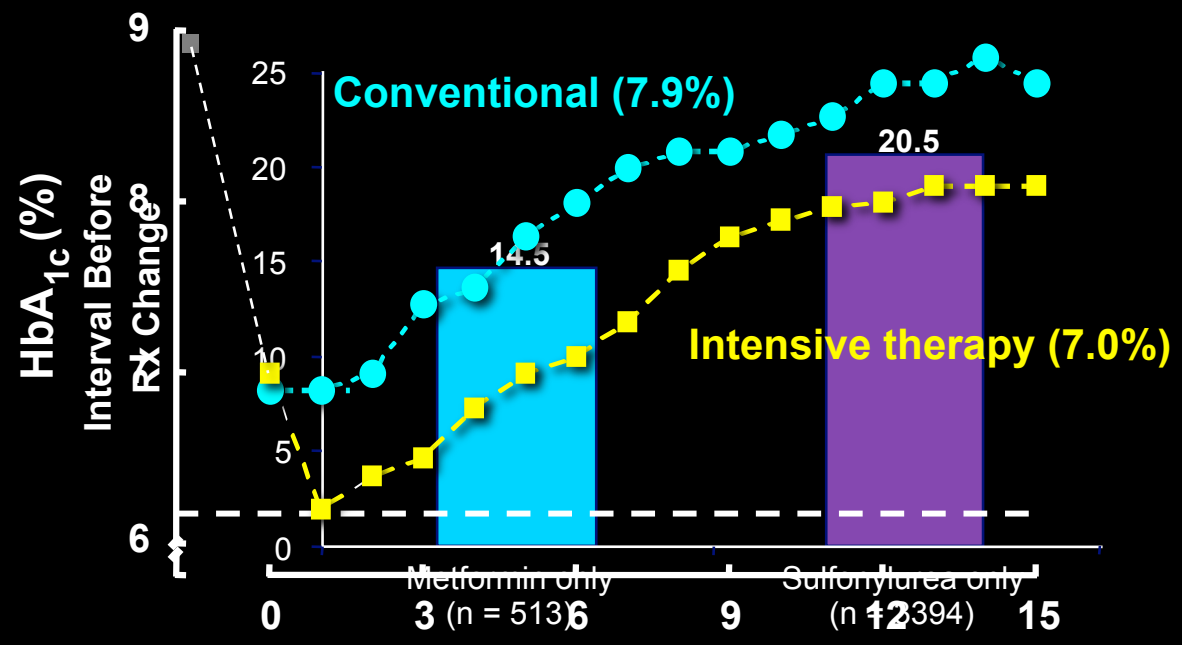
Diabetes Disease Progression:
β cell Dysfunction and Early Hyperglycemia



Ferrannini E. *J Clin Endocrinol Metab* 90: 493–500, 2005

Diabetes Disease Progression: Clinical Consequences

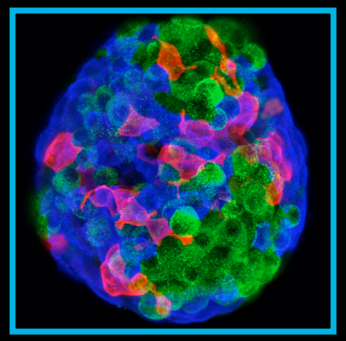
- Implications of disease progression
  - Progressive deterioration in glycemic control (UKPDS)
    - Increasing risk of complications
  - Stepped, failure-based therapeutic approach – delay in Rx



Brown JB, et al. *Diabetes Care.* 2004;27:1535-1540.
UKPDS 33. *Lancet* 352: 837–53, 1998

Clinical Impact of Diabetes Therapy

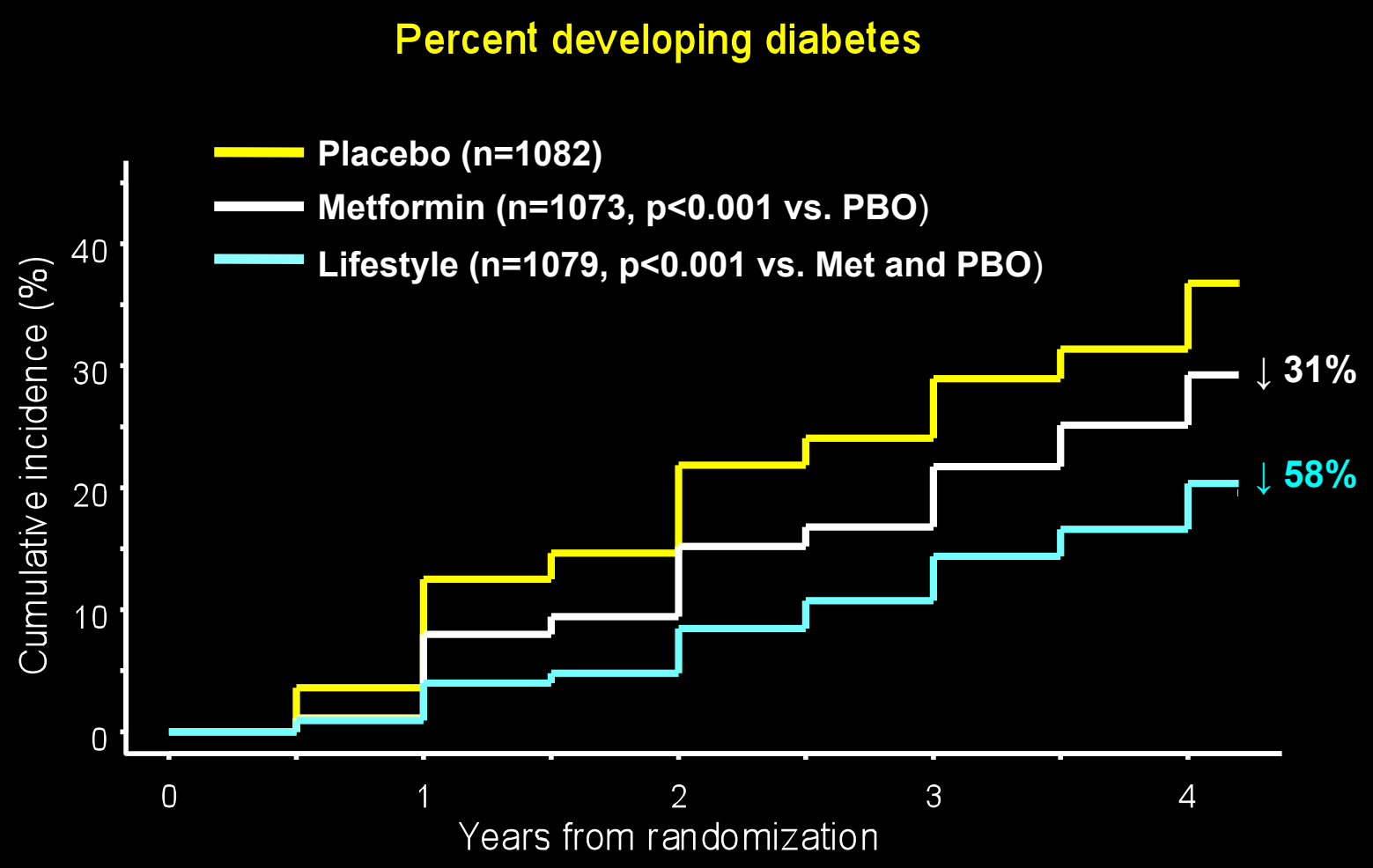
Diabetes Prevention and Disease Progression



Diabetes Disease Progression: Impact of Specific Therapies

Therapy	Improved Insulin Secretion	Increased β cell mass	Diabetes Prevention	Disease Modification
Lifestyle (MNT) Metformin Sulfonylurea Insulin AGI TZD Incretin based Rx	• Measures of fasting insulin • Stimulated insulin response	• Beta cell mass • Insulin content and mRNA • Stimulated (maximal) insulin secretion	• Prevent increase in FPG • Maintain or restore normal glucose response	• Diabetes prevention • Stability of glycemic control • Limit need for added therapies

