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Preventing Diabetes: From Theory to Reality

Vanita R. Aroda, MD

Director, Diabetes Clinical Research

Brigham and Women's Hospital, Boston, MA

Faculty, Harvard Medical School

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Disclosures

Consultant: Adocia, Astra Zeneca, BD, Novo Nordisk, Sanofi, Zafgen

Employee: Merck Research Laboratories (Spouse)

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Outline: Key Questions, Research Evidence, Clinical Guidance

1. What is the scope and potential impact of diabetes prevention?

2. Who should we screen (and therefore potentially intervene on)?

3. To treat or not to treat?

4. What does lifestyle intervention look like?

5. Is there evidence for pharmacotherapy?

6. Are there any clinically relevant targets that may guide treatment?

7. From the individual to society: Are there other areas to consider?

8. At the Patient Level: Conversation A vs Conversation B

A SNAPSHOT DIABETES IN THE UNITED STATES

PREDIABETES

9 OUT OF 10 don't know they have prediabetes

2 *out of* 5

2 out of every 5 Americans are expected to develop type 2 diabetes in their lifetime.

CDC

COST

$245 BILLION Total medical costs and lost work and wages for people with diagnosed diabetes

Risk of death for adults with diabetes is 

50% HIGHER 

than for adults without diabetes

More than 5,000 youth diagnosed each year in 2011 and 2012

People who have diabetes are at higher risk of serious health complications:


BLINDNESS


KIDNEY FAILURE

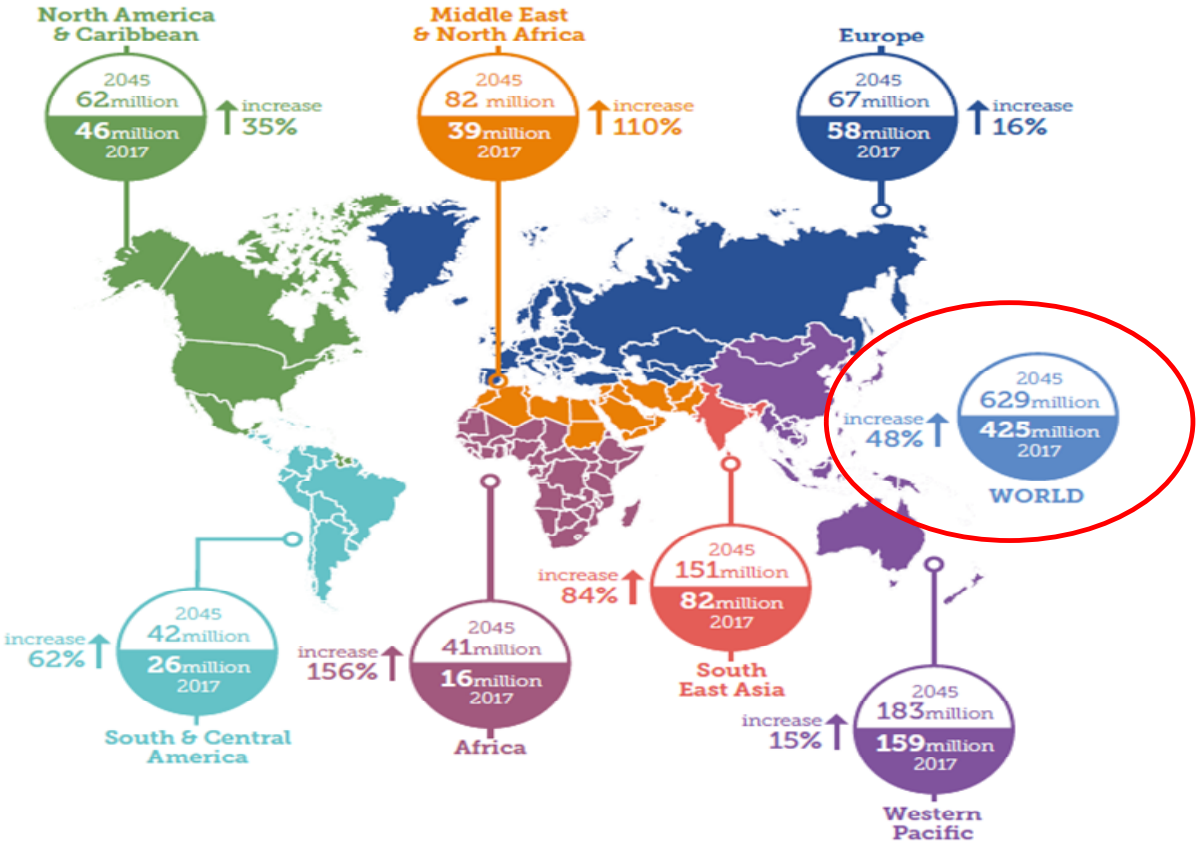

HEART DISEASE


STROKE


LOSS OF TOES, FEET, OR LEGS

https://www.cdc.gov/diabetes/library/socialmedia/infographics.html
Accessed 01 Nov 2019

Diabetes: A global emergency



International Diabetes Federation

Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years)

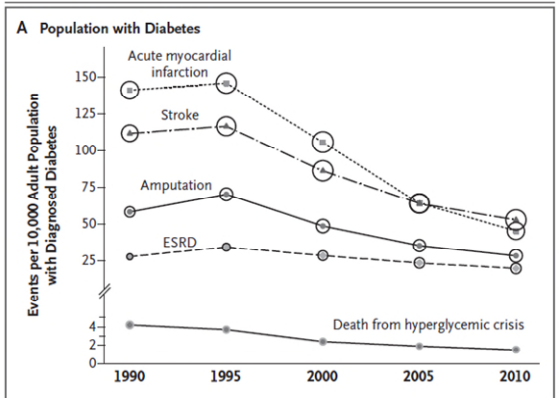
Prevalence of Prediabetes by BMI and Race/Ethnicity in the PORTAL Multisite Cohort (KP, HealthPartners, Denver Health)

- 4,906,238 individuals aged ≥ 20 years, 2012-2013
- Prediabetes prevalence: 33%
- Higher burden of prediabetes (and diabetes) at lower BMIs in racial/ethnic minorities than whites

Table 2—Age-standardized prevalence of diabetes and prediabetes by race/ethnicity and BMI category per 100 PORTAL Network cohort members: 2012–2013

	White	Black	Hispanic	Asian	Hawaiian/Pacific Islander	American Indian/Alaskan Native	All
No.	2,454,388	467,994	1,058,351	620,813	67,190	26,324	4,906,238
Prediabetes prevalence							
Overall	31.0 002830.9–31.1)	32.0 (31.9–32.1)	35.3 (35.2–35.4)	37.1 (37.0–37.2)	36.7 (36.4–37.1)	31.1 (30.6–31.7)	33.4 (33.3–33.5)
BMI*							
Underweight	21.1 (20.6–21.5)	23.9 (22.4–25.4)	23.8 (22.4–25.2)	29.5 (28.8–30.3)	29.5 (25.7–33.4)	17.5 (12.6–22.4)	23.9 (23.5–24.3)
Normal weight	24.4 (24.3–24.5)	26.9 (26.6–27.2)	29.3 (29.0–29.5)	33.0 (32.7–33.2)	33.7 (33.0–34.4)	26.3 (25.2–27.4)	26.8 (26.7–26.9)
Overweight	31.9 (31.8–32.0)	31.2 (31.0–31.5)	35.6 (35.4–35.7)	38.1 (38.0–38.3)	37.5 (36.9–38.2)	31.4 (30.5–32.4)	34.3 (34.2–34.3)
Obese class 1	35.0 (34.9–35.1)	33.3 (33.0–33.6)	37.5 (37.3–37.7)	39.3 (39.0–39.6)	37.1 (36.3–37.9)	32.3 (31.1–33.5)	36.7 (36.6–36.8)
Obese class 2	35.4 (35.2–35.6)	34.0 (33.6–34.4)	36.8 (36.5–37.1)	37.2 (36.6–37.7)	35.1 (33.9–36.4)	33.9 (32.1–35.6)	36.4 (36.3–36.5)
Obese class 3	35.1 (34.8–35.4)	34.8 (34.3–35.3)	35.6 (35.1–36.1)	34.1 (33.1–35.2)	34.9 (33.2–36.7)	34.3 (31.6–37.0)	35.8 (35.5–36.0)
Obese class 4	35.3 (34.5–36.0)	36.8 (35.5–38.2)	33.9 (32.5–35.3)	30.2 (26.4–33.9)	37.7 (32.5–43.0)	34.2 (29.6–38.8)	35.9 (35.3–36.5)
P for trend†	0.016	0.039	0.102	0.896	0.377	0.016	0.039

Zhu Y et al *Diabetes Care* 2019 Sep 19



"The annual numbers of amputations, cases of endstage renal disease, and strokes continue to increase because of the large increase in the number of prevalent cases of diabetes."

What is the potential impact of diabetes prevention?

Table 1. Age-Standardized Rates of Diabetes Complications among U.S. Adults with Diagnosed Diabetes.*

Variable	Year					Change, 1990–2010
	1990	1995	2000	2005	2010	Absolute Change (95% CI)
No. of adults with diagnosed diabetes	6,536,163	7,862,661	11,799,201	16,066,108	20,676,427	
Acute myocardial infarction						
No. of cases	140,122	183,605	191,011	158,616	135,743	−4379
No./10,000 persons (95% CI)	141.1 (125.3 to 156.8)	145.9 (130.9 to 160.9)	105.7 (96.1 to 115.2)	64.2 (57.4 to 70.9)	45.5 (34.6 to 56.4)	−95.6 (−114.6 to −76.6)
Stroke						
No. of cases	127,016	162,895	178,755	171,429	186,719	59,703
No./10,000 persons (95% CI)	111.8 (98.9 to 124.7)	116.6 (104.3 to 128.9)	86.2 (78.8 to 93.7)	64.1 (58.1 to 70.1)	52.9 (41.1 to 64.7)	−58.9 (−76.2 to −41.6)
Amputation						
No. of cases	50,364	76,531	80,658	69,074	73,067	22,703
No./10,000 persons (95% CI)	58.4 (49.3 to 67.4)	70.4 (59.1 to 81.7)	48.7 (41.6 to 55.9)	35.5 (30.9 to 40.1)	28.4 (19.4 to 37.3)	−30.0 (−42.6 to −17.4)
End-stage renal disease						
No. of cases	17,763	29,259	41,477	46,917	50,197	32,434
No./10,000 (95% CI)	27.9 (25.7 to 30.0)	34.5 (31.9 to 37.1)	28.6 (27.6 to 29.7)	23.6 (22.8 to 24.5)	20.0 (19.1 to 20.9)	−7.9 (−10.2 to −5.5)

Gregg EW *et al* NEJM 2014; 370:1514-23.

"While the average adult with diabetes in the USA has a lower risk of CVD than in previous decades, the average adult in the general population has an increased risk of diabetes-related CVD than in previous decades because of the **large increase in diabetes prevalence."**

Harding JL *et al; Diabetologia* 2019 Jan;62(1):3-16

Personal Take-Home #1 (On scope and potential impact)**:**

"The burden of the wide spectrum of complications in those with diabetes will ultimately be influenced by efforts to prevent diabetes."

Harding JL *et al; Diabetologia* 2019 ;62(1):3-16

1. What is the scope and potential impact of diabetes prevention?

2. Who should we screen (and therefore potentially intervene on)?

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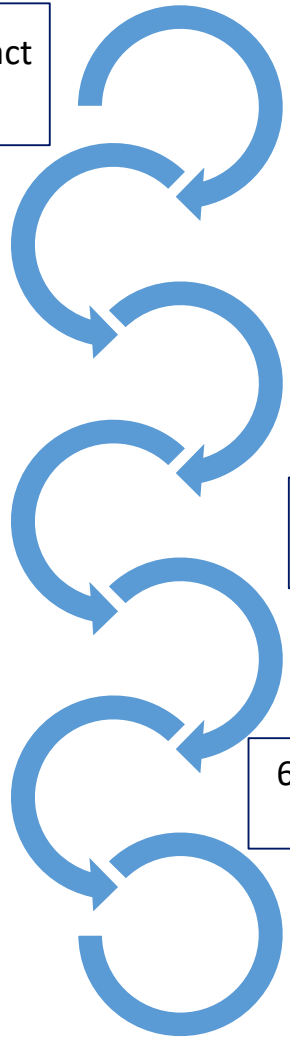
8. At the Patient Level: Conversation A vs Conversation B

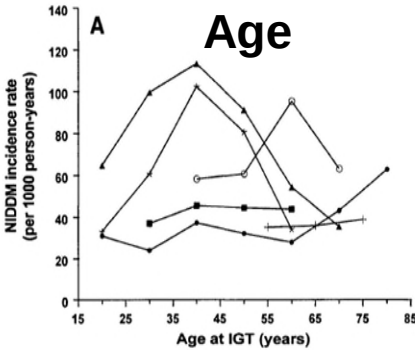


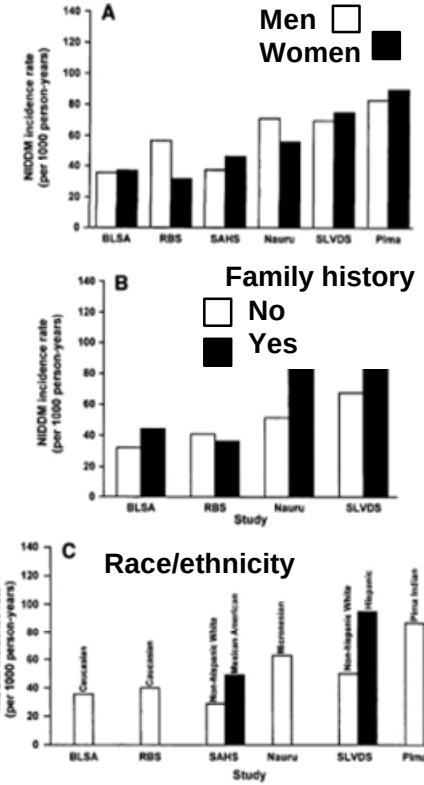
What We Knew About the Risk of Progression from Impaired Glucose Tolerance to Diabetes before the DPP

Diabetes Prevention Program

An Analysis of Six Prospective Studies

- Baltimore Longitudinal Study of Aging (MD)
- Rancho Bernardo Study (CA)
- San Antonio Heart Study (TX)
- Micronesian island of Nauru in Pacific Ocean
- San Luis Valley Diabetes Study (CO)
- Pima Indian Study (Gila River Indian Community, AZ)





Edelstein SL, et al. *Diabetes* 1997; 46: 701-710

Diabetes Prevention Program Eligibility Criteria

- High-risk individuals
  - Impaired Glucose Tolerance: 2 hour post-challenge glucose 140 - 199 mg/dl, and
  - Fasting glucose 95 - 125 mg/dl

    (American Indians < 125 mg/dl)
  - Body mass index ≥ 24 kg/m^2 (Asians ≥ 22 kg/m^2)
- Age ≥ 25 years
- All ethnic groups - goal of 50% from high risk populations

Screening for Prediabetes or Diabetes in Asymptomatic Adults

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

American Diabetes Association Standards of Care 2019

Criteria Defining "Prediabetes"

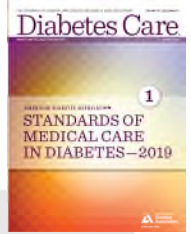


Table 2.5—Criteria defining prediabetes*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

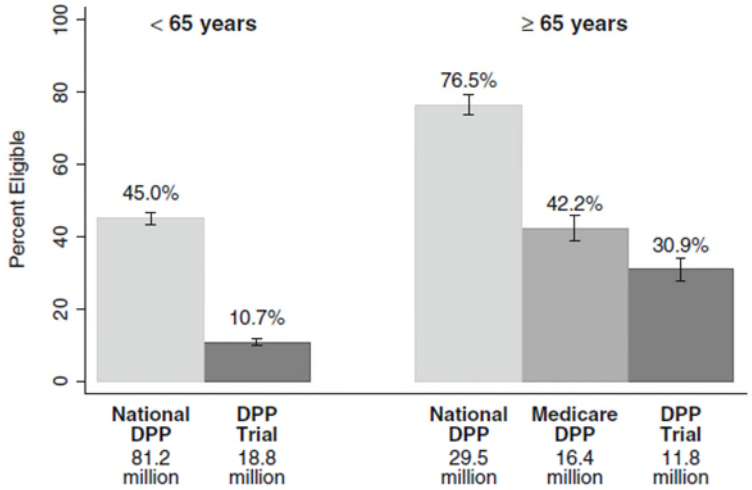
" 'Prediabetes' is the term used for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal... Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease."

