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Cardiovascular Risk in Type 2 Diabetes: New Therapeutic Approaches

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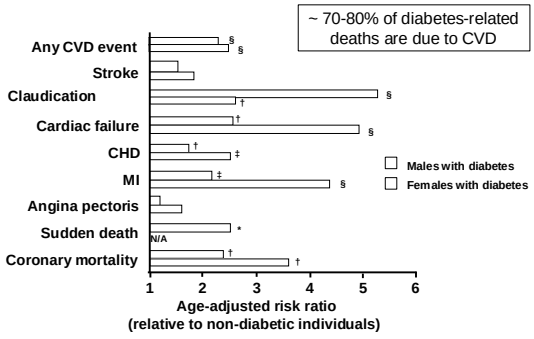
Cardiovascular Risk in the Spectrum of Type 2 Diabetes

- 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



*P < 0.1; †P < 0.05; ‡P < 0.01; §P < 0.001

Adapted from Kannel WB, *et al. Am Heart J* 1990; 120:672–676.

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Metabolic Syndrome: A Network of Atherogenic Factors

Insulin Resistance
↑FFA
↑Cytokines
↓Adiponectin

Type 2 Diabetes and Glycemic Disorders

Dyslipidemia
- Low HDL
- Small, dense LDL
- Hypertriglyceridemia

Hypertension

Endothelial dysfunction /inflammation

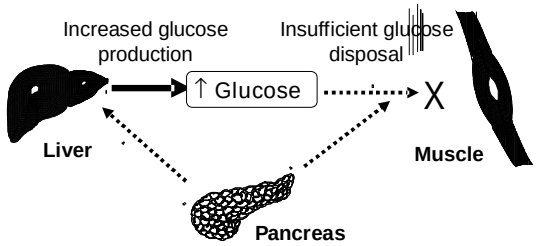
Impaired thrombolysis
- ↑PAI-1

Atherosclerosis

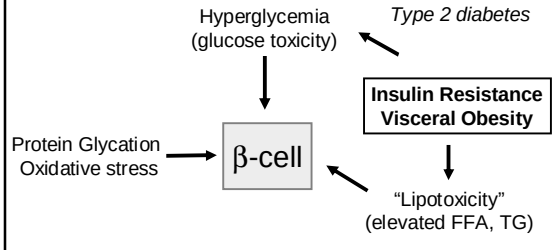
Goldstein BJ et al. *Am J Cardiol.* 2002

Causes of Hyperglycemia in Type 2 Diabetes

92% of patients with T2DM have insulin resistance



Multiple Factors Affect Function in Predisposed β-Cells



Reaven *Physiol Rev.* 1995;75:473; Unger Ann Rev Med 2002;53:319.

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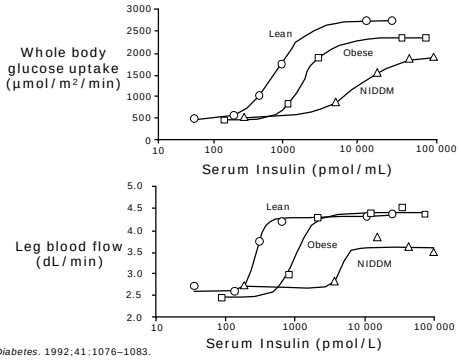
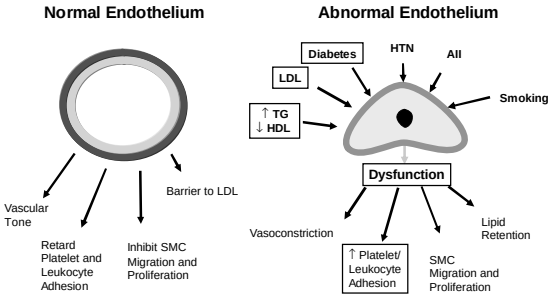
Diabetes Mellitus Impairs Endothelial Function



