The Growing Threat of Prediabetes

Act before its too late

Glucophage metformin

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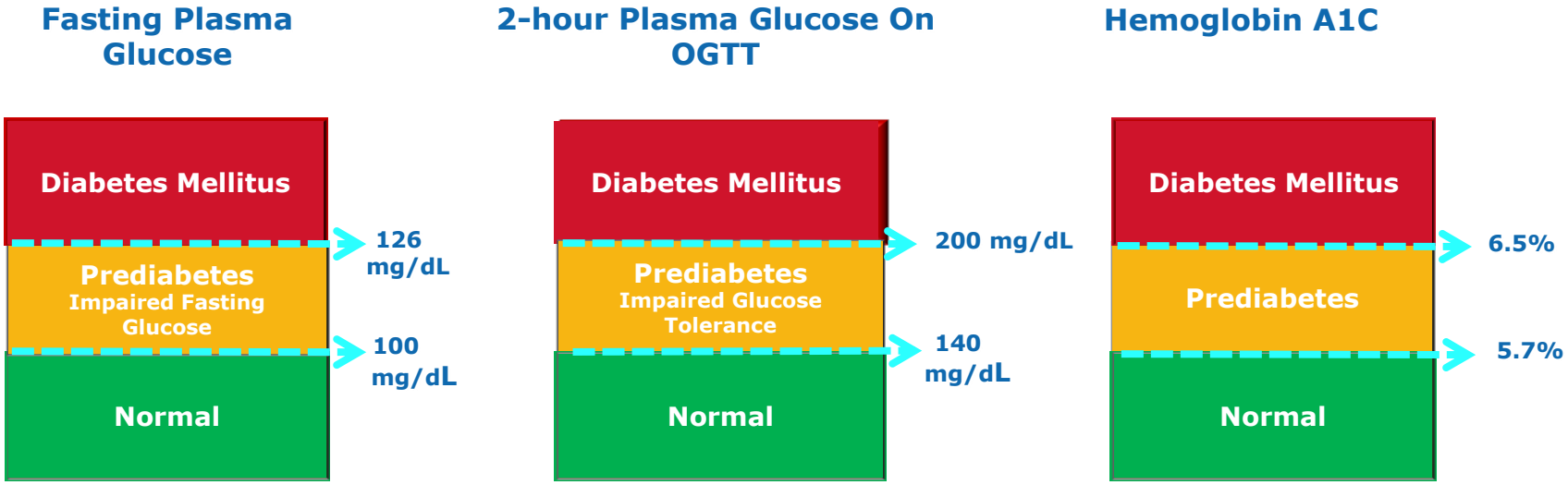
Defining of Prediabetes

A state of abnormal glucose homeostasis where blood glucose levels are elevated above those considered normal, but not as high as those required for a diagnosis of diabetes

It is often synonymous in the literature with a diagnosis of IGT, but neither the IDF nor the WHO support the use of this terminology, preferring instead “impaired glucose tolerance” and “intermediate hyperglycemia” respectively[5,6].

American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 Suppl 1:S81-90.

Prediabetes is an intermediate state between normal blood glucose and type II diabetes



Classification and Diagnosis of Diabetes:
Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S19-S40

Prediabetes is an intermediate state between normal blood glucose and type II diabetes

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)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *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.

Classification and Diagnosis of Diabetes:
Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S19-S40

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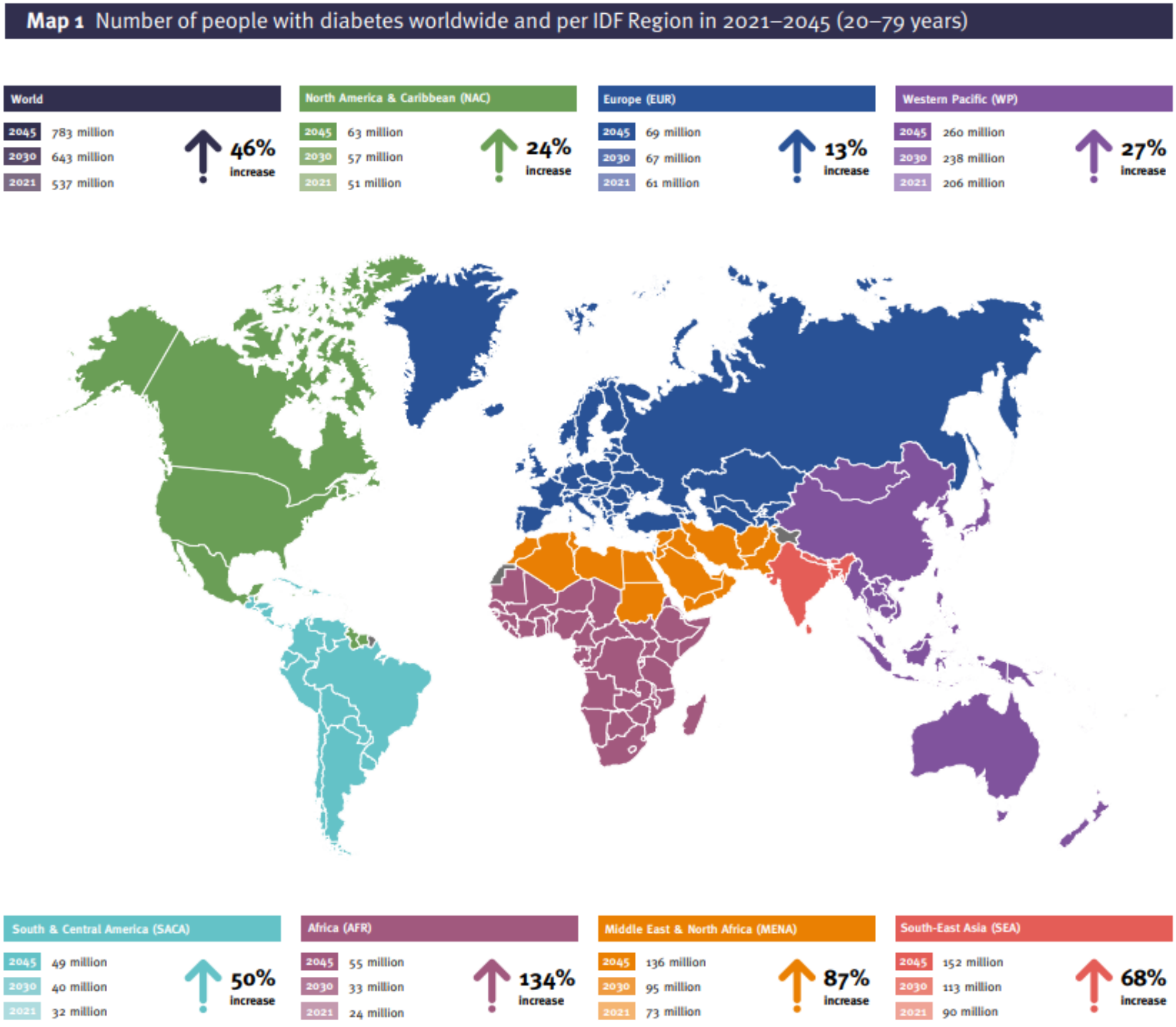

IDF Diabetes Atlas 2021 – 10th edition | www.diabetesatlas.org

Prediabetes Prevalence

Across epidemiological studies conducted in different countries during the last 5 years, the prevalence of prediabetes among adults varies widely, having been estimated to be in the range of **9.0–40.0%**.

Bullard KM, Saydah SH, Imperatore G, et al. Secular changes in U.S. Prediabetes prevalence defined by hemoglobin A1c and fasting plasma glucose: National Health and Nutrition Examination Surveys, 1999-2010. *Diabetes Care.* 2013;36:2286-2293.

