



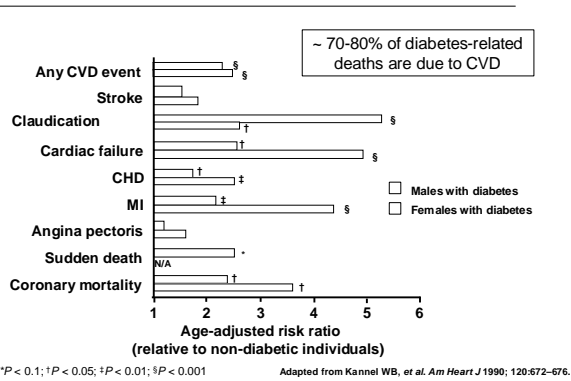
Cardiovascular Risk in Type 2 Diabetes: New Therapeutic Approaches

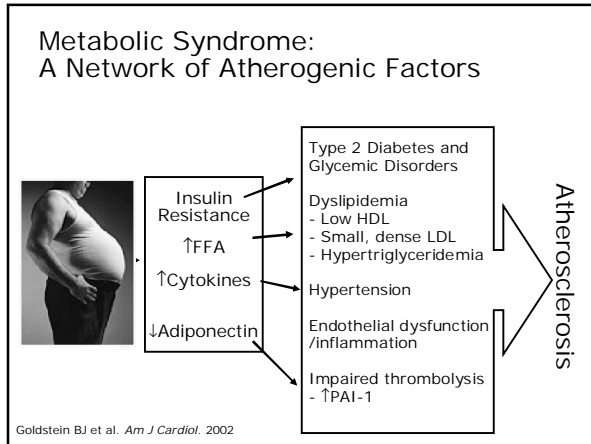
Barry J. Goldstein, MD, PhD
*Professor of Medicine, Biochemistry,
 and Molecular Pharmacology*
 Jefferson Medical College of
 Thomas Jefferson University
 Thomas Jefferson University Hospital
 Philadelphia, Pennsylvania

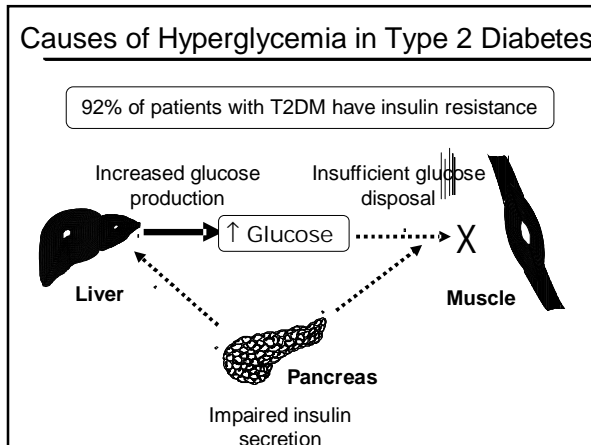
Cardiovascular Risk in the Spectrum of Type 2 Diabetes

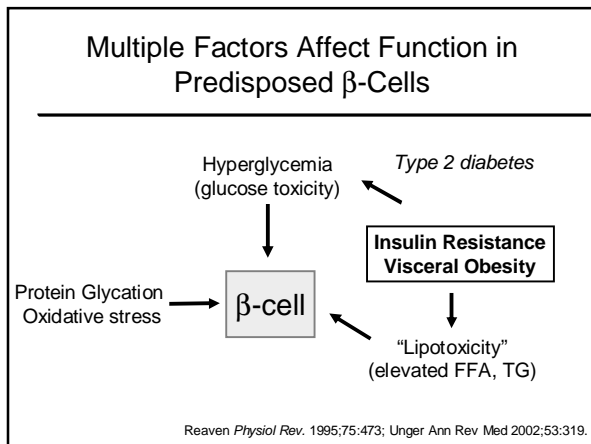
- Association of type 2 diabetes with CVD
- Opportunities for intervention
 - Provide aggressive and early treatment
 - Manage glucose along with CV risk factors
- Newer agents may prove useful
 - Exenatide (GLP-1 agonist)
 - Dual PPAR α/γ agonists (in development)

