

# Diabetes Risk Assessment and Treatment

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# Disclosures

- Consultant: Gilead Sciences, Merck, BMS, EMD-Serono, Theratechnologies

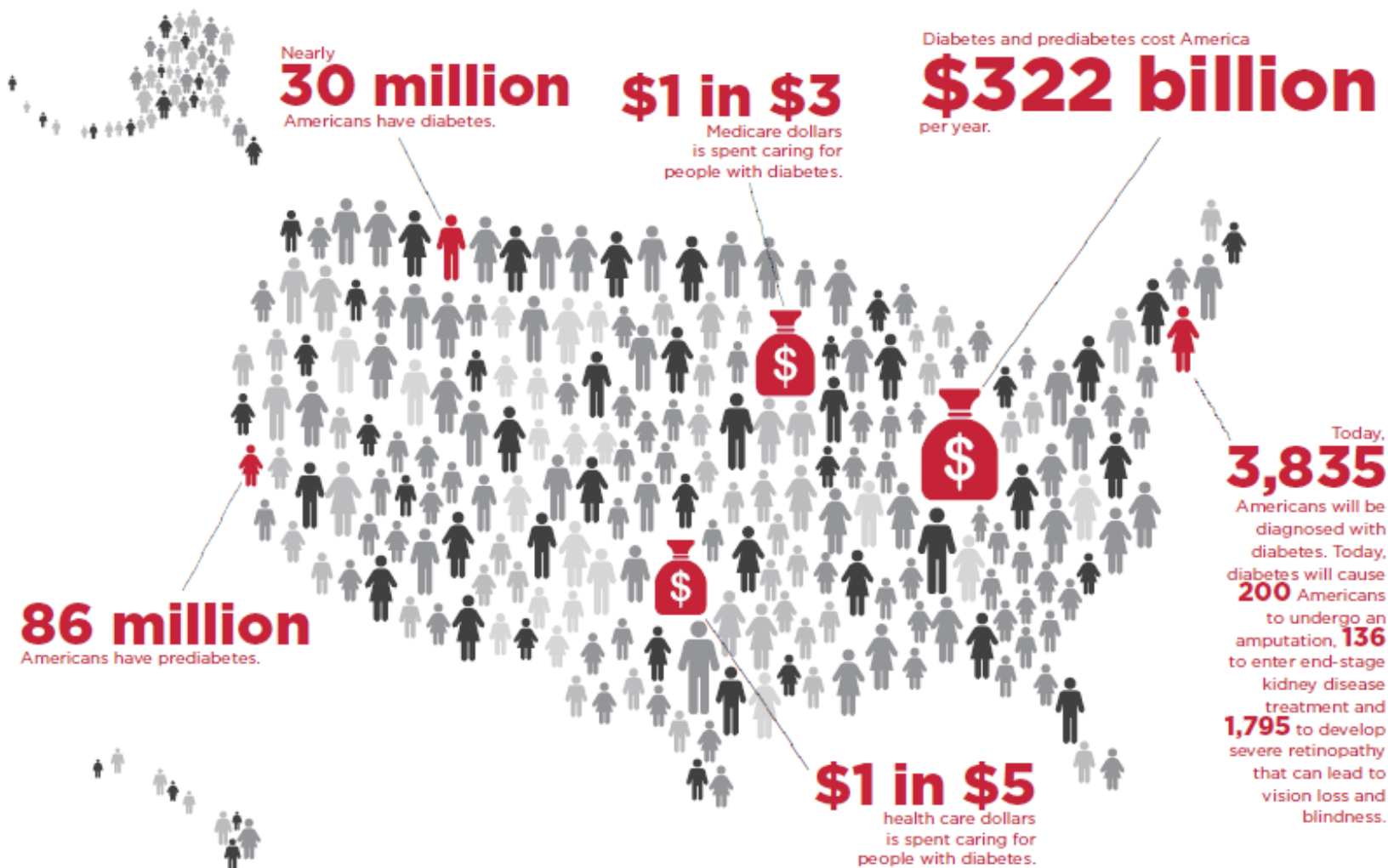
# Learning Objectives

- Explain how diabetes differs in persons with HIV infection compared to those without HIV
- Recommend how persons with HIV infection should be assessed for diabetes risk
- Summarize important considerations for managing patients with HIV infection and diabetes

# Why Care about Diabetes?

- Very common, with rapidly increasing prevalence
- One of leading causes of cardiovascular disease, blindness, ESRD, amputations, hospitalizations
- Common in HIV-infected populations
- Diabetes can be controlled, but management is complicated and requires individualization

# THE STAGGERING COSTS OF DIABETES IN AMERICA



Learn how to fight this costly disease at [diabetes.org/congress](http://diabetes.org/congress)



# Pathogenesis of Diabetes in HIV-infected Patients

- Antiretroviral Medication Factors
  - Thymidine analogues, older PIs
- HIV Factors
  - Residual immune activation/inflammation
- Host Factors
  - Adiposity
  - HCV
  - Genetic factors: family history, race
  - Coadministered medications: corticosteroids/atypical antipsychotics

# Case

- 53-year-old African American male, HIV+ for 20 years, on ART since 2000
- VL < 50 FTC/TDF/ EFV
- Mild/moderate lipoatrophy of face/buttocks/thighs
- Mild HTN, normal lipids, no smoking
- Strong family history of DM
- BMI 27 kg/m<sup>2</sup>

