APPROACHES TO IMPLEMENTING COMBINATION THERAPIES IN TYPE 2 DIABETES

From TZDs to GLP -1 Analogues

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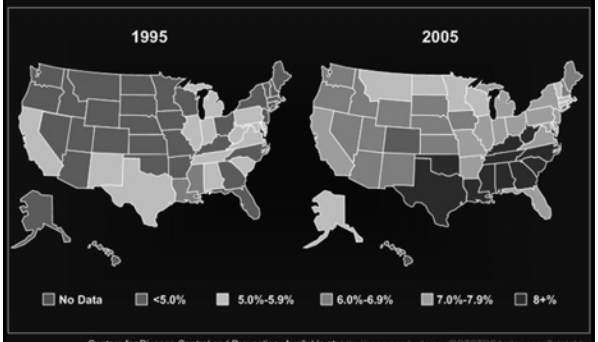
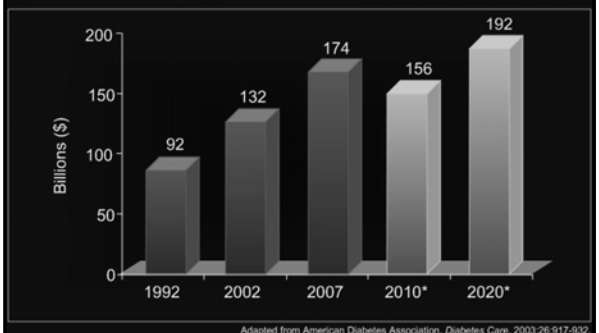
Prevalence of Diagnosed Diabetes in the United States



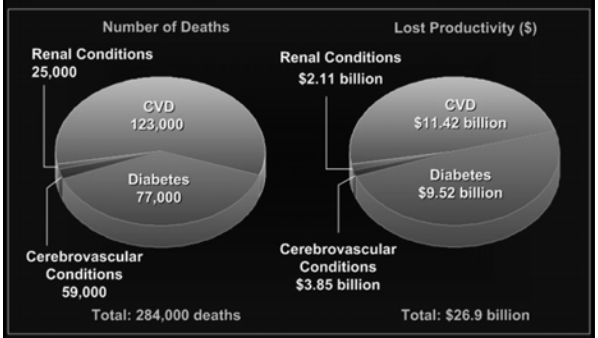
Centers for Disease Control and Prevention. Available at: http://apps.nccd.cdc.gov/DDTSTRS/index.aspx?stateId=17&state=Illinois&cat=prevalence&Data=map&view=TO&trend=prevalence&id=1. Accessed November 8, 2007.

Estimated Annual Costs of Diabetes in the United States—1992-2020



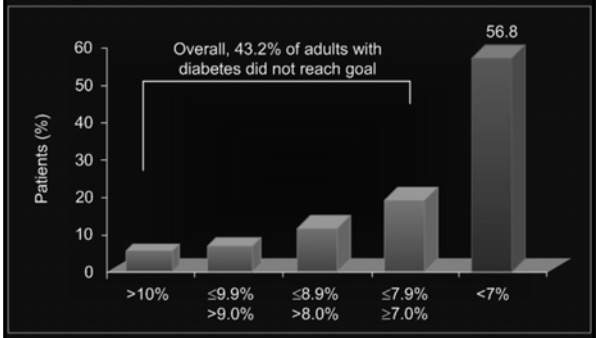
Adapted from American Diabetes Association. *Diabetes Care*. 2003;26:917-932.
Centers for Disease Control and Prevention. *Diabetes Public Health Resource*. Available at: http://www.cdc.gov/diabetes/pubs/costsdiabetes.htm Accessed July 2, 2003.
*Estimate.
Adapted from American Diabetes Association. *Diabetes Care*. 2008;31:596-615.

Impact of Diabetes in the United States—2007



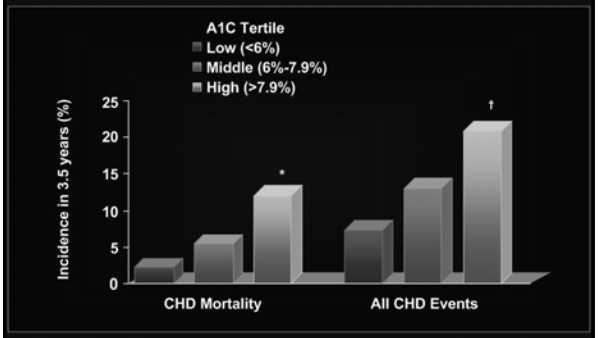
Adapted from American Diabetes Association. *Diabetes Care*. 2008;31:596-615.

