

The Optimal Evaluation and Management of Diabetes in People Living with HIV

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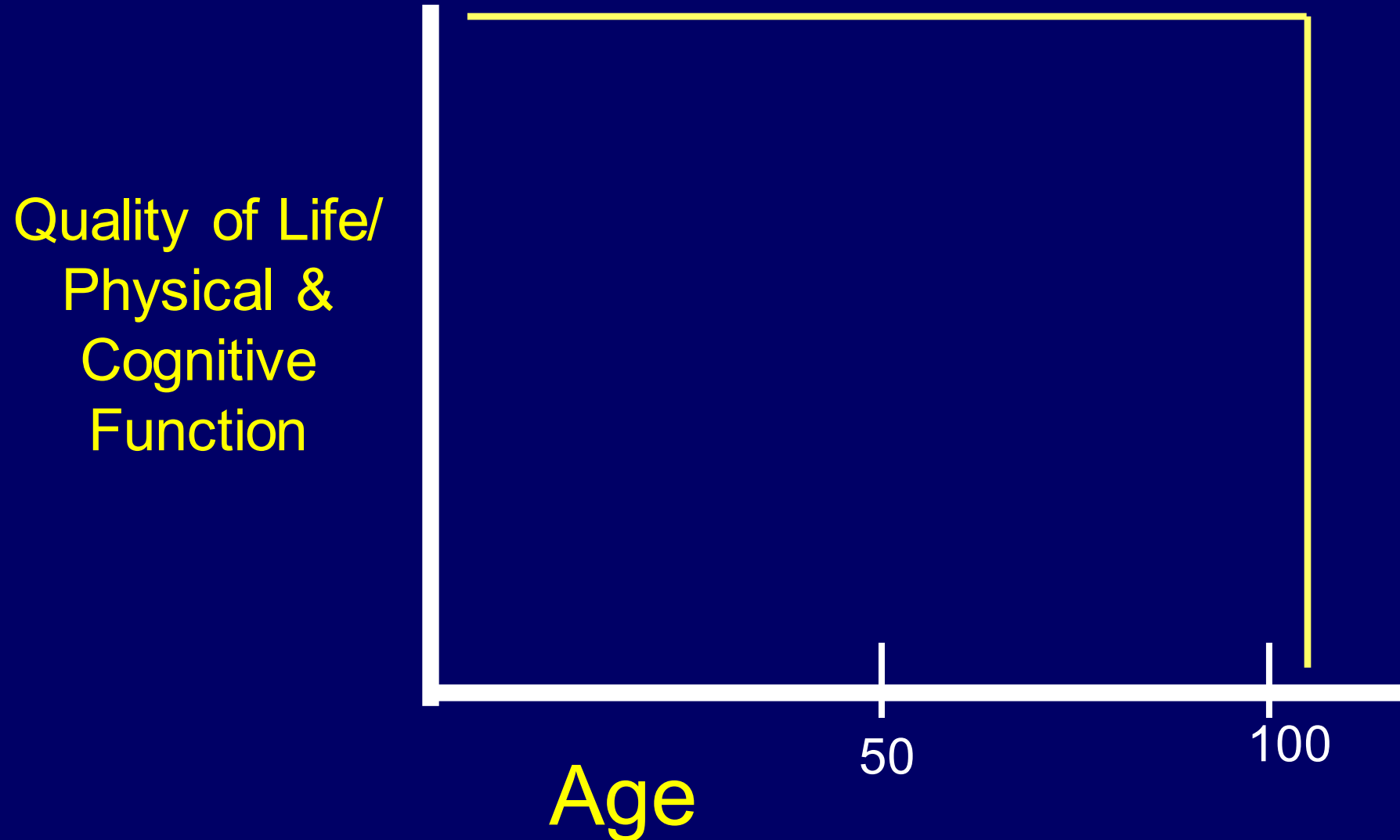
Learning Objectives

- Explain how diabetes differs in persons with HIV infection compared to those without HIV, as well as potential connections between antiretroviral therapy and diabetes risk
- Recommend how persons with HIV infection should be assessed for diabetes risk
- Summarize important considerations for managing patients with HIV infection and diabetes

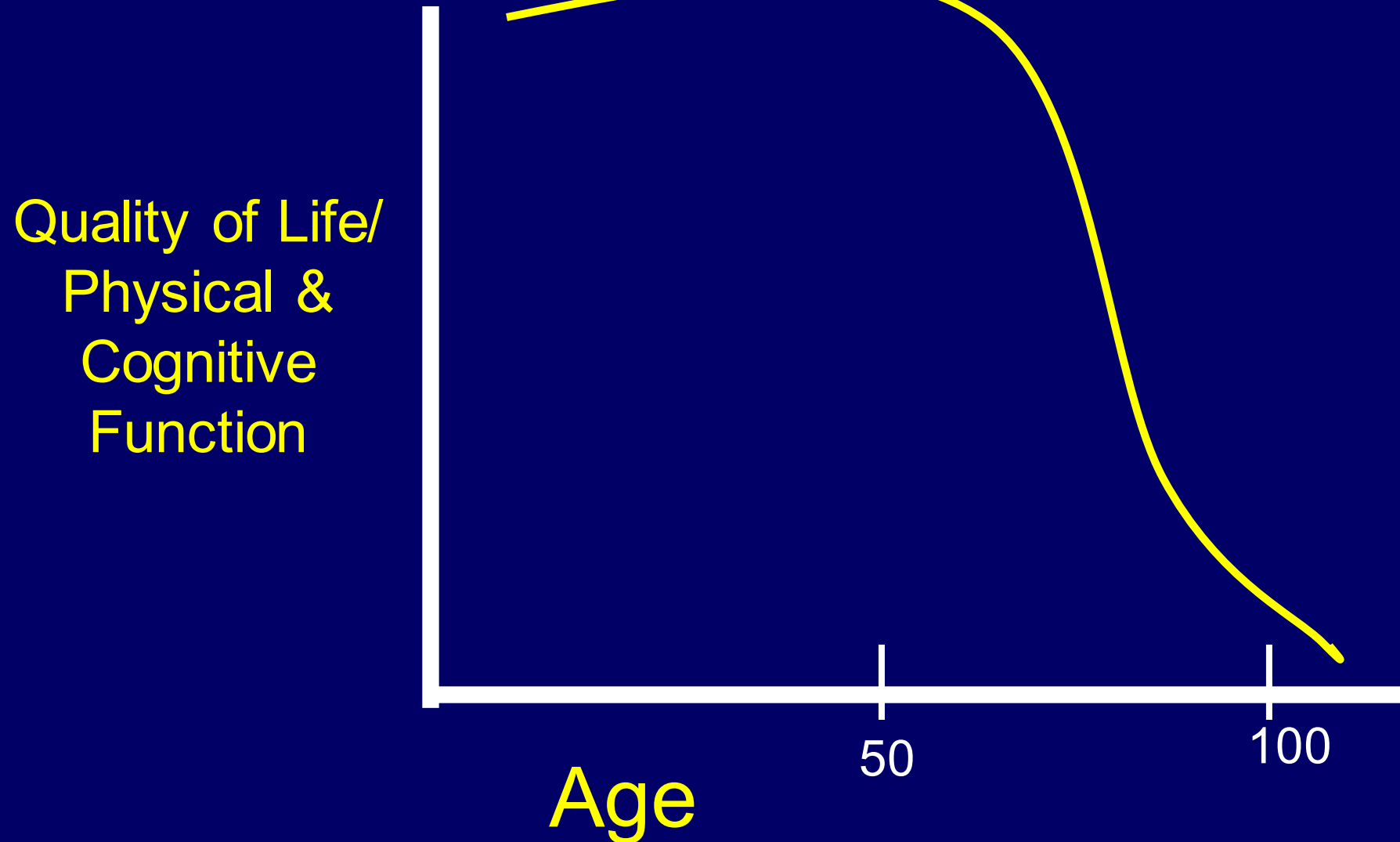
Disclosures

- Gilead Sciences
 - Merck
 - Janssen
 - ViiV Healthcare
-
- *This program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) under grant number U1OHA30535 as part of an award totaling \$4.2m. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS, or the U.S. Government. For more information, please visit [HRSA.gov](https://www.hrsa.gov).*
 - *“Funding for this presentation was made possible by cooperative agreement U1OHA30535 from the Health Resources and Services Administration HIV/AIDS Bureau. The views expressed do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. Any trade/brand names for products mentioned during this presentation are for training and identification purposes only.”*

The Ideal Life: Quality x Time

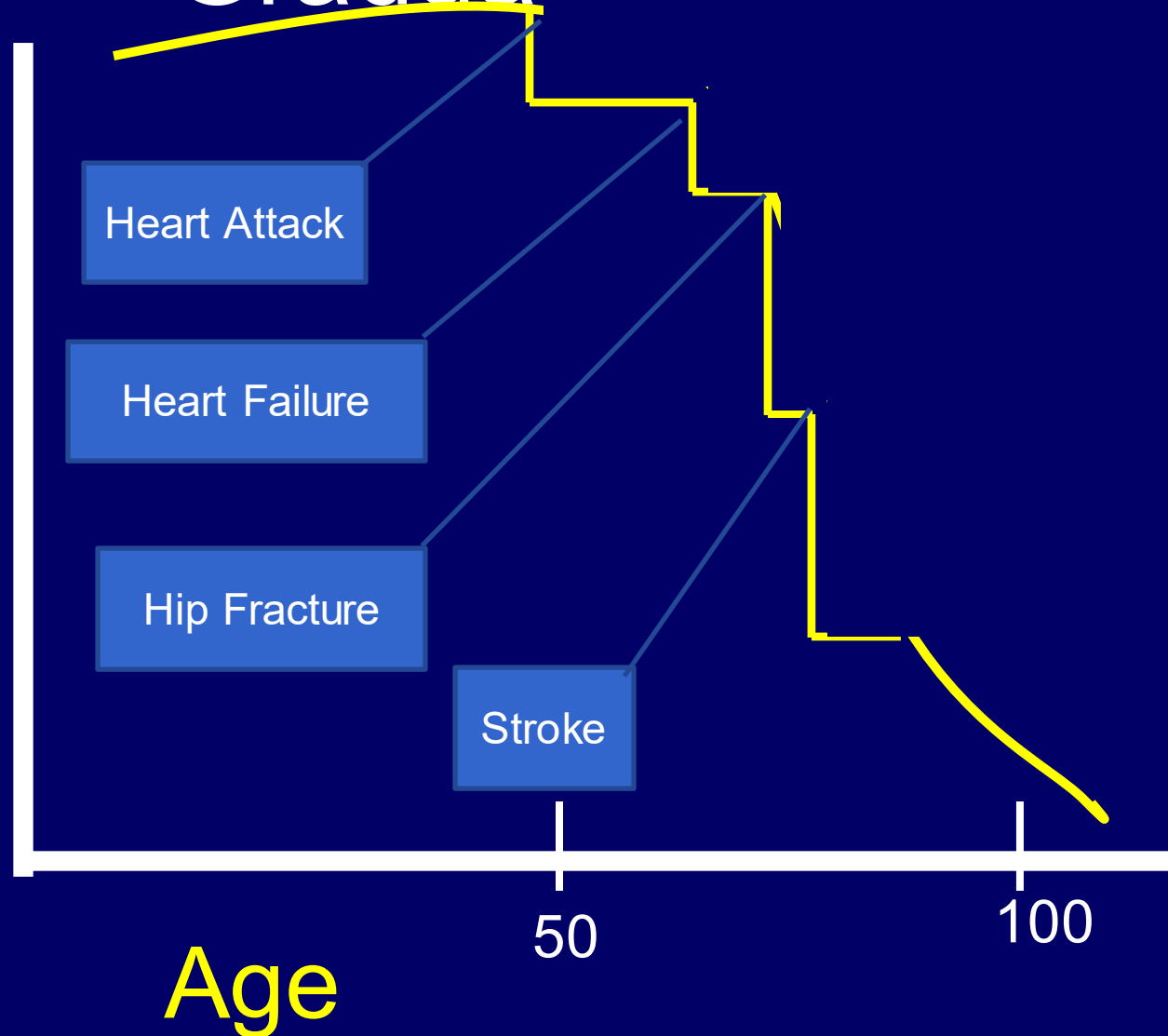


Physical & cognitive function generally declines over time



Decline in Function May Not Be Gradual

Quality of Life/
Physical &
Cognitive
Function



Prevention of Comorbid Events is Essential and Achievable: The Diabetes Example

- Good screening tests are available for diabetes
- Behavioral factors contribute to diabetes risk and can be modified
- Early treatment is important
- Good treatments exist that can decrease the risk of events (e.g., cardiovascular disease, ESRD, cognitive decline)
- Preventing complications can alter the aging process

