The Role of METFORMIN
نقش متفورمین
IN THE MANAGEMENT OF PREDIABETES AND DIABETES
در مدیریت پیش دیابت و دیابت

تاریخ برگزاری: ۲۸ بهمن ماه

ساعت برگزاری: ۱۰ الی ۱۳

GABRIC
Virtual Diabetes Academy
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MERCK

Diabetes Self-Management Education and Support

Dr Sara Sedaghat, MD

Gabric Diabetes Education Association

Gabric Virtual Academy

Renovating Diabetes Education

انجمن اطلاع رسانی دیابت گابریک

تنها مرکز آموزش فدراسیون بین المللی دیابت در ایران

عضو رسمی فدراسیون بین المللی دیابت

Member of the
International
Diabetes Federation
عضو فدراسیون بین المللی دیابت

International Diabetes
Federation
Centre of Education
مرکز آموزش فدراسیون بین المللی دیابت

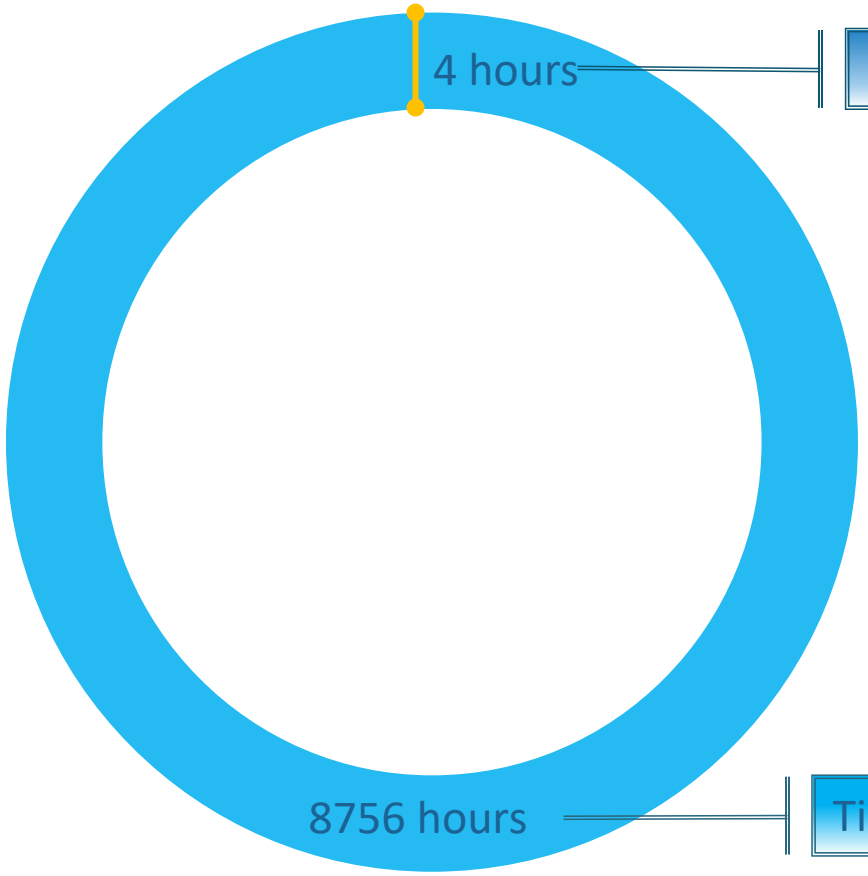
گابریک
انجمن اطلاع رسانی دیابت
نگرشی نو در آموزش دیابت

Member of the International Diabetes Federation
عضو فدراسیون بین المللی دیابت

ماموریت‌های گابریک

1. برگزاری دوره‌های آموزشی، مشاوره و بررسی وضعیت کنترل قند اعضا، آموزش و کنترل رژیم غذایی و فعالیت بدنی (آنلاین و حضوری)
2. برگزاری دوره‌های آموزشی علمی در قالب آکادمی آنلاین دیابت گابریک با همراهی داوطلبانه جمعی از اساتید برتر پزشکی کشور
3. اطلاع رسانی همگانی دیابت با استفاده از پلتفرم‌های اثرگذار همچون تبلیغات محیطی در سطح شهر و استفاده از ظرفیت‌های فضای مجازی
4. شناسایی مشکلات جامعه دیابتی در حوزه‌های مختلف و تلاش برای تاثیر بر سیاست‌گذاران و رفع موانع موجود در کنترل استاندارد دیابت
5. اهدای تجهیزات کنترل قند مددجویان، کمک هزینه دارو و درمان دیابت، تامین بخشی از نیازهای اساسی معیشتی و تحصیلی

Each patient has a doctor inside him



Direct HCP contact per year

Time needed to be self-managed

More than 95% of diabetes care is done by the patient.

Chaney, D. (2015). *Practical Diabetes*, *32*(6), 212.
Funnell, M. M. and R. M. Anderson (2000). JAMA 284(13): 1709-1709.

More time is needed!

TABLE 1. CDE Estimation of Time Needed for Self-Care Activities for an Adult With Established Type 2 Diabetes on Oral Medications and Performing SMBG Twice Daily

ADA-Recommended Task	Time Needed ± SD (minutes)
SMBG	11 ± 26
Recordk… and bl…	
Takin…	
Foot …	
Oral …	
Probl…	
Obta…	
Meal …	
Shop…	
Prepa…	
Exercise	32 ± 17
Stress management	16 ± 19
Support/support groups	13 ± 19
Scheduling medical appointments	9 ± 13

TABLE 2. CDE Estimation of Time Needed for Self-Care Activities for a Child (and Family) With Established Type 1 Diabetes on Basal-Bolus Insulin Therapy (Four Shots/Day) and Performing SMBG Four Times Daily

ADA-Recommended Task	Time Needed ± SD (minutes)
SMBG	17 ± 12
Recordkeeping (e.g., fasting serum glucose …	16 ± 18
…	…
Parental visits to school for problems (hypoglycemia/hyperglycemia)	15 ± 21
Support/support groups	14 ± 21
Obtaining supplies	11 ± 16
Scheduling medical appointments	9 ± 15

The total estimated time needed daily for recommended diabetes self-care:

~4 hours for adults and >5 hours for children

Shubrook JH et al. Diabetes Spectrum. 13, 2018

Extra decisions, Extra burden!

T1DM: 180 extra decisions every day, on average

2020 DSMES CONSENSUS REPORT

Diabetes Self-management Education and Support in Adults With Type 2 Diabetes

A Consensus Report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association

Consensus Report

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From HealthPartners, Bloomington, Minnesota (Powers); Medstar Health Research Institute, MedStar Diabetes Institute and MedStar Health System Nursing, Hyattsville, Maryland (Bardsley); Independent consultant, Albuquerque, New Mexico (Cypress); University of Michigan Medical School, Ann Arbor, Michigan (Funnell); MercyOne Clive Internal Medicine, Clive, Iowa (Harms); Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism, University of Chicago, Chicago, Illinois (Hess-Fischl); Martin Army Community Hospital, Fort Benning, Georgia (Hooks); Cleveland Clinic Diabetes Center, Cleveland, Ohio (Isaacs); Johnson & Wales University, Providence, Rhode Island (Mandel); Maryniuk & Associates, Boston, Massachusetts (Maryniuk); DiabetesSisters, Chicago, Illinois (Norton); Association of Diabetes Care & Education Specialists, Chicago, Illinois (Rinker, Uelmen); and University of Pittsburgh, Pittsburgh, Pennsylvania (Siminerio).

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This article contains Supplementary Data online at https://journals.sagepub.com/doi/suppl/10.1177/0145721720930959.

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Volume 46, Number 4, August 2020

Key clinical Benefits of DSMES

- Average A_{1C} reduction of 0.45–0.57% when compared with usual care for people with T_2D treated with a variety of modalities *(lifestyle alone, oral and injected medication)*
- Reduction in the onset and/or worsening of diabetes-related complications
- Reduction of all-cause mortality

Powers MA, et al. *Diabetes Care*. 2020, 43:1636-49.

Patient-centered DSME

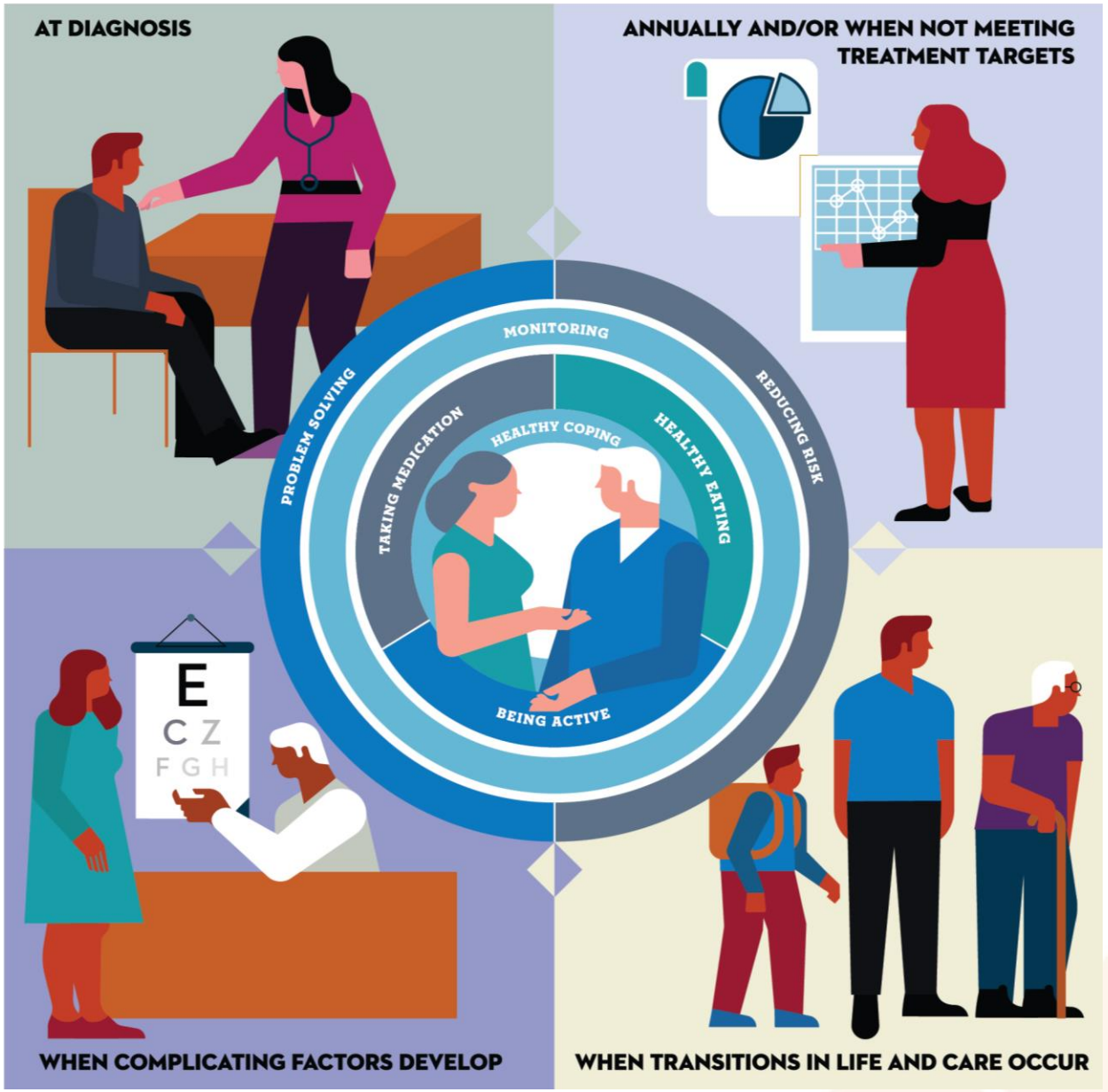
ADCES Association of Diabetes Care & Education Specialists

ADCES7™

ADCES7 SELF-CARE BEHAVIORS™

PROBLEM SOLVING
REDUCING RISKS
MONITORING
TAKING MEDICATION
HEALTHY EATING
HEALTHY COPING
BEING ACTIVE

Four critical times to provide and modify DSMES



Powers MA, Bardsley JK, et al. DSMES Consensus Report, Diabetes Care Jul 2020, 43 (7) 1636-1649

DSMES Consensus Report Recommendations

DSMES Improves Health Outcomes, Quality of Life, and Is Cost Effective, and People With Diabetes Deserve the Right to DSMES Services. Therefore, It Is Recommended That:
Providers:
1. Discuss with all persons with diabetes the benefits and value of initial and ongoing DSMES.
2. Initiate referral to and facilitate participation in DSMES at the 4 critical times: (1) at diagnosis, (2) annually and/or when not meeting treatment targets, (3) when complicating factors develop, and (4) when transitions in life and care occur.
3. Ensure coordination of the medical nutrition therapy plan with the overall management strategy, including the DSMES plan, medications, and physical activity on an ongoing basis.
4. Identify and address barriers affecting participation with DSMES services following referral.
Health policy, payers, health systems, providers, and health care teams:
5. Expand awareness, access, and utilization of innovative and nontraditional DSMES services.
6. Identify and address barriers influencing providers' referrals to DSMES services.
7. Facilitate reimbursement processes and other means of financial support in consideration of cost savings related to the benefits of DSMES services.

Powers MA, Bardsley JK, et al. DSMES Consensus Report, Diabetes Care Jul 2020, 43 (7) 1636-1649

Summary of DSMES Benefits to Discuss With People With Diabetes[15-28,30-33,40,89]

- Provides critical education and support for implementing treatment plan
- Reduces hypoglycemia
- Addresses weight maintenance or loss
- Enhances self-efficacy and empowerment
- Increases healthy coping
- Decreases diabetes-related distress
- Promotes lifestyle behaviors including healthful meal planning and engagement in regular physical activity
- Improves quality of life
- Reduces all-cause mortality
- Reduces emergency department visits, hospital admission, and hospital readmission
- Lowers A1C

No negative side effects

Medicare / most insurers covers costs

Powers MA, Bardsley JK, et al. DSMES Consensus Report, Diabetes Care Jul 2020, 43 (7) 1636-1649

If DSMES were a pill, would you prescribe it?

Comparing the benefits of DSMES/MNT vs metformin therapy

	Benefits rating	
CRITERIA	DSMES/MNT	METFORMIN
Efficacy	High	High
Hypoglycemia risk	Low	Low
Weight	Neutral/Loss	Neutral/Loss
Side effects	None	Gastrointestinal
Cost	Low/Savings	Low
Psychosocial benefits*	High	N/A

N/A, not applicable. *Psychosocial benefits include *improvements to* quality of life, self-efficay, empowerment, healthy coping, knowledge, self-care behaviors, meal planning, healthier food choices, more activity, use of glucose monitoring, lower blood pressure and lipids and *reductions in* problems in managing diabetes, diabetes distress, and the risk of long-term complications (and prevention of acute complications).

Powers MA, Bardsley JK, et al. DSMES Consensus Report, Diabetes Care Jul 2020, 43 (7) 1636-1649

The global challenge

Low Utilization of DSME despite its proven benefits

(Li, Shrestha et al. 2014)

Low Utilization of DSMES

5%

Of **MEDICARE** beneficiaries with newly diagnosed diabetes used DSMT services[1]

6.8%

Of individuals with newly diagnosed T2D with **PRIVATE HEALTH** insurance received DSMES within 12 months of diagnosis[2]

8.2%

UK:
of patients with T2DM attended DSME.