# ADA Screening Guidelines in General Population

Overweight or obese adults with one or more of the following:

- Previous pre-diabetes
- 1st-degree relative with DM
- High-risk race/ethnicity
- Women with h/o GDM
- H/O CVD
- HTN
- Low HDL or high TG
- Women with polycystic ovarian syndrome
- Physical inactivity
- Other conditions associated with IR



# Diabetes Screening Guidelines for HIV-infected Persons

- Who?
  - IDSA: Prior to ART, within 4-6 weeks after ART initiation, every 6-12 months thereafter

# How?: ADA Definitions 2017

## Diabetes Mellitus

1. A1C  $\geq 6.5\%$
2. Fasting plasma glucose  $\geq 126$  mg/dL, confirmed by repeat testing
3. Plasma glucose 2 hours after 75 g oral glucose tolerance test  $\geq 200$  mg/dL
4. Random plasma glucose  $\geq 200$  mg/dL with polyuria and polydipsia

#1-3 should be confirmed on repeat testing

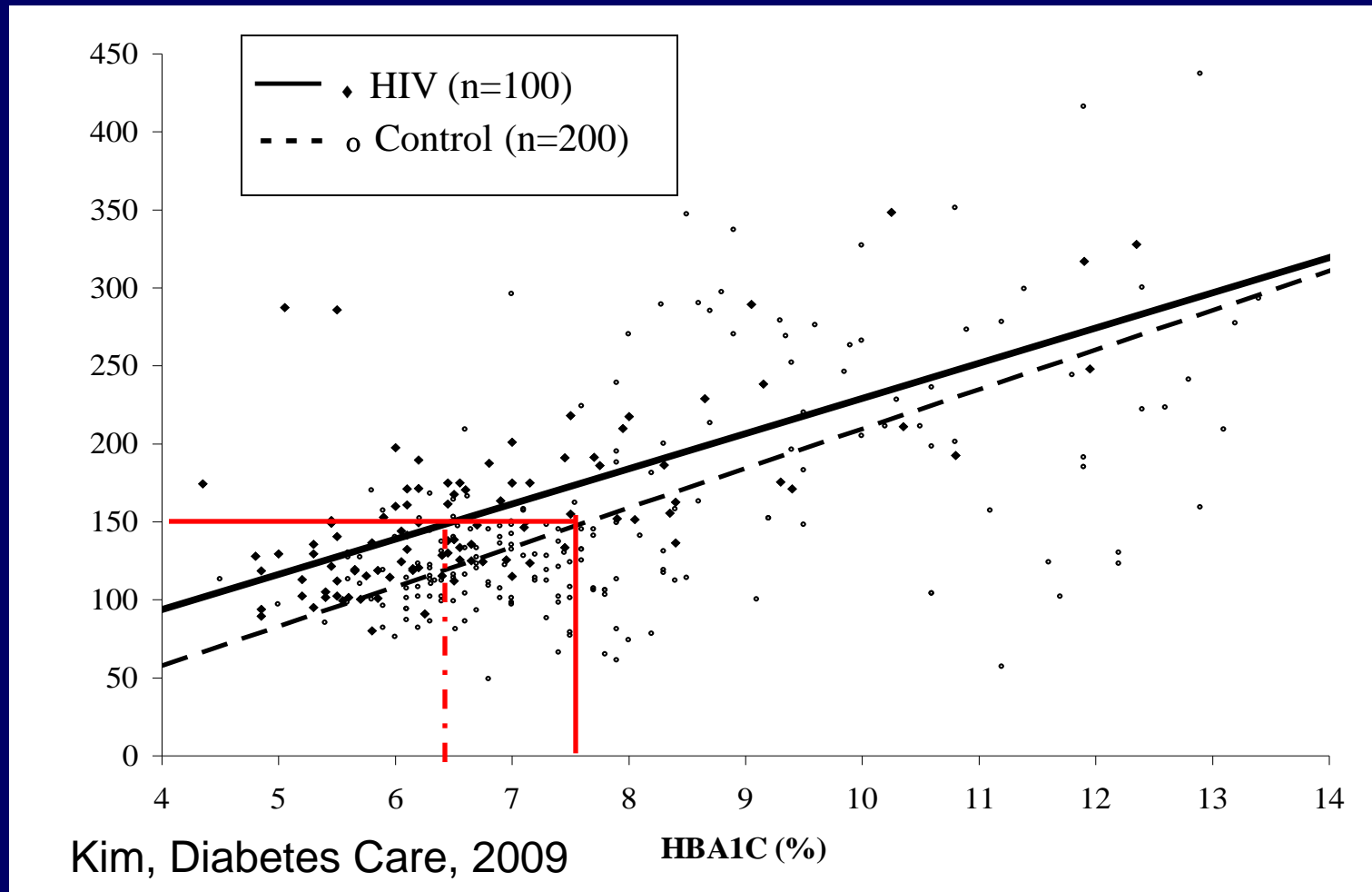
# Caveats for the Use of HgbA1c for Diagnosis

“For conditions with abnormal red cell turnover... the diagnosis of diabetes must employ glucose criteria exclusively.”