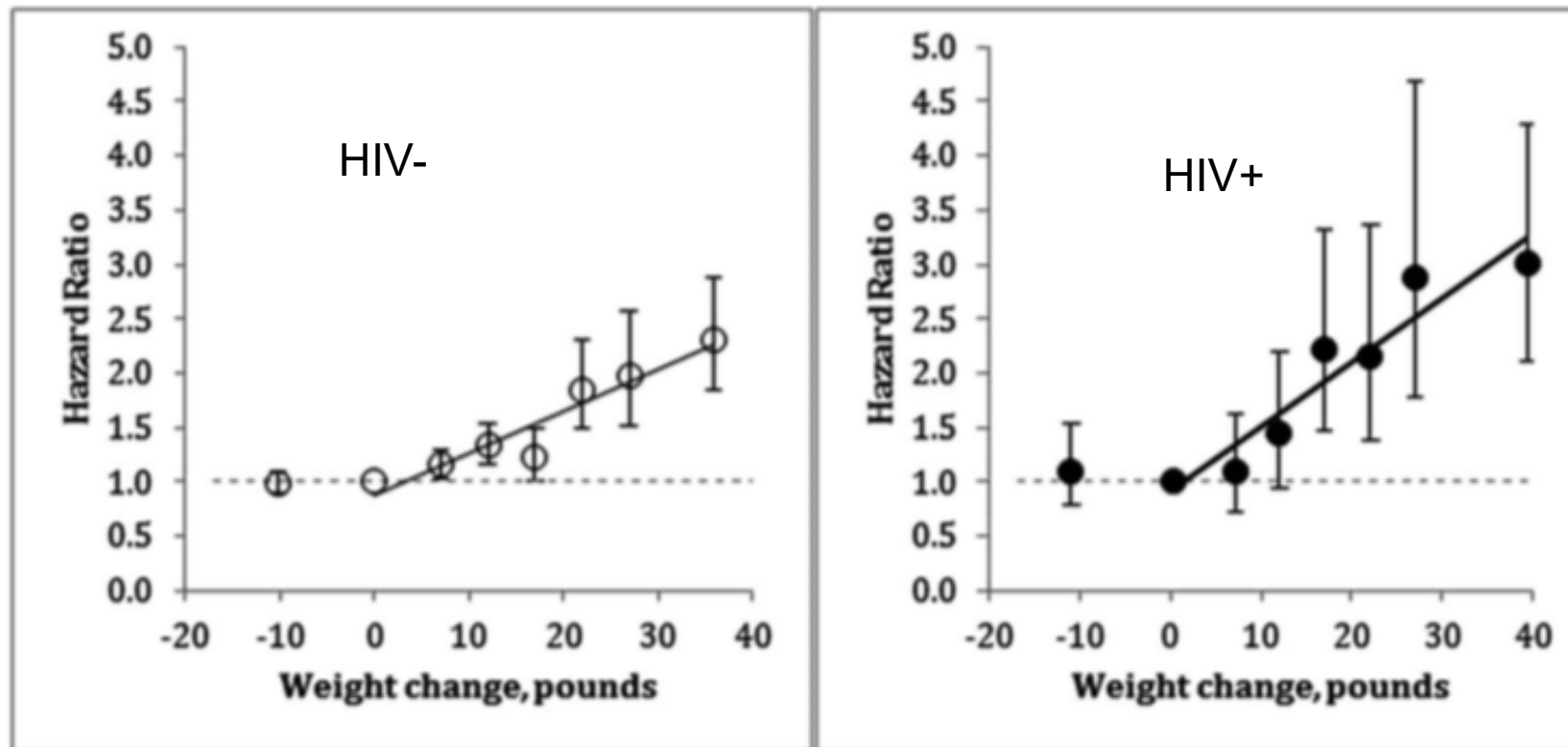
Why Care about Diabetes?

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

Pathogenesis of Diabetes in People with HIV

- **Host Factors**
 - **Adiposity**

Risk of DM with Weight Gain over 1 Year after ART Initiation



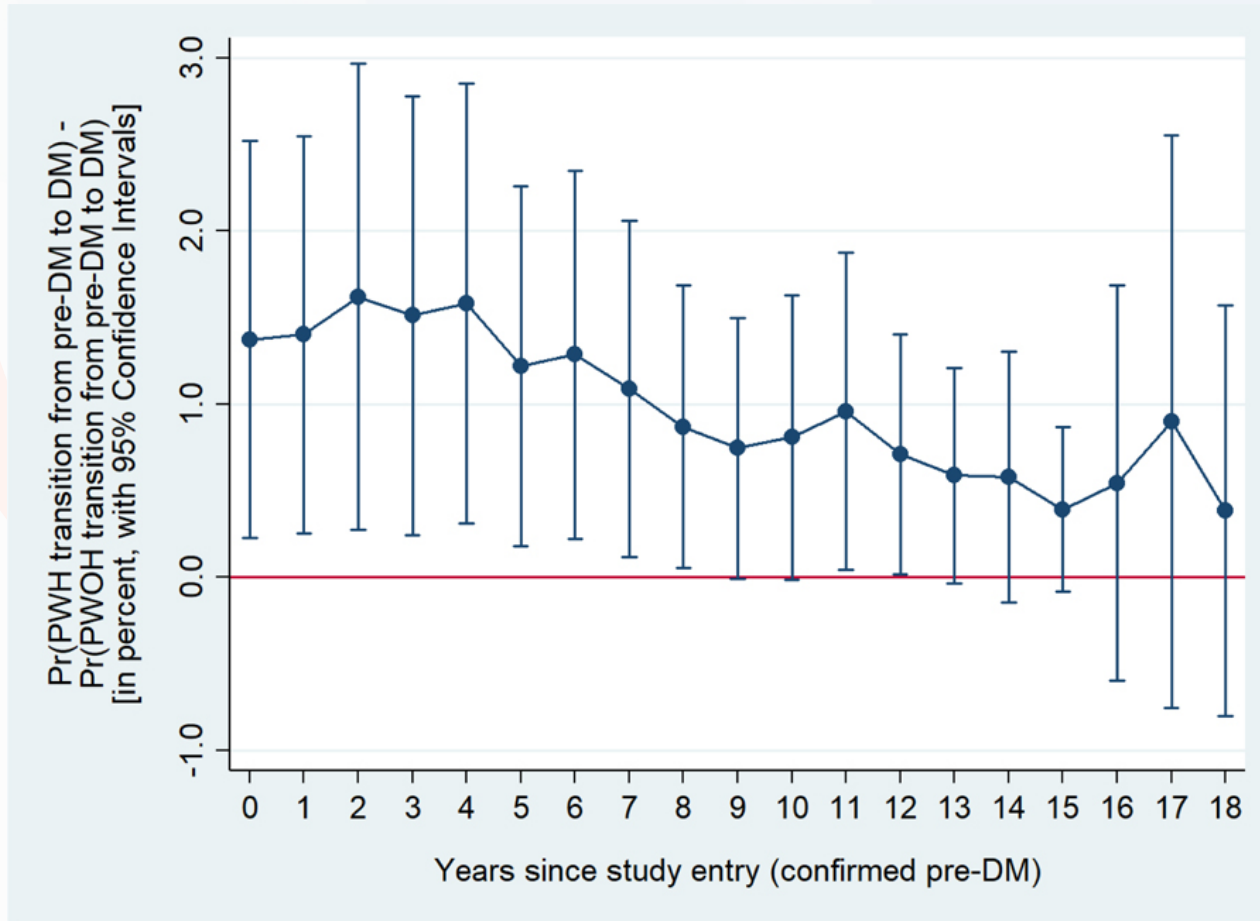
adjusted for age, race, sex, baseline BMI, smoking, HCV infection, and calendar year at baseline

Herrin, JAIDS, 2016

Pathogenesis of Diabetes in People with HIV

- **Host Factors**
 - **Adiposity**
 - **HCV**
 - **Genetic Factors: Family History, Race**
 - **Concomitant Medications: Corticosteroids/Atypical Antipsychotics**
- **Antiretroviral Medication Factors**
 - **Thymidine analogues, older PIs**

Men with HIV transition from pre-DM to DM at higher rates than men without HIV: MACS 1999-2019



Factors Associated with pre-DM → DM in MWH

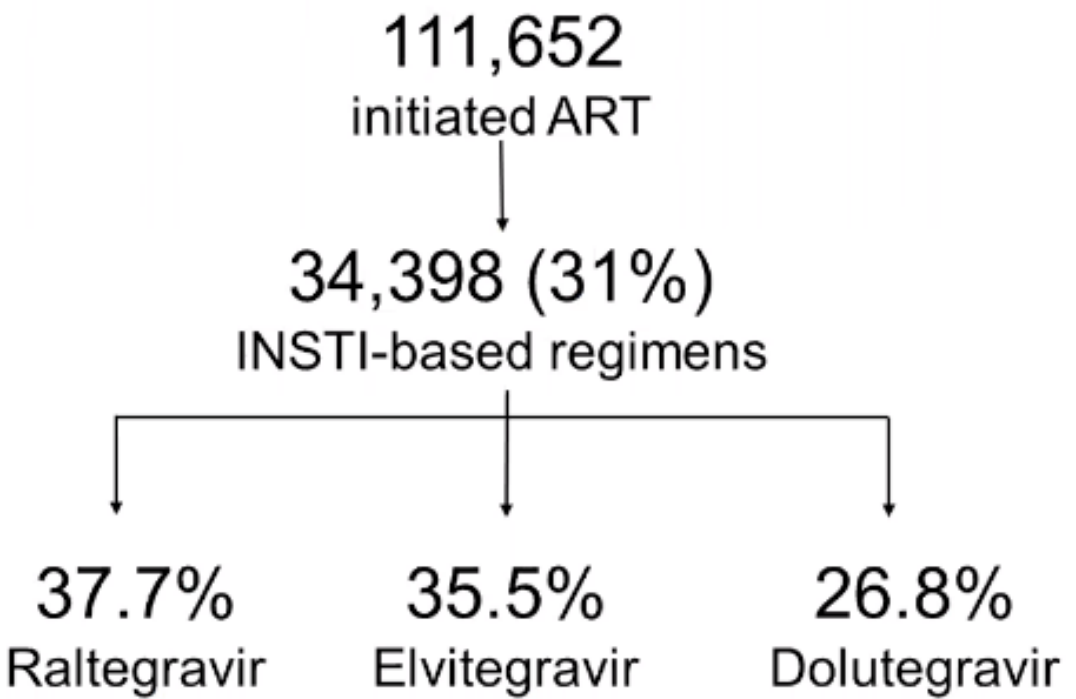
- Lipoatrophy OR 2.3
- Thymidine Analogue Use OR 1.7

Pathogenesis of Diabetes in People with HIV

- **Host Factors**
 - **Adiposity**
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 - **Genetic Factors: Family History, Race**
 - **Concomitant Medications: Corticosteroids/Atypical Antipsychotics**
- **Antiretroviral Medication Factors**
 - **Thymidine analogues, older PIs**
 - **? Integrase Inhibitors**

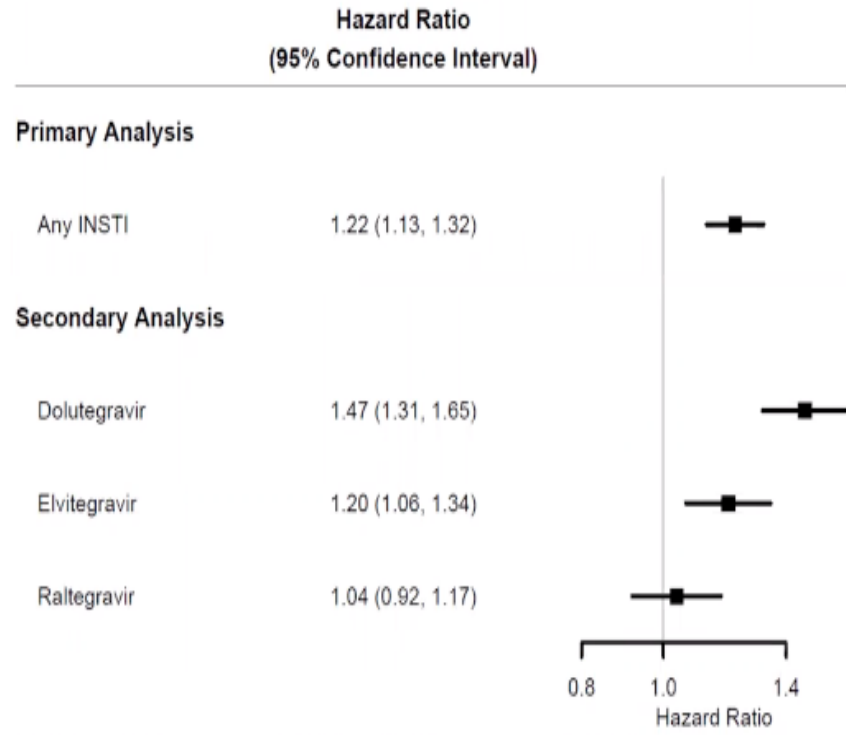
InSTI and Incident Diabetes after ART Initiation