Diabetes Prevention Program (DPP)
Prevention of Diabetes



The DPP Research Group, *NEJM 346*:393-403, 2002

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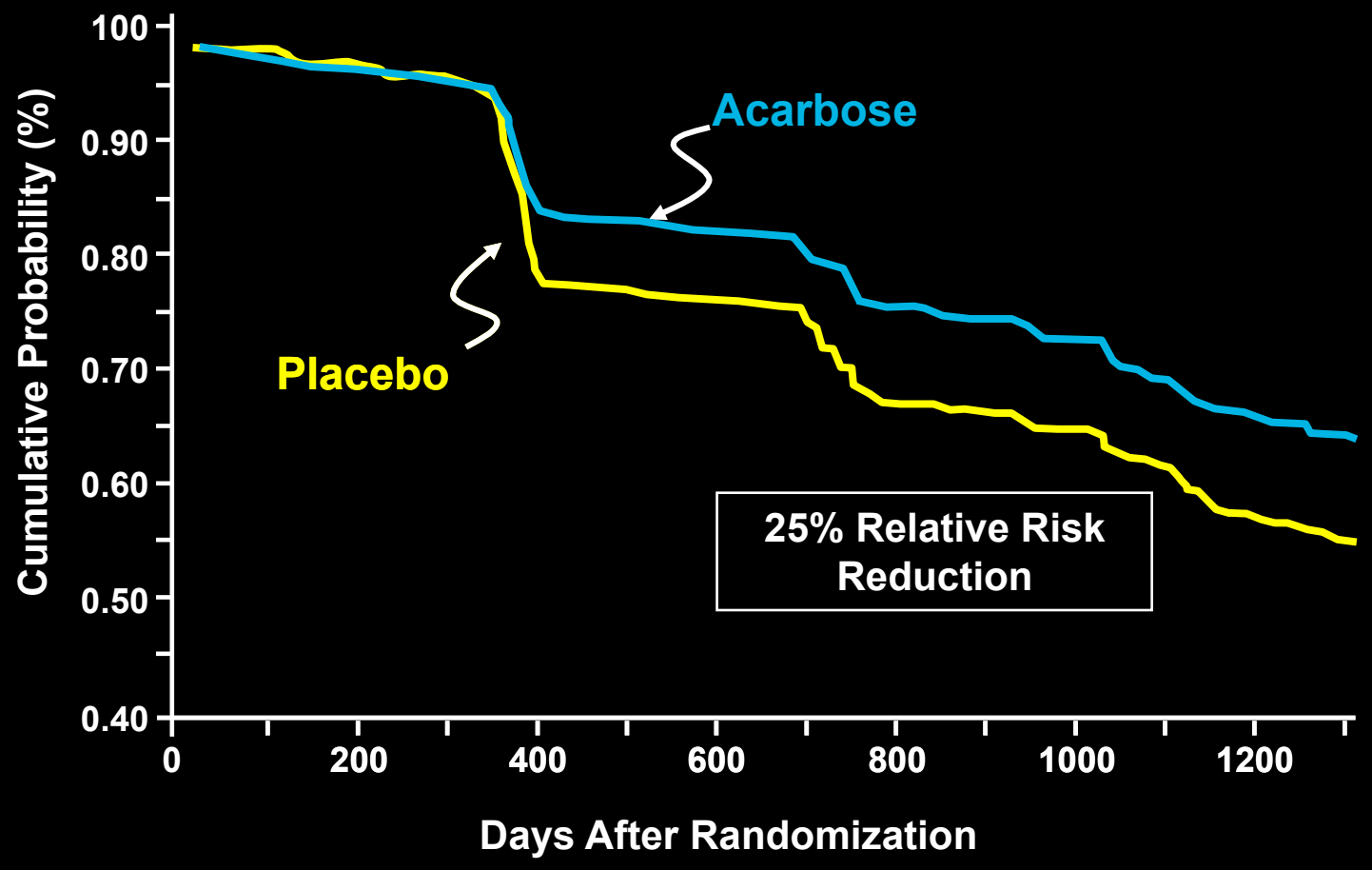
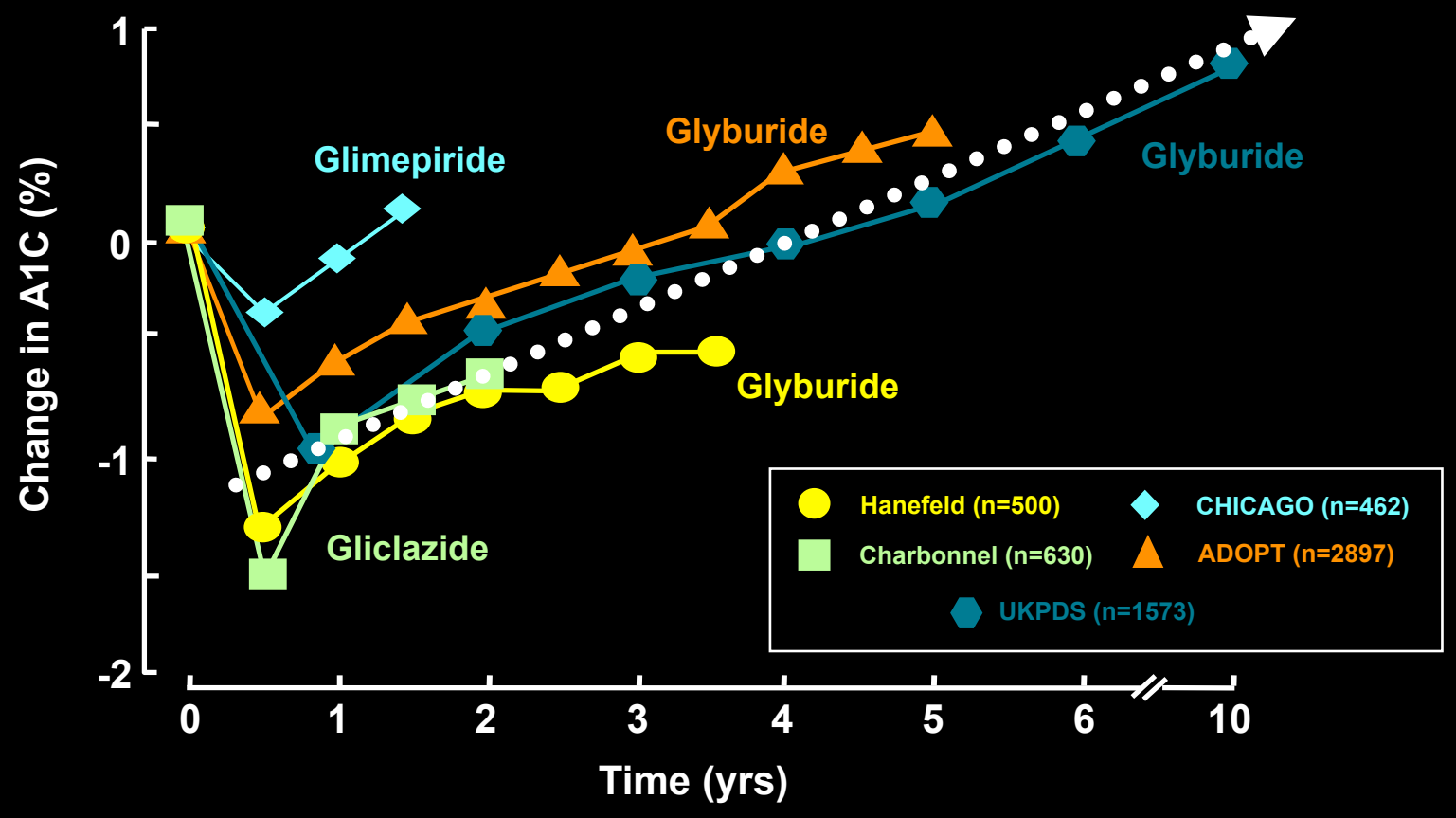
The STOP-NIDDM Study: Effect of Acarbose Therapy



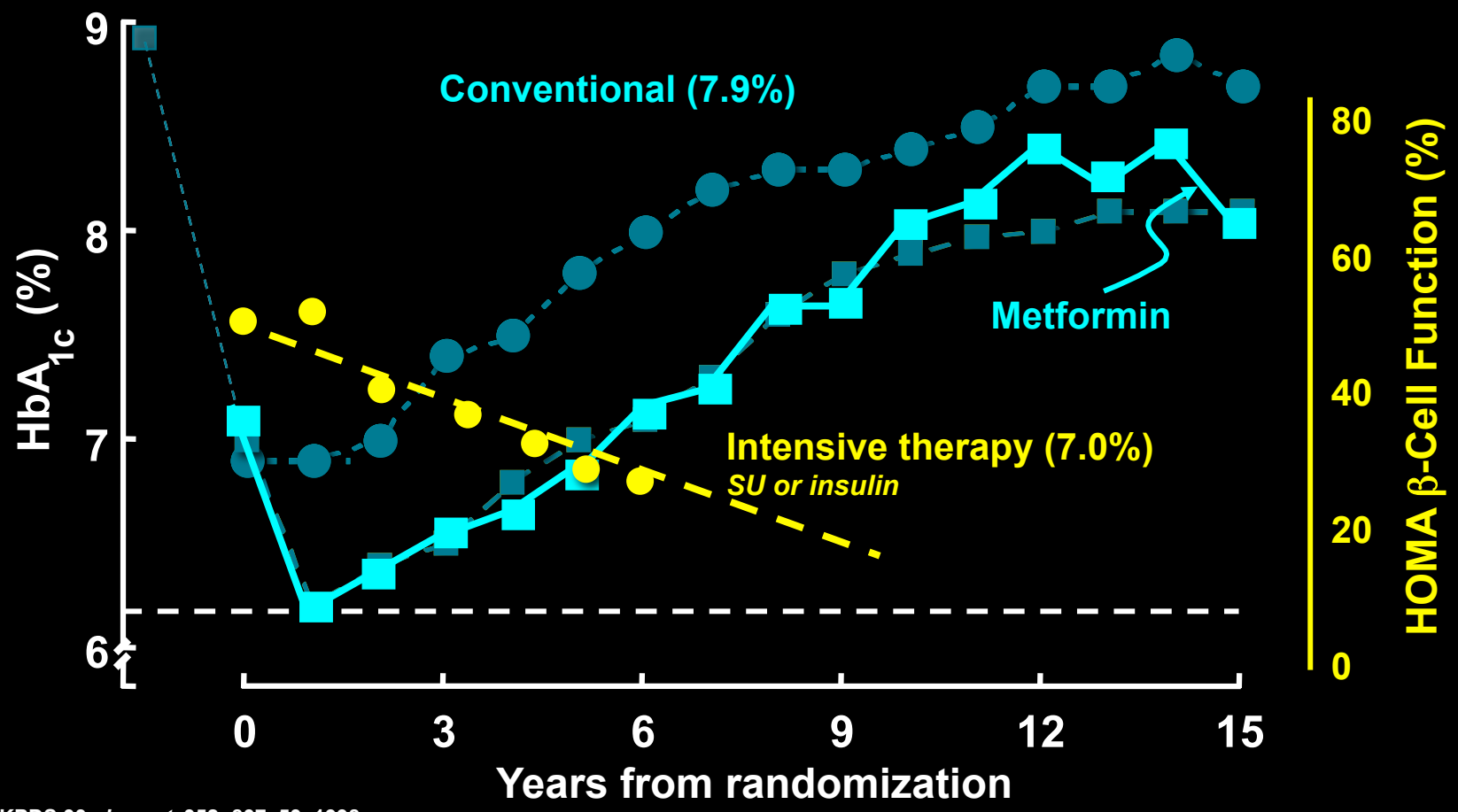
Chiasson JL et al. *Lancet* 2002;359:2072 and *JAMA* 2003;290:486