American Diabetes Association Standards of Care 2019

"Prediabetes": Are There Problems With This Label? Yes, the Label Creates Further Problems!

Diabetes Care 2016;39:1468–1471 | DOI: 10.2337/dc15-2113

- Risk of progressing to diabetes in the DPP (both Impaired Fasting Glucose and Impaired Glucose Tolerance): ~50% over 10 years
- ADA-defined prediabetes (86 million): 2%/year
- Risk of disease-labeling of many lower-risk people for whom no evidence exists
- [WHO: "Intermediate hyperglycemia"]



	National DPP Eligibility Criteria	Medicare DPP Eligibility Criteria	DPP Trial Eligibility Criteria
Age	≥ 18 years	≥65 years	≥ 25 years
BMI	Overweight or obese	Overweight or obese	Overweight or obese
Criteria	A1c 5.7-6.4% OR FPG 100-125 mg/dl OR 2-h glucose 140-199 mg/dl OR h/o GDM or CDC Risk Score ≥ 9	A1c 5.7-6.4% OR FPG 110-125 mg/dl OR 2-h glucose 140-199 mg/dL	FPG 95-125 mg/dl **AND** 2-h glucose 140-199 mg/dL

Lee AK *et al J Gen Int Med* 2019; 34(8):1400–2

"Prediabetes": Are There Problems With This Label? No, We Need Heightened Awareness of This Condition!

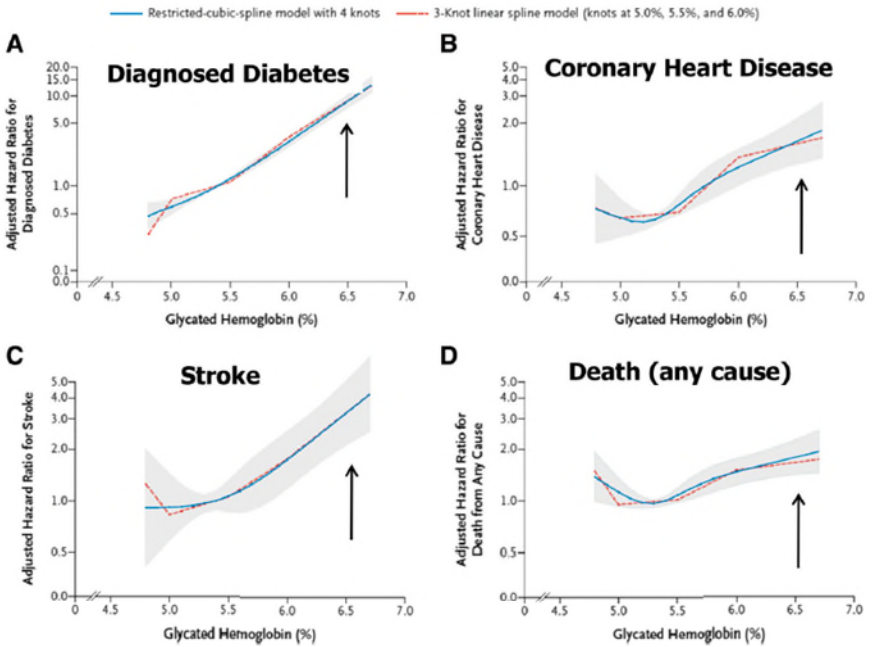
Diabetes Care 2016;39:1472–1477 | DOI: 10.2337/dc16-1143

1. The risk for progression of diabetes is present at the lower cut points suggested for diagnosing prediabetes.

2. There are significant clinical implications for prediabetes for microvascular disease.

3. Prediabetes identifies a cohort for which there needs to be a heightened awareness of cardiovascular disease risk and, therefore, further evaluation.

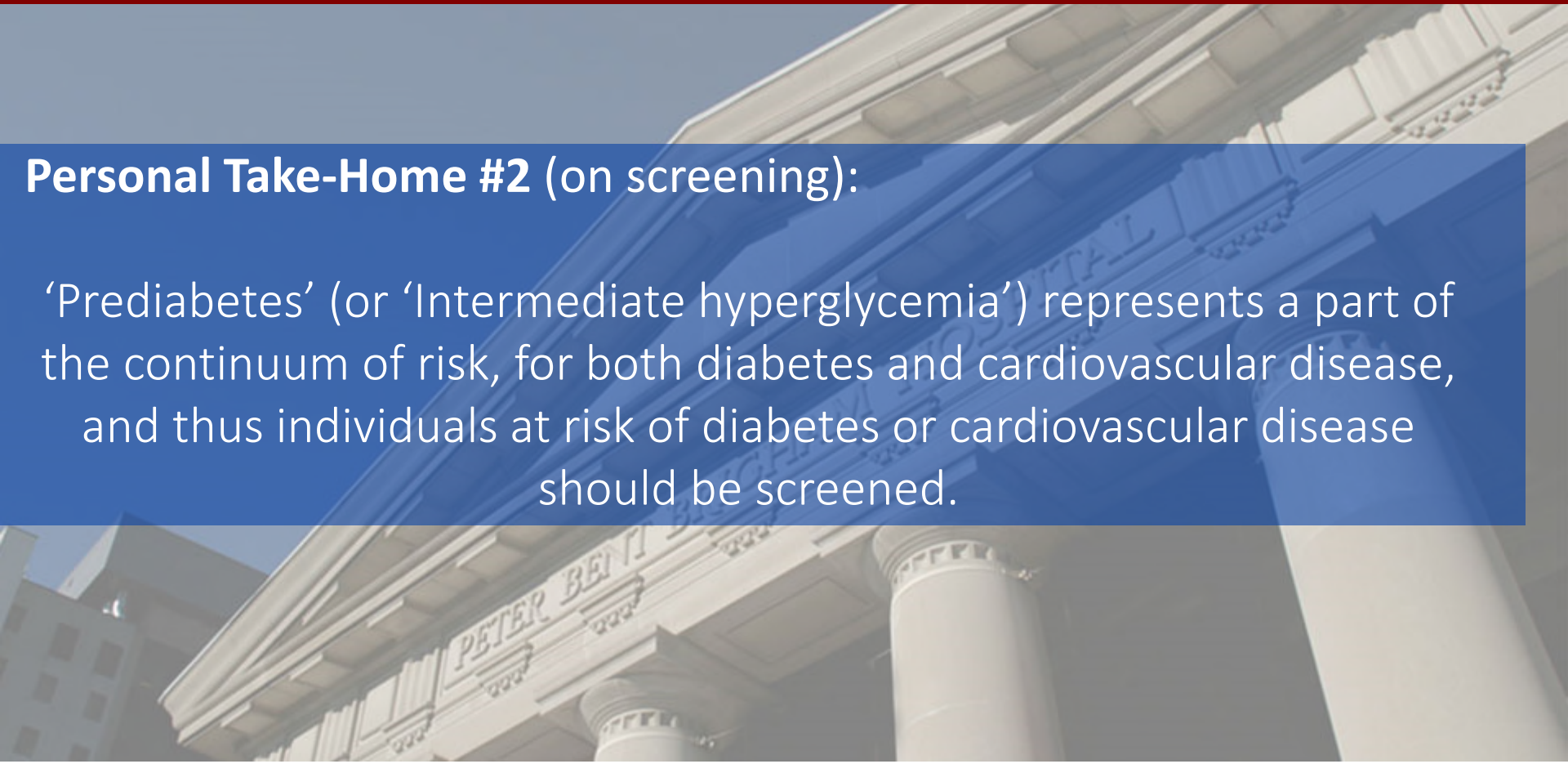
4. Lifestyle interventions to prevent type 2 diabetes are effective among persons at increased risk.



Atherosclerosis Risk in Communities (ARIC) Study: n=11,092

Recommendation

3.7 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease is suggested. **B**



Personal Take-Home #2 (on screening):

'Prediabetes' (or 'Intermediate hyperglycemia') represents a part of the continuum of risk, for both diabetes and cardiovascular disease, and thus individuals at risk of diabetes or cardiovascular disease should be screened.

1. What is the scope and potential impact of diabetes prevention?

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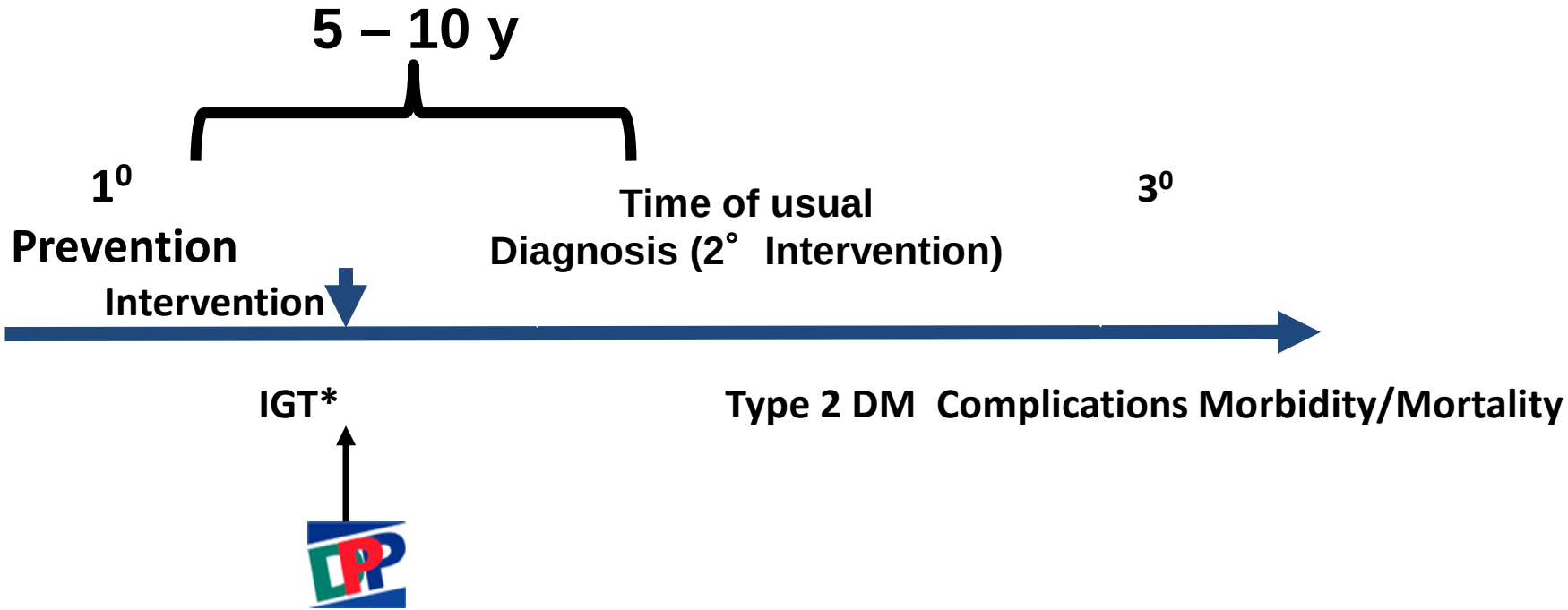
Spectrum of Dysglycemia: Potential for Intervention



*IGT: Impaired Glucose Tolerance

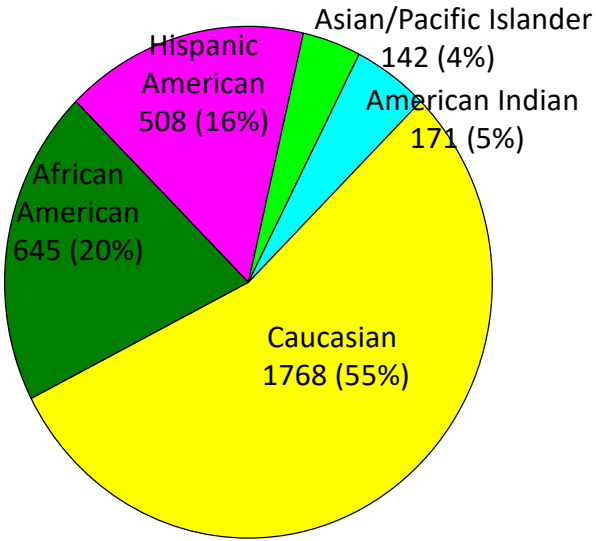
DPP Goals: Primary Objective

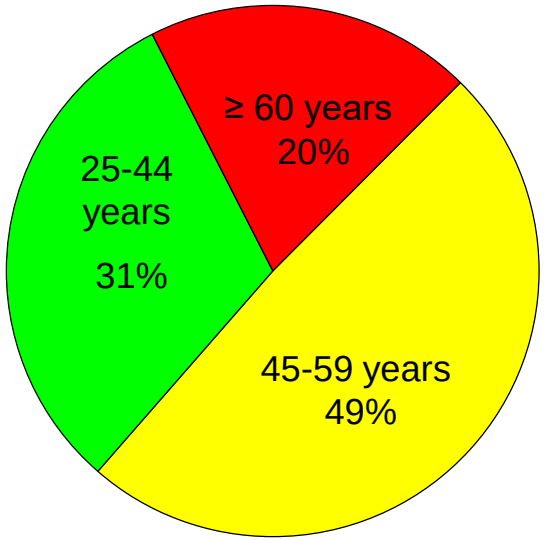
Can we prevent or delay the development of type 2 diabetes in persons at high risk?

(impaired glucose tolerance, elevated fasting glucose levels, and overweight or obese)

Diabetes Prevention Program

DPP Population was heterogeneous, facilitating generalizability and translation of results

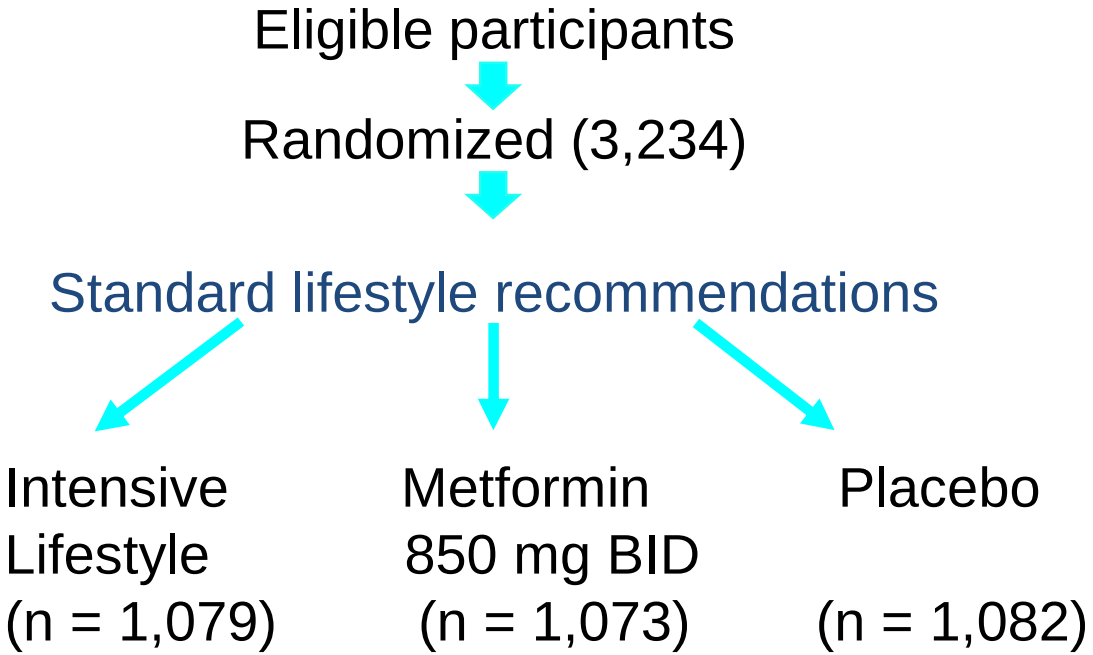




- 68% were women, including 350 women with a history of gestational diabetes
- Mean age: 51 years
- Mean BMI 34 kg/m2
- Mean FPG 107 mg/dl, mean 2-hour postchallenge glucose 165 mg/dl
- Baseline HbA1c 5.9%

The DPP Research Group, *Diabetes Care* 23:1619-29, 2000

DPP: Study Design



Primary Outcome: Development of diabetes based on annual OGTT (fasting and/or 2-hour glucose value) or semiannual FPG

Effects of intensive lifestyle intervention or metformin on diabetes prevention/delay: 1996-2001