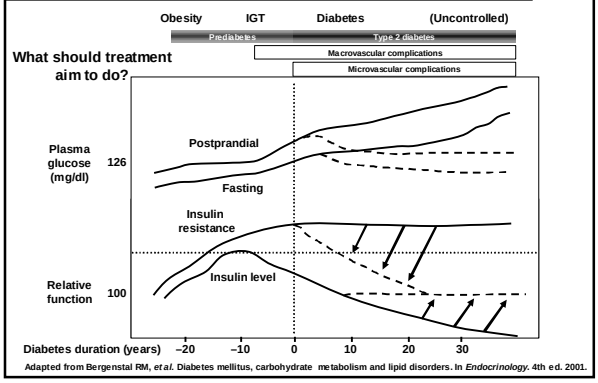
Laakso M et al. *Diabetes*. 1992;41:1076–1083.

Endothelial Dysfunction and Vascular Disease



After Vogel RA. *Am J Med*. 1999;107:479-487.

Modifying disease progression through treatment



Adapted from Bergenstal RM, *et al.* Diabetes mellitus, carbohydrate metabolism and lipid disorders. In *Endocrinology*. 4th ed. 2001.

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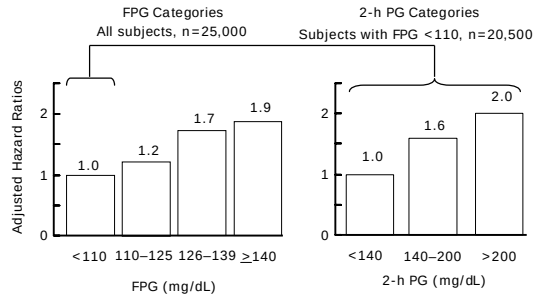
A Continuum of Glycemia and CV Risk?
Evidence for No Glycemic Threshold

- 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 glycemic goals

Biochemical index	ADA[1,2]		AACE[3]		IDF[4] (Global)	
HbA_{1c} (%)	< 7		≤ 6.5		≤ 6.5	
	mg/dl	*mmol/l*	mg/dl	*mmol/l*	mg/dl	*mmol/l*
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

[1] American Diabetes Association. *Diabetes Care* 2004; 27:S15–S35.
[2] American Diabetes Association. *Diabetes Care* 2002; 25:S35–S49.
[3] American Association of Clinical Endocrinologists. *Endocrine Pract* 2002; 8 (Suppl. 1):40–82.
[4] http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf.

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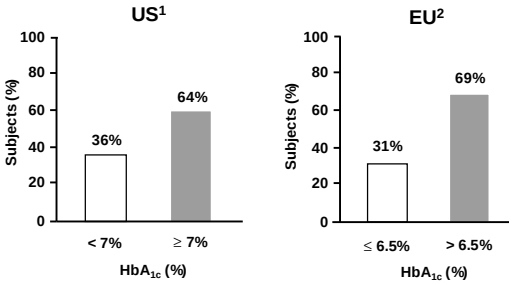
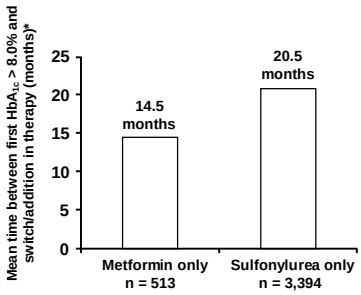
Majority of type 2 diabetes patients in US and EU have inadequate glycemic control



[1]Koro CE, *et al*. *Diabetes Care* 2004; 27:17–20. [2]Liebl A. *Diabetologia* 2002; 45:S23–S28.

