New Diabetes Treatments

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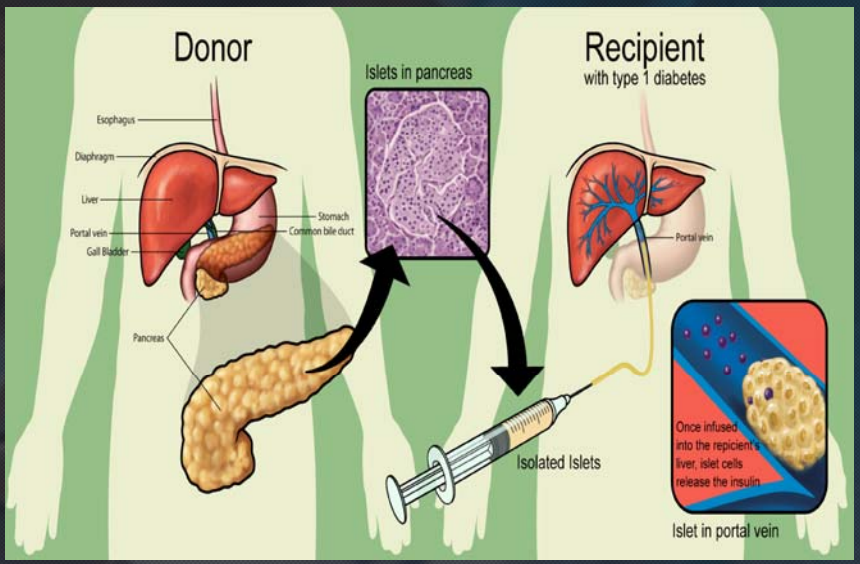
Islet cell transplantation

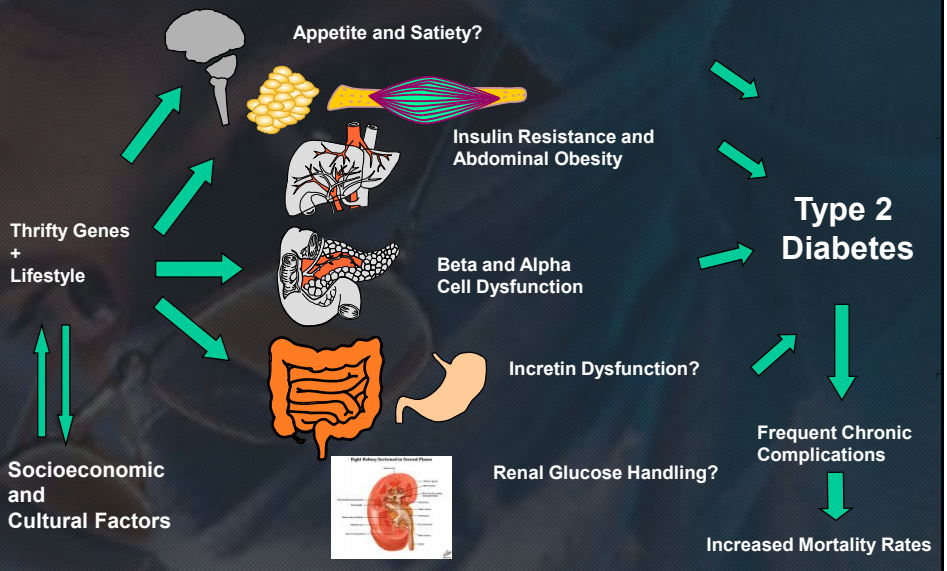


from Wikipedia, the free encyclopedia (Islet transplantation PLoS Medicine.jpg)

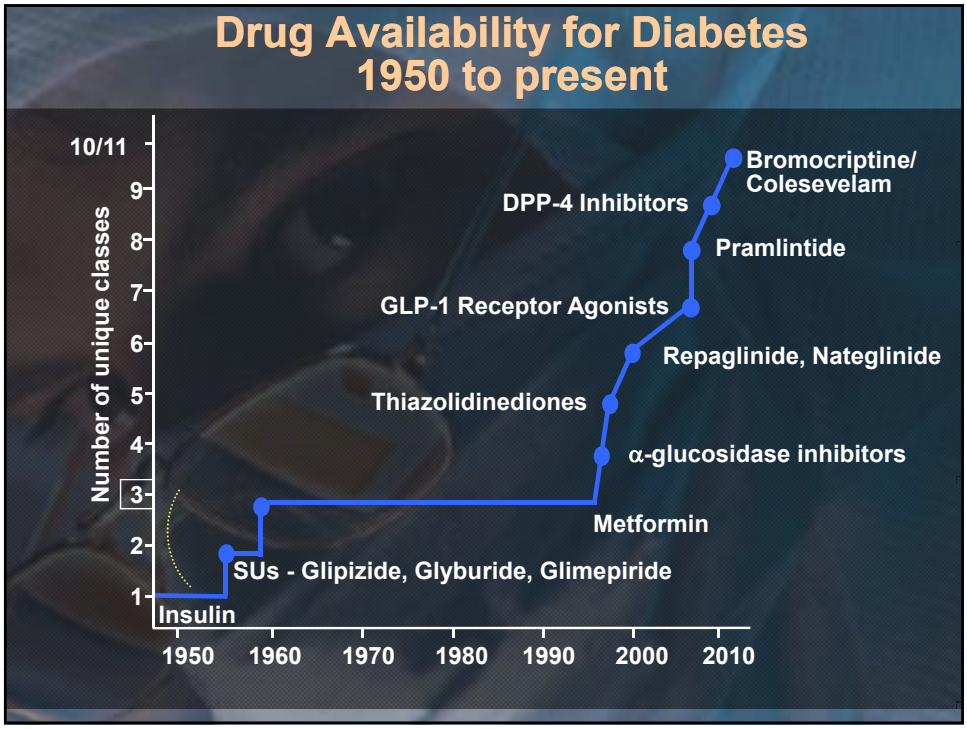
Embryonic Stem Cells (ESC)