January 2007 → June 2018



2,836 (2.5%) event

➤ 93% new-onset diabetes mellitus, 7% hyperglycemia



Pathogenesis of Diabetes in People with HIV

- **Host Factors**
 - **Adiposity**
 - **HCV**
 - **Genetic Factors: Family History, Race**
 - **Concomitant Medications: Corticosteroids/Atypical Antipsychotics**
- **Antiretroviral Medication Factors**
 - **Thymidine analogues, older PIs**
 - **? Integrase Inhibitors**
- **HIV Factors**
 - **Residual immune activation/inflammation**

ADA Screening Guidelines in General Population

- 1) Overweight or obese adults with one or more additional risk factors
- 2) Previous pre-diabetes
- 3) Women with a history of gestational diabetes
- 4) HIV

How?: ADA Definitions

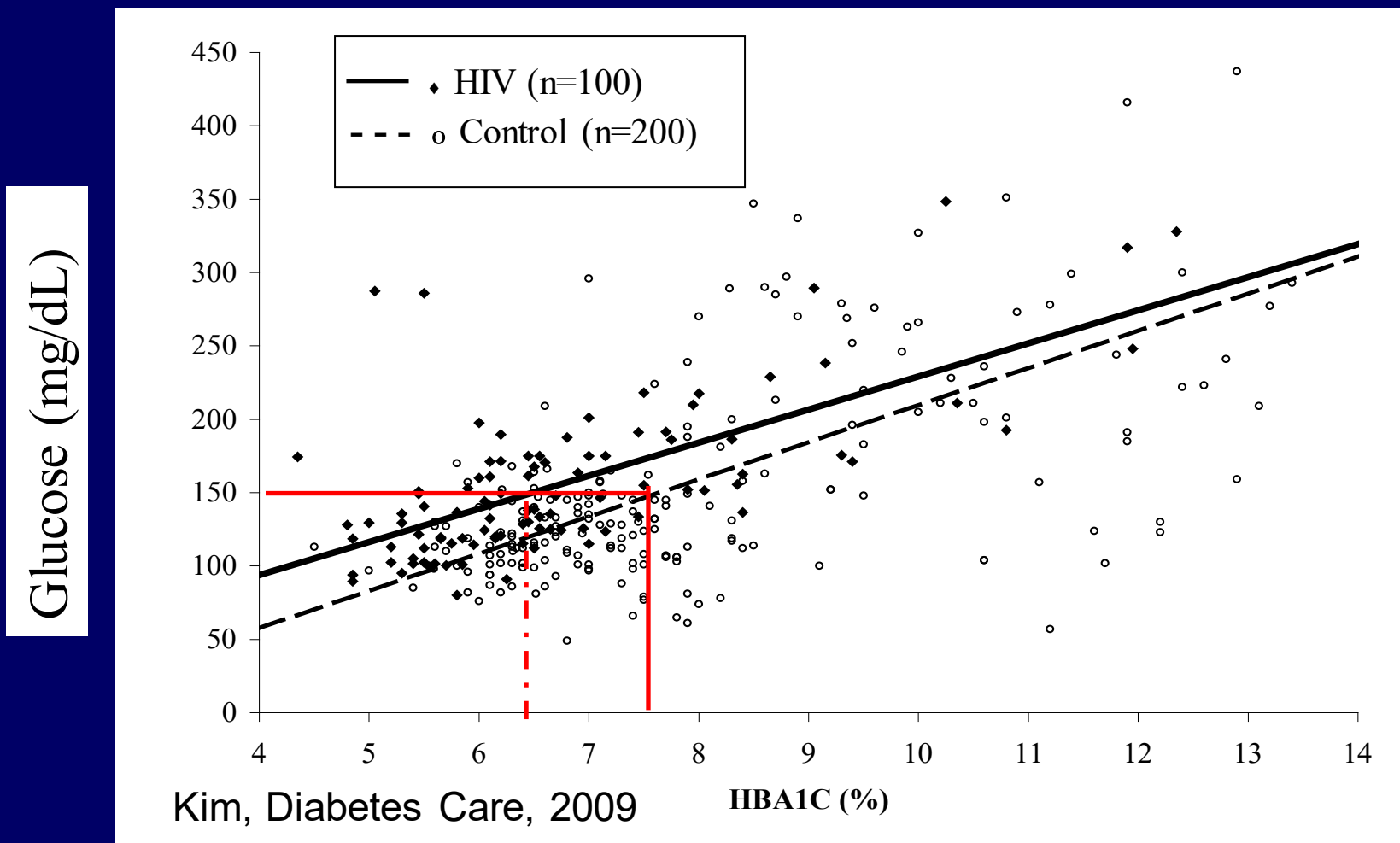
Diabetes Mellitus

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

Caveats for the use of HgbA1c for diagnosis

In conditions associated with increased red blood cell turnover..., only plasma blood glucose criteria should be used to diagnose diabetes. A1C is less reliable than blood glucose measurement in other conditions such as... HIV treated with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs)..

HbA1c Underestimates Glycemia in Persons with HIV



Diabetes Screening in People with HIV

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

Diabetes Screening Guidelines People with HIV: HIV Primary Care Guidelines

”Random or fasting blood glucose and hemoglobin A1c (HbA1c) should be obtained prior to starting ART. If random glucose is abnormal, fasting glucose should be obtained. After initiation of ART, only plasma glucose criteria should be used to diagnose diabetes.”

After DM is diagnosed, what should be the next steps?

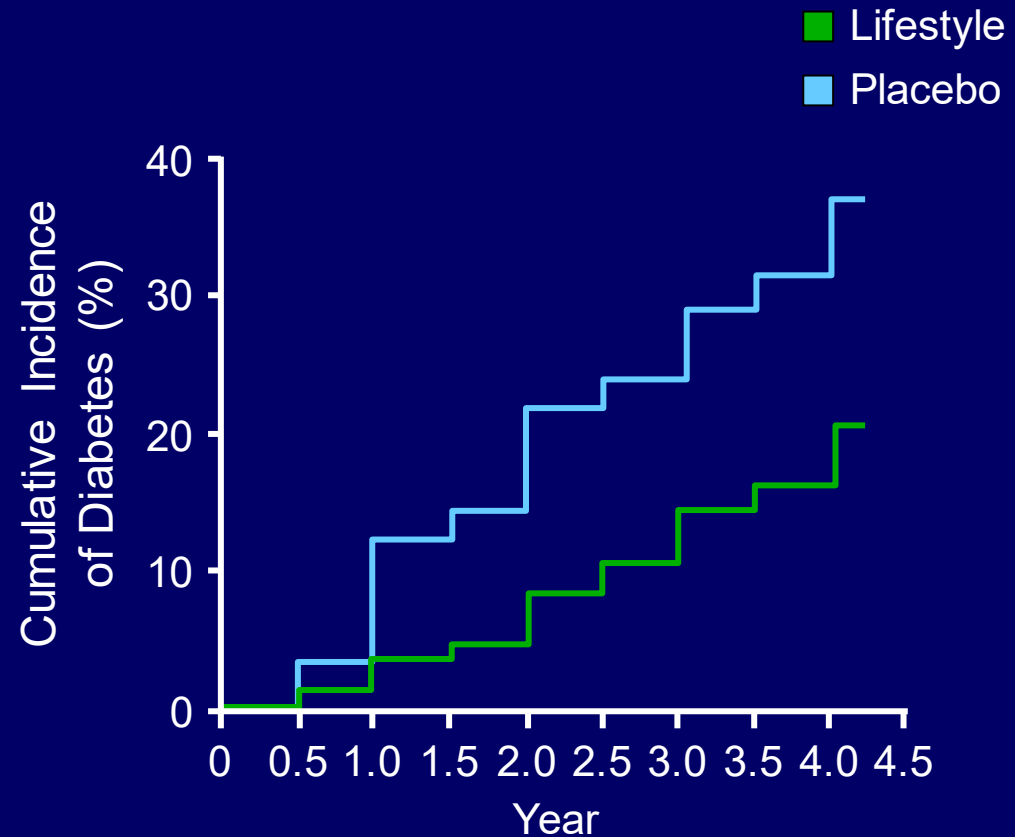
- **Lifestyle Modification**
- First-line Drug
- Combination Therapy

Lifestyle Modifications for Prediabetes

Diabetes Prevention

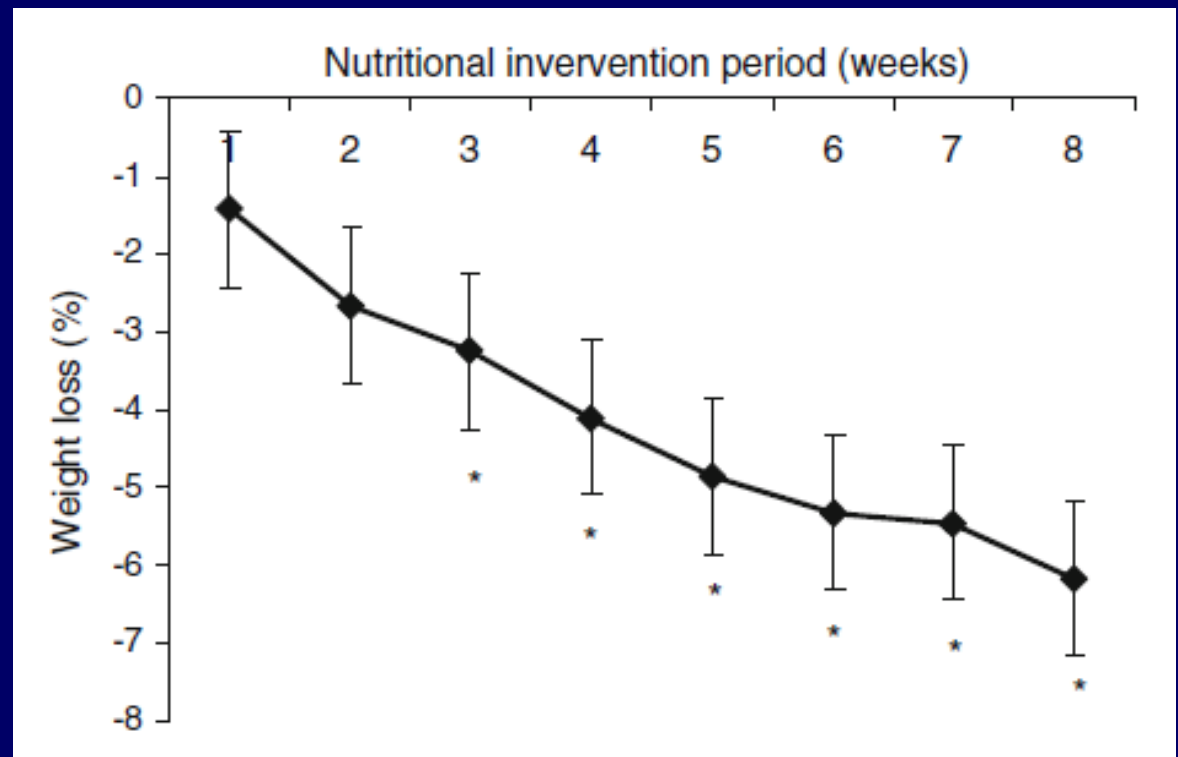
Program:

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

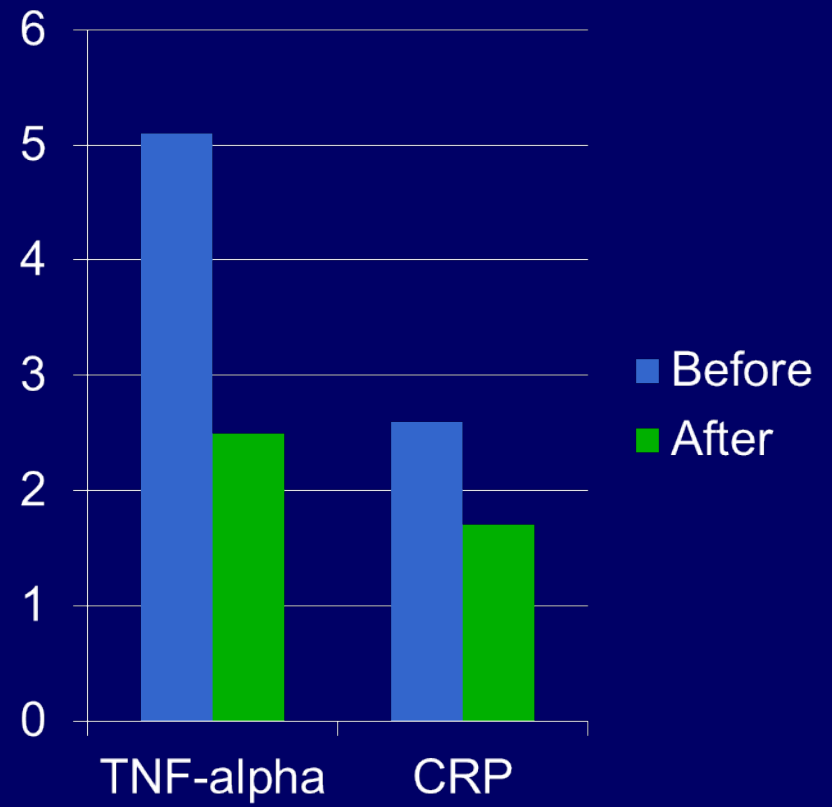


Effect of Cutting 500 cal/day over 8 weeks in Obese Persons

Effect on Weight



Effect on Inflammation





CrossMark

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

Sheri R. Colberg,¹ Ronald J. Sigal,² Jane E. Yardley,³ Michael C. Riddell,⁴ David W. Dunstan,⁵ Paddy C. Dempsey,⁵ Edward S. Horton,⁶ Kristin Castorino,⁷ and Deborah F. Tate⁸

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

**BEWARE
OF THE**



CHAIR

After DM is diagnosed, what should be the next steps?