ADA Clinical Practice Recommendations, 2017

# HbA1c Underestimates Glycemia in HIV-infected Persons

Glucose (mg/dL)



# Diabetes Screening in HIV-infected Persons

- How?
  - Fasting glucose
  - If 100-125 mg/dL, consider 75 g OGTT
  - Avoid A1c for screening (particularly in those on ABC, low CD4, PIs, high MCV)

# Case

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- Mild/moderate lipoatrophy of face/buttocks/thighs
- Mild HTN, normal lipids, no smoking
- Strong family history of DM
- BMI 27 kg/m<sup>2</sup>
- Fasting glucose 145 mg/dL (confirmed)
- A1c 6.8%

# After DM Is Diagnosed, What Should Be the Next Steps?

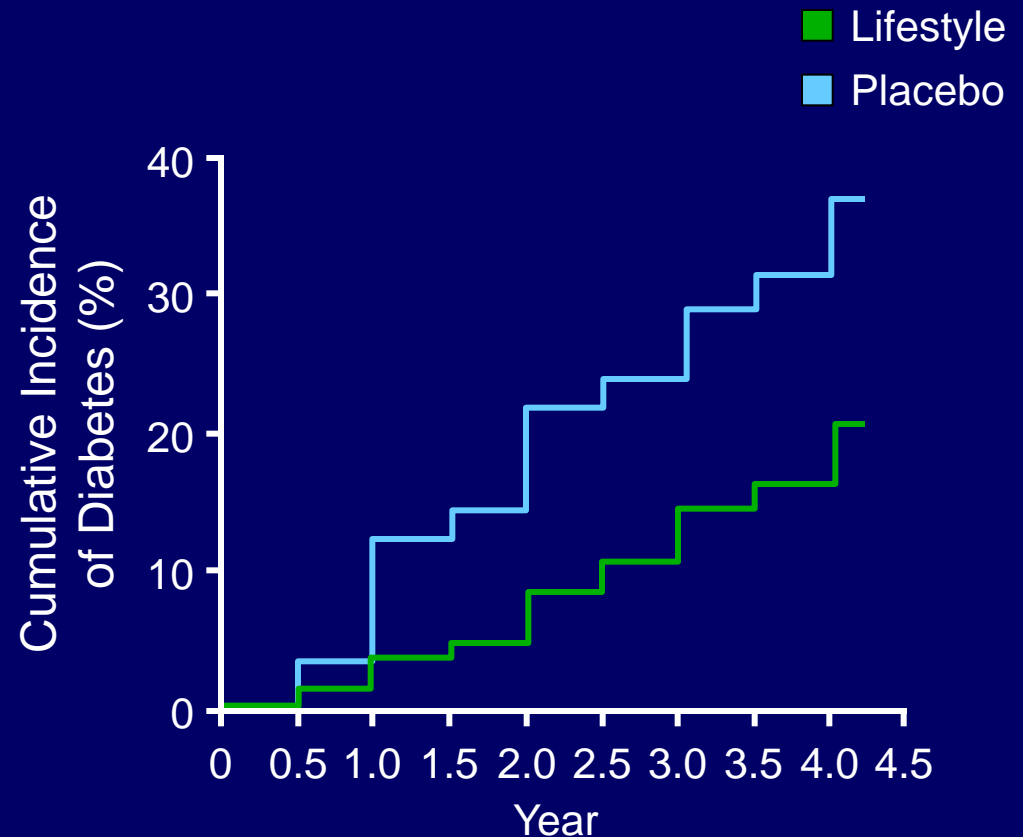
- Lifestyle modification
- First-line drug
- Combination therapy

# Lifestyle Modifications for Prediabetes

## Diabetes Prevention

### Program:

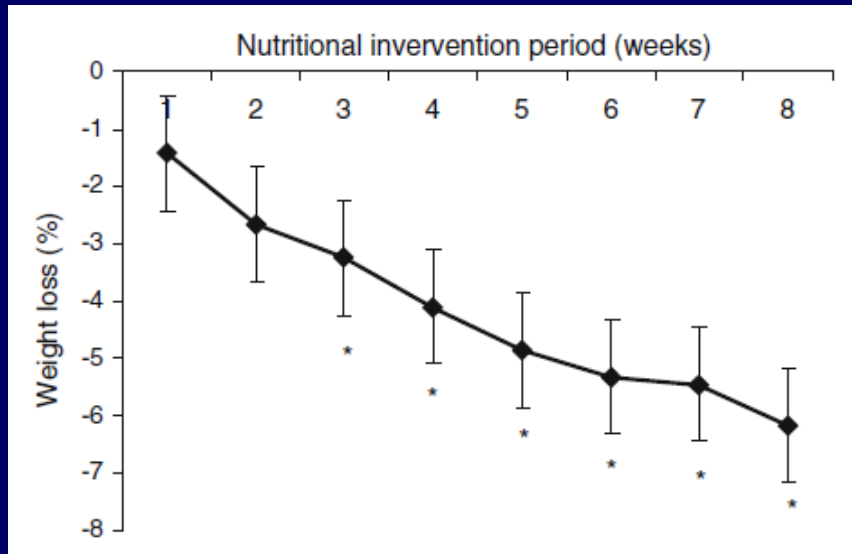
- 150 minutes/week of exercise and caloric restriction
- Goal: 7% weight loss
- ↓ 58% diabetes incidence