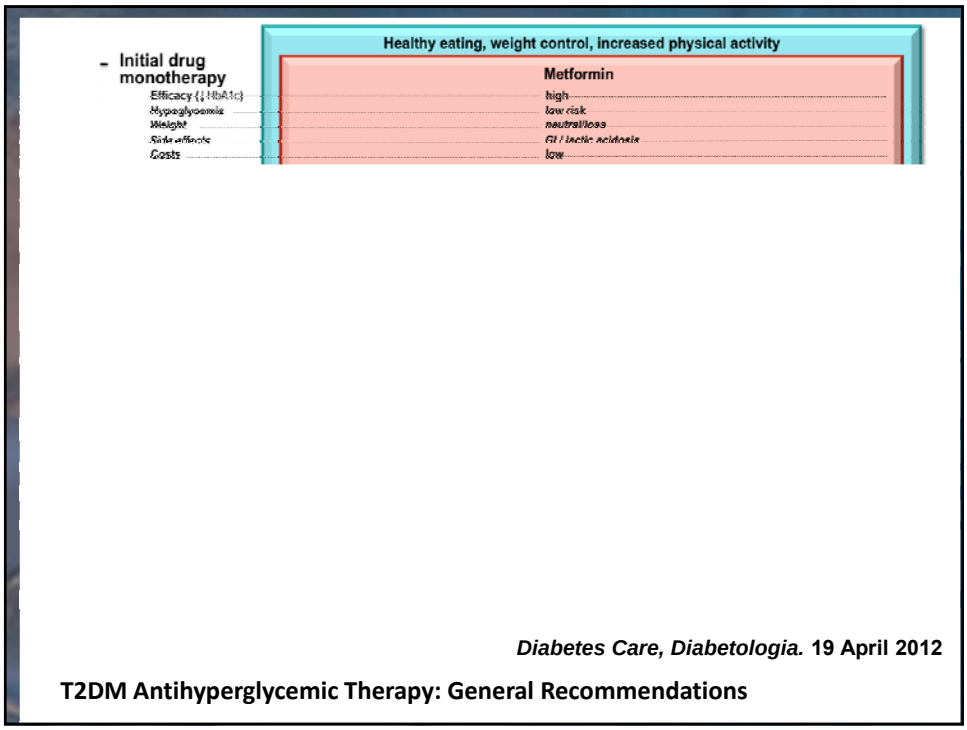
We need to understand mechanisms

Genes, Environment, and Social/Cultural Factors in Type 2 Diabetes in Racial/Ethnic Minorities



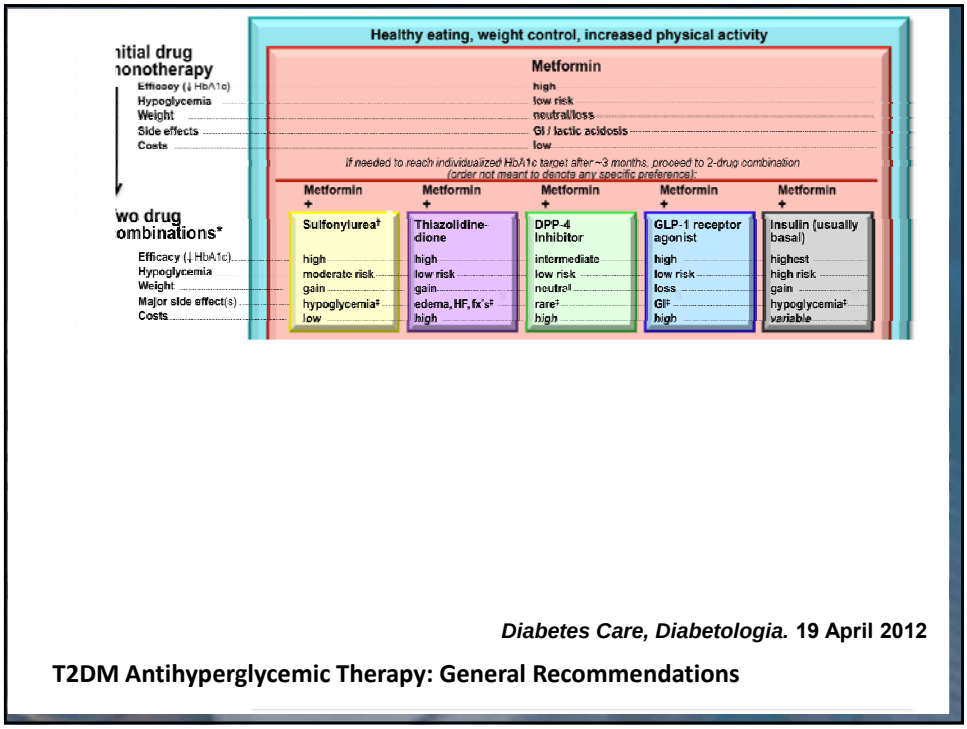
Modified from Caballero AE. *Curr Diab Endocrin Rep.* 2007;14:151-157.





Diabetes Care, Diabetologia. 19 April 2012

T2DM Antihyperglycemic Therapy: General Recommendations



Diabetes Care, Diabetologia. **19 April 2012**

T2DM Antihyperglycemic Therapy: General Recommendations

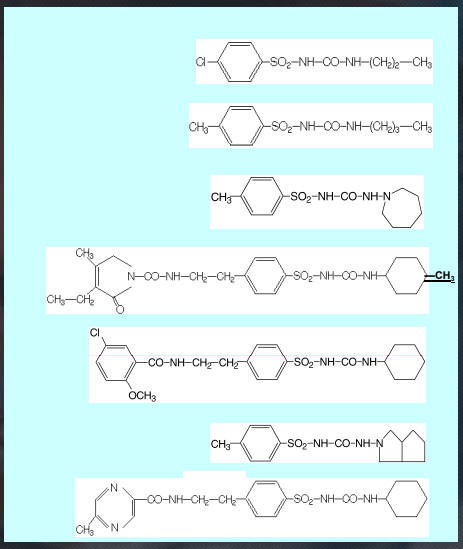
Sulfonlyureas

- **Advantages:**
  - World-wide, long-term experience
  - Very good effect on A1c levels
  - Do not seem to increase cardiovascular risk
  - Oral medication
  - Inexpensive

Sulfonlyureas

- **Disadvantages:**
  - Weight gain
  - Hypoglycemia
  - High rates of secondary failure
  - Blunting of ischemic preconditioning response?