- Lifestyle Modification
- First-line Drug
- Combination Therapy

Metformin: THE First Line Drug



FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)



TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis ≥50%, or LVH)



If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa¹
- TZD²
- DPP-4i if not on GLP-1 RA
- Basal insulin³
- SU⁴

+HF

Particularly HFREF (LVEF <45%)

SGLT2i with proven benefit in this population^{5,6,7}

+CKD

DKD and Albuminuria⁸

PREFERABLY SGLT2i with primary evidence of reducing CKD progression

OR SGLT2i with evidence of reducing CKD progression in CVOTs^{9,10}

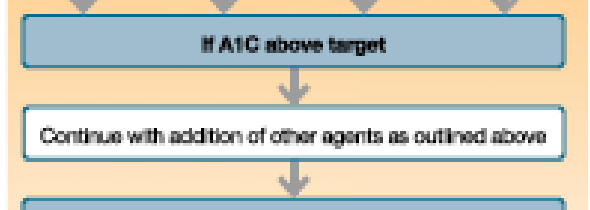
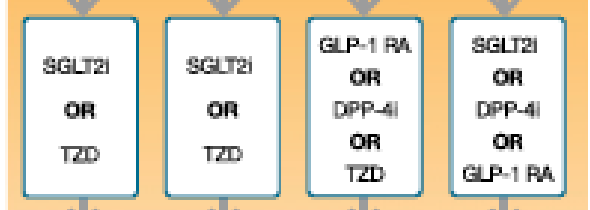
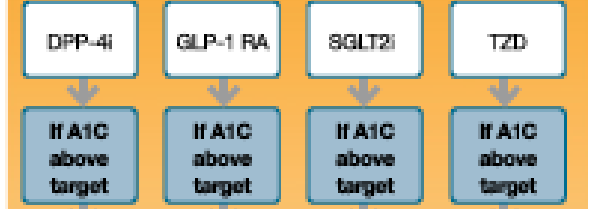
OR GLP-1 RA with proven CVD benefit¹¹ if SGLT2i not tolerated or contraindicated

For patients with T2D and CKD⁸ (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events

NO

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

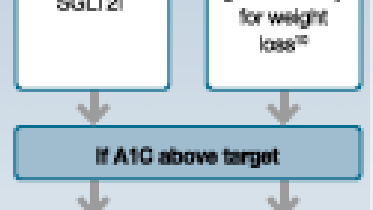
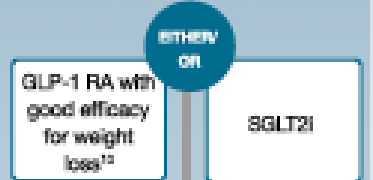
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA



Consider the addition of SU⁴ OR basal insulin³:

- Choose later generation SU with lower risk of hypoglycemia.
- Consider basal insulin with lower risk of hypoglycemia³

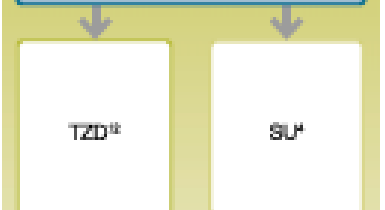
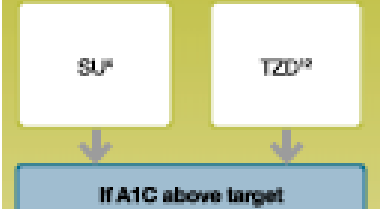
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



PREFERABLY

DPP-4i (if not on GLP-1 RA)

COST IS A MAJOR ISSUE^{1,13}



Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

† Proven benefit means it has label indication of

Metformin: Pros and Cons

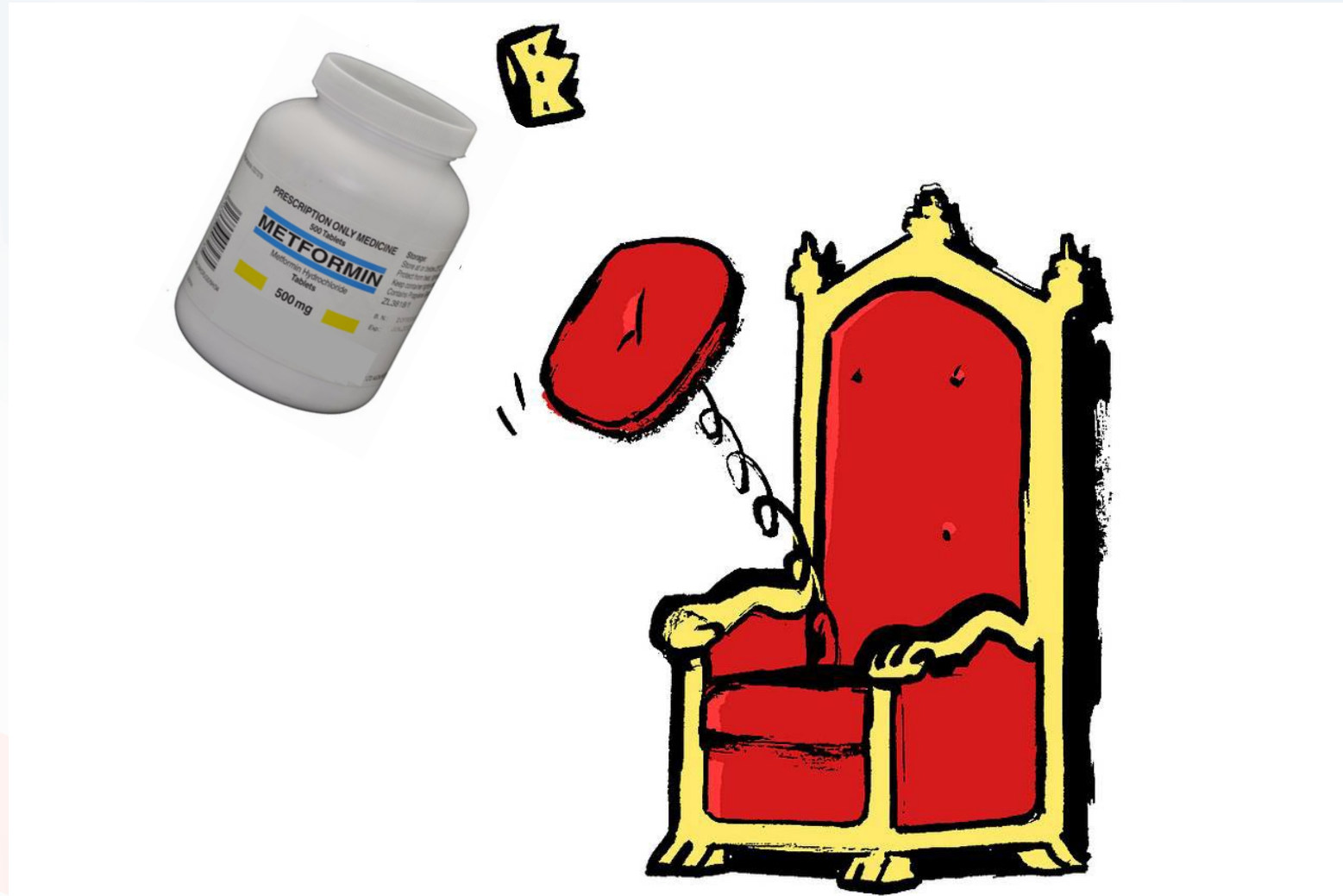
Pros

- ↓ A1c ~1%
- Long Track Record
- No Hypoglycemia
- No Weight Gain
- CVD benefit
- Low Cost (NADAC \$3/month)

Cons

- GI side effects
- Lactic Acidosis (rare)
- Contraindications:
 - CKD (OK eGFR > 30 cc/min/1.73 m²)
 - Hypoxia
 - Decompensated Liver Disease
 - Severe CHF
 - Alcohol Abuse
 - Past H/O Lactic Acidosis
- Interaction with DTG

New for 2023! Metformin dethroned!

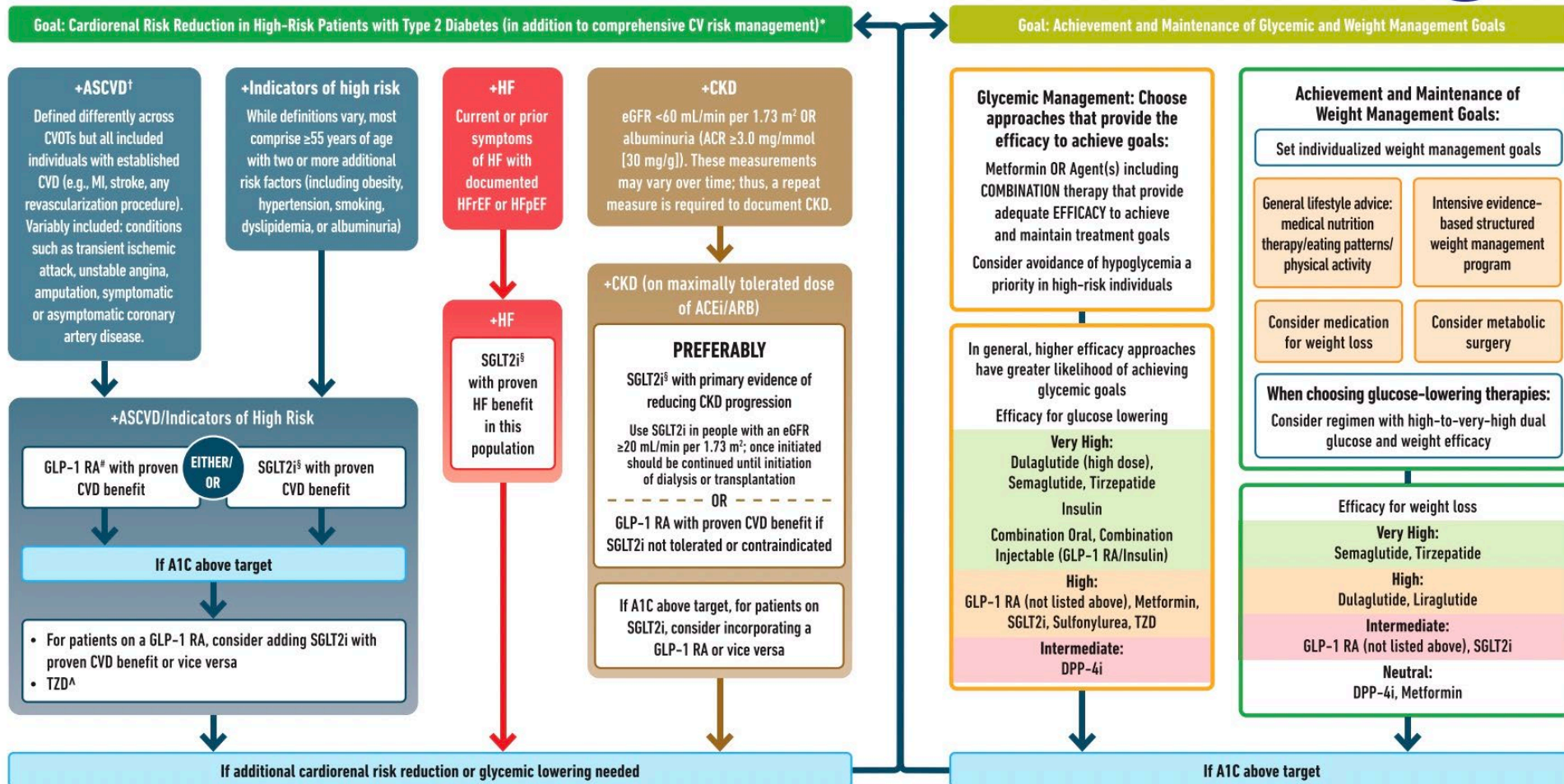


What's first line therapy for DM?