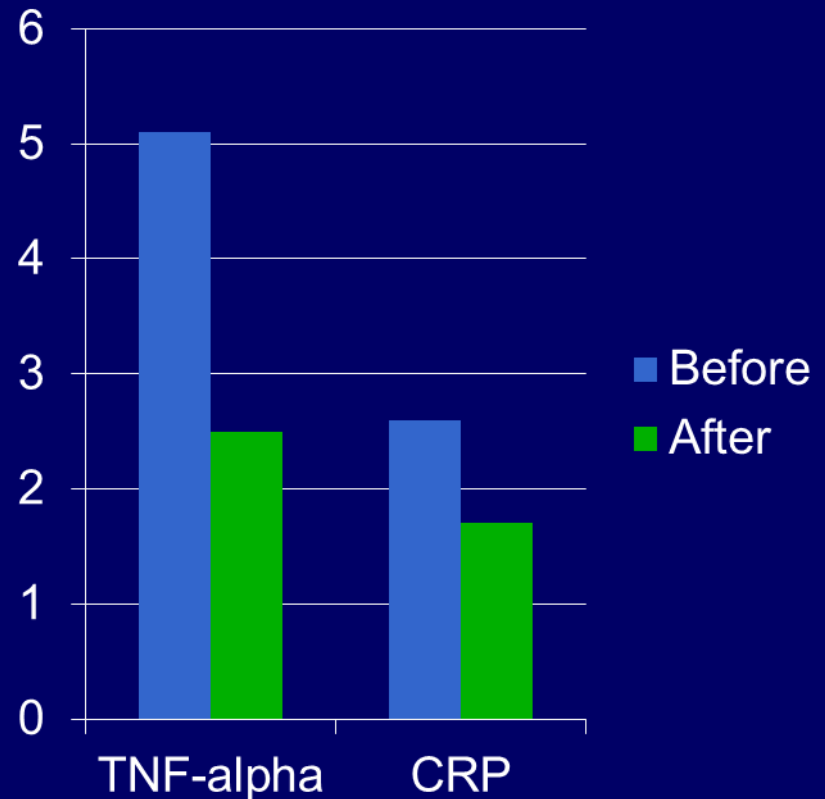


# Effect of Cutting 500 cal/day over 8 weeks in Obese Persons

## Effect on Weight



## Effect on Inflammation

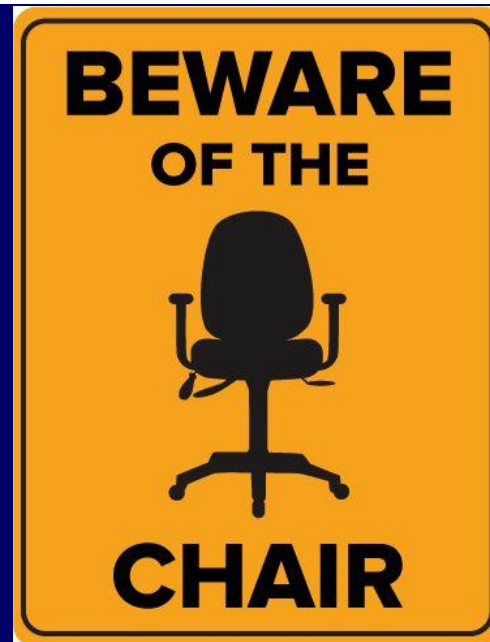




# Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association

*Sheri R. Colberg,<sup>1</sup> Ronald J. Sigal,<sup>2</sup> Jane E. Yardley,<sup>3</sup> Michael C. Riddell,<sup>4</sup> David W. Dunstan,<sup>5</sup> Paddy C. Dempsey,<sup>5</sup> Edward S. Horton,<sup>6</sup> Kristin Castorino,<sup>7</sup> and Deborah F. Tate<sup>8</sup>*

*Diabetes Care* 2016;39:2065–2079 | DOI: 10.2337/dc16-1728



# Benefits of and Recommendations for Reduced Sedentary Time

Prolonged sitting should be interrupted with bouts of light activity every 30 min for blood glucose benefits, at least in adults with type 2 diabetes.

# After DM Is Diagnosed, What Should Be the Next Steps?

- Lifestyle modification
- First-line drug
- Combination therapy

# Metformin: THE First Line Drug



# Metformin: Pros and Cons

## Pros

- ↓ A1c ~1%
- Long track record
- No hypoglycemia
- No weight gain
- ? CVD benefit
- Low cost (AWP \$86/month)

## Cons

- GI side effects
- Lactic acidosis (rare)
- Contraindications:
  - CKD (OK eGFR >30 cc/min/1.73 m<sup>2</sup>)
  - Hypoxia
  - Decompensated liver disease
  - Severe CHF
  - Alcohol abuse
  - Past H/O lactic acidosis
- ~~? Worsening lipodystrophy~~
- Interaction with DTG

# After DM Is Diagnosed, What Should Be the Next Steps?

- Lifestyle modification
- First-line drug
- Combination therapy



# What Drug to Add Next?

- Sulfonylureas
- Glitazones (pioglitazone)
- Insulin
- GLP-1 analogues
- DPP-IV inhibitors
- SGLT-2 inhibitors



