Non – Insulin Pharmacological Treatment of Type 2 Diabetes

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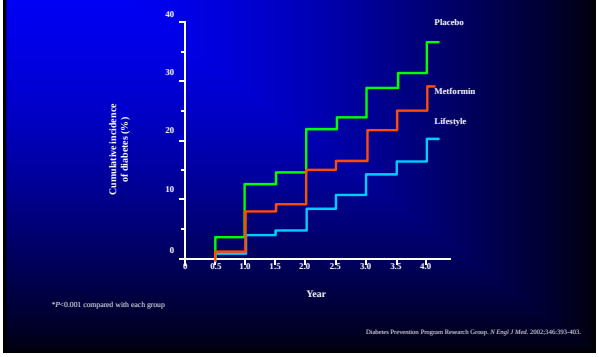
Disclosure Information
Vivian A. Fonseca, MD

- Research Support: American Diabetes Association, AstraZeneca, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, NIH, Novartis, Novo Nordisk, Pfizer, Takeda, sanofi-aventis
- Honoraria (Consulting and Lectures): AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Novartis, Novo Nordisk, Takeda, Pan American Laboratories, sanofi-aventis

Clinical Pearls

- **Prevention of type 2 diabetes is possible**
- **Cardiovascular and microvascular complications of type 2 diabetes begin prior to its clinical diagnosis**
- **Monotherapy fails in the majority of patients with type 2 diabetes**
- **Effective treatment strategies should include reduction in A1C, blood pressure, and cholesterol levels**
- **Improvement in cardiovascular outcomes in patients with type 2 diabetes remains a challenge**

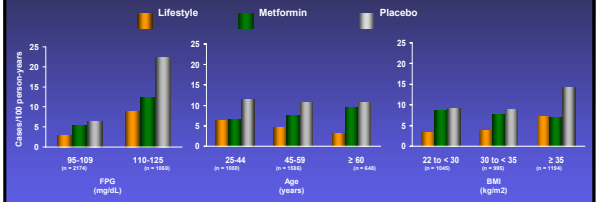
DPP: Incidence of Type 2 Diabetes



*P<0.001 compared with each group

Diabetes Prevention Program Research Group. *N Engl J Med.* 2002;346:393-403.

DPP: Baseline Predictors of Response to Metformin



- Lifestyle is more effective generally than metformin or placebo
- Metformin is more effective if FPG > 110 mg/dL, age < 60 years, and BMI > 30 kg/m2
- Gender, ethnicity, and 2-hour glucose were NOT predictive

DPP = Diabetes Prevention Program

Knowler WC, et al. *N Engl J Med.* 2002;346:393-403.

The ABCs of Diabetes Care

A1C
- ADA recommends < 7% = average glucose of 150 mg/dL
- AACE/IDF recommend ≤ 6.5% = average glucose of 135 mg/dL

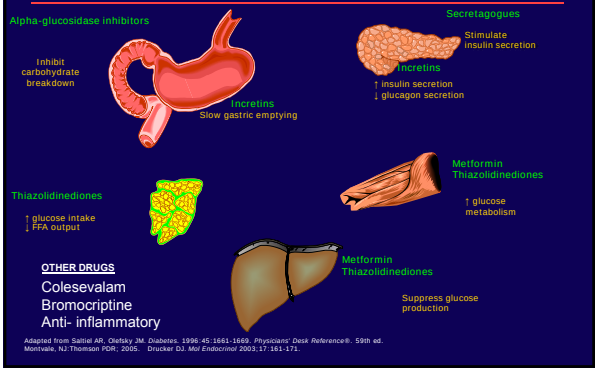
Blood pressure
- < 130/80 mm Hg

Cholesterol
- LDL-C: < 100 mg/dL (< 70 mg/dL in very high-risk patients)
- HDL-C: > 40 mg/dL in men and > 50 mg/dL in women
- Non-HDL-C: ≤ 130 mg/dL (< 100 mg/dL in high-risk patients)
- TGs: < 150 mg/dL

Don't forget aspirin!

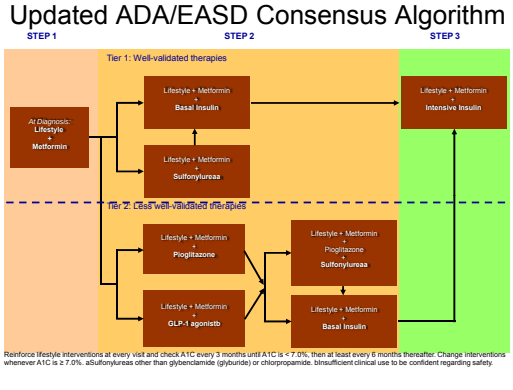
ADA Standards of Medical Care in Diabetes. *Diabetes Care.* 2005;28(suppl 1):S4-S36.
American Association of Clinical Endocrinologists. *Endocr Pract.* 2002;8(suppl 1):S8-S11.
International Diabetes Federation. *Diabetes Med.* 1999;16:716-730.