23%

Iran:

Phase 2 analysis from nationwide diabetes report of National Program for Prevention and Control of Diabetes (NPPCD-2018)

The prevalence of patients who received education for nutrition therapy or diabetes self-management was 16.3% and 23.3% respectively.

1. Li R, et al. Morbidity Mortality Weekly Report, 2014
2. Strawbridge LM, et al. Health Educator, 2015
3. Li, Shrestha et al. 2014
4. Esteghamati, A. et al. Primary Care Diabetes, 2020

- **Diabetes School Model:**
  - 20 different programs
  - 8 different target groups
  - Elementary to advanced level

Elementary			
Elementary (E)	★	1	Building motivation, correcting misconceptions Basics of diabetes and the pass to self-management
Keepo Adventures (E.KA)	D	2	Simplified educational concepts for children with diabetes
Gestational Diabetes (E.GDM)	H	1	Promoting mother/baby health to improve the outcome of GDM affected pegnancies through diabetes education. Addressing nutrition & Physical activity recomendations
Intermediate			
Type 1 (I.T1)	A,E	3	Addressing the daily skills for diabetes self-management i.e. SMBG, insulin injection, healthy nutrition and physical activity. Getting to know carbohydrates and nutritional needs as well as the path to prevention of diabetes complications.
Type 2-Insulin (I.T2I)	B	3	
Type 2-Oral Agents (I.T2O)	C	2	
Advanced			
Type 1 (I.T1)	A,E	2	Meal planning in practice, practical carbohydrate counting exercise program and blood glucose pattern and dose adjustment, sick day care
Type 2-Insulin (I.T2I)	B	2	
Type 2-Oral Agents (I.T2O)	C	2	

Complementary			
Stress Management (C.SM)	★	1	Stress symptoms and practical relaxation techniques
Weight Management (C.WM)	★	1	Counting calories and managing a weight loss plan
ABC of Diabetes Contorl (C.ABC)	★	1	Lifestyle modifications to manage HTN & dyslipidemia
Parents Discussion Club (C.PDC)	E	2	Strenghtening parents to play an effective role in the manegement of their child's diabetes
Gabric Support Session (C.GSS)	A	2	Empowering patients to implement "SMART" goal setting technique to promote self-assessment & overall care
Special			
Diabetes Prevention (S.HNDP)	G	1	Introducing practical modifications to lifestyle, including nutrition & activity, to effectively prevent diabetes
Insulin My Friend (S.IMF)	A,F	4	National educational program for diabetics, primary healthcare providers and healthcare professionals
Basics of Diabetes Education (S.BDE)	F	4	Advanced training workshop fo HCPs, addressing the importance and techniques of patient education
Diabetes Ambassadors Workshop (S.DAW)	F	1	National program focused on nurse education, addressing special skills i.e. sick day management
PsiTE-Type 1 (S.PSITE)	A,D	3	Innovative course for type 1 diabetics living in provincial areas, utilizing online solutions for education and support

Tailored Diabetes Education

- A Patients with T1DM
- B Patients with T2DM (Insulin)
- C Patients with T2DM (Oral agents)
- D Children with T1DM
- E Parents of children with T1DM
- F Healthcare professionals
- G General/at risk population
- H Women with GDM

Individualized Education Path

Gabric Diabetes School:

What we have learned

EMHJ
Eastern Mediterranean Health Journal
La Revue de Santé de la Méditerranée orientale
المجلة الصحية لشرق المتوسط

Report EMHJ – Vol. 24 No. 1 – 2018

GABRIC Diabetes School: an innovative education centre for people with diabetes

Alireza Esteghamati [1], Farhad Hosseinpanah [2], Seyed Adel Jahed [3], Hadi Harati [3], Mohammad Taghi Cheraghchi Bashi Astaneh [3], Hormoz Kaykhanzadeh [3] and Sara Sedaghat [3]

[1]Endocrinology and Meatbolism Research Center, Vali-Asr Hospital School of Medicine, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran [2]Obesity research center, Research institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran [3]Gabric Diabetes Education Association, Tehran, Islamic Republic of Iran (Correspondence to: Sara Sedaghat: s.sedaghat@gabric.ir).

Abstract

Diabetes prevalence and deaths attributable to diabetes continue to rise across globally. Diabetes Self-Management Education and Support (DSME/S) is a critical resource designed to help people with diabetes (PWD) successfully self-manage their disease; however, its utilization is too low. In the Islamic Republic of Iran, there are currently limited structured educational programmes and no national standards for DSME/S protocol. In response to this, the GABRIC Diabetes Education Association (GDEA) has been developed as a school for diabetics, which has a comprehensive DSME/S programme for PWD with 18 distinct courses on 5 levels for 8 target groups. In addition, GABRIC has developed a database registry with more than 100 000 members throughout the country, of whom 95% are diabetic with a proportion of 82% Type 2 diabetes and 13% Type 1 diabetes. The success of the GABRIC school model results is yet to be investigated through study trials, and offers a fruitful line of research.

Keywords: Diabetes, diabetic, education, self-management, noncommunicable diseases

Citation: Esteghamati A, Hosseinpanah F, Adel Jahed S, Harati H, Astaneh MTCB, Kaykhanzadeh H, et al. GABRIC diabetes school: an innovative education centre for diabetics. East Mediterr Health J. 2018;24(1):99–103. https://doi.org/10.26719/2018.24.1.99

Received: 06/01/18; accepted: 17/01/18

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GABRIC Diabetes School: an innovative education centre for people with diabetes

Report

PDF version

Alireza Esteghamati 1, Farhad Hosseinpanah 2, Seyed Adel Jahed 3, Hadi Harati 3, Mohammad Taghi Cheraghchi Bashi Astaneh 3, Hormoz Kaykhanzadeh 3 and Sara Sedaghat 3

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http://www.emro.who.int/emhj-volume-24-2018/volume-24-issue-1/gabric-diabetes-school-an-innovative-education-centre-for-people-with-diabetes.html

New initiative in HCP education
Based on 10 years of experience!

دیابت رویکرد کاربردی
Diabetes in Practice

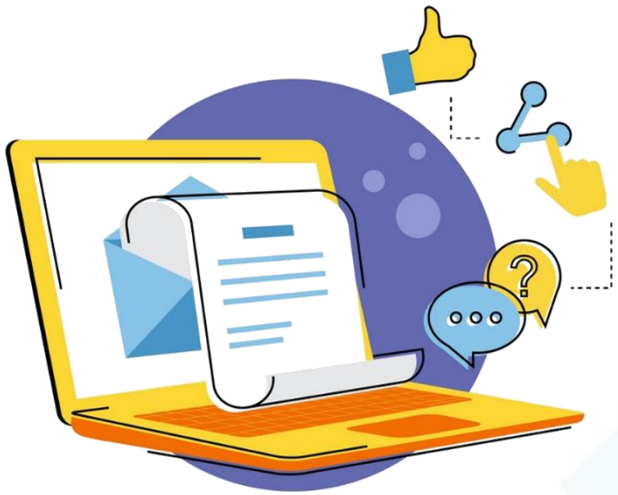
Basics of
Diabetes Education

Diabetes Care Approach
Fellowship Training Workshop

Providing online scientific courses

GABRIC
Virtual Diabetes Academy

Renovating Diabetes Education



Scientific platform for diabetes care

WWW.GABRICVIDA.COM

آکادمی مجازی دیابت گابریک

Gabric Virtual Diabetes Academy

چرا آکادمی مجازی گابریک

اگر به دنبال پلتفرمی هستید که در آن علاوه بر دوره های آموزشی مدیریت دیابت، به آخرین اخبار کنترل دارویی و تکنولوژی دیابت، وبینارهای علمی مرتبط با مدیریت بالینی دیابت، جلسات بحث و بررسی موارد بالینی، فایلها و ویدئوهای کمک آموزشی برای بیماران و ... دسترسی داشته باشید.

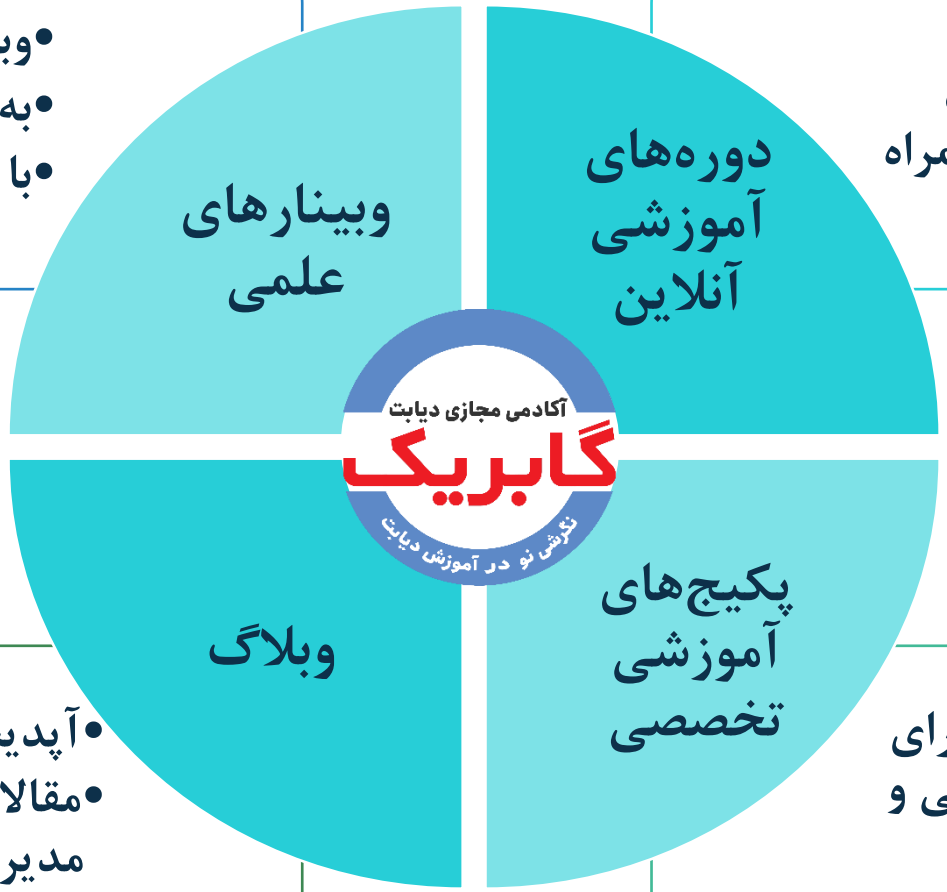
محتوای آموزشی آکادمی مجازی دیابت گابریک

- ۱۴۰ دوره آموزشی
- ۴۸۰ سرفصل آموزشی تخصصی
- ۲۲۰ ساعت آموزش آنلاین به همراه آزمون

دوره‌های آموزشی آنلاین

وبینارهای علمی

- وبینارهای Gabric ViDA Class
- به صورت Case discussion
- با رویکرد بیمار-محور



پکیج‌های آموزشی تخصصی

- پکیجهای آموزشی تخصصی برای گروه های هدف مختلف پزشکی و پیراپزشکی

وبلاگ

- آپدیت گایدلاینهای درمانی دیابت
- مقالات به روز و کاربردی حوزه مدیریت دیابت و تکنولوژی سلامت

معرفی بیمار برای دریافت
آموزش و مشاوره استاندارد خود-مدیریتی دیابت

Diabetes in Practice

Fellowship Practical workshop

Basics of Diabetes Education

Diabetes Care: A Holistic Approach

Fellowship Training Workshop

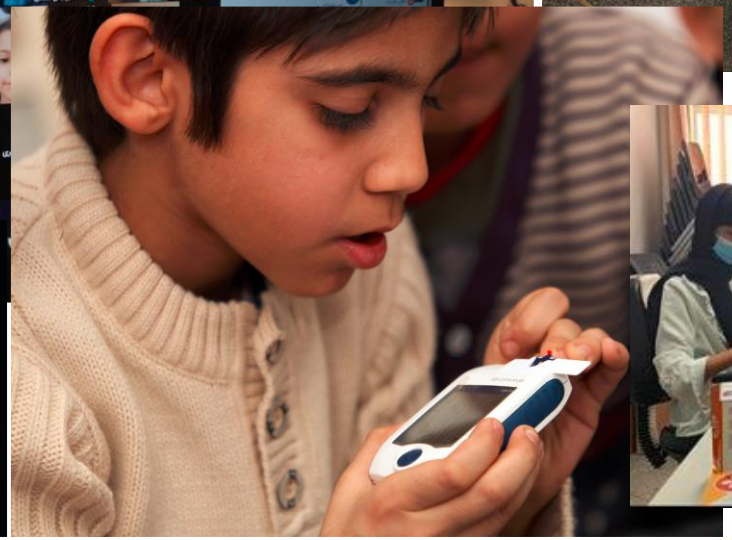
کارگاه آموزشی دستیاران فوق تخصص غدد – اطفال و بزرگسال

همایش سالانه دیابت، رویکرد کاربردی

Take home messages

- DSMES is a right for all.
- Know 4 critical times to refer for a DSMES program.
- Not every Education have benefits of DSME.
- Addressed psychosocial issues and behavioral strategies.
- A cost effective and accessible DSMES is needed!
- Still there is a gap in DSMES research!

همراه هم آینده ای را خواهیم ساخت که در آن دیابت برای هیچکس تهدید و نگرانی نبوده،
بلکه فرصتی جهت حرکت در مسیر سلامت و رشد انسان باشد.



Gabric Diabetes Education Association

@gabric_dia

A Journey from Pre-diabetes to diabetes

Case based discussion

Agenda

First, we will briefly review the evidence and new guidelines about prediabetes.

We will discuss the importance of prediabetes and its management in different scenarios.