Incretins



# Sulfonylureas: Pros and Cons

## Pros

- ↓ A1c ~1%
- Long track record
- ↓ Microvascular events
- Low cost (AWP \$74/month)

## Cons

- Weight gain
- Hypoglycemia
- High failure rate

# Pioglitazone: Pros and Cons

## Pros

- ↓ A1c ~1%
- No hypoglycemia
- ? CVD benefit
- ↑ HDL, ↓ TGs
- ↓ Liver fat
- ? ↓ Inflammation
- Low failure rate
- Modest effect on lipomatrophy (~200-500 g)

## Cons

- Weight gain
- Fluid retention/CHF
- Macular edema
- Osteoporosis/fracture
- Bladder cancer
- Cost (AWP \$349/month)

# Insulin: Pros and Cons

## Pros

- ↓ A1c: unlimited
- ↓ Microvascular events

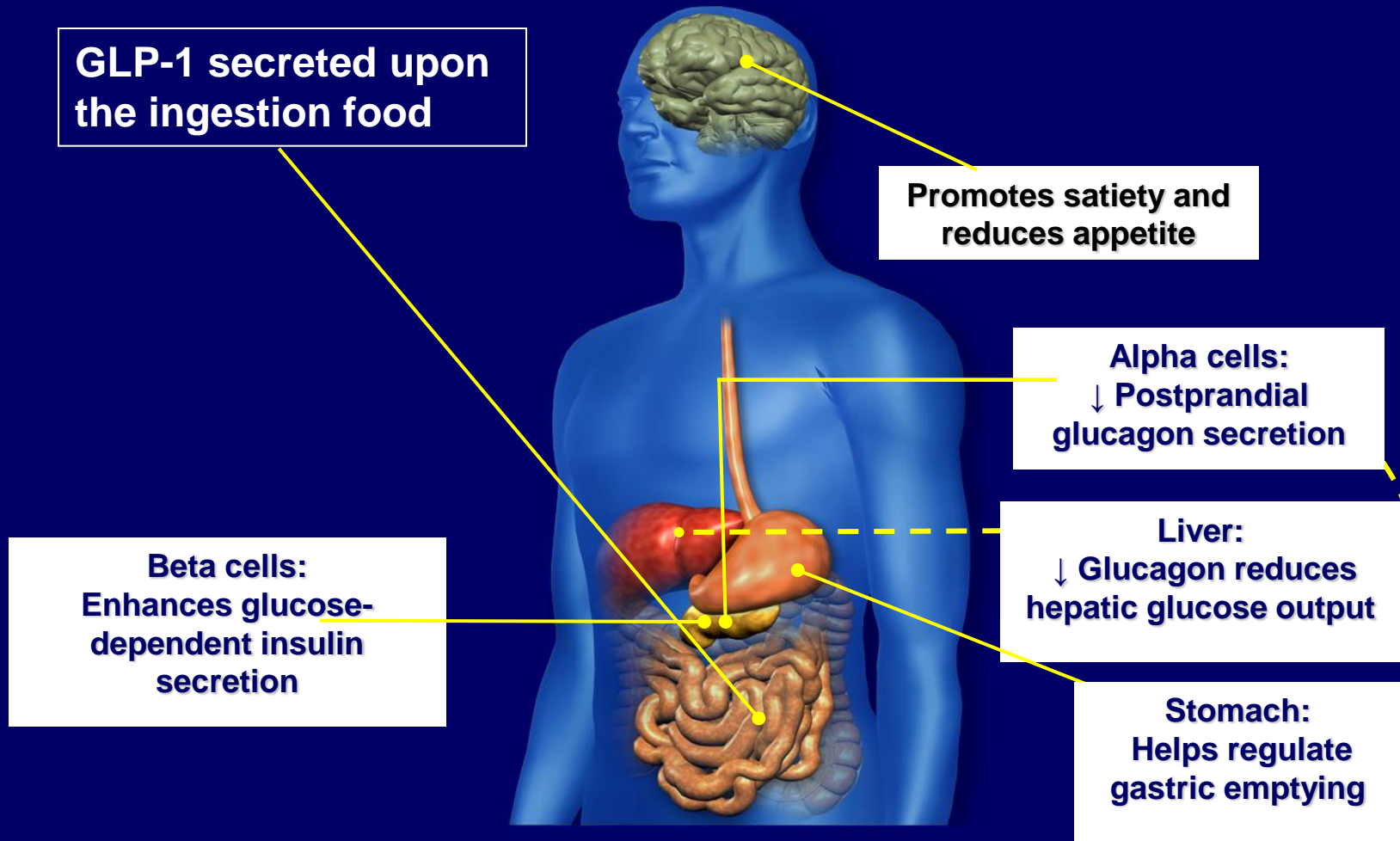
## Cons

- Hypoglycemia
- Weight gain
- Injectable
- Cost (insulin glargine AWP \$298/month; NPH vial AWP \$165/month)

# Starting Insulin in Type 2 DM

- Start with bedtime glargine, detemir, or NPH (10 units, increase by 2-3 units q 3 days until fasting is <120 mg/dl)
- Add prandial insulin (10% of basal dose before largest meal), GLP-1 analogue, or switch to 70/30 bid if not at goal
- Recommended as first line if A1c  $\geq 10\%$ , severe liver disease/kidney disease, hypertriglyceridemia

# GLP-1 Effects in Humans: Understanding the Glucoregulatory 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.* 1998;47:159-169.