Many Patients Not Reaching the ADA A1C Target Goal of <7%

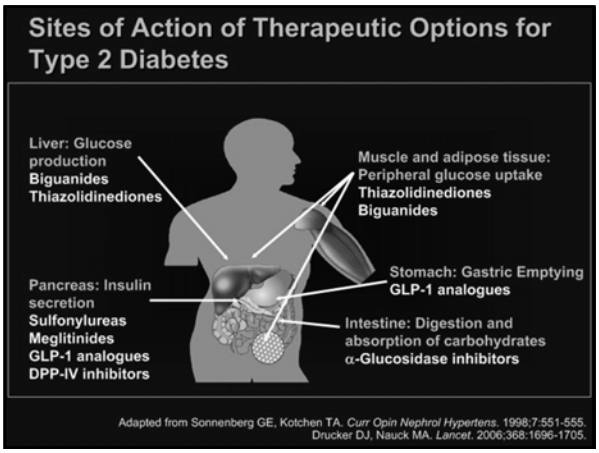


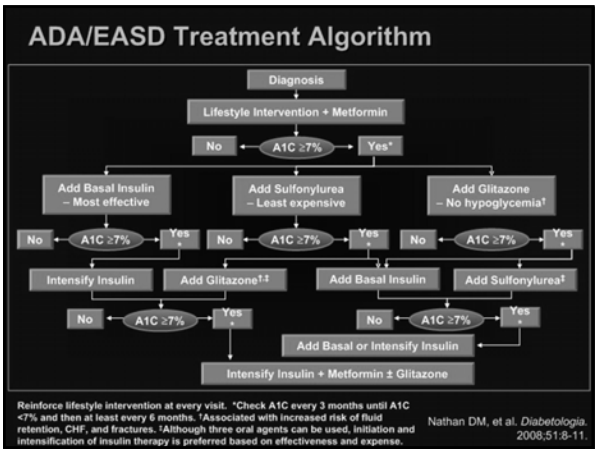
Hoerger TJ, et al. *Diabetes Care*. 2008;31:81-86.

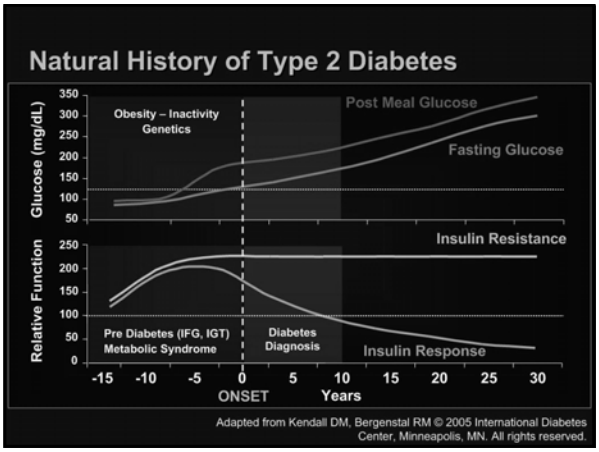
A1C as a Predictor of CHD in Type 2 Diabetes



*P<0.01 vs lowest tertile.
†P<0.05 vs lowest tertile.
Adapted from Kuusisto J, et al. *Diabetes*. 1994;43:960-967.







Choice of Therapies

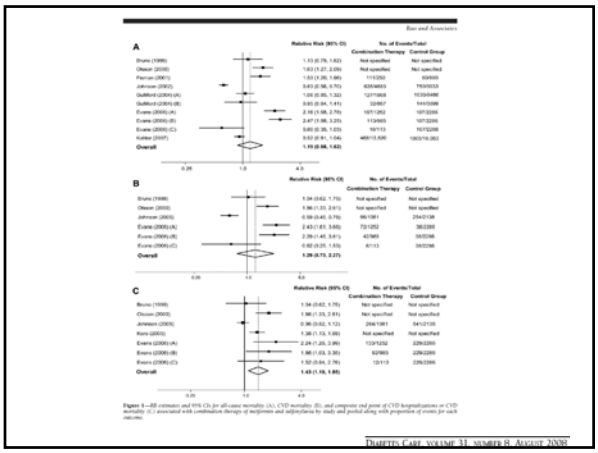
- Established Therapies
  - Metformin
  - Sulfonylureas
  - Insulin
- Newer Therapies
  - Rosiglitazone, Pioglitazone
  - Incretinmimetics
  - DPP-IV inhibitors
- Less favored therapies
  - Alpha-glucosidase inhibitors
  - Lipid lowering agents
  - Amylin