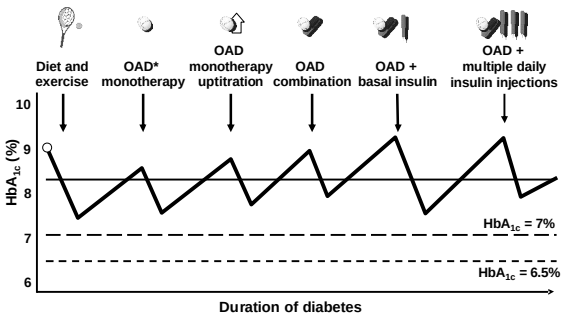
Patients remain on monotherapy > 1 year after first HbA_{1c} > 8.0%*



*May include uptitration

Brown JB, *et al. Diabetes Care* 2004; 27:1535–1540.

Conservative management of glycemia: traditional stepwise approach



*OAD = oral antidiabetic

Adapted from Campbell IW. *Br J Cardiol* 2000; 7:625–631.

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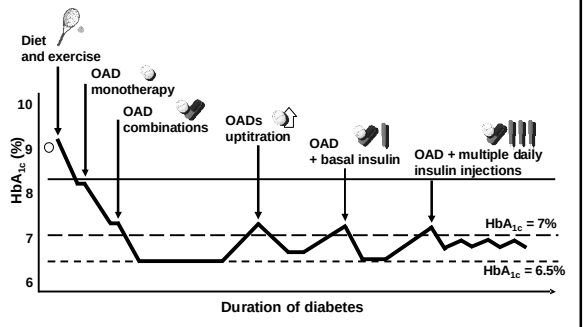
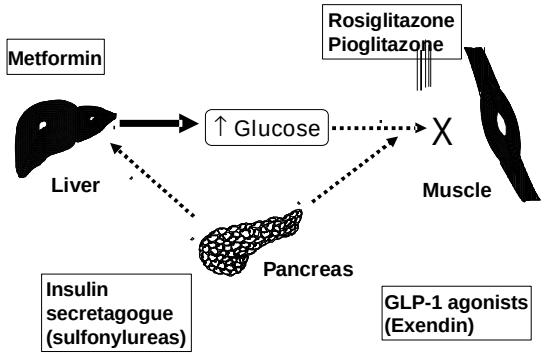
Proactive management of glycemia: early combination approach



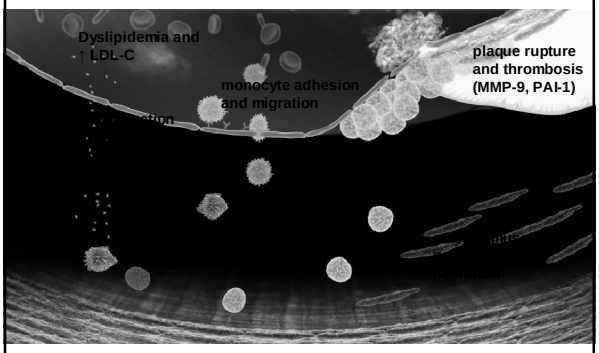
*OAD = oral antidiabetic

Del Prato S, *et al. Int J Clin Pract* 2000; 7:625–631.

Major Oral Therapy Options for Type 2 Diabetes



The atherosclerotic process



Modified from Plutzky J, *et al. J Diabetes Complications* 2002; 16:401–405.

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Metformin

Advantages

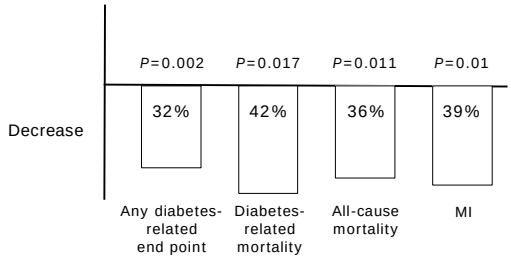
- Unique mechanism of action
- High initial response rate
- "Insulin-sparing" with rare hypoglycemia
- Long record of safety
- Limited weight gain
- Decreased macrovascular complications with monotherapy as observed in UKPDS

Disadvantages

- 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

DeFronzo. *Ann Intern Med.* 1999;131:281-303.
Inzucchi. *JAMA.* 2002;287:360-372.