Durability of Glycemic Control with Sulfonylurea Therapy



Mazzone T. *JAMA*. 2006;296:2572-2581. Hanefeldd M. *Cur Med Res Opin*. 2006;22:1211-1215.
Nissen SE. *JAMA*. 2008;299:1567-1573. UKPDS Study Group. *Lancet*.1998;352:837-853
Charbonnel B. *Diabetoogia*. 2005;48(6):1093-1104.

Intensive Treatment of Type 2 Diabetes: UKPDS



UKPDS 33. *Lancet* 352: 837–53, 1998
UKPDS 16. *Diabetes* 44:1249–1258, 1995

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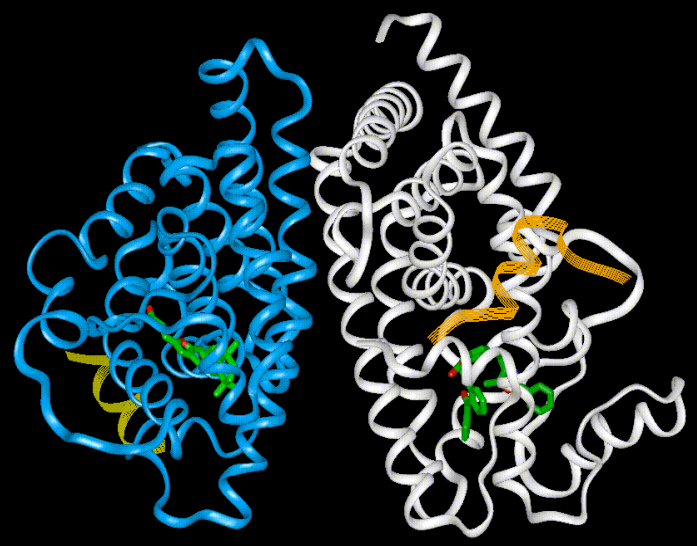
Diabetes Disease Progression: Impact of Specific Therapies

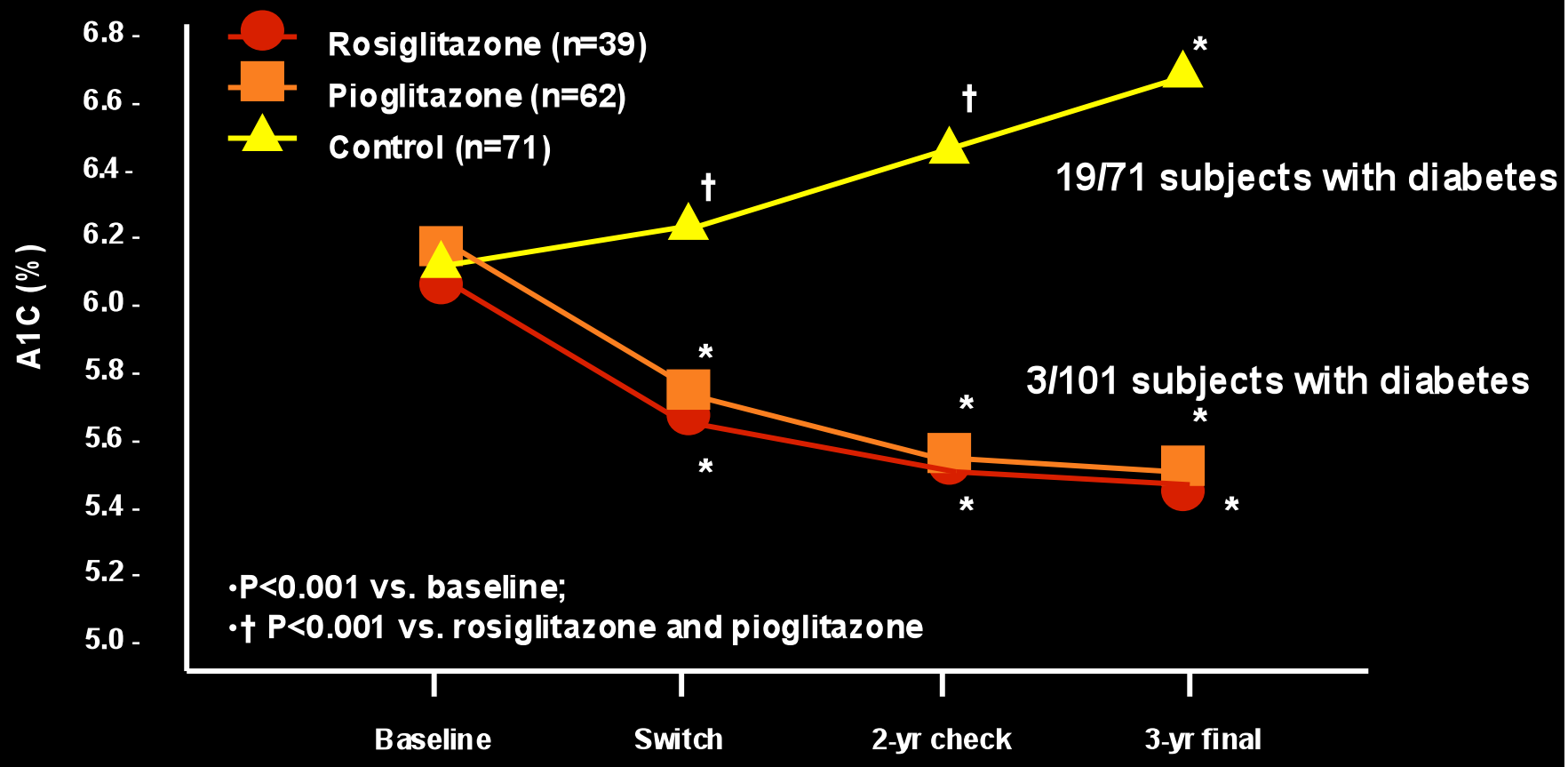
Therapy	Improved Insulin Secretion	Increased β cell mass	Diabetes Prevention	Disease Modification
Lifestyle (MNT)	Yes	No	Yes	No
Metformin	No	No	Yes	No
Sulfonylurea	Yes	No	No	No
Insulin	No	No	No	No
AGI	No	No	Yes	No
TZD				
Incretin based Rx				