Type 2 diabetes increases the risk of CVD



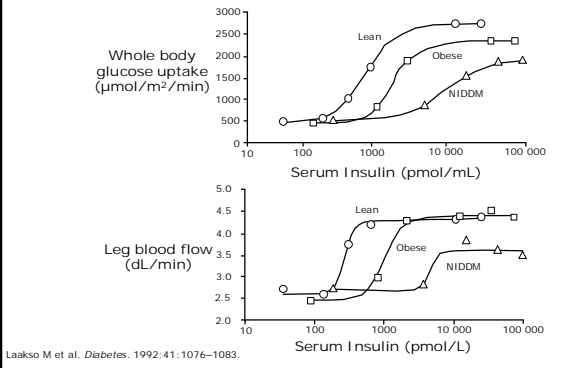




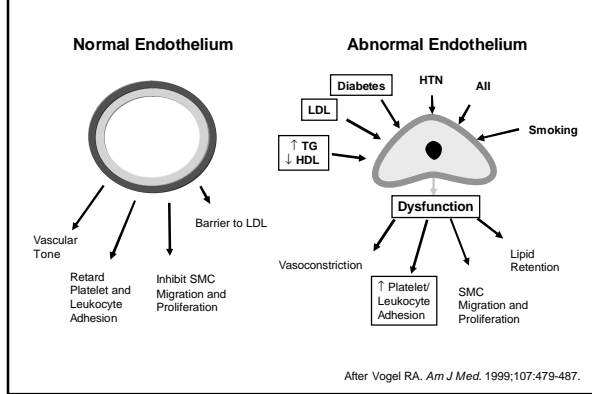




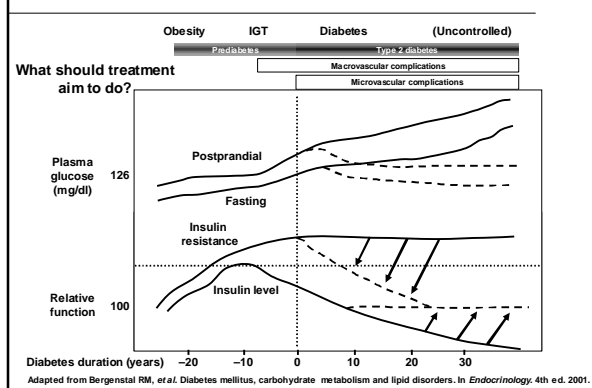
Diabetes Mellitus Impairs Endothelial Function



Endothelial Dysfunction and Vascular Disease



Modifying disease progression through treatment



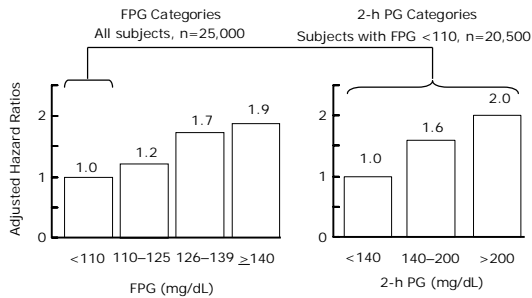


**A Continuum of Glycemia and CV Risk?
Evidence for No Glycemic Threshold**

- No A1C threshold is apparent
 - Finnish study by Kuusisto et al
 - UKPDS epidemiologic analysis
 - EPIC-Norfolk Study
- Impaired glucose tolerance (IGT) and postprandial hyperglycemia are CV risk factors
 - Funagata Diabetes Study
 - Honolulu Heart Program
 - DECODE Study
 - Rancho Bernardo Study

10

**FPG and 2-h PG Predict Mortality in Persons
Not Known to Have Type 2 Diabetes
DECODE Study**



FPG=fasting plasma glucose.
DECODE Study Group. *Lancet*. 1999; 354:617-621.