1- a person with impaired fasting blood glucose with hypertension and hyperlipidemia

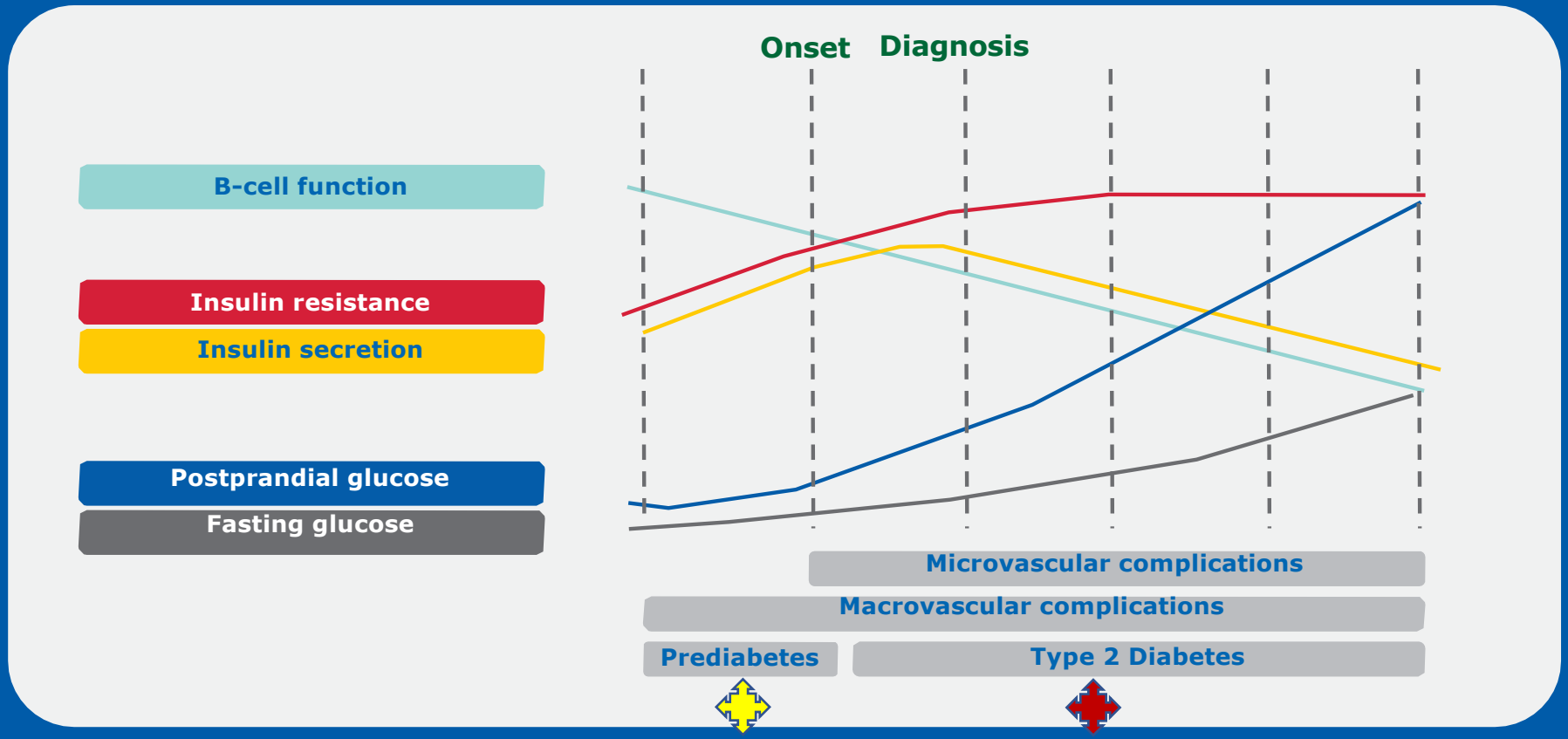
2- a woman with a history of GDM and impaired fasting glucose

3- a known case of ASCVD (previous CABG) with IFG and IGT.

4- a patient with newly diagnosed type 2 diabetes

The Defects in Glucose Metabolism May Begin Many Years Before Patients Are Diagnosed with T2D[1,2]

Prediabetes and Diabetes



T2D: Type 2 Diabetes.

References:
1.Nathan DM. *N Engl J Med* 2002; 347: 1342–9 [164]. **2.** Piya, M. et al. *British journal of clinical pharmacology* 70 5 (2010): 631-44.

Goals of diabetes prevention

The goals of diabetes prevention include:

1- Preventing or delaying the onset of diabetes

2- Preserving beta cell function

3- Preventing or delaying microvascular and cardiovascular complications

4- Reducing costs of diabetes care

First Case study

45 - year - old obese man referred for consultation

BP =140/95 mmHg

FBS = 115 mg/dl

Repeated 2 days later =118 mg/dl

Ch=265 mg/dl

LDL= 174 mg/dl

HDL= 35 mg/dl

Triglyceride=280 mg/dl

HbA1c= 6.3%

Questions?

How do you approach to his dysglycemia?

What do you recommend for management of hypertension and hyperlipidemia?

Definition and diagnostic criteria of prediabetes

Screening of diabetes and prediabetes in asymptomatic persons

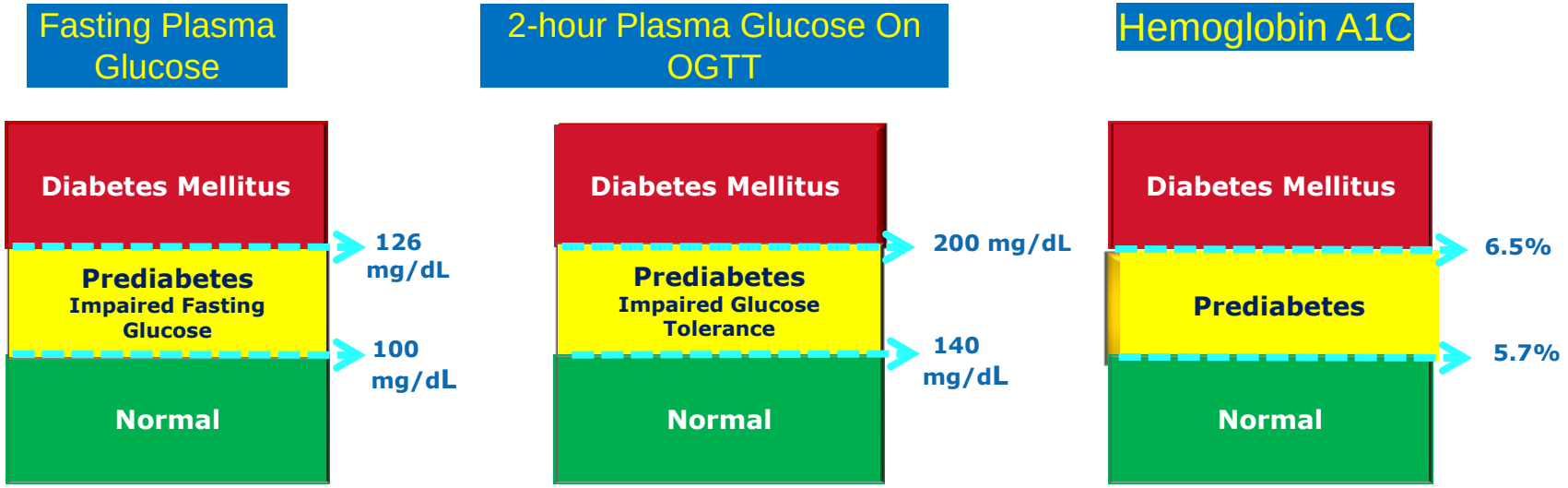
Diabetes Prevention Program & CV risk factors

Definition and diagnostic criteria of prediabetes

Screening of diabetes and prediabetes in asymptomatic persons

Diabetes Prevention Program & CV risk factors

Prediabetes is an intermediate state between normal blood glucose and type 2 diabetes



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

Prediabetes HbA1c limitation

"Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes yet have abnormal carbohydrate metabolism.

People with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7-6.4%.

The utility of A1C screening for prediabetes and diabetes may be limited in the presence of hemoglobinopathies and conditions that affect red blood cell turnover.

Definition and diagnostic criteria of prediabetes

Screening of diabetes and prediabetes in asymptomatic persons

Diabetes Prevention Program & CV risk factors

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

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

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)

Diabetes Risk Test | American Diabetes Association®

Figure 2.1—ADA risk test (diabetes.org/socrisktest).

Who should be screened for prediabetes and T2DM

1- Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated risk calculator should be done in asymptomatic adults. B

2-Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian American individuals) who have one or more risk factors B

3-For all people, screening should begin at age 35 years. B

Screening for prediabetes and T2DM in adults

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.

Prediabetes and Type 2 Diabetes follow up after screening

If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable

sooner with symptoms or change in risk (i.e., weight gain).C

To screen for prediabetes and type 2 diabetes:

fasting plasma glucose

2-h plasma glucose during 75-g OGTT

A1C

are each appropriate. B

Screening for Prediabetes and Type 2 Diabetes in **children & adolescent**

Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents

with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factors for diabetes. B

Screening for prediabetes and T2DM in children & adolescent

Table 2.4—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) A and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation A
- Family history of type 2 diabetes in first- or second-degree relative A
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) A
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) B

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

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

Prediabetes and Type 2 Diabetes
CV risk factors

When using OGTT as a screen for diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing. A

In people with prediabetes and type 2 diabetes, identify and treat cardiovascular disease risk factors. A

Prediabetes and Type 2 Diabetes HIV patients

- People with HIV should be screened for diabetes and prediabetes with a fasting glucose test
- Before starting antiretroviral therapy
- At the time of switching antiretroviral therapy
- 3–6 months after starting or switching antiretroviral therapy.

- If initial screening results are normal, fasting glucose should be checked annually. E

Definition and diagnostic criteria of prediabetes

Screening of diabetes and prediabetes in asymptomatic persons

Diabetes Prevention Program & CV risk factors

Table 1 Description of major diabetes prevention studies reporting long-term complications

Study	Total number of participants	Cohort	Duration[a]	Post-trial follow-up[b]	Intervention	HR (95% CI)[c]	HbA_{1c} at study end[d], active vs control (%) (mmol/mol)
DQDPS [7]	577	IGT	6		Lifestyle	0.49 (0.33, 0.73)	
DQDPOS [8]				20	Lifestyle	0.57 (0.41, 0.81)	NA
DQDPOS [12]	–	–	–	30	Lifestyle	0.61 (0.45, 0.83)	NA
DPP [13]	3234	IGT + IFG[e] + BMI ≥25	2.8		Lifestyle Metformin	0.42 (0.34, 0.52) 0.69 (0.57, 0.83)	5.9 vs 6.1 (41 vs 43) 6.0 vs 6.1 (42 vs 43)
DPPOS [14]				15	Lifestyle Metformin	0.73 (0.65, 0.83) 0.82 (0.72, 0.93)	6.2 vs 6.3 (44 vs 45) 6.1 vs 6.3 (43 vs 45)
FDPS [34]	522	IGT + BMI ≥25	3.9	–	Lifestyle	0.42 (0.3, 0.7)	NA
NAVIGATOR [22, 23]	9306	IGT + CVD or CVD risk factors	5	–	Nateglinide Valsartan	1.07 (1.0, 1.15) 0.86 (0.8, 0.92)	6.1 vs 6.3 (43 vs 45) NA
ACE [26]	6522	IGT + CHD	5	–	Acarbose	0.82 (0.71, 0.94)	5.88 vs 5.94 (41 vs 41)
ACT NOW [30]	602	IGT + IFG + BMI ≥25	2.3	–	Pioglitazone	0.28 (0.16, 0.49)	5.50 vs 5.70 (37 vs 39)
STOP-NIDDM [24]	1429	IGT + IFG + BMI ≥25	3.3	–	Acarbose	0.75 (0.63, 0.90)	NA
ORIGIN [32]	1456	CVD + IGT or IFG	6.2	–	Glargine	0.72 (0.58, 0.90)	6.3 vs 6.5 (45 vs 48)
DREAM [27, 28]	5269	IGT and or IFG	3	–	Rosiglitazone Ramipril	0.38 (0.33, 0.44) 0.91 (0.80, 1.03)	NA

The Diabetes Prevention Program
The role of lifestyle

Several major randomized controlled trials, including:

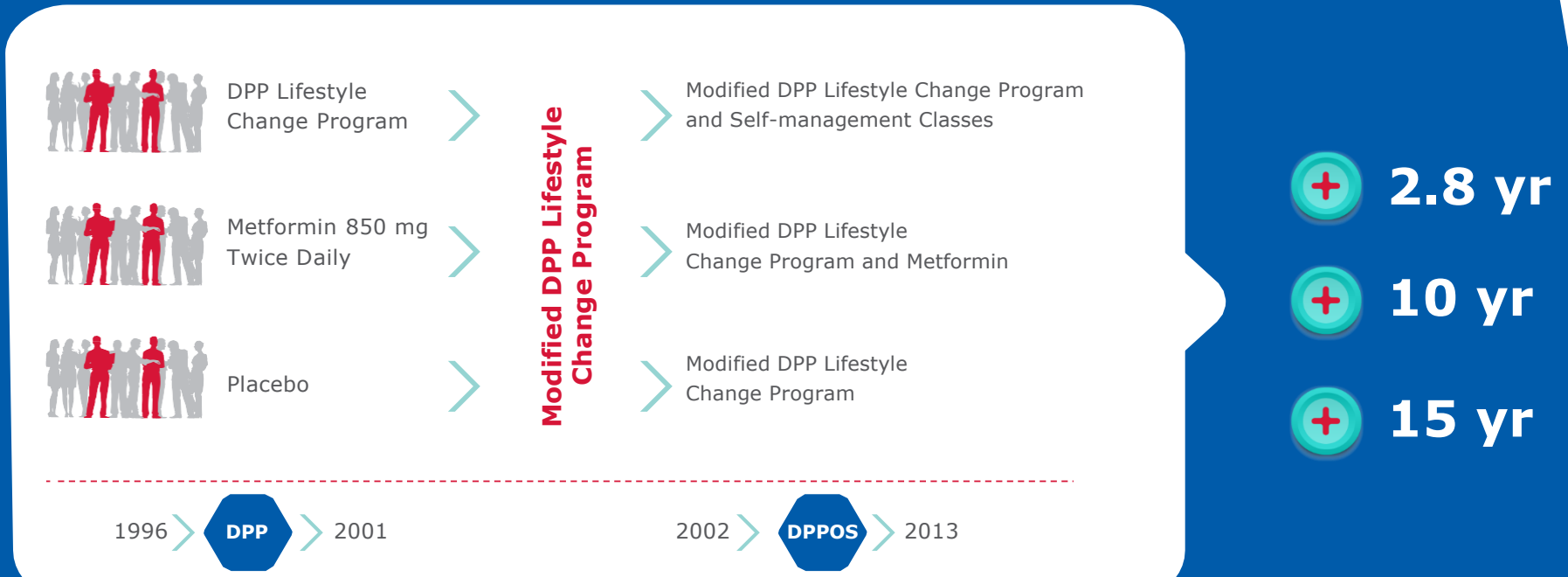
- The Diabetes Prevention Program (DPP) trial
- The Finnish Diabetes Prevention Study (DPS)
- The Da Qing Diabetes Prevention Study (Da Qing study)

- Demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic markers (such as BP, lipids, and inflammation).

The Diabetes Prevention Program

- Follow-up of three large studies of **lifestyle intervention** for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes:
- 39% reduction at 30 years in the Da Qing study
- 43% reduction at 7 years in the Finnish DPS
- 34% reduction at 10 years
- 27% reduction at 15 years in the U.S. DPPOS.

The Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study (DPP/DPPOS)[1]



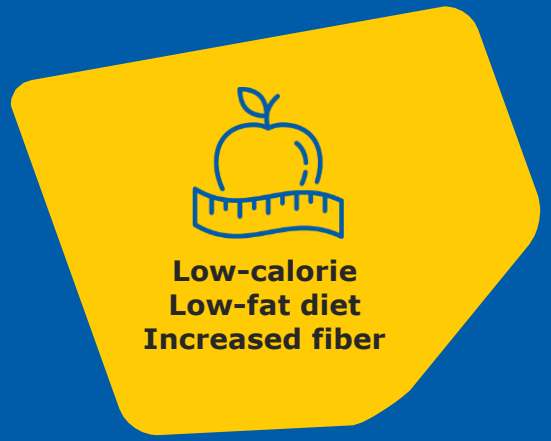
DPP: Diabetes Prevention Program; **DPPOS:** Diabetes Prevention Program Outcomes Study.