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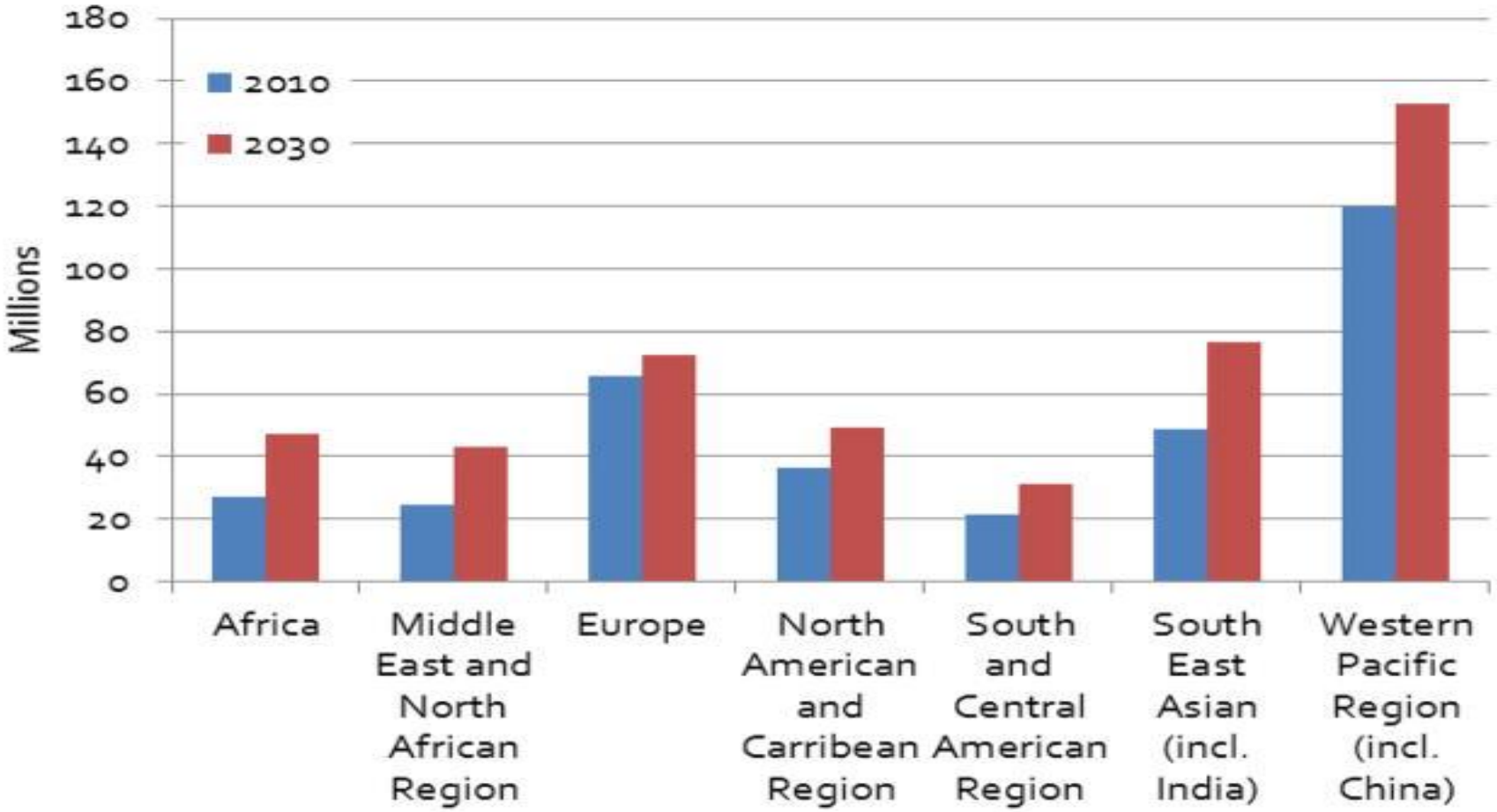
The number of people with IGT (in millions) by region among adults aged 20–79 years for the years 2010 and 2030



Tabak et al. Prediabetes: a high-risk state for diabetes development.Lancet. 2012 Jun 16;379(9833):2279-90.
doi: 10.1016/S0140-6736(12)60283-9.

Prediabetes Natural history

Prediabetes is a well characterized risk factor for the eventual development of overt type 2 diabetes

around 70% of all prediabetic individuals developing diabetes in the future

Bullard KM, Saydah SH, Imperatore G, et al. Secular changes in U.S. Prediabetes prevalence defined by hemoglobin A1c and fasting plasma glucose: National Health and Nutrition Examination Surveys, 1999-2010. *Diabetes Care.* 2013;36:2286-2293.
American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37 Suppl 1:S81-90.
American Diabetes Association. Standards of Medical Care in Diabetes—2014 *Diabetes Care*. 2014;37:S14-S80.

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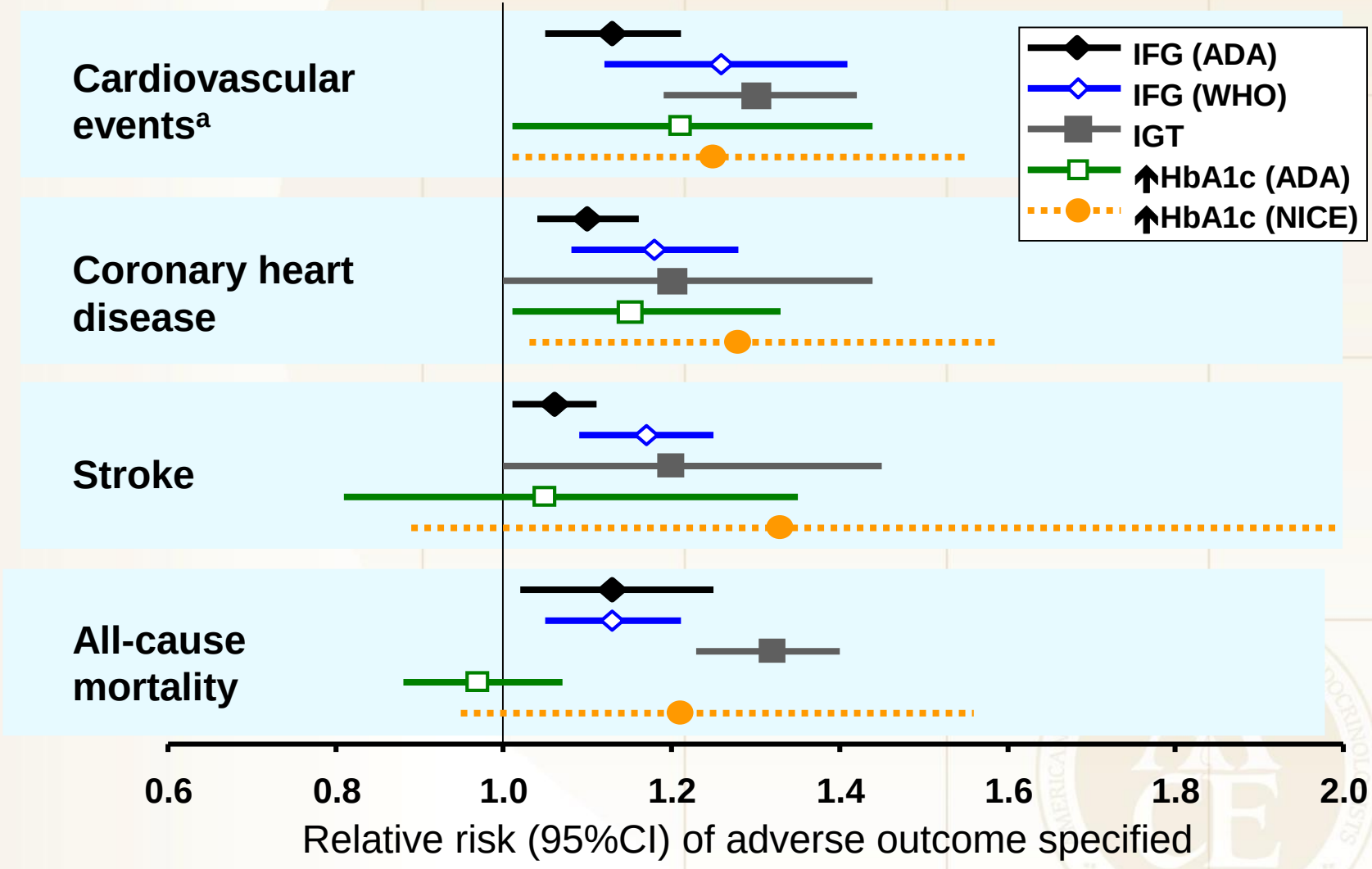
Prediabetes Associated complications

Prediabetes demonstrated association with development of

- Nephropathy.
- Chronic kidney disease.
- Small fiber neuropathy.
- Diabetic retinopathy.
- Cognitive dysfunction
- Macrovascular disease,
- Infertility in both men and women.

Tabak et al. Prediabetes: a high-risk state for diabetes development.Lancet. 2012 Jun 16;379(9833):2279-90.
doi: 10.1016/S0140-6736(12)60283-9.
Buysschaert, M et al (2014). *Prediabetes and associated disorders. Endocrine, 48(2), 371–393.* doi:10.1007/s12020-014-0436-2 .

Association of prediabetes with adverse clinical outcomes from a large meta-analysis in BMJ.



[a]As defined in original sources. IFG: impaired fasting glucose; IGT: impaired glucose tolerance ; ADA: American Diabetes Association; WHO: World Health organization ; NICE: National Institute for Health and Care Excellence.