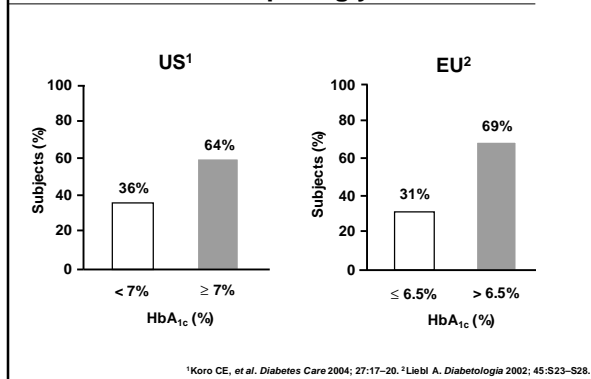
ADA, AACE and IDF glycemc goals

Biochemical index	ADA ^{1,2}		AACE ³		IDF ⁴ (Global)	
	mg/dl	mmol/l	mg/dl	mmol/l	mg/dl	mmol/l
HbA _{1c} (%)	< 7		≤ 6.5		≤ 6.5	
Fasting/preprandial plasma glucose	90-130	5.0-7.2	≤ 110	≤ 6.0	< 110	≤ 6.0
Postprandial plasma glucose	< 180	< 10.0	≤ 140	≤ 7.8	NA	NA
Bedtime plasma glucose	110-150	6.0-8.3	NA	NA	NA	NA

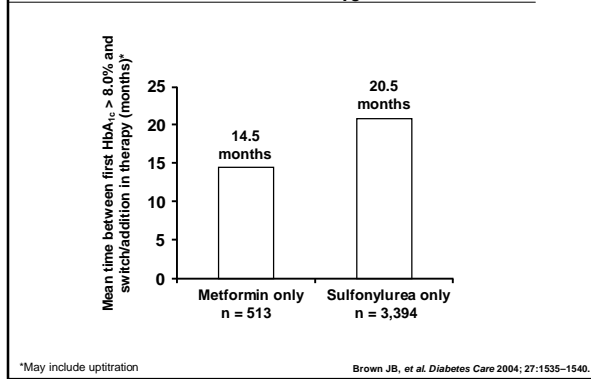
¹American Diabetes Association. *Diabetes Care* 2004; 27:S15-S35.
²American Diabetes Association. *Diabetes Care* 2002; 25:S35-S49.
³American Association of Clinical Endocrinologists. *Endocrine Pract* 2002; 8 (Suppl. 1):40-52.
⁴<http://www.idf.org/webdata/docs/IDF%20GGT20.pdf>.



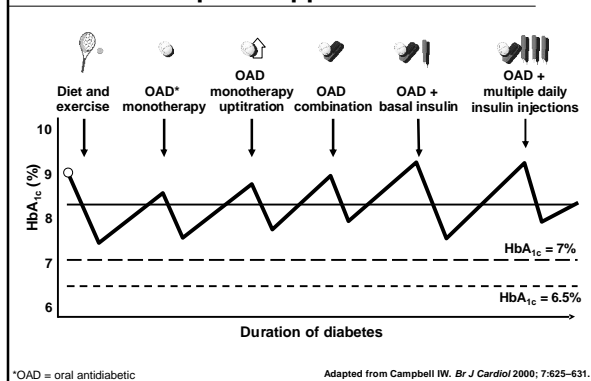
Majority of type 2 diabetes patients in US and EU have inadequate glycemic control

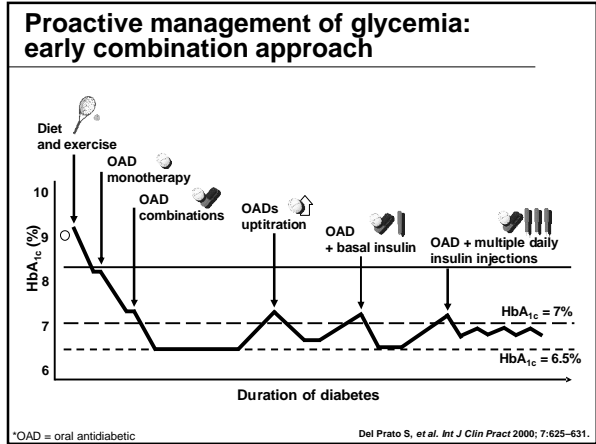


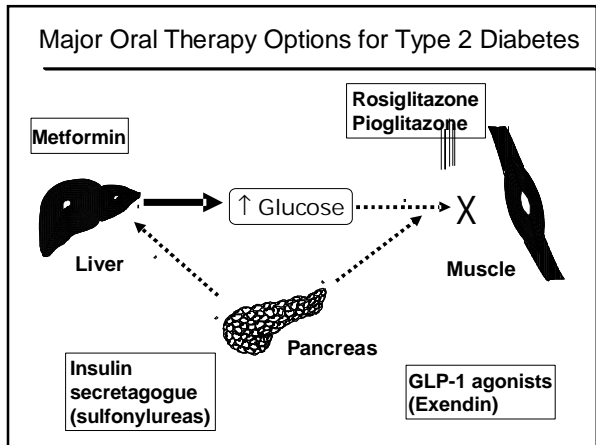
Patients remain on monotherapy > 1 year after first HbA_{1c} > 8.0%*

