Achieving Optimal Control In Type 2 Diabetes

Screening For Diabetes….

ADA's Recommendations:

FBS ≥ 126 mg/dl

Random Glucose ≥ 200 mg/dl

A1C ≥ 6.5%

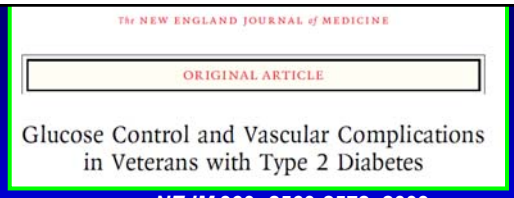
What's The Optimal A1C Goal??

Intensive Therapy for Diabetes Reduction in Incidence of Complications

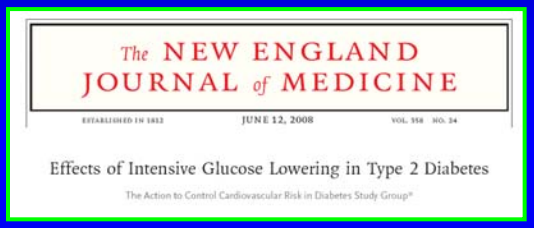
HbA1c	Type 1 DCCT 9 → 7%	Type 2 Kumamoto 9 → 7%	Type 2 UKPDS 8 → 7%
Retinopathy	76%	69%	17-21%
Nephropathy	54%	70%	24-33%
Neuropathy	60%	-	-

What About Glycemic Control And Macrovascular Disease?

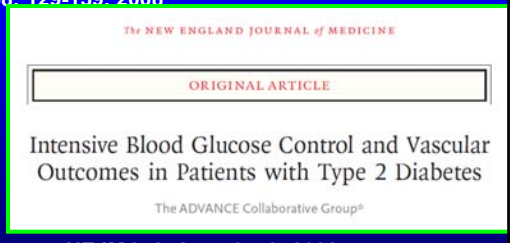
Recent Trials Modify The Paradigm



NEJM 360: 2560-2572, 2009



NEJM 358: 129-139, 2008



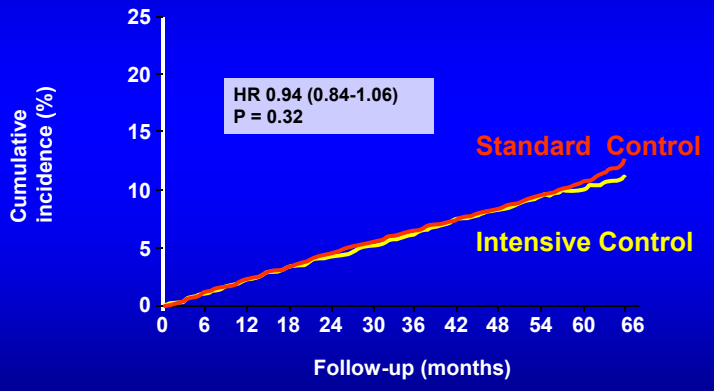
NEJM 358: 2545-2559, 2008

Diabetic Control and Macrovascular DIsease

	VADT	ACCORD	ADVANCE
Number	1,791	10,251	11,140
Age (Yrs)	60	62	66
Gender (% M/F)	97/3	62/38	58/42
DM Duration (Yrs)	11.5	10	8
HbA1c	9.4	8.1	7.5
CV Events (%)	~40	~35	~32
Insulin Use (%)	~50	~35	~1.5
Follow-Up (Yrs)	5.6	3.4	5

VADT, ACCORD, ADVANCE: Primary Outcome CV Events

CV Death, MI Stroke



Hypoglycemia In Recent Major Clinical Trials

- After the results became available, hypoglycemia was identified as an area of concern in 3 recent major clinical trials in which intensive glucose control was compared with standard glucose control:
  - ACCORD[1]
  - VADT[2]
  - ADVANCE[3]

ACCORD=Action to Control Cardiovascular Risk in Diabetes; ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; VADT=Veterans Affairs Diabetes Trial.

1. Action to Control Cardiovascular Risk in Diabetes Study Group et al. *N Engl J Med*. 2008;358(24):2545–2559.
2. Duckworth W et al. *N Engl J Med*. 2009;360(2):129–139.
3. ADVANCE Collaborative Group et al. *N Engl J Med*. 2008;358(24):2560–2572.

Hypoglycemia and CV Disease

Hemodynamic Responses To Hypoglycemia

- Heart Rate Increases
- Systolic BP Increases
- Diastolic BP Decreases
- Cardiac Output Increases
- Myocardial Contractility Increases
- EKG Changes
  - ✓ T wave flattening or inversion
  - ✓ ST depression
  - ✓ QT prolongation

Wright R et *al Diabetes/ Metabolism Research and Reviews* 2008

Hypoglycemia and CV Disease

Hematologic Responses To Hypoglycemia

- Increased RBCs Leading To Increased Blood Viscosity
- Enhanced Platelet Aggregation
- Increased Platelet Factor 4
- Increased Thromboglobulin
- Increased Coagulation Factor VIII
- Increased Von Willebrand Factor
- Increased Thrombin Generation

Wright R et *al Diabetes/ Metabolism Research and Reviews* , 2008

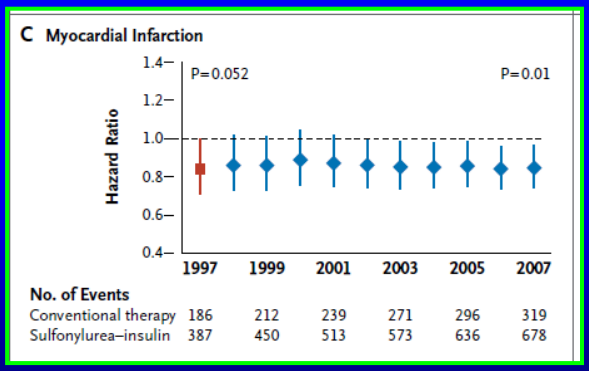
Is intensive glucose control ever beneficial to the vasculature?

UKPDS
United Kingdom Prospective Diabetes Study

	VADT	ACCORD	ADVANCE	UKPDS
Number	1,791	10,251	11,140	4,209
Age (Yrs)	60	62	66	53
Gender (% M/F)	97/3	62/38	58/42	61/39
DM Duration (Yrs)	11.5	10	8	0
HbA1c	9.4	8.1	7.5	7.1
CV Events (%)	~40	~35	~32	-
Insulin Use (%)	~50	~35	~1.5	0
Follow-Up (Yrs)	5.6	3.4	5	~10

UKPDS Group *Lancet* 352: 837-853 and 854-865, 1998

UKPDS
United Kingdom Prospective Diabetes Study Follow-Up
Myocardial Infarction



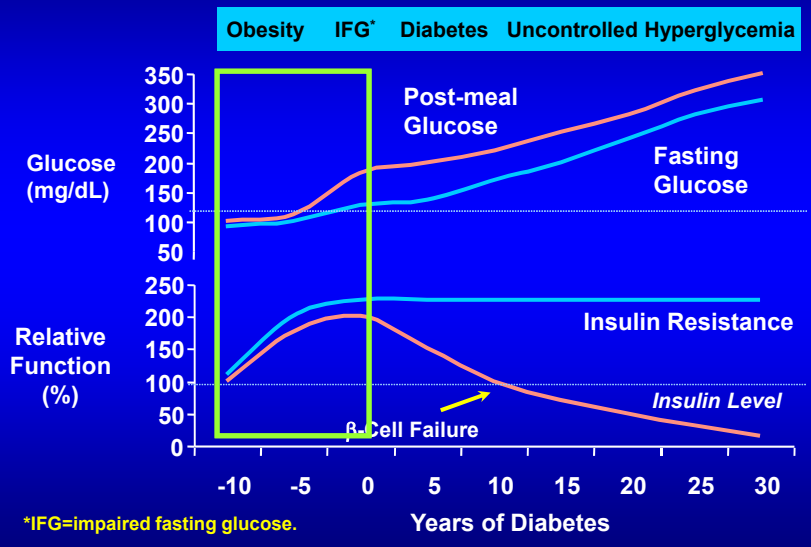
Holman R *et al NEJM* 359: 1565-1576, 2008.