Huang Y et al. BMJ. 2016;355:i5953.

Prediabetes Associated complications

Diabetic Retinopathy

It is one of the most common and severe microvascular complications of diabetes that is characterized by progressive loss of vision & can lead to eventual blindness; however, it develops over many years and only leads to visual impairment in some individuals.

Damage to the retinal microvasculature ➔ breakdown of the blood–-retinal barrier ➔ vessel leakage ➔ neovascularization and subsequent loss of vision.

Gabir MM, Hanson RL, Dabelea D, et al. Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organization criteria for diagnosis of diabetes. Diabetes Care. 2000;23:1113–8.
Tabak et al. Prediabetes: a high-risk state for diabetes development.Lancet. 2012 Jun 16;379(9833):2279-90. doi: 10.1016/S0140-6736(12)60283-9.

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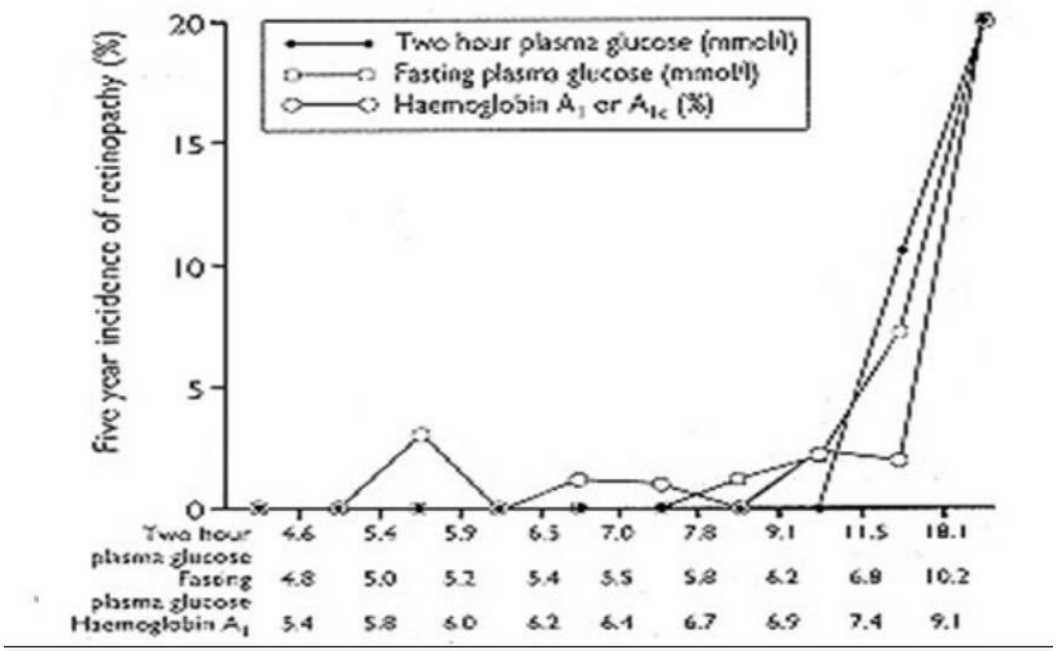
Prediabetes Associated complications

Retinopathy

In a large European cohort, DR was reported in **8.1%** of individuals diagnosed with prediabetes.

The Diabetes Prevention Program (DPP) & the Australian Diabetes, Obesity & Lifestyle Study reported that **7.9%** and **6.7%** individuals with IGT and IFG, respectively, had signs of retinopathy.

Evidence of retinopathy has been identified in individuals **7 years before** a diagnosis of type diabetes.



Prediabetes Associated complications

Nephropathy

Prediabetes is also associated with an increased risk of developing nephropathy and CKD.

In a US population, the prevalence of CKD was **17.7%** in individuals with prediabetes compared with **10.6%** in those with normal blood glucose levels, regardless of body mass index (BMI), and among the prediabetics with CKD, 56.2% were graded as stage 3 or 4.

A recent meta-analysis demonstrated that prediabetes is associated with an increased risk of CKD and that screening for nephropathy in individuals with prediabetes was justified, suggesting that more aggressive prediabetes treatment is potentially warranted.

Echouffo-Tcheugui J et al .Association between prediabetes and risk of chronic kidney disease: a systematic review and meta-analysis. Diabet Med. 2016 doi: 10.1111/dme.13113. Epub 2016 Apr 24.

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Prediabetes Associated complications

Neuropathy

Almost **50%** of patients with diabetes develop **diabetic neuropathy**; individuals with **prediabetes are similarly at higher risk** of a range of neuropathic complications.

These include autonomic neuropathy that may manifest as impaired cardiac autonomic function. Peripheral neuropathy is also an important factor in both diabetes and prediabetes; resulting from damage to motor, sensory or autonomic fibers, a spectrum of manifestations may present.

Ziegler D, Rathmann W, Dickhaus T, et al. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. Diabetes Care. 2008;31:464–9.

Prediabetes Associated complications

Cardiovascular Complication

Measures of atherosclerotic burden were significantly higher in prediabetic patients than in non-diabetic patients presenting with acute coronary syndrome; this burden was similar to that of patients with diabetes.

A meta-analysis reported that prediabetes was associated with increased composite cardiovascular events that include coronary heart disease and stroke. The relative risk was **1.30** (95% CI; 1.19 to 1.42) according to both the WHO and IDF criteria.

Tabak et al. Prediabetes: a high-risk state for diabetes development.Lancet. 2012 Jun 16;379(9833):2279-90. doi: 10.1016/S0140-6736(12)60283-9.

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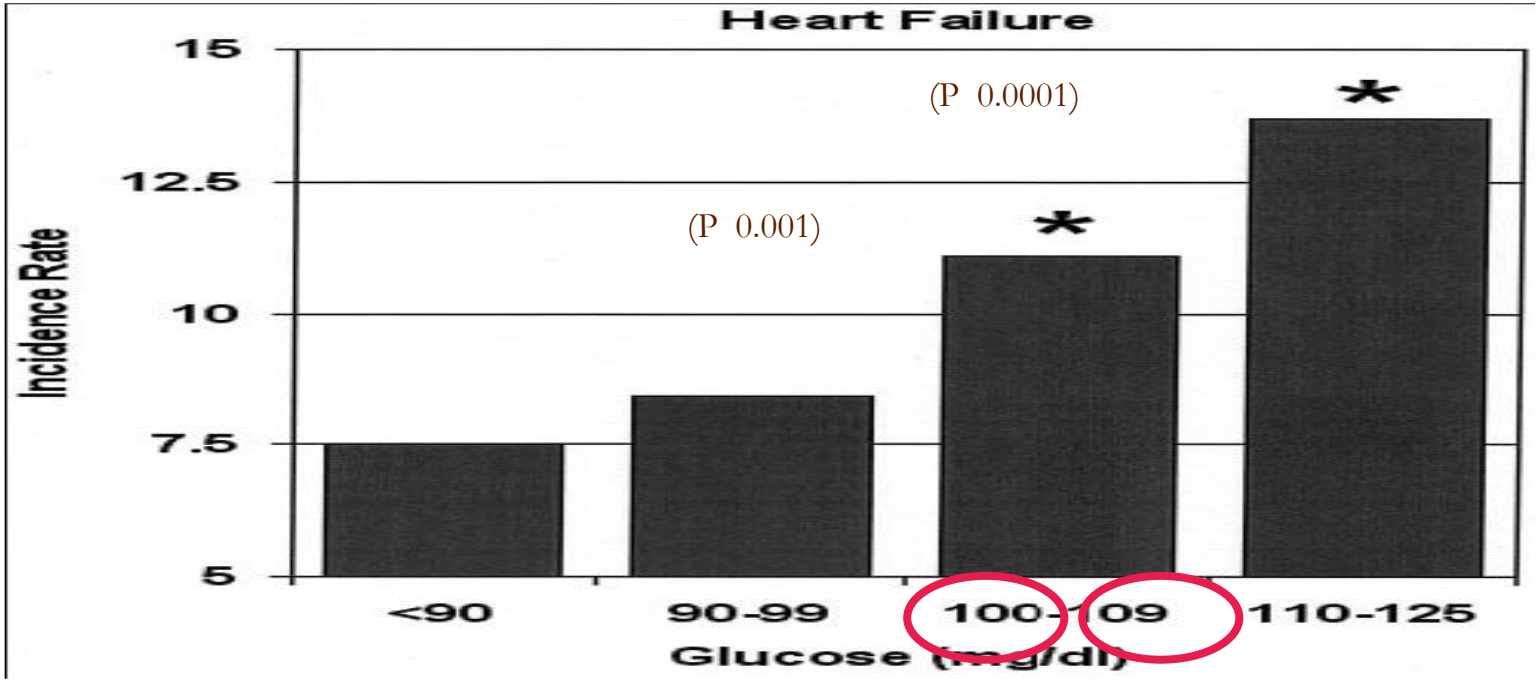
Prediabetes Associated complications