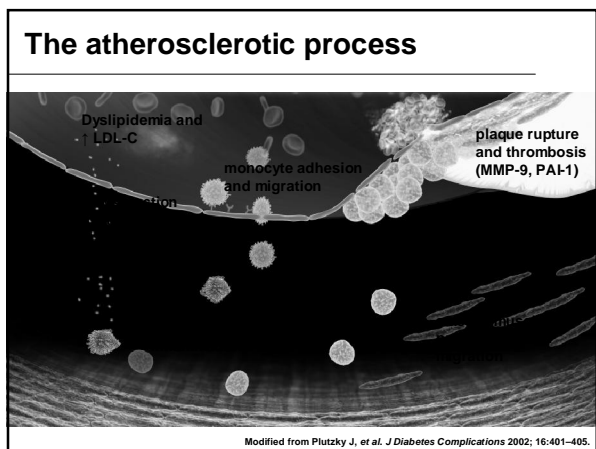


Conservative management of glycemia: traditional stepwise approach











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Metformin

<p>Advantages</p> <ul style="list-style-type: none"> • Unique mechanism of action • High initial response rate • "Insulin-sparing" with rare hypoglycemia • Long record of safety • Limited weight gain • Decreased macrovascular complications with monotherapy as observed in UKPDS 	<p>Disadvantages</p> <ul style="list-style-type: none"> • GI side effects in up to 50% • Not tolerated in up to 4% • Risk of lactic acidosis • Contraindicated in patients with impaired renal function and congestive heart failure
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DeFronzo. *Ann Intern Med.* 1999;131:281-303.
Inzucchi. *JAMA.* 2002;287:360-372.

UKPDS Intensive Therapy Risk Decrease: Benefit of Metformin

Endpoint	Decrease (%)	P-value
Any diabetes-related end point	32%	P=0.002
Diabetes-related mortality	42%	P=0.017
All-cause mortality	36%	P=0.011
MI	39%	P=0.01

American Diabetes Association. *Diabetes Care.* 1999;22(suppl 1):S27-S31.
UKPDS Group. *Lancet.* 1998;352:854-865.

Effect of Metformin on Cardiovascular Risk Factors

Meta-analysis of 32 studies involving a total of 2452 patients

Hgb A1c	-0.80% decrease	P<0.00001
Blood pressure	N.S.	
HDL-C	N.S.	
Triglycerides	10 mg/dL decrease	P=0.03
Total Chol	7.7 mg/dL decrease	P=0.0002
LDL-C	8.4 mg/dL decrease	P=0.00001

Wulfele et al., *Br J Clin Pharmacol* 2002 May



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Effect of Metformin on Endothelial Function and Inflammation

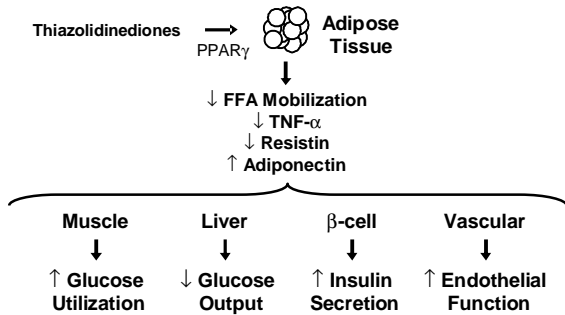
HOME trial: n=353, 16 wks Rx (MET vs. Placebo) + insulin

Albumin excretion	21% incr	P=0.06
vWF	6% decr	P= 0.0007
E-selectin	6% decr	P=0.08
VCAM-1	4% decr	P=0.0002
tPA	16% decr	P<0.0001
PAI-1	20% decr	P=0.0001
CRP, ICAM	No change	

MET improved endothelial fn, unrelated to glycemic control and weight, and without improvement of inflammatory markers