Reference:

1. Aroda VR et al. Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. *Diabetologia*.9. 2017.

Lifestyle Modification Program Goals

OBJECTIVE:
At least a **7%** weight loss and
at least **150 min** of physical activity/week[1]



Low-calorie
Low-fat diet
Increased fiber

First 24 weeks:
A one-on-one, 16-lesson curriculum
(diet, exercise, behavior modification)[1]

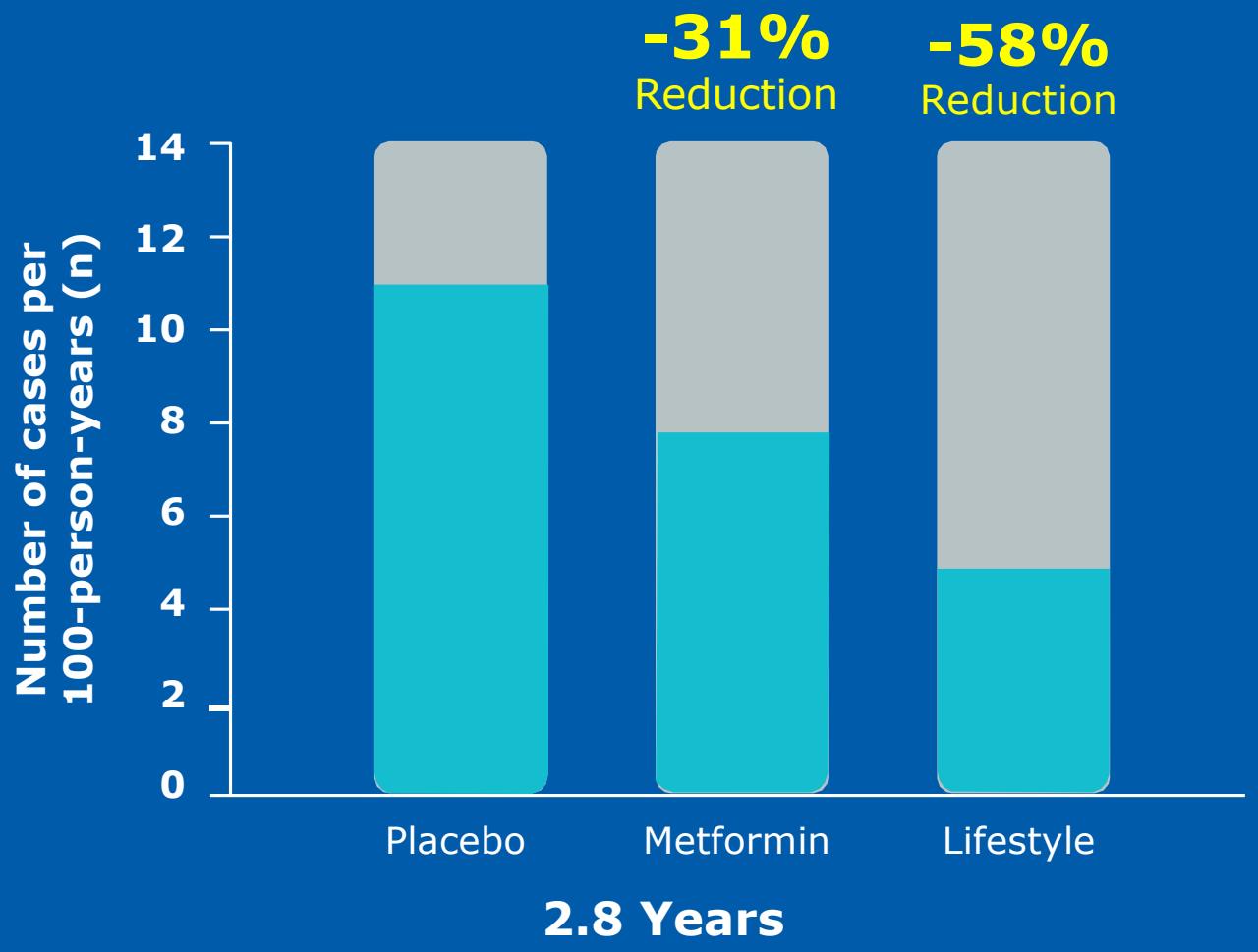
Moderate-intensity
Physical activity

Subsequent individual
sessions (usually monthly)
and group sessions[1]

Reference:
1. Diabetes Prevention Program Research Group, Knowler W, *et al. N Engl J Med*. 2002;346(6):393-403.

lifestyle/behavioral intervention

Diabetes Incidence Rates After 2.8 Years[1]



DPP

Reference:
1. Knowler WC, *et al.N Engl J Med.* 2002 Feb 7;346(6):393-403.

Challenges of Lifestyle Modification

Lifestyle modification is associated with adherence issues and high failure rates

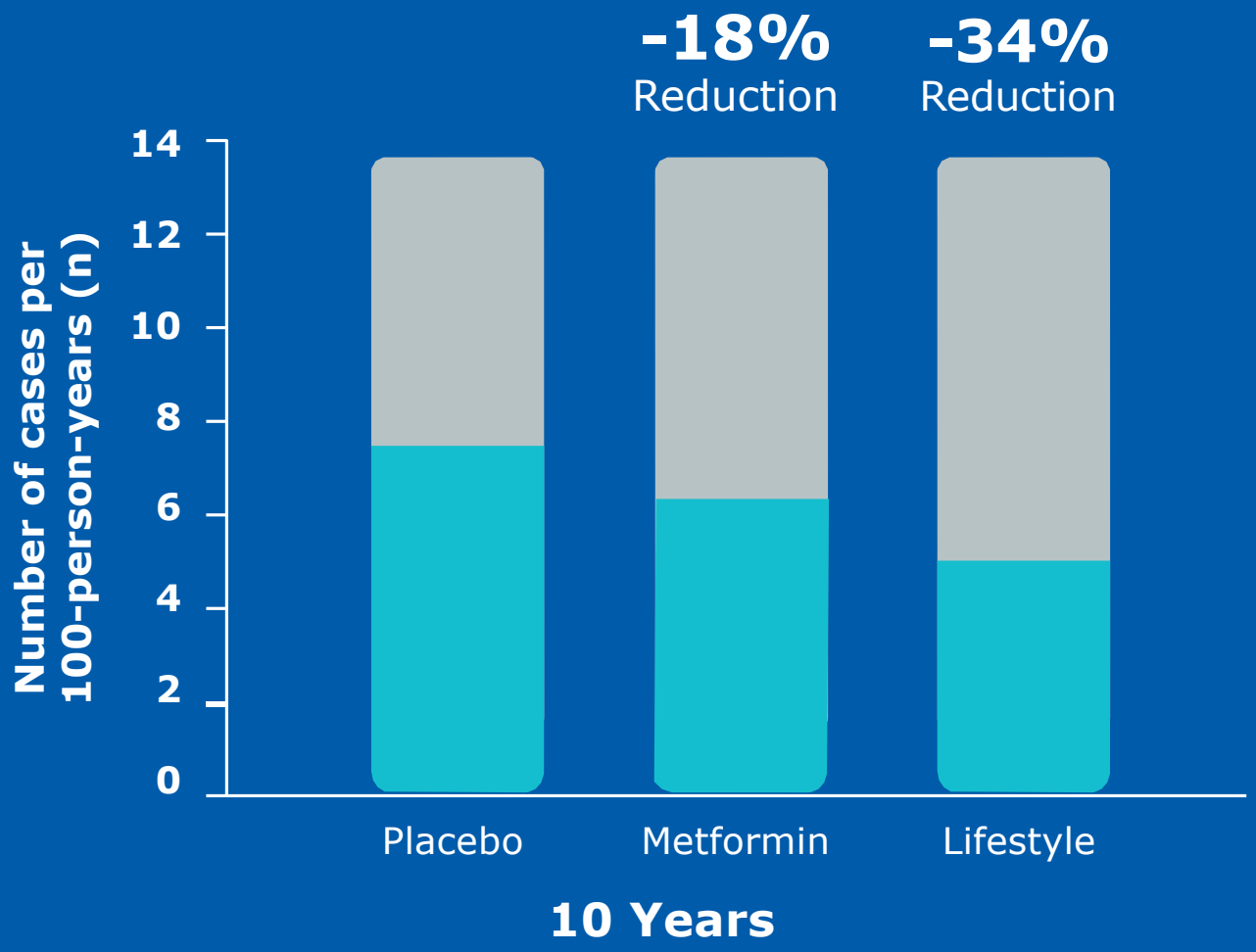
Difficult to maintain[1]

Poor compliance[2]

Regaining lost weight over time[1]

Pharmacotherapy can be considered for those who didn't improve despite lifestyle modification[3]

Diabetes Incidence Rates After 10 Years[2]



DPPOS

Reference:
2. Diabetes Prevention Program Research Group. *Lancet*. 2009 Nov 14;374(9702):1677-86.

Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study

*Diabetes Prevention Program Research Group**

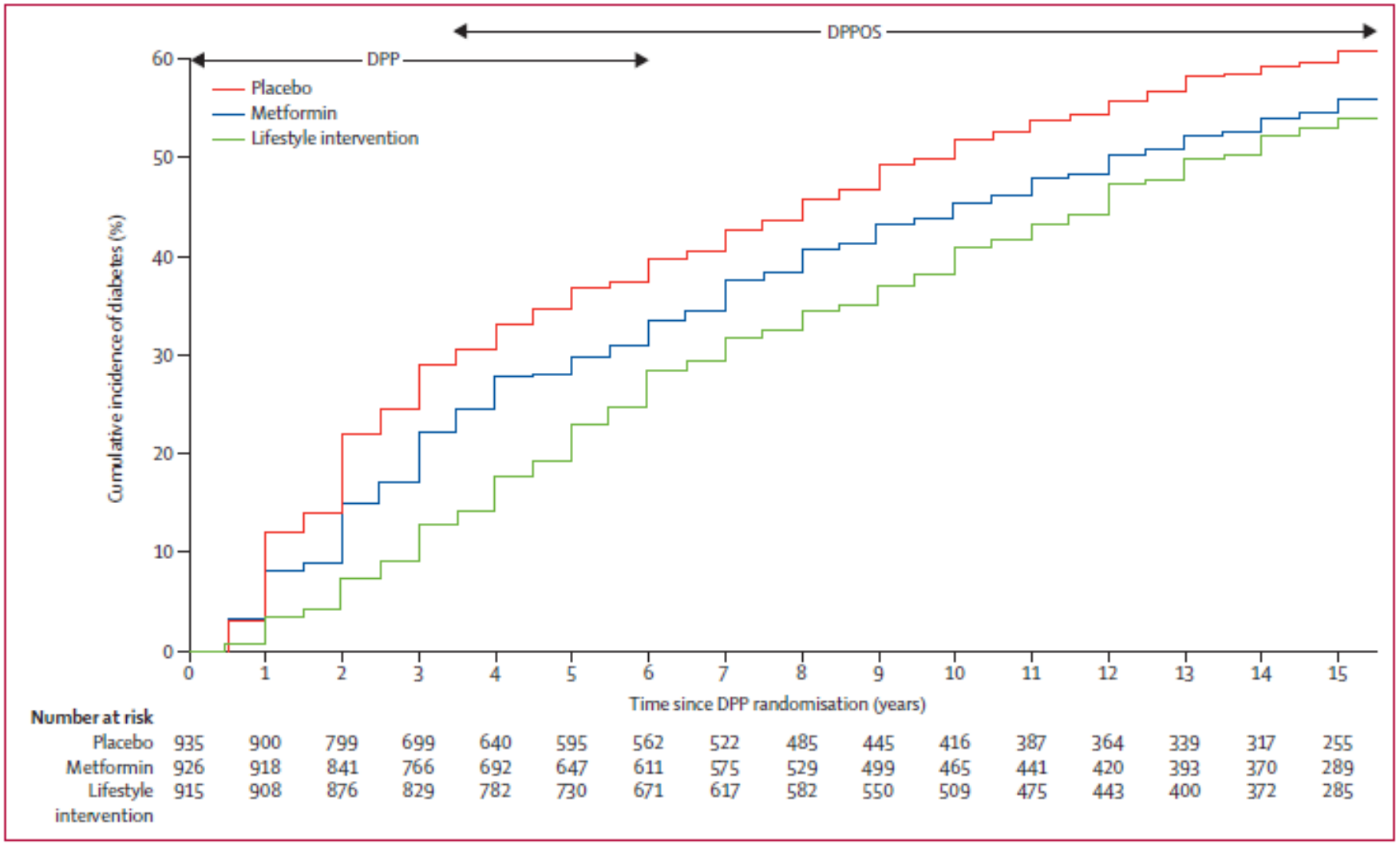
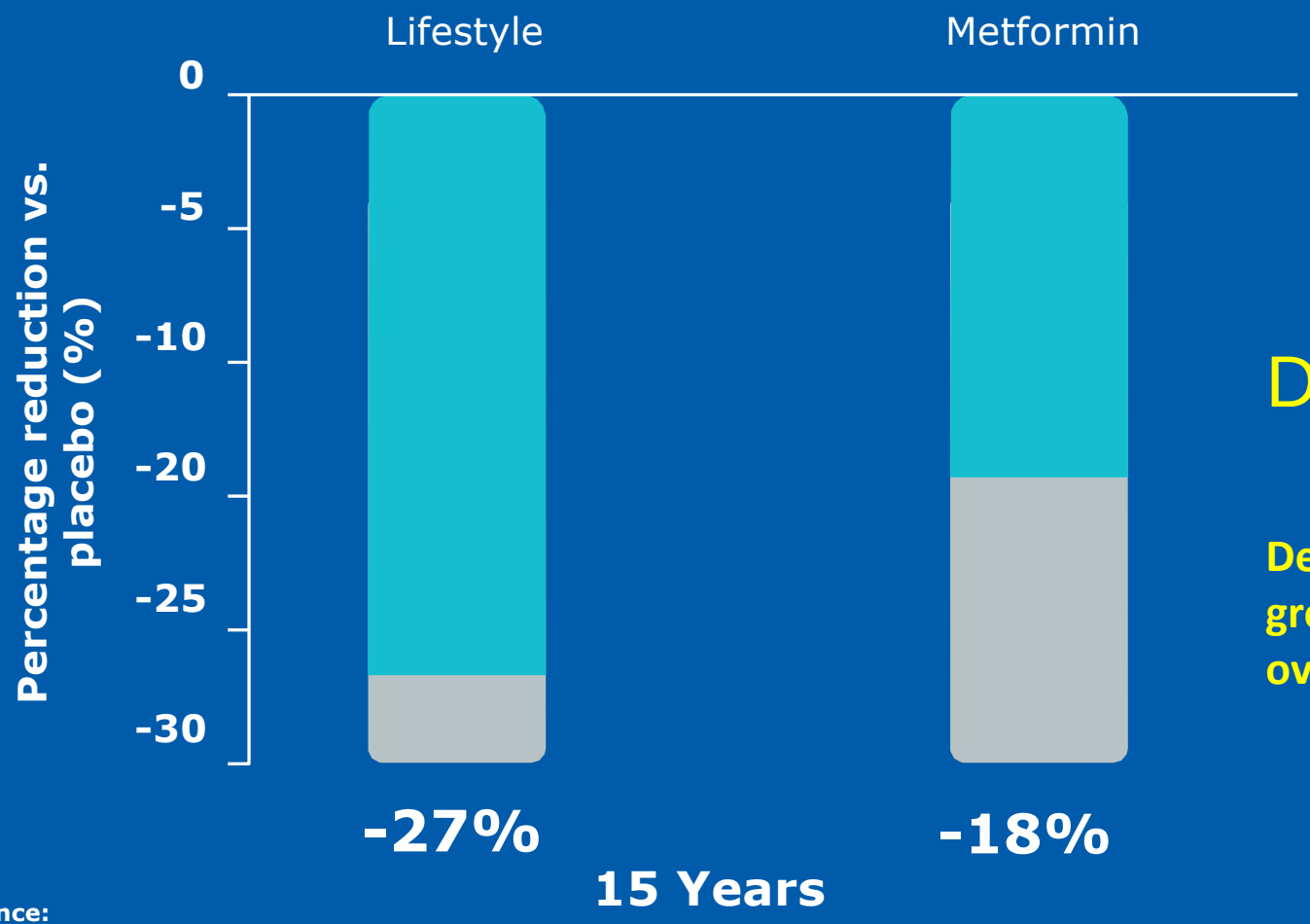


Figure 2: **Cumulative incidence of diabetes by treatment group in the 2776 DPP–DPPOS participants**

The Diabetes Prevention Program (DPP) and DPP Outcomes Study (DPPOS) periods, and the overlap between them, are shown. Over the entire study, the cumulative incidence was 27% lower for the lifestyle group than for the placebo group (p<0·0001) and 18% lower for the metformin group than for the placebo group (p<0·0001). The difference between the lifestyle and metformin groups was not significant (p=0·10).