Thiazolidinediones

A Closer Look at β Cell Function and Diabetes Disease Progression



Effect of Early TZD Use on A1C



Durbin RJ Diabetes, Obesity & Metabolism 6:280-285, 2004

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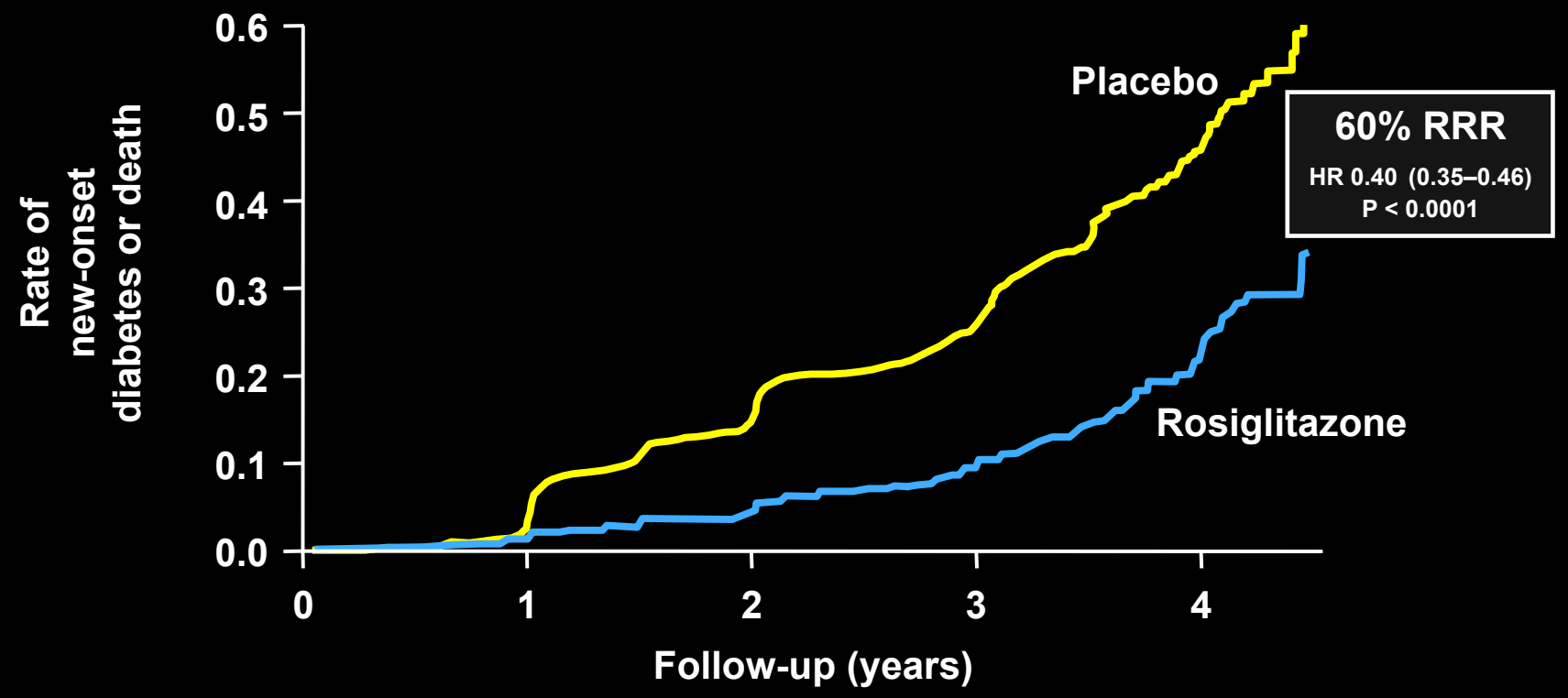
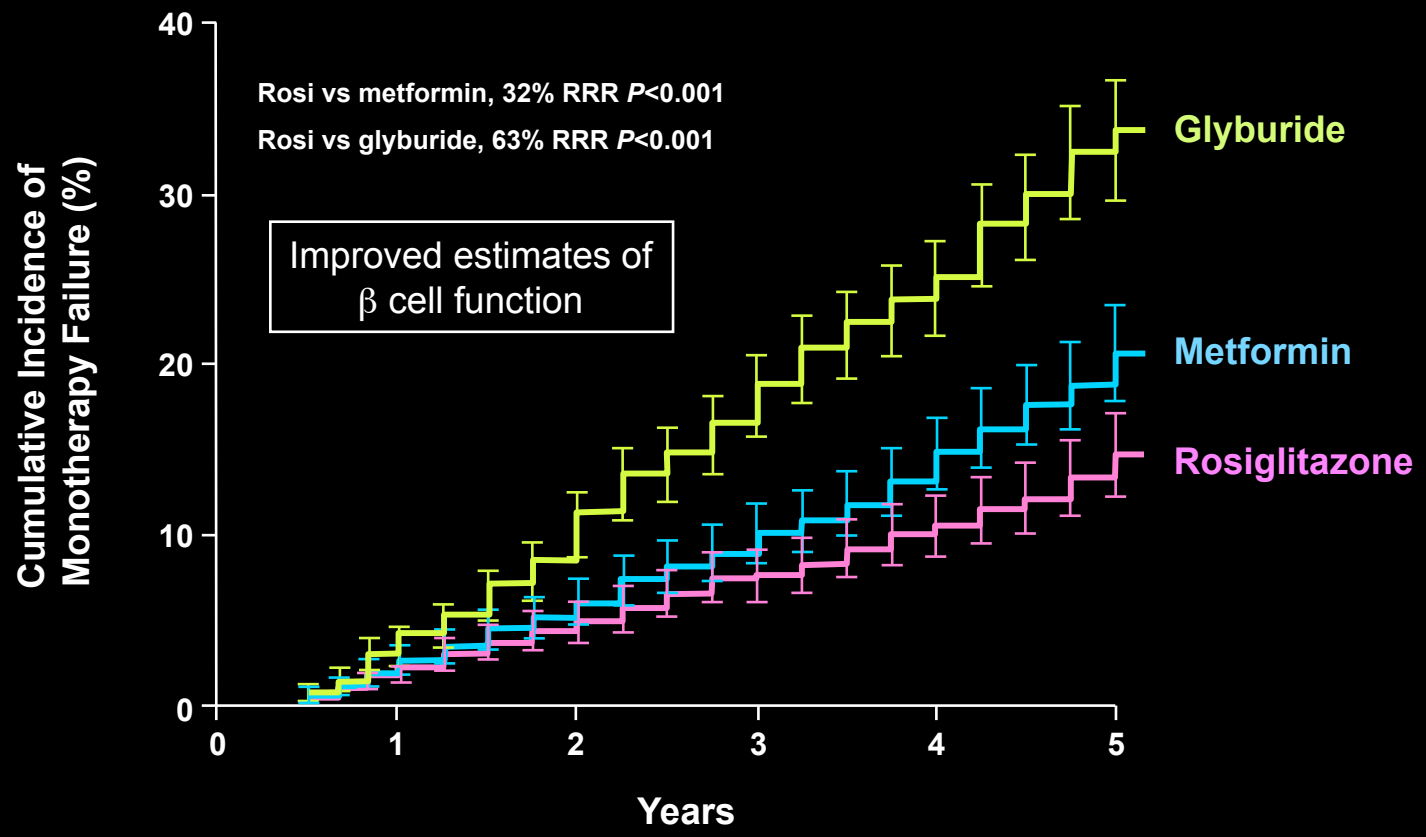
DREAM:
Investigation of Diabetes Prevention or Delay



No. at risk					
Placebo	2634	2470	2150	1148	177
Rosiglitazone	2635	2538	2414	1310	217

DREAM Trial Investigators. *Lancet 368(9541):1096-105, 2006*

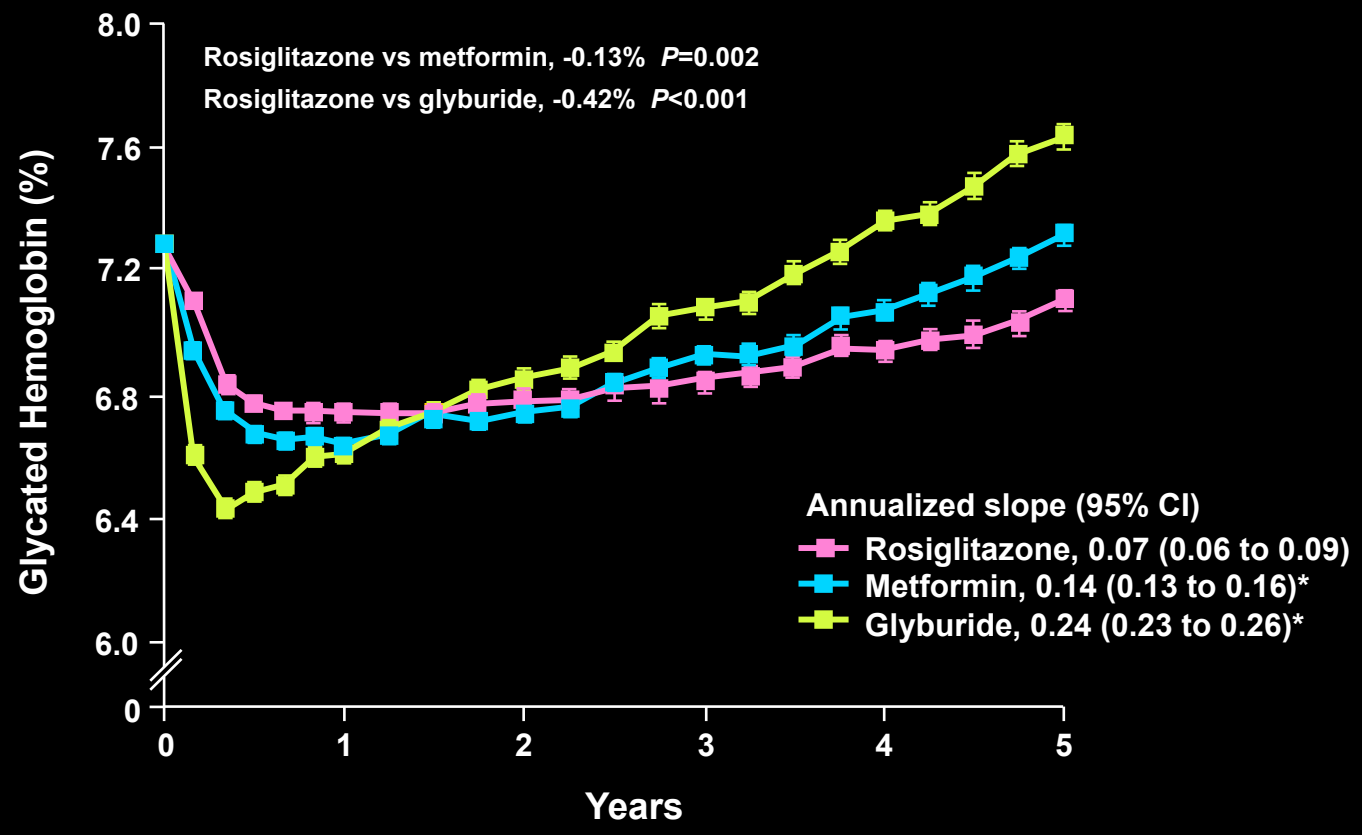
ADOPT
Cumulative Incidence of Treatment Failure



No. at risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

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

ADOPT
Impact of Initial Therapy on A1C



No. of Patients	4012	3308	2991	2583	2197	822

*Significant difference rosiglitazone vs other treatment groups with Hochberg adjustment.
Kahn SE, et al. *N Engl J Med* 2006;355:2427–2443.

