Diabetes in 2013-An Update

Sherwin D'Souza, M.D.

Objectives

- Burden of disease in 2013
- Type 2 DM Glucose Management Goals-understand the new guidelines by ADA/ AACE
- Drugs available for management of diabetes in 2013 (non insulin and insulin agents)
- Review incretin physiology and understand current controversies
- SGLT2 inhibitors-newest class of drugs for type 2 DM

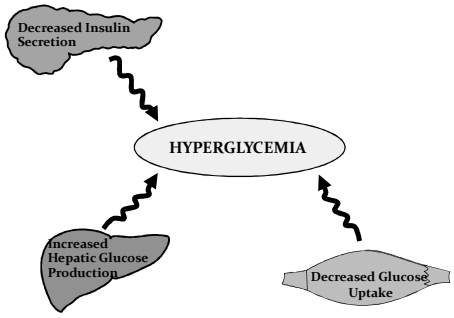
Burden of diabetes

- Diabetes affects 8.3% of the population of the United States, or approximately 25.8 million people.
- Of these, 7 million have not been diagnosed. Approximately 90% of all diabetes cases are type 2 diabetes.[1]
- In addition, another 79 million people—35% of US adults have prediabetes which raises short-term absolute risk of type 2 diabetes by 3- to 10-fold.[1-3]

Burden of diabetes

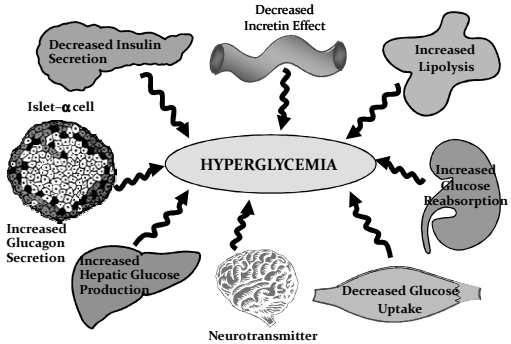
- Overall, up to 70% of people with prediabetes may develop type 2 diabetes during their lifetimes.[4]
- Thus, the prevalence of diabetes is projected to double in the next 10 years and, if current trends continue, this may affect 100 million people by 2050 !

Pathogenesis of Type 2 Diabetes: The Triumvirate



DeFronzo RA. *Diabetes*. 2009;58(4):773–795.

Pathogenesis of Type 2 Diabetes: The Ominous Octet



DeFronzo RA. *Diabetes*. 2009;58(4):773–795.

Pharmacologic Actions of Diabetes Drugs

Pancreas

Principle Action:
Insulin Secretion
- Glyburide
- GLP-1 agonists
- Glipizide
- DPP-4 inhibitors
- Glimepiride
- Repaglinide
- Nateglinide

Liver

Principle Action:
Hepatic Glucose Production
- Metformin
- Insulin
- GLP-1 agonists

Skeletal Muscle

Principle Action:
Insulin Sensitivity
- Rosiglitazone
- Pioglitazone

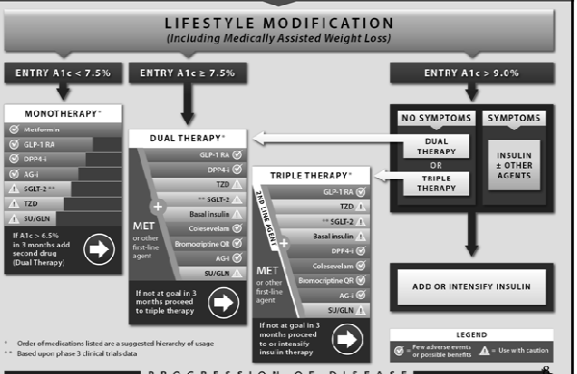
Hyperglycemia

Intestine

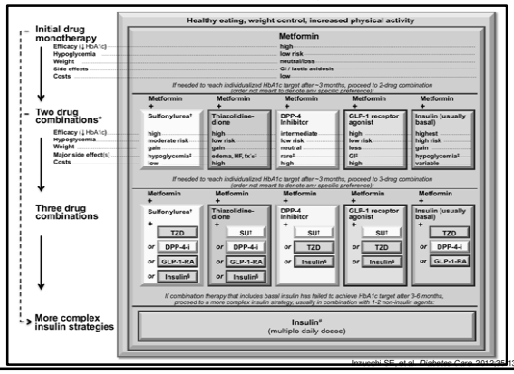
Principle Action:
Absorption
- Acarbose
- Miglitol
- Colesevelam

GI motility/satiety
- Pramlintide
- GLP-1 agonists

Glycemic Control Algorithm



ADA/EASD T2DM Treatment Algorithm



Inzucchi SE, et al. Diabetes Care. 2012;35:1364-1379.