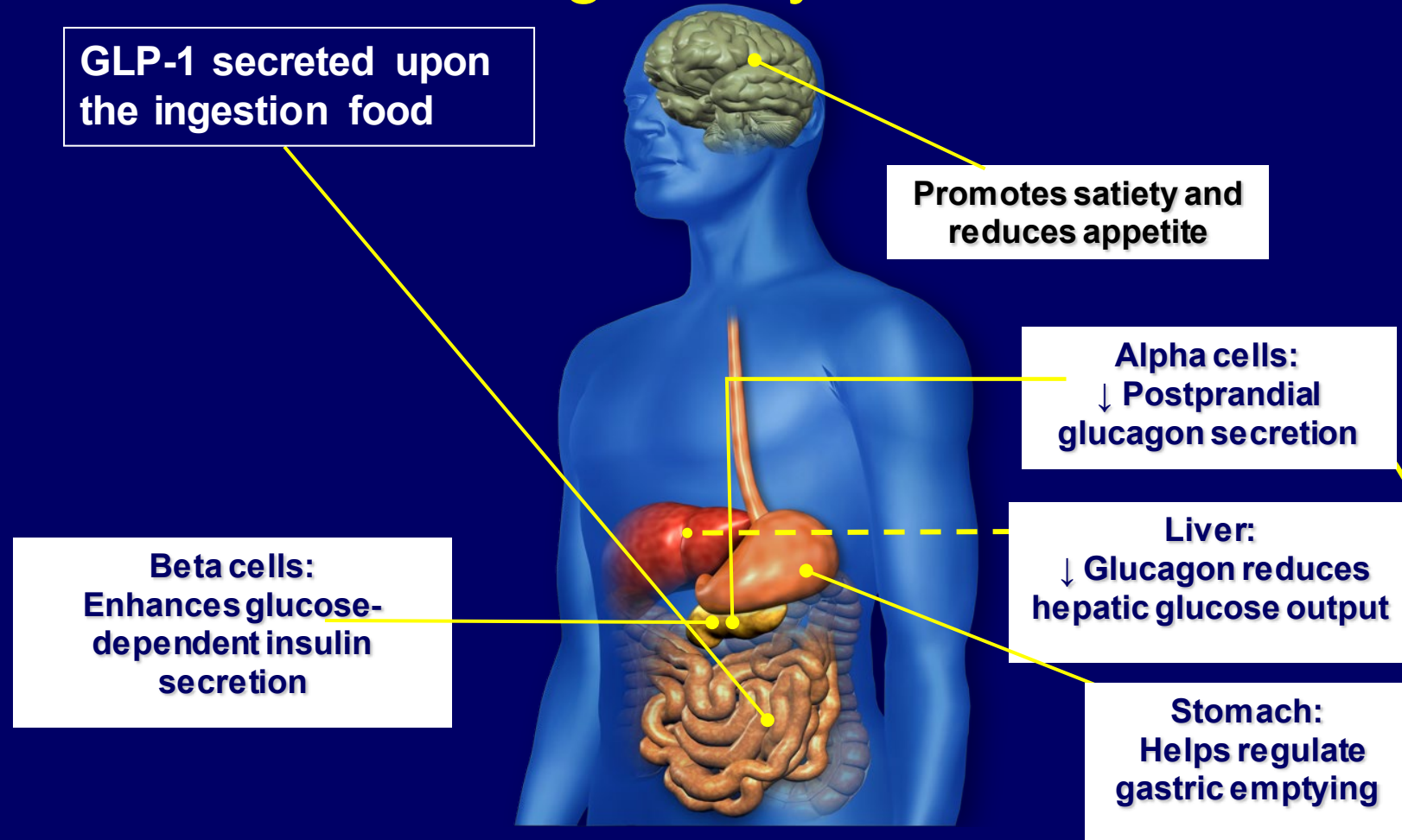
It depends...

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



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.

GLP1 Receptor Agonists: Pros and Cons

Pros

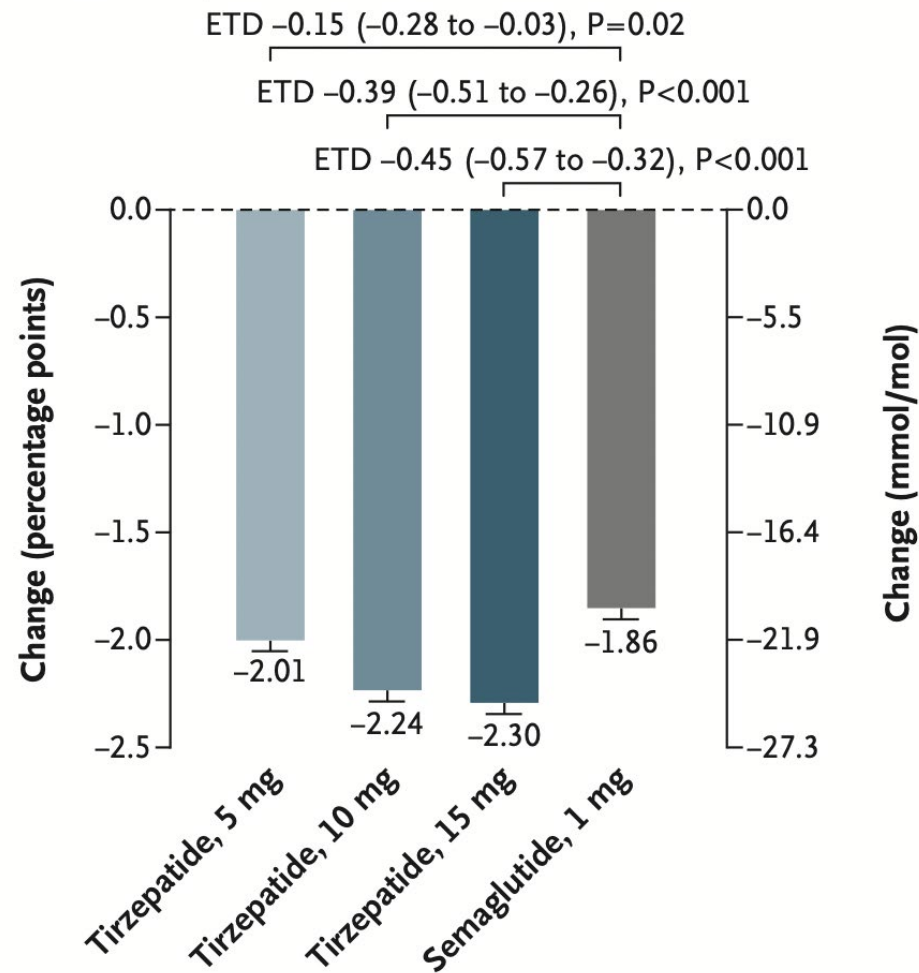
- ↓ A1c ~1.5%
- No Hypoglycemia
- CVD benefit
- Weight Loss
- ↓ Liver Fat
- Weekly Administration

Cons

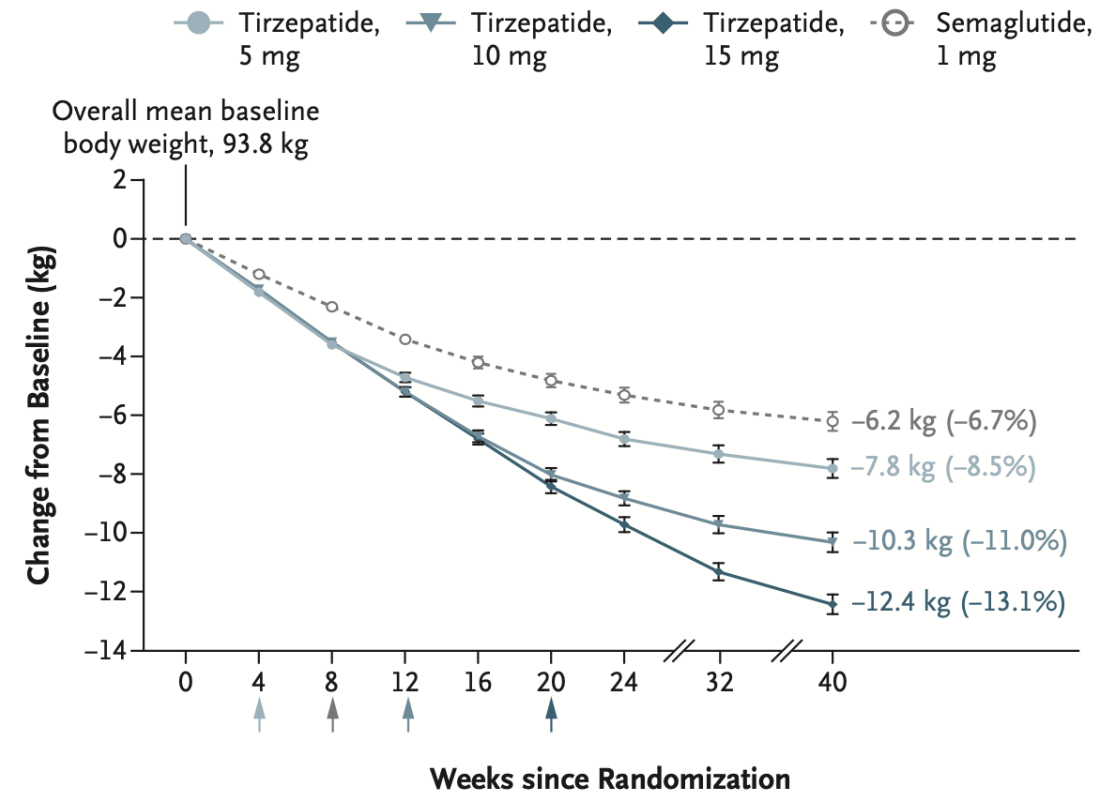
- Nausea
- ? Pancreatitis
- Cost

The Next Big Thing: Dual Incretin Agonist Tirzepatide

A Change in Glycated Hemoglobin Levels from Baseline



B Change in Body Weight from Wk 0 to Wk 40



Sodium Glucose Co-transporter 2 Inhibitors: Pros and Cons

Pros

- No hypoglycemia
- Weight Loss
- Lowers BP
- Preserves kidney function
- Decreases heart failure risk

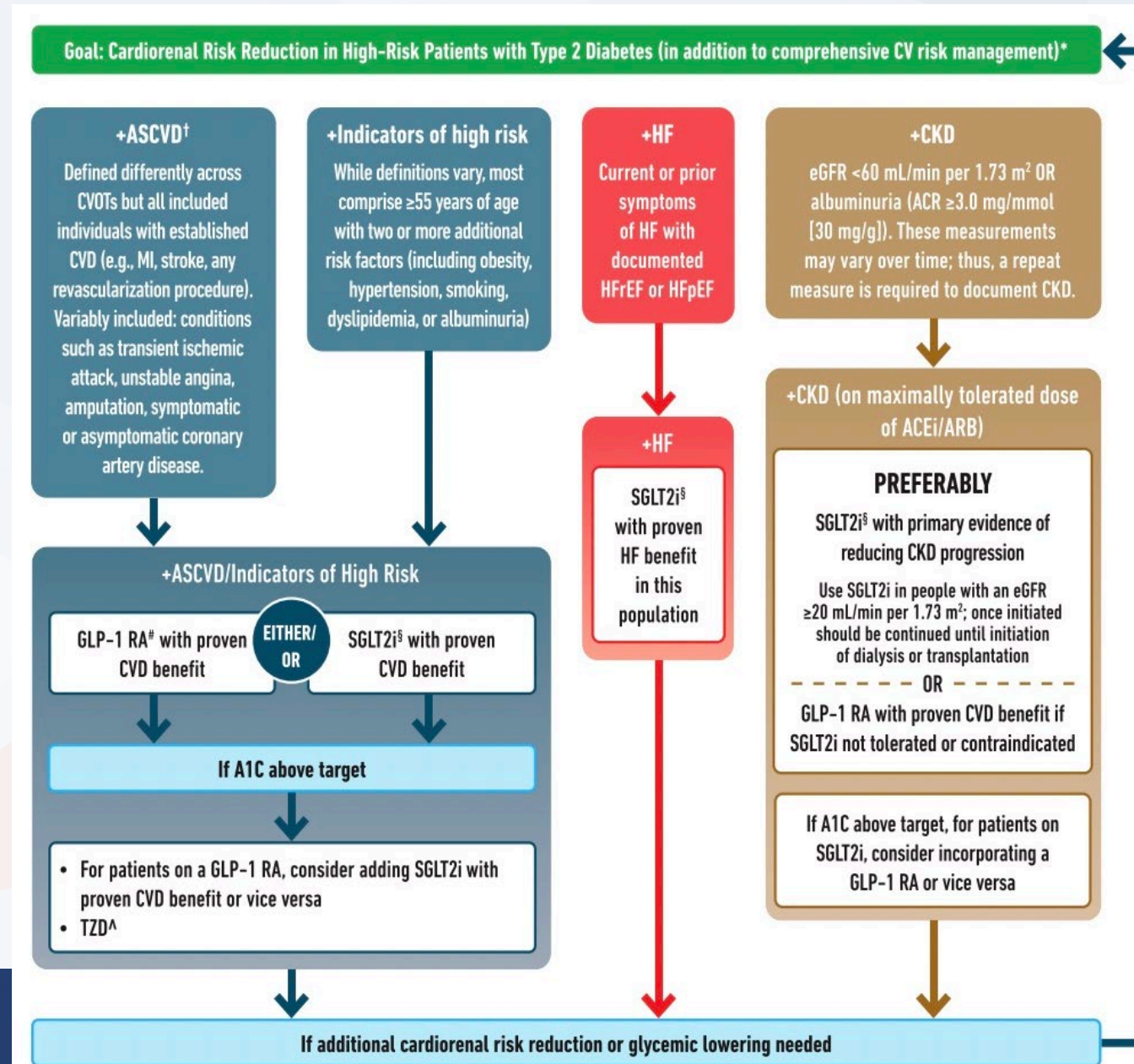
Cons

- ↓ A1c ~0.5-1%
- ↑ urinary tract infections/candidiasis
- Polyuria/dehydration
- ↑ DKA risk
- Cost

What's first line therapy for DM?