Sulfonylureas



Chlorpropamide

Tolbutamide

Tolazamide

Glimepiride

Glibenclamide (Glyburide)

Gliclazide

Glipizide

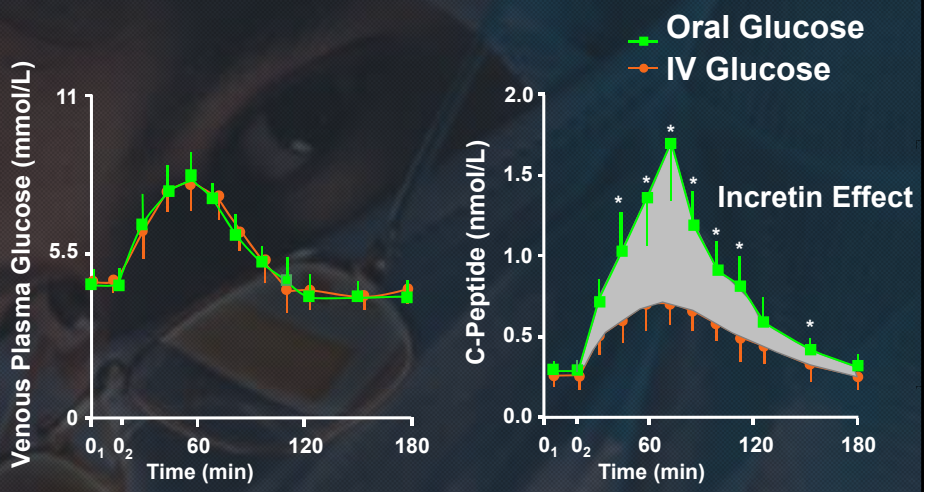
TZDs

- **Advantages:**
  - Good effect on A1c
  - Excellent reduction in insulin resistance
  - Reduction of intra-abdominal fat (liver and visceral fat)
  - Potential beneficial effect on beta cells
  - No hypoglycemia
  - Improvement on vascular function – animal, in vitro data and on markers of endothelial dysfunction and inflammation
  - Oral medication

TZDs

- **Disadvantages:**
  - Weight gain
  - Edema
  - CHF
  - CV risk?
  - Bone Fractures
  - Bladder Cancer?
  - Expensive in US
  -

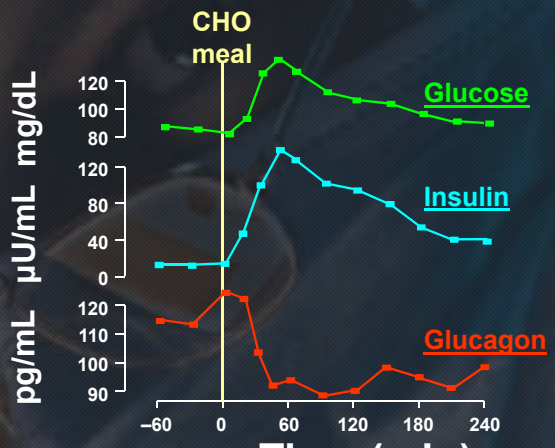
The Incretin Effect Demonstrates the Response to Oral vs IV Glucose



0_1-0_2: Glucose infusion time. IV: Intravenous.
Mean ± SE; n=6; *$p \leq 0.05$.

Nauck MA, et al. *J Clin Endocrinol Metab.* 1986;63:492-498.

The Normal Reciprocal Response of Insulin and Glucagon Regulates Postprandial Glucose Elevations



CHO = carbohydrate

Unger RH. *N Engl J Med.* 1971;285:443-449.

Comparison of the Incretins

	GLP-1	GIP
Site of majority of production	L cells (ileum and colon)	K cells (duodenum and jejunum)
↓ Secretion in T2DM	Yes	No
↓ Glucagon postprandially	Yes	No
↓ Food intake	Yes	No
Slows gastric emptying	Yes	No
Promotes expansion of beta-cell mass	Yes	Yes
Promotes insulin biosynthesis	Yes	Yes

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

Meta-analysis of DPP-4 Inhibitors

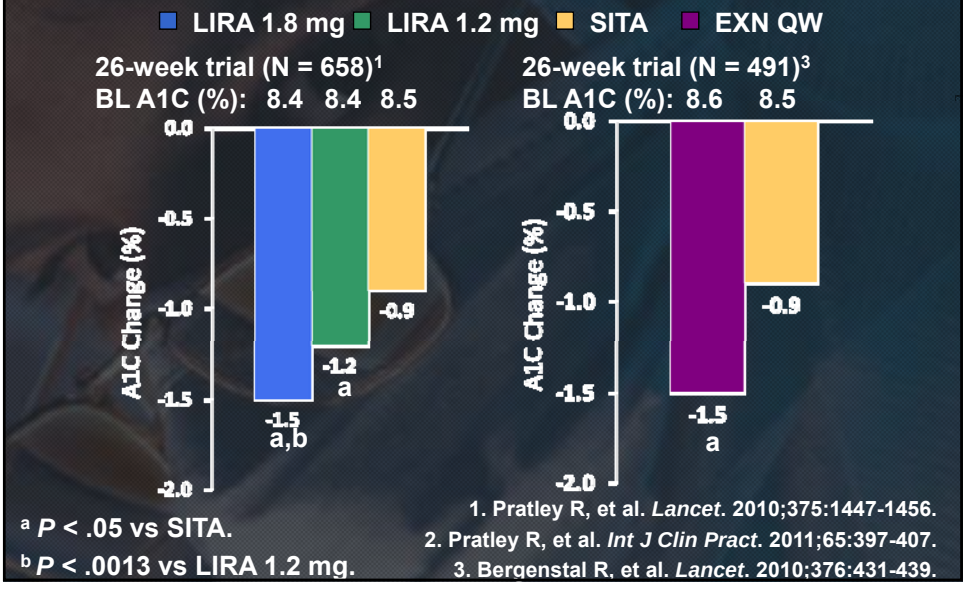
- Mean A1C reduction: -0.74% (-0.85 to -0.62)
- Significant reduction in postprandial glucose and very modest decrease of fasting plasma glucose
- Neutral effect on weight and lipids
- No hypoglycemia
- Side effects
  - Nasopharyngitis 1.2 RR (CI, 1.0–1.4)
  - Urinary tract infection 1.5 RR (CI, 1.0–2.2)
  - Headache 1.4 RR (CI, 1.1–1.7)

Amori RE et al. *JAMA.* 2007;298:194-206.