Therapy for Type 2 Diabetes: Sites of Action



Adapted from Saltiel AR, Olefsky JM. *Diabetes.* 1996;45:1661-1669. *Physicians' Desk Reference®.* 59th ed. Montvale, NJ:Thomson PDR; 2005. Drucker DJ. *Mol Endocrinol* 2003;17:161-171.

Updated ADA/EASD Consensus Algorithm



Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is < 7.0%, then at least every 6 months thereafter. Change interventions whenever A1C is ≥ 7.0%. aSulfonylureas other than glybenclamide (glyburide) or chlorpropamide. bInsufficient clinical use to be confident regarding safety.

Nathan DM, *et al. Diabetes Care.* 2008;31:1-11.

Selecting an Individualized Glycemic Regimen From Tier 1 or Tier 2

Tier 1 Agents

- When metformin is not tolerated or is contraindicated:
  - *Glomerular filtration rate < 30 mL/min*
- When a large reduction in A1C is needed:
  - *A1C reduction ≥ 1.5%*
- When medication cost is a hardship

Tier 2 Agents

- When avoidance of hypoglycemia is important:
  - *Certain occupations (eg, drivers, heavy equipment operators, using power tools, public safety jobs)*
  - *Certain populations (eg, history of hypoglycemia, alcohol use, elderly patients, renal insufficiency)*
- When promotion of weight loss is important

Adapted from Nathan DM, et al. *Diabetes Care.* 2009;32:193-203. Lassmann-Vague V. *Diabetes Metab.* 2005;31:5S53-5S57.

13 "Classes" of Agents Currently Available for Controlling Hyperglycemia

Class	A1C Reduction (%)	Fasting vs PPG	Hypoglycemia	Weight Change	Dosing (times/day)	Outcome Studies
Metformin	1.5	Fasting	No	Neutral	2	UKPDS
Insulin (Long Acting)	1.5-2.5	Fasting	Yes	Gain	1, injected	DIGAMI, UKPDS, (DCCT)
Insulin (Rapid Acting)	1.5-2.5	PPG	Yes	Gain	1-4, injected	DIGAMI, UKPDS, (DCCT)
Sulfonylureas	1.5	Fasting	Yes	Gain	1	UKPDS
Thiazolidinediones	0.5-1.4	Fasting	No	Gain	1	PROactive, RECORD
GLP-1 Agonists	0.5-1.0	PPG	No	Loss	2, injected	None

Adapted from Nathan DM, et al. *Diabetes Care*. 2006;29:1963-1972.
Nathan DM, et al. *Diabetes Care*. 2009;32:193-203.
American Diabetes Association. *Diabetes Care*. 2008;31(suppl 1):S12-S54.
U.S. Food and Drug Administration Center for Drug Evaluation and Research Web site. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA. Accessed August 11, 2009.

PPG: postprandial glucose

13 "Classes" of Agents Currently Available for Controlling Hyperglycemia (Cont.)

Class	A1C Reduction (%)	Fasting vs PPG	Hypoglycemia	Weight Change	Dosing (times/day)	Outcome Studies
Repaglinide	1.0-1.5	Both	Yes	Gain	3	None
Nateglinide	0.5-0.8	Both	Rare	Gain	3	NAVIGATOR (pending)
α-Glucosidase Inhibitor	0.5-0.8	PPG	No	Neutral	3	ACE (pending)
Amylin Mimetics	0.5-1.0	PPG	No	Loss	3, injected	None
DPP-4 Inhibitors	0.5-0.8	Both	No	Neutral	1	TECOS (pending)
Bile Acid Sequestrant	0.5	Fasting	No	Neutral	1-2	None
Bromocriptine	0.1	PPG	No	Neutral	1	None

DPP-4: dipeptidyl peptidase-4

Adapted from Nathan DM, et al. *Diabetes Care*. 2006;29:1963-1972.
Nathan DM, et al. *Diabetes Care*. 2009;32:193-203.
American Diabetes Association. *Diabetes Care*. 2008;31(suppl 1):S12-S54.
U.S. Food and Drug Administration Center for Drug Evaluation and Research Web site. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA. Accessed August 11, 2009.