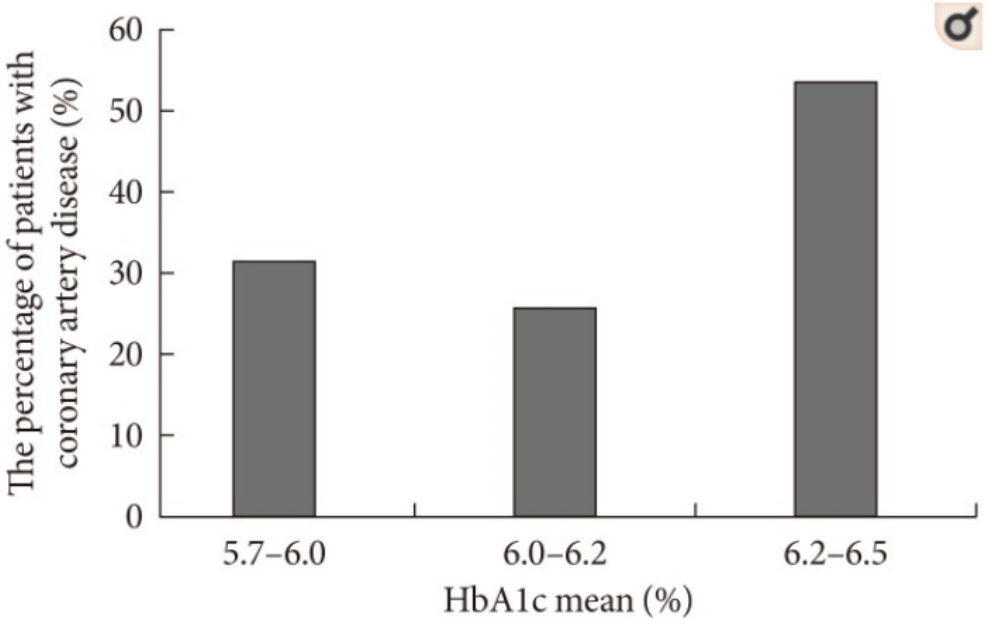
Cardiovascular Complication



Diabetes Care 28:607–611, 2005

Prediabetes Associated complications

Cardiovascular Complication



Diabetes Metab J. 2014 Feb; 38(1): 58–63.

Prediabetes Screening

Classification and Diagnosis of Diabetes

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

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian American individuals) 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)
   - Individuals with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. People with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. People who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other people, testing should begin at age 35 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.
6. People with HIV

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Classification and Diagnosis of Diabetes:
Standards of Care in Diabetes - 2023. *Diabetes Care* 2023;46(Suppl. 1):S19-S40

Classification and Diagnosis of Diabetes

Table 2.2—Criteria for the diagnosis of diabetes

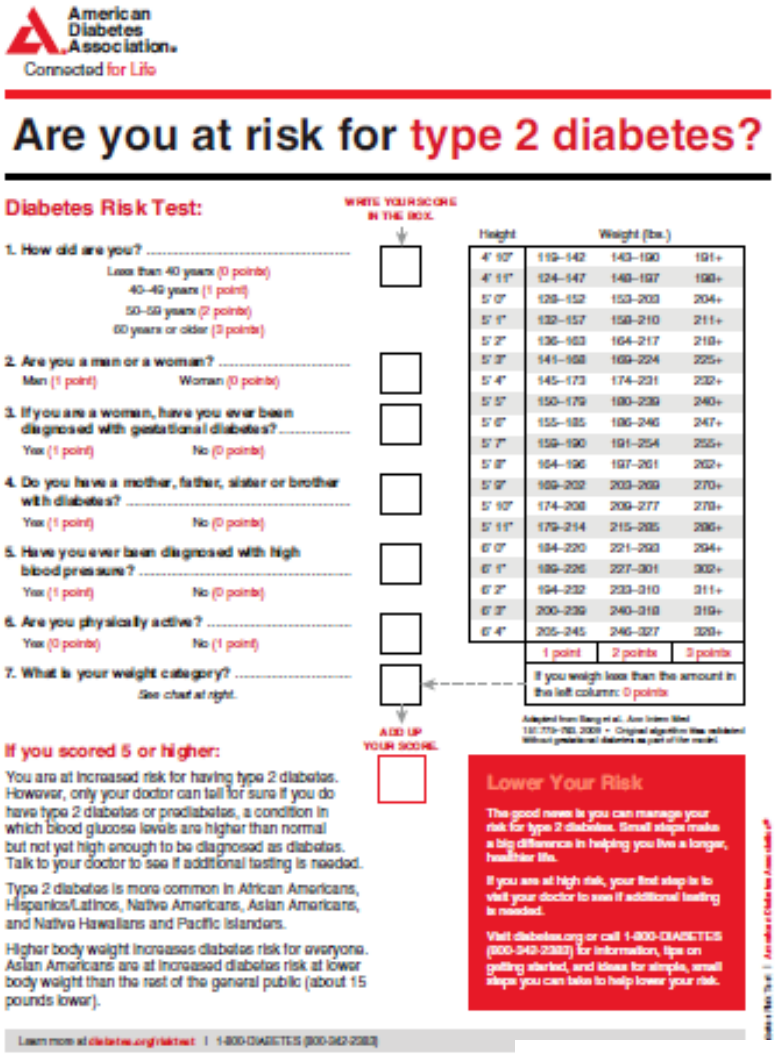
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Classification and Diagnosis of Diabetes:
Standards of Care in Diabetes - 2023. *Diabetes Care* 2023;46(Suppl. 1):S19-S40

Classification and Diagnosis of Diabetes

diabetes.org/socrisktest



American Diabetes Association.
Connected for Life

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you? .....
   - Less than 40 years (0 points)
   - 40–49 years (1 point)
   - 50–59 years (2 points)
   - 60 years or older (3 points)

2. Are you a man or a woman? .....
   - Man (1 point)
   - Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes? .....
   - Yes (1 point)
   - No (0 points)

4. Do you have a mother, father, sister or brother with diabetes? .....
   - Yes (1 point)
   - No (0 points)

5. Have you ever been diagnosed with high blood pressure? .....
   - Yes (1 point)
   - No (0 points)

6. Are you physically active? .....
   - Yes (0 points)
   - No (1 point)

7. What is your weight category? .....
   - See chart at right.

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

ADD UP YOUR SCORE.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Learn more at diabetes.org/risktest | 1-800-DIABETES (800-342-2383)

Classification and Diagnosis of Diabetes:
Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S19-S40

Prediabetes Management

PREVENTION OF DIABETES:

LIFESTYLE STUDIES

Prevention or Delay of Type 2 Diabetes

Overall Recommendation

3.1 Monitor for the development of type 2 diabetes in those with prediabetes at least annually; modified based on individual risk/benefit assessment. E

Standards of Care in Diabetes - 2023. *Diabetes Care* 2023;46(Suppl. 1):S19-S40

Prevention or Delay of Type 2 Diabetes

Lifestyle Behavior Change for Diabetes Prevention

3.2 Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 min/week of moderate intensity physical activity. A

3.3 A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. B

Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S19-S40

Prevention or Delay of Type 2 Diabetes

Lifestyle Behavior Change for Diabetes Prevention (continued)

3.4 Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. A Diabetes prevention programs should be covered by third-party payers, and inconsistencies in access should be addressed.