Metformin

- Decreases hepatic glucose output
- Inexpensive
- Well tolerated, no hypoglycemia
- GI upset (common), lactic acidosis (rare).
- Not to use when Cr >1.4, GFR <30
- Radiographic contrast
- Severe CHF

Sulfonylureas

- Enhance insulin secretion
- Inexpensive
- Long acting - Hypoglycemia – more in elderly, renal failure, can be severe
- Weight gain
- Rapid effect, wanes off rapidly
- Max efficacy at half max doses



DIABETES CARE, VOLUME 31, NUMBER 8, AUGUST 2008

Thiazolidinediones: Rationale for Type 2 Diabetes Therapy

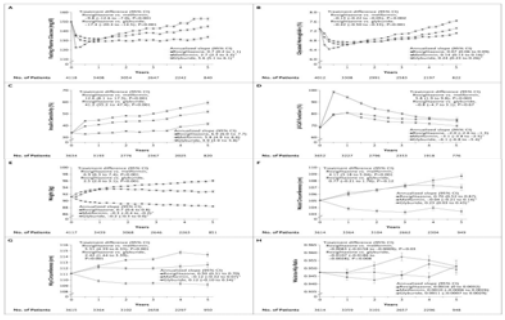
- Improve glycemic control
- Improve lipid profile (selected agents)
- Enhance insulin action
- Improve β-cell function (HOMA)
- Decrease hepatic glucose output
- Do not cause hypoglycemia in monotherapy

ACTOS Package Insert.
Diamant M, Heine RJ. *Drugs*. 2003;63:1373-1405.
Yki-Järvinen H. *N Engl J Med*. 2004;351:1106-1118.
Sonnenberg GE, Kotchen TA. *Curr Opin Nephrol Hypertens*. 1998;7:551-555.

Thiazolidinediones

- Weight gain
- Not to be used in CHF
- Watch for liver enzymes
- Macular edema reported but causal relationship is not established

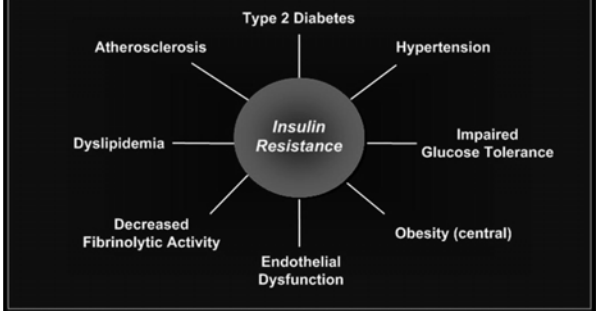
Fasting Plasma Glucose (Panel A), Glycated Hemoglobin (Panel B), Insulin Sensitivity (Panel C), beta-Cell Function (Panel D), Weight (Panel E), Waist Circumference (Panel F), Hip Circumference (Panel G), and Waist-to-Hip Ratio (Panel H) over Time, According to Treatment Group



Kahn S et al. N Engl J Med 2006;355:2427-2443

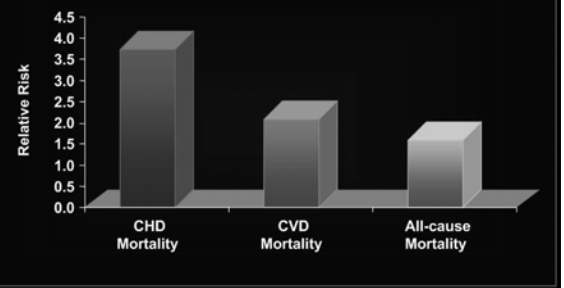
The NEW ENGLAND JOURNAL of MEDICINE

Insulin Resistance: Associated Conditions



Adapted from Consensus Development Conference of the American Diabetes Association. *Diabetes Care*. 1998;21:310-314.

Metabolic Syndrome* and Cardiovascular Disease Mortality in Middle-aged Men



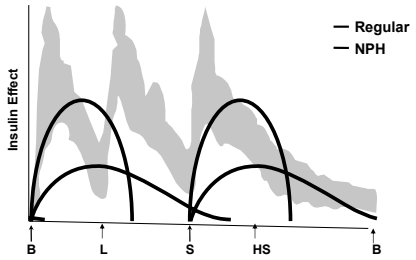
*NCEP definition.