Effect of Antidiabetic Agents on Weight

Weight Gain

- Insulin
- Sulfonylureas and other insulin secretagogues
- Thiazolidinediones

Weight Neutral or Slight Weight Loss

- α-Glucosidase inhibitors (acarbose, miglitol)
- Metformin
- DPP-IV inhibitors

Weight Loss

- GLP-1 mimetics
- Pramlintide

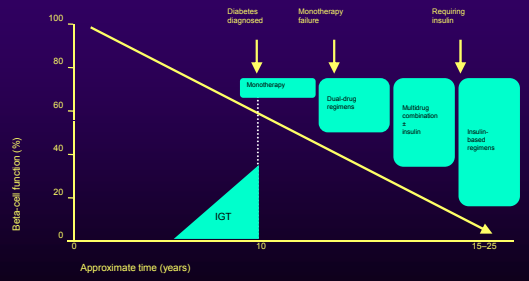
Changing Treatment Paradigm

Diet & exercise → Monotherapy → Combinations of oral agents → Insulin

- Problems
  - Glycemic targets often not met
  - Monotherapy not effective long-term
  - Treatment fails to address multiple impairments
  - Step-wise approach tends to perpetuate "failure"
  - Glucose toxicity interferes with treatment response

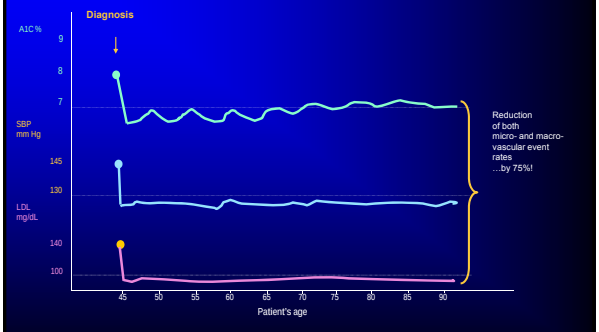
Harris, MI et al. *Diabetes Care*. 1999; 22: 403-408.
Harris, MI et al. *Diabetes Care*. 1998; 21: 518-524.

The Number of Medications Taken Usually Increases With Duration of Disease



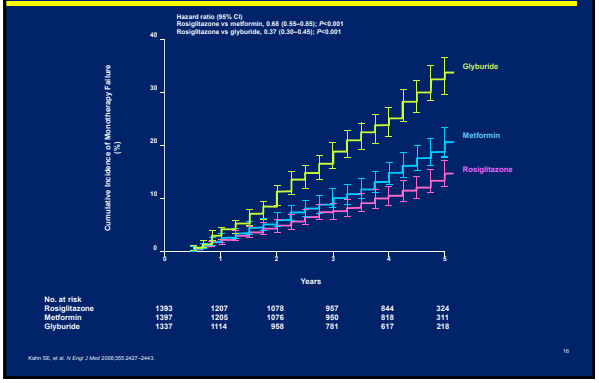
IGT = impaired glucose tolerance.
UKPDS 16 Group. *Diabetes*. 1995;44:1249–1258; Turner RC et al. *JAMA*. 1999;281:2005–2012; Warren RE. *Diabetes Res Clin Pract* 2004;65(suppl 1):S3–S8; Lebovitz HE. *Med Clin North Am*. 2004;88:847–863.

Primary Objectives of Effective Management



American Diabetes Association. *Diabetes Care*. 2003;26(suppl 1):S28-S32.
Gaede P et al. *N Engl J Med*. 2003;348:383-393.

Primary endpoint: Kaplan-Meier Estimates of the Cumulative Incidence of Monotherapy Failure



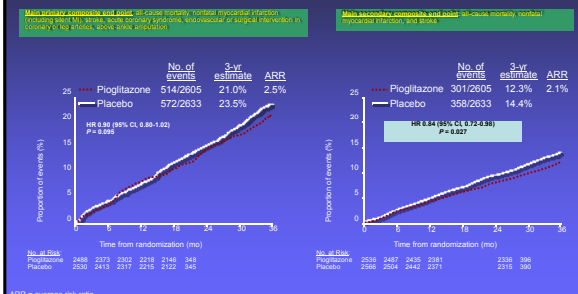
Kahn SE, et al. *N Engl J Med* 2006;355:2427–2443.

Thiazolidinediones (TZD's): Pioglitazone and Rosiglitazone

- Mechanism of action
  - Enhance insulin sensitivity in muscle, adipose tissue
  - Inhibit hepatic gluconeogenesis
  - Reduced rate of beta cell dysfunction
- Safety and efficacy
  - Decrease A1C 1-2%
  - Adverse effects: edema, weight gain, anemia; peripheral fractures in women, macular edema, (MIs - rosiglitazone*)
- Dosing
  - Initial dose (monotherapy): 1/2 to 2/3 maximum; dosing,1-2 x/day
  - Maximum effective dose: maximum dose
  - Titration frequency: weeks to month(s)

* Use no longer endorsed by ADA

PROactive Trial: Adding on Pioglitazone



ARR = average risk ratio
PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events

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

RECORD Trial

	Rosiglitazone (n = 2220)	Control (n = 2227)	Hazard Ratio (95 % CI)	*P* Value
Primary Outcome *(CV Hospitalization or CV Death)*	321	323	0.99 *(0.85-1.16)*	0.930
Death				
All cause	136	157	0.86 *(0.68-1.08)*	0.190
CV	60	71	0.84 *(0.59-1.18)*	0.320
MI*	64	56	1.14 *(0.80-1.63)*	0.470
Stroke*	46	63	0.72 *(0.49-1.06)*	0.100
CV Death, MI, or Stroke	154	165	0.93 *(0.74-1.15)*	0.500
Heart Failure*	61	29	2.10 *(1.35-3.27)*	0.001

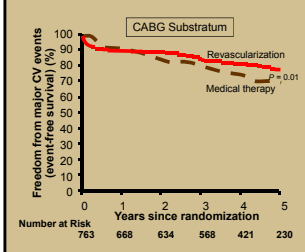
* Fatal and nonfatal

RECORD: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes

Home PD, et al. *Lancet.* 2009;373:2125-2135.

