Updates in Therapeutics® 2015:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

Diabetes Mellitus

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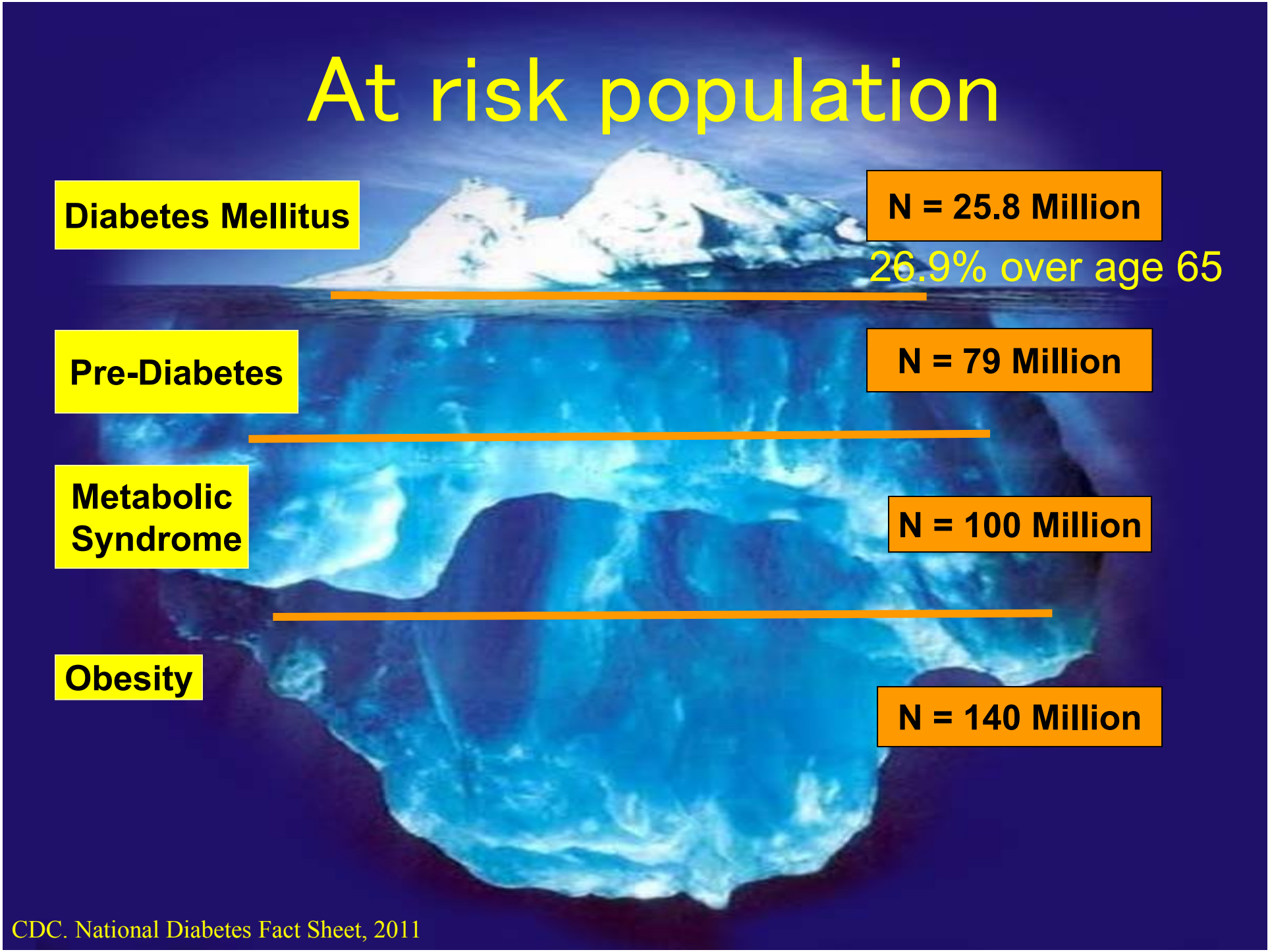
Conflict of Interest Disclosures

- L. Brian Cross, Pharm.D. has no conflicts of interest to disclose.

Learning Objectives

1. Describe the normal regulation of blood glucose with respect to the actions of insulin, cortisol, growth hormone, glucagon, and incretins in glucose homeostasis.
2. Identify differences between prediabetes, type 1 diabetes mellitus (T1DM), type 2 DM (T2DM), and gestational diabetes (GDM), including differences in diagnostic criteria and clinical presentation.
3. Explain sick-day rules for a patient with diabetes.
4. Compare agents used in the treatment of DM, including mechanisms of action, adverse effects, contraindications, and overall effectiveness.
5. Select appropriate insulin regimens for patients on the basis of desired onset, peak, and duration of insulin effects.
6. Individualize a comprehensive glycemic treatment and monitoring plan for a patient with DM.
7. State appropriate lipid and blood pressure targets for patients with DM.
8. Discuss acute and chronic complications associated with DM as well as strategies to prevent or slow its progression.

At risk population



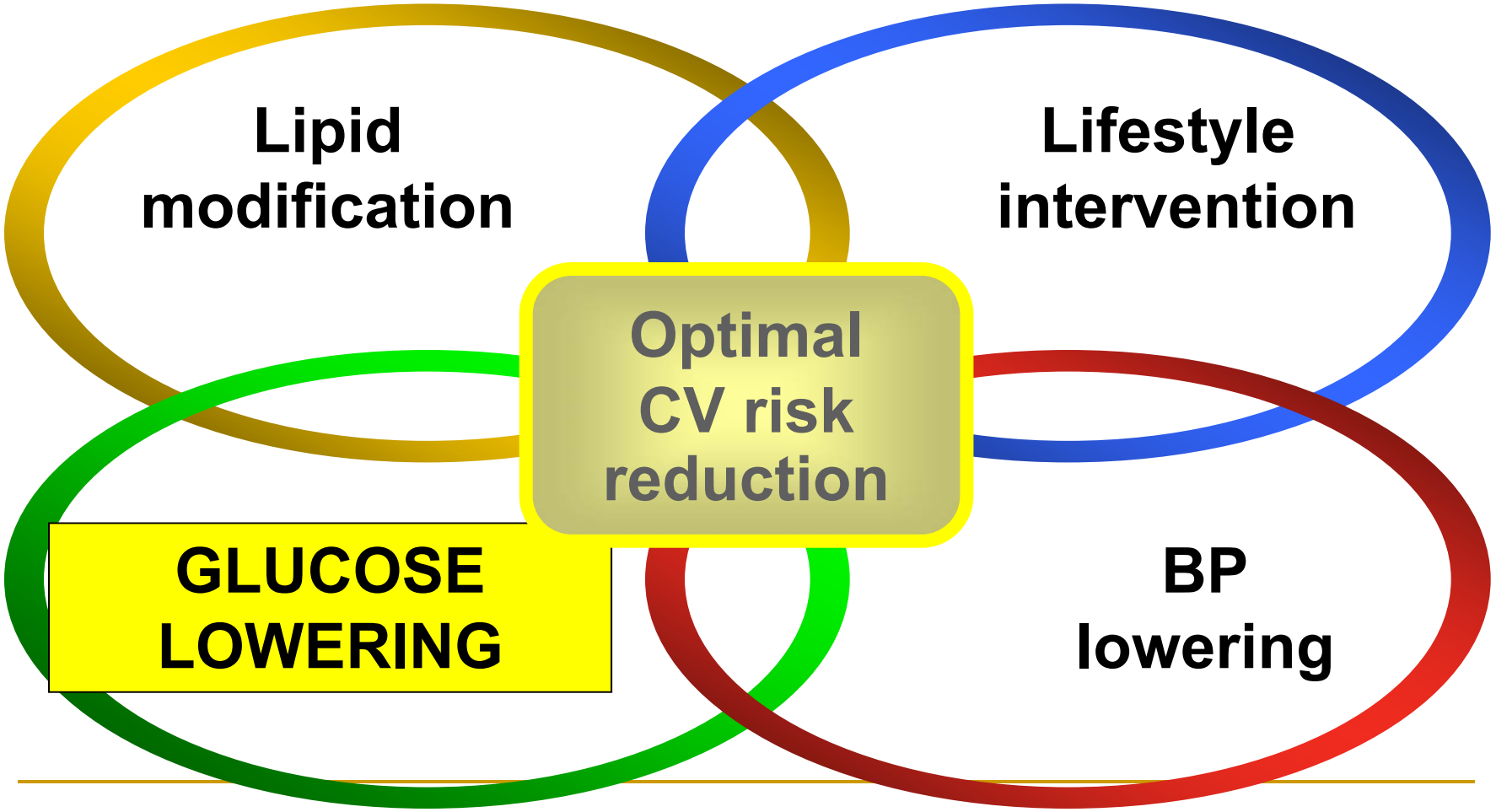
CDC. National Diabetes Fact Sheet, 2011

The Ticking Clock Hypothesis

- Type 2 DM is associated with microvascular and macrovascular complications.
- Duration of DM and severity of glycemia are primarily associated with microvascular disease.
- Metabolic disturbances during the prediabetic period may contribute to macrovascular disease.
- Macrovascular complications: the clock starts ticking years before the onset of clinical diabetes.

Haffner SM et al. JAMA. 1990;263:2893-8.

Benefit of multifactorial interventions



The ABC's of Diabetes

- A1C (and ASA)
  - < 7.0% (ACE < 6.5%)
- Blood Pressure*
  - < 140/80 mmHg (125/75 mmHg)
- Cholesterol** (and Cessation of smoking)
  - LDL-C < 100 mg/dL (<70 mg/dL?)
  - Non-HDL-C < 130 mg/dL (<100 mg/dL?)
  - HDL-C > 40 mg/dL (> 50 mg/dL in women)
  - TG's < 150 mg/dL

* JNC 8: < 140/90 mmHg

** NCEP 4: high-dose statin therapy recommended; ≥50% LDL-C reduction

ADA Diabetes Classification

- Type 1 Diabetes
  - Autoimmune Beta-cell destruction (includes LADA or Type 1 ½ DM)
  - Previously known as IDDM, juvenile onset, and ketosis prone diabetes
  - Absolute insulin deficiency
- Type 2 Diabetes
  - Progressive insulin secretory defect in the face of IR
  - Previously known as NIDDM, and adult onset diabetes
  - Makes up 90-95% of all diabetes cases, multiple RF's
  - Diabetes-related complication found in 50% at diagnosis

ADA. Diabetes Care 1997; 20:1183-97.