UKPDS Intensive Therapy Risk Decrease: Benefit of Metformin



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

Wulffele et al., Br J Clin Pharmacol 2002 May

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Effect of Metformin on Endothelial Function and Inflammation

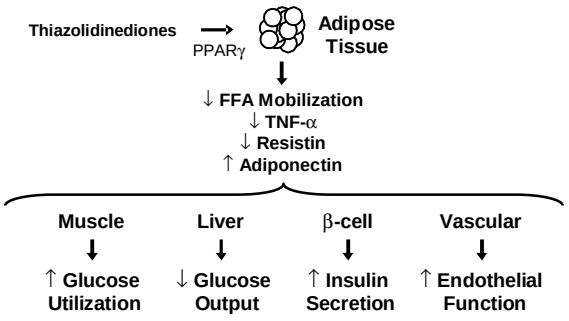
HOME trial: n=353, 16 wks Rx (MET vs. Placebo) + insulin

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

Advantages

- Unique mechanism of action
- Glycemic control without hypoglycemia
- Positive lipid effects
- Can be used in patients with renal insufficiency
- Preservation of β-cell function
- Durable efficacy
- Protective vascular effects
- Protective renal effects

Disadvantages

- Weight gain
- Fluid retention
- Delayed onset of action
- Clinical cardiovascular outcomes currently under study

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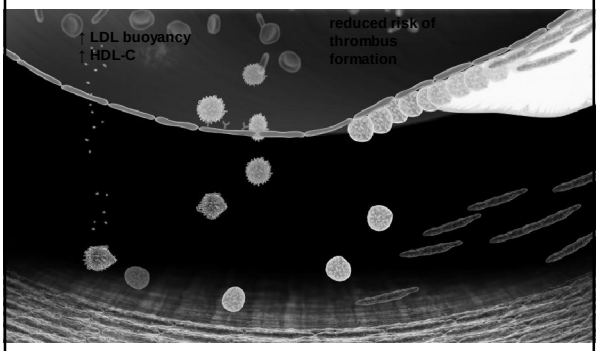
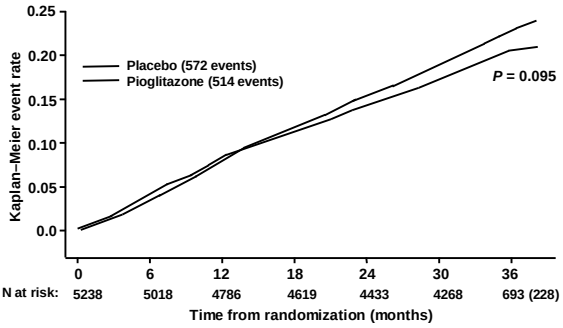
Thiazolidinediones: potential anti-atherogenic effects



Modified from Plutzky J, *et al. J Diabetes Complications* 2002; 16:401–405.

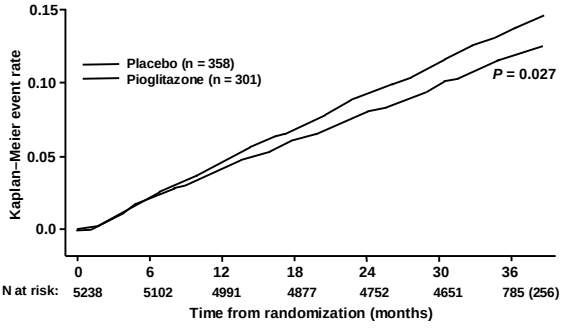
PROactive: no significant difference in primary composite endpoint*



*All-cause mortality, non-fatal MI (including silent MI), stroke, major leg amputation (above the ankle), acute coronary syndrome, cardiac intervention including CABG or percutaneous coronary intervention, leg revascularization. Pioglitazone vs. placebo: HR: 0.90; 95% CI: 0.80–1.02.

Dormandy JA, *et al. Lancet* 2005; 366:1279–1289.