De Jager et al, J Int Med 2005;1:2

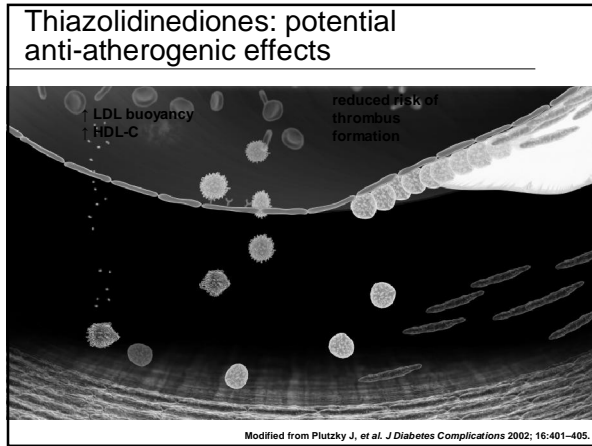
Effects of TZDs Mediated *via* Adipose Tissue

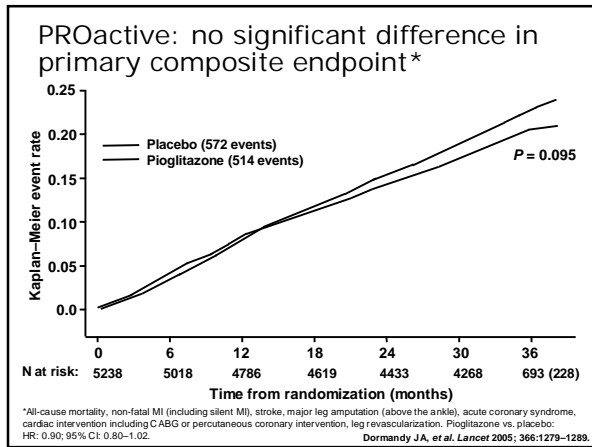


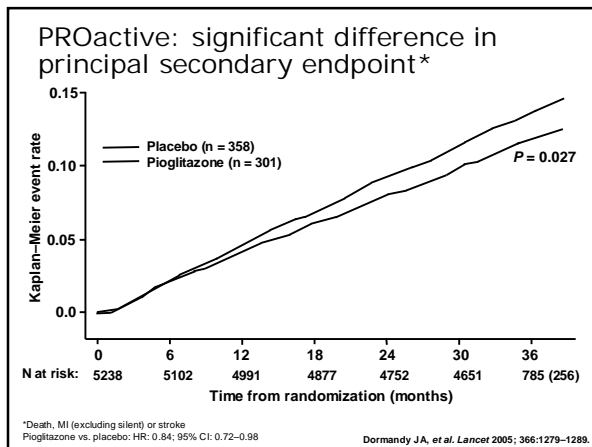
From Goldstein Am J Cardiol Suppl. 2002

Thiazolidinediones

<u>Advantages</u>	<u>Disadvantages</u>
<ul style="list-style-type: none"> • Unique mechanism of action • <u>Glycemic control without hypoglycemia</u> • Positive lipid effects • Can be used in patients with renal insufficiency • <u>Preservation of β-cell function</u> • Durable efficacy • Protective vascular effects • Protective renal effects 	<ul style="list-style-type: none"> • Weight gain • Fluid retention • Delayed onset of action • Clinical cardiovascular outcomes currently under study