Profiles of Antidiabetic Medications

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU / GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects

10

Principles of AACE/ACE Diabetes Algorithm for Glycemic Control

1. Minimize risk of hypoglycemia
2. Minimize risk of weight gain
3. Consider fasting *and* postprandial glucose
4. Consider total therapy cost, not just acquisition cost of drug
   - Hypoglycemic events; drug-related adverse events; treatment of complications from nonadherence; additional laboratory tests
5. Begin with metformin
   - Alone usually not sufficient; combination Tx usually indicated
   - Include all major classes of FDA-approved glycemic medications
6. Select therapy stratified by A1C level
7. Select therapy by A1C-lowering potential

ACE = American College of Endocrinology.

AACE/ACE 2011 Algorithm for Glycemic Control

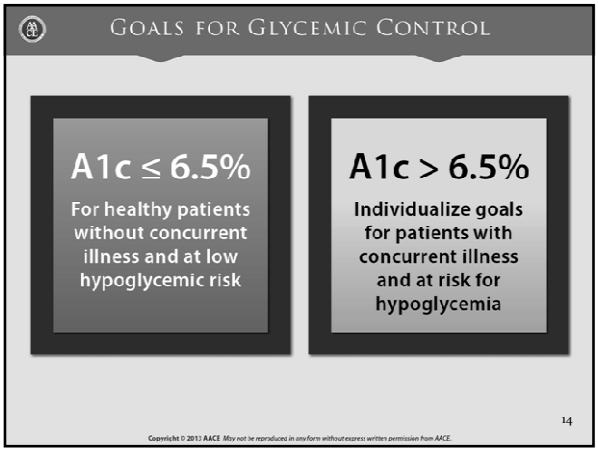
- Algorithm is stratified by A1C level
  - A1C: ≤7.5%
    - Start with monotherapy to achieve A1C goal of 6.5%
    - If monotherapy fails, progress to dual, then triple therapy
    - Finally, insulin therapy should be initiated, with or without additional agents
  - A1C: 7.6%–9.0%
    - Begin dual therapy; single agent is unlikely to achieve goal of 6.5%
    - If dual therapy fails, progress to triple therapy, then insulin, with or without additional orally administered agents
  - A1C: >9.0%
    - Asymptomatic: begin with triple therapy
    - Symptomatic, or medication failure: initiate insulin therapy, either with or without additional orally administered agents

Handelsman Y, et al. *Endocr Pract*. 2011;17(Suppl 2):1-53

Limitations of ADA/EASD Algorithm

- Assumes all diabetes patients are the same
- Overlooks risk of hypoglycemia
- Overlooks possible risks of blood sugar fluctuation independent of A1C level
- Doesn't discuss impact of medication choices on other complications of diabetes
- Uses primarily "cost" as a guide and overlooks key aspects of pathophysiology

Jellinger P. *Diabetes Care*. 2007;30(4):e16–e17.



AACE Comprehensive Diabetes Care: Glucose Goals

Parameter	Treatment Goal for Nonpregnant Adults
A1C (%)	Individualize based on age, comorbidities, and duration of disease* • ≤6.5 for most • Closer to normal for healthy • Less stringent for "less healthy"
FPG (mg/dL)	<110
2- hour PPG (mg/dL)	<140

*Considerations include

- Residual life expectancy
- Duration of T2DM
- Presence or absence of microvascular and macrovascular complications
- CVD risk factors
- Comorbid conditions
- Risk for severe hypoglycemia
- Patient's psychological, social, and economic status

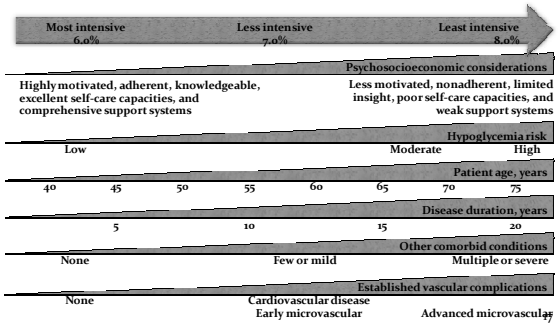
15

Handelsman Y, et al. *Endocr Pract*. 2011;17(suppl 2):1–53.