BARI 2D CABG Subgroup: Glycemic Control Reduces Risk of CV Events

BARI 2D tracked survival and freedom from major CV events in type 2 diabetes patients with heart disease following revascularization plus medical management vs medical management alone

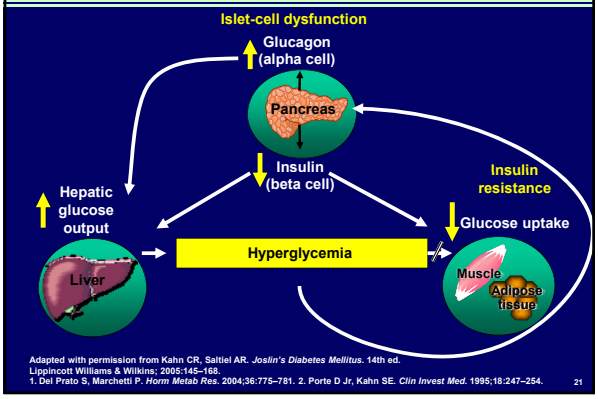


- Diabetes patients with coronary artery disease were stratified for either CABG or percutaneous coronary intervention
- Medical therapy: either insulin provision (*sulfonylurea/insulin*) or insulin sensitization (*metformin/thiazolidinedione*)
- In the CABG substratum, major CV events after revascularization were significantly lower than after medical therapy
- However, no difference in the overall analysis between prompt revascularization vs medical therapy
  - *Or between insulin provision vs insulin sensitization*

CABG: coronary-artery bypass graft

Frye RL, et al. *N Engl J Med.* 2009;360:2503-2515.

Major Pathophysiologic Defects in Type 2 Diabetes[1,2]



Adapted with permission from Kahn CR, Saltiel AR. *Joslin's Diabetes Mellitus.* 14th ed. Lippincott Williams & Wilkins; 2005:145–168.
1. Del Prato S, Marchetti P. *Horm Metab Res.* 2004;36:775–781. 2. Porte D Jr, Kahn SE. *Clin Invest Med.* 1995;18:247–254.

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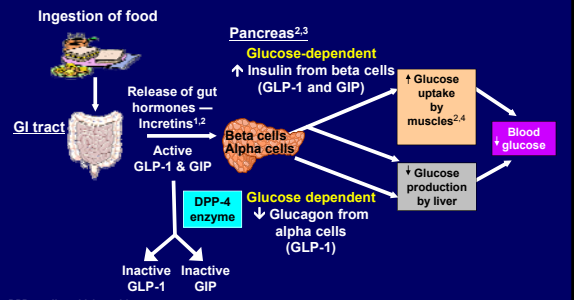
Role of Incretins in Glucose Homeostasis



DPP-4 = dipeptidyl-peptidase 4

1. Kieffer TJ, Habener JF. *Endocr Rev.* 1999;20:876–913.
2. Ahrén B. *Curr Diab Rep.* 2003;2:365–372.
3. Drucker DJ. *Diabetes Care.* 2003;26:2929–2940.
4. Holst JJ. *Diabetes Metab Res Rev.* 2002;18:430–441.

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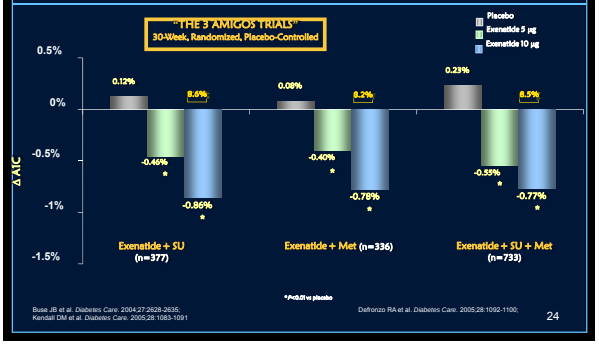
GLP–1 Replacement Therapy in T2DM in Developmetn

- Short-acting GLP–1 receptor agonists
  - ✓ Exenatide (Amylin/Lilly) - approved
  - ✓ Liraglutide (Novo Nordisk)- approved
  - ✓ AVE0010 (sanofi–aventis)
  - ✓ MKC253 Inhaled (MannKind)
- Long-Acting GLP–1 receptor agonists
  - ✓ LAR–exenatide (Amylin/Lilly)
  - ✓ Taspoglutide (R1583–Roche)
  - ✓ Albiglutide (Syncria®–GSK)
  - ✓ Lilly compound
  - ✓ Conjuchem compound