Summary: Trials and Metabolic Memory

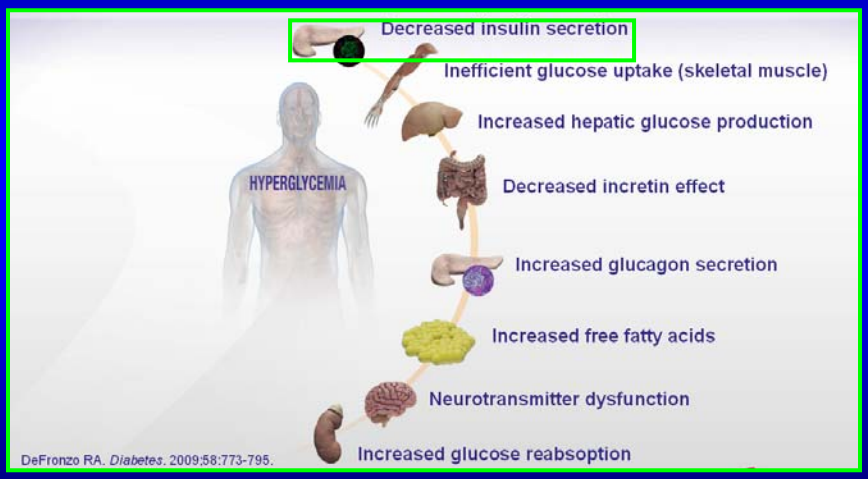
- Get In There Early With Tight Glycemic Control BUT Relax Glycemic Control Later!

- If CV Risk Factors Are Controlled, There Is No Benefit And Potential Harm To Intensive Glycemic Control In High Risk Patients With A Long Duration Of DM

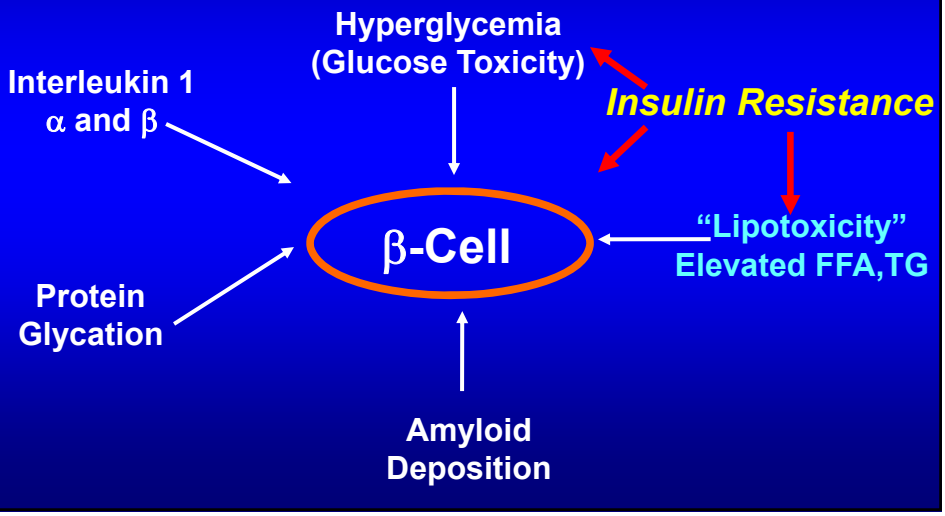
Natural History of Type 2 Diabetes



Multi-factorial Pathogenesis of Type 2 Diabetes



Multiple Factors Drive Progressive Decline Of β-Cell Function



The Sulfonylureas

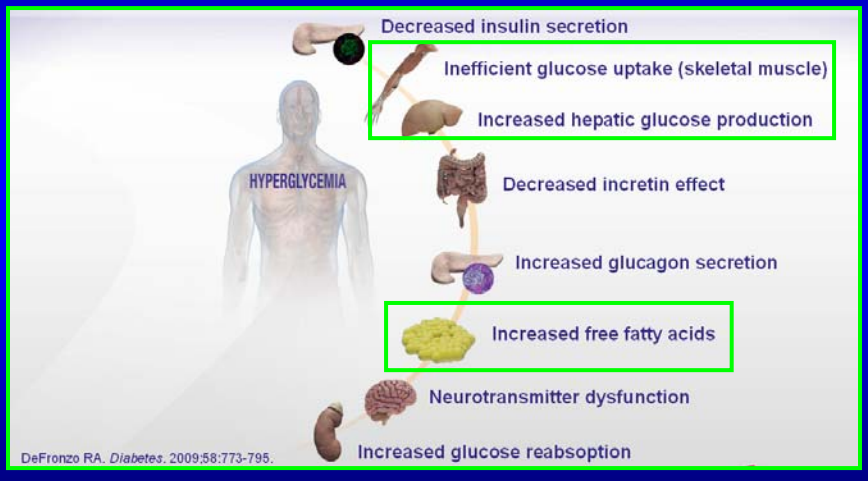
The Good

- Efficacious (↓A1C 1.2%)
- Increase Insulin Secretion
- Long Track Record
- Inexpensive

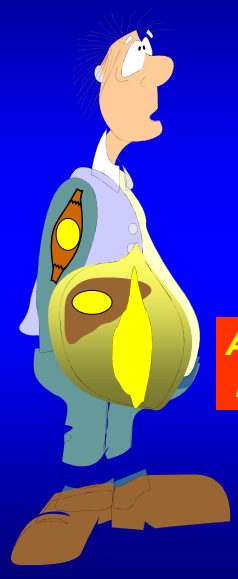
Not So Good

- Hypoglycemia
- Weight Gain
- Failure In 3-5 Years

Multi-factorial Pathogenesis of Type 2 Diabetes

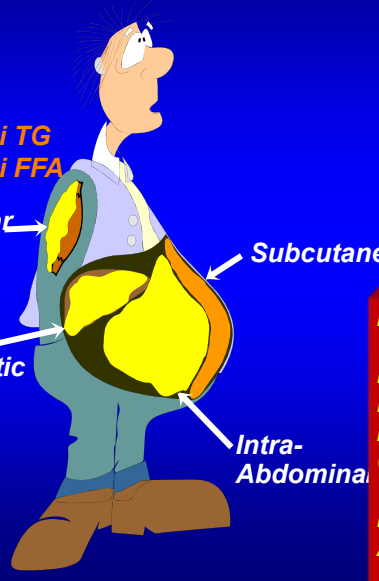


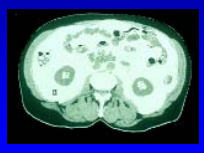
Fat Topography in Insulin Resistance



Adiponectin: Increases Insulin Sensitivity

Fat Topography In Insulin Resistance





- FFA
- TNF α
- Resistin
- Leptin
- IL-6
- CRP
- Tissue Factor
- PAI-1
- Angiotensinogen

Medications To Break Insulin Reistance: Metformin

The Good

- Efficacious (↓A1C 1.2%)
- Long Track Record
- ↓ Hepatic Glucose Production (90%)
- Helps Muscle Glucose Uptake (10%)
- Colon Cancer Protection