# Incretins

## GLP-1 Analogues

- Exenatide
- Liraglutide
- Exenatide LAR
- Dulaglutide
- Albiglutide
- Lixisenatide

## DPP-IV Inhibitors

- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

# GLP-1 Analogues: Pros and Cons

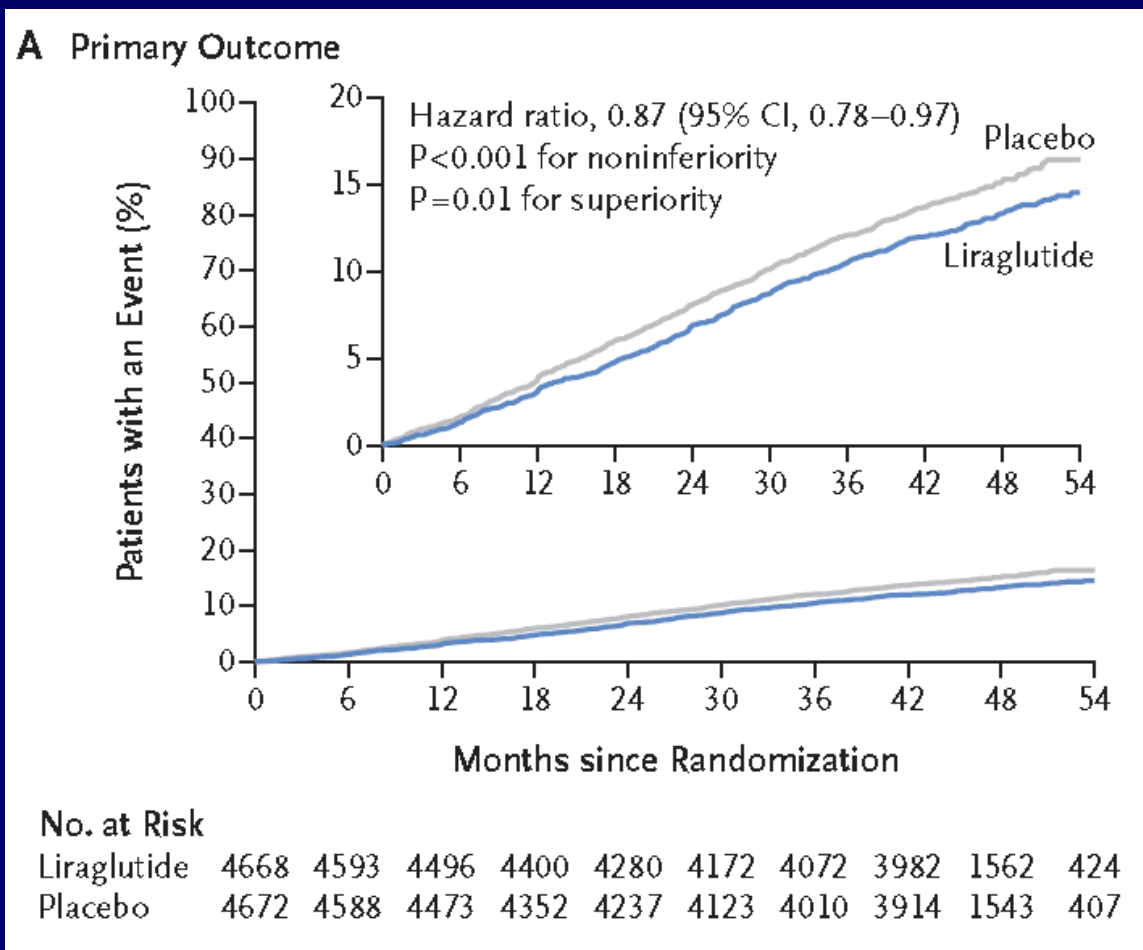
## Pros

- ↓ A1c ~1%
- No hypoglycemia
- Weight loss
- ? ↓ Inflammation
- CVD benefit

## Cons

- GI side effects
- ? ↑ pancreatitis
- Cost (AWP \$831/month)