Rationale for Combination Therapy in Type 2 Diabetes

- Multiple metabolic defects
- Polygenic basis of disease
- Progressive disease
- Limited efficacy of single drugs
- Hyperglycemia begets hyperglycemia
  - "Glucose toxicity"

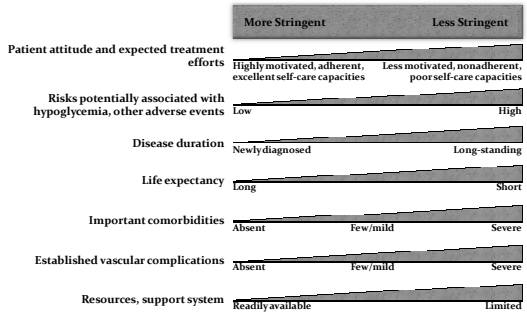
Algorithm for Individualizing Glycemic Targets



17

Ismail-Beigi F, Moghissi E, et al. *Ann Intern Med*. 2011;154:554-559.

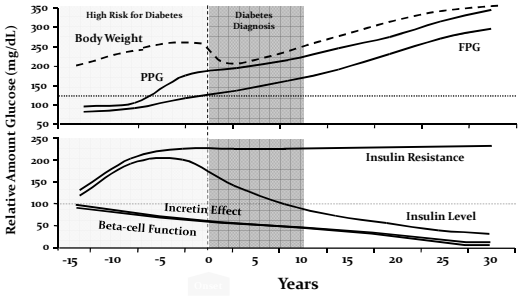
ADA-Recommended Approach to Management of Hyperglycemia



18

Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.

Natural History of T2DM



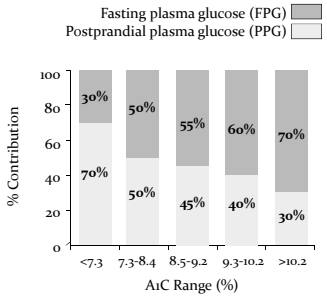
FPG = fasting plasma glucose; PPG = postprandial glucose.
Adapted from Kendall DM, Cuddihy, RM, Bergenstal RM.

Typical A1C Reduction by Treatment Regimen

Approved Antidiabetes Medications in the United States			
Medication	Route of Administration	Year of Introduction or FDA Approval	Efficacy as Monotherapy, Measured as a Reduction in the Glycated Hemoglobin Concentration (A1C; %)
Insulin	Parenteral	1921	≥2.5
Sulfonylureas	Oral	1946	1.5
Metformin*	Oral	1995	1.5
AGI	Oral	1995	0.5–0.8
TZDs	Oral	1997	0.8–1.0
Glinides	Oral	1997	1.0–1.5
GLP-1 agonists	Parenteral	2005	0.8–2.0
Amylin analogs	Parenteral	2005	0.6
DPP-4 inhibitors	Oral	2006	0.5–0.9

*Metformin has been available in other countries since 1957 but was approved in the United States in 1995.
Adapted from Unger J et al. *Postgrad Med*. 2010;122(30:145–157.

Fasting vs Postprandial Glucose: Relationship to A1C Level



Monnier L et al. *Diabetes Care*. 2003;26(3):881–885.

Insulins Available for the Treatment of Type 2 Diabetes

Class	Primary Mechanism of Action	Agent	Available as
Basal	• Increase glucose uptake • Decrease HGP	Detemir	Levemir
		Glargine	Lantus
		Neutral protamine Hagedorn (NPH)	Generic
Prandial		Aspart	NovoLog
		Glulisine	Apidra
		Lispro	Humalog
		Regular human	Humulin, generic
Premixed		Biphasic aspart	NovoLog Mix
		Biphasic lispro	Humalog Mix

22

Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.