PROactive: significant difference in principal secondary endpoint*



*Death, MI (excluding silent) or stroke
Pioglitazone vs. placebo: HR: 0.84; 95% CI: 0.72–0.98

Dormandy JA, *et al. Lancet* 2005; 366:1279–1289.

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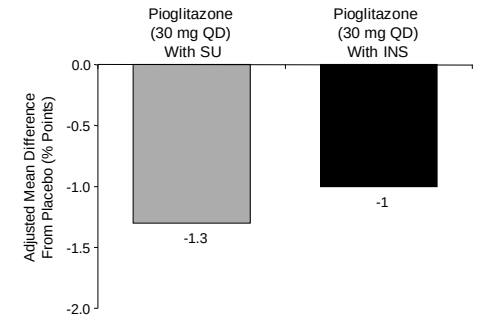
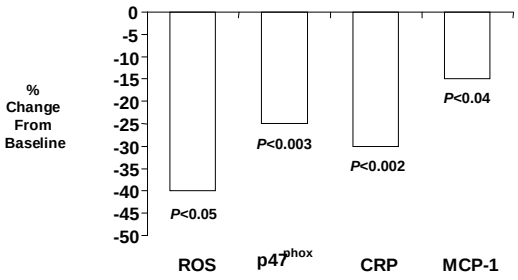
Pioglitazone: HbA1c Reduction vs Placebo in Combination Therapy



Adapted from Lebovitz HE. *Clinician's Manual on Insulin Resistance*. 2002:52.

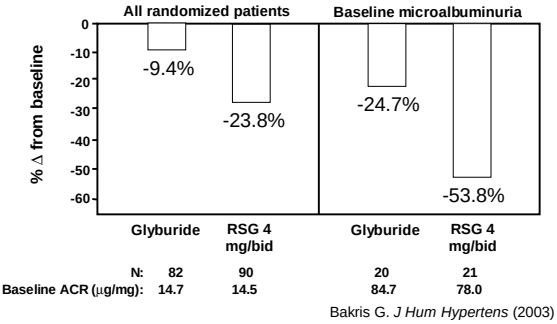
Effects Of Rosiglitazone On Markers Of Inflammation In Non-DM Obese Patients



N=11; rosiglitazone 4 mg/day × 6 weeks
Mohanty et al. *Diabetes*. 2001;50(Suppl 2):A68 (Abstract 276-OR).

Rosiglitazone Reduces Urinary Albumin Excretion

Data at Week 52



N:	82	90	20	21
Baseline ACR (μg/mg):	14.7	14.5	84.7	78.0

Bakris G. *J Hum Hypertens* (2003)

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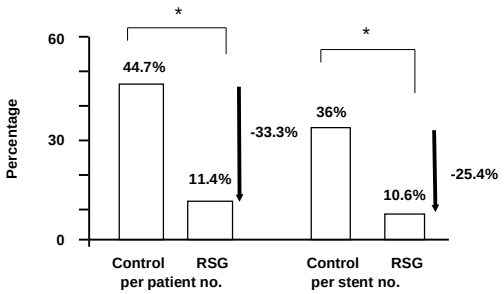
Rosiglitazone: Effect on in-stent Restenosis Rate After Coronary Angiography



*$P < 0.01$
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

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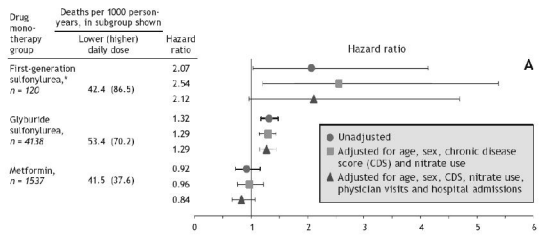
Insulin Secretagogues