Diabetes Incidence Rate After 15 Years[3]

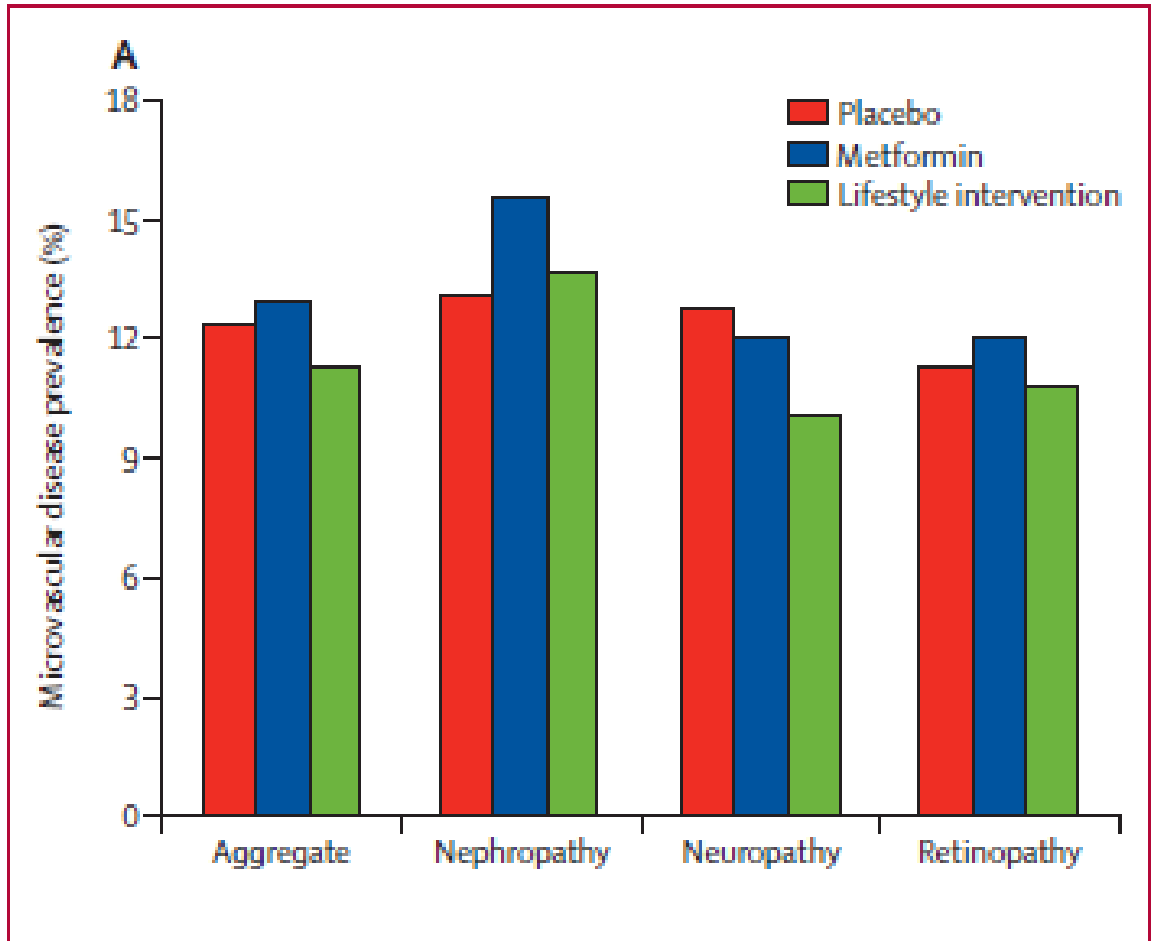


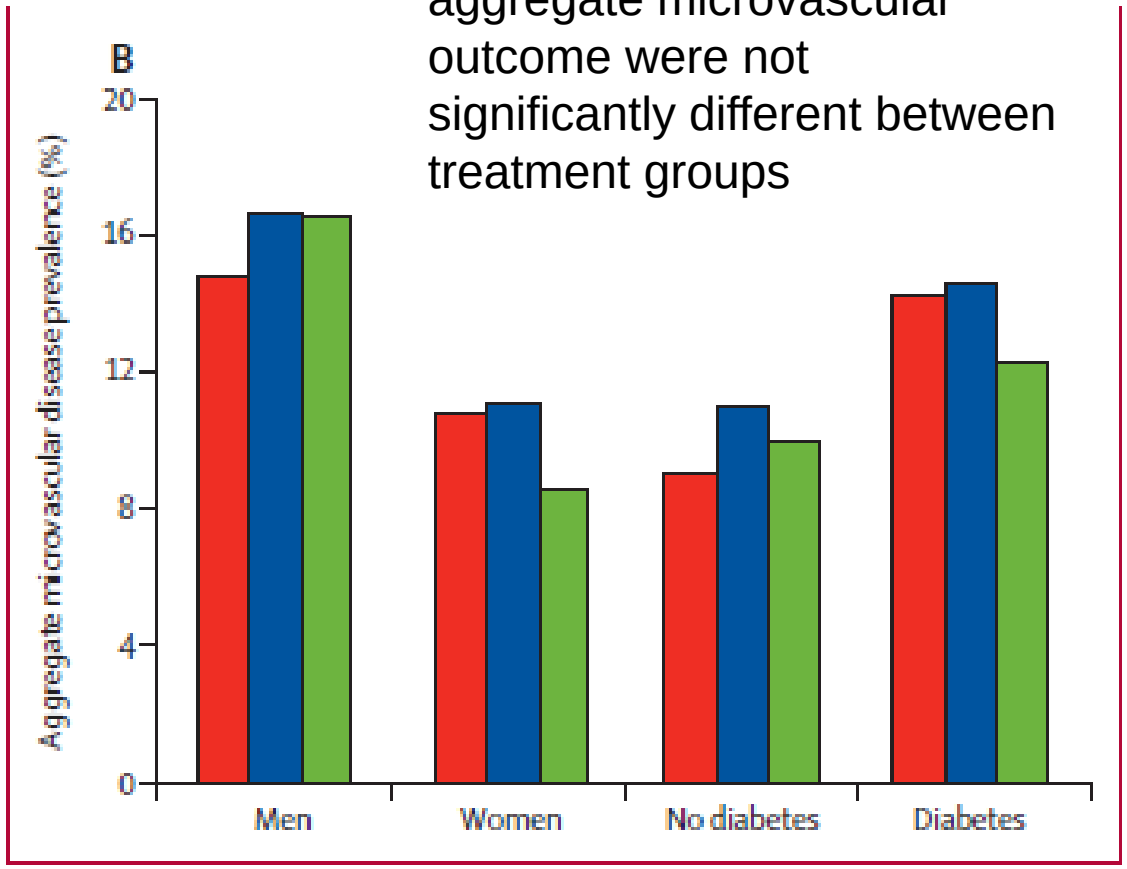
DPPOS

Declining between-group differences over time

Reference:
3. Diabetes Prevention Program Research Group.*Lancet Diabetes Endocrinol*. 2015 Nov; 3(11): 866–875.2015 Nov;3(11): 866–875.

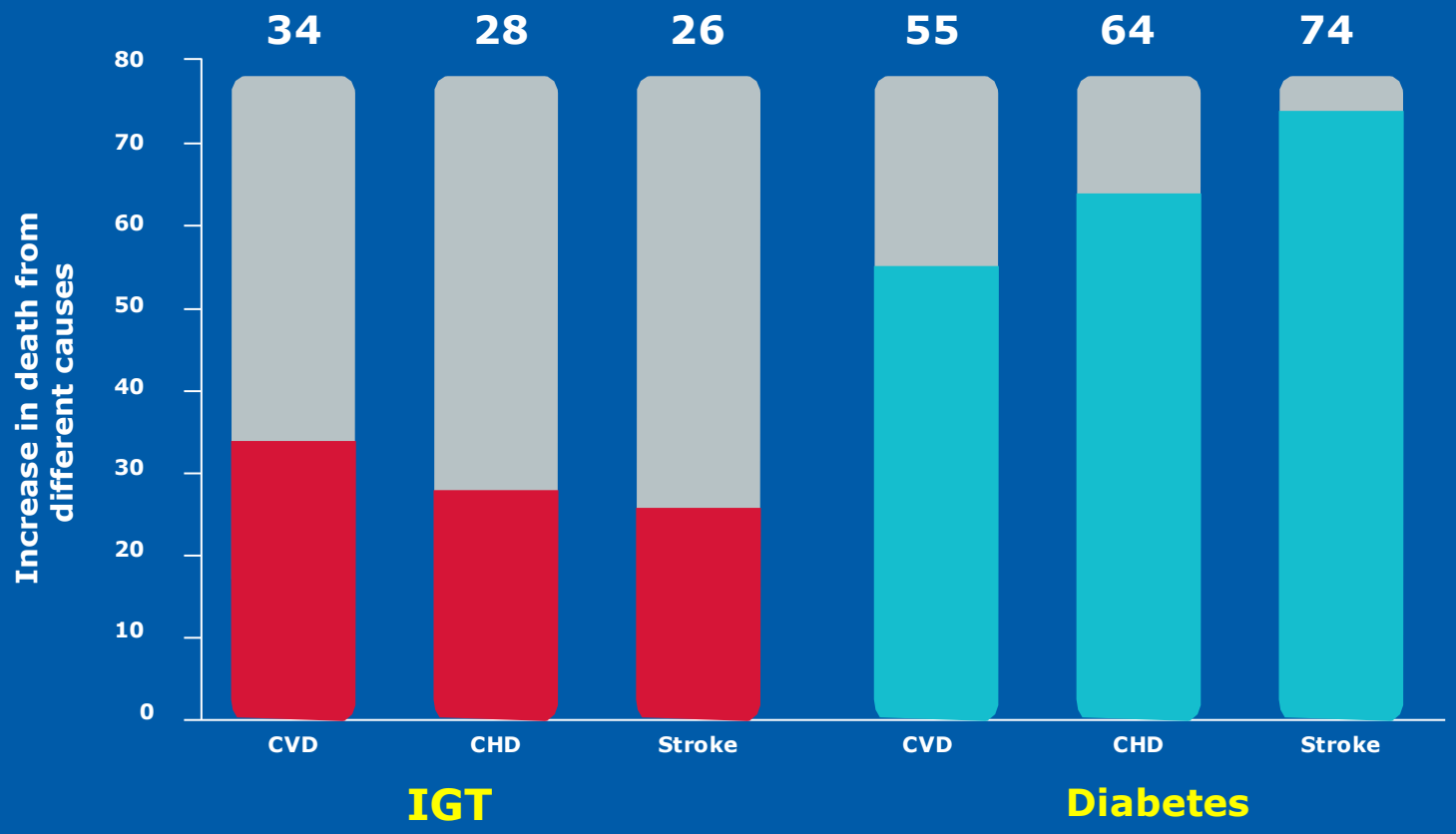
Figure 3: Prevalence of aggregate microvascular complications and individual microvascular components at DPPOS-end





The prevalence of the aggregate microvascular outcome were not significantly different between treatment groups

Both Prediabetes & Diabetes Increase the Risk of Macrovascular Complications[1,2]



IGT is a stronger predictor of CVD and total mortality than IFG.[1,2]

IGT: Impaired Glucose Tolerance; **IFG:** Impaired Fasting Glucose; **NGT:** Normal Glucose Tolerance.

References:
1. Milman S et al. Mechanisms of vascular complications in prediabetes. *Med Clin North Am*. 2. 2011. **2.** DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* . 3. 2001.

Prediabetes and Diabetes are Associated with Microvascular Complications[1-3]

Retinopathy[1]

59%

increase in retinopathy in diabetic subjects.[1]

Published in final edited form as:
Diabet Med. 2007 February ; 24(2): 137–144.

The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program

Diabetes Prevention Program Research Group

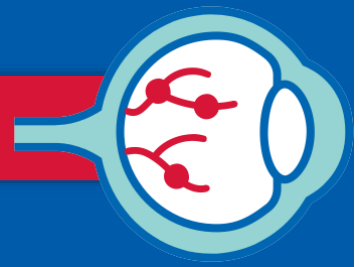
increase in polyneuropathy in impaired glucose tolerance subjects.[2]

increase in chronic kidney disease in prediabetic subjects.[3]

IGT: Impaired Glucose Tolerance; **IFG:** Impaired Fasting Glucose; **NGT:** Normal Glucose Tolerance.