Summary of Incretin Therapies

Agent	Administration	A1C Reduction	Weight Change	Main Adverse Effect
Incretin Mimetics: GLP-1 Agonists				
Exenatide	Twice daily injection	Up to -0.86%	↓	Nausea
Liraglutide	Once daily injection	Up to -0.75%	↓	Nausea
Incretin Enhancers: DPP-4 Inhibitors				
Vildagliptin	Oral	Up to 0.8%	↔	—
Sitagliptin	Oral	Up to 0.8%	↔	—
Saxagliptin	Oral	Up to 0.8%	↔	—
Linagliptin	Oral	Up to 0.8%	↔	—

A1c Change: Liraglutide or Weekly Exenatide Versus Sitagliptin (All Added to Metformin)



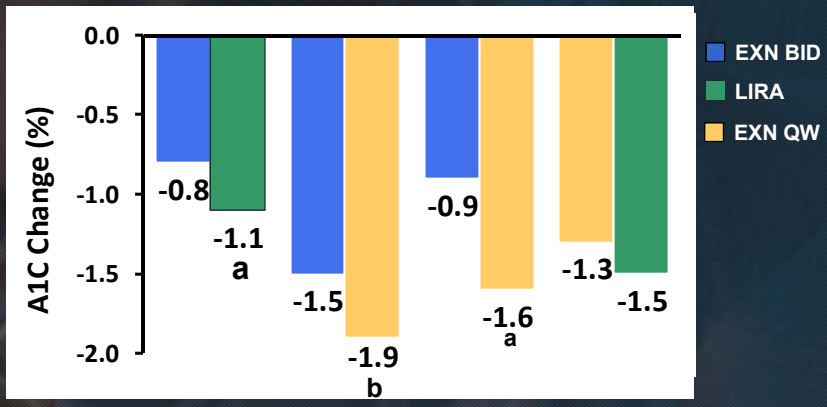
[a] *P* < .05 vs SITA.

[b] *P* < .0013 vs LIRA 1.2 mg.

1. Pratley R, et al. *Lancet*. 2010;375:1447-1456.
2. Pratley R, et al. *Int J Clin Pract*. 2011;65:397-407.
3. Bergenstal R, et al. *Lancet*. 2010;376:431-439.

Glycemic Control With GLP-1 RAs in Head-to-Head Clinical Trials

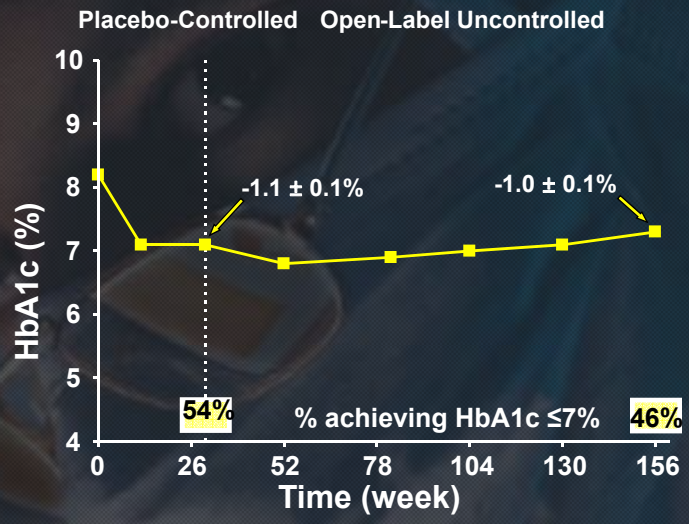
Trial:	LEAD-6[1]	DURATION-1[2]	DURATION-5[3]	DURATION-6[4]
Size (N):	464	303	254	912
Study length (weeks):	26	30	24	26



[a] *P* < .0001 vs EXN BID.
[b] *P* = .0023 vs EXN BID.

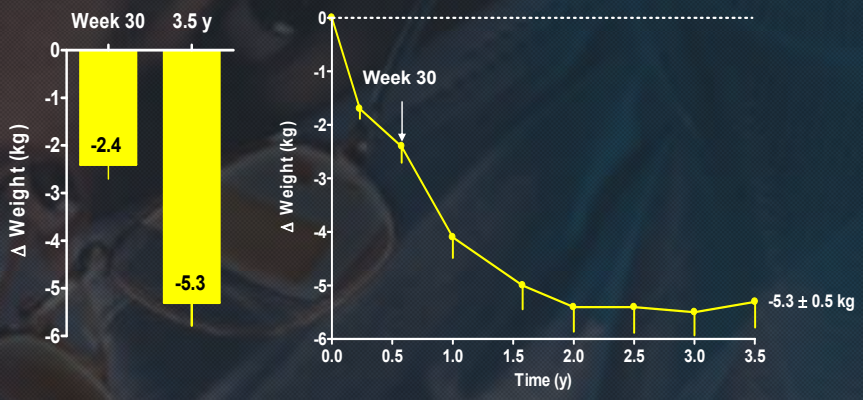
1. Buse J, et al. *Lancet*. 2009;374:39-47.
2. Drucker D, et al. *Lancet*. 2008;372:1240-1250.
3. Blevins T, et al. *J Clin Endocrinol Metab*. 2011;96:1301-3110.
4. Buse J, et al. EASD 47th Annual Meeting. 2011;75.

Exenatide Sustained HbA1c Reduction 3-Year Completers



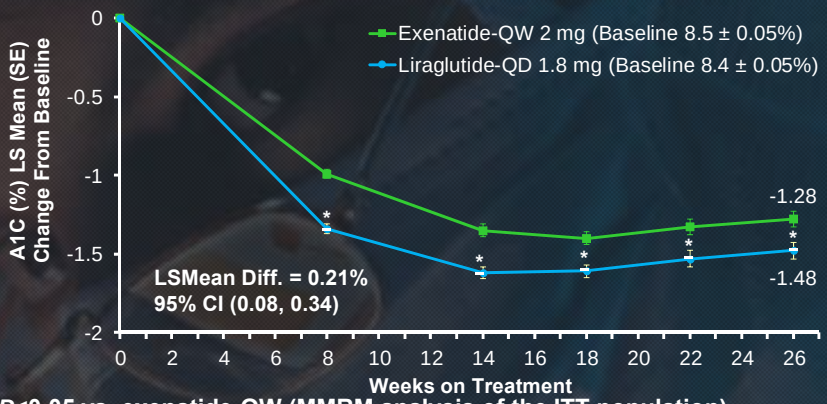
N = 217; Mean (- SE); p<0.0001 from baseline to 30 weeks and baseline to 3 years.
Klonoff DC, et al. Curr Med Res Opin. 2008;24:275–286.