Pharmacokinetics of Insulin

Agent	Onset (h)	Peak (h)	Duration (h)	Considerations
Basal				
NPH	2-4	4-10	10-16	Greater risk of nocturnal hypoglycemia compared to insulin analogues
Glargine	~1-4	No pronounced peak*	Up to 24 hours†	Less nocturnal hypoglycemia compared to NPH
Detemir				
Prandial				
Regular	~0.5-1	~2-3	Up to 8	• Must be injected 30-45 min before a meal • Injection with or after a meal could increase risk for hypoglycemia
Aspart	<0.5	~0.5-2.5	~3-5	• Can be injected 0-15 min before a meal • Less risk of postprandial hypoglycemia compared to regular insulin
Glulisine				
Lispro				

* Exhibits a peak at higher dosages.
† Dose-dependent.

23

Moghissi E, et al. *Endocr Pract*. 2013;Feb 20:1-33. [Epub ahead of print].

Carlos: 50-year-old African-American/Hispanic man diagnosed with T2DM 12 months ago

?

- Current labs: A1C = 8%
- Diabetes x 12 months treated with metformin 1000 mg bid and lifestyle intervention (increased physical activity, medical nutritional therapy)
- BMI = 29 kg/m²
- Social history: limousine driver

Which of the following would be an appropriate choice of next therapeutic strategy for a patient like this?

1. GLP-1 agonist
2. Insulin
3. Sulfonylurea
4. DPP-4 inhibitor

T2DM = type 2 diabetes mellitus; GLP-1 = glucagon-like peptide-1; DPP-4 = dipeptidyl dipeptidase-4.

Key Points to Consider When Selecting Pharmacotherapy for T2DM

- Duration/history of T2DM
- Which blood glucose level is not at target (fasting, postprandial, both)
- Patient administration preference (oral, injectable)
- Degree of A1C-lowering effect required to achieve goal
- Side-effect profile, patient's tolerability
- Coexisting conditions (CVD, depression, osteoporosis, obesity)

CVD = cardiovascular disease.

Burke S et al. *Clinician Reviews.* 2008; 18:28-34.

Basic Principles of Antihyperglycemic Drug Selection

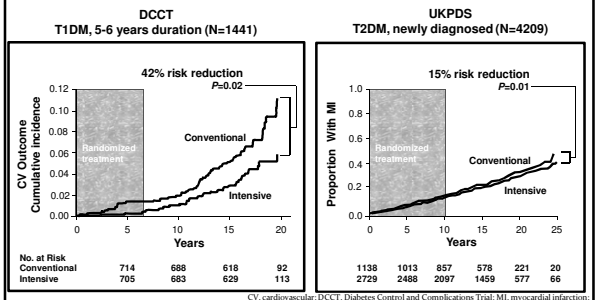
- Choice of which agent to use in a given individual should be based on:
  - Differing side-effect profiles of the various agents
  - Degree of glucose-lowering required
- Intensification of therapy requires monitoring and medication adjustment every 2 to 3 months

Which is your major consideration for selection of an antihyperglycemic agent?

?

1. Cost
2. Greatest glucose-lowering potential
3. Low hypoglycemia risk
4. Preference for oral agents

Intensive Glycemic Control Reduces Long-term Macrovascular Risk in Younger Patients With Shorter Duration of Disease



CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study.

Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653.
Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589.

28

Common Principles in AACE/ACE and ADA/EASD T2DM Treatment Algorithms

- Individualize glycemic goals based on patient characteristics
- Promptly intensify antihyperglycemic therapy to maintain blood glucose at individual targets
  - Combination therapy necessary for most patients
  - Base choice of agent(s) on individual patient medical history, behaviors and risk factors, ethno-cultural background, and environment
- Insulin eventually necessary for many patients
- SMBG vital for day-to-day management of blood sugar
  - All patients using insulin
  - Many patients not using insulin

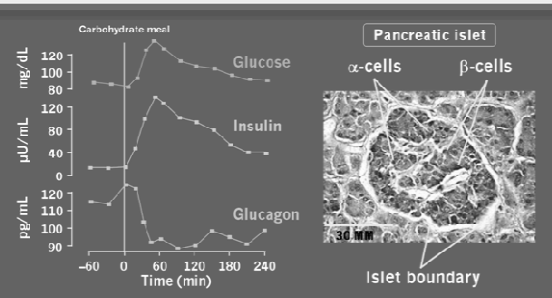
29

Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.
Garber AJ, et al. *Endocr Pract*. 2013;19:327-336.