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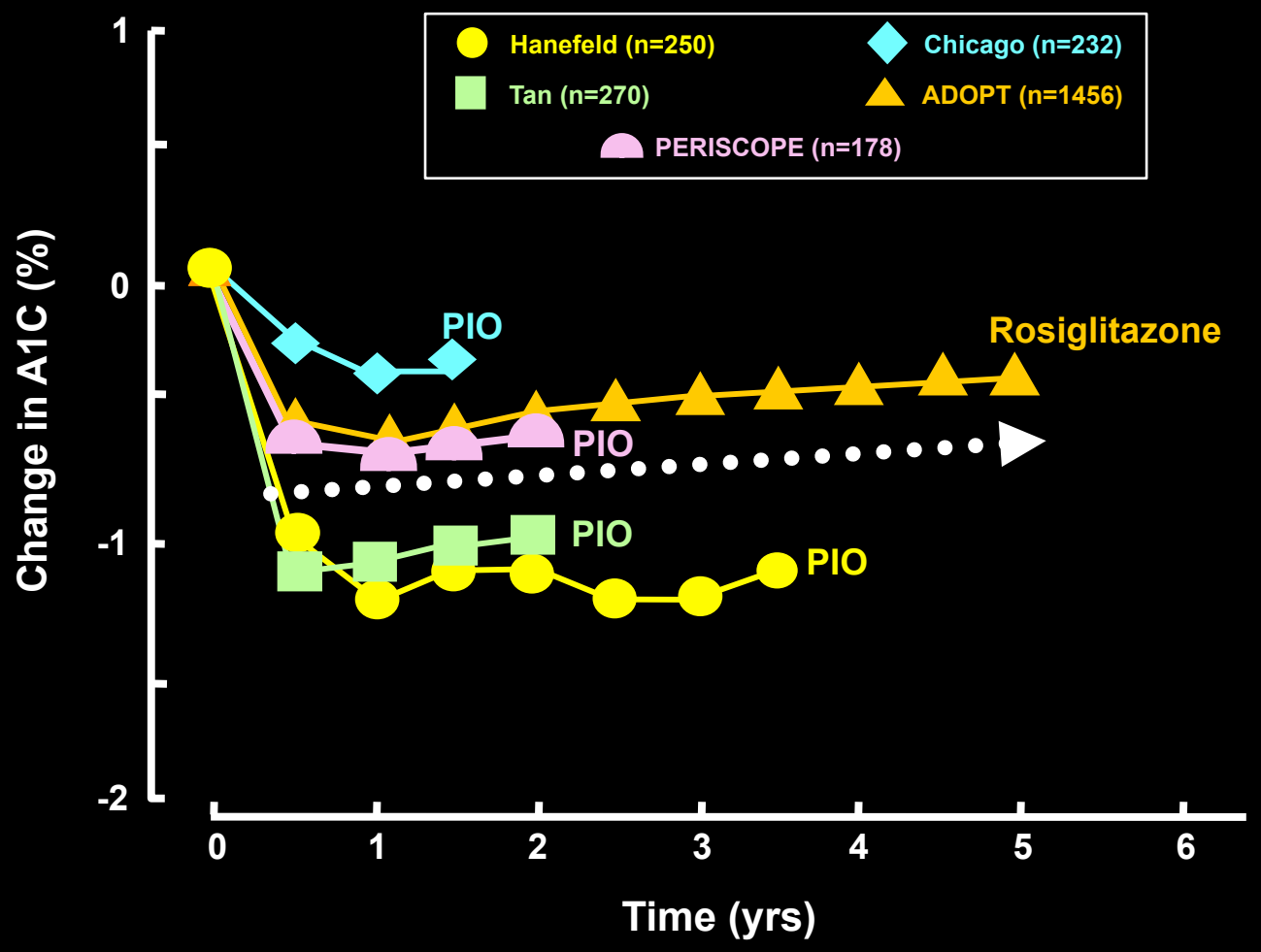
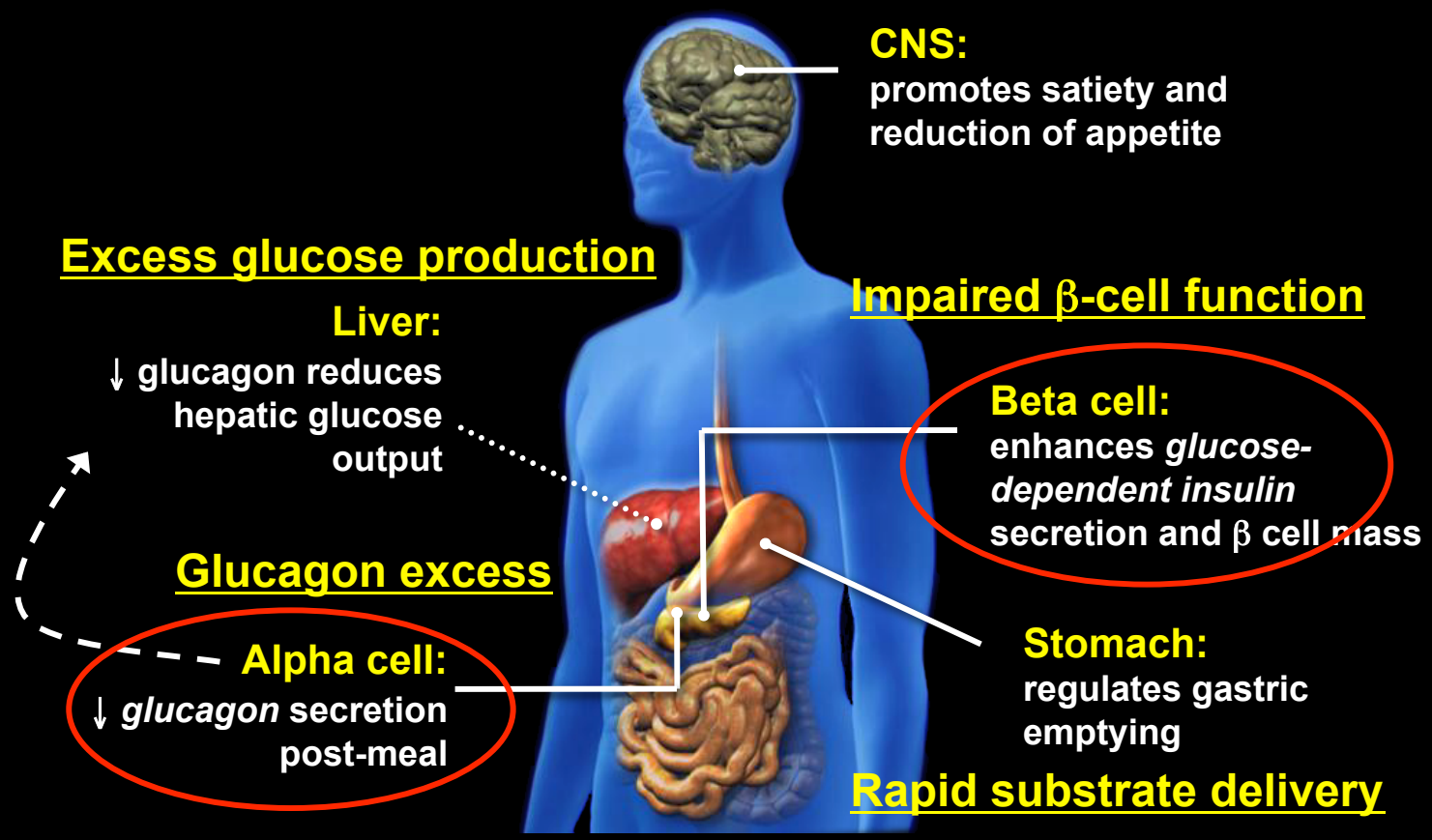
Durability of Glycemic Control with Thiazolidindiones