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

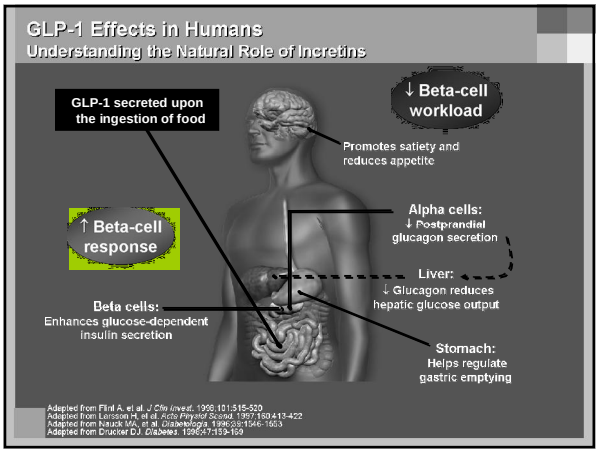
Advantages	Disadvantages
• Improve insulin secretion	• No insulin sensitization or vascular effects
• High initial response rate	• Hypoglycemia possible
• No lag time	• May exacerbate visceral fat accumulation
• Once-a-day or multiple dosing schemes possible	• Cardiovascular concerns: ischemic pre-conditioning
	• 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



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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	H G E G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S-NH_2
GLP-1 Human	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R-NH_2

Site of DPP-IV inactivation

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

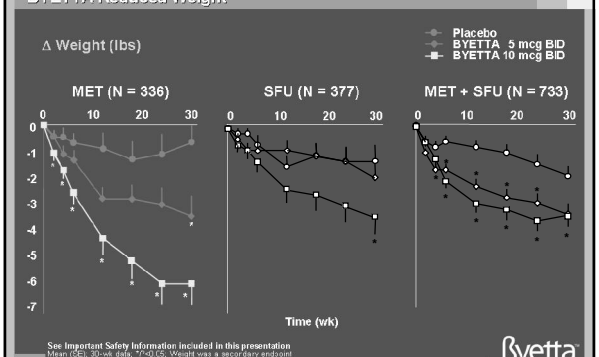
Adapted from Nielsen LL, et al. *Regul Pept.* 2004;117:77-88.
Adapted from Kolterman OG, et al. *Am J Health-Syst Pharm.* 2005;62:173-181.

Large Phase 3 Clinical Studies (ITT) — Exenatide
BYETTA Lowered A1C

See Important Safety Information included in this presentation
Mean (SE), $^{*}P<0.005$
Data from DeFronzo RA, et al. *Diabetes Care.* 2005;28:1092-1100.
Data from Buse JB, et al. *Diabetes Care.* 2004;27:2628-2635.
Data from Kendall DM, et al. *Diabetes Care.* 2005;28:1083-1091.

Byetta exenatide injection

Large Phase 3 Clinical Studies (ITT) — Exenatide
BYETTA Reduced Weight



See Important Safety Information included in this presentation
Mean (SE), 30-wk data, $^{*}P<0.05$. Weight was a secondary endpoint.
Data from DeFronzo RA, et al. *Diabetes Care.* 2005;28:1092-1100.
Data from Buse JB, et al. *Diabetes Care.* 2004;27:2628-2635.
Data from Kendall DM, et al. *Diabetes Care.* 2005;28:1083-1091.

Byetta exenatide injection

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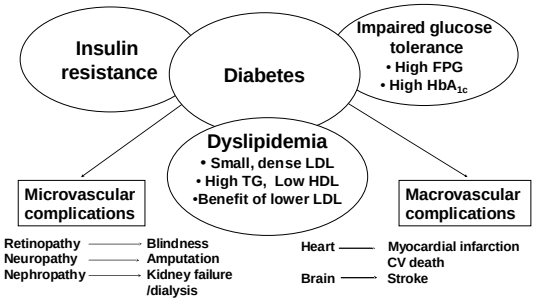
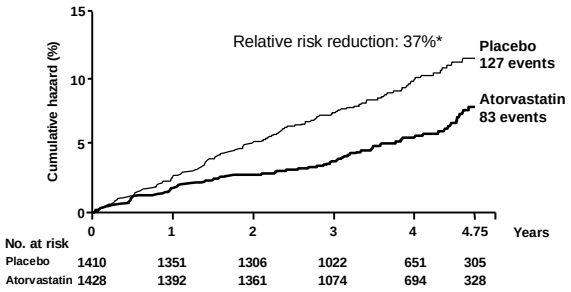
Cardiovascular Disease in T2DM