Incretins

- Review physiology
- Controversies

Normal Insulin and Glucagon Response in the Postprandial Period



Photomicrograph courtesy of Michael Sarras, PhD, Rosalind Franklin University of Medicine and Science

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

NOVARTIS

Incretins

- An incretin is a substance (hormone) that:
  - Originates in the GI tract
  - Is released during nutrient absorption[1]
  - Augments insulin secretion
- Some incretins also decrease glucagon secretion
- Actions on insulin and glucagon are glucose-dependent[2]

[1]Pugh MB, et al, eds. *Stedman's Medical Dictionary*. 27th ed. 2000.
[2]Vilsbøll T, Holst JJ. *Diabetologia*. 2004;47:357-366.

NOVARTIS

What is DPP-4?

- A serine protease widely distributed throughout the body[1]
- Cleaves N-terminal amino acids and inactivates a number of biologically active peptides, including the glucostatic incretins GLP-1 and GIP[1,2]
- DPP-4 effects on GLP-1 and GIP play a key role in incretin activity and glucose homeostasis[3]:
  - Inactivates GLP-1 >50% in ~1–2 min
  - Inactivates GIP >50% in ~7 min

[1]Mentlein R. *Regul Pept*. 1999;85:9-24.
[2]Deacon CF, et al. *J Clin Endocrinol Metab*. 1995;80:952-957.
[3]Ahrén B, Hughes TE. *Endocrinology*. 2005;146:2065-2069.

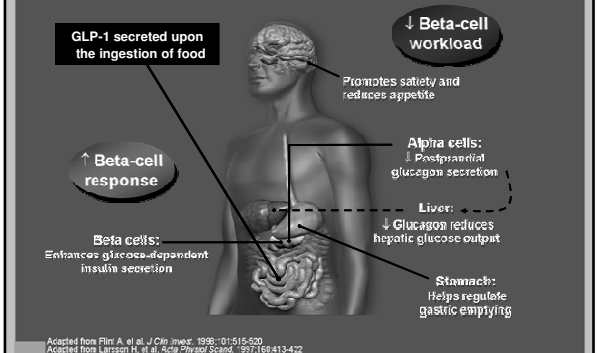
NOVARTIS

The "Incretin Effect" in Normal Subjects

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

NOVARTIS

GLP-1 Effects in Humans
Understanding the Natural Role of Incretins



Adapted from Flint A, et al. *J Clin Invest.* 1998;101:515-520.
Adapted from Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422.
Adapted from Nauck MA, et al. *Diabetologia.* 1996;39:1546-1553.
Adapted from Drucker DJ. *Diabetes.* 1996;47:159-169.

Incretin-Based Therapies for T2DM

GLP-1 and GIP have extremely short half-lives due to DPP-4 degradation

Degradation-resistant GLP-1 receptor agonists
Injectables

Exendin-4 based:
- **Exenatide**
- **Exenatide once weekly[a]**
- **Lixisenatide**

GLP-1 analogs:
- **Liraglutide**
- **Albiglutide**
- **Taspoglutide**

DPP-4 inhibitors
Oral agents
- **Sitagliptin**
- **Saxagliptin**
- **Alogliptin[a]**
- **Linagliptin**
- **Vildagliptin[a]**
- **Dutogliptin**

Indicates FDA-approved agent

[a] Under FDA consideration.

Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm; NIH. http://www.clinicaltrials.gov; Exenatide once weekly. http://phx.corporate-ir.net/phoenix.zhtml?c=101911&p=irol-newsArticle&ID=1423378; Alogliptin. http://www.takeda.com/press/article_34760.html.; Vildagliptin. http://www.novartis.com/downloads/investors/Novartis-20-F-2008.pdf; Baggio LL, Drucker DL. *Gastroenterology.* 2007;132:2131-2157.

Comparison

Effects/ Parameters	GLP 1 Receptor Agonists	DPP 4 INHIBITORS
ROUTE	SQ	Oral
A1C REDUCTION	-0.6 to -1.9 %	-0.5-0.8%
BODY WEIGHT	Reduced	Reduced
APPETITE	Suppressed	No effect
GASTRIC EMPTYING	Slowed significantly	No effect
HYPOGLYCEMIA	Minimal	Minimal
CVD risk factors	Improved with weight loss	No effect
GI AEs	Nausea, diarrhea	None
TIMING OF DRUG	Once or twice daily/ weekly	Once or Twice daily
INSULIN SECRETION	Enhanced	Enhanced
GLUCAGON SECRETION	Suppressed	Suppressed