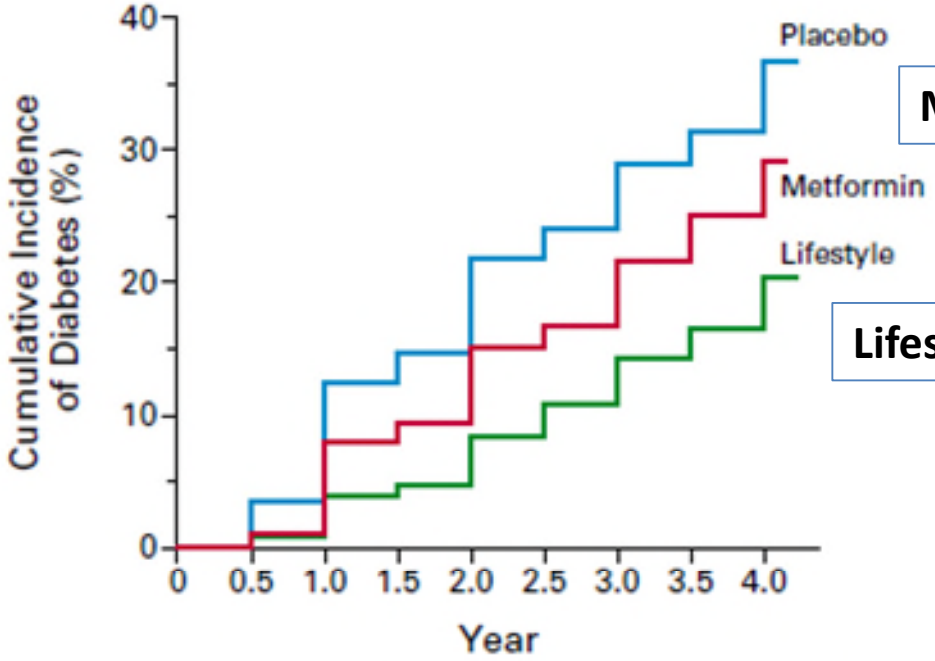


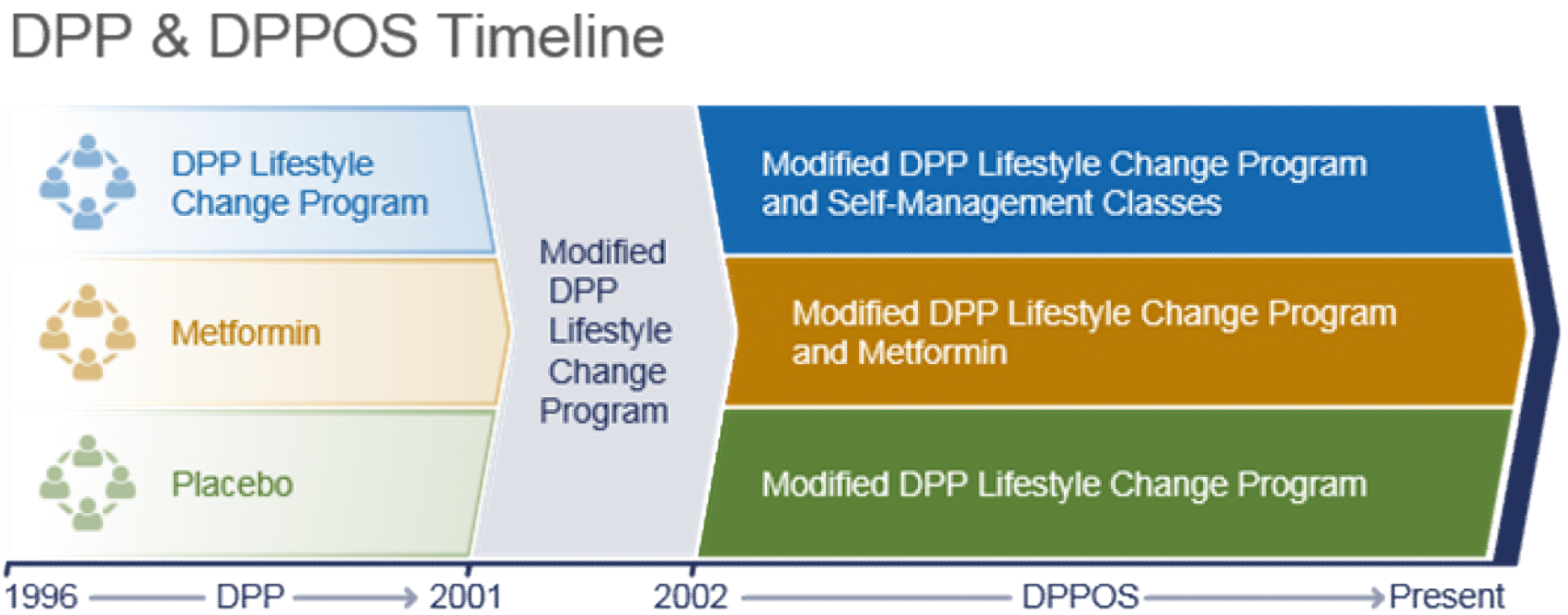
Figure 2. Cumulative Incidence of Diabetes According to Study Group.

Metformin vs placebo: -31%

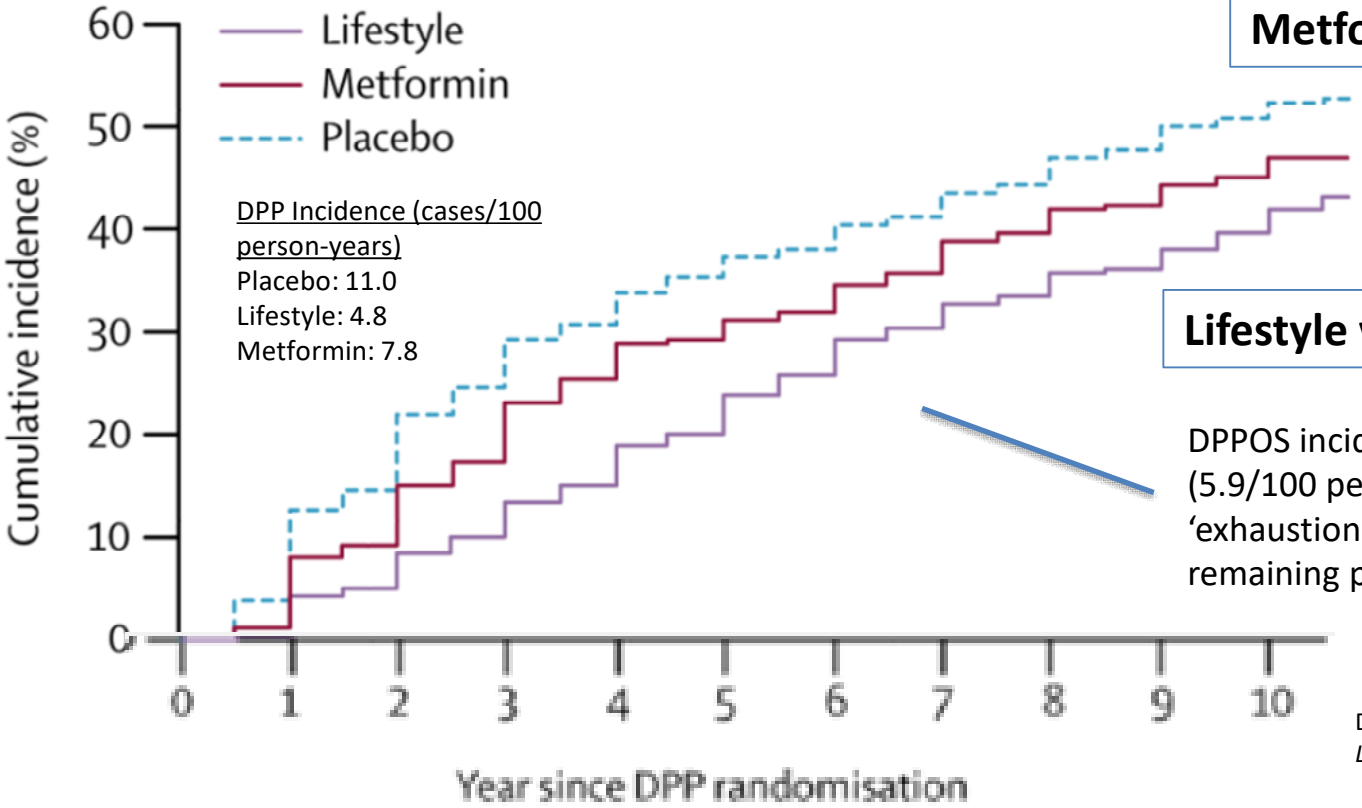
Lifestyle vs placebo: -58%

Diabetes Prevention Program Research Group *NEJM* 2002; 346:393-403

Continued follow up of DPP Cohort (86% eligible) in DPPOS



DPPOS: 10 years post-randomization



DPP Incidence (cases/100 person-years)
Placebo: 11.0
Lifestyle: 4.8
Metformin: 7.8

Metformin vs placebo: -18%

Lifestyle vs placebo: -34%

DPPOS incidence rates converged during (5.9/100 person-years), likely related to 'exhaustion of susceptibles' (lower risk of remaining participants)

Diabetes Prevention Program Research Group; *Lancet* 2009; 374(9702): 1677–1686.

Hamman RF et al; Diabetes 2015; 64:989-998

10-years: Diabetes Prevention is Cost-Effective

Compared to the placebo intervention:

- The lifestyle intervention cost ~$1,700 more per person over 10 years but substantially improved quality-of-life

  “cost-effective”

- The metformin intervention cost ~$100 less per person over 10 years and marginally improved quality-of-life

  “cost-saving”

Diabetes Prevention Program

Diabetes Care 2012;35:723-30

DPPOS

Translational Impact of DPP

Congressionally-established National Diabetes Prevention Program

National Diabetes Education Program/HHS

Health System Programs

State Programs

CMS

ADA Consensus

US Department of Veterans Affairs

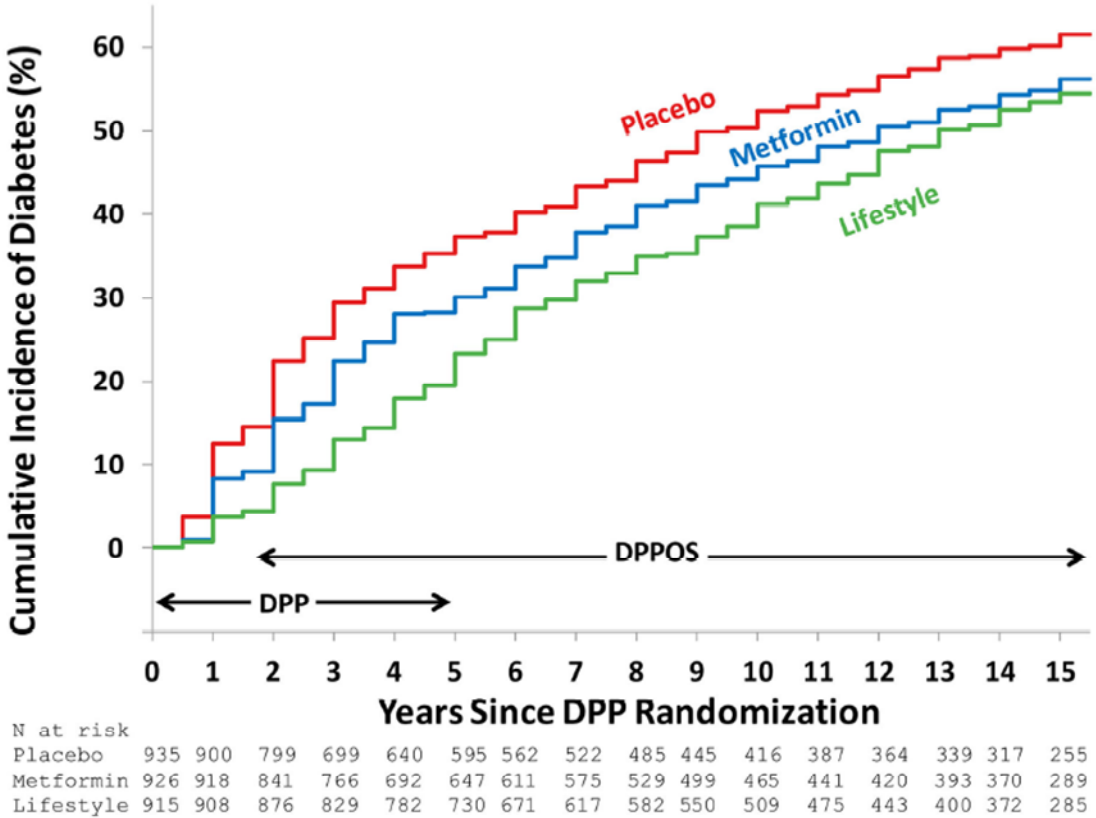
International Programs

Indian Health Service

Community Programs (e.g. Y-DPP; United Health Group)

Workplace Intervention Programs

DPP/DPPOS: 15-year follow-up (1996-2013)



Metformin vs placebo: -18%

Lifestyle vs placebo: -27%

<u>Cumulative incidence of diabetes:</u>

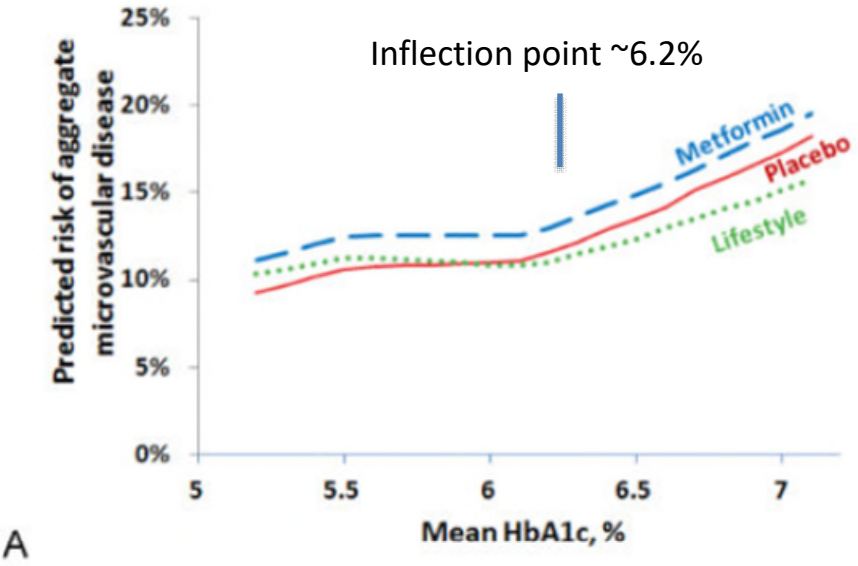
Placebo: 62%

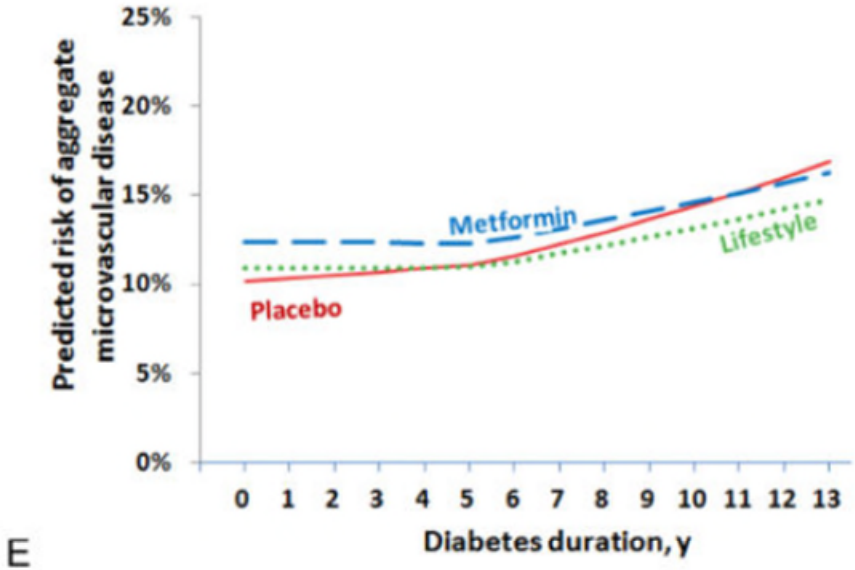
Lifestyle: 55%

Metformin: 56%

Approximately one-half of DPP participants have <u>not</u> developed diabetes during the entire study (or… approximately half did)

Composite of microvascular outcomes (nephropathy, neuropathy, retinopathy) at 15 years was 28% less in those who did not progress to diabetes, without difference by treatment