It depends....

- CVD → GLP-1 RA
- HF → SGLT2i
- CKD → SGLT2i

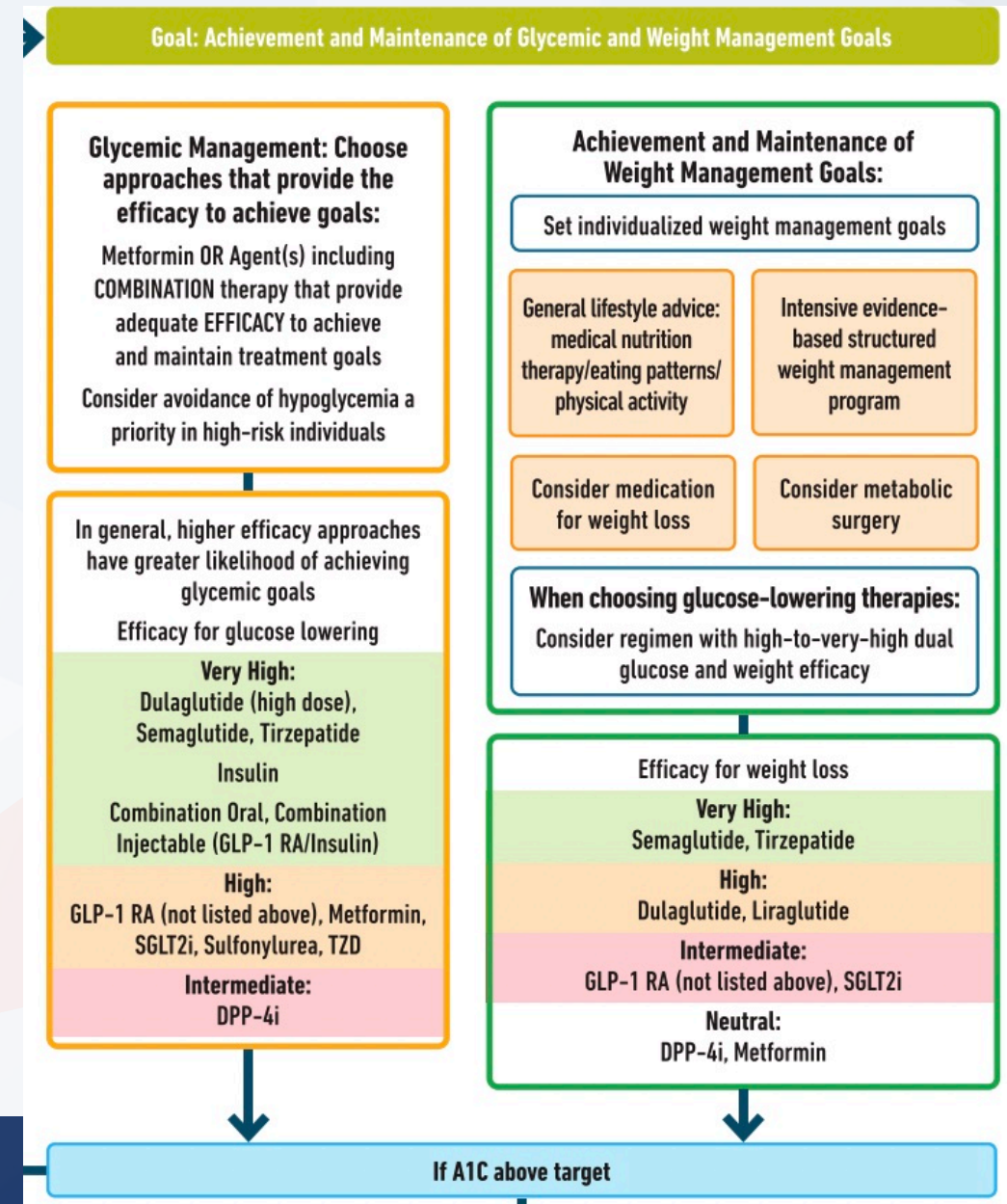


What's first line therapy for DM?

It depends....

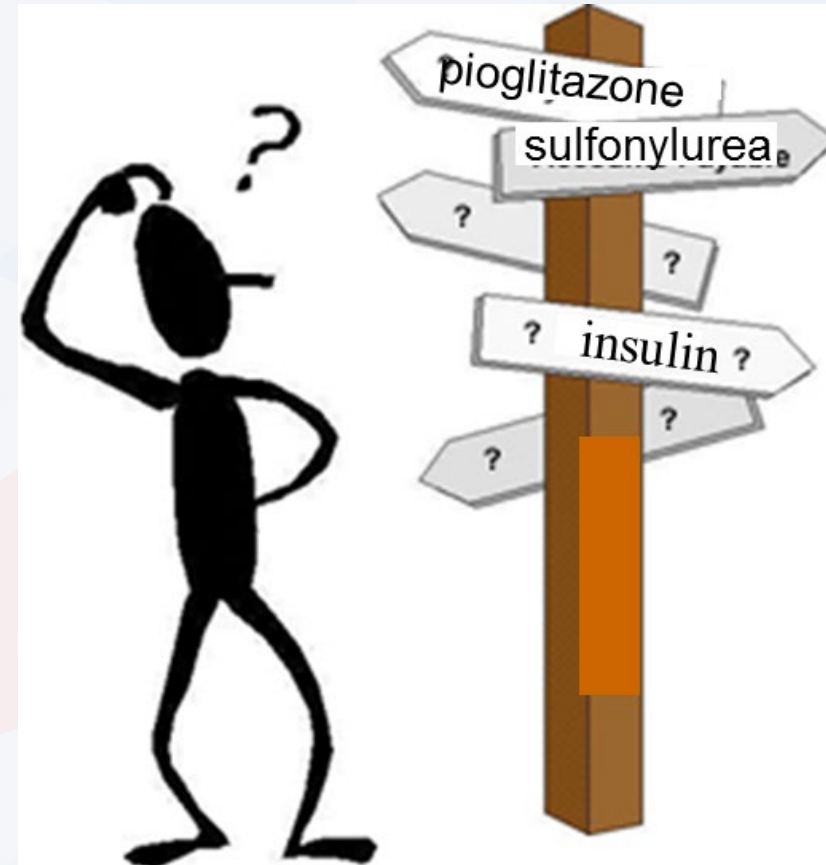
Additional Considerations:

- Glucose Lowering
- Weight Effects
- Avoidance of Hypoglycemia



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
- DPP-IV Inhibitors

Sulfonylureas: Pros and Cons

Pros

- ↓ A1c ~1%
- Long Track Record
- ↓ Microvascular Events
- Low Cost

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 lipoatrophy (~200-500 g)
- Cost

Cons

- Weight Gain
- Fluid Retention/CHF
- Macular Edema
- Osteoporosis/Fracture
- Bladder Cancer

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
- Cost

Insulin: Pros and Cons

Pros

- ↓ A1c: Unlimited
- ↓ Microvascular events

Cons

- Hypoglycemia
- Weight Gain
- Injectable
- Cost

Starting Insulin in Type 2 DM

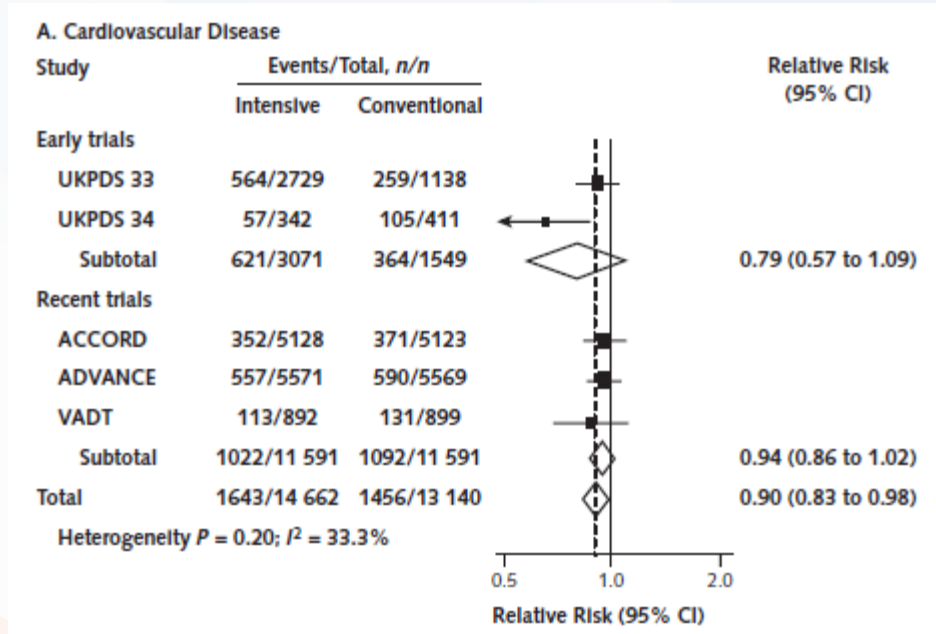
- Start with bedtime glargine, detemir, or NPH (10 units, increase by 2-3 units q 3 days until fasting is < 120 mg/dl)
- Add prandial insulin (10% of basal dose before largest meal), or switch to 70/30 bid if not at goal.
- Recommended as first line if A1c $\geq 10\%$, severe liver disease/kidney disease,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



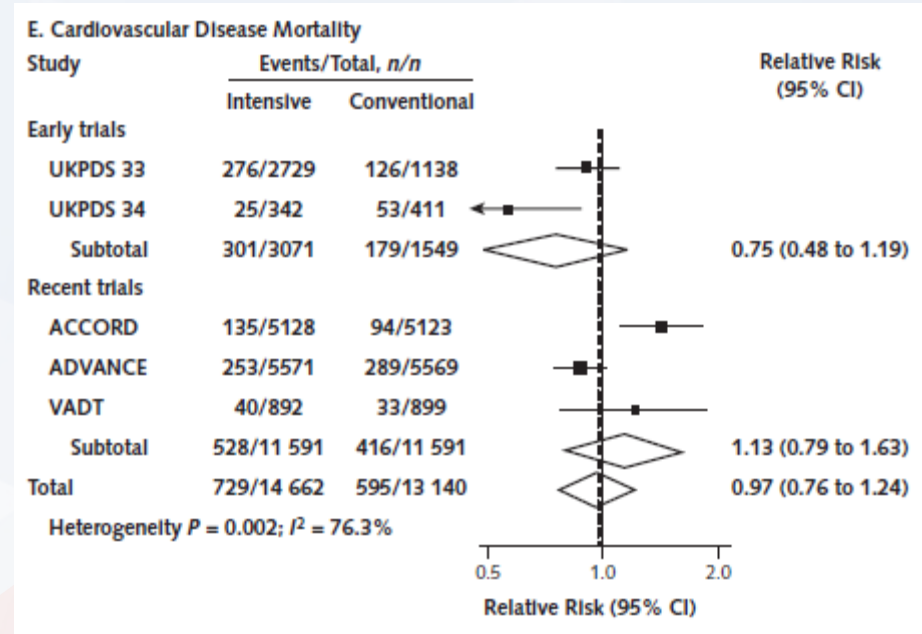
What should be the glycemic target?