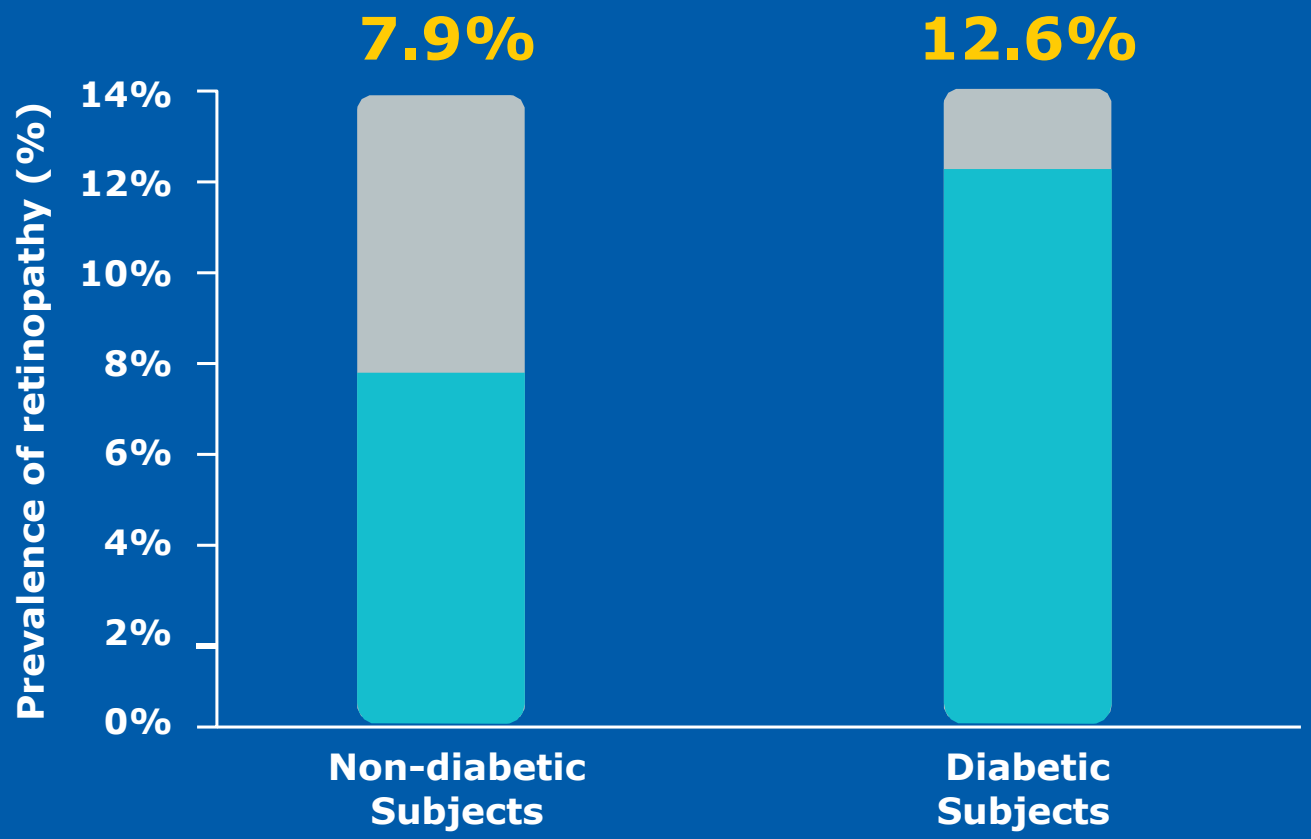
References:
1. Diabetes Prevention Program Research Group. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabet Med*. 2. 2007. **2.** Ziegler D et al. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. *Diabetes Care*. 3. 2008. **3.** Plantinga LC et al.Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. *Clin J Am Soc Nephrol.4*. 2010.

Retinopathy[1]



Results—Retinopathy consistent with diabetic retinopathy was detected in 12.6 and 7.9% of the diabetic and non-diabetic participants, respectively ($P = 0.03$, comparing prevalence in the two groups). Systolic blood pressure and HbA_{1c} were higher at baseline in the diabetic participants who had retinopathy compared with the diabetic participants without retinopathy.

Conclusions—Retinopathy characteristic of diabetes is present in persons with elevated fasting glucose and impaired glucose tolerance and no known history of diabetes. The prevalence of retinopathy is significantly higher in persons who develop diabetes, even within 3 years of diagnosis.



References:
1. Diabetes Prevention Program Research Group. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabet Med*. 2. 2007.

Prediabetes and Diabetes are Associated with Microvascular Complications[1-3]

Retinopathy[1]

59%

increase in retinopathy in diabetic subjects.[1]

Polyneuropathy[2]

75%

increase in polyneuropathy in impaired glucose

Nephropathy[3]

67%

increase in chronic kidney disease in prediabetic subjects.[3]

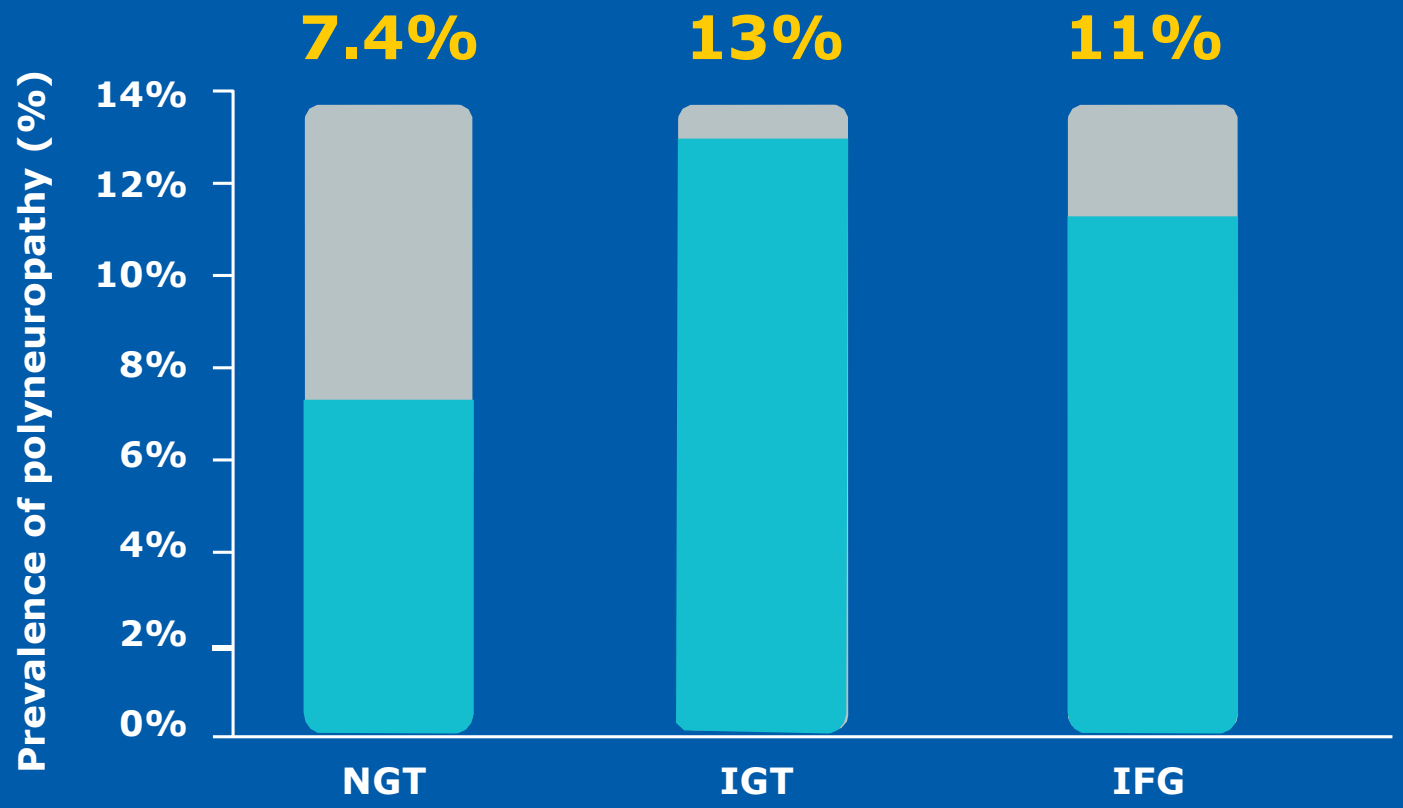
Prevalence of Polyneuropathy in Pre-Diabetes and Diabetes Is Associated With Abdominal Obesity and Macroangiopathy

The MONICA/KORA Augsburg Surveys S2 and S3

References:

1. Diabetes Prevention Program Research Group. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabet Med*. 2. 2007. **2.** Ziegler D 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*. 3. 2008. **3.** Plantinga LC et al.Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. *Clin J Am Soc Nephrol.4*. 2010.

Polyneuropathy[2]



The prevalence of polyneuropathy was:

28.0% in DM 13.0% in IGT 11.3% in IFG 7.4% in NGT

(P 0.05 for diabetes vs. NGT, IFG, and IGT)

2. Ziegler D 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.* 3. 2008

Prediabetes and Diabetes are Associated with Microvascular Complications[1-3]

Retinopathy[1]

59%

increase in retinopathy in diabetic subjects.[1]

Polyneuropathy[2]

75%

increase in polyneuropathy in impaired glucose tolerance subjects.[2]

Nephropathy[3]

67%

increase in chronic kidney disease in prediabetic subjects.[3]

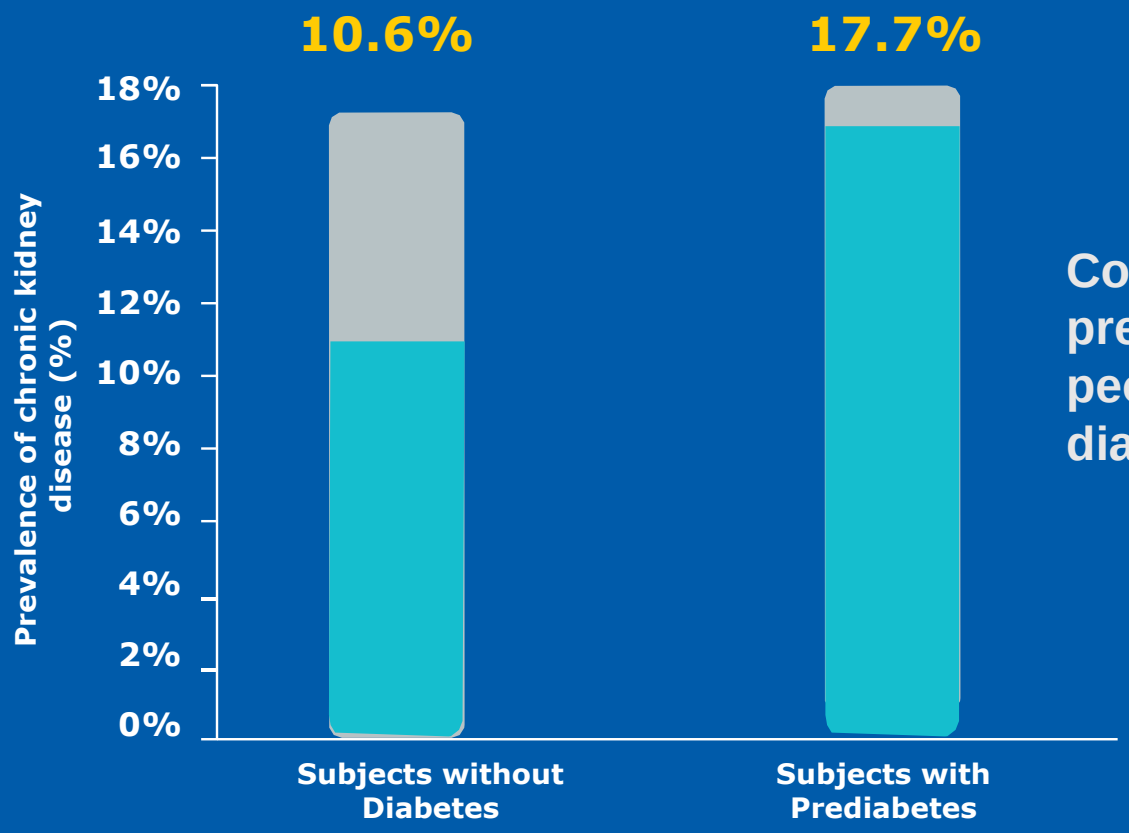
IGT: Impaired Glucose Tolerance; **IFG:** Impaired Fasting Glucose; **NGT:** Normal Glucose Tolerance.

References:

1. Diabetes Prevention Program Research Group. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabet Med*. 2. 2007. **2.** Ziegler D 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*. 3. 2008. **3.** Plantinga LC et al.Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. *Clin J Am Soc Nephrol.4*. 2010.

Nephropathy[3]

The 1999 through 2006 National Health and Nutrition Examination Survey
N = 8188



Conclusions: CKD prevalence is high among people with undiagnosed diabetes and prediabetes

References:
3. Plantinga LC et al.Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. *Clin J Am Soc Nephrol.*4. 2010.

Reviews/Commentaries/ADA Statements

REVIEW ARTICLE

A1C Level and Future Risk of Diabetes: A Systematic Review

Zhang X, Gregg EW, Williamson DF, et al. A1C level and future risk of diabetes: a systematic review. Diabetes Care 2010;33:1665–1673

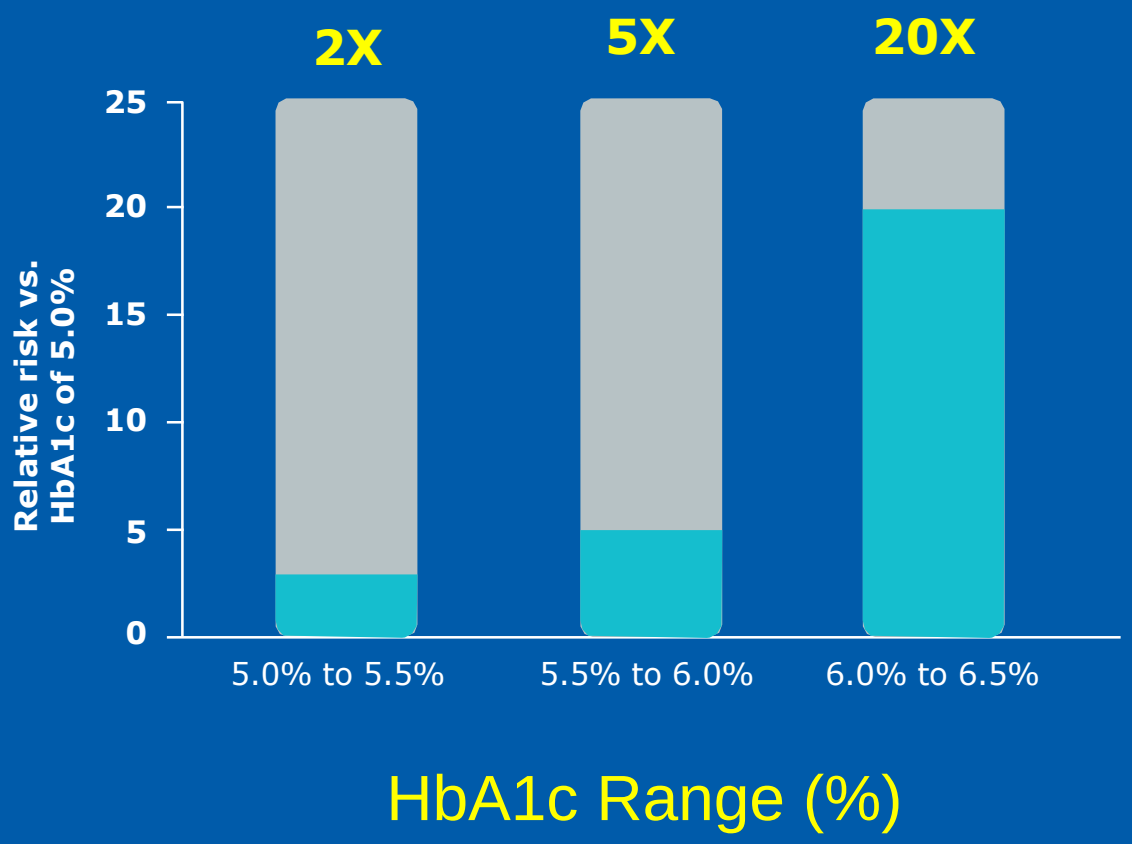
In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years)

1-Those with A1C between 5.5% and 6.0% had a substantially increased risk of diabetes (5-year incidence from 9% to 25%).

2-Those with an A1C range of 6.0–6.5% had a 5-year risk of developing diabetes between 25% and 50% and a relative risk 20 times higher compared with A1C of 5.0%.