Not So Good

- GI Upset
- Hold For Procedures and CT Dye Load
- Watch Creat→ Stop If > 1.5mg

Medications To Break Insulin Reistance: Thiazoladinediones

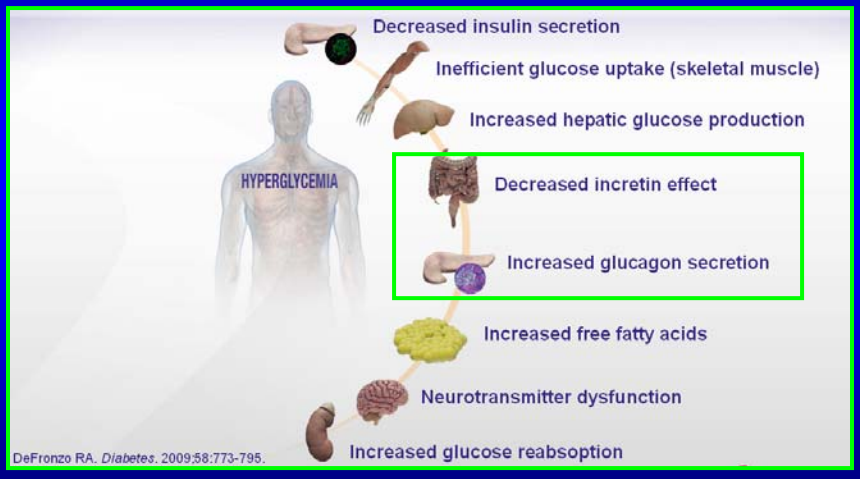
The Good:

- Efficacious (↓A1C 1.2%)
- Reasonably Long `Experience
- No Hypoglycemia
- β Cell Preservation

Thiazoladinediones (TZD's)

The Good:	Not So Good
➥Efficacious	➥Increased CV Risk?
➥Reasonably Long Experience	➥Edema
➥No Hypoglycemia	➥Weight Gain
➥β Cell Preservation	➥Fractures
	➥Bladder Cancer ?

Multi-factorial Pathogenesis of Type 2 Diabetes

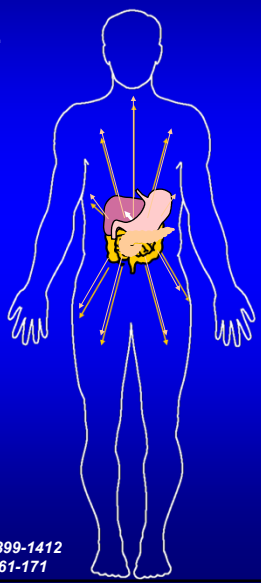


GLP-1 Modes of Action in Humans

Upon Ingestion of Food…

GLP-1 Is Secreted From the L-cells In the Intestine

This in Turn…

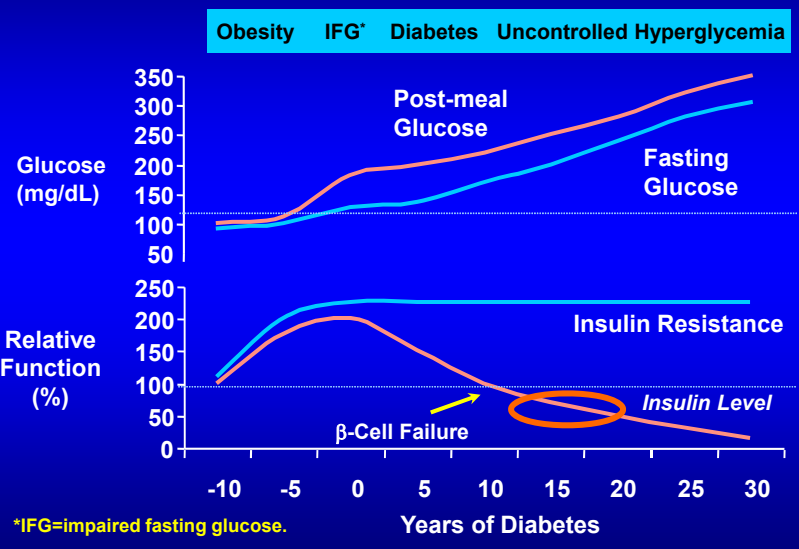


- ✓ Stimulates Insulin Secretion
- ✓ Suppresses Glucagon
- ✓ Slows Gastric Emptying
- ✓ Reduces Food Intake

Drucker DJ. Curr Pharm Des 2001; 7:1399-1412
Drucker DJ. Mol Endocrinol 2003; 17:161-171

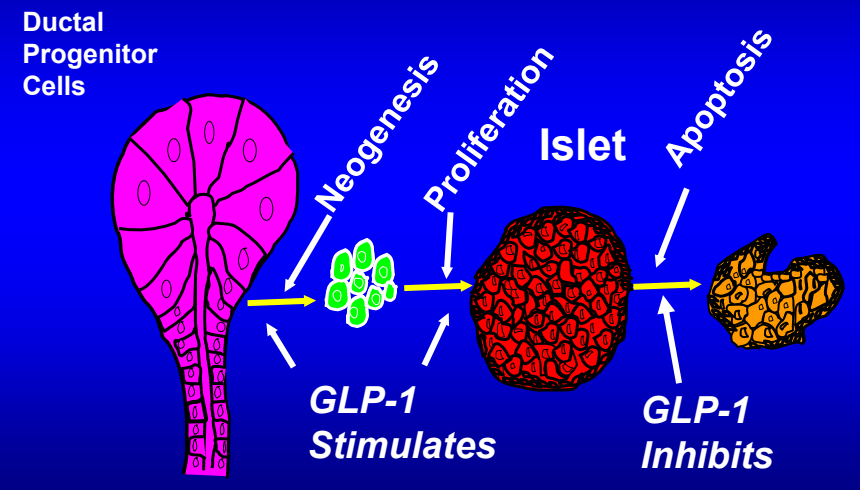
One More Point Going Back to Those β Cells…..

Natural History of Type 2 Diabetes

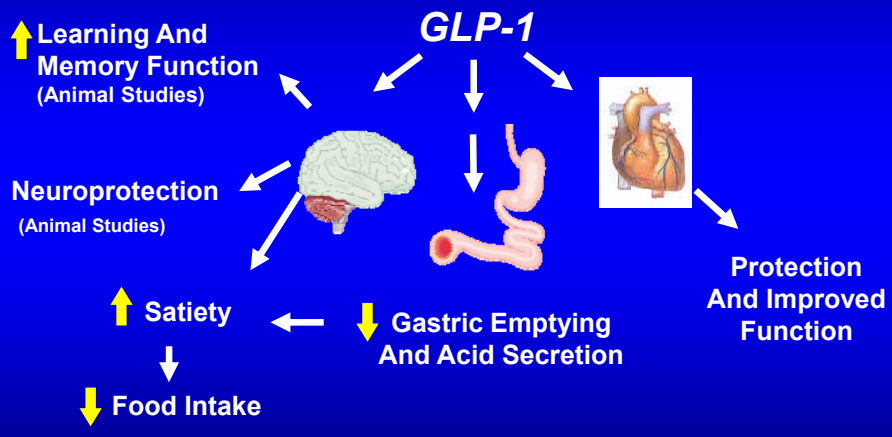


*IFG=impaired fasting glucose.

β-cell Neogenesis, Proliferation and Apoptosis



GLP-1: Effects On The Gastrointestinal, Cardiac And Central Nervous Systems



Kieffer, Habener. Endocr Rev 1999;20:876–913. Flint Et Al. J Clin Invest 1998;101:515–520. Wettergren Et Al. Dig Dis Sci 1993;38:665–673. During Et Al. Nat Med 2003;9:1173–1179. Perry Et Al. J Pharmacol Exp Ther 2002;302:881–888. Perry Et Al. J. Neurosci Res 2003;72:603–612. Bose Et Al. Diabetes 2005;54:146-151. Kavanipour Et Al. Peptides 2003;24:569-578. Thrainsdottir Et Al. Diab Vasc Dis Res 2004;1:40-43. Nikolaidis, Mankad Et Al. Circulation 2004;109:962-965. Nystrom Et Al. Am J Physiol Endocrinol Metab 2004;287:E1209-1215. Nystrom Et Al. Regul Pept 2005;125:173-177.