ADA Diabetes Classification

- Gestational Diabetes Mellitus
  - Onset of diabetes during pregnancy; 200,000^{+}/year
- Other Specific Types
  - Genetic Defects (includes MODY)
  - Exocrine pancreatic disease
  - Endocrinopathies
  - Drug/Chemical Induced
- Additional Terms
  - Type 1 ½ diabetes (LADA)
  - MODY
  - Double-double diabetes

ADA. Diabetes Care 1997; 20:1183-97.

ADA 1997 Diagnostic Guidelines

- Symptoms of diabetes with casual Plasma Glucose $\geq$200 mg/dL
- Fasting Plasma Glucose $\geq$126 mg/dL*
- 2 hr Plasma Glucose $\geq$200 mg/dL* (after a 75-g OGTT)
- A1C > 6.5%
  Point-of-care A1C assays are not sufficiently accurate at this time to use for diagnostic purposes.

ADA. Diabetes Care 1997; 20:1183-97.

Diagnosis of Diabetes

	Normal	Pre-Diabetes	Diabetes
Fasting Plasma Glucose	<100mg/dl	100-125mg/dl	≥126mg/dl
2-hour Post-prandial Glucose	<140mg/dl	140-199mg/dl	≥200mg/dl
A1C	<5.7%	5.7-6.4%	≥6.5%
Casual blood sugar and DM symptoms	N/A	N/A	≥200mg/dl

ADA. Standards of Medical Care in Diabetes. Diabetes Care. 2010;33(Suppl 1):S11-S61.

Diagnosis of Gestational Diabetes

- Screen between weeks 24 and 28 of gestation if no diabetes risk factors
- Screen at first prenatal visit in patient with even one diabetes risk factor, and if normal, repeat between weeks 24 and 28
- ADA: **One-step** or **Two-step** screening is now recommended. Strike what is written in your book and read below.

- One-step Screening (WHO, IADPSG): One abnormal blood glucose result makes the diagnosis following a single, fasted 75-g OGTT

75-g Glucose Tolerance Test:

	Cut-Points
Fasting	92 mg/dL
1-hour	180 mg/dL
2-hour	153 mg/dL

ADA. Diabetes Care. 2014;37:S14-S80.

Diagnosis of Gestational Diabetes

- Two-step Screening (NIH)
  - Non-fasted 50-g, 1-hour glucose challenge; if 50-g 1-hr glucose is ≥ 130 mg/dL, follow with
  - Fasted 100-g, 3-hour oral glucose tolerance test (OGTT)
  - Two abnormal blood glucose result makes the diagnosis

100-g Glucose Tolerance Test:	Cut-Points
Fasting	95 mg/dL
1-hour	180 mg/dL
2-hour	155 mg/dL
3-hour	140 mg/dL

ADA. Diabetes Care. 2014;37:S14-S80.

Add to page 5-6

Gestational Diabetes: Follow-up

- Women with a history of GDM should be screened for diabetes 6-12 weeks postpartum using non-pregnant OGTT criteria.
- Women with a history of GDM should subsequently be screened at least every 3 years for diabetes.

Patient Case #1

An obese 50-year-old Hispanic American woman with a history of gestational DM presents to the clinic for her annual physical examination. Her family history is significant for type 2 DM in her parents, both sets of grandparents, and several aunts and uncles. A FPG is 160 mg/dL. She has no concerns. Which one of the following best conveys how this patient's treatment should be managed?

A. Rescreen in 3 years.

B. Obtain another FPG level next week

C. Order an OGTT before she leaves her appointment

D. Diagnose type 2 DM and initiate LS changes

Workbook Page 1-6; Answer: Page 1-34

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D. Diagnose type 2 DM and initiate LS changes

Workbook Page 1-8; Answer: Page 1-34

Prediabetes

- Hyperglycemia that does not meet diagnostic threshold for DM
  - Impaired Fasting Glucose (IFG):
    100-125 mg/dl
  - Impaired Glucose Tolerance (IGT):
    140-199 mg/dl 2 hours after a 75g oral glucose load
  - A1C:
    5.7-6.4%

Pre-Diabetes

- 26 million Americans with DM / 79 million Americans with pre-DM
- 50-70% of patients with pre-DM will progress to DM over their lifetimes (5-10% per year).
  - Risk increases with blood sugar
  - IGT and IFG = twice DM risk as either alone
- The risk of progression to DM depends on the degree of insulin resistance and deficiency of insulin secretion (as well as age, family hx, weight/BMI, hx of GDM or PCOS).
- Risk factor for macrovascular disease

National Diabetes Fact Sheet, 2011 (www.cdc.gov/diabetes/pubs/factsheet11.htm).
Gerstein HC et al. Diabetes Res Clin Pract. 2007;78:305-12.
Tabak AG et al. Lancet. 2012;379:2279-90. Levitan EB et al. Arch Intern Med. 2004;164:2147-55.

Pathophysiology of Pre-diabetes

- Impaired Fasting Glucose (IFG)
  - Elevated *hepatic insulin resistance*
  - Normal skeletal muscle insulin sensitivity
  - *Impaired early insulin release*
- Impaired Glucose Tolerance (IGT)
  - Normal hepatic insulin sensitivity
  - Moderate-severe *skeletal muscle insulin resistance*
  - *Impaired early and late-phase insulin release*

Total body glucose disposal worsens from NGT to IGT to IFG to T2DM

Ferrannimi E et al. Med Clin N Amer. 2011;95:327-39.
DeFronzo RA et al. J Clin Endocrinol Metab. 2011;96:2354-66.
Basu A et al. Diabetes. 2012;61:270-1.

Interventions for the Prevention of Diabetes in Patients with Prediabetes

- Weight loss of 7%
- Increase in physical activity to at least 150 minutes/week of moderate activity (such as walking). Follow-up counseling appears to be important for success
- Drug Therapy
  - Metformin
  - α-Glucosidase inhibitors
  - Orlistat
  - TZD
- Monitor for development of DM annually

Prevention of Type 2 Diabetes: Completed Trials in IGT or GDM

Trial	Journal/Year	Treatment		Results (Risk reduction)
Da Qing IGT & Diabetes Study	*Diabetes Care* 1997 (*Diabetologia* 2011)	Diet +/ exercise	6 yrs (20yrs)	31- 46% (43%)
Finnish Diabetes Prevention Study	*N Engl J Med* 2001 (*Lancet* 2006)	Intensive lifestyle	4 yrs (7 yrs)	58% (43%)
Diabetes Prevention Program (DPP)	*N Engl J Med* 2002 (*Diabetes* 2005) (*Lancet* 2012)	Lifestyle changes		58% (58%)
		Metformin	2.8 yrs	31% (44%)
		Troglitazone	(5.7 yrs)	23% (75%)
STOP-NIDDM	*Lancet* 2002	Acarbose	3.3 yrs	25%
TRIPOD	*Diabetes* 2002	Troglitazone	2.5 yrs	55%

Prevention of Type 2 Diabetes: Completed Trials in IGT or GDM

Trial	Journal/Year	Treatment		Results (Risk reduction)
XENDOS	*Diabetes Care* 2004	Orlistat	4 yrs	37%
DREAM	*Lancet* 2006 (*Diabetologia* 2011)	Rosiglitazone	3 yrs	60% (39%)
		Ramipril	(4.5 yrs)	0% (0%)
Indian Diabetes Prevention Program	*Diabetologia* 2006	Lifestyle +/- Metformin	2.5 yrs	14%
PIPOD	*Diabetes* 2006	Pioglitazone	3 yrs	62%
Vildagliptin	*Diabetes Care* 2004	Vildagliptin	12 wks	32% ↓AUC
Voglibose Study Group	*Lancet* 2009	Voglibose	48 wks	42%
Liraglutide Obesity Study	*Lancet* 2009	Liraglutide 1.8 - 3 mg	20 wks	84-96% (normalized BS)

Prevention of Type 2 Diabetes: Completed Trials in IGT or GDM

Trial	Journal/Year	Treatment		Results (Risk reduction)
NAVIGATOR	*N Engl J Med* 2010	Valsartan	5 yrs	14%
		Nateglinide		No change
CANOE	*Lancet* 2010	Low dose Rosi/Met	3.9 yrs	66%
Exenatide for Weight Loss	*Diabetes Care* 2010	Exenatide	6 mos	52% (normalized BS)
Fenofibrate	Diabet Med 2010	Fenofibrate	6 mos	53%
		Metformin		70%
ACT NOW	*N Engl J Med* 2011	Pioglitazone	2.4 yrs	82%
ORIGIN	*N Engl J Med* 2012	Insulin Glargine	6.2 yrs	28%
Phen/Topiramate	*Diabetes Care* 2013	Phentermine/Topir	2 yrs	70-79%

ADA Consensus Conference Recommendation

- Lifestyle Modification
  - Weight loss
  - Increased physical activity
- Metformin 850 mg BID in high-risk patients with IFG or IGT
  - A1C ≥ 6%
  - BMI ≥ 35 kg/m2
  - Age ≤ 60 years

Nathan DM et al. Diabetes Care. 2007;30:753-9.

Type 1 Diabetes
PATHOPHYSIOLOGY

- Autoimmune B-cell Destruction
  - Islet cell cytoplasmic autoantibodies
  - Insulin autoantibodies
  - Antibodies to glutamic acid decarboxylase (GAD)
- Loss of Insulin Secretion
  - Molecular mimicry model
  - Direct environmental toxin

The Ominous Octet

- Beta cell—Insulin deficiency (relative or absolute)
- Muscle—Insulin resistance
- Liver—Increased gluconeogenesis
- Fat cell (adipocytes)—Accelerated lipolysis
- Gastrointestinal (GI) tract—Incretin deficiency (glucagon-like peptide [GLP]) and/or resistance (glucose-dependent insulinotropic polypeptide[GIP])
- Alpha cell—Hyperglucagonemia
- Kidney—Increased glucose absorption
- Brain—Neurotransmitter dysfunction

Glycemic Goals of Therapy in Diabetes

Goal	ADA	AACE
A1C	**< 7%***	**≤ 6.5%**
Premeal plasma glucose (mg/dL)	**70-130**	**< 110**
Postprandial plasma glucose (mg/dL)	**< 180†**	**< 140**

*An A1C of ≥ 7% should serve as a call to action to initiate or change therapy with the goal of achieving an A1C level as close to the nondiabetic range as possible or, at a minimum, decreasing the A1C to 7%.