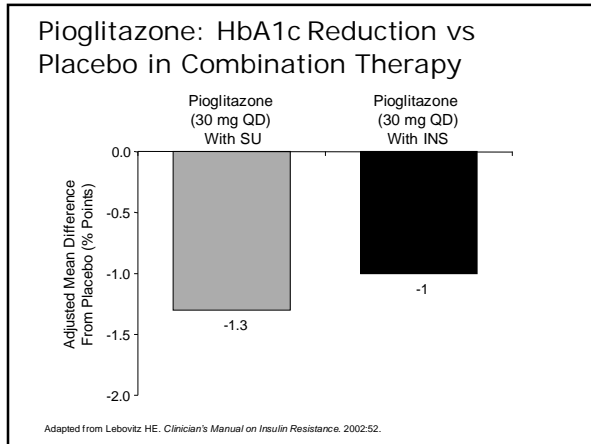


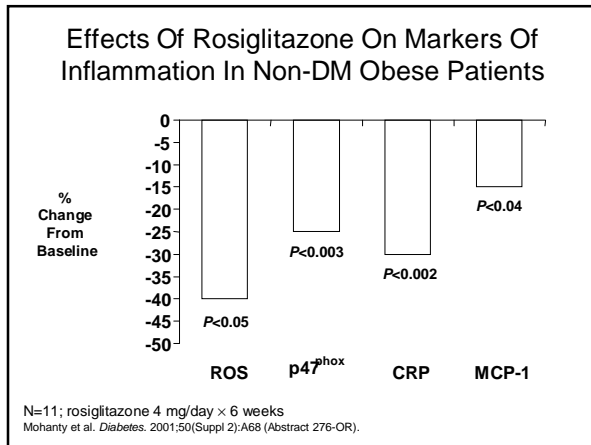


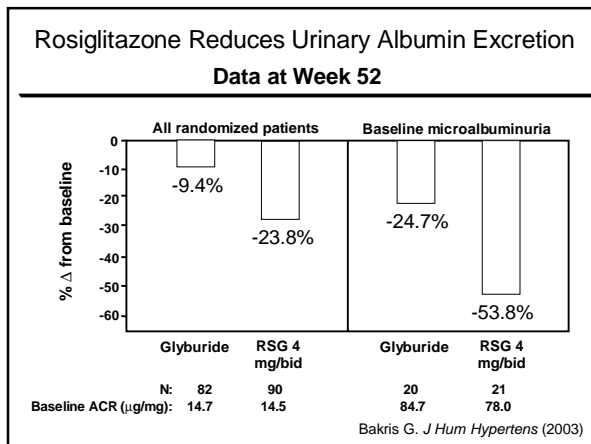




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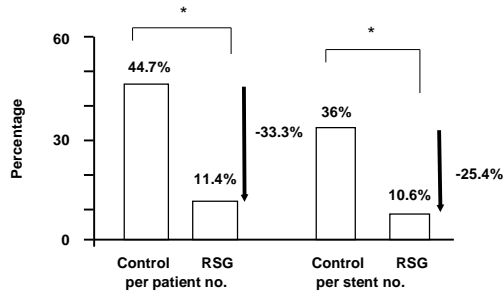








Rosiglitazone: Effect on in-stent Restenosis Rate After Coronary Angiography



*P < 0.01
Control n = 38 RSG n = 35
Quantitative coronary angiography (QCA)
Rosiglitazone 4 mg/day for 6 months

Choi et al. Diabetes Care 2004

Metabolic Effects of Oral Agents for T2DM

	TZD	Metformin	SU /Meglit	α-GI
Weight	↑	↓ or ↔	↑	↔
LDL-cholesterol	↑	small ↓	↔	↔
HDL-cholesterol	↑↑	small ↑	↔	↔
Triglycerides	↓ or ↔	small ↓	↔	↔
Free Fatty Acids	↓↓↓	↓	↓	↔
Insulin Resistance	↓↓	↓ or ↔	↔	↔
Hypertension	↓	↔	↔	↔
PAI-1	↓↓	↓	↔	↔
CRP	↓	↓ or ↔	↔	↔

Potential Advantages of Metformin-TZD Combination

- Reduced insulin resistance (TZD)
- Cardiovascular protection (Met and TZD)
- Potential preservation of pancreatic β cells (TZD)
- Minimal hypoglycemia (no ↑ insulin)
- Less weight gain (Met)
- Effective early in course of type 2 diabetes, when sufficient endogenous insulin is available



Insulin Secretagogues

Long Acting - sulfonylureas (glyburide, glipizide, glimepiride)
Short Acting (repaglinide, nateglinide)

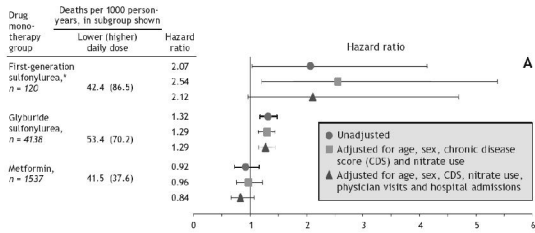
Advantages

- Improve insulin secretion
- High initial response rate
- No lag time
- Once-a-day or multiple dosing schemes possible