HbA1c < 7%

Meta-Analysis of Glycemic Control and CVD in Diabetes



10% Risk Reduction for CVD



No Benefit on CVD Mortality

2-fold Increase Risk of Severe Hypoglycemia with Intensive Control

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, Co-morbidities

Continuous Glucose Monitoring



AGP Report

February 4, 2022 - February 17, 2022 (14 Days)

GLUCOSE STATISTICS AND TARGETS

February 4, 2022 - February 17, 2022 **14 Days**

% Time CGM is Active 82%

Ranges And Targets For		Type 1 or Type 2 Diabetes
Glucose Ranges		Targets % of Readings (Time/Day)
Target Range 70-180 mg/dL		Greater than 70% (16h 48min)
Below 70 mg/dL		Less than 4% (58min)
Below 54 mg/dL		Less than 1% (14min)
Above 180 mg/dL		Less than 25% (6h)
Above 250 mg/dL		Less than 5% (1h 12min)

Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.

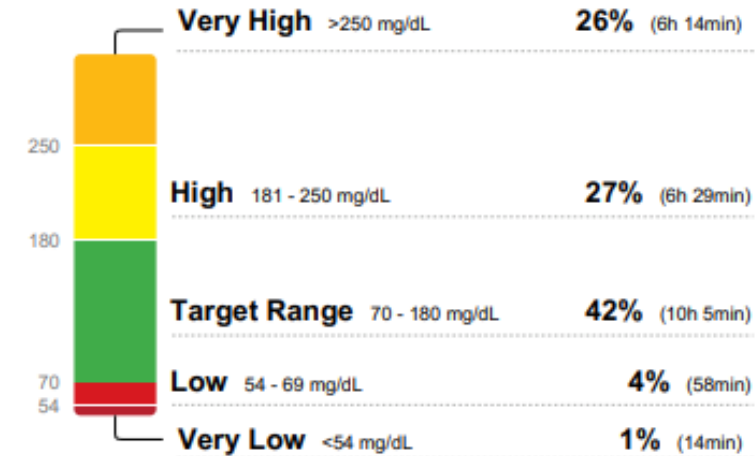
Average Glucose 192 mg/dL

Glucose Management Indicator (GMI) 7.9%

Glucose Variability 46.1%

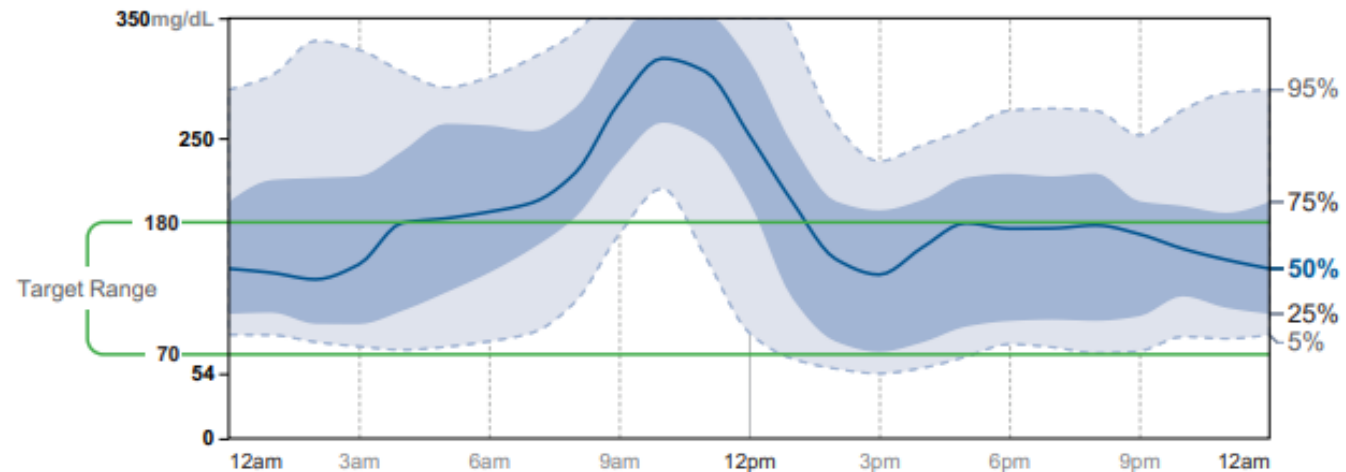
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES



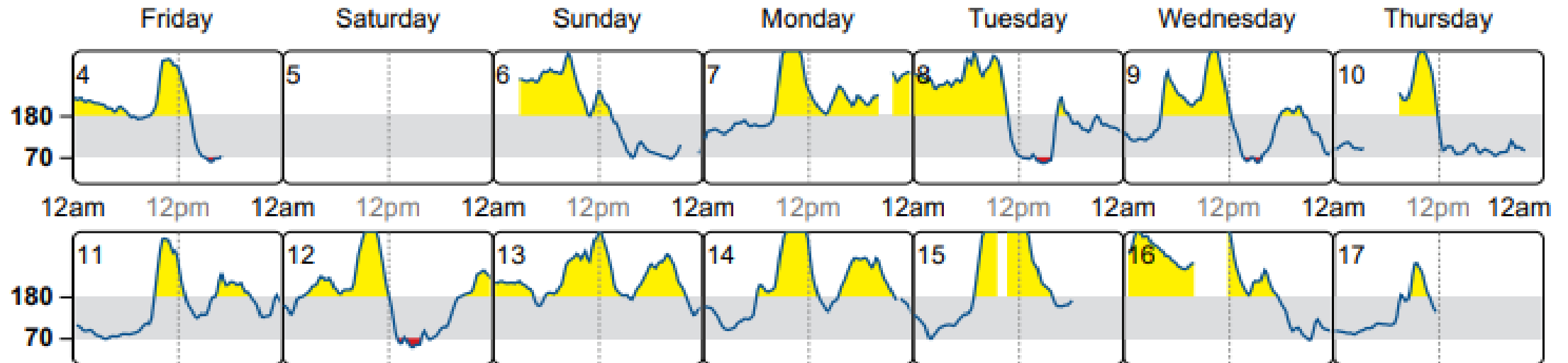
AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



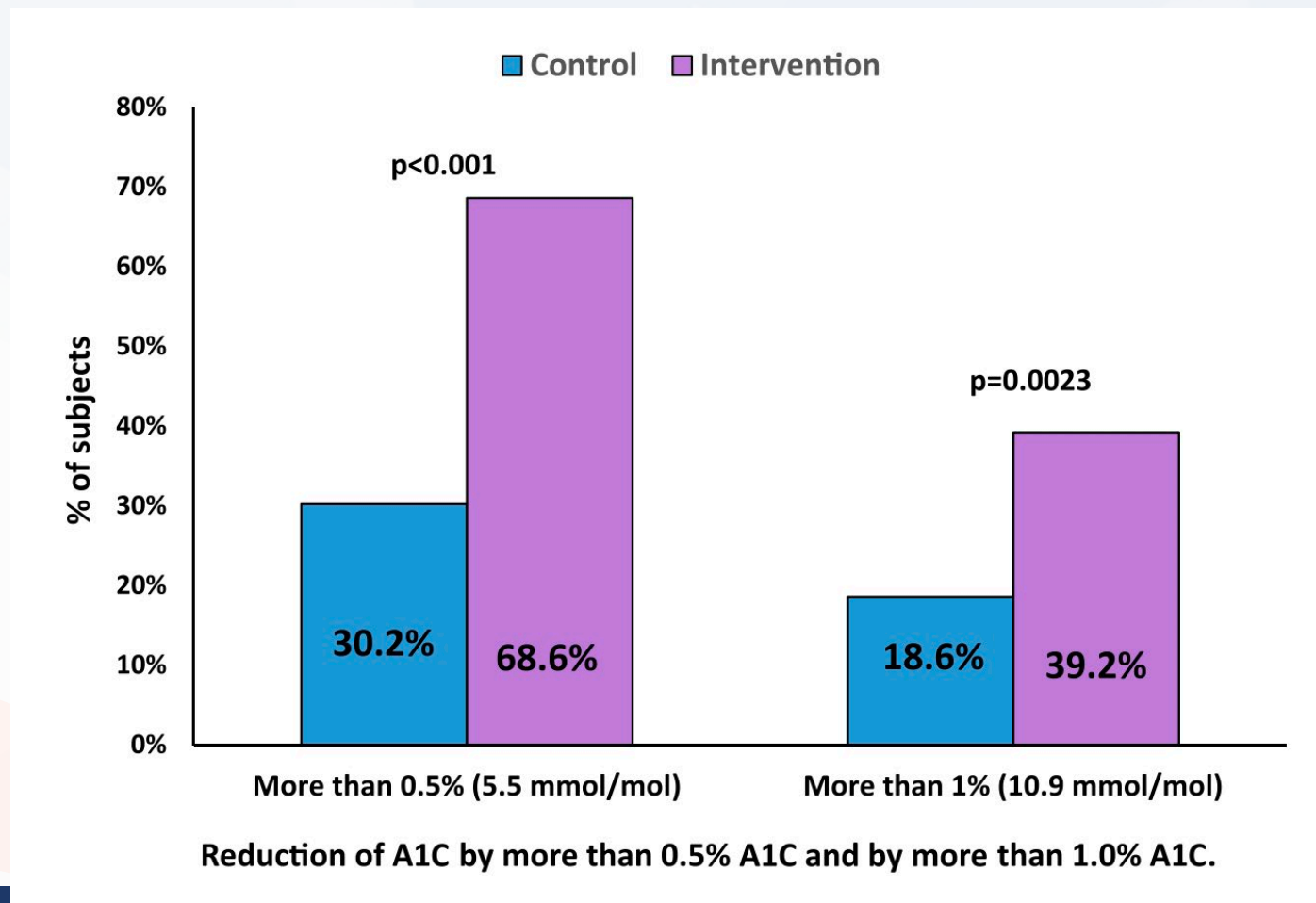
DAILY GLUCOSE PROFILES

Each daily profile represents a midnight to midnight period with the date displayed in the upper left corner.



Source: Battelino, Tadej, et al. "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range." *Diabetes Care*, American Diabetes Association, 7 June 2019, <https://doi.org/10.2337/dci19-0028>.