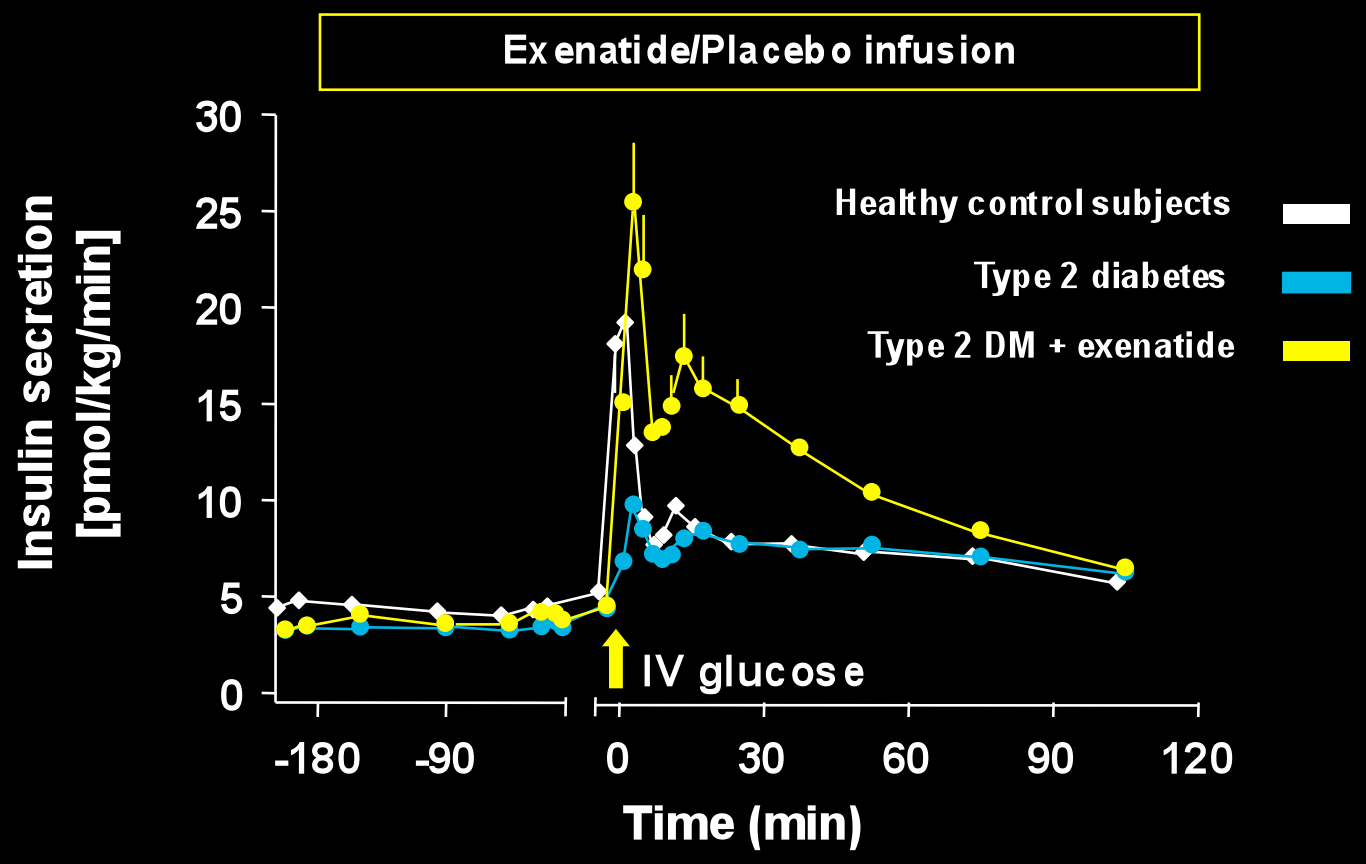
Kahn SE. *N Engl J Med*. 2006;355:2427-2443. Mazzone T. *JAMA*. 2006;296:2572-2581
Hanefeld M. *Cur Med Res Opin*. 2006;22:1211-1215. Tan MH. *Diabetes Care*. 2005;28:544-550
Nissen SE, et al. *JAMA*. 2008;299:1567-1573.

Incretin Based Therapy with GLP-1
Potential Impact on Disease Progression



Flint A et al. *J Clin Invest*. 1998;101:515-520. Larsson H et al. *Acta Physiol Scand*. 1997;160:413-422
Nauck MA et al., *Diabetologia*. 1996;39:1546-1553. Drucker DJ. *Diabetes*. 1998;47:159–169.

Exenatide Improves Phasic Insulin Secretion in Type 2 Diabetes



Fehse F et al. *J Clin Endocrinol Metab*. 2005 Nov;90(11):5991-7

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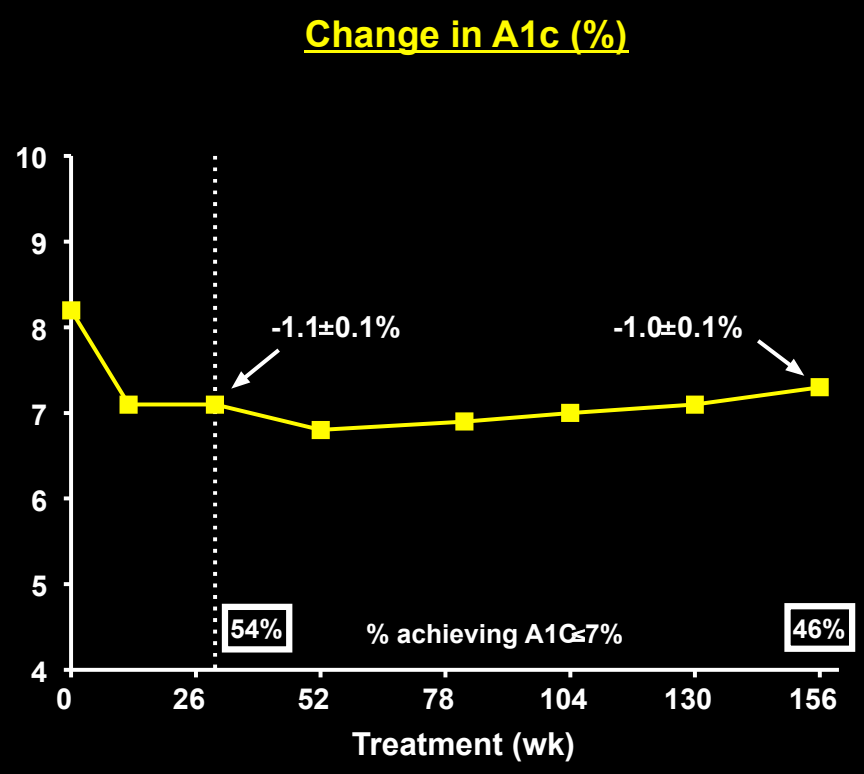
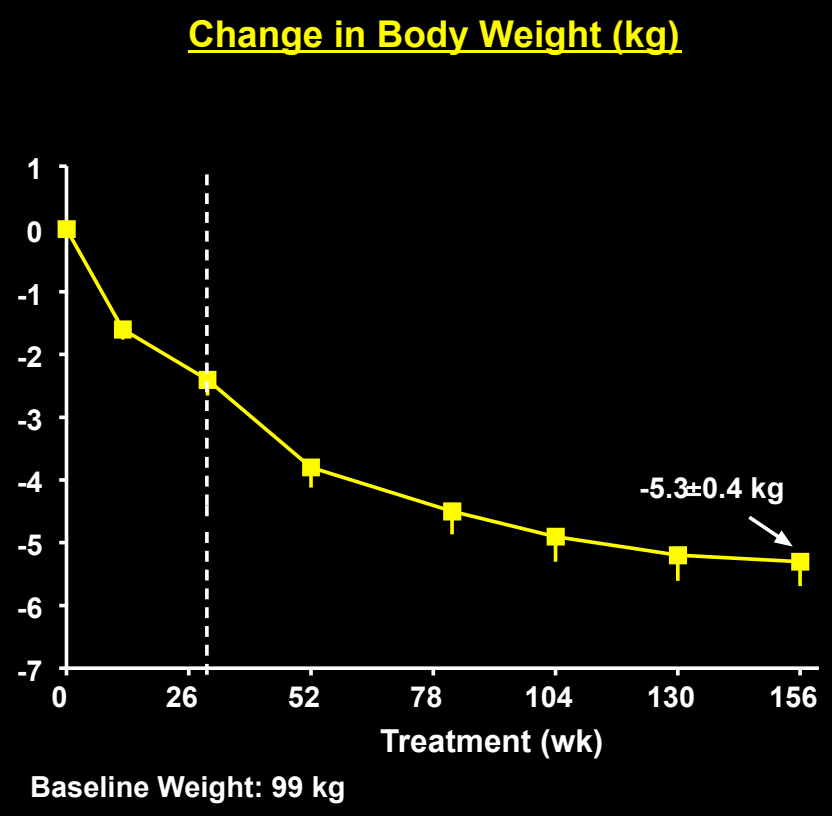
Incretin Based Therapies and Disease Progression
Impact of Exenatide Over 3 Years