Nathan DM et al, Lancet Diabetes Endocrinol 2015; 3(11): 866-875

Favorable effects of intervention on cardiovascular risk factors

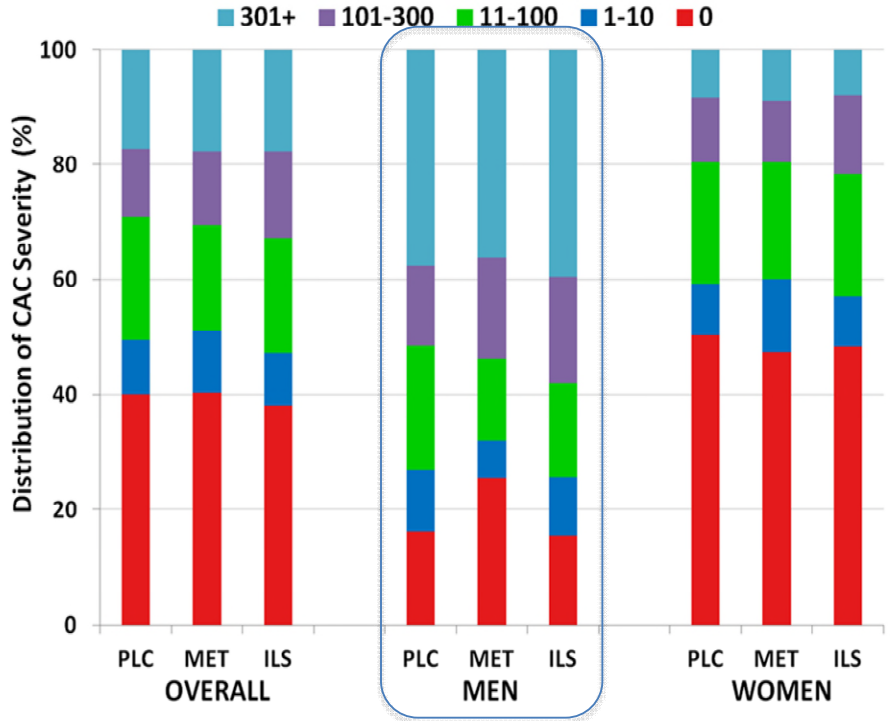
- DPP:
  - Lifestyle: improvements in blood pressure, HDL, TG, LDL particle size, biomarkers of inflammation, coagulation, endothelial dysfunction, metabolic syndrome (fewer BP and lipid meds)
  - Metformin: modest effects on TG and novel biomarkers

- DPPOS (10 years): no significant differences between treatment groups

Development of diabetes accompanied by unfavorable changes in cardiometabolic factors in all 3 arms

Nathan, D.M. *et al; Diabetologia* 2019; 62: 1319.

Metformin reduces presence and severity of Coronary Artery Calcification (CAC) in men



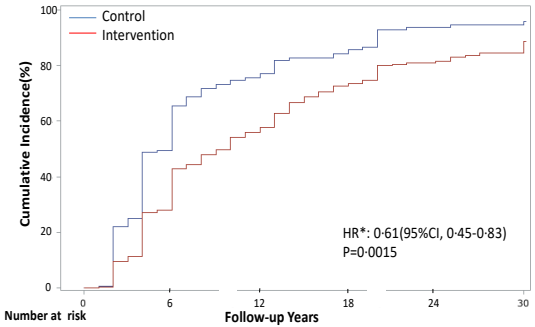
- MET vs. Placebo lowered the presence and severity of CAC in men, with no effect in women
- No reduction in the prevalence of clinically significant plaque (Agatston score > 100), suggesting that metformin affects smaller more recently calcified plaques, rather than well-established plaques

Goldberg RB, Aroda VR, et al. Circulation May 2017

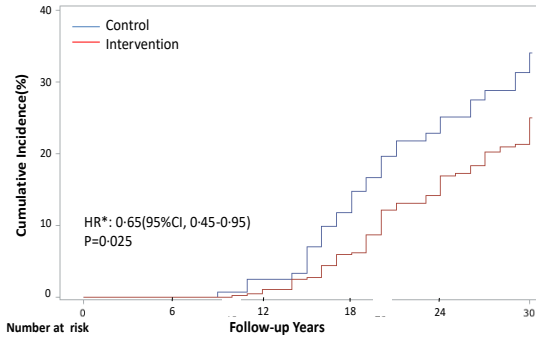
30-year follow up of the Da Qing Diabetes Prevention Study

(n=577, 6 years of lifestyle intervention vs control in IGT)

Diabetes



Microvascular Disease

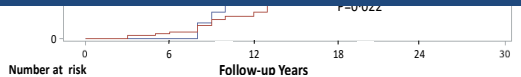


At 30 years:

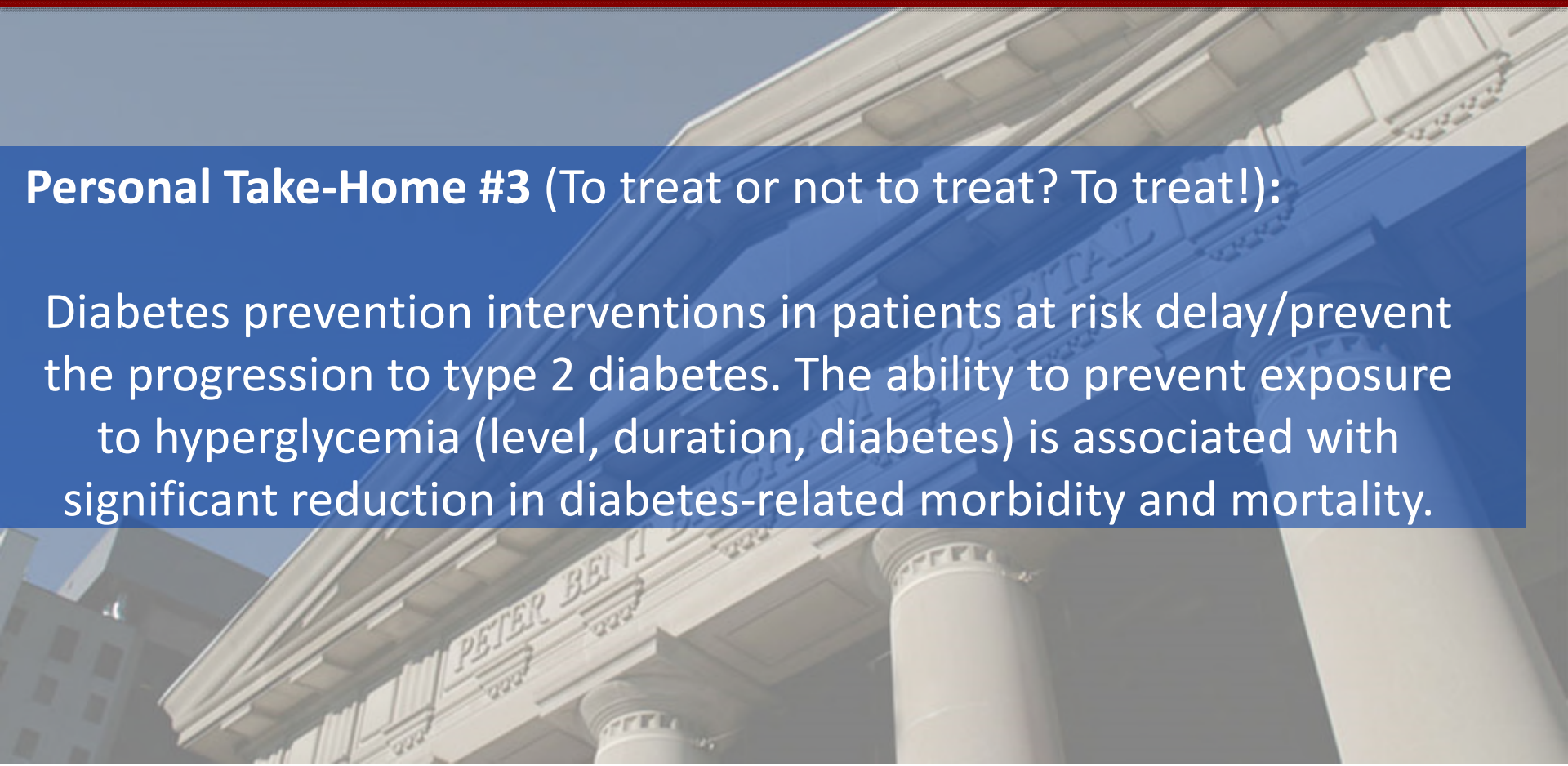
- 39% reduction in diabetes, median delay in diabetes by 3.96 years
- 33% reduction in CV death
- 26% reduction in CVD events
- 26% reduction in all-cause mortality
- 35% reduction in microvascular complications
- Increase in 1.44 life years

Multivariate models that corrected for time of onset of diabetes nullified the significance of the intervention effect for each of the primary outcomes.

I.e. Reduced incidence of these outcomes is accounted for by the **delay in diabetes onset** in the intervention group.



Gong Q *et al* *Lancet Diabetes Endocrinol.* 2019;7(6):452-461



Personal Take-Home #3 (To treat or not to treat? To treat!)**:**

Diabetes prevention interventions in patients at risk delay/prevent the progression to type 2 diabetes. The ability to prevent exposure to hyperglycemia (level, duration, diabetes) is associated with significant reduction in diabetes-related morbidity and mortality.

1. What is the scope and potential impact of diabetes prevention?

2. Who should we screen (and therefore potentially intervene on)?

3. To treat or not to treat?

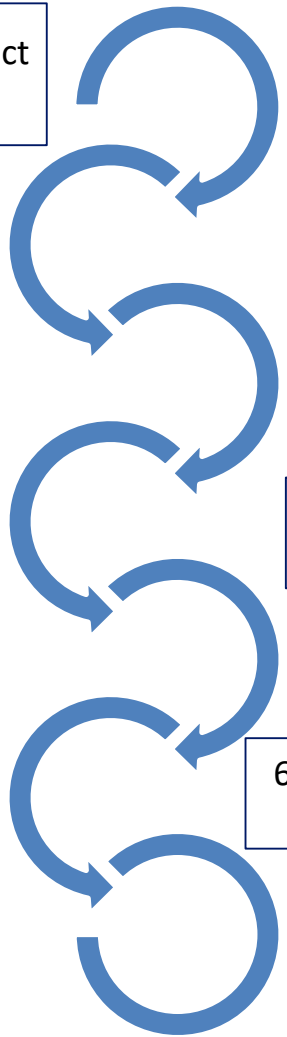
4. What does lifestyle intervention look like?

5. Is there evidence for pharmacotherapy?

6. Are there any clinically relevant targets that may guide treatment?

7. From the individual to society: Are there other areas to consider?

8. At the Patient Level: Conversation A vs Conversation B



Intensive Lifestyle Intervention

Behavioral Modification

An intensive program with the following specific goals:

- ≥ 7% loss of body weight and maintenance of body weight loss
- ≥150 minutes per week of moderate physical activity

Reminder: DPP was an EFFICACY study!

- Intensive lifestyle intervention:
  - Individual lifestyle coaches and access to support staff:
    - Dietitian
    - Behavioral counselor
    - Exercise specialist
  - 16-session individual curriculum, covering nutrition, exercise, and behavioral self-management
  - Kept food journals (mandatory requirement in run-in period)

- The “Toolbox”

Lifestyle Intervention in the DPP

"The lifestyle participants went through what amounts to a kind of graduate-level education in how to change their lives."

"In some respects, the coaches and others in the trial became the *federally funded equivalent of nagging relatives*, determined to keep participants adherent to the trial interventions and deeply motivated."

"Nike shoes, gym memberships, grocery vouchers, digital scales…We even bought one participant a treadmill."

"Vanita, we even went knocking on doors. We did whatever it took."

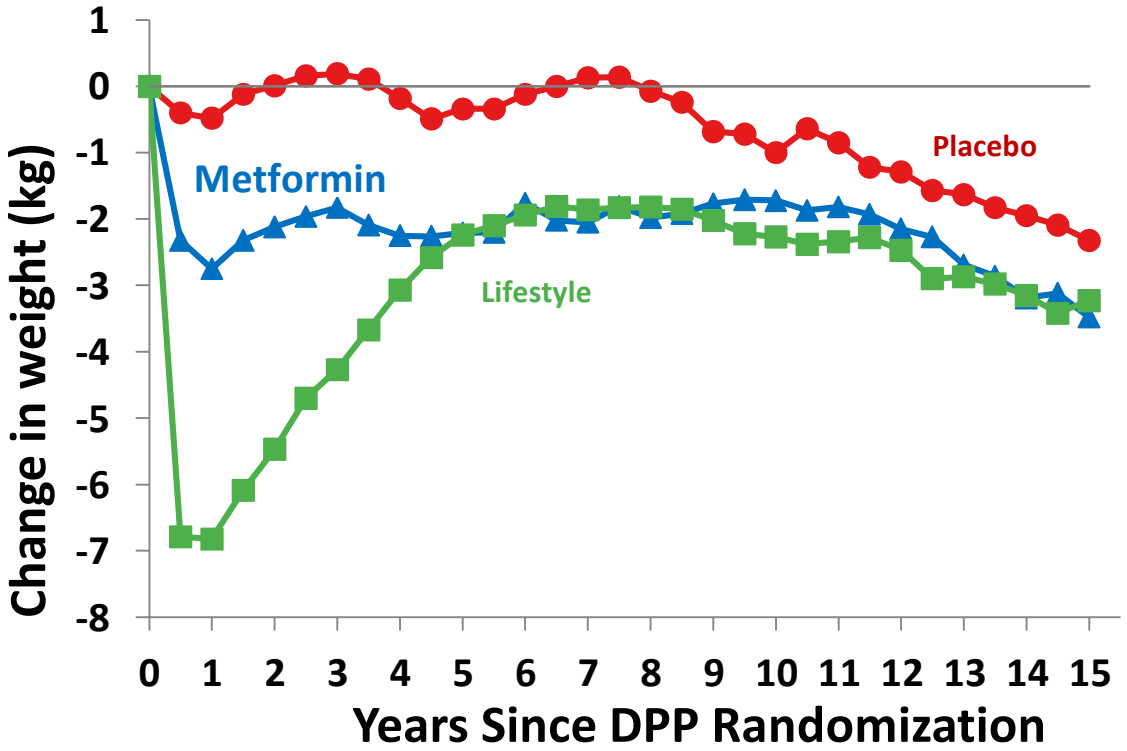
Brink S. *Health Affairs* 2009; 28(1):57-62.

“Standard lifestyle education” (1996-2002)

- Both metformin and placebo received standard lifestyle recommendations
- Written information, plus
  - Annual 20-30 minute individual session, emphasizing the importance of a healthy lifestyle

- All participants encouraged to follow the Food Guide Pyramid and the equivalent of a National Cholesterol Education Step 1 diet, to reduce weight, and increase their physical activity

Effects of Intervention on Body Weight during DPP and DPPOS



National Diabetes Prevention Program

PREVENT T2
A PROVEN PROGRAM TO PREVENT OR DELAY TYPE 2 DIABETES

1st 6 months

Module names
Burn More Calories Than You Take In
Shop and Cook to Prevent T2
Manage Stress
Find Time for Fitness
Cope with Triggers
Keep Your Heart Healthy
Take Charge of Your Thoughts
Get Support
Eat Well Away from Home
Stay Motivated to Prevent T2

Module names
Introduction to the Program
Get Active to Prevent T2
Track Your Activity
Eat Well to Prevent T2
Track Your Food
Get More Active

Next 6 months

Module names
When Weight Loss Stalls
Take a Fitness Break
Stay Active to Prevent T2
Stay Active Away from Home
More About T2
More About Carbs
Have Healthy Food You Enjoy
Get Enough Sleep
Get Back on Track
Prevent T2—for Life!

https://nccd.cdc.gov/DDT_DPRP/Registry.aspx

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

SEARCH

CDC A-Z INDEX

National Diabetes Prevention Program

Diabetes Home > National Diabetes Prevention Program

Registry of All Recognized Organizations

The national registry of recognized diabetes prevention programs lists contact information for all CDC-recognized organizations that deliver evidence-based type 2 diabetes prevention programs in communities across the United States. All of these programs have agreed to use a CDC-approved curriculum that meets the duration, intensity, and reporting requirements described in the *DPRP Standards* [PDF - 728KB]. Full recognition means that a program has demonstrated effectiveness by achieving all of the performance criteria detailed in the *DPRP Standards*.