GLP-1 Modes of Action in Humans

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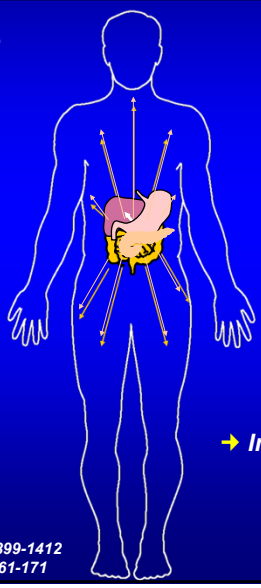


- ✓ Stimulates Insulin Secetion
- ✓ Suppresses Glucagon
- ✓ Slows Gastric Emptying
- ✓ Reduces Food Intake

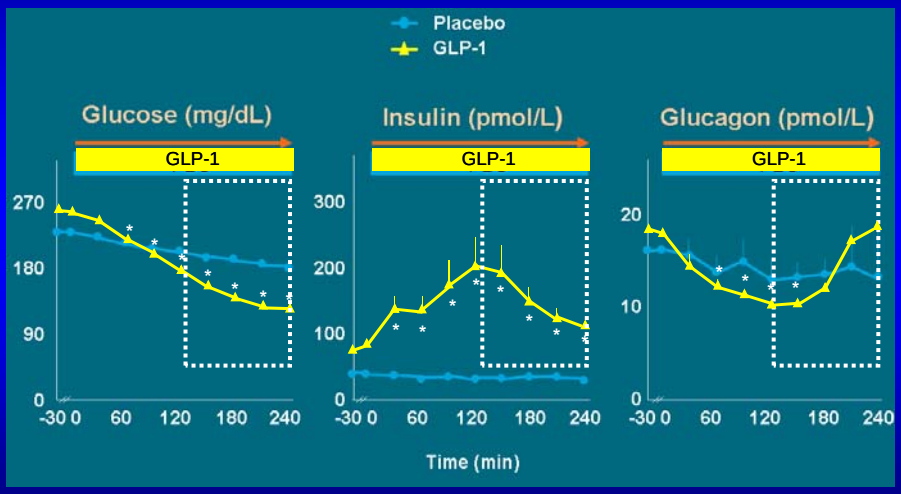
Long Term Effects Demonstrated in Animals…

→ *Increases β Cell Mass & Efficiency*

Drucker DJ. Curr Pharm Des 2001; 7:1399-1412
Drucker DJ. Mol Endocrinol 2003; 17:161-171

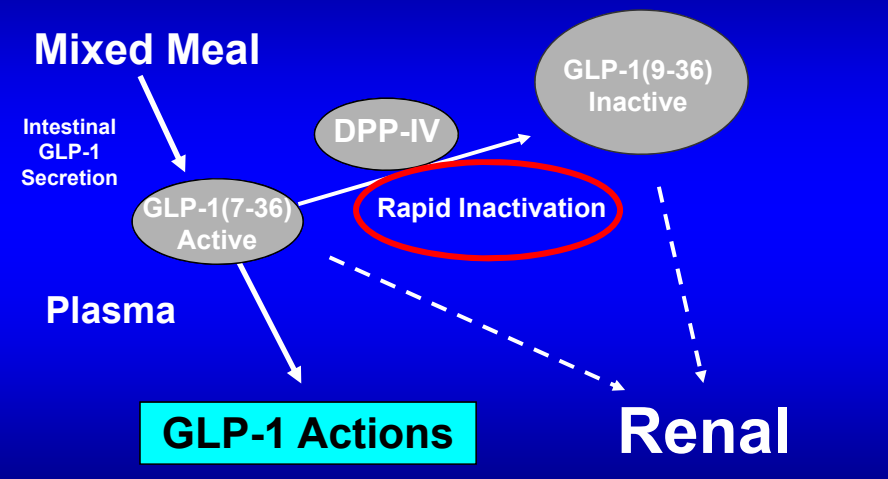
Glucose Dependent Effects of GLP-1

Type 2 Diabetics (n=10)



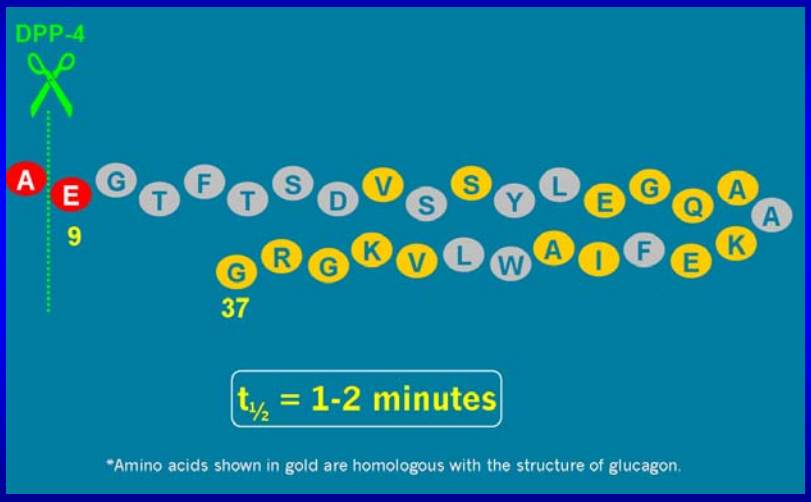
Mean (se) <p.05 Nautack MA Diabetelogia 1983

GLP-1 Effect : Blocked By DPP-4



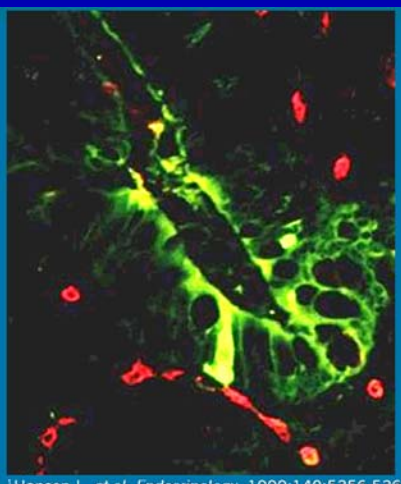
Deacon *et al.* Diabetes 1995; 44:1126

GLP-1: Rapidly Degraded by DPP-4



Mentlein, R *Regulatory Peptides* 85:9-24, 1999

Secreted GLP-1 Rapidly Degraded



- GLP-1 (green) released into intestinal capillaries is immediately exposed to DPP-4 (red)[1]
- >50% of secreted GLP-1 is already degraded before it reaches the general circulation[2]
- >40% of circulating GLP-1 is already degraded before it reaches β-cells[2]

[1]Hansen L, *et al. Endocrinology.* 1999;140:5356-5363;
[2]Deacon CF, *et al. Am J Physiol.* 1996;271(3 pt 1):E458–E464.