Effect of Libre System on A1c over 10 Weeks in People with Type 2 DM on MDI



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: Anti-platelet therapy

B: Blood pressure

C: Cholesterol

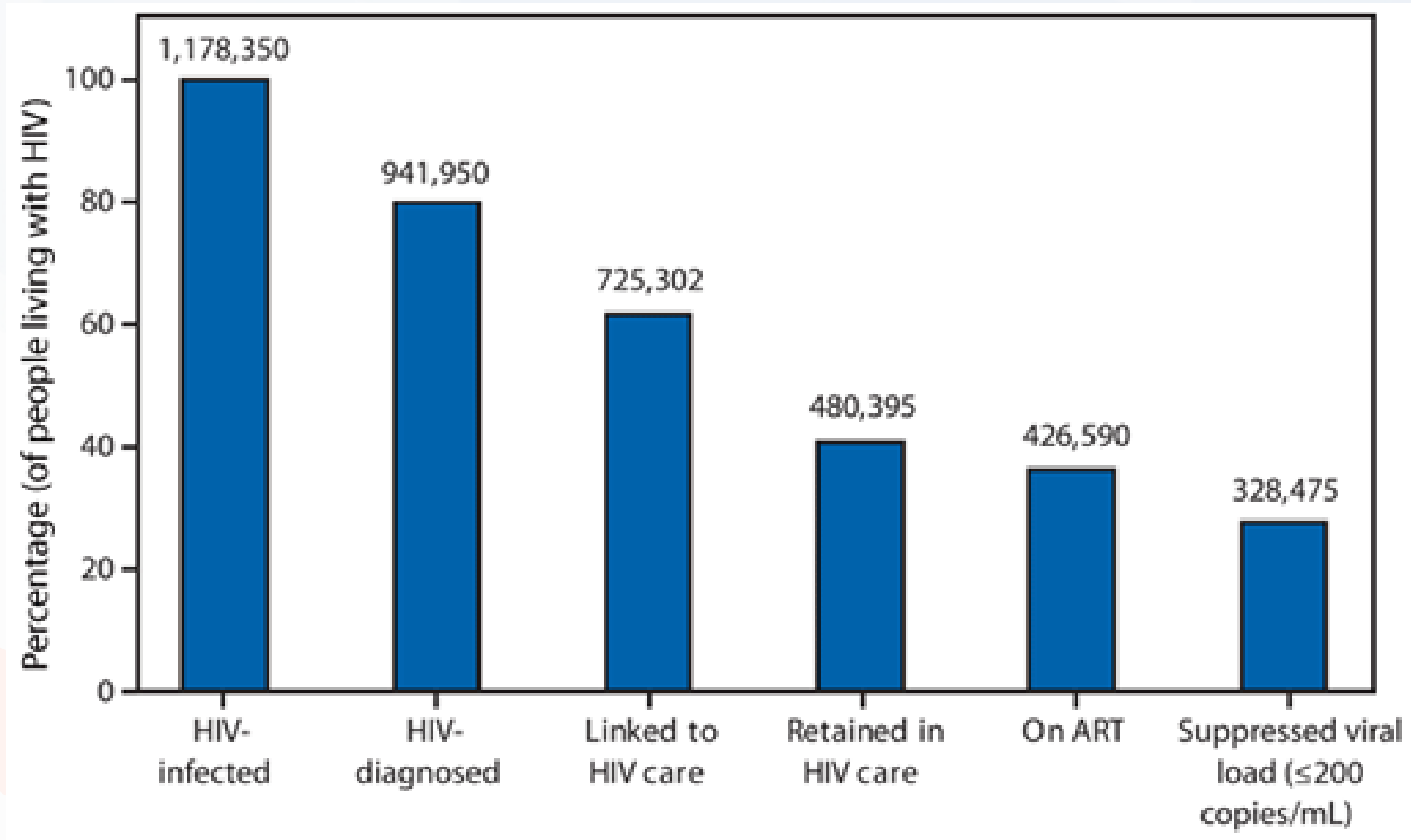
D: Diabetes/Glucose Management

S: Smoking Cessation

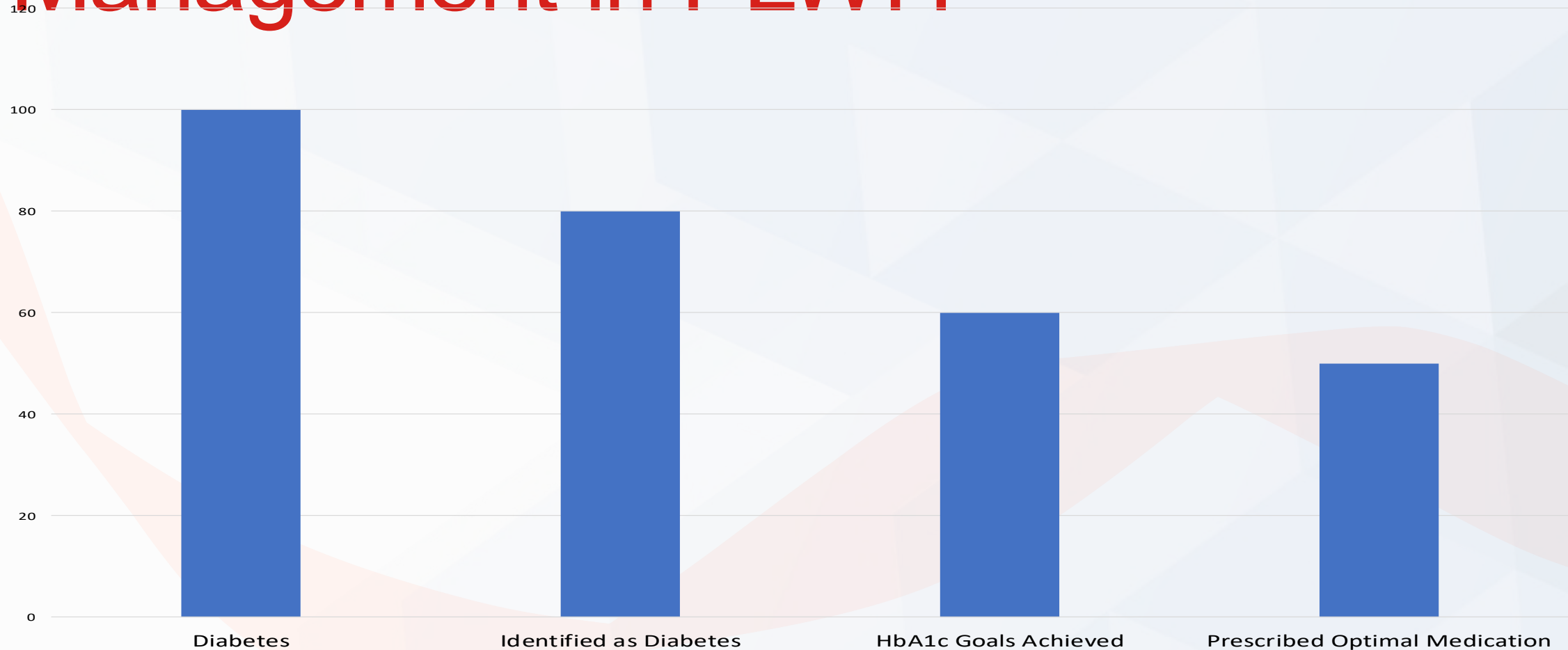
Conclusions

- Lifestyle changes are critical : 5-10% Wt loss!
- Use GLP1RA in those at risk for ASCVD
- Use SGLT2i in those with heart failure or CKD
- Use GLP1RA or dual agonists for weight loss
- Decisions re: 2nd and 3rd drugs should be individualized.
- A1c goal < 7% in most, but should be individualized
- Multiprong approach to prevent complications

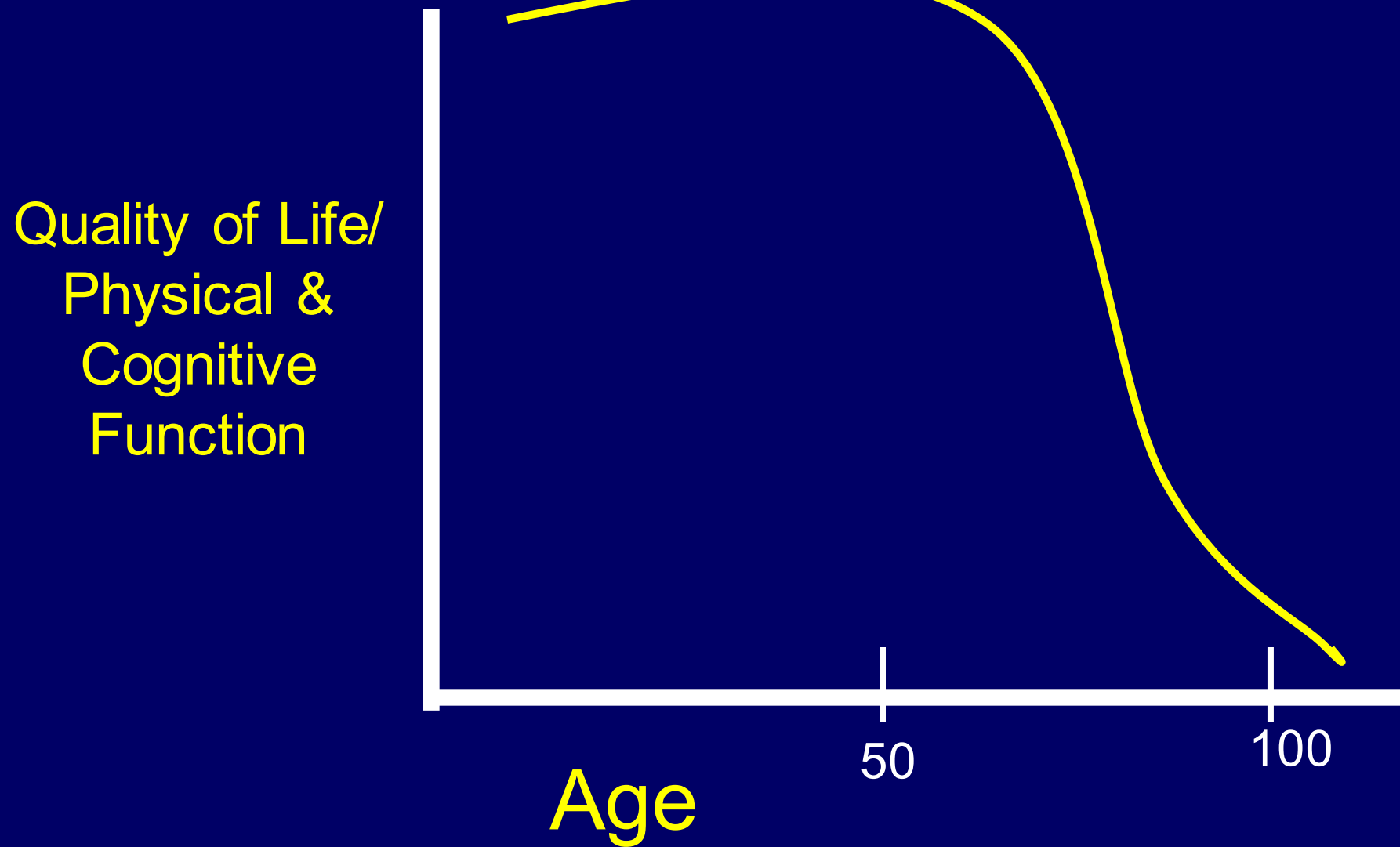
HIV Treatment Cascade: Identifying and Closing the Gaps in Care



Closing the Gaps for Diabetes Management in PLWH



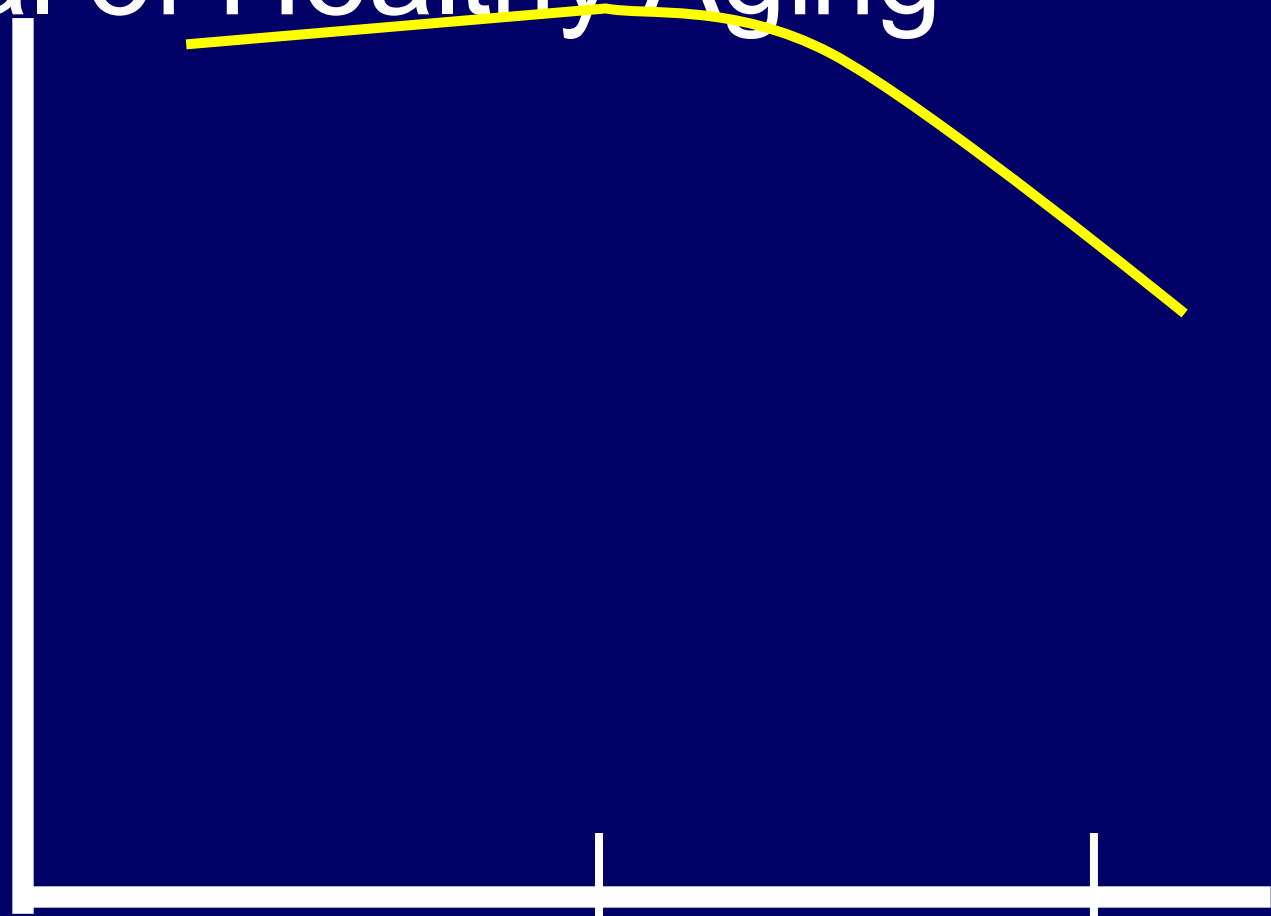
Physical & cognitive function generally declines over time



Bending the Curve Upwards is the Essential

Goal of Healthy Aging

Quality of Life/
Physical &
Cognitive
Function



Age

50

100

Thank you for your attention!

Please put any questions or comments in
the chat

Further questions? tbrown27@jhmi.edu