Exenatide + Oral Agents

Summary of A1C Changes

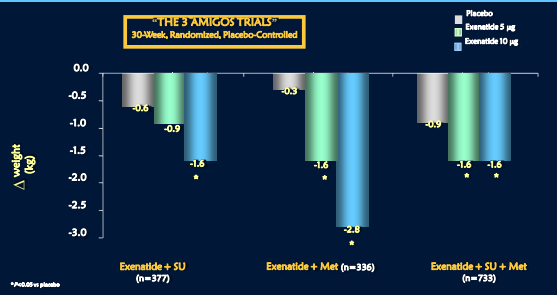


Buse JB et al. *Diabetes Care.* 2004;27:2628-2635;
Kendall DM et al. *Diabetes Care.* 2005;28:1083-1091
DeFronzo RA et al. *Diabetes Care.* 2005;28:1092-1100;

24

Exenatide + Oral Agents

Summary of Weight Changes



Buse JB et al. *Diabetes Care*. 2004;27:2628-2635; Kendall DM et al. *Diabetes Care*. 2005;28:1083-1091

DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100;

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Exenatide:
Potential for Type 2 Diabetes

Benefits

- Beta Cell Effect
  - Restored first-phase insulin
- Three AMIGOs Endpoints
  - A1C ↓ of ~ 0.8-0.9%
  - A1C ≤7% in ~35-45%
  - Weight Loss 1.6-2.8 kg
- Ongoing Open Label Study in Completers/Responders
  - Sustained A1C reductions ~1%
  - Sustained Weigh Loss ~3 kg

Limitations

- Nausea
  - Mild-Moderate ~40%
    - Tend to subside over time
  - Severe ~5%
  - Causing Withdrawal ~3%
- Vomiting
  - 13%
  - Causing Withdrawal ~1%
- Twice Daily Injections
- Cost
- No Long-Term Controlled Study

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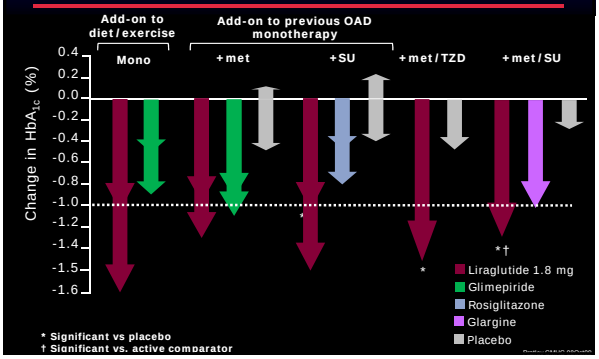
Exenatide Added to Ongoing Therapy Improves Risk Factors

Parameter	Change From Baseline	*P* Value (n = 151)
Body Weight (kg)	– 5.3 ± 0.5	< 0.0001
A1C (%)	– 0.8 ± 0.1	< 0.0001
Total Cholesterol (mg/dL)	– 10.8 ± 3.1	0.0007
Triglycerides (mg/dL)	– 44.4 ± 12.1	0.0003
LDL-C (mg/dL)	– 11.8 ± 2.9	< 0.0001
HDL-C (mg/dL)	+ 8.5 ± 0.6	< 0.0001
Systolic Blood Pressure (mm Hg)	– 3.5 ± 1.2	0.0063
Diastolic Blood Pressure (mm Hg)	– 3.3 ± 0.8	< 0.0001

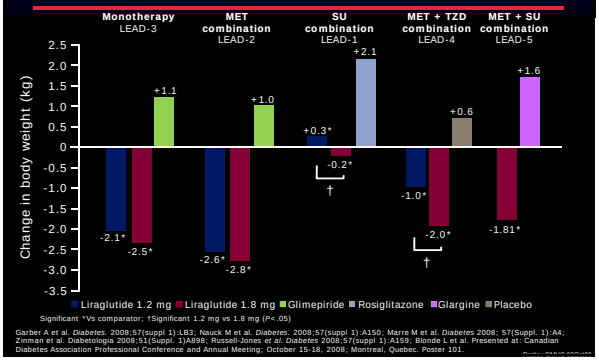
Open-label extension study; 527 patients using metformin and/or sulfonylurea added exenatide 5 µg BID for 4 weeks followed by 10 µg BID thereafter; 151 subjects with baseline lipid measurements completed 3.5 years of treatment

Klonoff DC, et al. *Curr Med Res Opin*. 2008;24:275-286.