Lakka H-M, et al. *JAMA*. 2002;288:2709-2716.

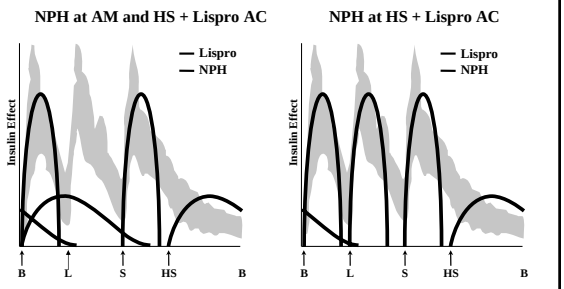
Insulin

- Long Acting
  - Glargine (Lantus)
  - Detemir (Levemir)
- Intermediate Acting
  - Novolin N
  - Humuljn N
- Short Acting
  - Lispro (Humalog)
  - Aspart (Novolog)
  - Glulisine (Apidra)
- Combinations – 70/30, 75/25, 50/50

Twice-daily Split-mixed Regimens



Multiple Daily Injections (MDI)
NPH + Mealtime Lispro



6-29

Glargine Once Daily,
Premeal Rapidly Acting Insulin

Pros:
- Postprandial control at each meal
- Improve fasting glucose
- Provides basal coverage throughout the day

Cons:
- Inconvenient, multiple dosing
- Cannot mix insulins

Combinations

Metformin + Sulfonylureas + Insulin

Metformin + Sulfonylureas + Rosiglitazone

Metformin + Sulfonylureas + Pioglitazone + Insulin

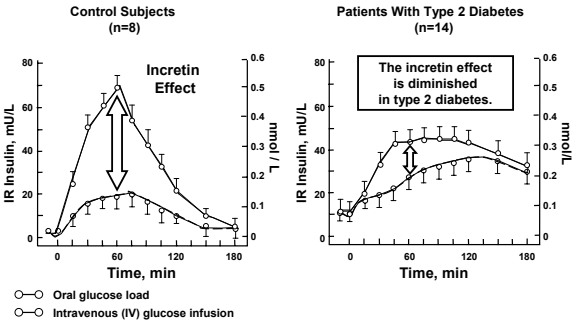
Pioglitazone + high doses of insulin
= increased fluid retention

Combinations

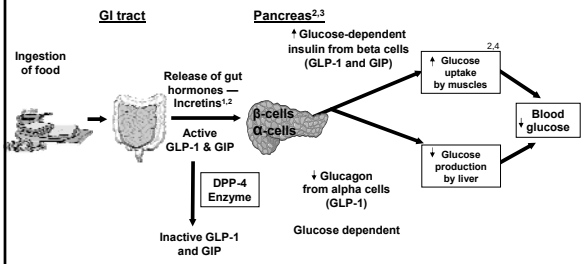
- Early in disease
  - Basal Insulin – self titration
  - To control fasting sugar
  - Combined with sulfonylurea, Metformin and/or TZD
- Long standing diabetes
  - Basal + Bolus insulin
  - Combined with Metformin, TZD

Incretinmimetics

The Incretin Effect in Subjects Without & With Type 2 Diabetes



Adapted with permission from Nauck M et al. *Diabetologia*. 1986;29:46–52. Copyright © 1986 Springer-Verlag.



- Active incretins physiologically regulate glucose by modulating insulin secretion in a glucose-dependent manner.
- GLP-1 also modulates glucagon secretion in a glucose-dependent manner.

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.

GLP – 1 Mechanism of Action

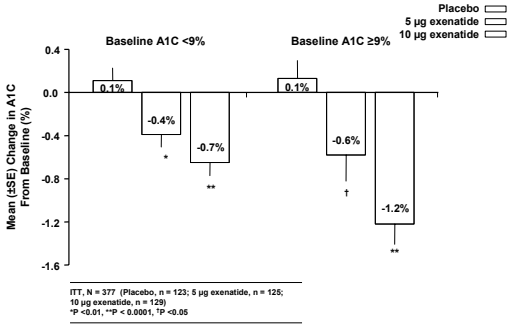
- Stimulates insulin response from beta cells
- Reduces food intake and body weight
- Inhibits gastric emptying
- Inhibits glucagon secretion

Exenatide

- GLP-1 analogue
- Adjunctive therapy for uncontrolled type 2 DM
- Patients on metformin, a sulfonylurea, a TZD or a combination
- Not for
  - Type 1 DM
  - Treatment of ketoacidosis
  - Patients with gastroparesis and indigestion
  - Severe kidney disease or on dialysis