CUSTOMER SERVICE CENTER

Diabetes Prevention Recognition Program – Registry of Recognized Organizations

Show organizations by location:

State: California City: Show all cities

Download Full Registry

Personal Take-Home #4 (What does lifestyle intervention look like?)

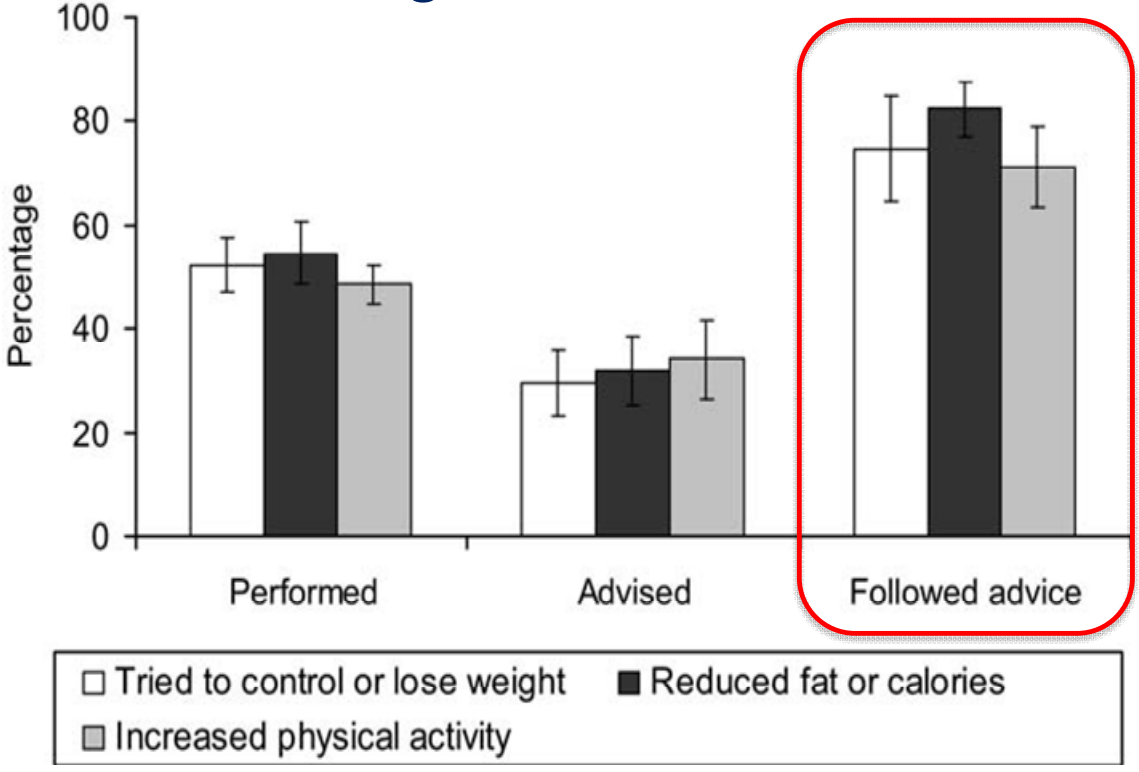
1. Favorite Dotphrase counseled on healthy lifestyle, handout provided etc etc

≠

Intensive Lifestyle Intervention

2. Know (and utilize!) your local resources and support!

Post-script (Take-Home #4): Diabetes Risk Reduction Behaviors among US adults with Prediabetes



AMERICAN JOURNAL OF
Preventive Medicine

Geiss LS et al, Am J Prev Med 2010 38:403-

1. What is the scope and potential impact of diabetes prevention?

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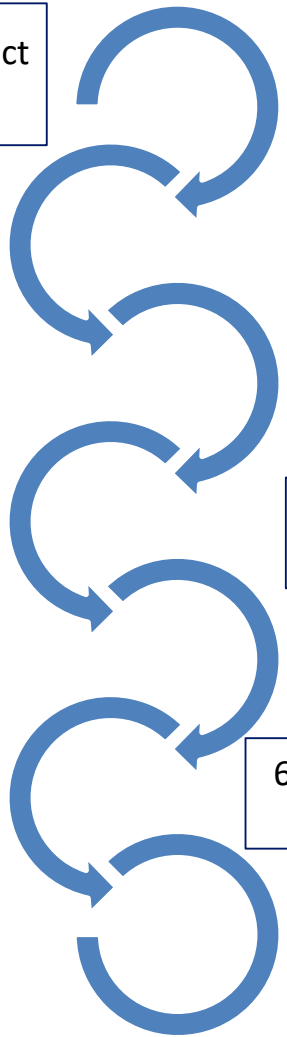


Summary of select randomized controlled trials evaluating the prevention of progression to diabetes, 1997-2006

Study Title (country of conduct, year of publication, n)	Risk eligibility criteria	Duration of follow-up	Intervention	Risk reduction in diabetes incidence compared to control
Da Qing Study (China, 1997, n=577)	IGT; age ≥ 25 years	6 years	Diet	31%
			Exercise	46%
			Diet + Exercise	42%
			Control	--
Finnish Diabetes Prevention Study (Finland, 2001, n=522)	IGT; age 40-65 years; BMI > 25 kg/m^2	3.2 years	Diet and activity	58%
			Control	--
Diabetes Prevention Program (US, 2002, n=3,234)	IGT; elevated fasting glucose 95 – 125 mg/dl (5.3 – 6.9 mmol/l) (< 125 mg/dl (6.9 mmol/l) for native American ancestry); age ≥ 25 years; BMI ≥ 24 kg/m^2 (≥ 22 kg/m^2 in Asians)	2.8 years	Intensive lifestyle intervention	58%
			Metformin 850 mg BID	31%
			Placebo	--
STOP-NIDDM (multiple countries, 2002, n=1,429)	IGT; elevated fasting glucose 5.6-7.7 mmol/l; age 40-70 years; BMI 25-40 kg/m^2	3.3 years	Acarbose 100 mg TID	25%
			Placebo	--
XENDOS (Sweden, 2004, n=3,305)	BMI ≥ 30 kg/m^2; age 30-60 years	4 years	Orlistat 120 mg TID	37%
			Placebo	--
Japanese IGT study (Japan, 2005, n=458)	Males with IGT	4 years	Diet and exercise	67%
			Control	--
Indian Diabetes Prevention Programme (India, 2006, n=531)	IGT, age 35-55 years	30 months	Lifestyle modification	29%
			Metformin 250 mg BID	26%
			Lifestyle modification + metformin 250 mg BID	28%
			Control	--

**composite primary outcome of incident diabetes or death from any cause

Aroda VR *et al; Diabetologia* 2017; 60(9):1601-1611

Summary of select randomized controlled trials evaluating the prevention of progression to diabetes, 2006-2017

DREAM (rosiglitazone) (multiple countries, 2006, n=5,269)	IFG and/or IGT, age ≥ 30 years	3.0 years	Rosiglitazone 8 mg daily	60%**
			Placebo	--
DREAM (ramipril) (multiple countries, 2006, n=5,269)	IFG and/or IGT, age ≥ 30 years	3.0 years	Ramipril (up to 15 mg per day)	No reduction**
			Placebo	--
Voglibose Ph-3 (Japan, 2009, n=1,780)	IGT, age 30-70 years, with additional risk factor for type 2 diabetes	48.1 weeks	Voglibose 0.2 mg TID	41%
			Placebo	--
NAVIGATOR (valsartan) (multiple countries, 2010, n=9,306)	IGT, fasting plasma glucose 95 - <126 mg/dl (5.3 - <7.0 mmol/l) + cardiovascular disease/cardiovascular risk	5.0 years	Valsartan (up to 160 mg daily), and lifestyle modification	14%
			Placebo	--
NAVIGATOR (nateglinide) (multiple countries, 2010, n=9,306)	IGT, fasting plasma glucose 95 - < 126 mg/dl (5.3 - < 7.0 mmol/l) + cardiovascular disease/cardiovascular risk	5.0 years	Nateglinide (60 mg before meals three times daily)	No reduction
			Placebo	--
CANOE (Canada, 2010, n=207)	IGT, age 30-75 years (18-75 for native Canadian ancestry), with at least one risk factor for type 2 diabetes	3.9 years	Rosiglitazone + metformin (2 mg/500 mg BID)	66%
			Placebo	--
ACT NOW (USA, 2011, n=602)	IGT, fasting plasma glucose between 95 and 125 mg/dl (5.3 and 6.9 mmol/l), age 18 years or older, BMI ≥ 25 kg/m^{2,} at least one risk factor type 2 diabetes	2.4 years	Pioglitazone 45 mg daily	72%
			Placebo	--
SCALE Prediabetes (multiple countries, 2017, n=2,254)	Prediabetes, adults 18 years or older; BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with comorbidities	3 years	Liraglutide 3.0 mg	66%
			Placebo	--

**composite primary outcome of incident diabetes or death from any cause

Aroda VR *et al; Diabetologia* 2017; 60(9):1601-1611

ADA Standards of Care on Pharmacotherapy for Diabetes Prevention

- Pharmacologic agents have been shown to decrease the incidence of diabetes to various degrees in those with prediabetes
- None are approved by the US FDA specifically for diabetes prevention
- Metformin has the strongest evidence base and demonstrated long-term safety as pharmacologic therapy for diabetes prevention

PHARMACOLOGIC INTERVENTIONS

Recommendations

3.5 Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those aged <60 years, and women with prior gestational diabetes mellitus. **A**

American Diabetes Association Standards of Care 2019

Effects of intensive lifestyle intervention or metformin on diabetes prevention/delay: 1996-2001

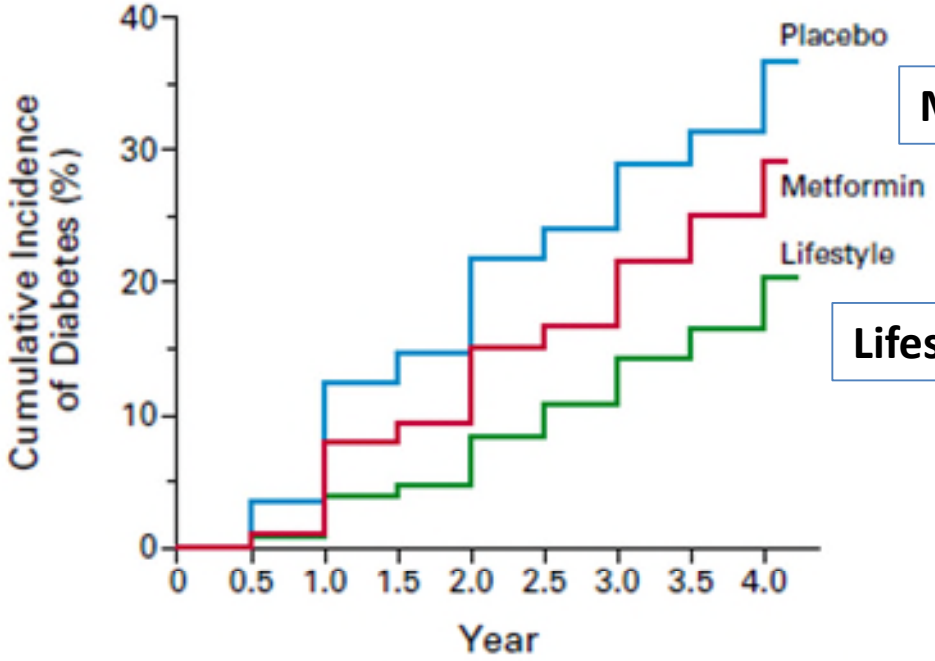


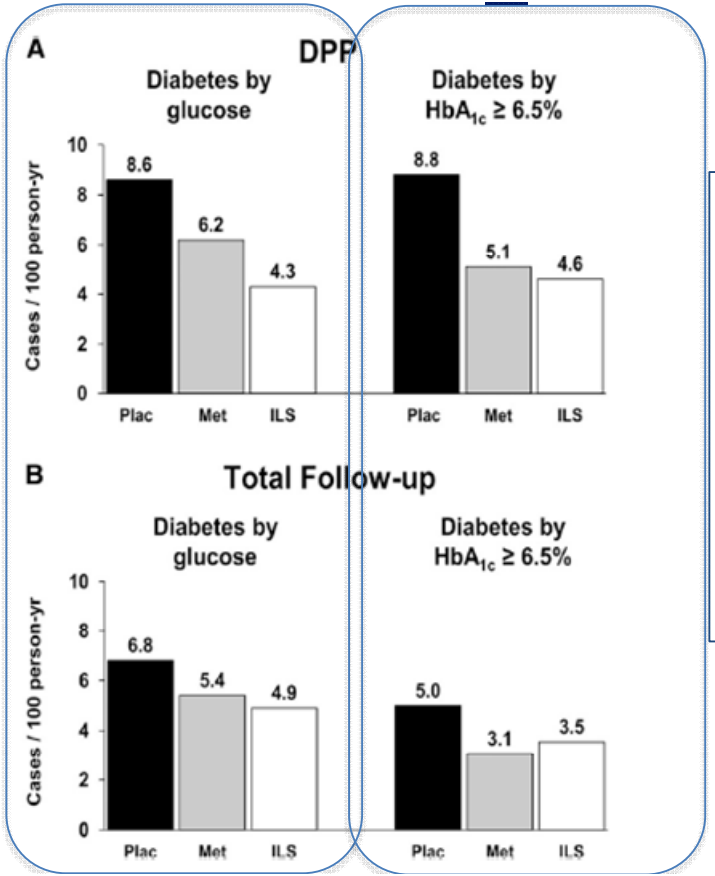
Figure 2. Cumulative Incidence of Diabetes According to Study Group.

Metformin vs placebo: -31%

Lifestyle vs placebo: -58%

Diabetes Prevention Program Research Group *NEJM* 2002; 346:393-403

What if we look at diagnosis of diabetes based on HbA1c >6.5%? (2010 ADA definition)

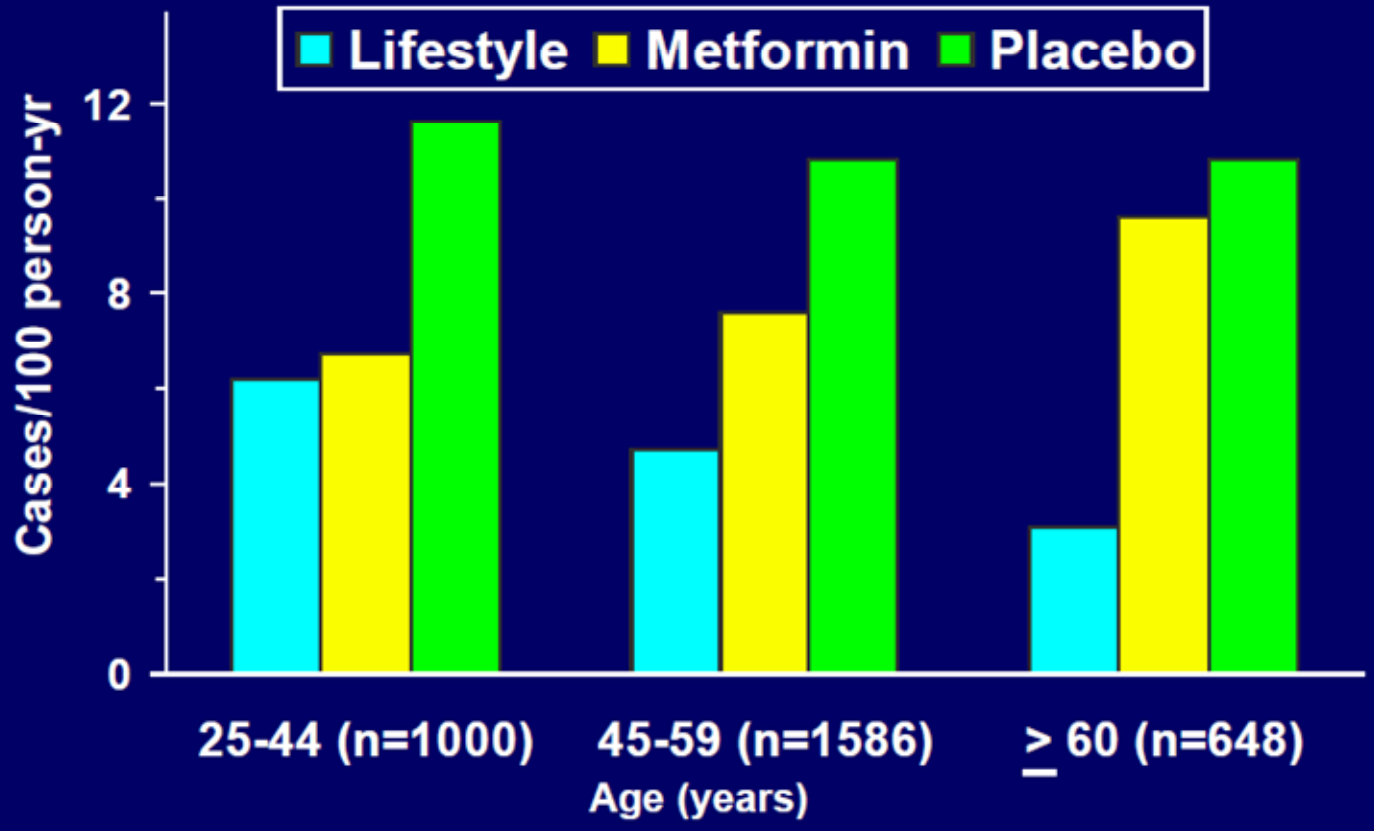


- By glucose criteria (FPG, OGTT): ILS was more effective than metformin in reducing the incidence of diabetes