Liraglutide Reduces HbA_{1c} as Monotherapy and in Combination Therapy



LEAD: Weight Reduction With Liraglutide



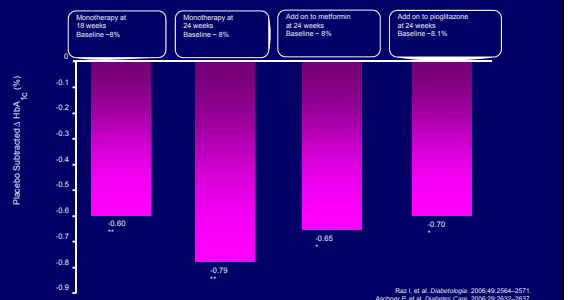
Significant *Vs comparator; †Significant 1.2 mg vs 1.8 mg ($P<.05$)

Garber A et al. *Diabetes.* 2008;57(suppl 1):LB3; Nauck M et al. *Diabetes.* 2008;57(suppl 1):A150; Marre M et al. *Diabetes* 2008; 57(Suppl. 1):A4; Zinman et al. Diabetologia 2008;51(Suppl. 1)A898; Russell-Jones *et al. Diabetes* 2008;57(suppl 1):A159; Blonde L et al. Presented at: Canadian Diabetes Association Professional Conference and Annual Meeting; October 15-18, 2008; Montreal, Quebec. Poster 101.

Comparison of DPP-4 Inhibitors

	Sitagliptin	Alogliptin	Saxagliptin	Vildagliptin
Usual Phase 3 Dose	100 mg QD	25 mg QD	5mg QD	50 mg BD
Half Life (t1/2)	12.4h	12.5 to 21.1h (25mg)	2.2 to 3.8h	1.3-2.4h
DPP-4 inhibition at 24h	~80% at 24h	~78% at 24h (25 mg)	5 mg: ~55% at 24h	~50% at 24h (100 mg)
Elimination	Kidney (mostly unchanged)	Kidney (mostly unchanged)	Liver and kidney Active metabolite	Kidney>>Liver Inactive metabolite
Renal Dose Adjustments Required	Yes	Yes	Yes	None for mild impairment; not recommended for moderate or severe impairment
Selectivity for DPP-4	>2600 fold vs DPP-8 >10,000 fold vs DPP-9	>10,000 fold vs DPP-8/9	>400 fold vs DPP-8 >100 vs DPP-9	>90 fold vs DPP-8
Potential for DDI	Low	Low	Strong CYP3A4/5 inhibitors[d]	Low
Food effect	No	No	No	No

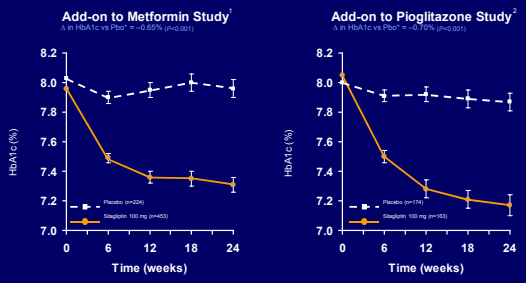
HbA_{1c} Reductions with Sitagliptin in Monotherapy and Add-on Combination Therapy



Raz I, et al. *Diabetologia*. 2006;49:2564–2571.
Aschner P, et al. *Diabetes Care*. 2006;29:2632–2637.
Charbonnel B, et al. *Diabetes Care*. 2006;29:2638–2643.
Rosenstock J, et al. *Clin Ther*. 2006;28:1556–1568.

Efficacy of Add-on Sitagliptin

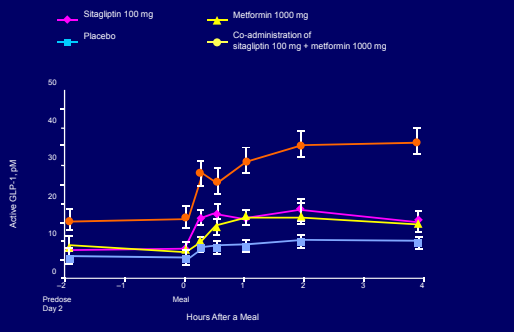
24-week placebo-adjusted results



*LSM between-group differences at Week 24. LSM = least squares mean.

1. Charbonnel B et al. *Diabetes Care*. 2006;29:2638–2643.
2. Rosenstock J et al. *Clin Ther*. 2006;28:1556–1568.

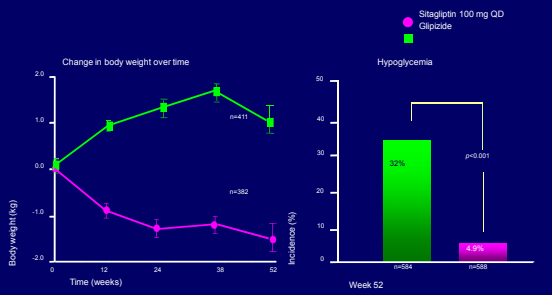
Both Sitagliptin and Metformin Increased Active GLP-1 Concentrations



Values represent mean ± SE., n=16

Adapted from Migoya E, et al. 286-OR. Presented at 2007 ADA.