†If A1C remains above the desired target, postprandial levels, usually measured 90-120 minutes after a meal, may be checked. They should be < 180 mg/dL to achieve A1C levels in the target range.

Nathan DM, et al. Diabetes Care. 2006;29:1963-72.
American Association of Clinical Endocrinologists. Endocr Pract. 2007;13(suppl 1):3-68.

All recommendations are general guidelines: always consider each patient on an individual basis.

- Examples:
  - A 42-year-old otherwise healthy patient taking metformin and pioglitazone.
    Goal A1C less than 6.5%.
  - An 80-year-old patient post–myocardial infarction (MI) on insulin therapy.
    Goal A1C less than 8%.
  - A 28-year-old woman with T1DM without complications at 16 weeks' gestation.
    Goal A1C less than 6%.
  - A 49-year-old man with T2DM for 15 years, HTN, and hyperlipidemia on basal/bolus insulin therapy. Goal A1C less than 7%.

A1C and Average Blood Glucose

A1C	Average Blood Glucose
6.0%	126 mg/dL
7.0%	154 mg/dL
8.0%	183 mg/dL
9.0%	212 mg/dL
10.0%	240 mg/dL
11.0%	269 mg/dL
12.0%	298 mg/dL

eAG = (28.7 X HbA1c) – 46.7

Nathan DM et al. Diabetes Care. 2006;29:1963-72.

THERAPY OF DIABETES MELLITUS

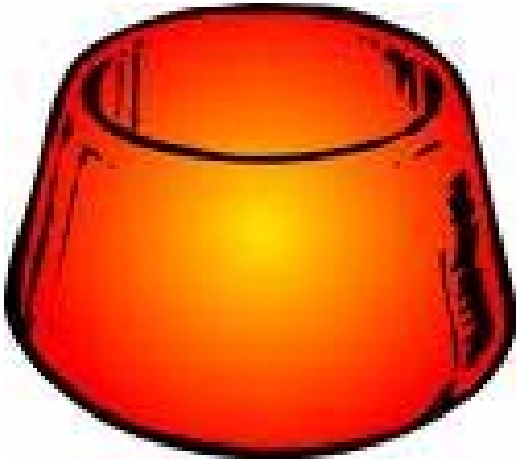
- D iet
- E xercise
- E ducation
- D rugs
- S elf-monitoring

Diabetes Management

In The Old Days:

Simple but tasteless

Animal Insulins
Sulfonylureas



TODAY:

A tantalizing array of choices …

Biguanide
a-glucosidase inh
Insulin analogs
TZD
Meglitinides
Amylin analog
Incretin mimetics
DPP-4 Inhibitors
Resin Binder
Dopamine agonist
SGLT-2 Inhibitors

Treatment Options

Oral Options

- Sulfonylureas
- Biguanide
- Alpha-Glucosidase Inhibitors
- TZD
- Meglitinides
- DPP-4 Inhibitors
- Resin Binder
- Dopamine Agonist
- SGLT-2 Inhibitors

Parenteral Options

- Amylin Analogue
  - Pramlintide (Symlin)
- Incretin Mimetic
  - Exenatide (Byetta)
  - Liraglutide (Victoza)
  - Exen LAR (Bydureon)
- Insulin
  - Basal
  - Prandial
  - Mixed

Drug & Primary Glycemic Effect

Fasting	Mixed	PPG
Metformin	Sulfonylurea	Regular insulin
NPH insulin (HS)	TZD	Lispro/Aspart/ Glulisine insulins
Detemir insulin	SGLT-2 Inhibitor	Alpha-glucosidase
Glargine insulin	Liraglutide	Meglitinide
Bile Acid Resin	Exenatide weekly	DPP-4 Inhibitor
	Mixed Insulin	Bromocriptine
		Pramlintide
		Exenatide

Sulfonylureas
(Glimipizide, Glipizide, Glyburide)

- Mechanism of Action
  - Insulin secretagogue
- Efficacy
  - A1C lowering of 1-2% (The bigger they are…)
  - Mixed glucose effect (Fasting and PP)
  - 50% of max dose; 80% of effect
  - 5-10% primary failure rate; 5-10%/yr secondary
- Dose
  - Glimepiride 1-8 mg QD, glyburide 2.5 mg – 10 mg BID, glipizide up to 5-20 mg BID, 20 mg QD for XL
- Adverse Effects
  - Hypoglycemia (esp. glyburide in elderly)
  - Weight gain
  - Less common: Rash, photosensitivity, dyspepsia, nausea

Sulfonylureas

(Glimepiride, Glipizide, Glyburide)

- Contraindications
  - Hypoglycemic unawareness
  - Severe liver or kidney disease
- Advantages
  - Works quickly (within hours)
  - Effective
  - High initial response rate
  - Inexpensive
- Disadvantages
  - Hypoglycemia
  - Weight gain
  - Eventual treatment failure
  - Cardiovascular concerns?

Metformin
(Glucophage, Fortamet, Riomet, Glumetza)

- Mechanism of Action
  - Decrease hepatic glucose production
  - Secondarily some improvement of peripheral insulin resistance
  - May decrease intestinal absorption of glucose (small intestine)
- Efficacy
  - ADA recommended drug of choice
  - Hemoglobin A1c lowering of 1%–2%
  - Primarily reduces FPG
  - 5%–10% per year secondary failure rate
- Dose
  - 500 mg once or twice daily with food to start (decrease GI adverse effects); maximum of 2550 mg/day (1 gm BID)
- Adverse Effects
  - Common: GI - nausea, vomiting, diarrhea (especially early)
  - Uncommon: Macrocytic anemia (caused by vitamin B12 deficiency); lactic acidosis (uncommon but life threatening! Use only in appropriate patients)

Metformin (Glucophage, Fortamet, Riomet, Glumetza)

- Contraindications
  - Serum creatinine of ≥ 1.5 mg/dL in men; ≥ 1.4 mg/dL or greater in women
  - Creatinine clearance less than 60 mL/minute? 50?
  - Severe hepatic, pulmonary, or cardiac disease
  - Hold for 24 hrs before and 48 hrs after procedures using contrast dye
- Advantages
  - Improved CV outcomes? (UK Prospective Diabetes Study obese patients)
  - No hypoglycemia as monotherapy
  - Weight neutral
  - High initial response rate
  - Positive lipid effects
  - Inexpensive
- Disadvantages
  - Patients eventually stop responding to therapy (2^o failure)
  - Gastrointestinal SE's especially early
  - Lactic Acidosis (in inappropriate candidates)

Meglitinides
(Repaglinide-Prandin, Nateglinide-Starlix)

- Mechanism of Action
  - Short-acting Insulin secretagogue
- Efficacy
  - Hemoglobin A1c reduction of 0.5%–1% (Repag > Nateg) as monotherapy or add-on therapy
  - A1C reductions of 1.5%–1.8% in combination with metformin or thiazolidine
  - Reduces postprandial blood glucose
  - Mealtime (e.g., 3 times/day) dosing may reduce adherence
- Dose
  - Repaglinide (Prandin): 0.5–1 mg 1–15 minutes before meals; max daily dose 16 mg
  - Nateglinide (Starlix): 60-120 mg before meals
- Adverse Effects
  - Hypoglycemia (< sulfonylurea)
  - Modest weight gain (< sulfonylurea)

Meglitinides

(Repaglinide-Prandin, Nateglinide-Starlix)

- Contraindications
  - Hypoglycemic unawareness
  - Severe renal / hepatic impairment
  - Repaglinide together with gemfibrozil or conivaptan
- Advantages
  - Rapid onset of action
  - Less hypoglycemia and weight gain compared with sulfonylurea
  - Targets postprandial glucose
- Disadvantages
  - Hypoglycemia
  - Weight gain
  - Frequent dosing
  - Eventual treatment failure

Alpha-glucosidase inhibitors (Acarbose-Precose, Miglitol-Glyset)

- Mechanism of Action
  - Inhibits the enzyme α-glucosidase, found along the brush border of the small intestine; responsible for the breakdown of complex carbohydrates into glucose, thus delaying and reducing post-meal carbohydrate absorption (and postprandial blood glucose)
- Efficacy
  - Hemoglobin A1c reduction of 0.5%–1%
  - Reduces postprandial blood glucose
  - Mealtime (e.g., 3 times/day) dosing (may reduce adherence)
- Dose
  - Acarbose (Precose): 25 mg with first bite of meal; start every day and then increase weekly to 2 times/day; then 3 times/day with meals to decrease GI adverse effects; up to 100 mg TID
  - Miglitol (Glyset): 25 mg with first bite of meal, and as above
- Adverse Effects
  - Common: Flatulence, abdominal discomfort, diarrhea; occur in up to 80% of patients but may diminish after 4–8 weeks of therapy
  - Rare: Liver function test (LFT) elevation

Alpha-glucosidase inhibitors (Acarbose-Precose, Miglitol-Glyset)

- Contraindications
  - IBD - Ulcerative Colitis, Crohn's, bowel obstruction, Short bowel
  - Intestinal obstruction
  - Malabsorption
  - Creatinine clearance less than 25 mL/minute or serum creatinine greater than 2 mg/dL
  - Cirrhosis
- Advantages
  - No hypoglycemia as monotherapy (Note: Use only simple sugar [e.g., glucose, fructose, lactose] to treat hypoglycemia in patient receiving combination therapy, not sucrose.)
  - Weight neutral (adverse GI side effects may lead to some weight loss)
- Disadvantages
  - Modest efficacy
  - Poorly tolerated GI adverse effects
  - Frequent dosing

Thiazolidinediones
(Rosiglitazone-Avandia, Pioglitazone-Actos)

- Mechanism of Action
  - PPAR-gamma agonist
    - Increase peripheral muscle and adipose tissue insulin sensitivity
      - Decreases insulin resistance
    - Decrease hepatic glucose production

TZD's

(Rosiglitazone-Avandia, Pioglitazone-Actos)