# Liraglutide Decreases CVD Events in High-Risk Type 2 Patients: LEADER Trial





# DPP-IV Inhibitors: Pros and Cons

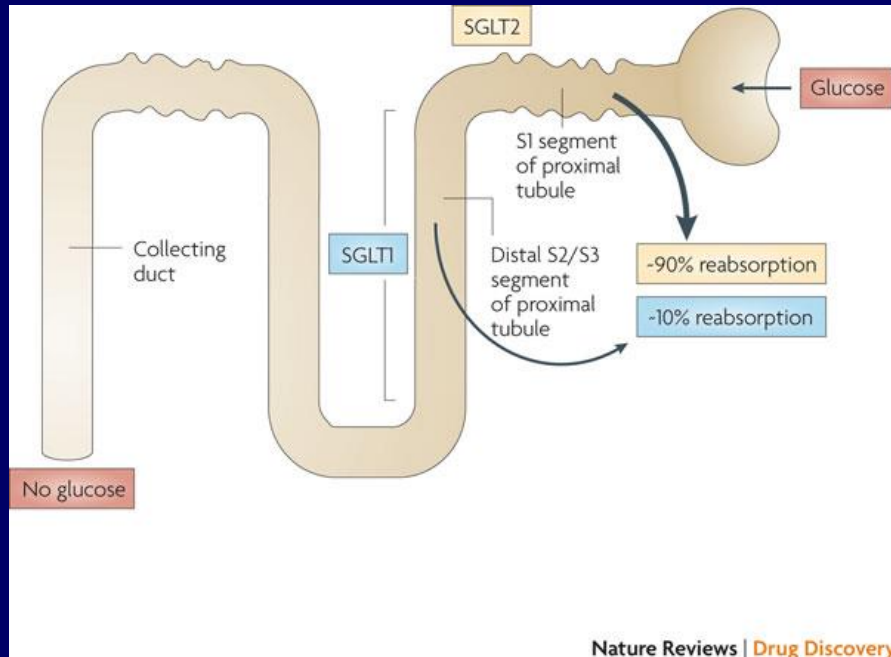
## Pros

- No hypoglycemia
- Weight neutral
- ? ↓ inflammation

## Cons

- ↓ A1c ~0.5%
- GI side effects
- ? pancreatitis
- Hypersensitivity reaction
- No CVD benefit
- Heart failure
- Cost (AWP \$436/month)

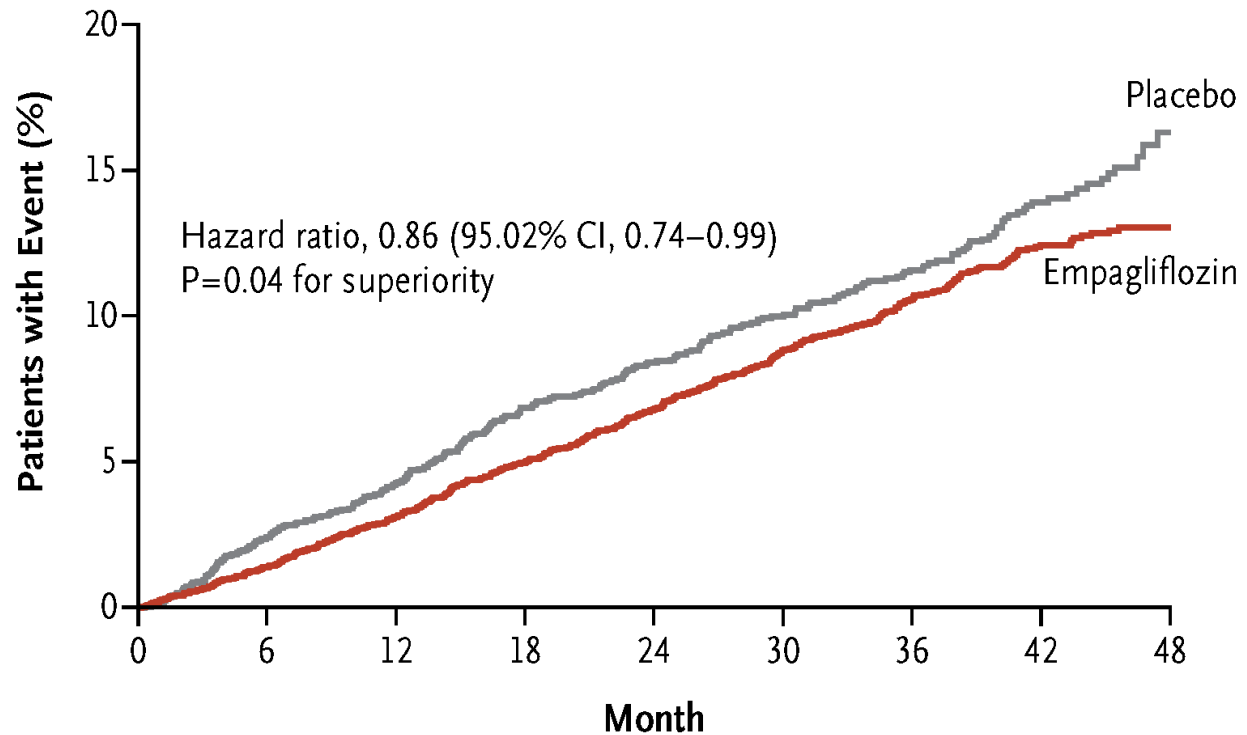
# Sodium Glucose Cotransporter-2 Inhibition: The “Gliflozins”



- Insulin-independent reduction in glucose
  - dapagliflozin
  - canagliflozin
  - empagliflozin
- 0.5%-1% A1c reductions
- Weight loss (~2kg)
- Lowers BP
- No hypoglycemia
- ↑ urinary tract infections/candidiasis
- Polyuria/dehydration
- ↑ DKA risk
- ↑ Bone fractures
- High cost (AWP \$470/month)

# Empagliflozin Reduced CVD Events in DM Patients with High CVD Risk

## A Primary Outcome



### No. at Risk

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

# What Drug to Add Next?

- Sulfonylureas
- Glitazones (pioglitazone)
- Insulin
- GLP-1 analogues
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Incretins



***COST***

**RISKS**

**BENEFITS**

# What Drug to Add Next?

- Sulfonylureas
- Glitazones (pioglitazone)
- Insulin
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Incretins

# ADA Recommendations 2017

“Consider empagliflozin or liraglutide in patients with established CVD to reduce the risk of mortality.”