GLP-1 agonists and Thyroid Tumors

- Animal studies: Thyroid C-cell tumors in rats and mice
- Clinical trials
  - Papillary thyroid cancer: 5 cases with liraglutide vs 1 case with comparators
  - Neoplastic C-cell hyperplasia: 1 case in comparator group
  - Calcitonin levels
    - Mean concentrations higher for liraglutide vs placebo
    - Mean concentrations not higher for liraglutide vs active comparators
    - Small, similar calcitonin decreases for exenatide and liraglutide in head-to-head trial
- Label information
  - Relationship between tumors in animals and risk to humans unclear
  - Counsel patients regarding risks and symptoms of thyroid tumors

FDA briefing materials – liraglutide. http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4422b2-01-FDA.pdf; Buse JB, et al. *Lancet* 2009;374:39-47; Victoza (liraglutide) [prescribing information]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf.

Dosing Incretin-Based Therapies in Renal Insufficiency

Renal Function	GLP-1 Agonists	DPP-4 Inhibitors
Mild renal insufficiency (GFR > 50 mL/min	• Exenatide: No change	• No changes
	• Liraglutide: Use with caution due to limited clinical experience[a]	
Moderate renal insufficiency (GFR ≥ 30-50 mL/min)	• Use with caution due to limited clinical experience[a]	• Decrease sitagliptin to 50 mg daily
		• Decrease saxagliptin to 2.5 mg daily
Severe renal insufficiency (GFR < 30 mL/min)	• Exenatide: Contraindicated	• Sitagliptin 25 mg daily
	• Liraglutide: Use with caution due to limited clinical experience[a]	• Saxagliptin 2.5 mg daily

[a] Nausea and vomiting can worsen hypovolemia

Byetta® [prescribing information]. San Diego, CA: Amylin Pharmaceuticals, Inc; 2009. Onglyza™ [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2009. Januvia™ [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc; 2008. Victoza® [prescribing information]. Princeton, NJ: Novo Nordisk Inc; 2010.

Summary

- Approved GLP-1 receptor agonists can decrease A1C
  - ≈ 0.7%-1.1% as monotherapy
  - ≈ 0.8%-1.5% in combination with other agents
- Approved DPP-4 inhibitors can decrease A1C
  - ≈ 0.4%-0.5% as monotherapy
  - ≈ 0.5%-0.9% in combination with other agents
- Emerging data demonstrate improved glycemic control over periods ≥ 1 years for some incretin-based therapies
- Incretin-based therapies are generally associated with low risk of hypoglycemia, although risk is increased in combination with SUs
- In clinical trials, long-acting GLP-1 receptor agonists offer less frequent injections, greater A1C benefits, and better control of fasting plasma glucose than short-acting agents

PANCREATITIS AND INCRETIN-BASED THERAPIES

- The estimated risk of acute pancreatitis in the population at large is reported as 0.33 to 0.44 events per 1,000 adults per year; 15% to 20% of cases are considered severe, and 2% to 4% result in death. A relatively small number (1%–2%) are believed to be drug-induced.

INCRETINS and PANCREATIC CANCER

- The US Food and Drug Administration (FDA) is evaluating an increased risk for pancreatitis and precancerous cellular changes called pancreatic-duct metaplasia associated with incretin mimetic drugs used to treat patients with type 2 diabetes.
- This covers the glucagon-like peptide-1 (GLP-1) agonists and the DPP-4 inhibitors.

Incretins and pancreatic cancer

- A group of researchers came up with a study showing that there is a link between incretin mimetics and pancreatic cancer.
- In the unpublished study, researchers examined a small number of pancreatic tissue specimens taken from patients after they died from unspecific cause. FDA requested the researchers to provide the methodology of the study as well as the tissue samples for further investigation.

- Diabetes, 2013 Peter Butler, M.D.

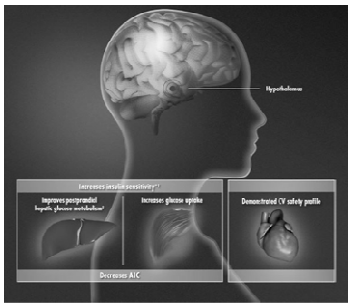
FDA statement

- This is the first time the FDA has issued a communication with regard to the potential risk for precancerous findings of the pancreas with incretin mimetics. It emphasizes, however, that it "has not concluded these drugs may cause or contribute to the development of pancreatic cancer."