Weight Reductions With 3.5 y of Exenatide



3.5-y completer cohort N = 151. Baseline weight 99.9 kg. Mean ± SE
Kendall D, et al. *Diabetes.* 2007:56(Suppl1):A149;

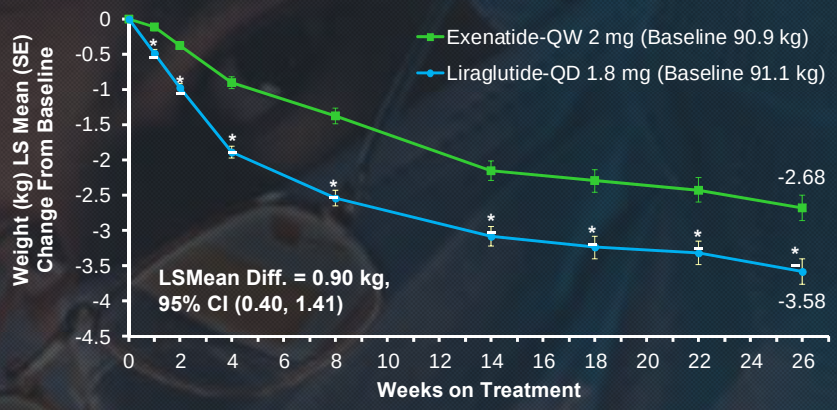
A1C: LS Mean Change From Baseline to Week 26 (ITT, N=911)



*P<0.05 vs. exenatide-QW (MMRM analysis of the ITT population)
More subjects taking liraglutide-QD achieved A1C <7% (271 [60.2%]) than those taking exenatide-QW (241 [52.3%]; P=0.008, LOCF).

Abbreviations: LOCF = last observation carried forward
MMRM = mixed model repeated measures analysis
SE = standard error

Weight (kg): LS Mean Change From Baseline to Week 26 (ITT, N=911)



*$P<0.05$ vs exenatide-QW (MMRM analysis of the ITT population)

Incretin Mimetics and DPP- 4 Inhibitors

Properties / Effect	GLP-1 Analogs	DPP-4 Inhibitors
Glucose-dependent insulin secretion	Yes	Yes
Restoration of biphasic insulin responses	Yes	Not tested
Suppression of glucagon secretion	Yes	Yes
Slowing of gastric emptying	Yes	Marginal
Effect on body weight	Weight loss	Weight neutral
Differentiation of islet precursor cells into β cells (animal data)	Yes	Unknown
Predominant adverse event	Nausea	None observed
Administration	Subcutaneous, QD,BID	Oral, QD/BID

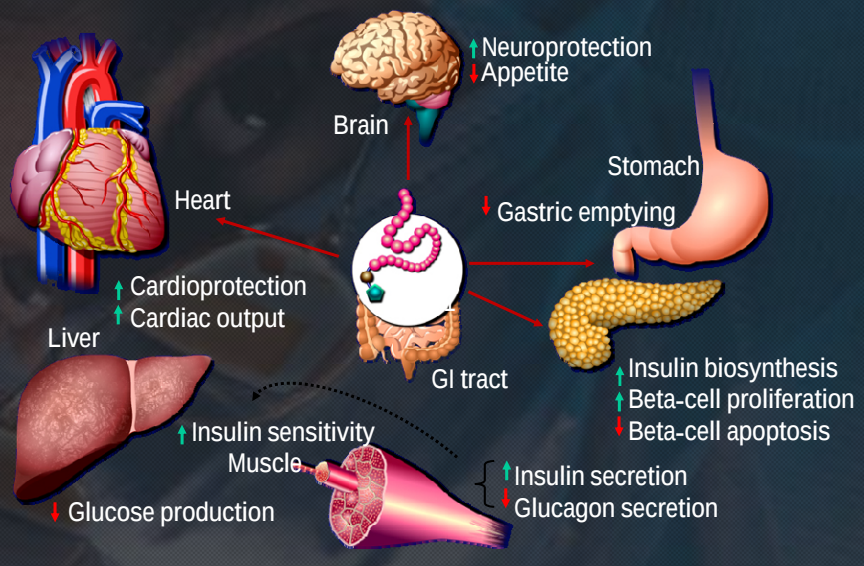
BID: Twice-daily dosing; QD: Once-daily dosing.

Abbreviated from Drucker DJ et al. *Lancet.* 2006;368:1696-1705.

GLP-1R Agonists: Unanswered Questions

- Optimal pharmacokinetics?
- Intermittent vs continuous administration?
- Effects of sustained vs transient levels?
- Responders vs nonresponders?
- Data in real clinical practice?
- Islet mass and β-cell function in humans?
- Safety and immunogenicity?

Summary of Incretin Actions on Different Target Tissues

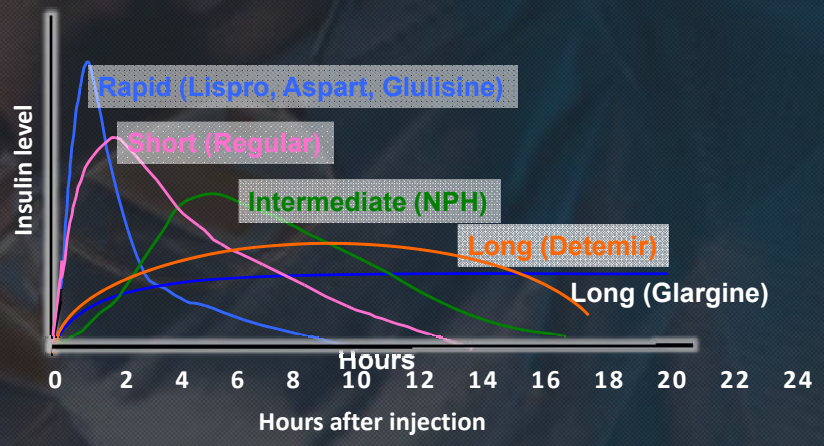


Adapted from Drucker DJ. *Cell Metab.* 2006;3:153–165.