Disadvantages

- No insulin sensitization or vascular effects
- Hypoglycemia possible
- May exacerbate visceral fat accumulation
- Cardiovascular concerns: ischemic preconditioning
- May need caution in patients with hepatic and renal dysfunction

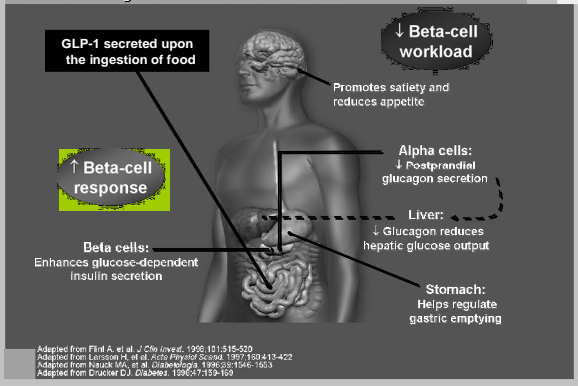
Higher Hazard Ratio for All-cause Mortality in SU Users vs. Metformin



Error bars indicate 95% confidence intervals. *Either chlorpropamide or tolbutamide.

Simpson et al. CMAJ 2006;174:169

GLP-1 Effects in Humans
Understanding the Natural Role of Incretins





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The Beginning

Exenatide

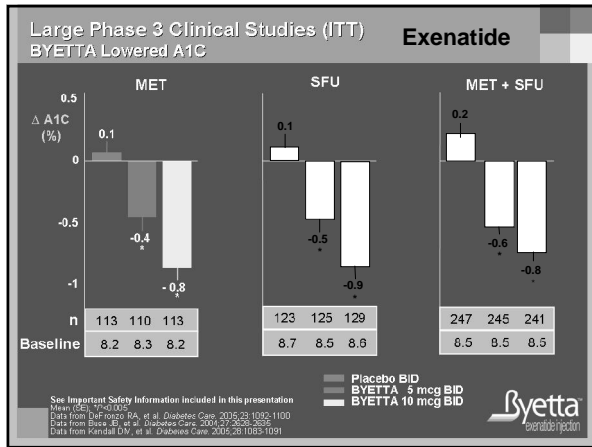
- Exenatide
 - Synthetic version of salivary protein found in the Gila monster
 - More than 50% overlap with human GLP-1
 - Binds to known human GLP-1 receptors on beta cells (*in vitro*)
 - Resistant to DPP-IV inactivation

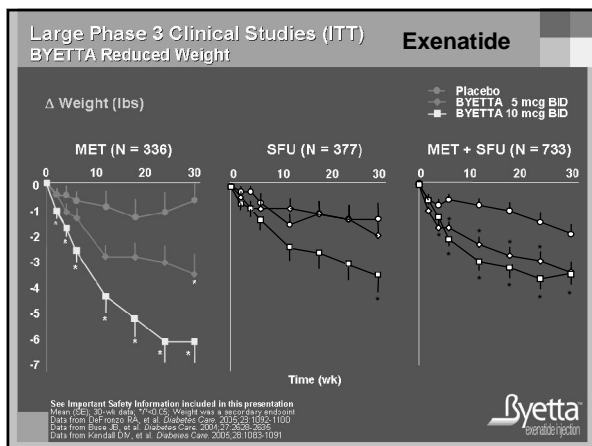
Exenatide	HCEGTF TSDLSKQMEEEAVRLFIEWLKNCGPSSGAPPPS-NH ₂
GLP-1 Human	HAEGTF TSDVSYLEGQAAKEFI AWLVKGR-NH ₂