Zhang X, Gregg EW, Williamson DF, et al. A1C level and future risk of diabetes: a systematic review. Diabetes Care 2010;33:1665–1673

A1C Level and Future Increased Risk of Diabetes[1]



Reference:
1. Zhang X. Gregg EW. et al. A1C Level and Future Risk of Diabetes: A Systematic Review. *Diabetes Care*. 33:1665–1673, 2010.

HbA_{1c} as a Predictor of Diabetes and as an Outcome in the Diabetes Prevention Program: A Randomized Clinical Trial

*Diabetes Prevention Program Research Group**

Diabetes Care 2015;38:51–58 | DOI: 10.2337/dc14-0886

Diabetes Prevention Program Research Group. HbA1c as a predictor of diabetes and as an outcome in the diabetes prevention program: a randomized clinical trial. Diabetes Care 2015; 38:51–58

Diabetes defined by HbA1c

Evaluation of treatment effects in the 2,765 participants who did not have diabetes at baseline according to FPG, 2hPG, or HbA1c

RESULTS

Baseline HbA1c predicted incident diabetes in all treatment groups.

Diabetes incidence defined by HbA1c > 6.5% :

was reduced by 44% by metformin and 49% by lifestyle during the DPP

and by 38% by metformin and 29% by lifestyle throughout follow-up.

Unlike the primary DPP and DPPOS findings based on glucose criteria, **metformin and lifestyle were similarly effective in preventing diabetes defined by HbA1c.**

CONCLUSIONS

HbA1c predicted incident diabetes

In contrast to the superiority of the lifestyle Intervention on glucose-defined diabetes, **metformin and lifestyle interventions had similar effects in preventing HbA1c-defined diabetes.**

The long-term implications for other health outcomes remain to be determined.

In the most recent NIH Diabetes Prevention Program Outcomes Study (DPPOS) report, prevention of progression from prediabetes to diabetes resulted in lower rates of developing retinopathy and nephropathy.

Perreault L, Pan Q, Aroda VR, et al.; Diabetes Prevention Program Research Group. Exploring residual risk for diabetes and microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS). Diabet Med 2017;34:1747–1755

Nathan DM, Bennett PH, Crandall JP, et al.; Research Group. Does diabetes prevention translate into reduced long-term vascular complications of diabetes? Diabetologia 2019; 62:1319–1328

Diabet Med. 2017 December ; 34(12): 1747–1755. doi:10.1111/dme.13453.

Exploring residual risk for diabetes and microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS)

L. Perreault[1], **Q. Pan**[2], **V. R. Aroda**[3], **E. Barrett-Connor**[4], **D. Dabelea**[5], **S. Dagogo-Jack**[6], **R. F. Hamman**[5], **S. E. Kahn**[7], **K. J. Mather**[8], and **W. C. Knowler**[9] **for the Diabetes Prevention Program Research Group**

[1]University of Colorado, Aurora, CO

Approximately half of the participants in the DPPOS had diabetes after 15 years of follow-up, whereas nearly all the others remained with pre-diabetes.

We examined whether formerly unexplored factors in the DPPOS coexisted with known risk factors that posed additional risk for, or protection from, diabetes as well as microvascular disease.

Results: In models adjusted for demographics and known diabetes risk factors, two formerly unknown factors were associated with risk for both diabetes and microvascular disease

Number of medications taken

HR = 1.07, for diabetes

OR = 1.10 for microvascular disease

Variability in HbA1c

HR = 1.02, for diabetes

OR = 1.06, for microvascular disease per SD.

Diabetologia (2019) 62:1319–1328
https://doi.org/10.1007/s00125-019-4928-8

REVIEW

Does diabetes prevention translate into reduced long-term vascular complications of diabetes?

David M. Nathan[1] · Peter H. Bennett[2] · Jill P. Crandall[3] · Sharon L. Edelstein[4] · Ronald B. Goldberg[5] · Steven
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Does diabetes prevention translate into reduced long-term vascular complications of diabetes?

- The limited long-term data, largely from the Da Qing Diabetes Prevention Study (DQDPS) and the Diabetes Prevention Program (DPP) and their respective follow-up studies **(DQDPOS and DPPOS)**

Suggest :

- **Reduction in microvascular** complications and
- Amelioration of **CVD risk factors.**

Does diabetes prevention translate into reduced long-term vascular complications of diabetes?

- Only the **DQDPOS** and Study to Prevent Non-Insulin- Dependent Diabetes Mellitus **(STOP-NIDDM)** studies have shown:
- A reduction in CVD events
- Only DQDPOS has demonstrated a decrease in CVD and overall mortality.

Diabetologia (2019) 62:1385–1390
https://doi.org/10.1007/s00125-019-4895-0

SHORT COMMUNICATION

Reversion from prediabetes to normoglycaemia and risk of cardiovascular disease and mortality: the Whitehall II cohort study

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What is already known about this subject?

- Prediabetes is associated with an increased risk of cardiovascular disease (CVD) and death
- Reversion from prediabetes to normoglycaemia has been shown to improve cardiovascular risk factors

What is the key question?

- Is reversion from prediabetes to normoglycaemia associated with a lower risk of CVD and death?

What are the new findings?

- Individuals reverting from fasting glucose- or from HbA_{1c}-defined prediabetes to normoglycaemia were not at reduced risk of future CVD or death
- Reversion to normoglycaemia from prediabetes defined by 2 h glucose was associated with a halving in future risk of CVD and death

How might this impact on clinical practice in the foreseeable future?

- People with elevated 2 h glucose seem to have a strong potential to decrease their CVD risk through reducing glucose levels, and therefore this group should be identified for early preventive strategies

Glycated Hemoglobin, Prediabetes, and the Links to Cardiovascular Disease: Data From UK Biobank

Diabetes Care 2020;43:440–445 | https://doi.org/10.2337/dc19-1683

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Naveed Sattar[1]

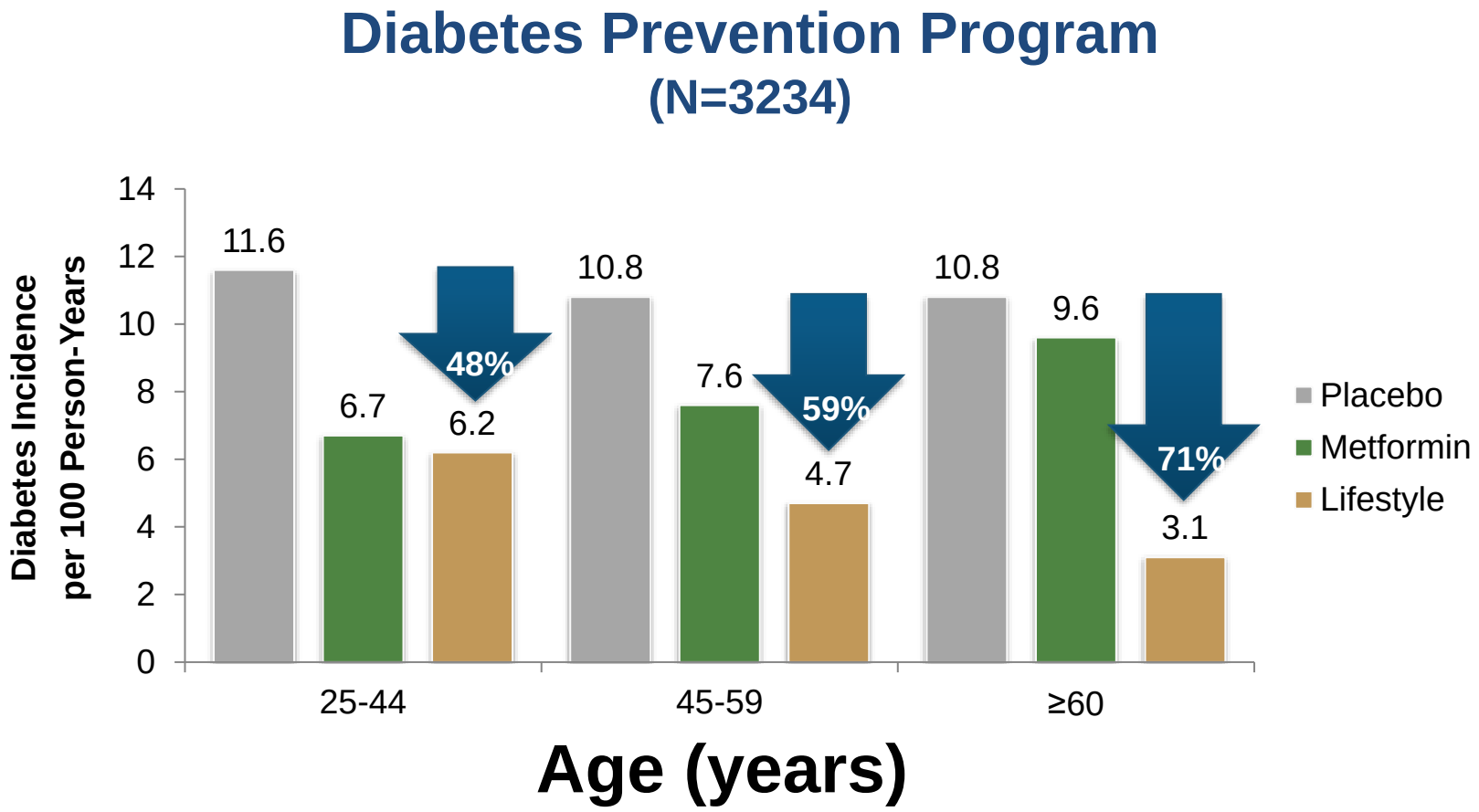
Glycated Hemoglobin, Prediabetes, and the Links to Cardiovascular Disease

- HbA1c levels are increasingly measured in screening for diabetes
- We investigated whether HbA1c may simultaneously improve CVD risk assessment, using QRISK3, (ACC/AHA),and (SCORE) scoring systems.
- UK Biobank participants without baseline CVD or known diabetes (n 5 357,833) were included

CONCLUSIONS

- The near twofold higher unadjusted risk for CVD in people with prediabetes is driven mainly by abnormal levels of conventional CVD risk factors.
- While HbA1c adds minimally to cardiovascular risk prediction, those with prediabetes should have their conventional cardiovascular risk factors appropriately measured and managed.

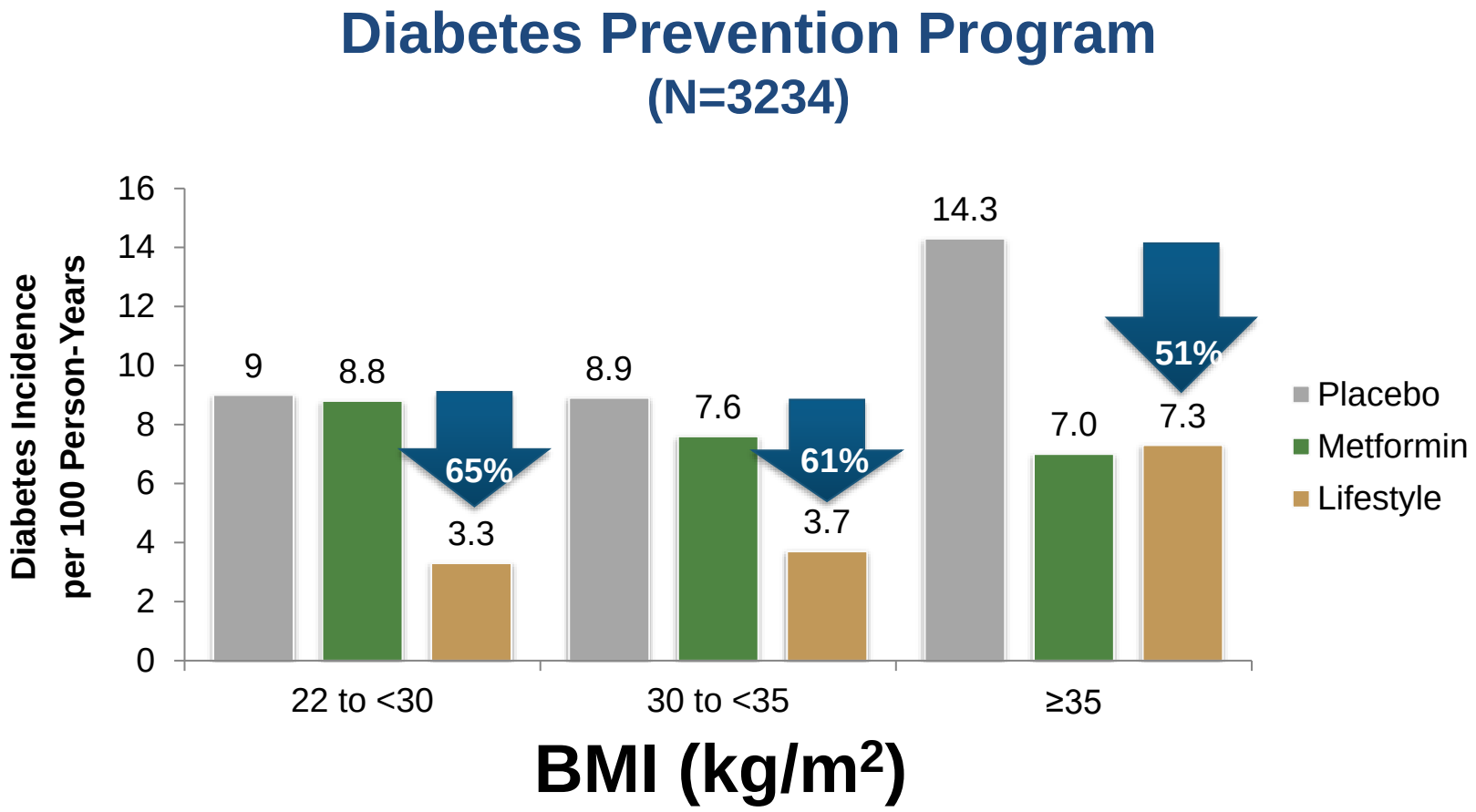
Lifestyle Intervention More Effectively Prevents Diabetes as Populations Age



*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.