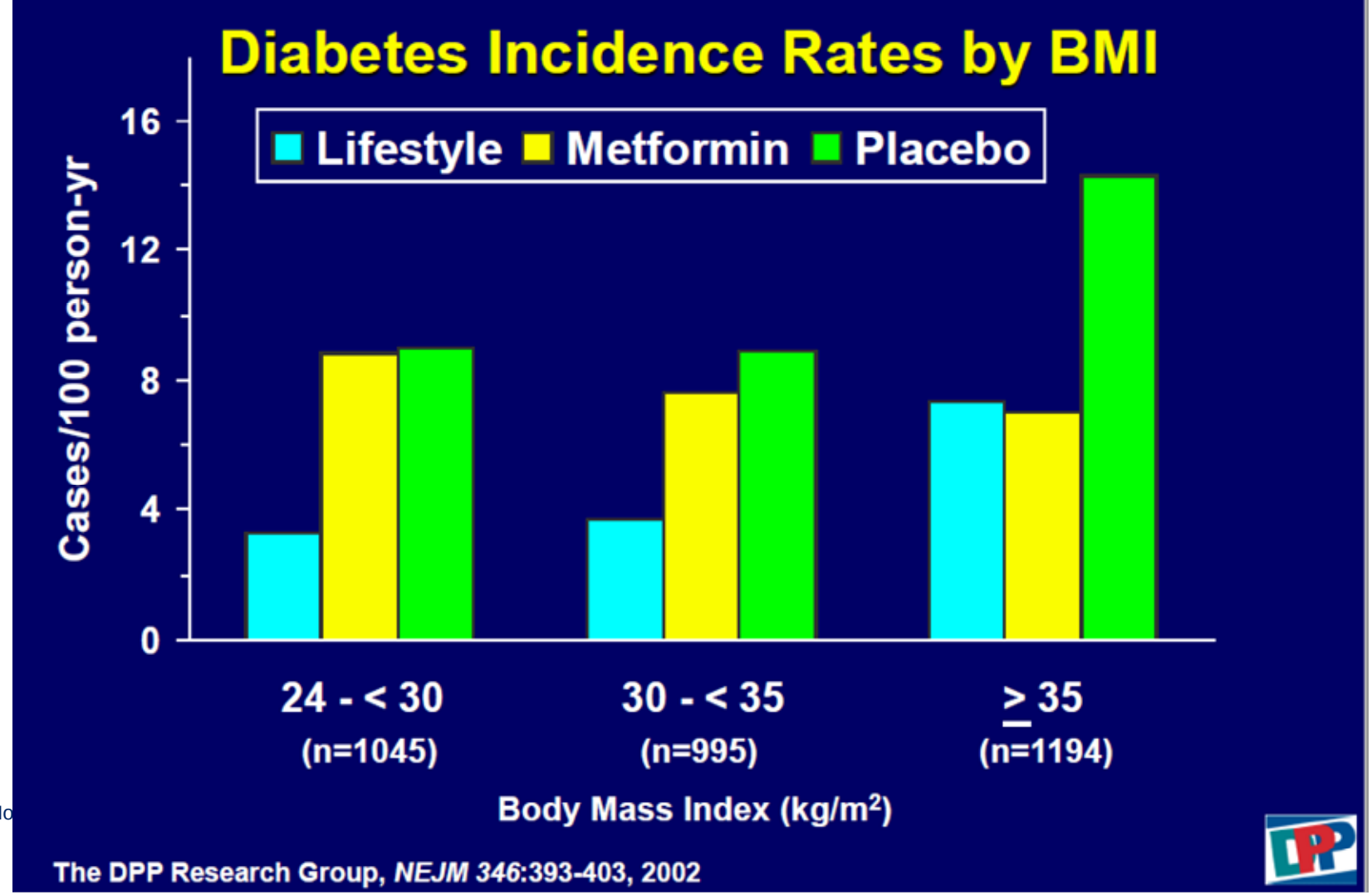
- By HbA1c criteria: Metformin no different than ILS
  - DPP: 44% (met) vs 49% (ILS) reduction
  - DPP/DPPOS: 38% (met) vs 29% (ILS) reduction

Knowler WC et al Diabetes 2015

Diabetes Incidence Rates by Age

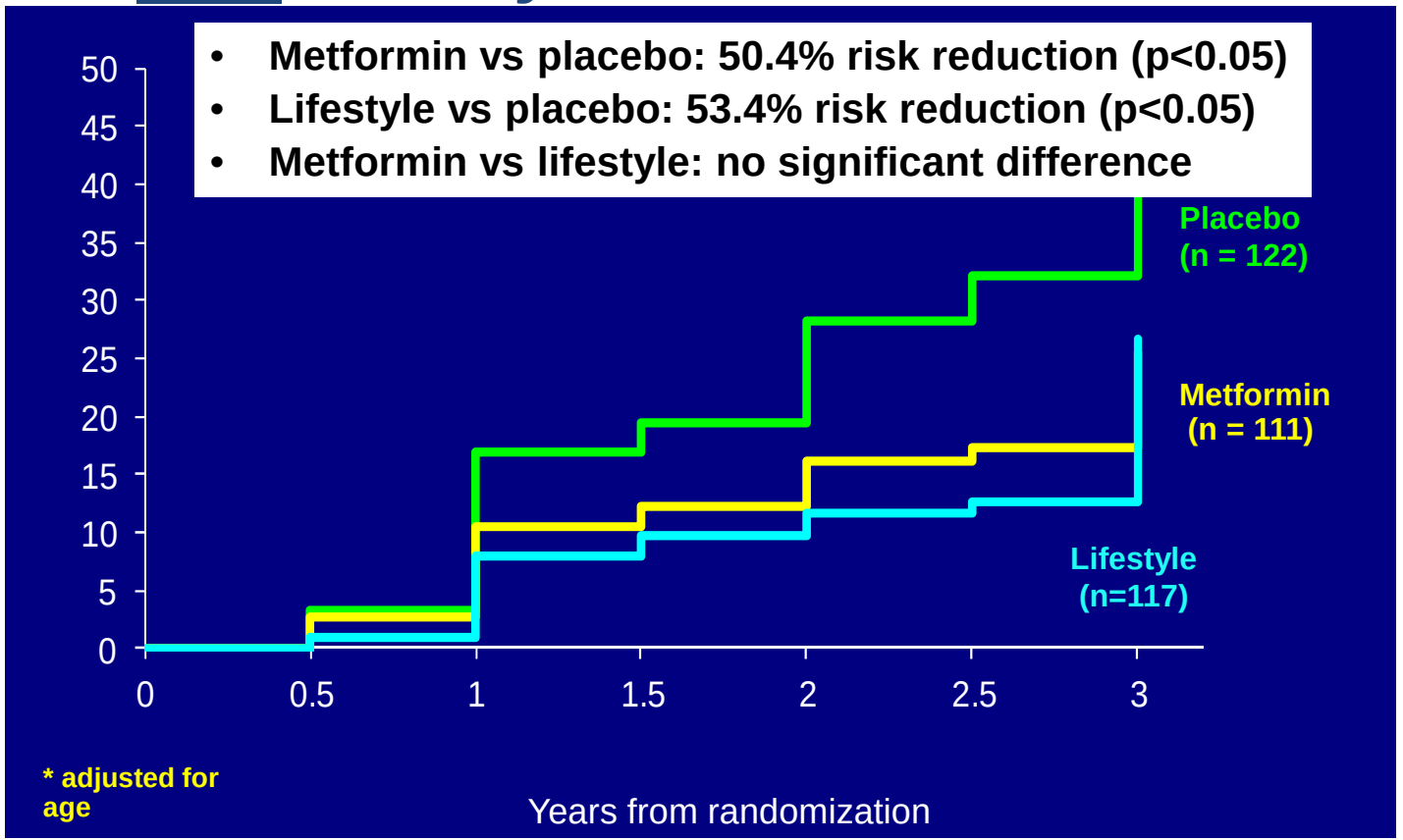


The DPP Research Group, *NEJM 346*:393-403, 2002


Diabetes Incidence Rates by BMI
Lifestyle
Metformin
Placebo
Cases/100 person-yr
16
12
8
4
0
24 - < 30
(n=1045)
30 - < 35
(n=995)
≥ 35
(n=1194)
Body Mass Index (kg/m²)
The DPP Research Group, NEJM 346:393-403, 2002

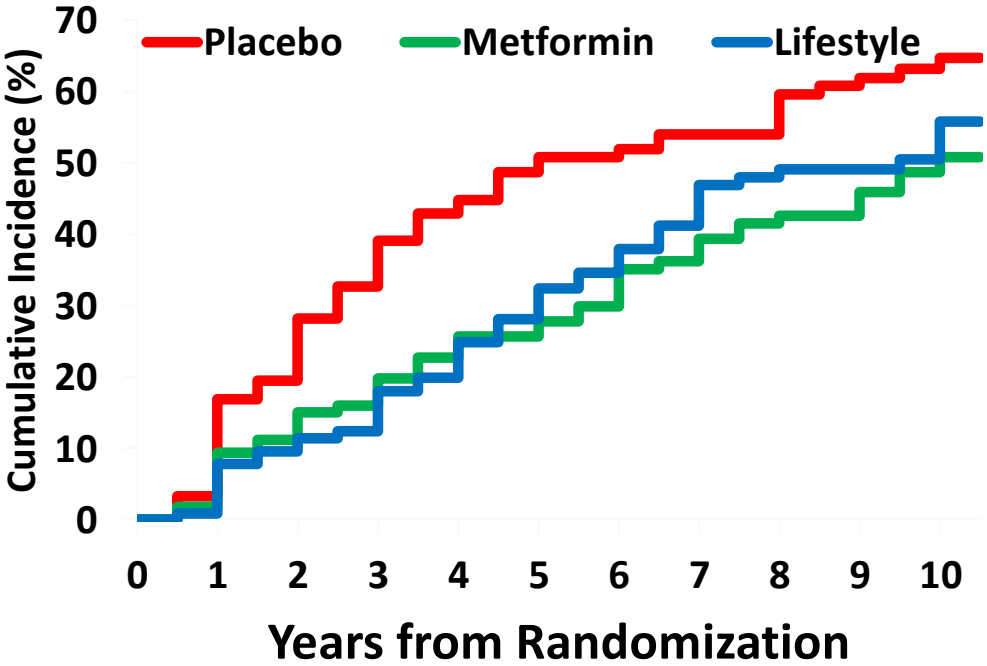
Cumulative Incidence of Diabetes in DPP – Women with History of GDM

71% increased risk of progression to diabetes in women with h/o GDM in DPP compared to women without h/o GDM



Ratner RE et al JCEM 2008

10-Year Cumulative Incidence of Diabetes in Parous Women with a History of GDM



Lifestyle vs placebo: 35% risk reduction ($p<0.05$)

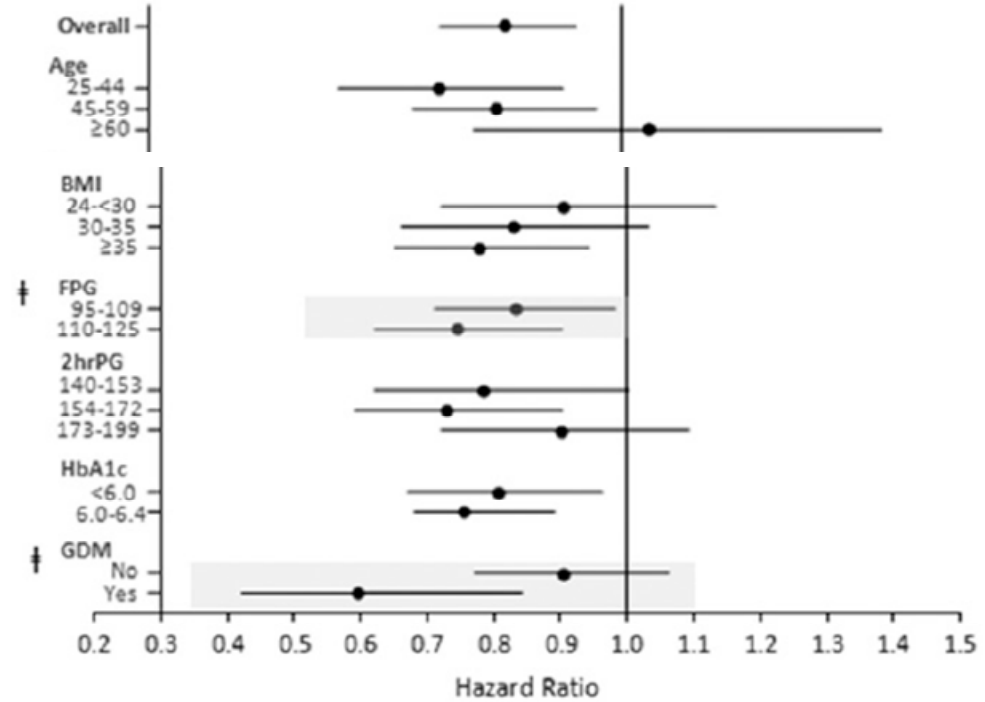
Metformin vs placebo: 41% risk reduction ($p<0.05$)

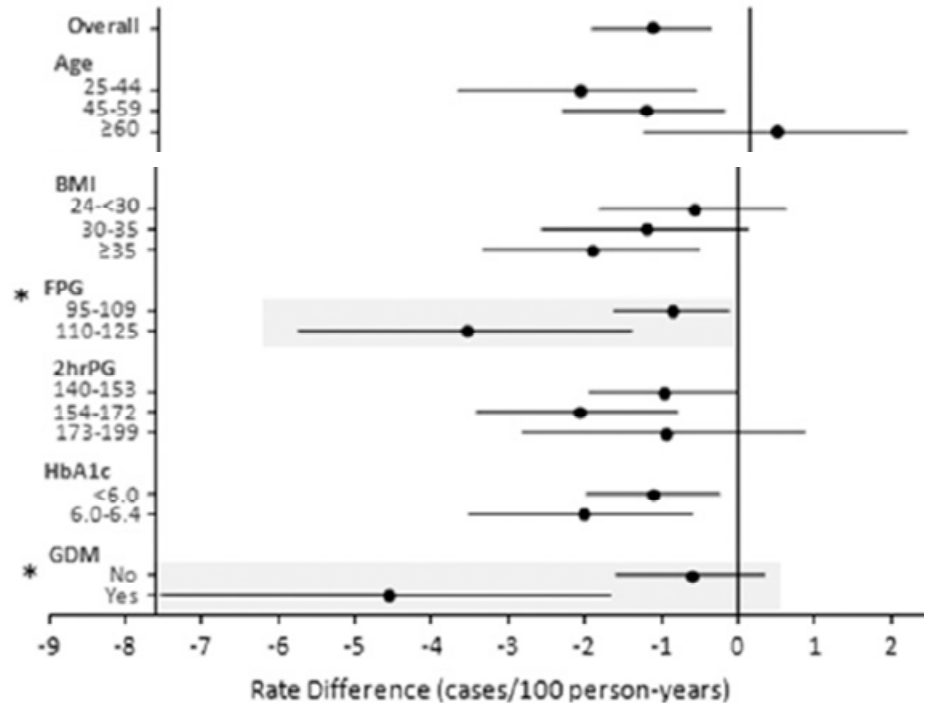
Lifestyle vs metformin: -9.6% ($p=ns$)

Women with a history of GDM in the placebo group had a 65% higher risk of developing diabetes compared with women without a GDM history (11.4/100 vs 6.9/100 person-years).