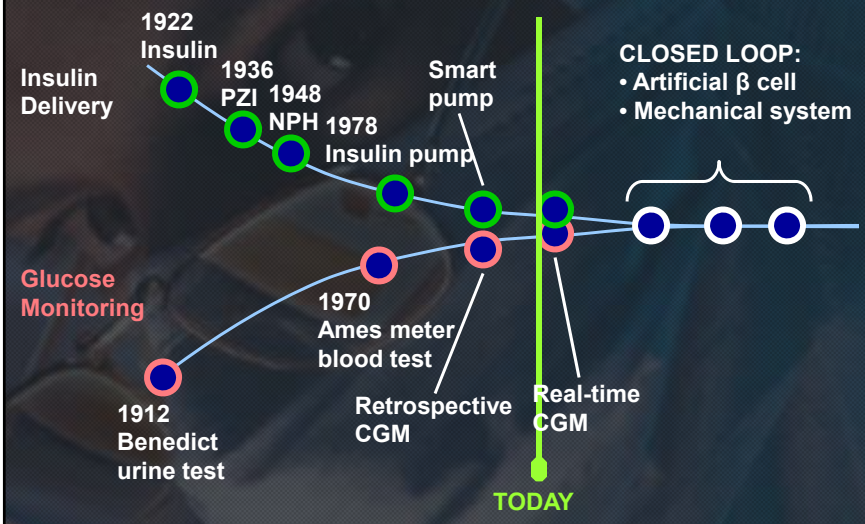
ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

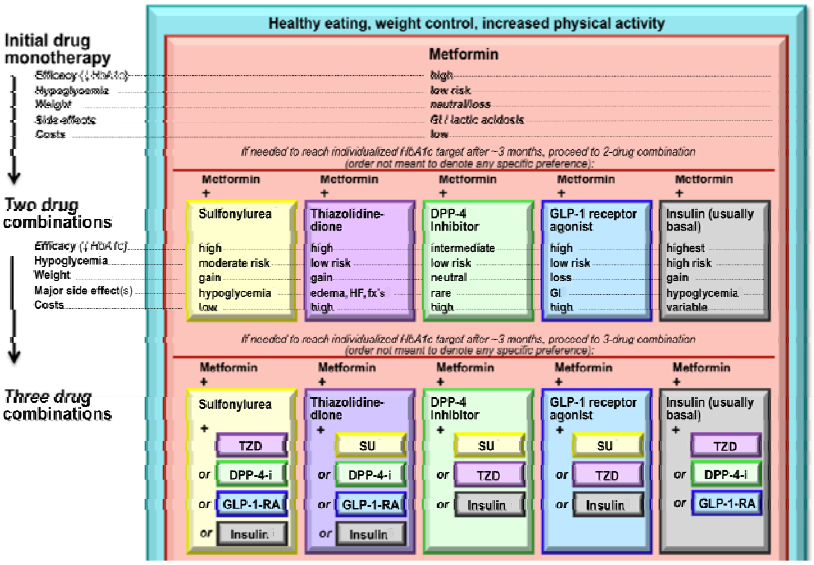
ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: Insulin



Insulin delivery – closing the loop





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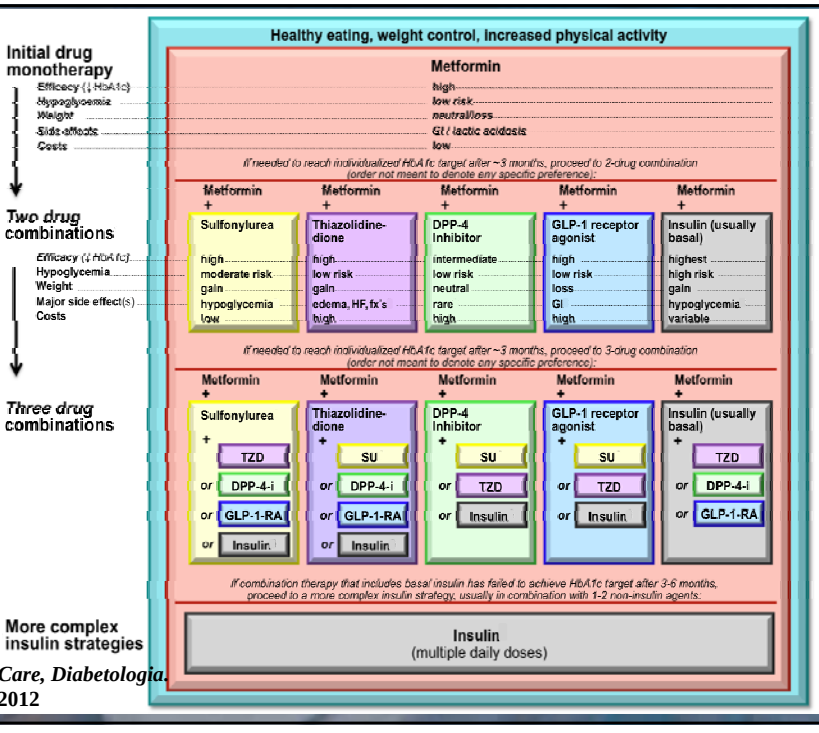
T2DM Antihyperglycemic Therapy: General Recommendations



Diabetes Care, Diabetologia. **19 April 2012**

Pharmacologic options for Type 2 DM

- **Insulin Resistance**
  - Biguanides
  - Thiazolidinediones (TZD)
- **β-cell dysfunction/failure**
  - Sulfonylureas (SU)
  - Meglitinides
  - DPP4 inhibitors
  - GLP-1 analogs
  - Insulin
- **Other Mechanisms**
  - Alpha glucosidase inhibitors
  - Bile Acid Sequestrants
  - Bromocriptine

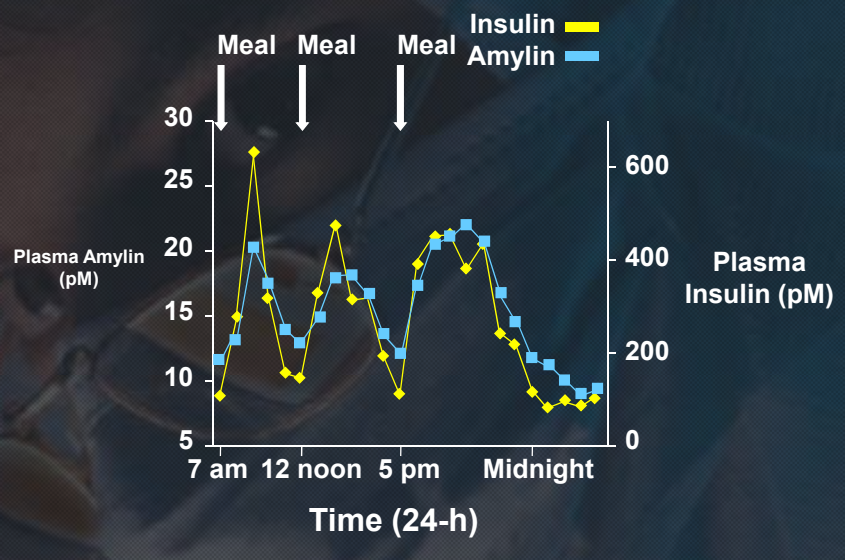
Alpha Glucosidase Inhibitors: Acarbose, Miglitol and Voglibose