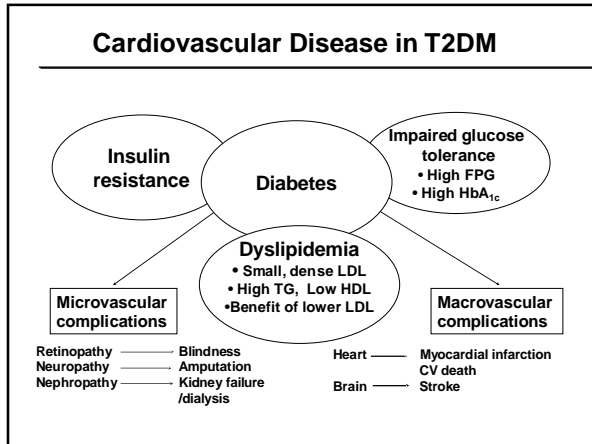
↑ Site of DPP-IV Inactivation

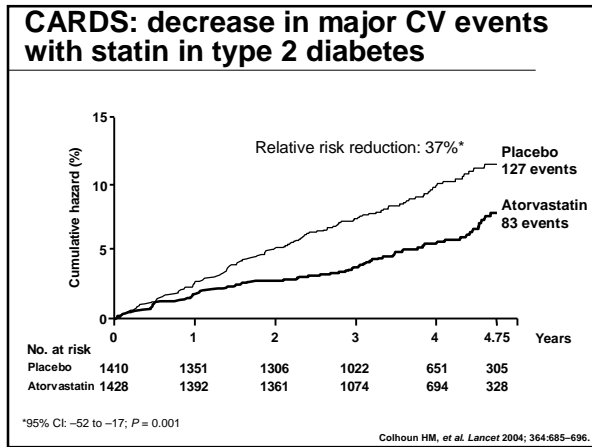
- Following injection, exenatide is measurable in plasma for up to 10 hours

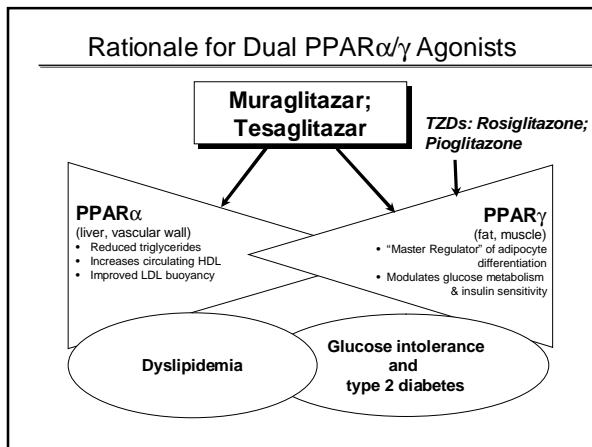
Adapted from Nielsen LL, et al. *Regul Pept*. 2001;117:77-88
Adapted from Koltman GG, et al. *Am J Health-Syst Pharm*. 2005;62:173-181













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Muraglitazar vs. Pioglitazone added to Metformin: results at week 50

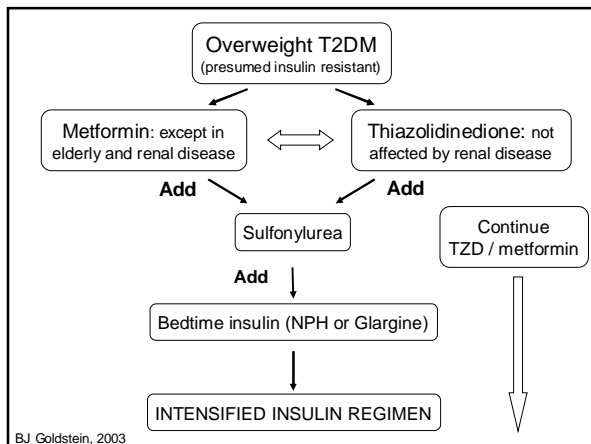
EFFICACY	PIO+MET	MURA+MET	Δ
TGs	↓ 11%	↓ 25%	16% (P<0.0001)
HDL-c	↑ 13%	↑ 17%	3% (P<0.0001)
SAFETY			
Body weight	↑ 1.5kg	↑ 2.5kg	
Edema-related events	8.9%	11.8%	
Additional CHF	n=1	n=2	
Additional deaths	0	4 (2 CV, 1 stroke, 1 cancer)	

26-week extension

Kendell DM. ADA 2005. Late breaker oral presentation.

Dual PPAR α / γ Agonists in Late Clinical Development for Type 2 Diabetes

- § **PPAR- γ Receptor – mediated effects**
 - § Dose limited glucose lowering \approx current TZD agents
 - § Dose-related side effects are similar
 - § weight gain
 - § fluid retention
- § **PPAR- α Receptor – mediated effects**
 - § Improved \uparrow HDL and \downarrow TG
 - § Effects on LDL lowering are dose-limited



BJ Goldstein, 2003