Enhance GLP-1 Effect By…

GLP-1 RECEPTOR AGONISTS

- Exenatide (Byetta/Bydureon) sc
- Liraglutide (Victoza) sc
- Dulaglutide (Trulicity) sc
- Albiglutide (Tanzeum) sc
- Lixisenatide sc

GLP-1 Mimetics

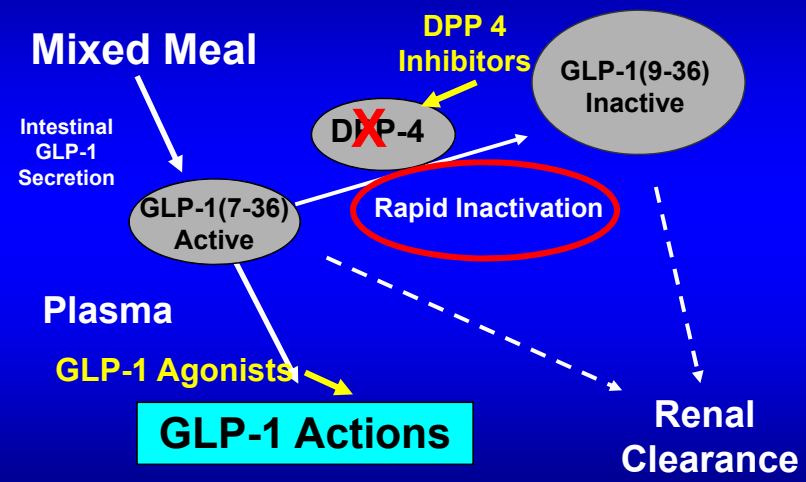
The Good:

- ✓ Efficacious (↓A1C 1.2-1.5%)
- ✓ Decrease Post-Prandial Glucose
- ✓ No Hypoglycemia
- ✓ Potential For Weight Loss
- ✓ Perhaps ß Cell Preservation

The Not So Good:

- ✓ *Daily/Twice Daily/Weekly Injection*
- ✓ *GI Upset*
- ✓ *Rare Reports Of Pancreatitis*
- ✓ *Cost*

GLP-1 Effect : Blocked By DPP-4



Deacon *et al.* Diabetes 1995; 44:1126

Enhance GLP-1 Effect By…

GLP-1 RECEPTOR AGONISTS

- Exenatide (Byetta/Bydureon)
- Liraglutide sc (Victoza)
- Dulaglutide (Trulicity) sc
- Albiglutide (Tanzeum) sc
- Lixisenatide sc

DPP-4 INHIBITORS

- Sitagliptin po (Januvia)
- Saxagliptin po (Onglyza)
- Linagliptin po (Tradjenta)
- Alogliptin po (Nesina)

DPP-4 Inhibitors

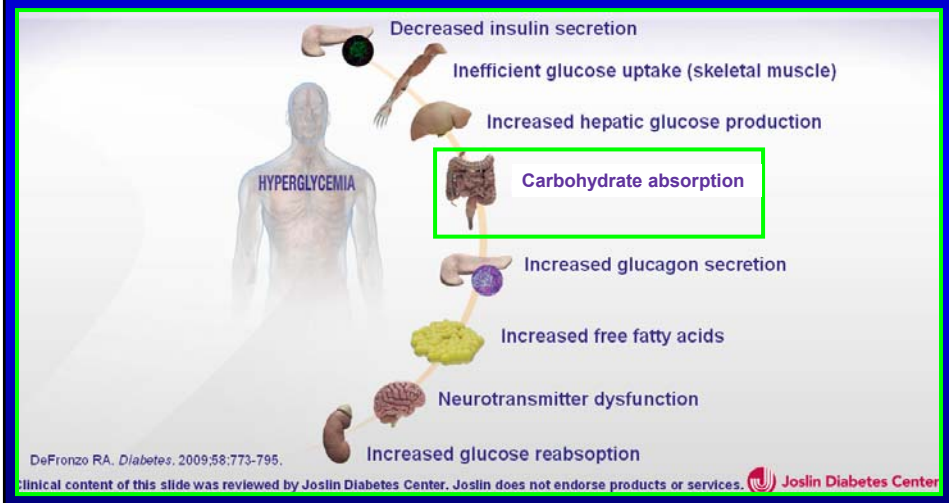
The Good:

- ✓ Efficacious (↓A1C 0.7%)
- ✓ Decrease Post-Prandial Glucose
- ✓ No Hypoglycemia
- ✓ Weight Neutral
- ✓ Safe In Renal Disease
- ✓ No GI Upset
- ✓ Perhaps ß Cell Preservation

The Not So Good:

- ✓ *Cost*
- ✓ *Rare Reports Of Pancreatitis*

Multi-factorial Pathogenesis of Type 2 Diabetes



α Glucosidase Inhibitors

Good

- Efficacious (↓A1C 0.5%)
- Long Experience
- No Hypoglycemia
- No Weight Gain

Not So Good

- Dosing With Meals
- GI Intolerance

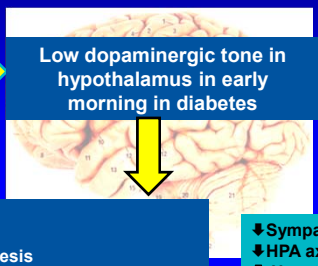
Multi-factorial Pathogenesis of Type 2 Diabetes

Dopamine Receptor Agonists

Type 2 Diabetics Have Low Levels Of Brain Dopamine

Quick Release Bromocriptine Increases Brain Dopamine Levels

Bromocriptine Mesylate : Proposed Mechanism Of Action



Morning administration (within 2 hours of waking) of Cycloset **Corrects** Low dopaminergic tone in hypothalamus in early morning in diabetes → Restoration of morning peak in dopaminergic activity (via D2 receptor-mediated activity)

⬆Sympathetic tone
⬆HPA axis tone
⬆ Hepatic gluconeogenesis
⬆ FFA and TG
⬆ Insulin resistance
⬆ Inflammation/hypercoagulation

→ Impaired glucose metabolism, hyperglycemia and insulin resistance
Adverse cardiovascular pathology

⬇Sympathetic tone
⬇HPA axis tone
⬇ Hepatic gluconeogenesis
⬇ FFA and TG
⬇ Insulin resistance
⬇ Inflammation/hypercoagulation

→ Decreased postprandial glucose levels
Reduction in insulin resistance
Day-long reduction in plasma glucose, TGs and FFAs

Fonseca. Use of Dopamine agonists in Type-2-Diabetes. Oxford American Pocket Cards. OUP, 2010
Cincotta. Hypothalamic role in Insulin Resistance and insulin Resistance Syndrome. Frontiers in Animal Diabetes Research Series. Taylor and Francis, Eds Hansen, B Shafrir, E London, pp 271-312, 2002

Quick Release Bromocriptine

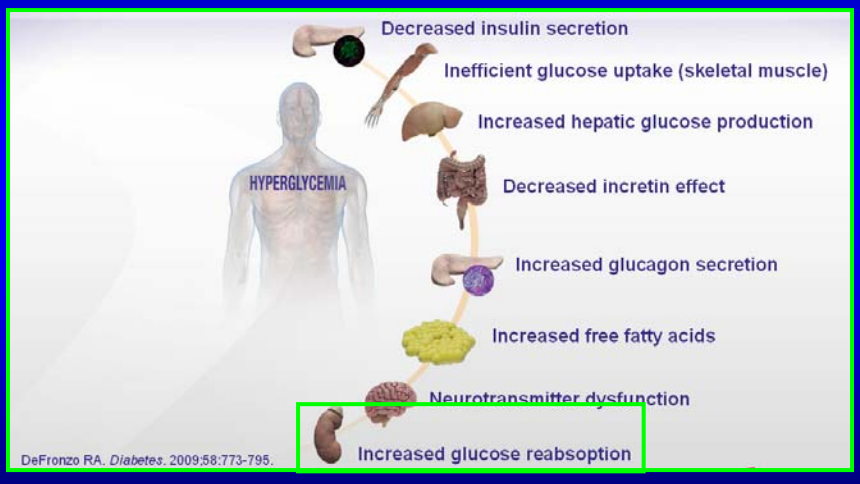
The Good

- Efficacious (↓A1C 0.5%)
- Resets Hypothalamic Circadian Clock
- Surprisingly Good CV Profile