Aroda VR et al, JCEM 2015

Long-term Effects of Metformin on Diabetes Prevention: Identification of Subgroups that Benefited most in the DPP/DPPOS





Hazard Ratio: chance of event occurring in the treatment arm relative to chance of event occurring in the control/comparison arm

Rate Difference: focuses on absolute effect between metformin and placebo, calculated as number of diabetes events divided by the total number of person-years of follow up.

Diabetes Prevention Program Research Group; *Diabetes Care* 2019; 42(4):601-608.

Long-term Effects of Metformin on Diabetes Prevention: Identification of Subgroups that Benefited most in the DPP/DPPOS

- Regardless of how diabetes is diagnosed in follow up, long-term effects of metformin in DPP/DPPOS suggest that it remains effective overall, and its effect is enhanced in specific subgroups:
  - Those with higher baseline fasting glucose
  - Those with higher baseline HbA1c
  - Women with a history of GDM

"These results should help to prioritize those groups at high risk of developing diabetes who will benefit most from being treated with metformin."

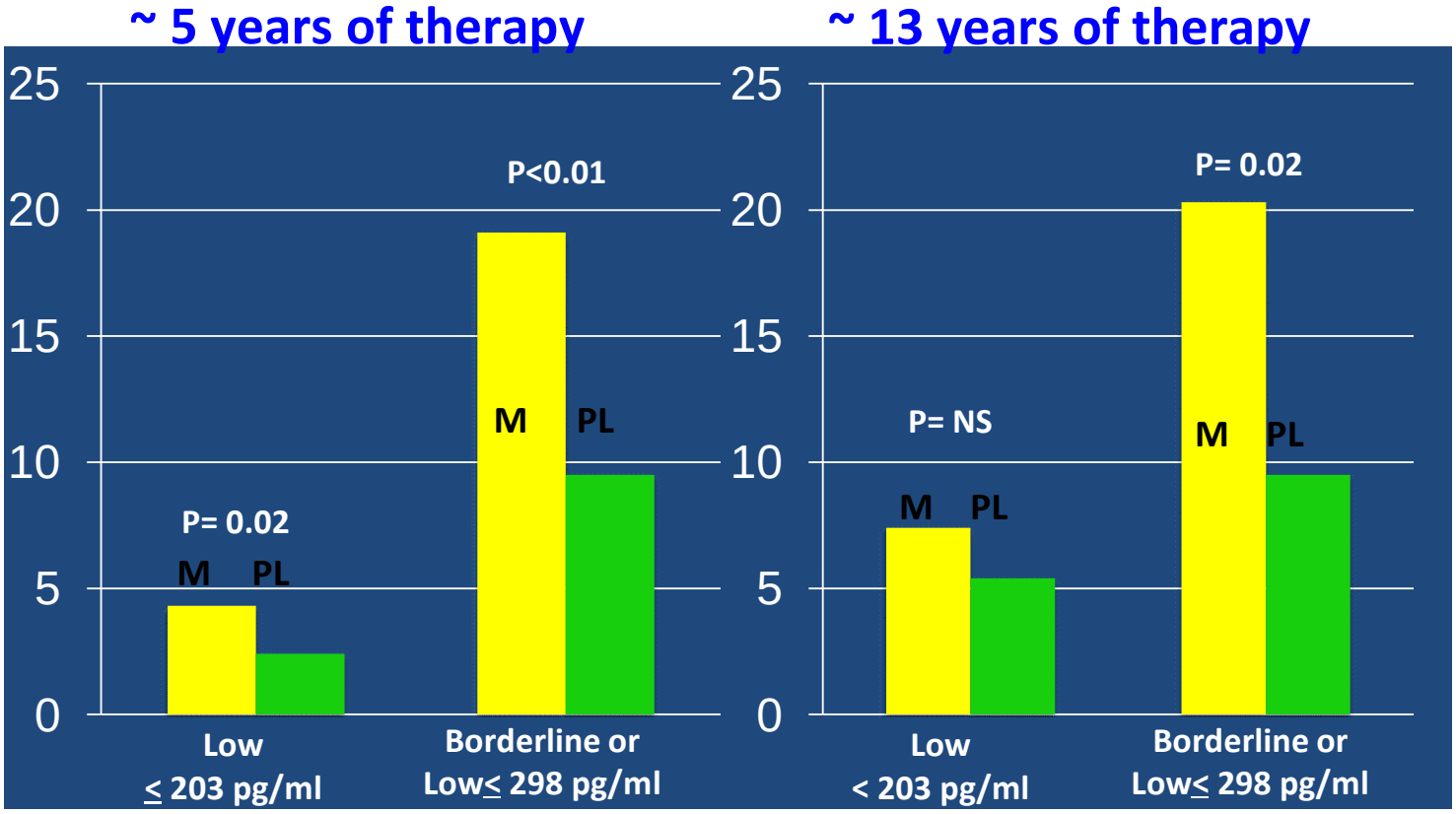
Diabetes Prevention Program Research Group; *Diabetes Care* 2019; 42(4):601-608.

Metformin and B12 Deficiency

Background

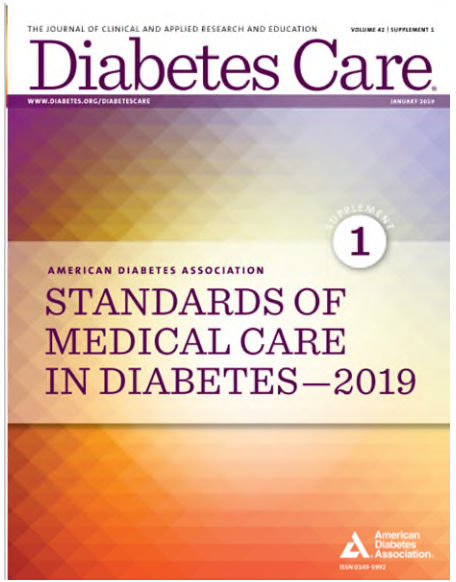
- **Metformin has long been recognized to be associated with vitamin B12 deficiency**
- **Clinician awareness of this is variable; routine B12 testing is not common in clinical practice**
  - Hematologic monitoring (CBC) used as surrogate
- **Until recently, no guidelines recommend routine B12 testing**

Long-term Metformin Use and Vitamin B12 Deficiency in the DPP/DPPOS



Aroda VR, Crandall J ,et al J Clin Endo Metab 2016; 101: 1754-61.

3.6 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. **B**



Personal Take-Home #5 (Pharmacotherapy?)

No agent has a label indication specifically for diabetes prevention. The longest term evidence is for metformin, with particular benefit seen in the DPP population in:

-younger age groups

-higher BMI (BMI $\geq$ 35 kg/m^2)

-higher fasting glucose

-higher HbA1c

-history of gestational diabetes

1. What is the scope and potential impact of diabetes prevention?

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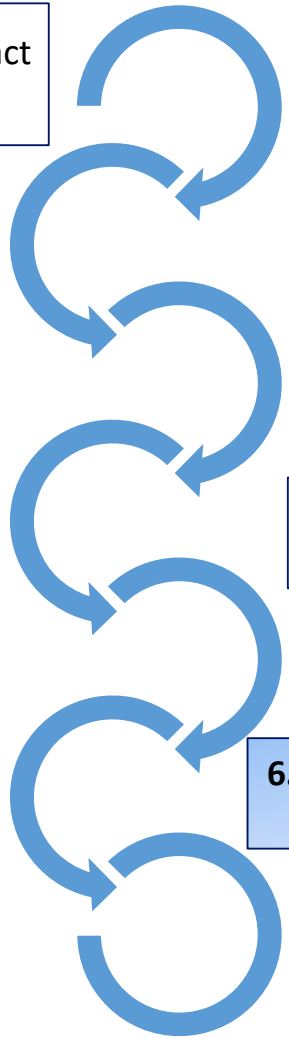
6. Are there any clinically relevant targets that may guide treatment?

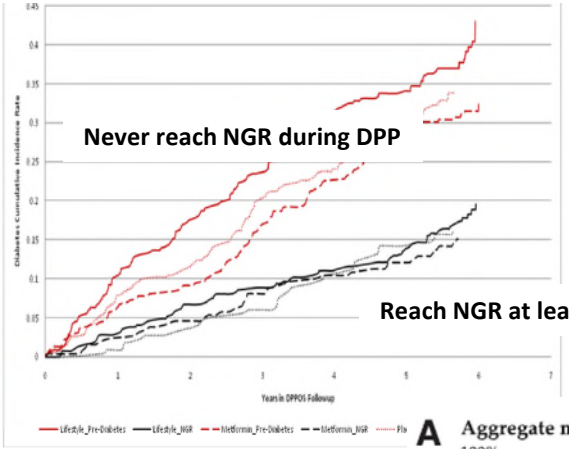
7. From the individual to society: Are there other areas to consider?

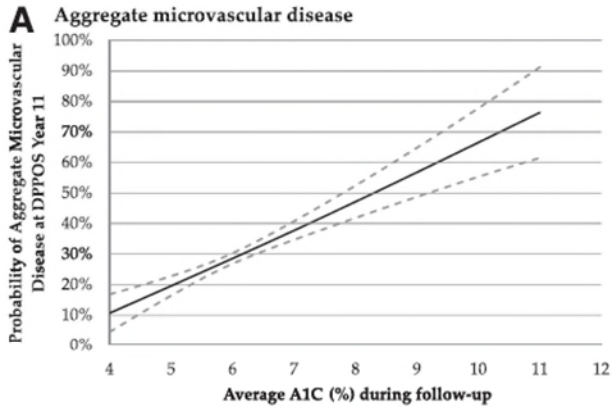
8. At the Patient Level: Conversation A vs Conversation B



Regression from Prediabetes to Normal Glucose Regulation at least once (vs never) during the **DPP:**

- 56% lower risk of diabetes during DPPOS follow up (compared to remaining with prediabetes)
- Lower aggregate microvascular disease, and nephropathy and retinopathy individually
  - This association was lost in models that included average HbA1c during follow up or diabetes status at end of follow-up
  - Thus, this lower risk was likely due to lower glycemic exposure over time





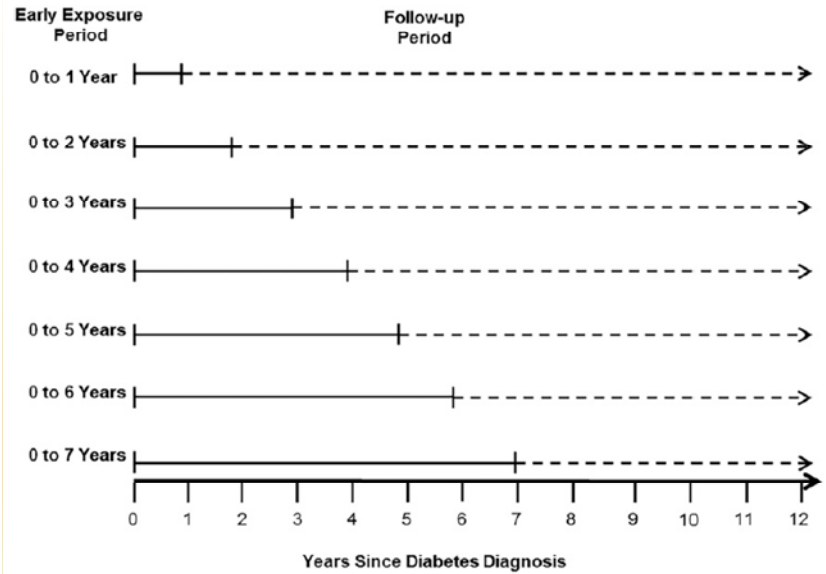
Perreault L *et al; Lancet* 2012; 379(9833): 2243–2251
Perreault L *et al; Diabetes Care* 2019;42(9):1809-1815

The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study)

[1]Department of Medicine, The University of Chicago, Chicago, IL
[2]Center for Health and the Social Sciences, The University of Chicago, Chicago, IL
[3]Division of Research, Kaiser Permanente, Oakland, CA

Compared with HbA1c <6.5% for the 0-to-1-year early exposure period after diagnosis of T2DM, mean HbA1c levels ≥ 6.5% were associated with:

- Increased risk of microvascular events
- Increased risk of macrovascular events
- Increased mortality



Laiteerapong N *et al*; *Diabetes Care* 2019; 42:416-426

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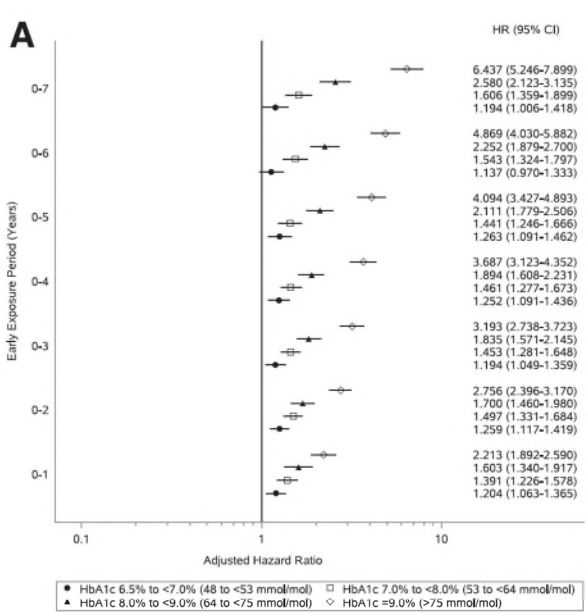
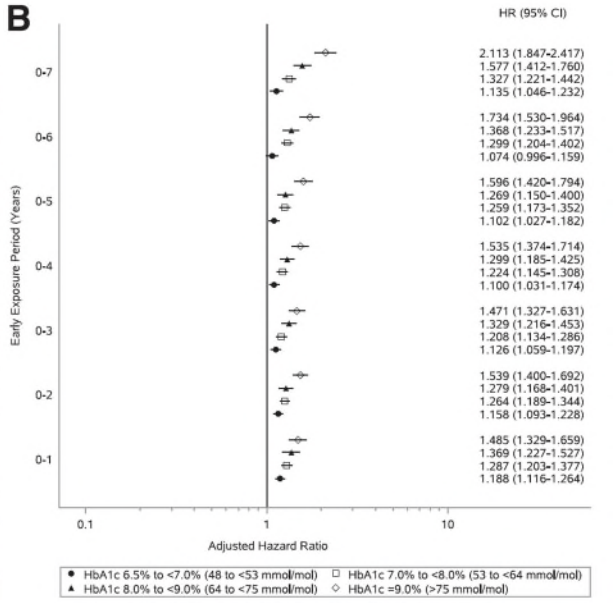
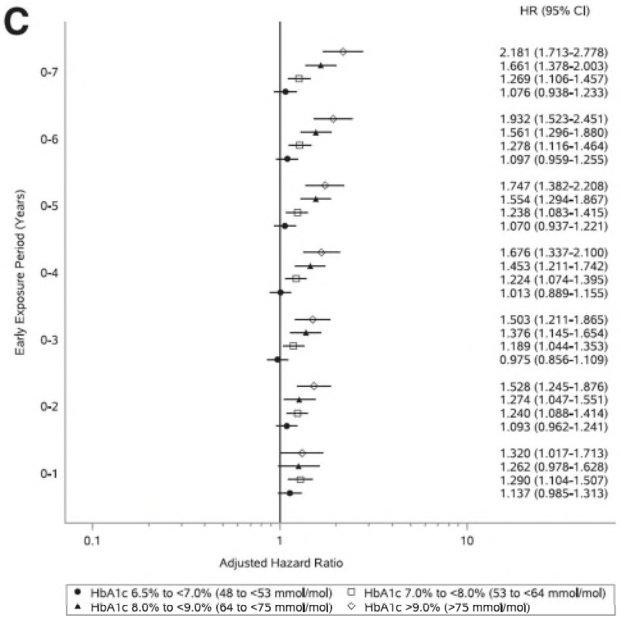


Microvascular Events (vs HbA1c < 6.5%)