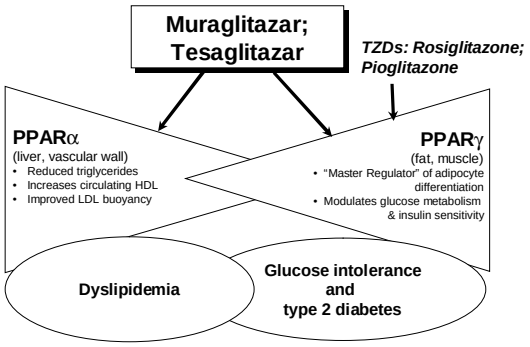
CARDS: decrease in major CV events with statin in type 2 diabetes



*95% CI: –52 to –17; *P* = 0.001

Colhoun HM, *et al. Lancet* 2004; 364:685–696.

Rationale for Dual PPARα/γ Agonists



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

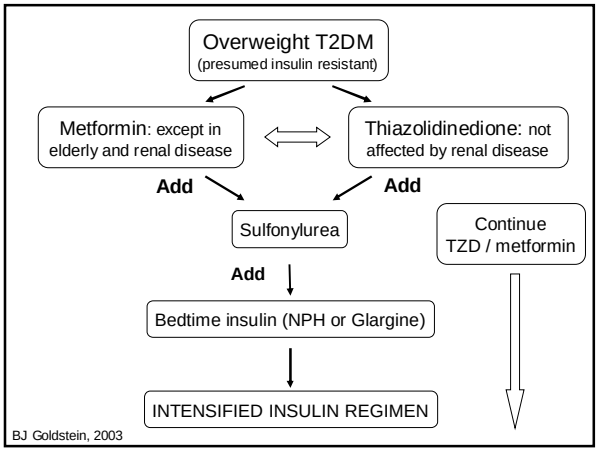
EFFICACY	PIO+MET	MURA+MET	Δ
TGs	↓ 11%	↓ 25%	16% (*P*<0.0001)
HDL-c	↑ 13%	↑ 17%	3% (*P*<0.0001)
SAFETY	**PIO+MET**	**MURA+MET**	
Body weight	↑ 1.5kg	↑ 2.5kg	
Edema-related events	8.9%	11.8%	
Additional CHF	n=1	n=2	
Additional deaths	0	4 (2 CV, 1 stroke, 1 cancer)	

26-week extension

Kendell DM. ADA 2005. Late breaker oral presentation.

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

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



BJ Goldstein, 2003

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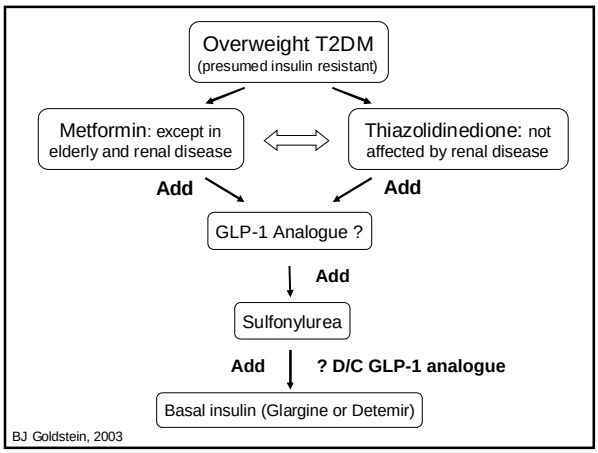

Outcome studies in IGT/IFG/T2DM: building the picture