- Efficacy
  - Hemoglobin A1c lowering of 0.8%–1.5%
  - Mixed blood glucose lowering effect
  - Long lag time before observe glycemic effect (weeks); maximal effect 8–12 weeks
  - Increases HDL-C (both) and lowers TG (pioglitazone)
- Dose
  - Pioglitazone (Actos): 15–45 mg/day
  - Rosiglitazone (Avandia): 1–2 mg/day, up to 8 mg/day (twice-daily is more effective); no longer restricted access
- Adverse Effects
  - Weight gain
  - Fluid retention (especially with insulin, NSAID, GC, or DHP-CCB use)
  - Heart failure exacerbation
  - "Atypical" bone fractures (hands and feet)
  - Potential myocardial infarctions (rosiglitazone)?
  - Bladder cancer? (pio)
  - Rare hepatotoxicity and macular edema

TZD's
(Rosiglitazone–Avandia, Pioglitazone–Actos)

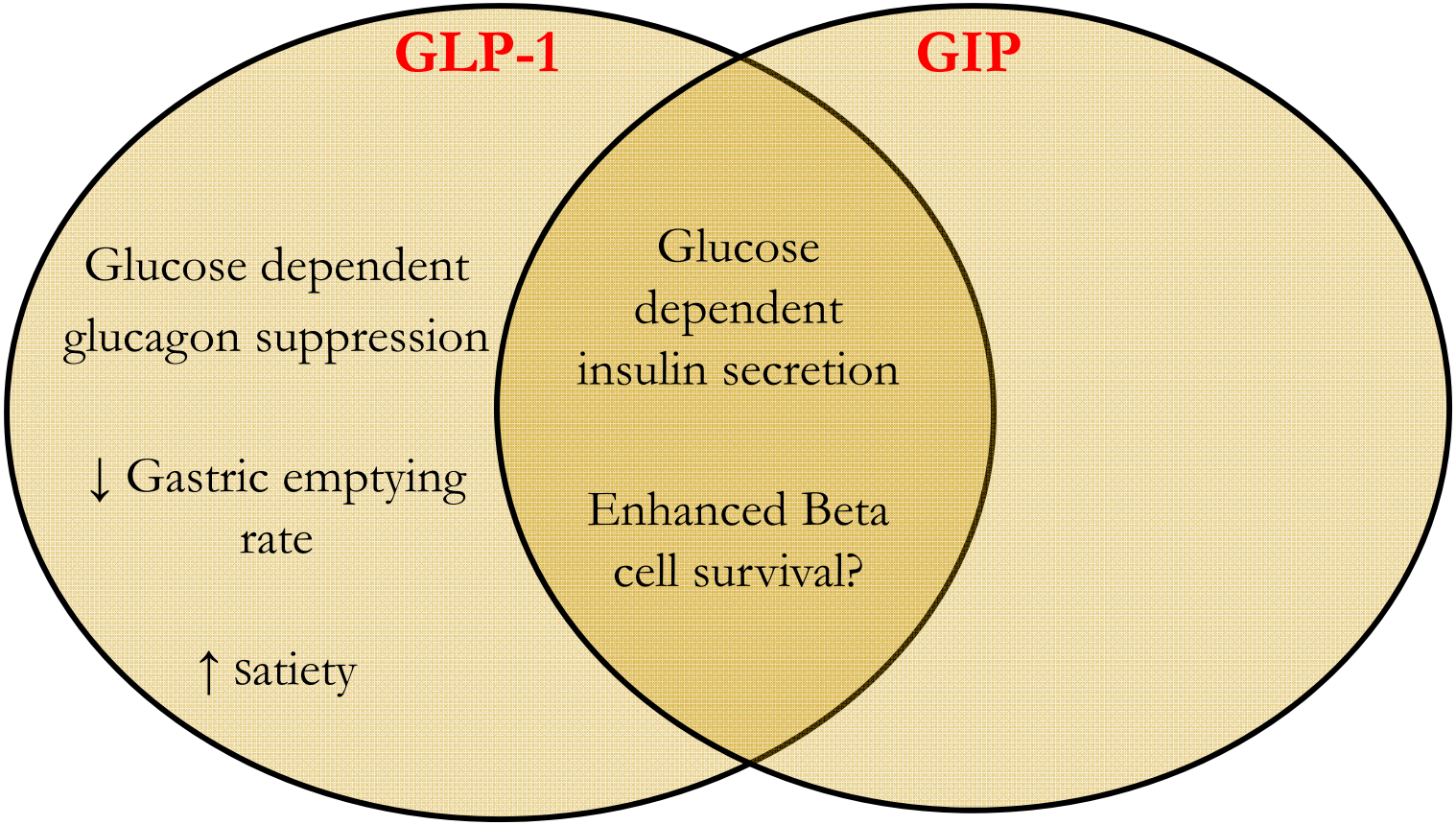
- Contraindications
  - ALT > 2.5 ULN
  - NYHA Class III and IV HF
- Advantages
  - No hypoglycemia as monotherapy
  - Several favorable metabolic effects
  - Can use in renal insufficiency
  - Potential B-cell sparing effect?
  - Can induce ovulation in women with PCOS
- Disadvantages
  - Delayed onset of action
  - Adverse effects (weight gain, edema, fractures)
  - Periodic LFT monitoring recommended
  - Can induce ovulation in women with PCOS

The Incretin Effect

- Insulin secretory response is greater to oral glucose than IV glucose
- Accounts for up to 60% of post-prandial insulin secretion in healthy individuals
- Attributed to hormones released from intestinal mucosal cells upon GI exposure to nutrients
  - GLP-1 (Glucagon-like peptide-1)
  - GIP (Glucose-dependent insulinotropic polypeptide)

Idris I and Donnelly R. Diabetes Obes Metab. 2007;9:153-65.

Incretins: GLP-1 and GIP



Drucker DJ et al. Lancet. 2006;368:1696-705.

Endogenous Incretin Limitations In DM

- Incretin response is impaired in T2DM
  - Decreased response to GIP
  - Decreased secretion of GLP-1
- GLP-1 therapy limited by short half-life
  - Rapidly degraded by DPP-4
  - Inhibition of inactivation? (Incretin Enhancers)
    - Sitagliptin, Saxagliptin, Linagliptin, Alogliptin

Drucker DJ et al. Lancet. 2006;368:1696-705.

DPP-IV Inhibitors: Mechanisms of Action

- Prolong $t_{1/2}$ of endogenous GLP-1 & GIP by inhibiting their inactivation by DPP-4
  - Increase GLP-1 levels 2-3x normal
- Target T2DM pancreatic defects
  - Increase glucose-dependent insulin secretion
  - Decrease inappropriate glucagon secretion
- No effect on gastric emptying, satiety, or weight
- May help preserve Beta-cell function?

Drucker DJ et al. Lancet. 2006;368:1696-705.

Dipeptidyl peptidase-4 inhibitors

Sitagliptin *(Januvia)*, Saxagliptin *(Onglyza)*,
Linagliptin *(Tradjenta)*, Alogliptin *(Nesina)*

- Mechanism of Action
  - Inhibits the enzyme DPP-4 from breaking down endogenous GLP-1 and GIP, resulting in 2-3X increased endogenous incretin levels. This results in
    - Glucose-dependent increase in insulin secretion
    - Glucose-dependent inhibition of glucagon secretion
- Efficacy
  - Hemoglobin A1c lowering of 0.6%–0.8%.
  - Primarily lowers postprandial glucose levels
- Dose
  - Sitagliptin: 100 mg/day (50 mg/day CrCl 30–49 mL/minute; 25 mg/day for CrCl < 30 mL/minute)
  - Saxagliptin: 5 mg/day (2.5 mg/day CrCl <50 mL/minute)
  - Linagliptin: 5 mg daily (no dose adjustment necessary)
  - Alogliptin: 25 mg daily (12.5 mg/day CrCl 30–59 mL/minute; 6.25 mg/day for CrCl < 30 mL/minute)

Baetta R, Corsini A. Drugs. 2011;71:1441-67.

Dipeptidyl peptidase-4 inhibitors

Sitagliptin *(Januvia)*, Saxagliptin *(Onglyza)*,
Linagliptin *(Tradjenta)*, Alogliptin *(Nesina)*

- Adverse Effects
  - Placebo-like incidence of adverse effects (upper respiratory, headache, UTI's)
  - Rare: Pancreatitis, skin reactions
- Contraindications
  - History of pancreatitis?
- Advantages
  - No hypoglycemia as monotherapy
  - Weight neutral
  - Placebo-like adverse effect profile
  - Potential B-cell sparing effect?
- Disadvantages
  - Modest A1c lowering; expensive

Colesevelam Indications

Reduction of Elevated LDL-Cholesterol

Indicated as an adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in patients with primary hyperlipidemia (Fredrickson Type IIa) as monotherapy or in combination with an hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor

Reduction of Blood Glucose

Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Colesevelam - Welchol

- Mechanism of Action
  - Farnesoid X receptor (FXR) antagonist. Bile acids activate the farnesoid X receptor (FXR), which leads to increased expression of phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting enzyme necessary for hepatic gluconeogenesis. Colesevelam inhibits bile acid reabsorption, thus preventing FXR activation and upregulation of PEPCK, leading to decreased hepatic glucose production.
- Efficacy
  - Hemoglobin A1c lowering of 0.4%–0.6%
  - Primarily a fasting blood glucose–lowering effect
  - LDL-C reduction of 15%–18%
- Dose
  - 625-mg tablets, 3 tablets twice daily or 6 tablets every day with meals
  - Suspension 3.75 g/packet, 1 every day with largest meal
- Adverse Effects
  - Constipation/dyspepsia
  - Potential TG increase (don’t use if TG > 500 mg/dL)

Colesevelam - Welchol

- Contraindications
  - Bowel obstruction
  - Triglycerides greater than 500 mg/dL
  - History of hypertriglyceridemia-induced pancreatitis
- Advantages
  - No hypoglycemia as monotherapy
  - Low-density lipoprotein cholesterol lowering of 15%–18%
- Disadvantages
  - Modest A1C efficacy
  - High pill burden
  - May raise TG
  - Potential for drug interactions (levothyroxine, ezetimibe, phenytoin)