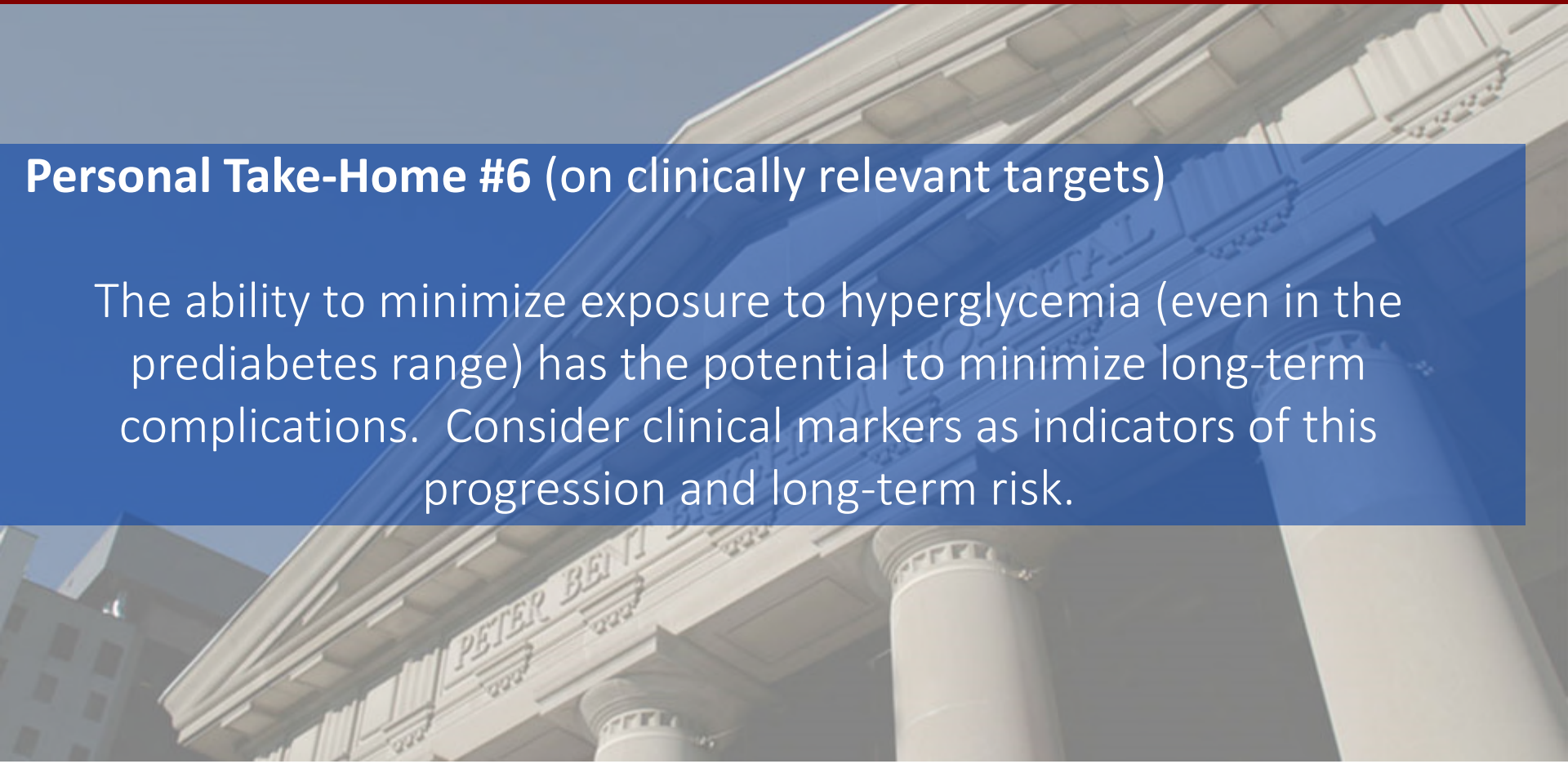


Macrovascular Events (vs HbA1c < 6.5%)



Mortality (vs HbA1c < 6.5%)

Laiteerapong N *et al*; *Diabetes Care* 2019; 42:416-426



Personal Take-Home #6 (on clinically relevant targets)

The ability to minimize exposure to hyperglycemia (even in the prediabetes range) has the potential to minimize long-term complications. Consider clinical markers as indicators of this progression and long-term risk.

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4. What does lifestyle intervention look like?

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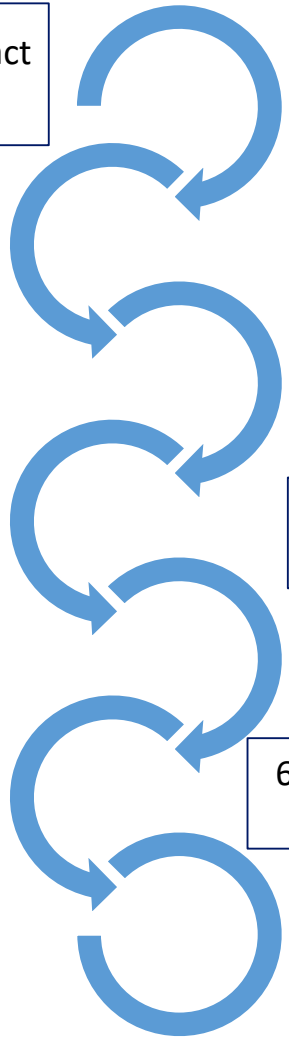
7. BONUS: From the individual to society: Are there other areas to consider?

8. At the Patient Level: Conversation A vs Conversation B



MEDICAL MODEL

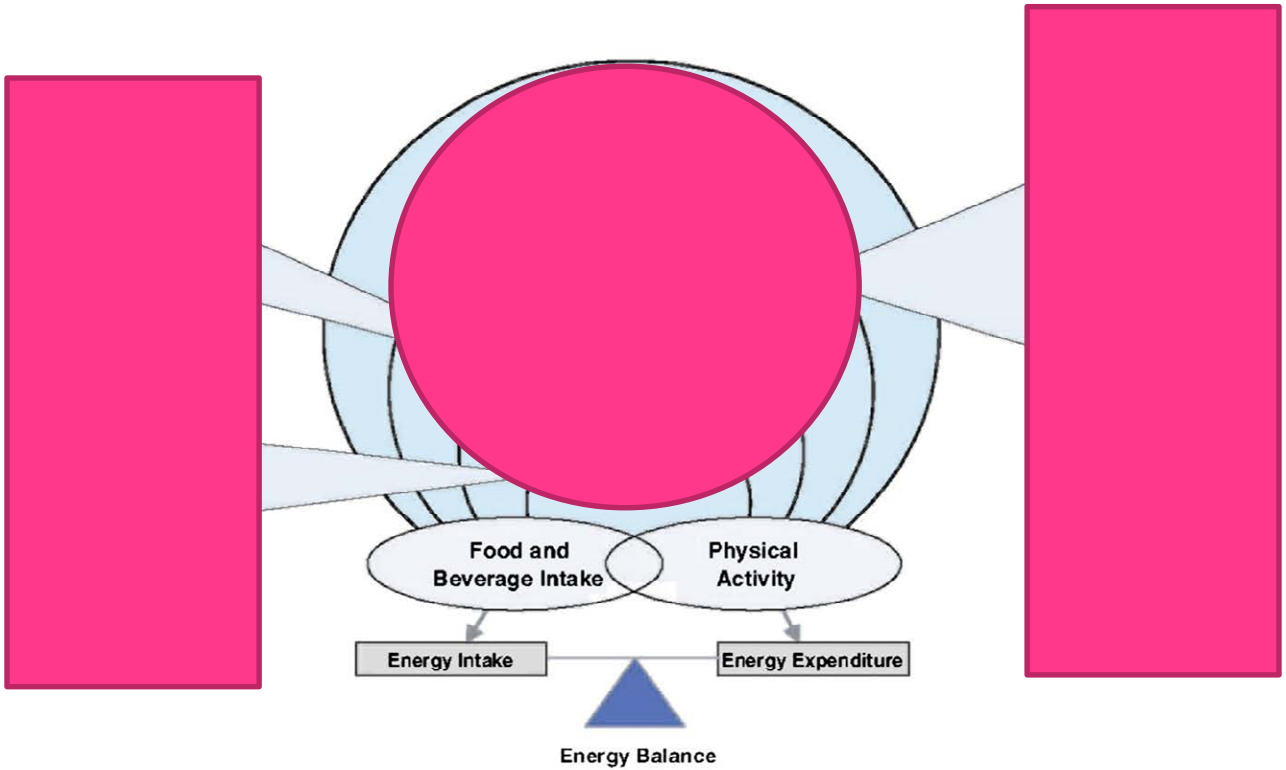


Figure 1—*Levels and sectors of influence on obesity and diabetes risk (progress in preventing childhood obesity) (© 2007 the National Academies Press). SES, socioeconomic status.*

Institute of Medicine. *Accelerating Progress in Obesity Prevention.* 2012

SOCIOECOLOGICAL MODEL

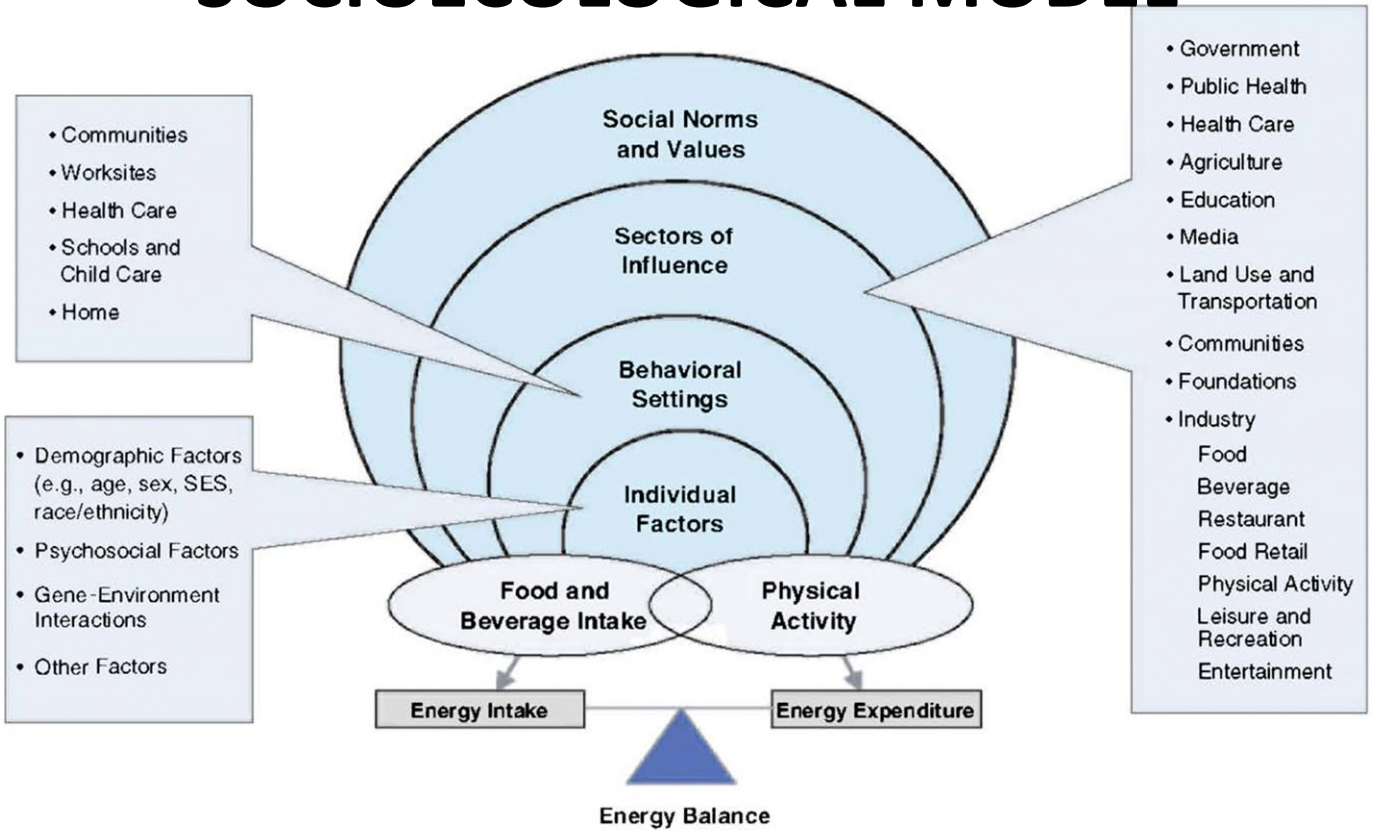
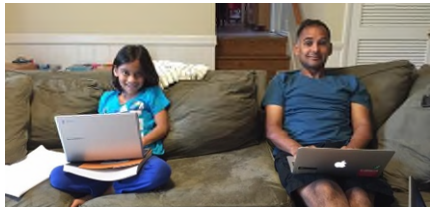
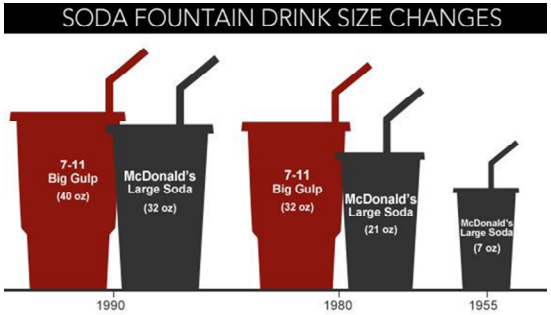


Figure 1—*Levels and sectors of influence on obesity and diabetes risk (progress in preventing childhood obesity) (© 2007 the National Academies Press). SES, socioeconomic status.*

Institute of Medicine. *Accelerating Progress in Obesity Prevention.* 2012
Hill JO, Aroda VR, Diabetes Care 2013; 36:2430-2439



“Venus of Cupertino” (Scott Eaton)



Hill JO, Aroda VR, Diabetes Care 2013; 36:2430-2439

1. What is the scope and potential impact of diabetes prevention?

2. Who should we screen (and therefore potentially intervene on)?

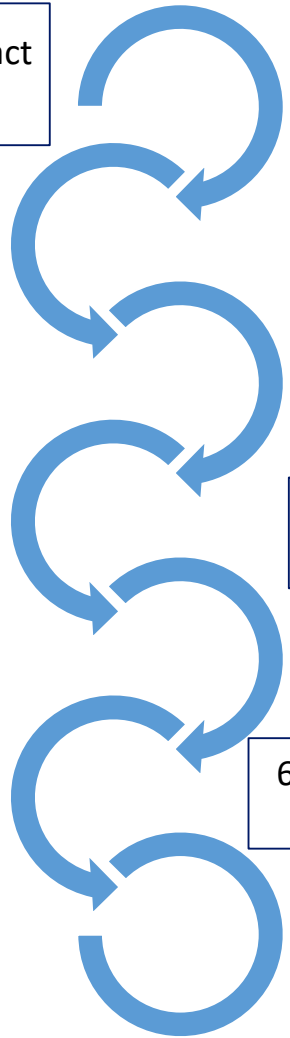
3. To treat or not to treat?

4. What does lifestyle intervention look like?

5. Is there evidence for pharmacotherapy?

6. Are there any clinically relevant targets that may guide treatment?

7. From the individual to society: Are there other areas to consider?



8. BONUS: At the Patient Level: Conversation A vs Conversation B

Conversation A vs Conversation B

Conversation A

- "Your lab tests su[illegible]est you have increased risk of di[illegible]betes (a condition we call prediabete[illegible]st you make healthie[illegible]oices and increase your physical [illegible]goal of 150 [illegible]k of moderate physical acti[illegible]lo[illegible]eight. I will see you in 6 months a[illegible]e will need to put you on a medicine."
- "Yes, your labs show [illegible]ised you to lose weight. People in the DP[illegible]vent diabetes. If you don't make [illegible]dia[illegible]e to put you on a medicine…"
- "Oh, you didn't [illegible]es, diabetes is prevent[illegible]ur doctor should have told you tha[illegible]. Your doctor should have advise[illegible] you to lose weight or take metformin and you could have prevented your diagnosis of diabetes."

Conversation B

Your lab values suggest that you are at an increased risk of developing diabetes. We term this condition 'prediabetes', and it signals to us that we should monitor you more closely and pay more attention to your long-term risks of diabetes and cardiovascular disease. Our primary goal to optimize health is to try to keep your blood sugar values (e.g. HbA1c) as close to normal as possible, safely, as we know that higher levels are associated with higher risk of progression to diabetes and complications related to diabetes.

Studies have shown that losing ~7% of one's body weight through healthy lifestyle changes can decrease the risk or delay progression to diabetes, and we have a local diabetes prevention program that can provide the coaching and educational tools to support this effort. We also have medications that have been studied in large programs that we can consider. We will monitor your glucose values (e.g. HbA1c) and consider additional therapy as needed with the goal of minimizing long-term risks of higher than normal blood sugars.

Conversation C?

Special thanks:
DPP
DPPOS
SCPMG
Patricia (and KP colleagues!)

thrive...

Vanita
Thanks for forwarding your slide set—thorough, informative and exciting. Enjoy Southern California. As one of our true health care systems, K-P is capable of implementing prevention effectively and efficiently.

Best regards

David