3.5 Based on patient preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. B

Standards of Care in Diabetes - 2023. *Diabetes Care* 2023;46(Suppl. 1):S19-S40

Prevention or Delay of Type 2 Diabetes

Pharmacologic Interventions

3.6 **Metformin therapy for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes**, as typified by the Diabetes Prevention Program, especially those aged 25–59 years with BMI ≥35 kg/m^2, higher fasting plasma glucose (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus. A

3.7 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. B

Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S19-S40

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Prevention or Delay of Type 2 Diabetes

Prevention of Vascular Disease and Mortality

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

3.9 Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be discontinued. B

3.10 In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fracture. A Lower doses may mitigate the risk of adverse effects. C

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Prevention or Delay of Type 2 Diabetes

Patient-Centered Care Goals

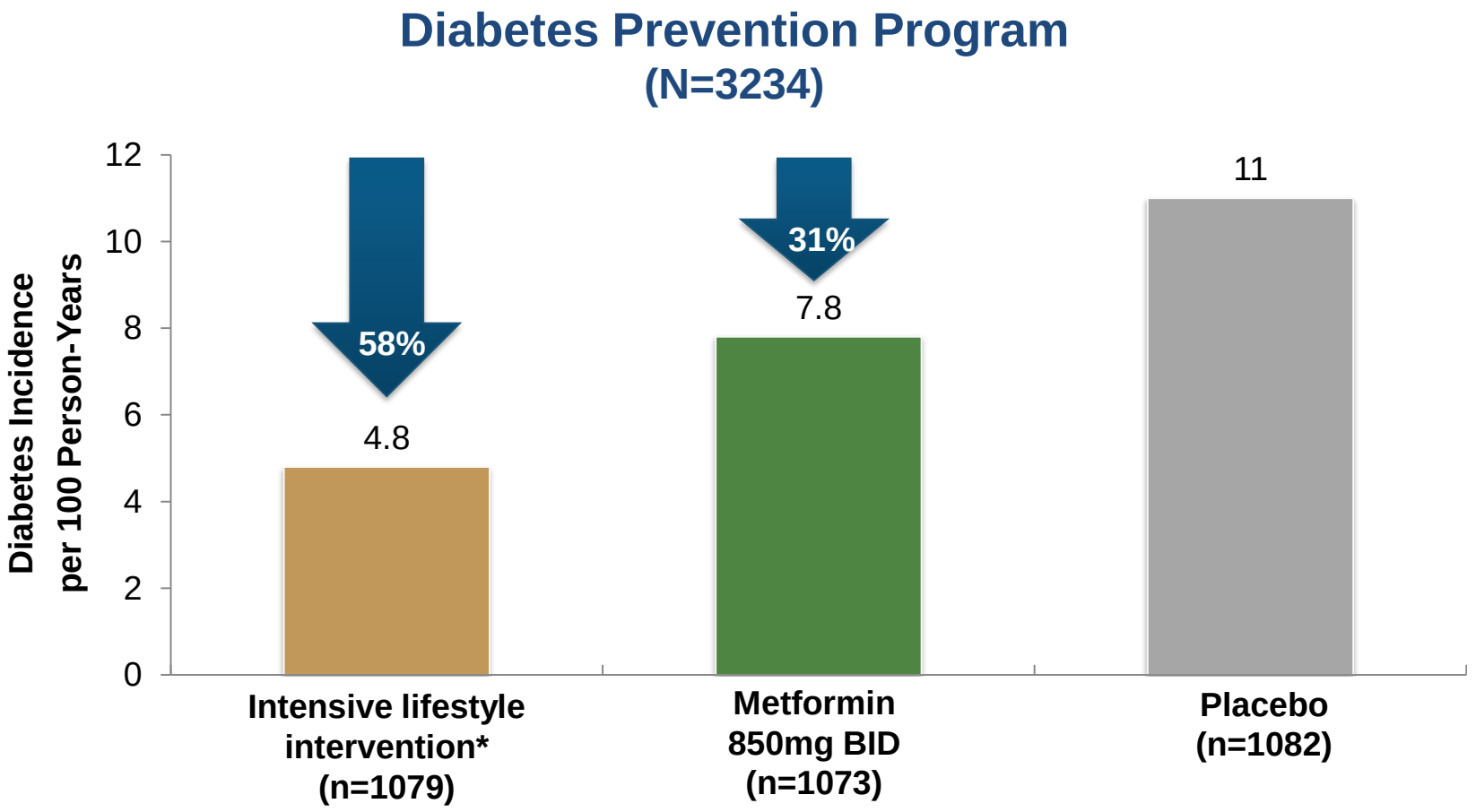
3.11 In adults with overweight/obesity at high risk of type 2 diabetes, care goals should include weight loss or prevention of weight gain, minimizing the progression of hyperglycemia, and attention to cardiovascular risk and associated comorbidities. B

3.12 Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, cardiovascular risk reduction) may be considered to support person-centered care goals. B

3.13 More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥35 kg/m^2, those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, A1C ≥6.0%), and individuals with a history of gestational diabetes mellitus. A

Standards of Care in Diabetes - 2023. *Diabetes Care* 2023;46(Suppl. 1):S19-S40

Intensive Lifestyle Intervention Effectively Prevents Progression From IGT to T2D



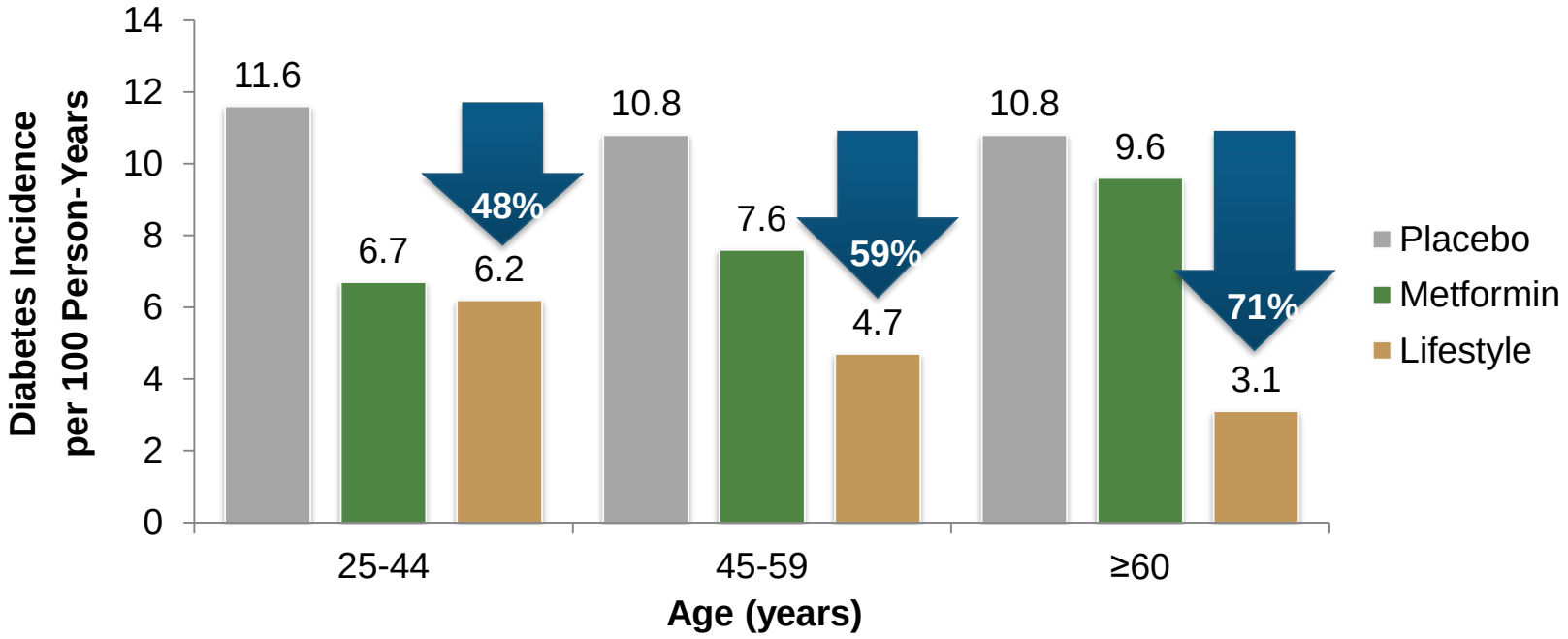
*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

IGT, impaired glucose tolerance; T2D, type 2 diabetes.

DPP Research Group. *N Engl J Med*. 2002;346:393-403.