So what do you tell your patient?

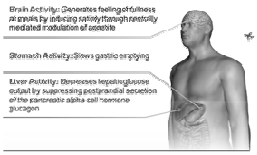
- Studies are difficult because diabetes is a risk factor for pancreatitis, both acute and chronic; acute and chronic pancreatitis can cause diabetes; plus chronic pancreatitis can cause cancer; and cancer causes pancreatitis. And the development of diabetes in itself can be an early indicator of cancer!
- In general, you wouldn't use incretin in people with a prior history of pancreatitis. And in people who develop pancreatitis on the drug, you certainly discontinue it. It's not an absolute contraindication, but it does seem prudent.

Cycloset-Bromocriptine agonist



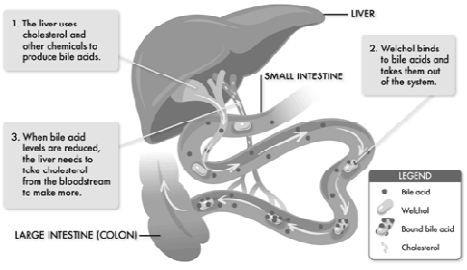
Dose is 0.8 mg daily in am, titrated upwards as tolerated

Symlin (Pramlinitide)



Synthetic analog of human amylin, a naturally occurring neuroendocrine hormone in the pancreatic beta cells that contributes to postprandial glucose control.

Welchol(Colveselam)



Available as pills or as oral suspension

Welchol(Colveselam)

Mechanism of action in lowering blood sugar is not exactly known. Approved for use with metformin, insulin and sulfonylureas. Should not be used for TGs > 500 or if any intestinal blockage.

SGLT-2 Inhibitors

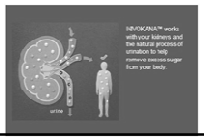
- A New Modality for Treating Type 2 Diabetes

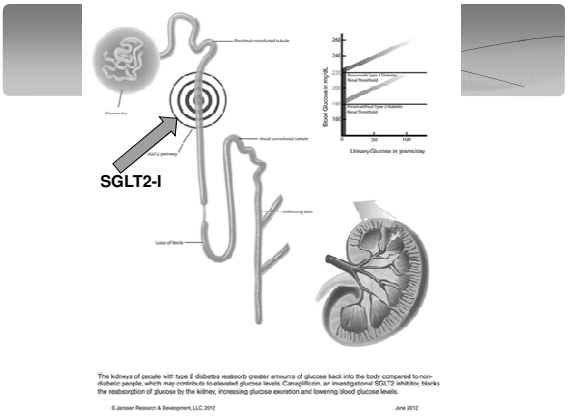
SGLT-1 and SGLT-2

- Two sodium glucose transporters, cause glucose reabsorption, have been identified: SGLT-1 and SGLT-2
- SGLT-2 is found only in the proximal tubule of the kidney, accounts for 90% of the re-absorption of glucose
- SGLT-1 is found in the gut and other tissues, account for approximately 10% of glucose reabsorption

SGLT-2 Inhibitor - Canagliflozin

- **Invokana** (Canagliflozin) 1st SGLT-2 inhibitor, approved March 2013
- Once daily dosing before 1st meal of day, 100mg or 300mg tablets
- **MOA**: Inhibition of SGLT2 reduces reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion, with a consequent lowering of plasma glucose levels as well as weight loss.
- Blocks approximately 50-80 grams of glucose per day from being reabsorbed





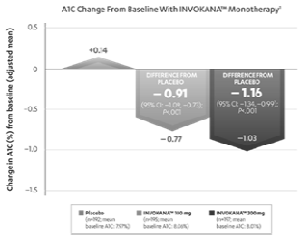
SGLT-2 Inhibitor-Canagliflozin

- **Positive effects**: Reduction in body weight and systolic blood pressure
- **Side effects**: Most common: Vaginal yeast infection, urinary tract infection and increased urination. Hypoglycemia (<5%), dehydration, dizziness or fainting, hyperkalemia
- **Contraindications**: Clinicians should not use canagliflozin to treat patients with type 1 diabetes, patients with type 2 diabetes who have increased ketones in their blood or urine, severe renal impairment, end-stage renal disease or patients receiving dialysis

SGLT-2 Inhibitor: Canagliflozin

- 100 mg once daily in am before first meal
- Do not use if GFR is < 45 mg/dl
- Dose can be titrated up to 300 mg once daily if tolerated and if GFR is > 60%
- If GFR is 45-60% then use 100 mg qd.