Not So Good

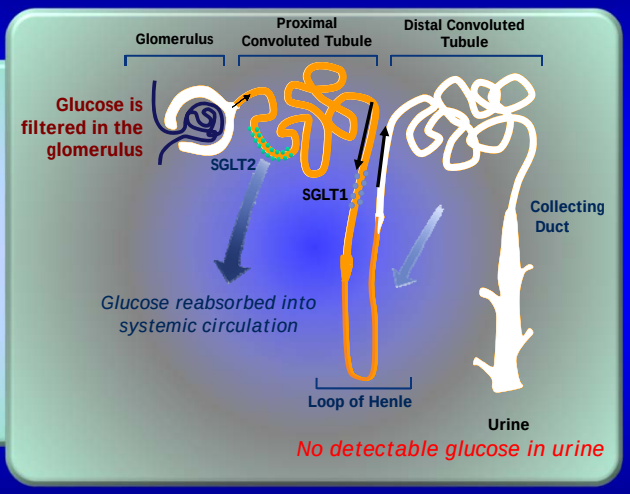
- Hypotension
- Short Track Record
- Cost

Multi-factorial Pathogenesis of Type 2 Diabetes



Sodium-Glucose Co-transporters (SGLTs) and Normal Renal Handling of Glucose

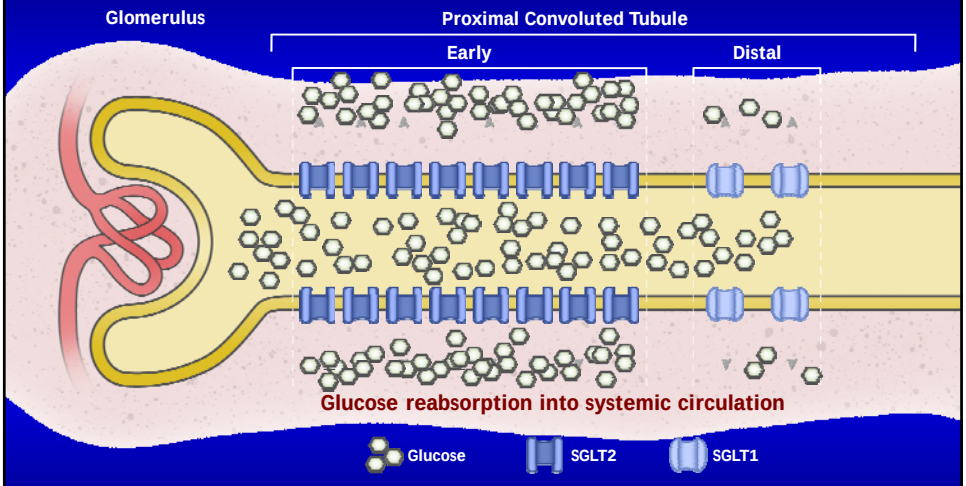
- 180 g/day/1.73 m^2 is filtered glucose load[1]
- SGLT2 transports 90% of filtered glucose out of the tubular lumen[1-4]
- SGLT1 transports the remaining 10% of filtered glucose[1-4]
  - SGLT1 is the primary SGLT in the small intestine[1,2]



SGLT = sodium-glucose co-transporter.

1. Wright EM et al. *J Intern Med.* 2007;261(1):32-43. 2. Kanai Y et al. *J Clin Invest.* 1994;93(1):397-404. 3. You G et al. *J Biol Chem.* 1995;270(49):29365-29371. 4. Wright EM. *Am J Physiol Renal Physiol.* 2001;280(1):F10-F18.

Normal Kidney: Glucose Reabsorption (Plasma Glucose ≤180 mg/dL)

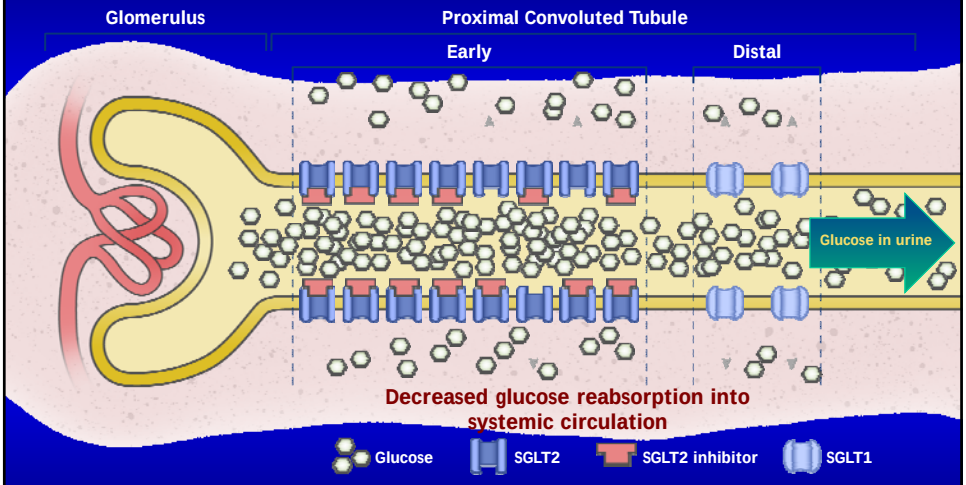


Rothenberg PL et al.

SGLT = sodium-glucose co-transporter.

1. Kanai Y et al. *J Clin Invest.* 1994;93(1):397-404. 2. You G et al. *J Biol Chem.* 1995;270(49):29365-29371.

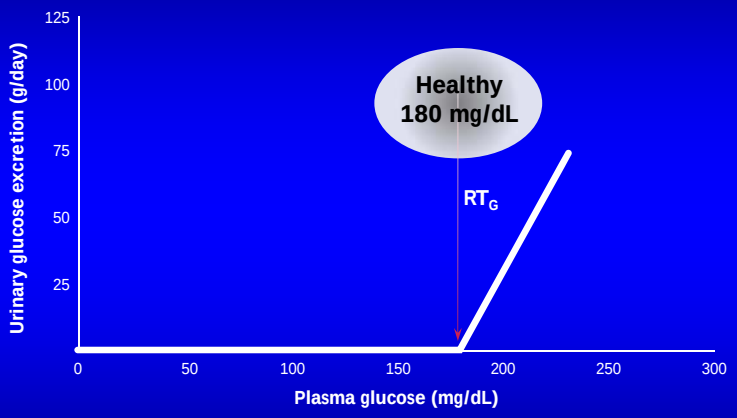
SGLT2 Inhibition Reduces Renal Glucose Reabsorption and Increases Urinary Glucose Excretion



SGLT = sodium-glucose co-transporter.

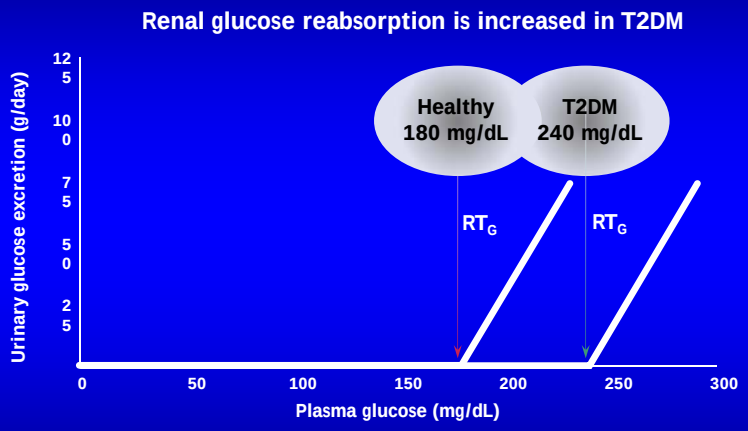
1. INVOKANA™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013. 2. Rothenberg PL et al. Poster presented at: 46th European Association for the Study of Diabetes Annual Meeting; September 20-24, 2010; Stockholm, Sweden. 3. Cowart SL, Stachura ME. In: Walker HK et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Boston, MA: Butterworths; 1990:653-657. 4. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14(6):782-790. 5. Oku A et al. *Diabetes*. 1999;48(9):1794-1800.