Bromocriptine - Cycloset

- Mechanism of Action
  - Dopamine receptor agonist
  - Glucose-lowering mechanism is unknown but improves glucose and energy metabolism and does NOT increase plasma insulin concentration; acts to reset aberrant central neurometabolic control of peripheral metabolism toward normal in patients with diabetes, resulting in a reduction in insulin resistance; improves glucose and energy metabolism through activation of central nervous system dopaminergic pathways responsible for metabolic control (Cylcoset PI).
- Efficacy
  - Hemoglobin A1c lowering of 0.4%–0.6%
  - Postprandial glucose effect primarily.
- Dose
  - 0.8-mg tablet each morning (within 2 hours of waking) with food; titrate by 0.8 mg/week to mean daily dose of 4.8 mg (6 tablets) q AM
- Adverse Effects
  - Nausea/vomiting
  - Asthenia
  - Constipation
  - Dizziness
  - Somnolence

Rationale for Sodium-glucose transporter-2 (SGLT2) Inhibition

- SGLT2: a low-affinity transport system, specifically expressed in the kidney
- Plays an important role in renal glucose reabsorption in the proximal tubule (expressed exclusively in the S1 segment of the proximal tubule)
- Accounts for 90% of tubular reabsorption of glucose
- Inhibition enhances glucose and energy loss through the urine
- Insulin independent glucose lowering poses little risk of hypoglycemia
- Individuals with familial renal glycosuria maintain normal long-term kidney function

Canagliflozin (Invokana)

- Mechanism of Action
  - Blocks the reabsorption of glucose by the kidney, increasing glucose excretion directly into the urine
- Efficacy
  - A1C lowering of 1%
  - Reduces fasting and postprandial blood sugars
- Dose
  - Recommended starting dose of 100 mg, taken before the first meal of the day; can increase to 300 mg once daily (if eGFR>60) if require additional glycemic control.
  - Do not initiate if eGFR is below 45 mL/min
- Adverse Effects
  - Vaginal yeast infections
  - UTI's

Canagliflozin (Invokana)

- Contraindications
  - Severe renal impairment, ESRD, or dialysis
  - History of serious hypersensitivity reaction
- Advantages
  - No hypoglycemia as monotherapy
  - Potential for weight loss
  - Decreases in blood pressure (5 mmHg SBP)
- Disadvantages
  - Ineffective in patients with renal dysfunction
  - Potential HoTN in patients receiving diuretic therapy
  - Polyuria?
  - UTI's/GU fungal infections

Dapagliflozin (Farxiga)

- Mechanism of Action
  - Blocks the reabsorption of glucose by the kidney, increasing glucose excretion directly into the urine
- Efficacy
  - A1C lowering of 1%
  - Reduces fasting and postprandial blood sugars
- Dose
  - Recommended starting dose of 5 mg, taken in the morning with or without food; can increase to 10 mg once daily if additional glycemic control is required.
  - Do not initiate if eGFR is below 60 mL/min
- Adverse Effects
  - Vaginal yeast infections, UTI's, nasopharyngitis

Dapagliflozin (Farxiga)

- Contraindications
  - Severe renal impairment (eGFR < 30mL/min), ESRD or dialysis
  - History of serious hypersensitivity reaction
- Advantages
  - No hypoglycemia as monotherapy
  - Potential for weight loss
  - Decreases in blood pressure (5 mmHg SBP)
- Disadvantages
  - Ineffective in patients with renal dysfunction
  - Potential HoTN in patients receiving diuretic therapy
  - Polyuria?
  - UTI's/GU fungal infections

Combination Oral Diabetes Medications

- Actoplus Met—Pioglitazone and metformin
- Avandamet—Rosiglitazone and metformin
- Avandaryl—Rosiglitazone and glimepiride
- Duetact—Pioglitazone and glimepiride
- Glucovance—Glyburide and metformin
- Invokamet—Canagliflozin and metformin
- Janumet—Sitagliptin and metformin
- Janumet XR—Sitagliptin and metformin XR
- Jentadueto—Linagliptin and metformin
- Kombiglyze XR—Saxagliptin and ER-metformin
- Kazano—Alogliptin and metformin
- Metaglip—Metformin and glipizide
- Oseni—Alogliptin and pioglitazone
- Prandimet—Repaglinide and metformin

Case #2

- A 65-year-old patient with type 2 DM, diagnosed 3 years ago, is currently treated with sitagliptin. He notes that his FBG is too high (180–200 mg/dL). He has a seafood allergy, no known drug allergies, and normal organ function. Which one of the following medication recommendations is best?

A. Acarbose

B. Bromocriptine

C. Metformin

D. Repaglinide

Workbook Page 1-17; Answer: Page 1-34.

Case #2

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C. Metformin

D. Repaglinide

Workbook Page 1-17; Answer: Page 1-34.

Amylin Analog - Pramlintide (Symlin)

- Mechanism of Action
  - Synthetic analog of human amylin
    - Inhibits glucagon secretion in a glucose-dependent manner
    - Reduces the rate of gastric emptying
    - Increases satiety
- Efficacy
  - Hemoglobin A1c lowering of 0.5%–0.7%
  - Primarily lowers postprandial glucose levels
- Dose
  - Type 1 DM: Initiate at 15 mcg subcutaneously with meals daily, increase by 15 mcg per dose every 3–7 days based on tolerability and response; maximum of 60 mcg with meals
  - Type 2 DM: Initiate at 60 mcg with meals, increase to 120 mcg with meals in 3–7 days
- Adverse Effects
  - Nausea
  - Vomiting
  - Hypoglycemia with insulin (mealtime insulin doses must be reduced by 50% at drug initiation!)

Pramlintide (Symlin)

- Contraindications
  - Gastroparesis
  - Hypoglycemic unawareness
  - Hemoglobin A1c greater than 9%
  - Patients unwilling to self-monitor blood glucose
- Advantages
  - Use is associated with weight loss
- Disadvantages
  - Gastrointestinal adverse effects
  - Requires three additional injections per day (cannot be mixed with insulin)
  - Modest A1C reduction
  - May reduce the rate and extent of absorption of drugs that require rapid absorption (pain relievers, antibiotics, and oral contraceptives); separate administration by at least 1 hour

Endogenous Incretin Limitations In DM

- Incretin response is impaired in T2DM
  - Decreased response to GIP
  - Decreased secretion of GLP-1
- GLP-1 therapy limited by short half-life
  - Rapidly degraded by DPP-4
  - Inhibition of inactivation? (Incretin Enhancers)
    - Sitagliptin, Saxagliptin, Linagliptin, Alogliptin
  - Analogues resistant to DPP-4? (Incretin Mimetics)
    - Exenatide, Liraglutide, et al.

Drucker DJ et al. Lancet. 2006;368:1696-705.

Incretin Mimetics

- Mechanism of Action
  - Synthetic analog of human glucagon-like peptide-1, resistant to DPP-4, results in supraphysiologic (pharmacologic) incretin levels, causing
    - a glucose-dependent increase in insulin secretion
    - a glucose-dependent inhibition of glucagon secretion
    - reduced gastric emptying
    - increased satiety

Incretin Mimetics

- Efficacy
  - Hemoglobin A1c lowering of 0.6%–1.9%
  - Primarily a postprandial glucose reduction with exenatide
  - Mixed postprandial and fasting glucose reduction with liraglutide and weekly exenatide
- Dose
  - Exenatide (Byetta): 5 mcg subcutaneously 2 times/day (thigh, abdomen, or upper arm) 1–60 minutes before morning and evening meals, increase to 10 mcg 2 times/day after 4 weeks if tolerated
  - Liraglutide (Victoza): 0.6 mg subcutaneously every day (independent of meals; inject into thigh, abdomen, or upper arm); increase by weekly intervals to 1.2 mg subcutaneously every day; then 1.8 mg subcutaneously every day if needed
  - Exenatide LAR (Bydureon): 2 mg subcutaneously weekly (thigh, abdomen, or upper arm); two weeks before see effect
  - Albiglutide (Tanzeum): 30-50 mg subcutaneously weekly (independent of meals; inject into thigh, abdomen, or upper arm); inject 15 minutes after powder is reconstituted within pen
- Adverse Effects
  - GI: Nausea, Vomiting, Diarrhea
  - Headache
  - Rare: Pancreatitis/Renal dysfunction

Incretin Mimetics

- **Contraindications**
  - Gastroparesis
  - Pancreatitis
  - Exenatide and Ex LAR: Creatinine clearance < 30 mL/minute
  - Liraglutide and Ex LAR: Personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 (MEN2)
- **Advantages**
  - Use is associated with weight loss (2-3 kg)
  - Convenient dosing
  - B-cell sparing effect?
- **Disadvantages**
  - Gastrointestinal adverse effects
  - Requires 1-2 injections per day (except Ex LAR & albiglutide)
  - May reduce the rate and extent of absorption of drugs that require rapid absorption (pain relievers, antibiotics, and oral contraceptives); separate administration by at least 1 hour
  - Cost

Incretin Comparison

	GLP-1 Activation	DPP-4 Inhibition
↕ Insulin	+++	+++
↓ Glucagon	+++	++
↓ Gastric emptying	+++	--
↑ Satiety	+++	--
Hypoglycemia	+/-	+/-
Nausea/Vomiting	+++	--
Weight	Loss	No Change
Route of admin	Injection	Oral
	e.g. exenatide, liraglutide, exenatide LAR	e.g. sitagliptin, saxagliptin, linagliptin, alogliptin

Case #3

- A patient with type 2 DM receiving premeal insulin is interested in a “new” drug that he heard will allow him to significantly decrease his premeal insulin doses and allow better glycemic control. This drug is which one of the following?

A. Liraglutide

B. Metformin

C. Pramlintide

D. Bromocriptine

Workbook Page 1-17; Answer: Page 1-34.

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Workbook Page 1-17; Answer: Page 1-34.