- **Advantages:**
  - Effective in reducing postprandial hyperglycemia
  - Neutral effect on weight, lipids and BP
  - Oral medication
  - Positive results for acarbose in the Stop-NIDDM Study (DM prevention and Reduction of CV events)

Alpha Glucosidase Inhibitors:

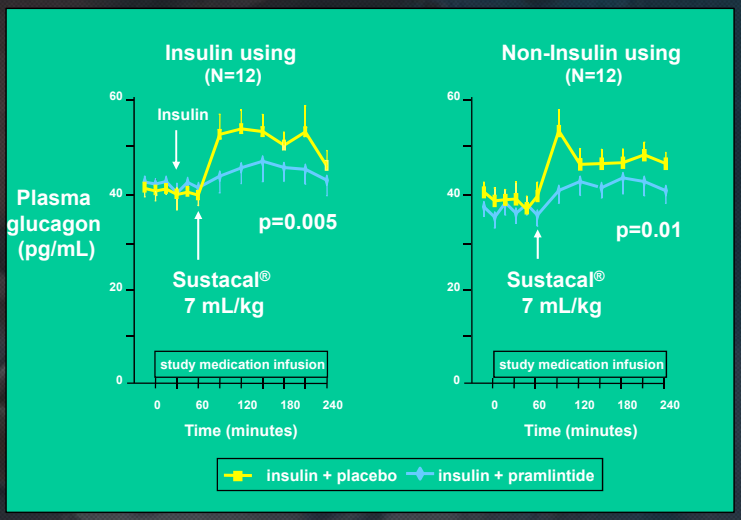
- **Disadvantages:**
  - Modest reduction in A1c levels
  - Need to be taken 3 times a day
  - Rare liver enzyme elevations
  - GI side effects
  - Expensive

Amylin is co-secreted with insulin



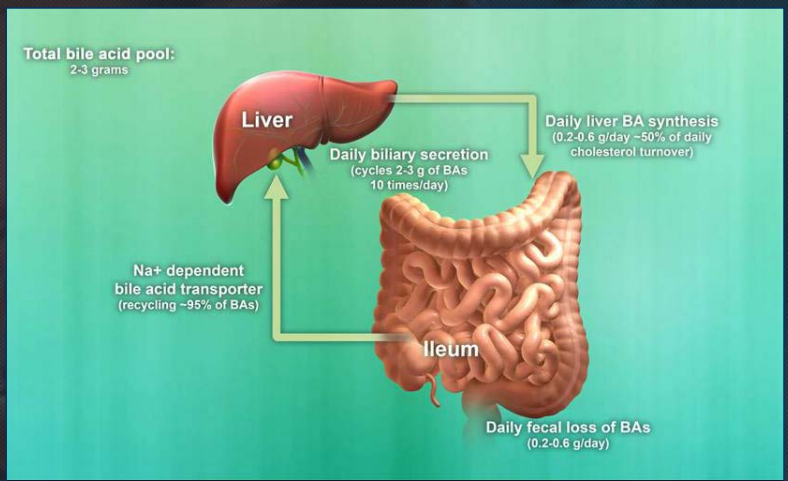
Data from Kruger D, et al. *Diabetes Educ* 1999; 25:389-398

Pramlintide Reduces Postmeal Glucagon in Insulin using and Non-Insulin using Type 2 Patients



Fineman, Diabetologia. 1998; 41 (s1-abstract 653).

Enterohepatic Circulation of Bile Acids (BA)



The Target: Bile Acids—From Detergents to Hormones

- Bile acids have long been known to facilitate digestion and absorption of lipids in the small intestine
- Recently, it has been demonstrated that bile acids also fulfill the criteria for hormones as they activate specific receptors including nuclear receptors (FXR) and G-protein coupled receptor (TGR5), and cell signaling pathways in the liver and GI tract
- Activation of nuclear receptors and cell signaling pathways results in modulation of multiple metabolic pathways including: bile acid, triglyceride, cholesterol, energy, and glucose homeostasis
- Bile acids appear to function as nutrient signaling molecules primarily during the feed/fast cycle as there is a flux of the molecules returning from the intestines to the liver following a meal

Goldfine AB. *Curr Opin Cardiol.* 2008;23:502-511.
Levy P. *Endocr Pract.* 2008;14:644-647.

Bile Acid sequestrants - Colesevalam

- **Advantages:**
  - Dual effect on LDL-cholesterol and A1c
  - Two effects with one drug
  - Neutral effect on weight and BP
  - Oral medication

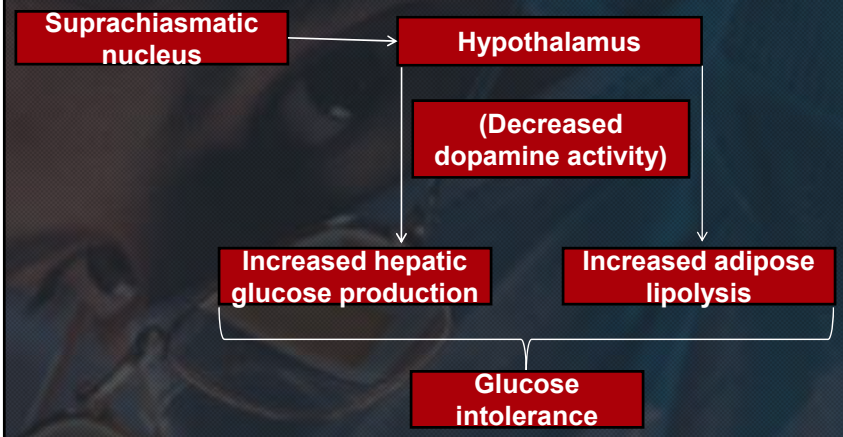
Bile Acid sequestrants - Colesevalam

- **Disadvantages:**
  - Modest effect on A1c (0.5%)
  - Unclear mechanism of action to reduce glucose levels
  - Main side effects: constipation, indigestion, nausea
  - Six tablets a day
  - No long term data
  - Expensive