Lifestyle Intervention More Effectively Prevents Diabetes as Populations Age

Diabetes Prevention Program
(N=3234)

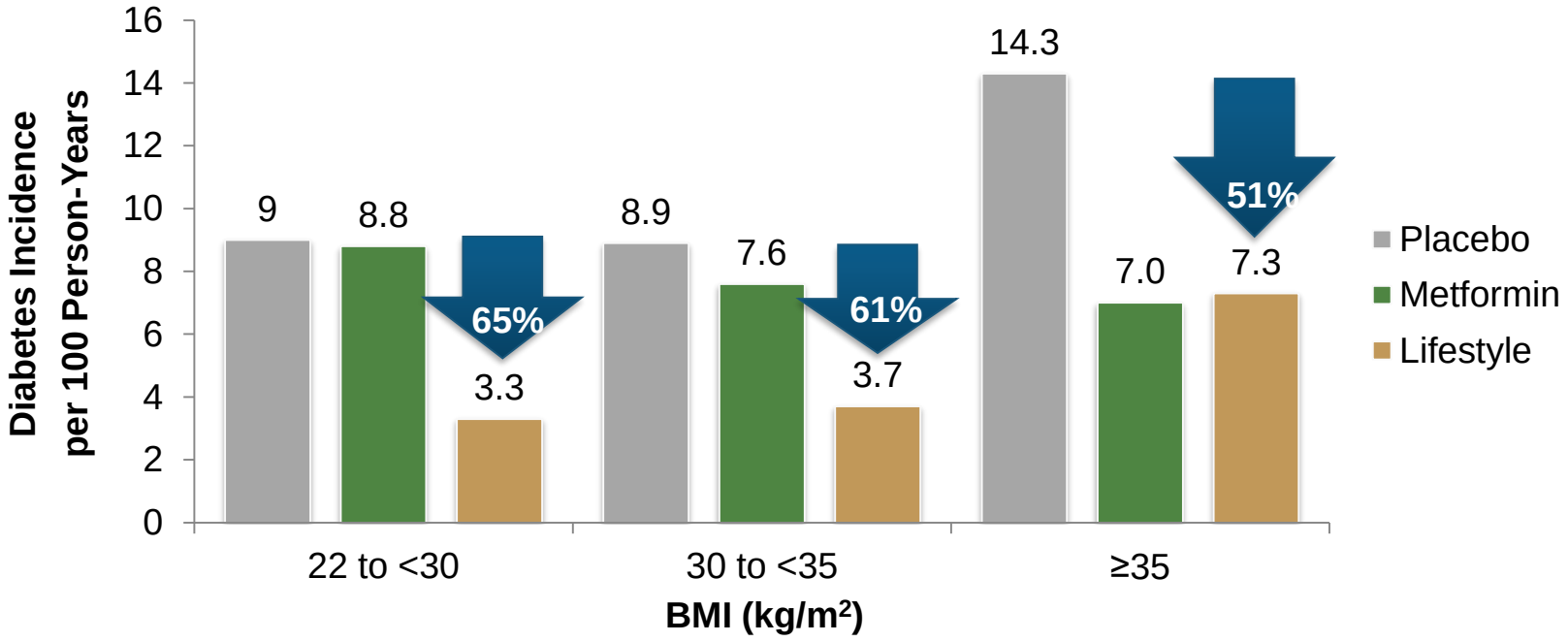


*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

DPP Research Group. *N Engl J Med*. 2002;346:393-403.

Effectiveness of Lifestyle Intervention for Diabetes Prevention Wanes as Weight Increases

Diabetes Prevention Program
(N=3234)

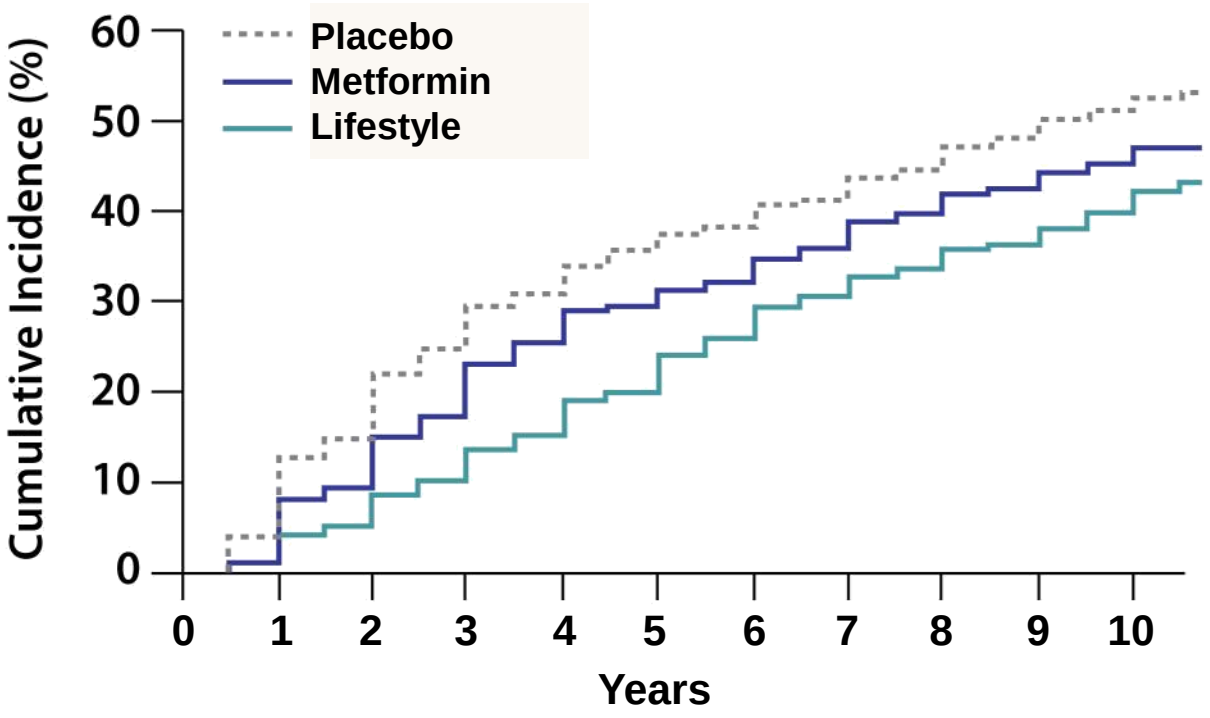


*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

DPP Research Group. *N Engl J Med*. 2002;346:393-403.

10-Year Incidence of T2D

DPP Outcomes Study (N=2766)

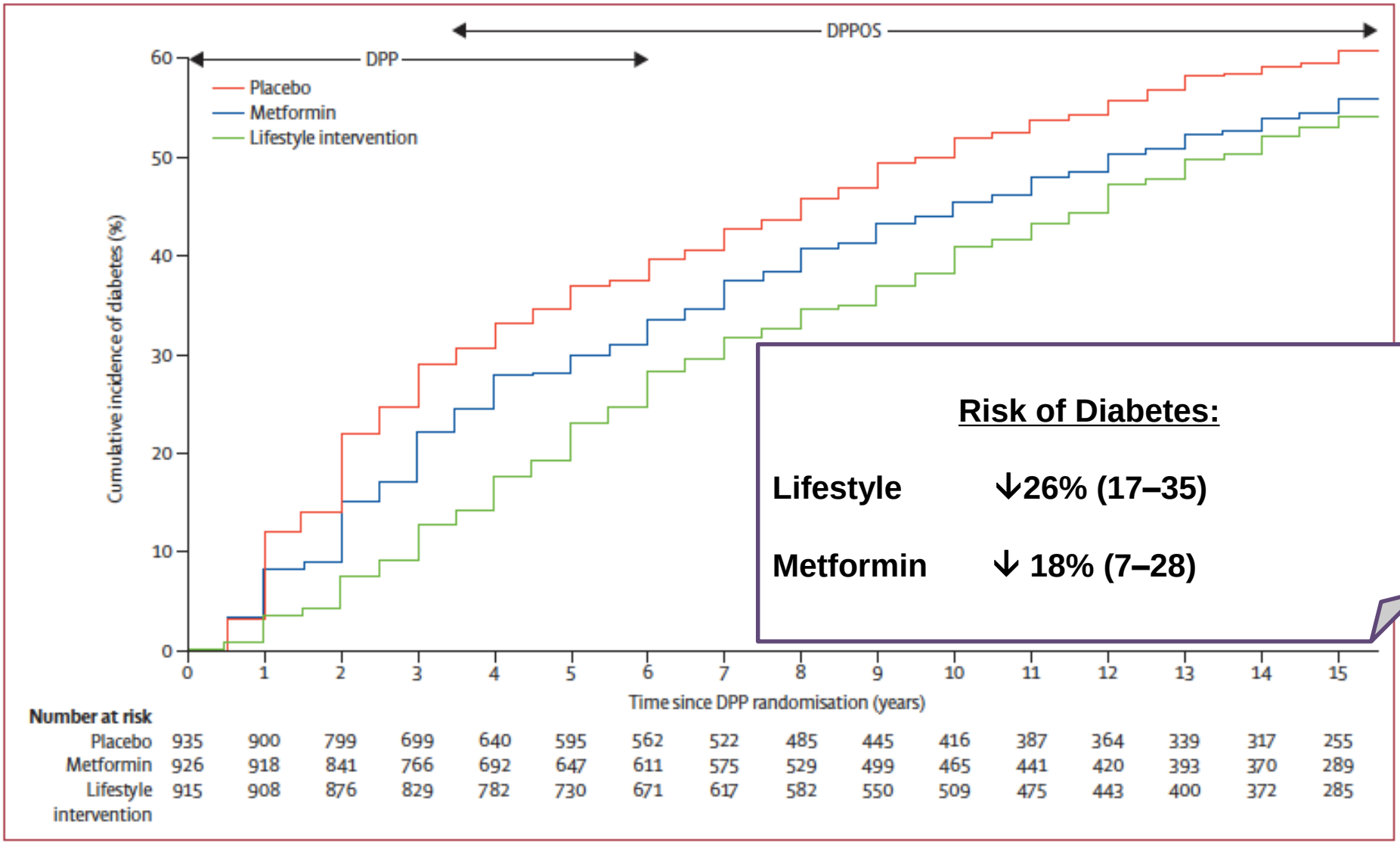


DPP, Diabetes Prevention Program; T2D, type 2 diabetes.