Renal Threshold for Glucose Excretion (RT_G) in Healthy Adult Subjects



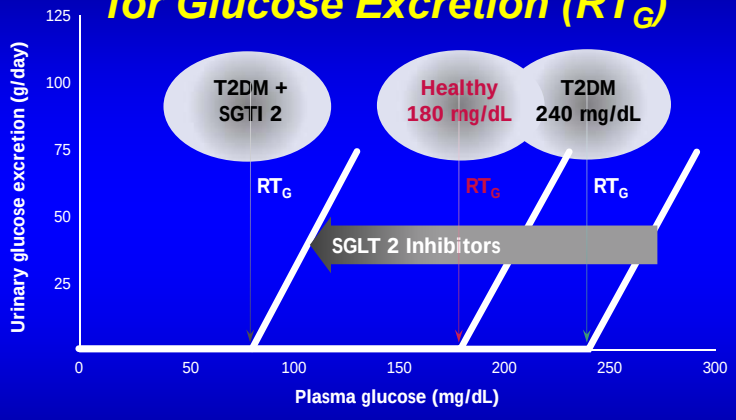
Abdul-Ghani MA, DeFronzo RA.
1. Cowart SL, Stachura ME. In: Walker HK et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Boston, MA: Butterworths; 1990:653-657. 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14(6):782-790. 3. Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95(1):34-42.

Renal Threshold for Glucose Excretion (RT_G) Is Increased in T2DM



Abdul-Ghani, DeFronzo RA.
1. Cowart SL, Stachura ME. In: Walker HK et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Boston, MA: Butterworths; 1990:653-657. 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14(6):782-790. 3. Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95(1):34-42.

SGTI-2's Lower Renal Threshold for Glucose Excretion (RT_G)



Abdul-Ghani MA, DeFronzo RA.
T2DM = type 2 diabetes mellitus.
1. Cowart SL, Stachura ME. In: Walker HK et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Boston, MA: Butterworths; 1990:653-657. 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14(6):782-790. 3. Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95(1):34-42.

The Gliflozin's

- *Canagliflozin (Invokana)*
- *Dapagliflozin (Farxiga)*
- *Empagliflozin (Jardiance)*
- *Ipragliflozin*

The SGLT-2 Inhibitors

The Good

- **Efficacious (↓A1C 1.0%)**
- **Inhibits Glucose Reabsorption At Renal Level**
- **Weight Reduction**
- **No Drug Interactions**

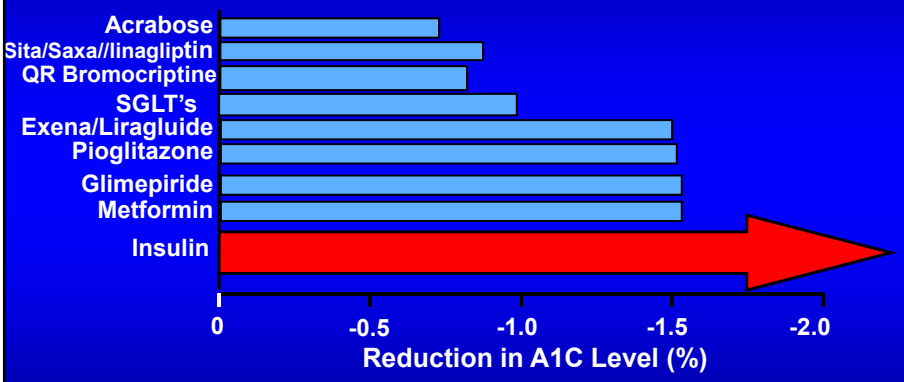
Not So Good

- **Increased UTI's/Vaginitis**
- **Short Track Record**
- **Cost**

Combination Pills for Type 2 Diabetes

Glyburide/Metformin (Glucovance)
Sitagliptin/Metformin (Janumet)
Saxaglitin/Metformin (Kombiglyze)
Linagliptin/Metformin (Jentadueto)
Canaglifozin/Metformin (Invokamet)
Dapaglifozin/Metformin (Xigduo)
Empaglifozin/Metformin (Jardamet)
Empaglifozin/Linagliptin(Glyxambi)

Anti-Hyperglycemic Monotherapy: Maximum Therapeutic Effect on A1C

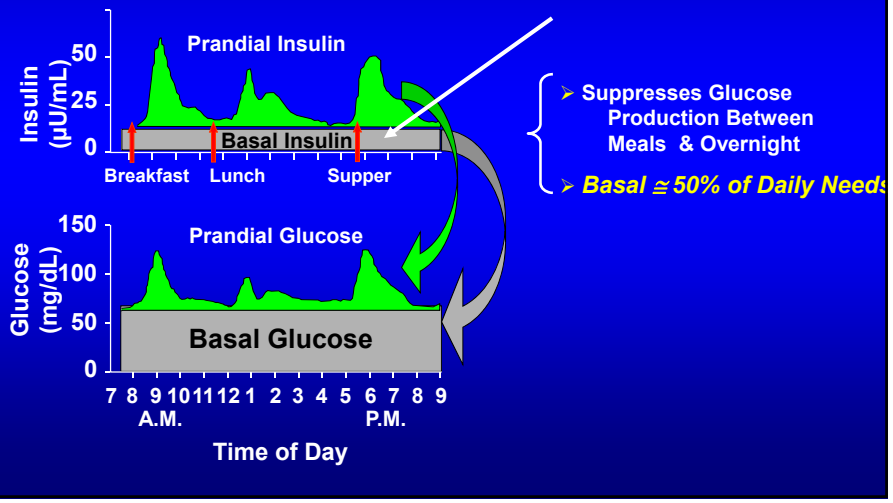


Precose [PI]. West Haven, CT: Bayer; 2003; Aronoff S, et al. *Diabetes Care.* 2000;23:1605–1611; Garber AJ, et al. *Am J Med.* 1997;102:491–497; Goldberg RB, et al. *Diabetes Care.* 1996;19:849–856; Hanefeld M, et al. *Diabetes Care.* 2000;23:202–207; Lebovitz HE, et al. *J Clin Endocrinol Metab.* 2001;86:280–288; Simonson DC, et al. *Diabetes Care.* 1997;20:597–606; Wolfenbuttel BH, van Haeften TW. *Drugs.* 1995;50:263–288; Nelson P, et al. *Diabetes Technol Ther.* 2007;9:317–326. Garber AJ, et al. ADA 2008; 07–LB.

A Basic Principle:

Fix The Fasting First

Physiologic Insulin Secretion : Basal/Bolus Concept



Basal Insulins

- Neutral Protamine Hagedorn (1946)
- Glargine (Lantus-2001 &Trujedo-2015)
- Detemir (2006)
- Degludec (2015)

Starting Basal Insulin

Continue Oral Agent(s) at Same Dosage (Eventually Reduce)

Add Single Insulin Dose (~ 15 units)

- ✓ Glargine (Anytime)
- ✓ Increase Insulin Dose 1 unit Daily Until FBS<100 mg &/or HbA1C < 7%

Suggested Titration Options For Glargine

Start with 10-15 units basal insulin and adjust weekly[2*]

Mean of self-monitored FPG values from preceding 2 days	Increase in insulin dose (IU/d)
≥180 mg/dL	+8
140-179 mg/dL	+6
120-139 mg/dL	+4
100-119 mg/dL	+2