Monotherapy study



Effects on Weight, BP

Canagliflozin Side Effects

Adverse Reactions Reported in ≥2% of Patients Treated With INVOKANA™ in Four Pooled 26-Week Placebo-Controlled Trials[1]

Adverse reaction	Placebo (n=646)	INVOKANA™ 100 mg (n=833)	INVOKANA™ 300 mg (n=834)
Female genital mycotic infection*	3.2%	10.4%	11.4%
Urinary tract infection†	4.0%	5.9%	4.3%
Increased urination‡	0.8%	5.3%	4.6%
Male genital mycotic infection§	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst¶	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

http://www.invokanahcp.com/safety-information/safety-and-tolerability-profile?utm_source=google&utm_medium=cpc&utm_campaign=Invokana+HCP&utm_term=canagliflozin%20side%20effects&utm_content=Side+Effects+-+Exact|mkwid|suZLUen2m|pcrid|24016786155

Canagliflozin

- **Drug Interactions**:

1. UGT Inducers (Rifampin, Phenytoin, Phenobarbitol, Ritonavir)- Decreased canagliflozin, consider increasing dose of canagliflozin
2. Digoxin- Increased digoxin concentration, monitor levels

- **Pregnancy Category C**
- **Do Not Use:** GFR <30mL/min, end stage renal disease, or patients on dialysis

SGLT-2 Inhibitor-Canagliflozin

- **Pre-Marketing Study Results**:

✓ Average decrease in A1C levels 1%
✓Weight Loss average 5-10 pounds
✓Decrease in systolic blood pressure approximately 4%
✓Increase HDL approximately 7.6%
✓Increase LDL approximately 11.7%
✓Low risk of hypoglycemia

SGLT-2 Inhibitors

Pipeline:

1. Empagliglozin (Eli Lilly/Behringer)
2. Dapagliflozin (AstraZeneca)
3. Remogliflozin Etabonate (GlaxoSmithKline)
4. Sergliflozin Etabonate (GlaxoSmithKline)
5. Tofoglitazone (Roche & Chugal)

Which Combination Therapy Options Should Be Used?

- Any of multiple rational combinations can be used
  - Considerations
    - Relative effectiveness
    - Cost, side-effect profile, intercurrent illness
- Metformin
  - Relatively safe, inexpensive, associated with less weight gain, and may reduce CV complications (UKPDS)
- Sulfonylureas
  - Have high rate of secondary failure and hypoglycemia
- Consider effects on other manifestations of cardiometabolic disease

Summary

- Oral agents often fail to maintain long-term glycemic control in many patients with T2DM
- Progressive beta-cell failure plays a major role in the lack of durable A1C control
- Weight gain and hypoglycemia are major factors limiting the effectiveness of current therapies

DeFronzo RA. *Diabetes*. 2009;58(4):773–795.

Post-test Question 3:
Carlos: 50-year-old African-American/Hispanic man diagnosed with T2DM 12 months ago

?

- Current labs: A1C = 8%
- Diabetes x 12 months treated with metformin 1000 mg bid and lifestyle intervention (increased physical activity, medical nutritional therapy)
- BMI = 29 kg/m²
- Social history: limousine driver

Which of the following would be an appropriate choice of next therapeutic strategy for a patient like this?

1. GLP-1 agonist
2. Insulin
3. Sulfonylurea
4. DPP-4 inhibitor
5. SGLT2 inhibitor

Questions? Comments!

POST TEST QUESTIONS

- 1. The ADA/ EASD algorithm takes into account the following
- a.efficacy and hypoglycemia
- b.weight , side effects and costs
- c. a and b

- 2 True or false
- Two SGLT (sodium glucose co transporters) have been identified. SGLT 2 which accounts for 90% of the reabsorption is located in the distal tubule of the kidney.

- 3. Which one of the following statements is true
- a. Exenatide can be used in severe renal insufficiency (GFR < 30 ml/min)
- b. Liraglutide may be used with caution in severe renal insufficiency (GFR < 30 ml/min) due to limited clinical experience.
- c. sitagliptin and saxagliptin do not require dosage adjustments for GFR < 50 ml/min