DPP Research Group. *Lancet*. 2009;374:1677-1686.

Diabetes Prevention Program Outcomes Study (DPPOS)

15 years follow-up in 2015 & 22 years in 2022



Risk of Diabetes:

Lifestyle **↓26% (17–35)**

Metformin **↓ 18% (7–28)**

Diabetes Prevention Program Research Group Lancet 2015;3: 866-875

Overview of Trials in Prediabetes
Lifestyle Modification Intervention

- **Lifestyle intervention continues to have an effect, even after 20 years**

Study		N	Intervention	Treatment	Risk Reduction
Da Qing[1,2]	IGT	577	Lifestyle	6 years 20 years	34% - 69%
Finnish DPS[3,4]	IGT	523	Lifestyle	3+ years 7 years	58%
Diabetes Prevention Program (DPP)[5,6]	IGT	3324	Lifestyle	3 years 10 years	58% 34%

American Diabetes Association.

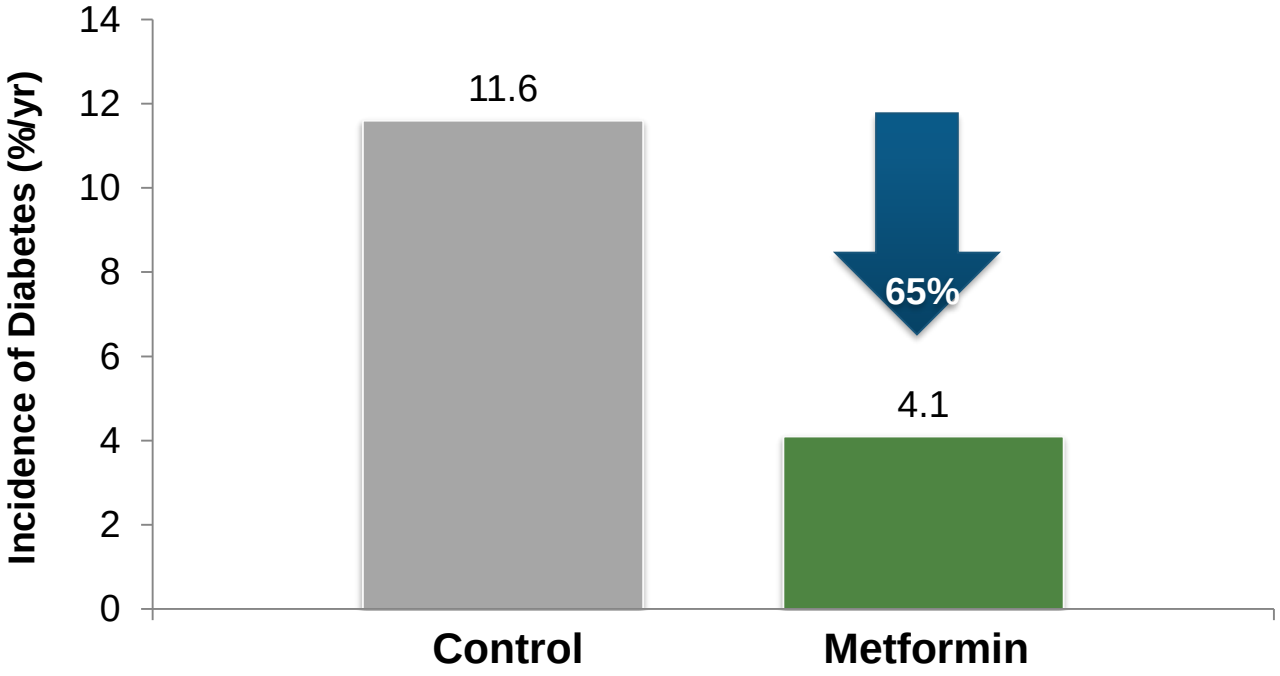
1. *Diabetes Care*. 1997;20:537-544.
2. *Lancet*. 2008;371:1783-1789.
3. *N Engl J Med*. 2001;344:1343-1350.
4. *Lancet*. 2006;368:1673-1679.
5. *N Engl J Med*. 2002;346:393-403.
6. *Lancet*. 2009;374:1677-1686.

PREVENTION OF DIABETES:

METFORMIN ROLE

The Effect of Metformin on the Progression of IGT to Diabetes Mellitus

The Chinese Prevention Study (N=321)

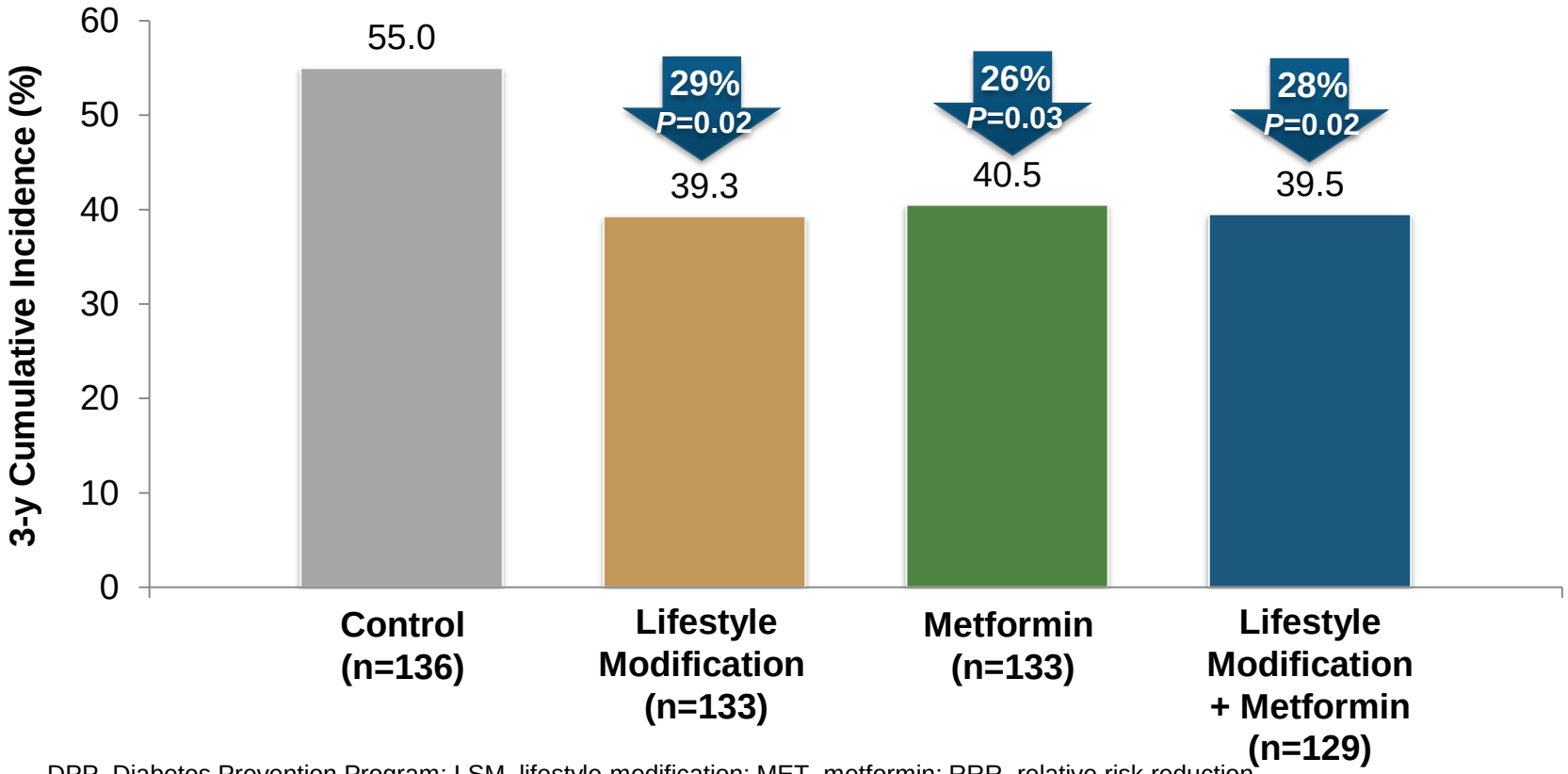


IGT, impaired glucose tolerance; RRR, relative risk reduction.