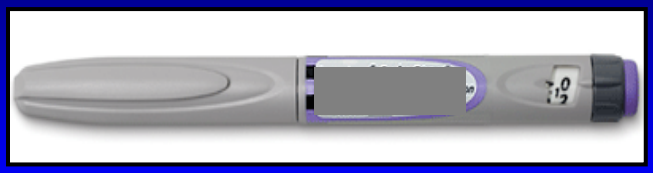
Or

Increase by 1 unit daily until FBS ≤ 100mg/dl

REPEAT

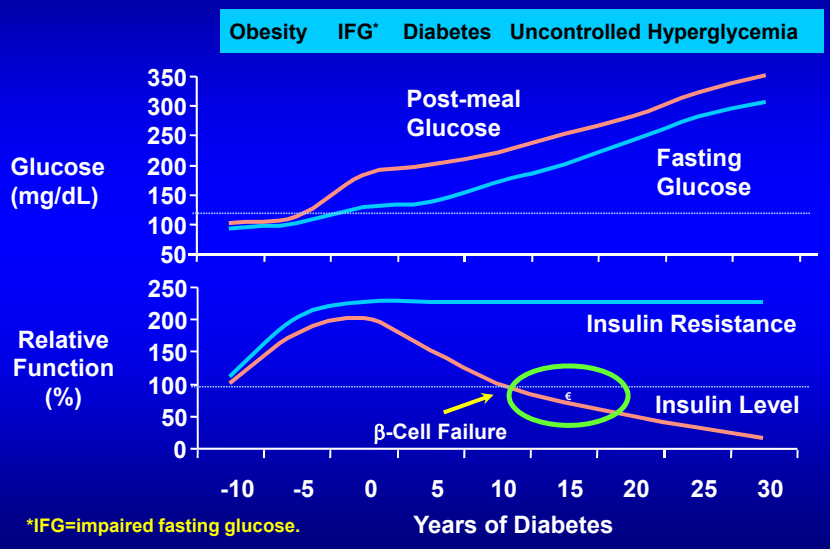
1. Gerstein HC et al. *Diabet Med*. 2006;23:736-742.
2. Riddle MC et al. *Diabetes Care*. 2003;26:3080-3086.

Insulin Pens



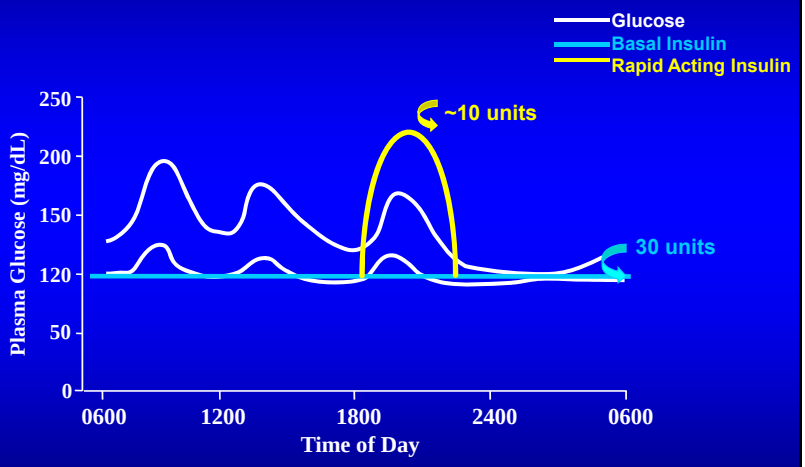
- ✓ More Convenient Than Vial And Syringe
- ✓ Repeatedly More Accurate Dosages
- ✓ Easier To Use For Those With Visual Or Fine Motor Skills Impairments
- ✓ Less Injection Pain
  - Coated Needles Not Dulled By Insertion Into A Vial Before Insertion Into The Skin

Natural History of Type 2 Diabetes



*IFG=impaired fasting glucose.

Glucose Patterns in Type 2 Diabetes Mellitus



Continue SU/Tide/DPP-4 Inhibitor, Metformin, TZD

Currently Available Bolus Insulins

- Regular (1921)
- Insulin Lispro (1996)
- Insulin Aspart (2000)
- Insulin Glulisine (2006)
- Inhaled Insulin (2015)

Fine Tuning The Bolus

The Bolus Has 2 Components:

Prandial→

Fine Tune By Carbohydrate Counting

Correction Factor →

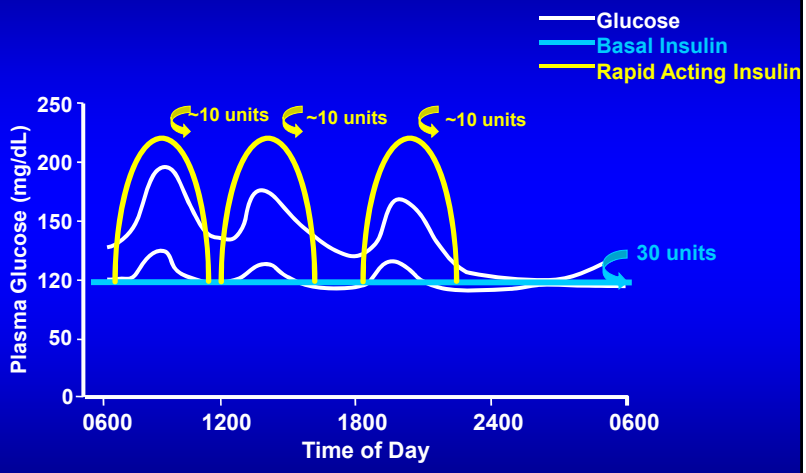
Adjustment For Pre-Meal Hyperglycemia

Dosing Prandial Insulin

- ✓ Considerations For Initial Dosing[1-3]
  - ✓ 5-10 u/meal OR 0.1 - 0.15 u/kg/meal
  - ✓ Prandial Insulin Should Cover 50% Of Total Daily Dose→ 30% At Breakfast, 30% Lunch, 40% Dinner
- ✓ Considerations For Dosing Adjustments[1-3]
  - ✓ Titration To Adjust For Patterns In BG Levels
  - ✓ Variable Meal Dosing To Adjust For Carbohydrate Intake
  - ✓ Supplemental Dosing To Correct For BG Before Meals

1. Mooradian AD et al. *Ann Intern Med.* 2006;145:125-134.
2. Dailey GE. *J Fam Pract.* 2007;56:735-742.
3. Leahy JL. *Am J Med Sci.* 2006;332:24–31.

Glucose Patterns in Type 2 Diabetes Mellitus



Discontinue SU/Tide/DPP-4 Inhibitor; Continue Metformin, TZD

Finally, For Your Larger Patients….

Extreme Insulin Resistance > 200 units/day→ Consider Using U500

- ✓5 Times As Concentrated---> 500 units/ml
- ✓Dosed BID or TID
- ✓Huge Cost Savings

Don't Forget The ABCs

✓**A** = Aspirin **(if over age 50)**

✓**B** = Blood Pressure

✓**C** = Cholesterol

BP Goals:

- SBP < 140
- SBP < 130 If Can Achieve Without Undue Treatment Burden, Such As Younger Pts.
- DBP < 90
- At Least One Anti-hypertensive At Bedtime

Lipid Goals:

- Goal LDL<100 If No Overt CVD
- Goal LDL<70 If CVD Or > 40 With One Or More CVD Risk Factor (Fam Hx, HTN, Smoking, Albuminuria)
- HDL > 40 and TG <150 Desirable However LDL Targeted Statin Therapy Is Preferred Strategy

Lipids: Statins Trump Other Meds

- Combination Therapy Provides No Additional CVD Benefit Over Statin And Is Not Recommended
- If Goal LDL Not Reached On Max Tolerated Statin, Treat To Goal Of 30-40% Reduction In LDL From Baseline

Coronary Disease

- Screening Asymptomatic Patients Not Recommended
- Beta-blocker For At Least 2 Years After MI
- Metformin May Be Used In Patients With Stable Compensated CHF If Renal Function Normal; Avoid If Unstable CHF Or Hospitalized

Thanks For Listening