Exenatide

Change in A1C at 30 Weeks

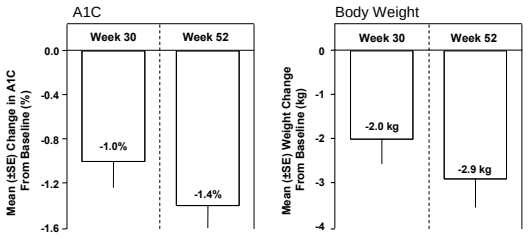


ITT, N = 377 (Placebo, n = 123; 5 µg exenatide, n = 128; 10 µg exenatide, n = 129)
*P <0.01, **P < 0.0001, †P <0.05

Buse J, et al. *Diabetes* 2004; 53(suppl 2):A82

Exenatide

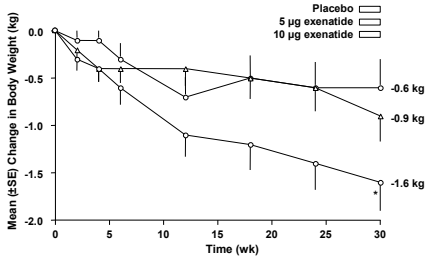
52 weeks -10 µg Arm



Baseline (week 0) A1C = 8.5 ± 0.1;
Baseline Body Weight (week 0) = 95.9 ± 2.5 kg

Buse J, et al. *Diabetes* 2004; 53(suppl 2):A82

Change in Body Weight From Baseline, ITT



N = 377 (Placebo, n = 123; 5 µg exenatide, n = 125; 10 µg exenatide, n = 129), P <0.05

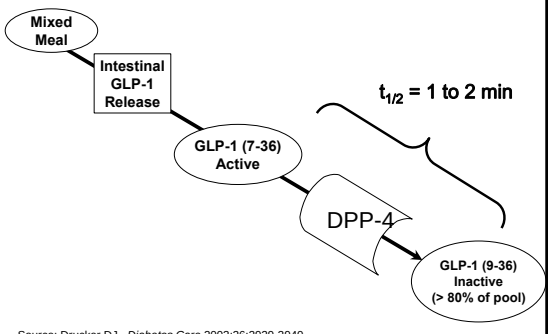
Buse J, et al. *Diabetes* 2004; 53(suppl 2):A82

Combinations with exenatide

- Studied with
  - Metformin
  - Sulfonylurea
  - TZD
- Not studied with insulin

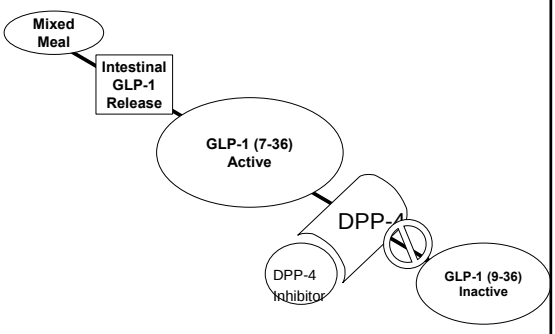
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

GLP-1 Secretion and Inactivation



Source: Drucker DJ. *Diabetes Care* 2003;26:2929-2940.

Inhibition of DPP-4 to Increase Active GLP-1



Source: Drucker DJ. *Diabetes Care* 2003;26:2929-2940.

Sitagliptin

- Once a day oral dose
- 2- to 3-fold ↑ in circulating levels of active GLP-1 and GIP
- ↓ glucagon concentrations
- ↑ glucose mediated insulin release
- ↑ plasma levels of insulin and C-peptide
- ↓ fasting glucose and ↓ glucose excursion after an oral glucose load or a meal
- Does not cause hypoglycemia

Sitagliptin

- Not used in
  - Type 1 diabetes
  - Ketoacidosis
- Dose adjusted for renal function
  - Normal - 100 mg
  - CrCl 30-50 - 50 mg
  - CrCl < 30 - 25 mg
- Weight Neutral

Combinations with Sitagliptin

- Studied with
  - Metformin
  - Sulfonylurea
  - TZD
- Not studied with insulin

Summary

- Various combination options are available for treatment of type 2 diabetes
- The choice depends on stage of disease, additive mechanisms of the agents used
- TZDs and basal insulin early in the disease make physiological sense
- Combination of newer therapies like incretinmimetics with insulin is not studied

Thank You!