Yang W, et al. *Chin J Endocrinol Metab.* 2001;17:131-136.

Effect of Lifestyle Modification and Metformin on Cumulative Diabetes Incidence

The Indian DPP (N=531)

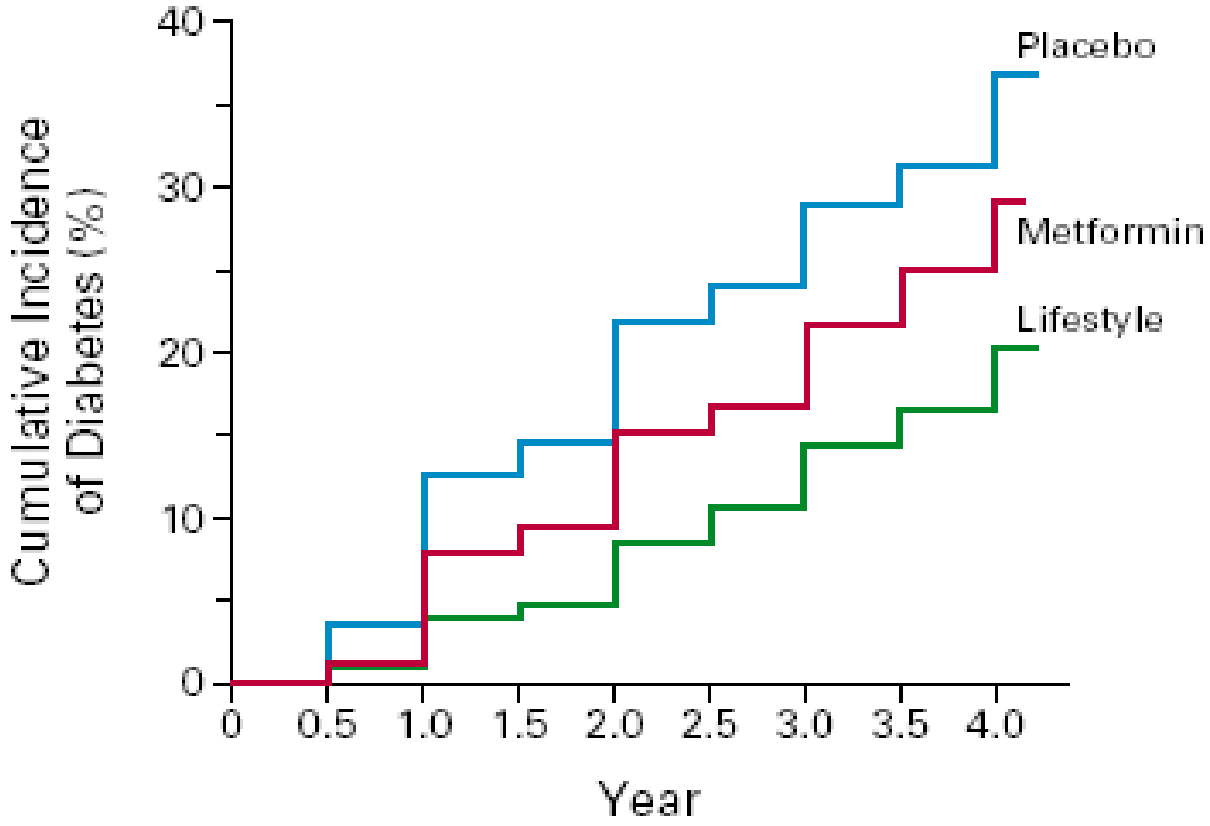


DPP, Diabetes Prevention Program; LSM, lifestyle modification; MET, metformin; RRR, relative risk reduction.

Ramachandran A, et al. *Diabetologia.* 2006;49:289-297.

Type 2 Diabetes Can Be Prevented

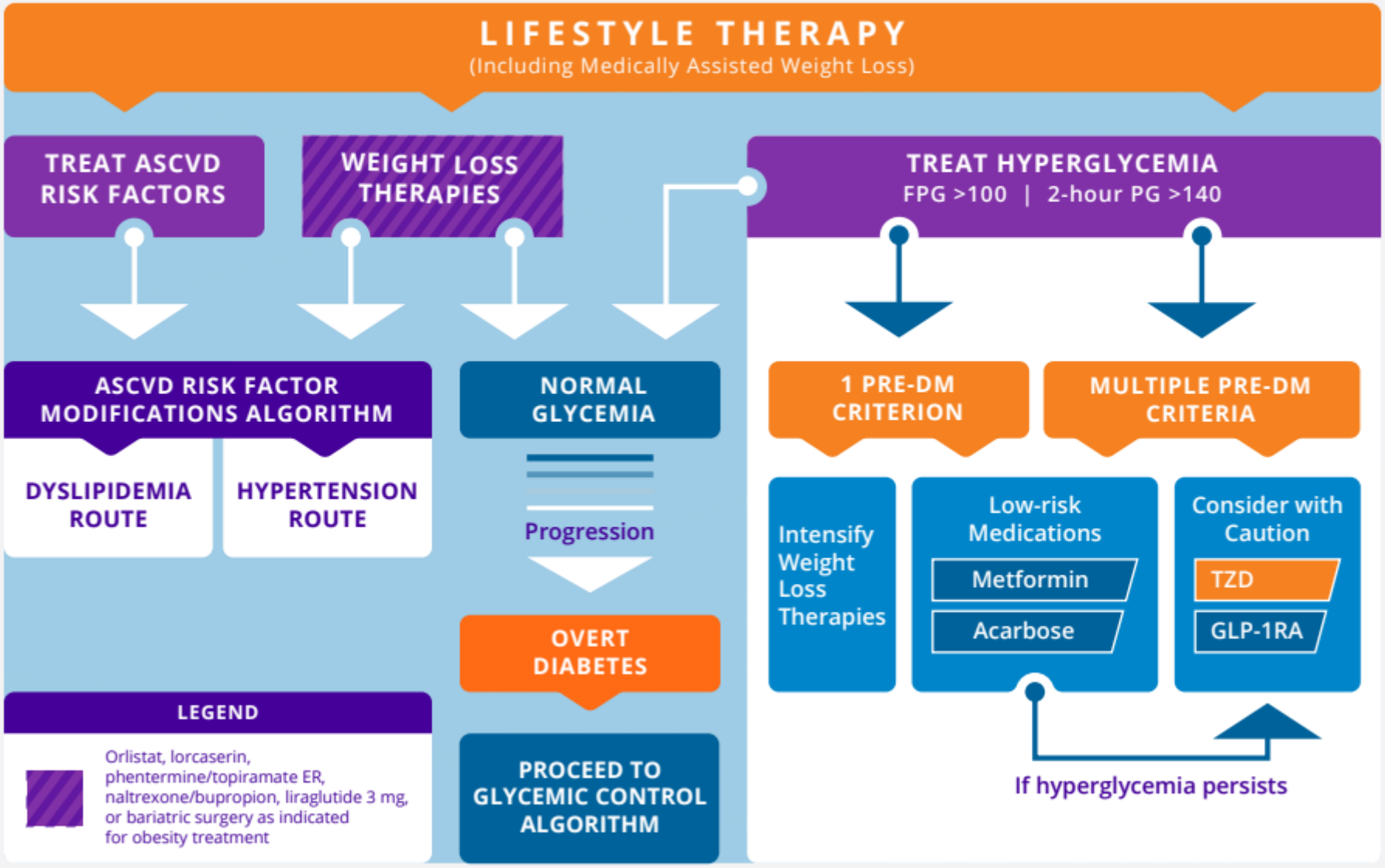
58% decreased risk with lifestyle modification
31% decreased risk with metformin



*From New England Journal of Medicine, Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin, Vol. 346, pp. 393-403, Copyright © 2002, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)



NICE Guidance on metformin use in prediabetes

- Add metformin to lifestyle support when plasma glucose blood test has deteriorated over 3-6 months, particularly for overweight (BMI>35)

- **Check renal function initially then every 6 months**

- **Start with 500mg then increase gradually to 2000mg daily**

- **Prescribe for 12 months initially and stop if no benefit has been noted**

NICE Guidance on diabetes Prevention 2018

MERCK