Sitagliptin Provided Weight Reduction (vs. Weight Gain) and a Much Lower Incidence of Hypoglycemia

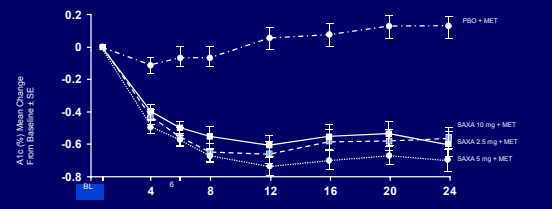


Δ between groups = –2.5 kg (p<0.001)
At 52 weeks: Glipizide: +1.2 kg; sitagliptin: – 1.3 kg

Nauck MA, et al. *Diabetes Obes Metab.* 2007;9:194–205.

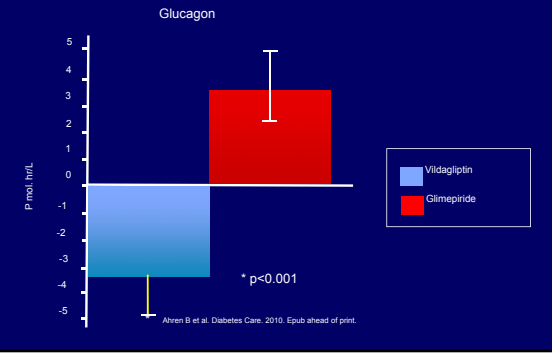
Saxagliptin Add-on to Metformin

Reduction in HbA1c in Patients With Inadequately Controlled Type 2 Diabetes on Metformin Alone



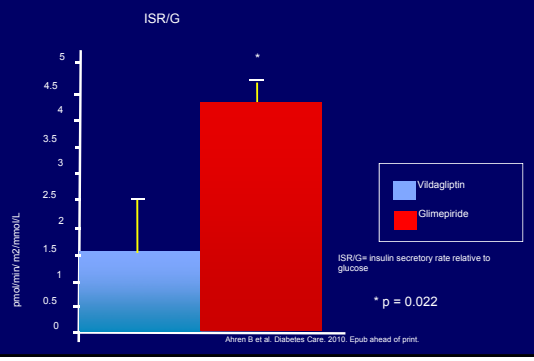
DeFronzo RA et al. *Diabetes Care.* 2009;32:1649–1655.

Prandial Glucagon After Up To 2 Years Add-on Treatment In T2D Patients Inadequately Controlled with Metformin



Ahren B et al. Diabetes Care. 2010. Epub ahead of print.

ISR / G After Up To 2 Years Add-on Treatment In T2D Patients Inadequately Controlled with Metformin



Ahren B et al. Diabetes Care. 2010. Epub ahead of print.

GLP-1 Receptor Agonists vs DPP-4 Inhibitors

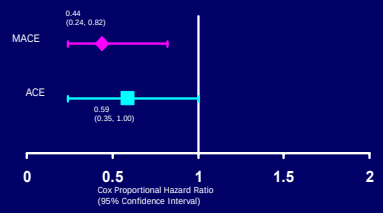
	GLP-1R Agonists	DPP-4 Inhibitors
Administration	Injection	Oral
GLP-1 concentrations	Pharmacological	Physiological
Mechanisms of action	GLP-1	GLP-1 + GIP
↑Activation of portal glucose sensor	No	Yes
↓Insulin secretion	+++	+
↓Glucagon secretion	++	++
↓Gastric emptying	Inhibited	+/-
Weight loss	Yes	No
Expansion of beta-cell mass in preclinical studies	Yes	Yes
Nausea and vomiting	Yes	No
Potential immunogenicity	Yes	No

Adapted from Drucker DJ. Cell Metab. 2006;3:153–165.

Cardiovascular Risk in Saxagliptin Trials

Data from 8 randomized, double-blind, phase 2b/3 trialsa

MACE = major adverse cardiovascular eventsb
ACE = acute clinically significant eventsc



a Saxagliptin exposure = 3758 patient-years, comparator exposure = 1293 patient-years.
b Stroke, myocardial infarction, cardiovascular death.
c Includes revascularization.

Wolff R, et al. ADA 69th Scientific Sessions. Late Breaking Abstract Handout. 2009;8-LB.LB3.

Other Considerations: Pancreatitis

Sitagliptin and Sitagliptin/metformin

- FDA Adverse Event Reporting System
  - 88 reports of acute pancreatitis, including 2 cases of hemorrhagic or necrotizing pancreatitis (October 16, 2006-February 9, 2009)
  - 58 (66%) of the patients were hospitalized, 4 of whom were admitted to the intensive care unit
  - 47 (53%) of cases resolved once sitagliptin was discontinued
  - 45 (51%) of cases were associated with at least one other risk factor for developing pancreatitis (diabetes, obesity, high cholesterol, high triglycerides)
- FDA is working with manufacturer to revise prescribing information to include post-marketing reports of acute pancreatitis, and recommendations for healthcare professionals for monitoring patients