The VMH

- Has rich connections with other hypothalamic nuclei
- Plays a major regulatory role in the peripheral metabolic activities
- Functions as a central glucose sensor
- Is able to induce hepatic glucose production via the autonomic and endocrine system

Role of Central Pathways in Glucose and Fat Metabolism



In obese-glucose intolerant, insulin resistant conditions (characterized by type 2 diabetes), central ventromedial hypothalamic noradrenergic and serotonergic activities are increased

Exp. Opin. Invest. Drugs.1999;8(10):1683-1707

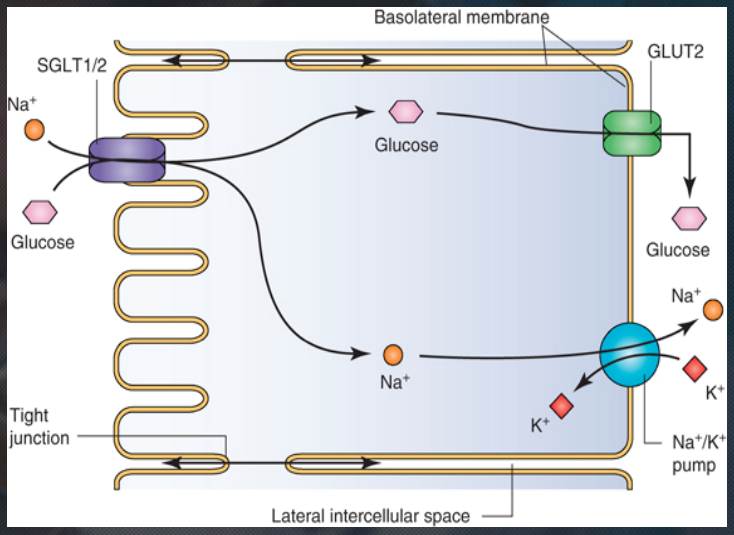
Bromocriptine

- Bromocriptine is a NOVEL oral anti diabetic drug
- Bromocriptine HELPS to RESET circadian rhythms
- Bromocriptine is a Dopamine receptor (D2) agonist
- Bromocriptine is sympatholytic by (alpha2-adrenoceptor agonistic and an alpha1-adrenoceptor antagonistic) actions

Bromocriptine

- Increases peripheral insulin sensitivity, decreases hepatic glucose production, reduces lipolysis,
- Can be used as monotherapy or as adjunct therapy with metformin, SU, TZDs
- A1c reduction of 0.2 to 0.9% along with small changes in Tg and BP
- Dose 1.6 – 4.8 mg qd (0.8 mg tablets) every morning
- Side effects: Nausea in 10% of patients. Hypoglycemia depending on concomitant therapies
- Longer term data needed

THE ROLE OF THE KIDNEY IN GLUCOSE HOMEOSTASIS



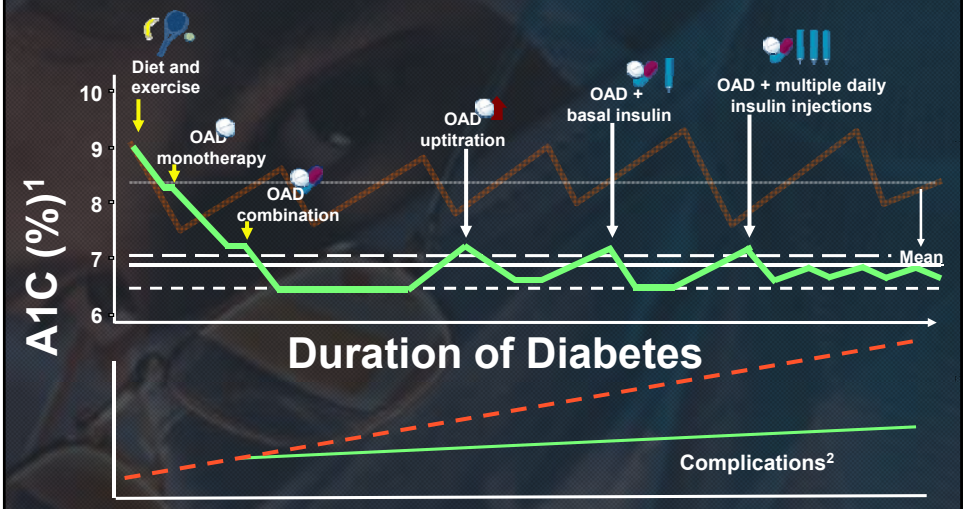
SGLT-2 Inhibitors

- **Advantages:**
  - Good effect on A1c levels
  - No frequent hypoglycemia
  - Potential weight loss
  - Oral medication

SGLT-2 Inhibitors

- **Disadvantages:**
  - Counterintuitive mechanism of action
  - New class!
  - Urinary and vaginal infections
  - Long term data are needed
  - Cost?

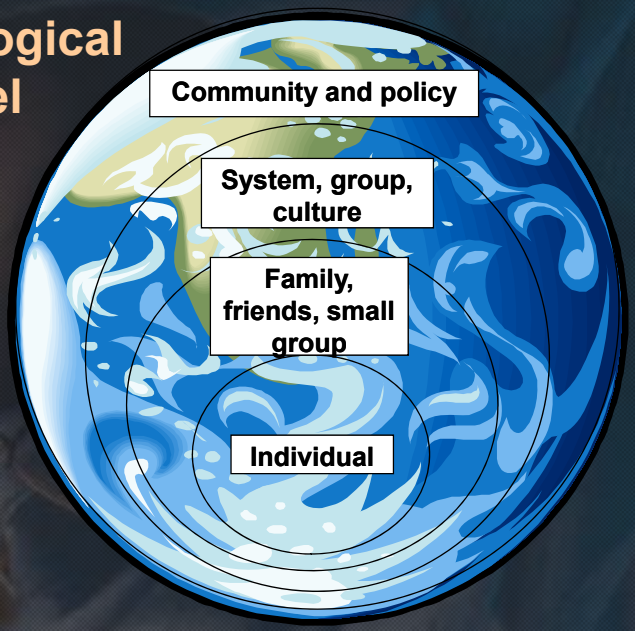
The Case for Early Combination Therapy: Reaching and Maintaining Glycemic Goals



OAD = oral antidiabetic drug

1. Adapted from Del Prato S et al. *Int J Clin Pract*. 2005;59:1345-1355.
2. Stratton IM et al. *BMJ*. 2000;321:405-412.

Ecological Model



The health of individuals is inseparable from the health of communities (Healthy People 2010)