Considerations for Initiation of Drug Therapy

- Baseline A1C/ Blood sugars
- Organ Function
- CI's to therapy
- Duration of DM
- SMBG
- Hypoglycemic Unawareness
- Baseline Weight
- Route of administration
- Start with single or combination drug therapy?
- Cost

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Silvio E. Inzucchi, MD[1]
Richard M. Bergenstal, MD[2]
John B. Buse, MD, PHD[3]
Michaela Diamant, MD, PHD[4]
Ele Ferrannini, MD[5]
Michael Nauck, MD[6]
Anne L. Peters, MD[7]
Apostolos Tsapas, MD, PHD[8]
Richard Wender, MD[9]
David R. Matthews, MD, DPHIL[10,11,12]

Glycemic management in type 2 diabetes mellitus has become increasingly complex and, to some extent, controversial, with a widening array of pharmacological agents now available (1–5), mounting concerns about their potential adverse effects and new uncertainties regarding the benefits of intensive glycemic control on macrovascular complications (6–9). Many clinicians are therefore perplexed as to the optimal strategies for their patients. As a consequence, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) information on the benefits/risks of glycemic control, recent evidence concerning efficacy and safety of several new drug classes (16,17), the withdrawal/restriction of others, and increasing calls for a move toward more patient-centered care (18,19).

This statement has been written incorporating the best available evidence and, where solid support does not exist, using the experience and insight of the writing group, incorporating an extensive review by additional experts (acknowledged below). The document refers to glycemic control; yet this clearly needs to

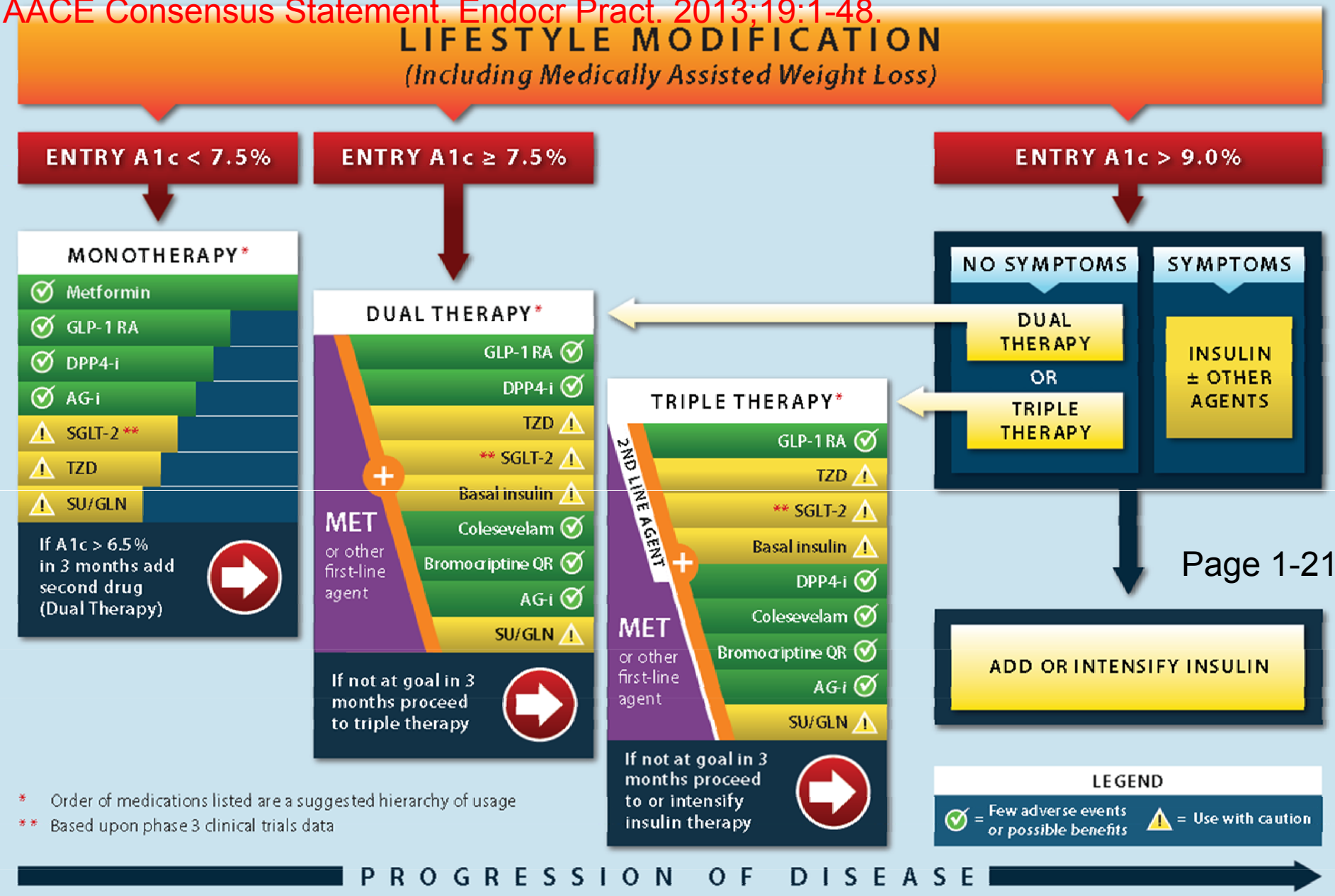
These recommendations should be considered within the context of the needs, preferences, and tolerances of each patient; individualization of treatment is the cornerstone of success. Our recommendations are less prescriptive than and not as algorithmic as prior guidelines. This follows from the general lack of comparative-effectiveness research in this area. Our intent is therefore to encourage an appreciation of the variable and progressive nature of type 2 diabetes, the specific role of each drug, the patient and disease factors that drive clinical decision making (20–23), and the constraints imposed by age and comorbidity (4,6). The implementation of these guidelines will require thoughtful clinicians to integrate current evidence with other constraints and imperatives in the context of patient-specific factors.

ADA/EASD Key Points

- Glycemic targets and glucose-lowering therapies must be individualized.
- Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.
- Unless there are prevalent contraindications, metformin is the optimal first-line drug.
- After metformin, there are limited data to guide us. Combination therapy with an additional 1–2 oral or injectable agents is reasonable, aiming to minimize side effects where possible.
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.
- All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.
- Comprehensive cardiovascular risk reduction must be a major focus of therapy.

Glycemic Control Algorithm

AACE Consensus Statement. Endocr Pract. 2013;19:1-48.



Page 1-21

Case #4

- J.L. is a 48-year-old obese white woman with type 2 DM, currently receiving metformin 1 g twice daily, whose postprandial blood glucose is higher than desired, and her most recent hemoglobin A1c is 7.5%. Which one of the following best represents how J.L.'s diabetes regimen should be changed?
- A. Increase the metformin dose to 850 mg three times/day.
- B. Substitute metformin with a sulfonylurea.
- C. Add a bedtime dose of neutral protamine Hagedorn (NPH) insulin.
- D. Add sitagliptin 100 mg orally every day.

Workbook Page 1-19; Answer: Page 1-34.

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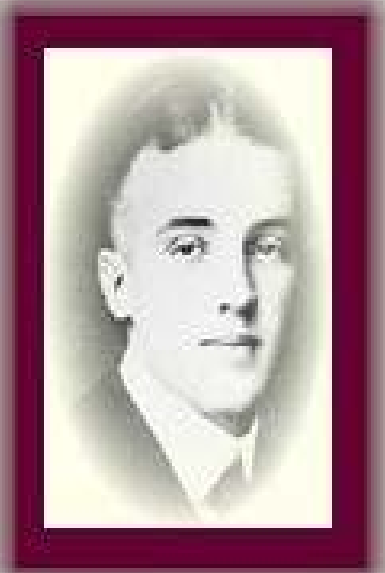
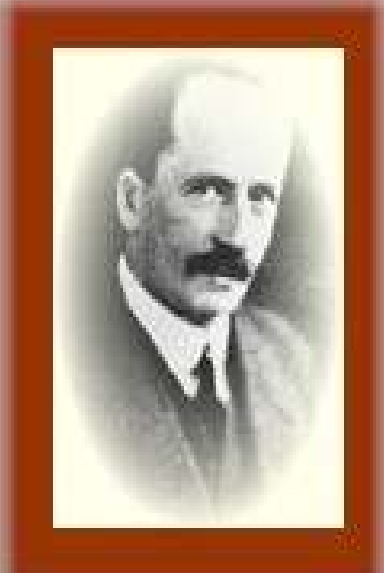
Workbook Page 1-19; Answer: Page 1-34.