DPP-4 Inhibitors: Role in T2DM Therapy

- Oral therapy, once daily
- Endogenous GLP-1 and GIP levels are increased in response to meal and are transient
- Monotherapy, add-on to metformin, TZD, SU, insulin
- Clinically significant A1c reductions
  - Comparable efficacy to rosiglitazone, glipizide

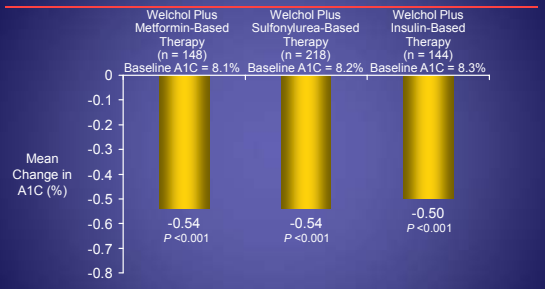
DPP-4 Inhibitors: Safety and Tolerability

- Low risk of hypoglycemia
- No weight gain
- No edema
- No GI effects
- No cardiac issues
- No immunologic effects
- No adverse events attributable to DPP-4 inhibition
- Low risk of drug-drug interactions
- Hypersensitivity reactions with sitagliptin

DPP-4 Inhibitors: Cardiovascular Effects

- Weight neutral
- No effect on BP
- No effect on fasting lipids
- Possible effect on post-prandial lipemia
- Enhance insulin sensitivity
- No CVD signal in clinical trials

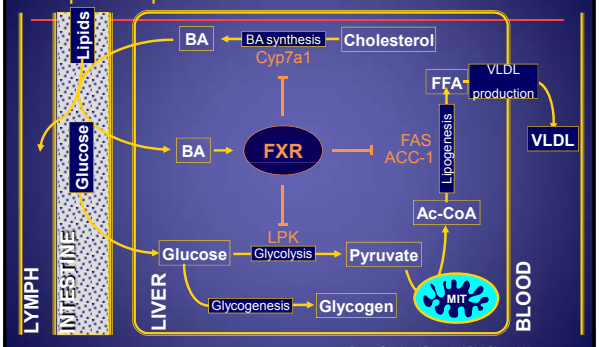
Welchol™ Consistently Lowers A1C* by An Additional Mean 0.5%



*From baseline, placebo-adjusted. Data on file, Daiichi Sankyo, Inc.

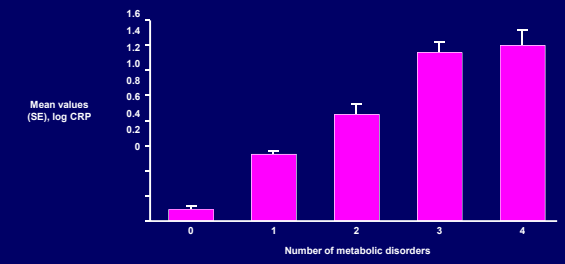
ITT Population, Last Observation Carried Forward (LOCF), patients on background monotherapy and combination therapy.

FXR: Metabolic Modulator of Post-prandial Hepatic Lipid and Glucose Metabolism



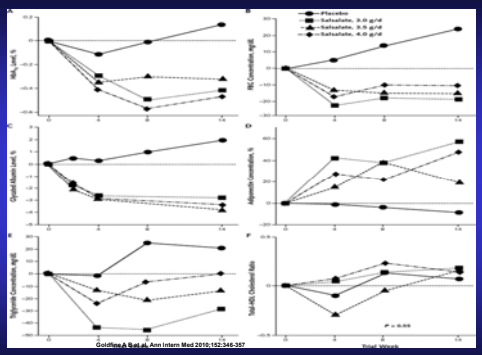
Duran-Sandoval D. et al. J Biol Chem 2005.

Chronic Subclinical Inflammation: Part of the Insulin Resistance Syndrome



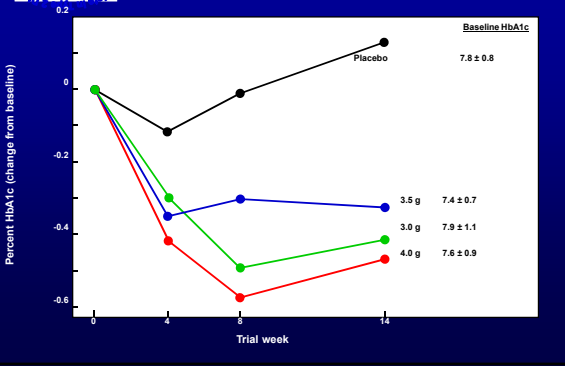
Festa. *Circulation*. 2000.

TINSAL-T2D Stage 1



Annals of Internal Medicine

TINSAL-T2D Stage 1: HbA1c (primary endpoint)



SUMMARY

TYPE 2 DIABETES IS A COMPLEX DISEASE
MULTIPLE NEW TARGETS FOR TYPE 2 DIABETES
WHICH TREATMENT WILL PROVIDE VALUE?