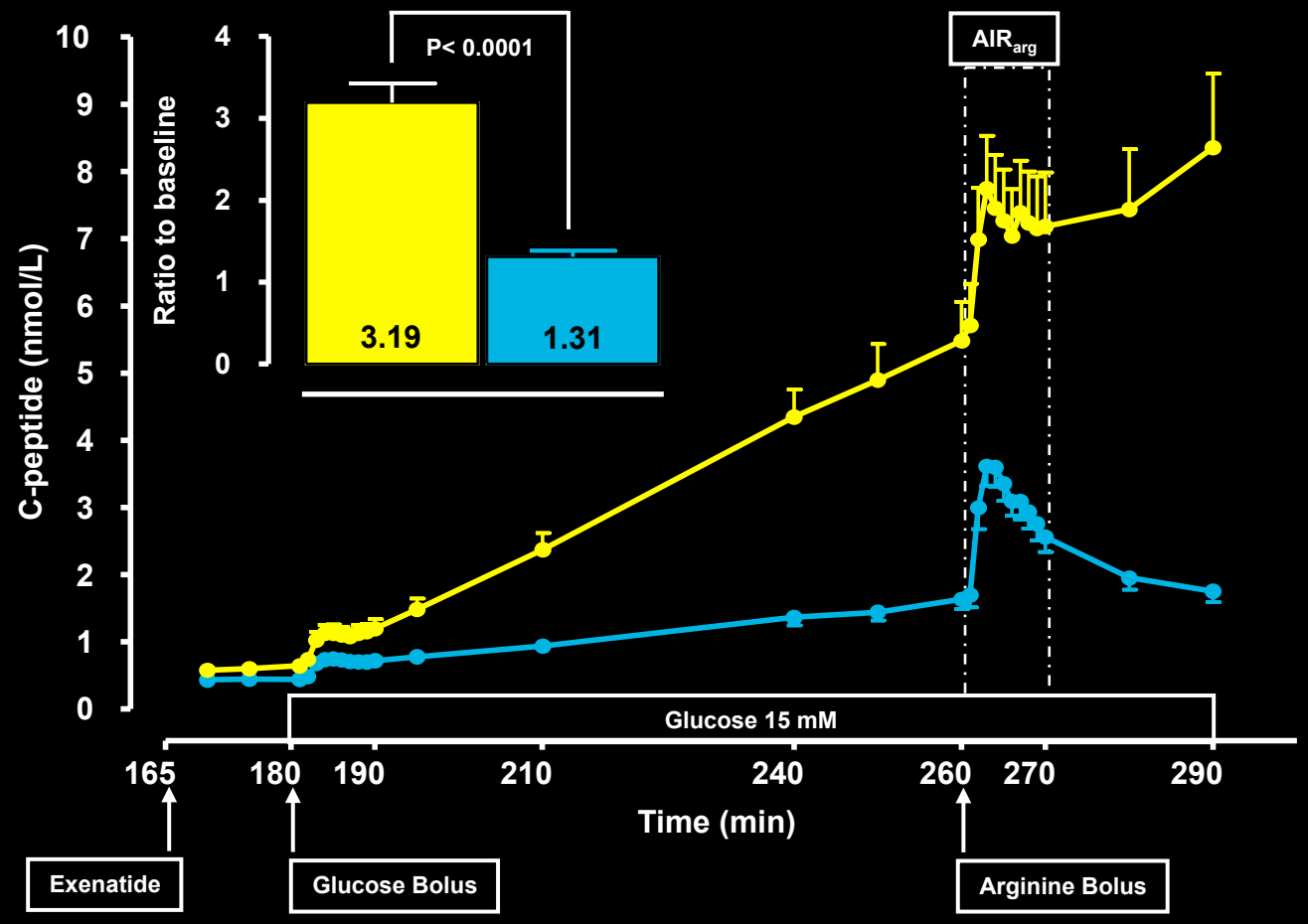




N = 217; Mean ± SE
Klonoff DC, et al. *Curr Med Res Opin* 2008; 24:275-286

Exenatide vs Glargine Over 1 Year

Impact on C-peptide Secretion During Hyperglycaemic Clamp



Mean (SE)

Bunck M. *Diabetologia.* EASD 2007/2008

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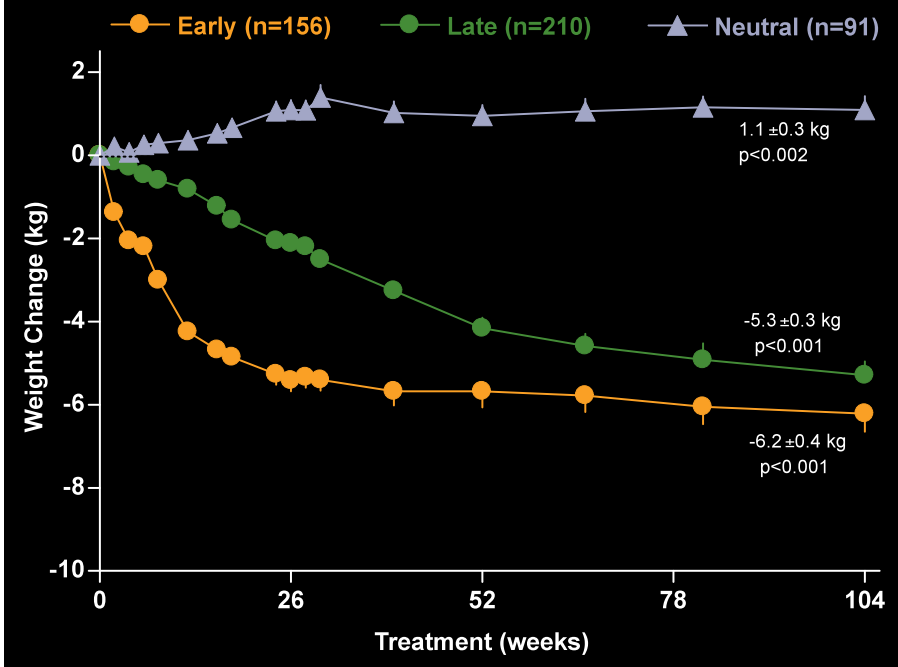
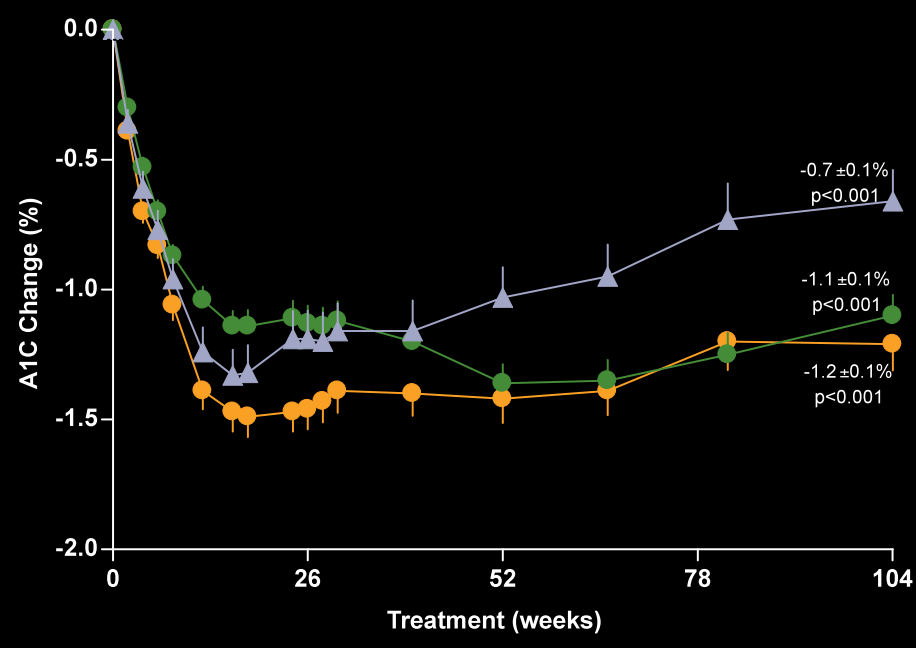
The Temporal Pattern of Weight Loss with Exenatide Therapy