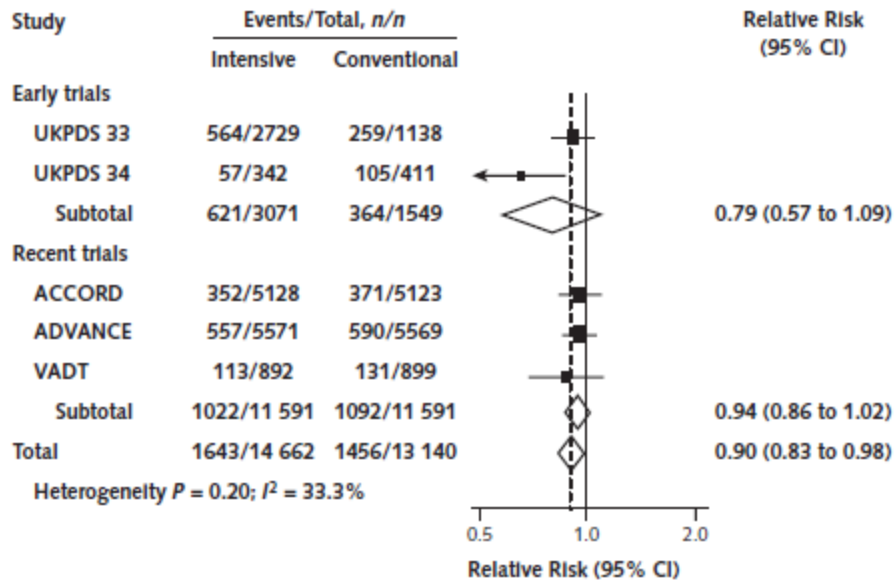
# What Should Be the Glycemic Target?

HbA1c <7%



# Meta-Analysis of Glycemic Control and CVD in Diabetes

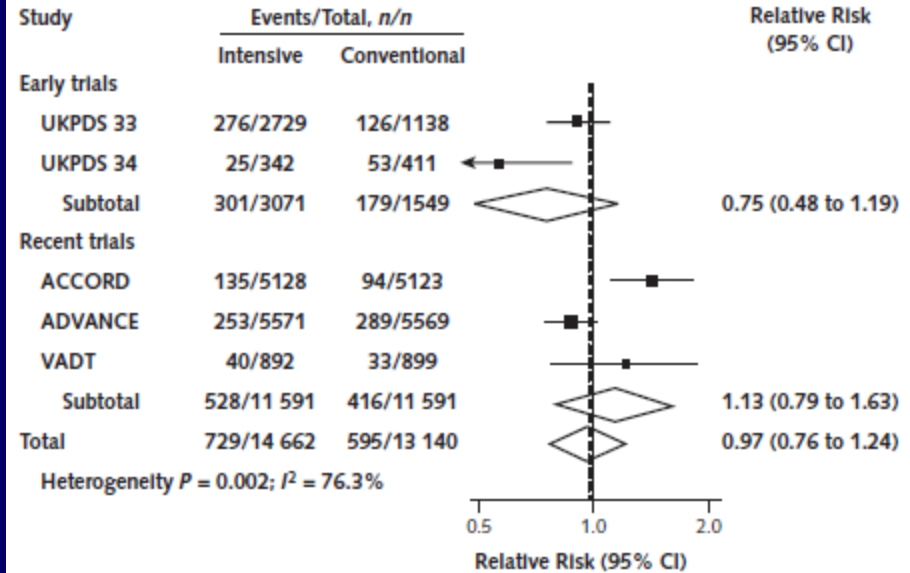
## A. Cardiovascular Disease



10% Risk Reduction for CVD

2-fold increase risk of severe hypoglycemia with intensive control

## E. Cardiovascular Disease Mortality



No Benefit on CVD Mortality

Kelly, Annals of Int Med, 2009

# A1c Goal

# HbA1c <7%

## Individualization Is Key:

- Tighter control (A1c 6.0-6.5%): younger, healthier
- Looser control (A1c 7.5-8.0%+): older, hypoglycemia-prone, comorbidities

# What Else Should I Be Doing to Prevent Complications?: Microvascular

- Retinopathy: yearly ophthalmologic exams
- Nephropathy:
  - BP control
  - Spot urine microalbumin every 6-12 months
  - ACE-I/ARB with microalbuminuria or HTN
  - Lipid control
- Neuropathy:
  - Foot exams every 6-12 months
  - Instruction in foot care
  - Podiatry if evidence of neuropathy

# What Else Should I Be Doing to Prevent Complications?: Macrovascular

- Attention to all CV risk factors
  - A: Antiplatelet therapy
  - B: Blood pressure
  - C: Cholesterol
  - D: Diabetes/glucose management
  - S: Smoking cessation

Steno-2 Trial (Gaede, NEJM, 2003):  
CV events ↓ by 50% with intensive control  
of all CV risk factors

# Conclusions

- Regular DM screening is important
- Avoid A1c for diagnosis in HIV+ patients
- Lifestyle changes are critical
  - 5%-10% wt loss!
- Metformin first
- Decisions re: 2nd and 3rd drugs should be individualized
- A1c goal <7% in most, but should be individualized
- Multiprong approach to prevent complications

HIV Management  
Hepatitis Management

# THE NEW YORK COURSE