The Discovery of INSULIN: 1921

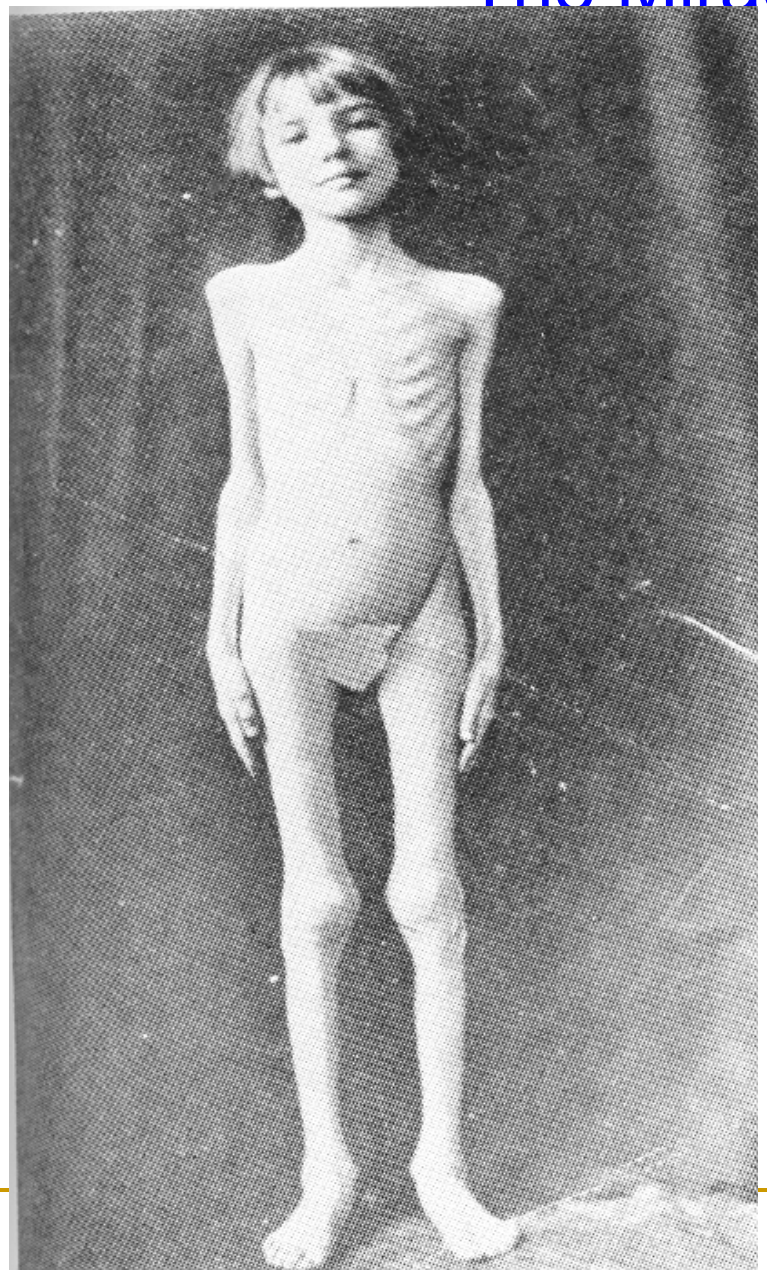

Sir Frederick Grant Banting


Charles Herbert Best

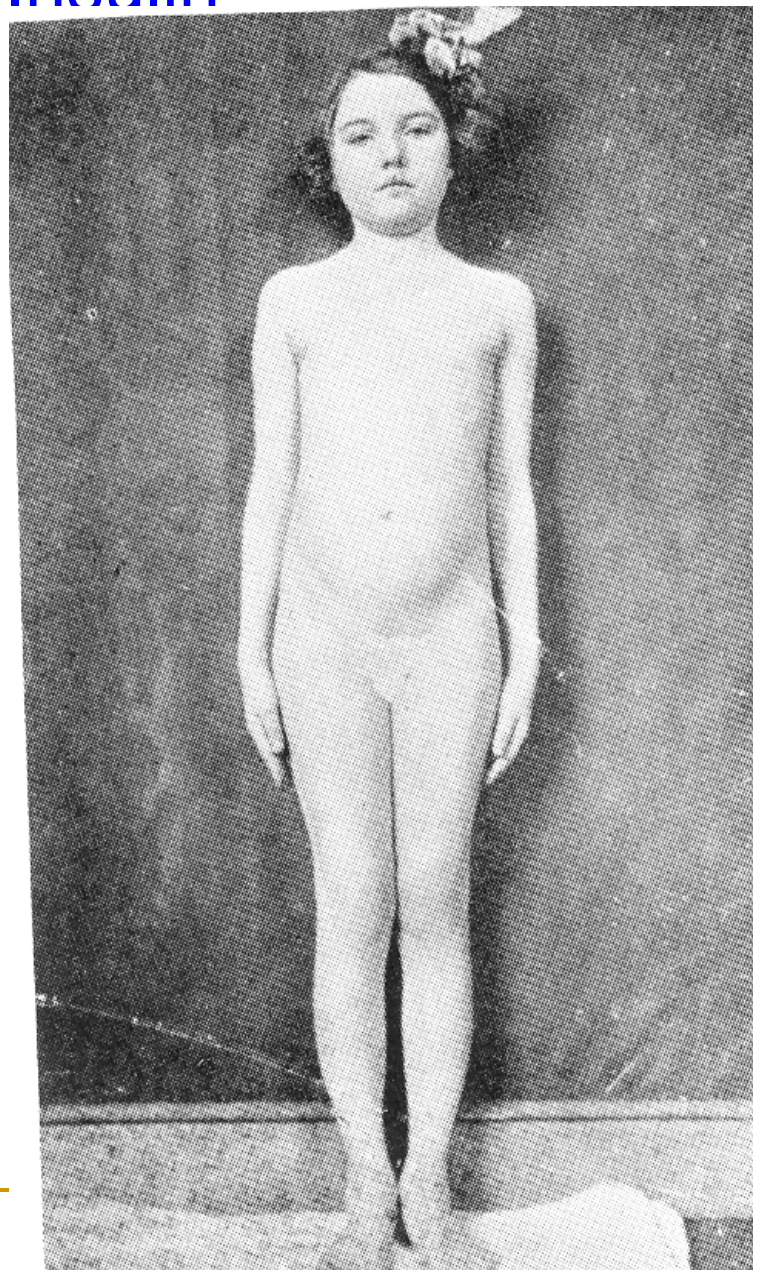

James Bertram Collip


John James Rikard Macleod

The Miracle of Insulin

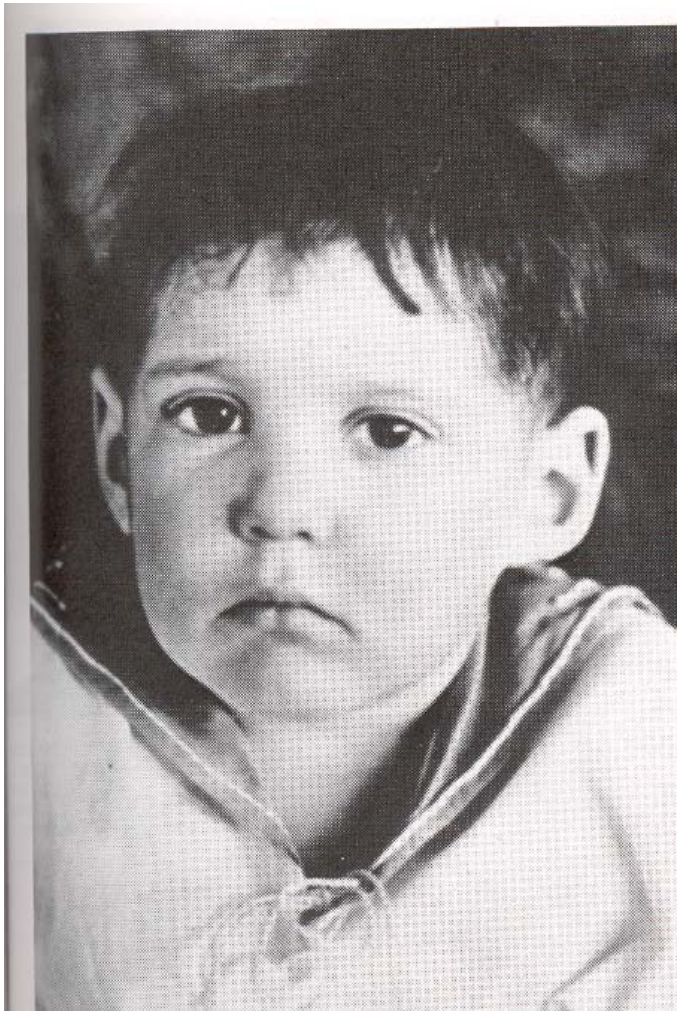


1922: Before Insulin



1923: After Insulin

JI: December 15, 1922.



JI: February 15, 1923.

Comparison of Human Insulins

Insulin	Onset	Peak	Duration
Lispro, Aspart, Glulisine	5-15 mins	1-2 hrs	3-5 hrs
Human Regular	30-60 mins	2-4 hrs	6-8 hrs
Human NPH	1-2 hrs	6-12 hrs	10-16 hrs
Insulin Detemir	3-4 hrs	Peakless	6-24 hrs
Insulin Glargine	4-6 hrs	Peakless	~24 hrs

The Concept of Basal/Bolus

- **Basal Insulin (detemir, glargine, NPH)**
  - Decreases fasting glucose production
  - Requires consistent (constant) insulin levels
  - Approximates 50% of daily insulin needs
  - Equivalent doses
- **Bolus Insulin (regular, aspart, glulisine, lispro)**
  - Limits PPHG
  - Requires immediate insulin peak
  - Each meal requires 10-20% of daily insulin requirements

Glucose Monitoring and Insulin Titration

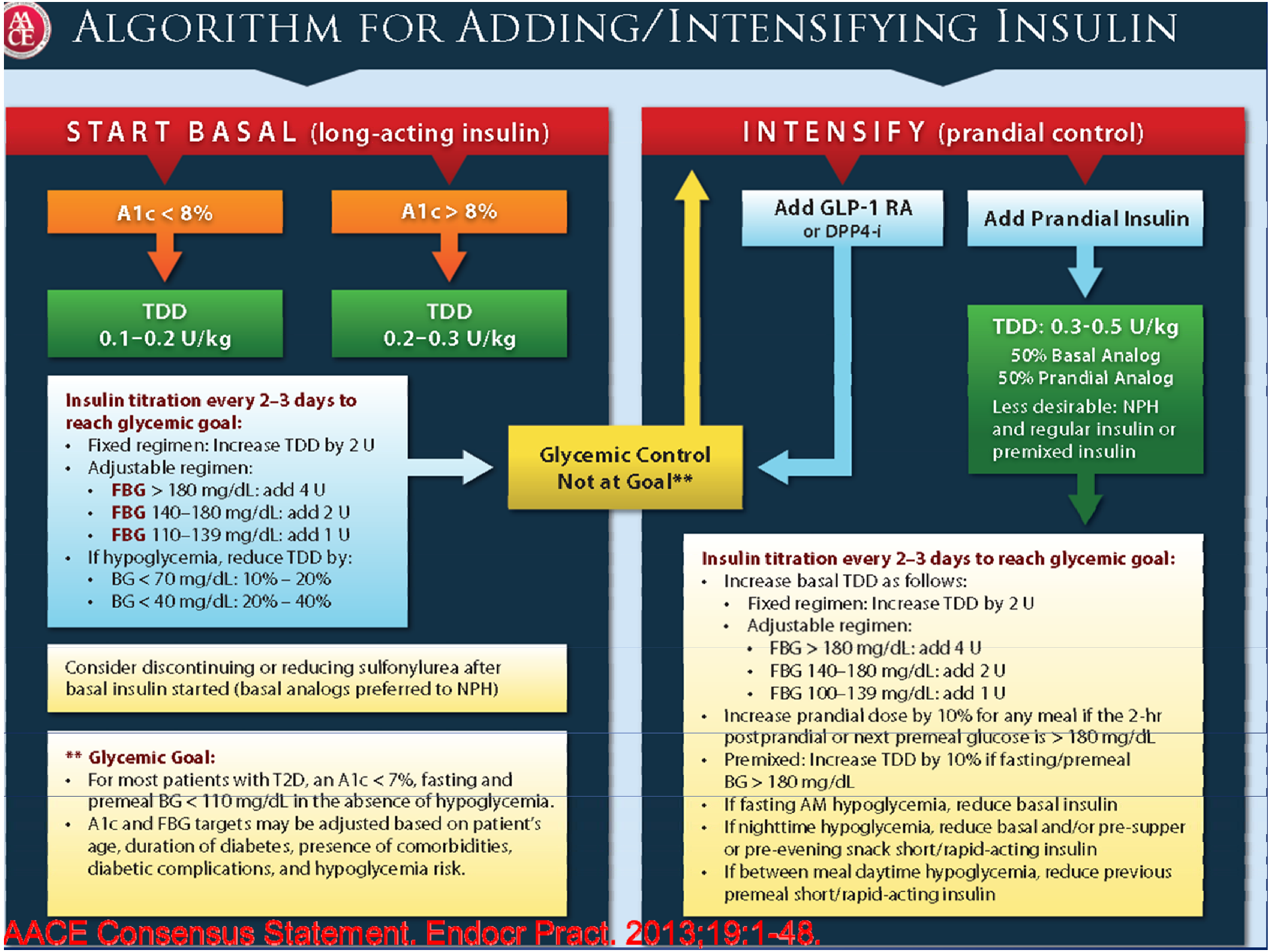
Target Blood Glucose	Target Insulin
Fasting (Pre-breakfast)	Bedtime or pre-dinner NPH, detemir, glargine
Pre-lunch (post-breakfast)	Pre-breakfast regular, aspart, glulisine, lispro
Pre-dinner (post-lunch)	Pre-breakfast NPH or detemir; Pre-lunch regular, aspart, glulisine, lispro
Bedtime (post-dinner)	Pre-dinner regular, aspart, glulisine, lispro