Weight

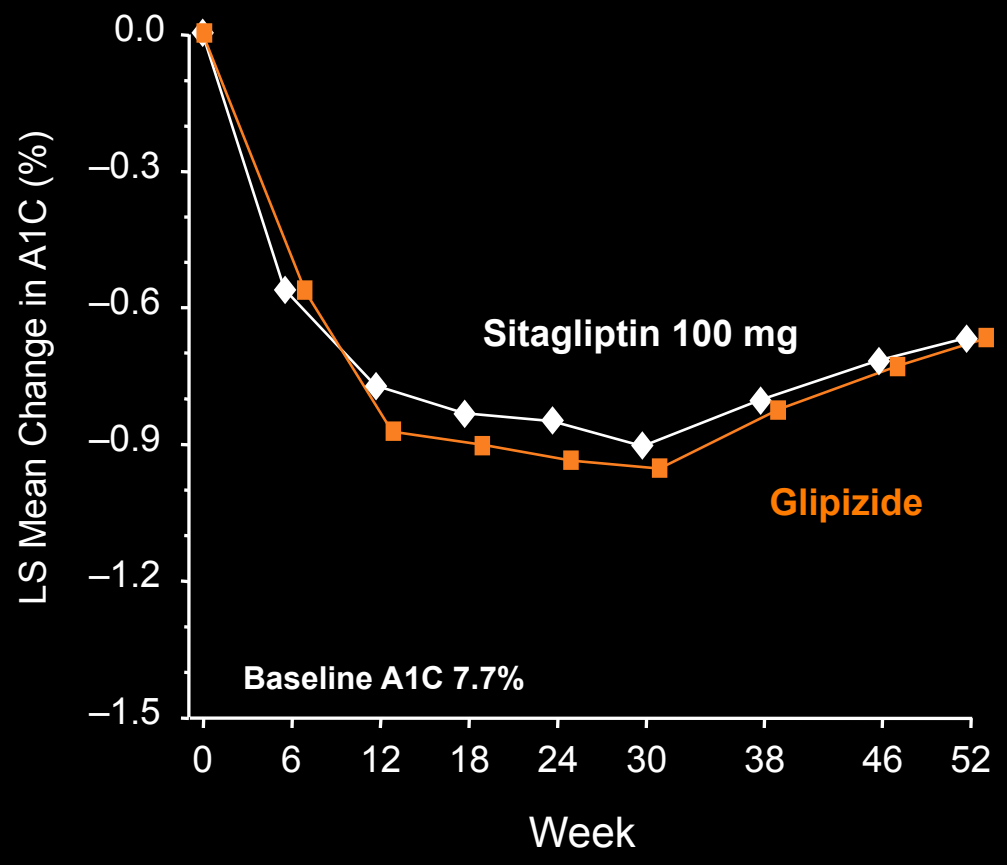


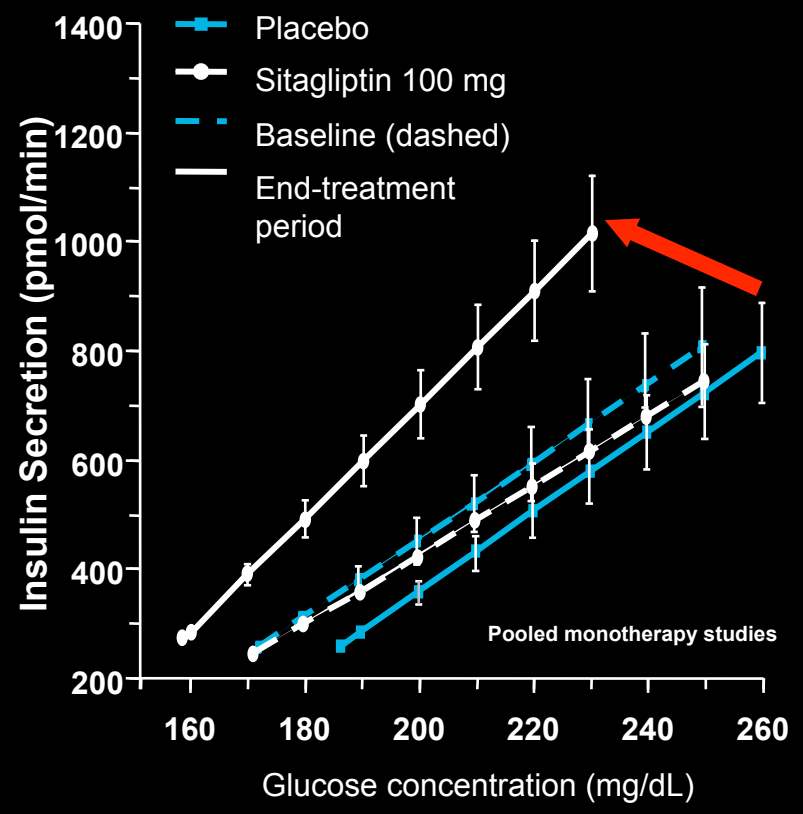
HbA1c



Kendall DM et al. Diabetes 2008. ADA Annual Scientific Sessions

Impact of DPP-4 Inhibitor on Glycemic Control and Beta Cell Function





Nauck M. *Diabetes Obes Metab*, 2007; 9:195-205
Xu L, et al. Diabetes Obes Metab. 2008;10:1212-20

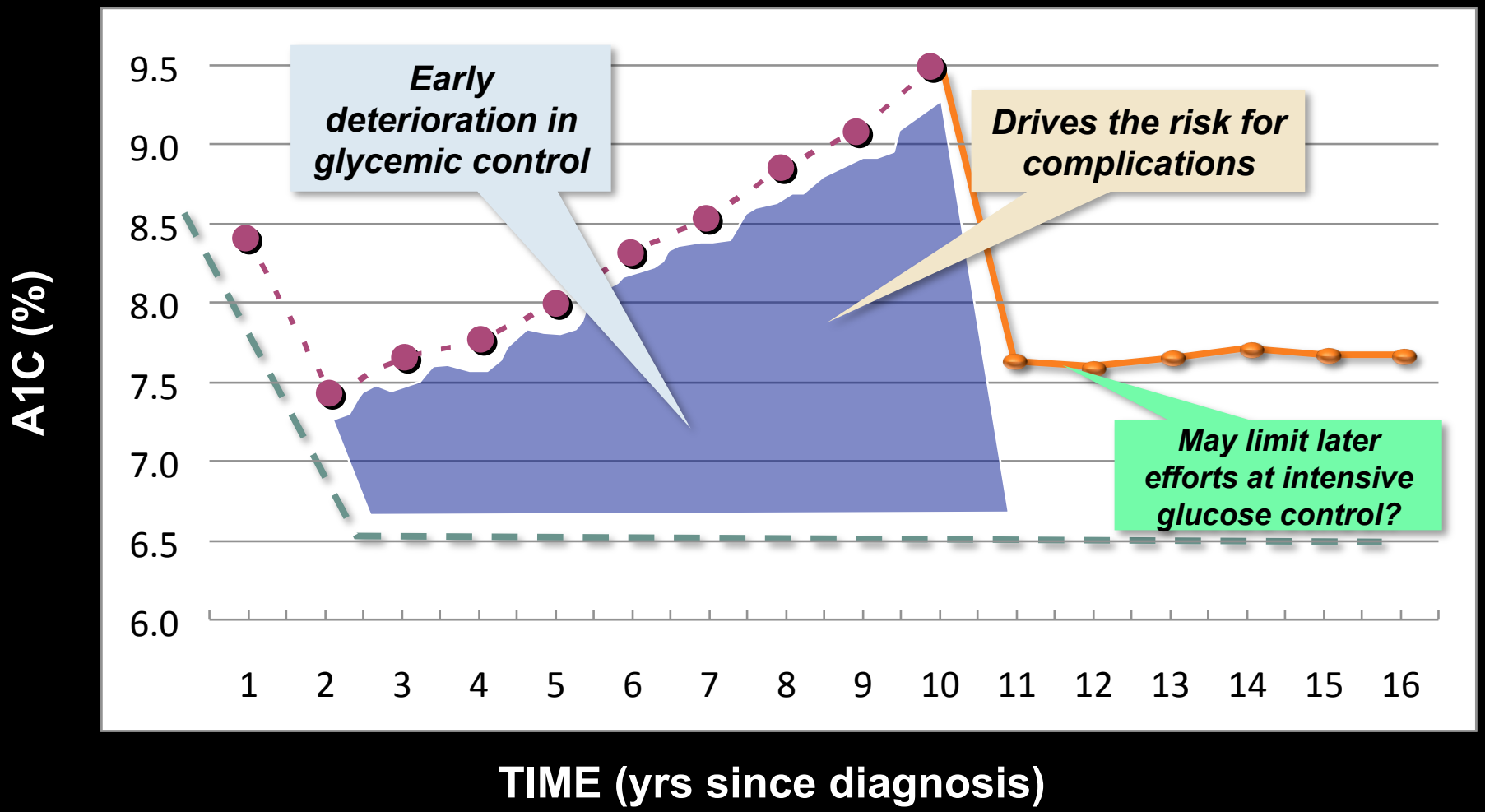
Impact of Type 2 Diabetes Therapy on Disease Progression: A Checklist

Therapy	Improved Insulin Secretion	Increased β cell mass	Diabetes Prevention	Disease Modification
Lifestyle (MNT)	No	No	Yes	No
Metformin	No	No	Yes	No
Sulfonylurea	Yes	No	No	No
Insulin	No	No	No	No
AGI	Yes	No	Yes	No
TZD	No	Yes	Yes	Yes
Incretin based Rx	Yes	Yes	?	?

A Glimpse of the Future: Implications for Clinical Care

- Early intervention and diabetes treatment response
  - Achieve and sustain glucose control
  - Legacy effect on risk of complications
- Therapeutic Options
  - Disease modification – targeting pathophysiologic defects
  - Sustain beta-cell responsiveness
  - Early combination therapy
- Limit factors that negatively impact treatment response
    - ? Hypoglycemia
    - ? Weight gain
    - ? Treatment tolerability and concordance

Clinical Implications of Disease Progression: The "Natural History" of Type 2 Diabetes



TIME (yrs since diagnosis)

Adapted from Prof. Stefano del Prato. EASD Commentary, Rome ITALY, 2008. With permission

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