Basal Insulin Therapy

Fix the Fasting First

Initiating Basal Insulin Therapy

- Continue oral agent(s) at same dosage (may eventually reduce or DC - especially secretagogue therapy)
- Add single HS insulin dose (10-20 Units or 0.1-0.2 units/kg)
  - Detemir Insulin
  - Glargine insulin
  - NPH insulin
- Adjust insulin dose according to Fasting Blood Sugars
- Adjust the insulin dose every 3-4 days as needed
  - Increase 2 U if FBG 100–120 mg/dL
  - Increase 4 U if FBG 121–140 mg/dL
  - Increase 6 U if FBG 141–180 mg/dL
  - Increase 8 U if FBG >180 mg/dL
- Reduce dose immediately if experience fasting hypoglycemia.
- Treat to target (usually FPG 80–100 mg/dL)



AACE Consensus Statement. Endocr Pract. 2013;19:1-48.

Initiating MDI (multiple daily injections)Therapy

- Empiric Dosing - Insulin Analogues
  - Type 1 0.5 units/kg/d
  - Type 2 0.7-1.0 units/kg/d (obesity, activities)
  - Calculate Daily Dose
- Give 50% as Basal Insulin
- Give 50% as Bolus Insulin
  - Split into three doses
- Adjust accordingly:
  - Algorithm (The Rule of 1800)
  - Carbohydrate Counting

Case 5

- C.D. is a 19-year-old white woman, just given a diagnosis of type 1 DM. She weighs 80 kg and has normal renal function (serum creatinine 0.6 mg/dL). Which one of the following is the most appropriate empiric basal insulin and dose?

A. Aspart 20 units at bedtime.

B. Glargine 20 units at bedtime.

C. Regular insulin 40 units at bedtime.

D. NPH 40 units at bedtime.

Workbook Page 1-21; Answer: Page 1-34.

Case 5

- C.D. is a 19-year-old white woman, just given a diagnosis of type 1 DM. She weighs 80 kg and has normal renal function (serum creatinine 0.6 mg/dL). Which one of the following is the most appropriate empiric basal insulin and dose?

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B. Glargine 20 units at bedtime.

C. Regular insulin 40 units at bedtime.

D. NPH 40 units at bedtime.

Workbook Page 1-21; Answer: Page 1-34.

Correctional Insulin Dosing

- Rule of 1800 (Rapid acting insulin)
  - 1800/current ***daily*** insulin dose equals the mg/dl change of glucose per 1 unit insulin
  - Titrate dose using algorithm
  - Example: Patient from last example
    - 40 units insulin/day 1800/40= 45 mg/dl per unit

Blood Glucose

< 80	Subtract 1 unit from usual premeal dose
80-125	Use usual premeal dose
126-170	Add 1 unit to usual premeal dose
171-215	Add 2 units to usual premeal dose
216-260	Add 3 units to usual premeal dose

Correctional Insulin Dosing

- Rule of 1500 (Regular insulin)
  - 1500/current ***daily*** insulin dose equals mg/dl change of glucose per 1 unit insulin
  - Titrate dose using algorithm
  - Example:
    - 50 units insulin/day 1500/50= 30 mg/dl per unit

Blood Glucose

< 80	Subtract 1 unit from usual premeal dose
80-110	Use usual premeal dose
111-140	Add 1 unit to usual premeal dose
141-170	Add 2 units to usual premeal dose
171-200	Add 3 units to usual premeal dose

Insulin to Carbohydrate Ratio

- Rule of 500
  - (500/total current ***daily*** insulin dose) equals the insulin/carbohydrate ratio
  - Titrate dose using algorithm
  - Example:
    - 50 units insulin/day 500/50 = 10
    - Insulin/carbohydrate ratio equals 1 unit of insulin for every 10 grams of CHO ingested

Case #6

- B.L. is a 70-year-old patient with type 2 DM, diagnosed 28 years ago. His indirect measure of endogenous insulin secretion (C-peptide level) is undetectable, and he receives a basal/bolus insulin regimen of glargine and lispro insulins. His insulin requirements total 100 units of insulin per day.

- 6. Which one of the following is Bill's insulin sensitivity?
  - A. 5 mg/dL
  - B. 10 mg/dL
  - C. 15 mg/dL
  - D. 18 mg/dL

Workbook Page 1-22; Answer: Page 1-34.

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Case #7

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- 7. Which of the following is Bill's insulin/carb ratio?
  - A. 5
  - B. 10
  - C. 15
  - D. 18

Workbook Page 1-22; Answer: Page 1-34.

Case #7

- B.L. is a 70-year-old patient with type 2 DM, diagnosed 28 years ago. His indirect measure of endogenous insulin secretion (C-peptide level) is undetectable, and he receives a basal/bolus insulin regimen of glargine and lispro insulins. His insulin requirements total 100 units of insulin per day.

- 7. Which of the following is Bill's insulin/carb ratio?
  - A. 5
  - B. 10
  - C. 15
  - D. 18

Workbook Page 1-22; Answer: Page 1-34.

Case #8

- B.L. is a 70-year-old patient with type 2 DM, diagnosed 28 years ago. His indirect measure of endogenous insulin secretion (C-peptide level) is undetectable, and he receives a basal/bolus insulin regimen of glargine and lispro insulins. His insulin requirements total 100 units of insulin per day.

- Bill's presupper reading today is 184 mg/dL (goal of 130 mg/dL), and he plans to eat 60 carbohydrates at dinner. Which one of the following represents what his pre-dinner lispro insulin dose should be?

A. 5
B. 10
C. 15
D. 18

Workbook Page 1-22; Answer: Page 1-34.

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Workbook Page 1-22; Answer: Page 1-34.

Mixed Insulins

- Humulin 70/30
  - 70% NPH, 30% Regular
- Novolin 70/30
  - 70% NPH, 30% Regular
- Humalog Mix 75/25
  - 75% lispro protamine, 25% lispro
- Humalog Mix 50/50
  - 50% lispro protamine, 50% lispro
- Novolog Mix 70/30
  - 70% aspart protamine, 30% aspart

Diabetes Complications - Acute

- Hypoglycemia: Signs/symptoms of hypoglycemia (CNS/SNS)
  - Blood glucose usually below normal (less than 60 mg/dL)
  - Patient may:
    - Feel tremulous
    - Feel nervous/anxious
    - Be diaphoretic
    - Be tachycardic
    - Feel hungry
    - Experience a headache
  - Provider/family member may notice:
    - Irritability
    - Confusion
    - Sleepiness
- Diabetic Ketoacidosis
- Hyperglycemic hyperosmolar state

Sick Day Rules for Insulin-treated Pts

- DO NOT STOP INSULIN !
- Keep usual basal insulin
- Cover with quick-acting insulin
- Frequent finger stick monitoring (q 1-2 hrs)
- Check urine ketones
- Use sport drinks to maintain hydration
- Supplement calories to support insulin coverage (glucose affected prior to ketones)
- If vomit, go to ER

Diabetes Complications - Chronic

- Microvascular
  - Retinopathy
  - Nephropathy
- Macrovascular
  - Coronary Artery Disease
  - Cerebrovascular Disease
  - Peripheral Arterial Disease

Diabetes Complications - Chronic

- Neurologic
  - Peripheral Neuropathy
  - Autonomic Neuropathy
    - Erectile Dysfunction
    - Gastroparesis
    - Urinary Retention
    - Hypoglycemic Unawareness
    - Cardiovascular Autonomic Neuropathy
      - Orthostatic Hypotension
      - Resting Tachycardia
      - Silent Angina
    - Diabetic Diarrhea

The ABC's of Diabetes

- A1C (and ASA)
  - < 7.0% (ACE < 6.5%)
- Blood Pressure*
  - < 140/80 mmHg (125/75 mmHg)
- Cholesterol** (and Cessation of smoking)
  - LDL-C < 100 mg/dL (<70 mg/dL?)
  - Non-HDL-C < 130 mg/dL (<100 mg/dL?)
  - HDL-C > 40 mg/dL (> 50 mg/dL in women)
  - TG's < 150 mg/dL

* JNC 8: < 140/90 mmHg

** NCEP 4: high-dose statin therapy recommended; ≥50% LDL-C reduction

My Diabetes Check-List

- Epidemiologic and interventional evidence define these interventions/targets
  - HbA_{1c} ≤7% (6%?) (Metabolically friendly)
  - Blood Pressure ≤140/80 mm Hg (ACEI/ARB)
  - LDL-cholesterol ≤70 mg/dL (Statin)
  - Daily ASA use for vascular protection
  - Smoking Cessation
  - Immunizations (Influenza, Pneumococcus)
  - Urinalysis
  - Daily Feet Inspection
  - Annual Dilated Eye Exams
  - Realistic Exercise Program
  - Weight Loss (5-10%)
  - Dental Exams (Peridontal Disease)