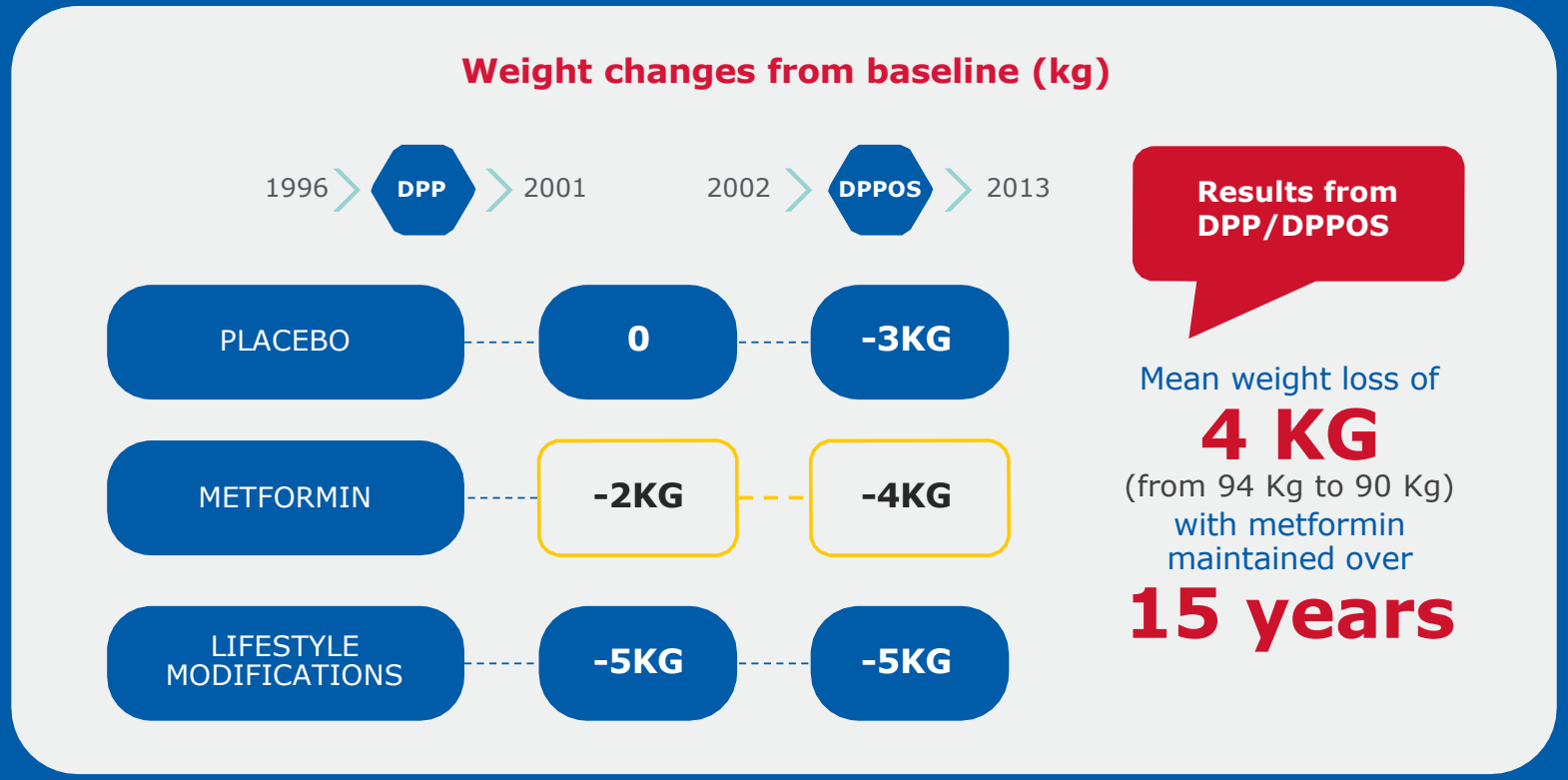
Effectiveness of Lifestyle Intervention for Diabetes Prevention Wanes as Weight Increases



*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.

Metformin Is Associated with a Long-term and Sustained Body Weight Loss in Prediabetic Subjects[1]



DPP: Diabetes Prevention Program.
Metformin is not indicated for weight loss or obesity treatment.

Reference:

1. Diabetes prevention program research group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol*, 2015.

Weight loss in DPP

- In the DPP, weight loss was an important factor in reducing the risk of progression
- With every kilogram of weight loss conferring a 16% reduction in risk of progression over 3.2 years.
- In postpartum individuals with GDM, the risk of type 2 diabetes increased by 18% for every 1unit BMI above the preconception baseline.

Importance of prediabetes

Prediabetes and CV risk factors

1- Prediabetes should not be viewed as a clinical entity in its own right but rather as a risk factor for progression to diabetes and cardiovascular disease (CVD).

2- Prediabetes is associated with:

- Obesity (especially abdominal or visceral obesity)
- Dyslipidemia with high triglycerides and/or low HDL cholesterol
- Hypertension.

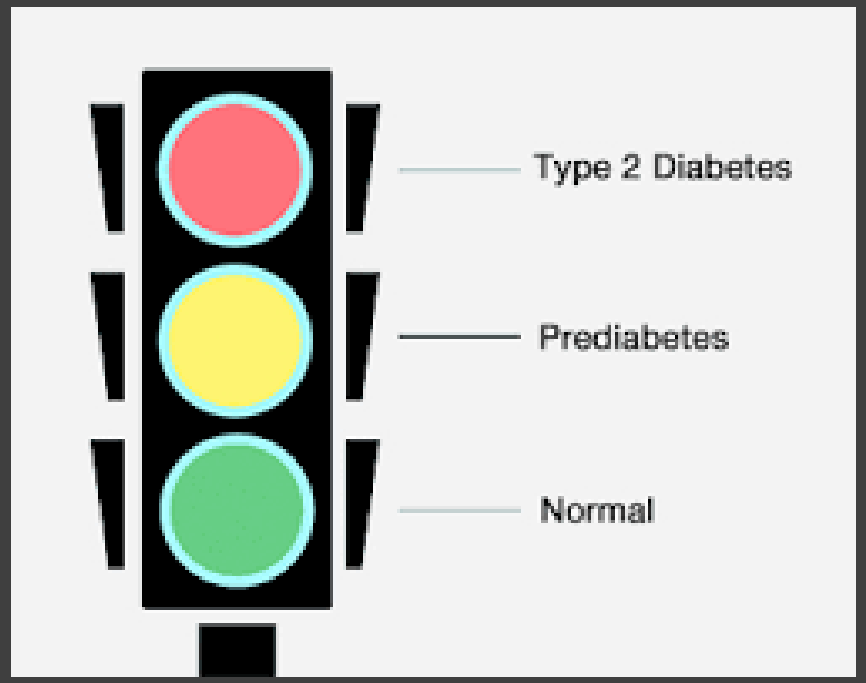
3- The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors.

Prediabetes and CV risk factors

Similar to those with IFG and/or IGT, individuals with A1C of 5.7–6.4% should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks

Similar to glucose measurements, **the continuum of risk is curvilinear, so as A1C rise**s, the diabetes risk rises disproportionately.

Aggressive interventions and vigilant follow-up should be pursued for those considered at **very high risk (e.g., those with A1C >6.0%.**



Pharmacologic diabetes prevention

Pharmacologic diabetes prevention

- Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention.

- Metformin
- a-glucosidase inhibitors
- GLP-1 RA (liraglutide, semaglutide)
- Thiazolidinediones
- Testosterone
- Insulin

have been shown to lower the incidence of diabetes in specific populations.

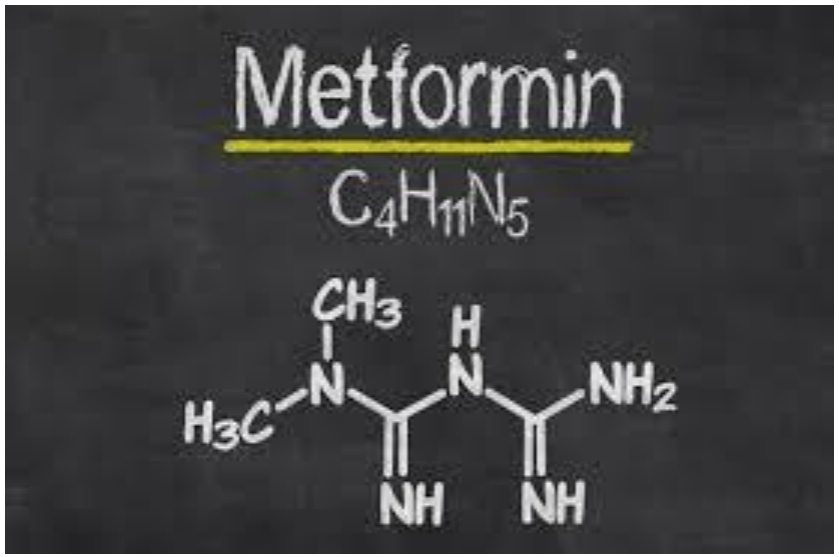
- Whereas diabetes prevention was not seen with nateglinide

Pharmacologic diabetes prevention

- No pharmacologic agent has been approved by the U.S. FDA for a specific indication of type 2 diabetes prevention

PREVENTION OF DIABETES:

METFORMIN ROLE

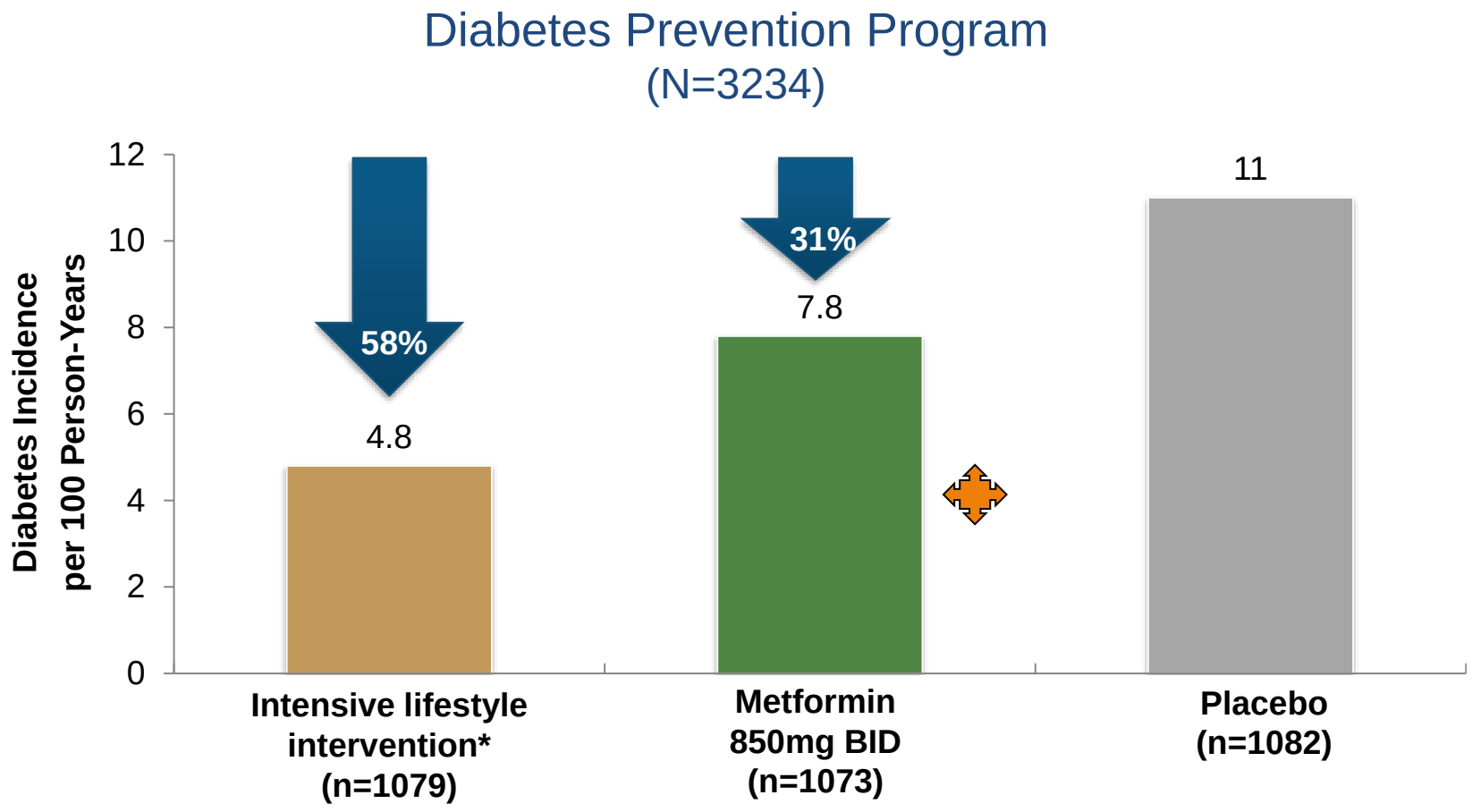


Metformin role

Metformin has the longest history of safety data as a pharmacologic therapy for diabetes prevention.

Metformin was overall less effective than lifestyle modification in the DPP, though group differences declined over time in the DPPOS, and metformin may be **cost-saving** over a 10-year period.

Intensive Lifestyle Intervention Effectively Prevents Progression From IGT to T2D



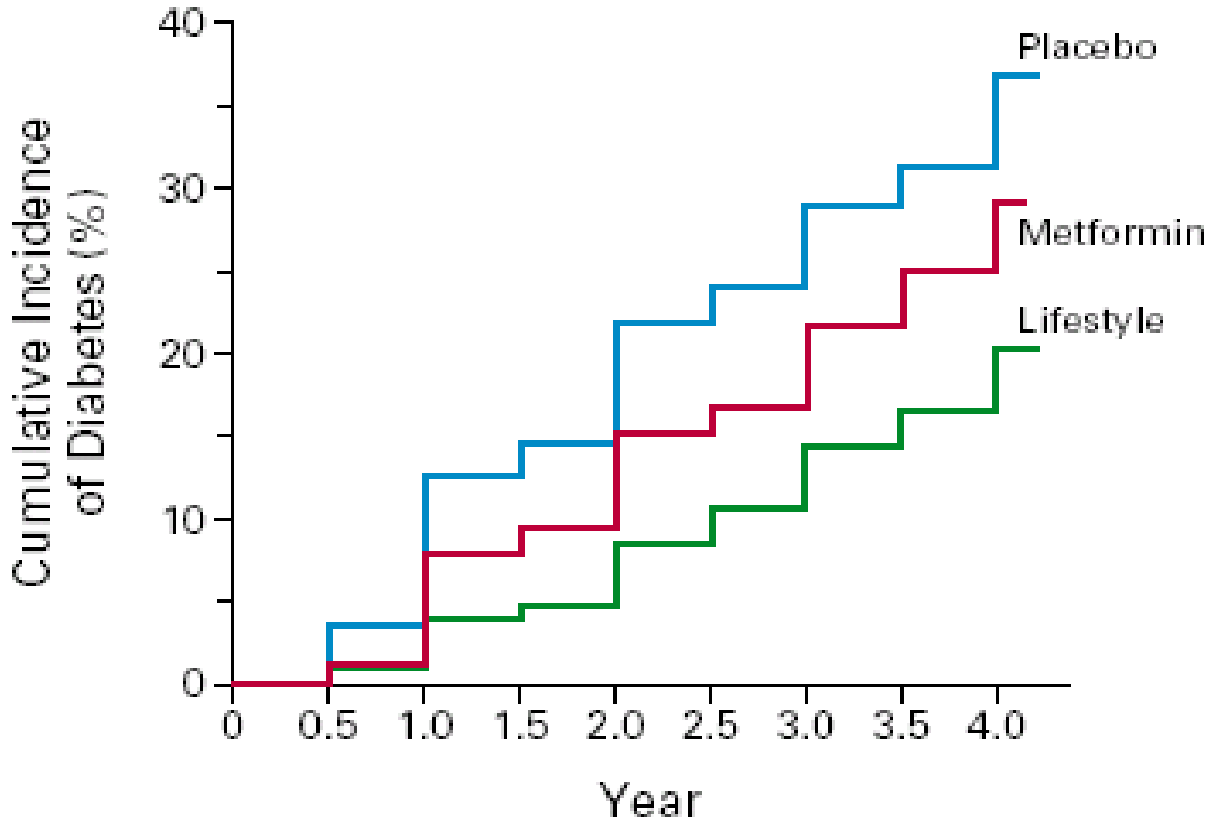
*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

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

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

Type 2 Diabetes Can Be Prevented

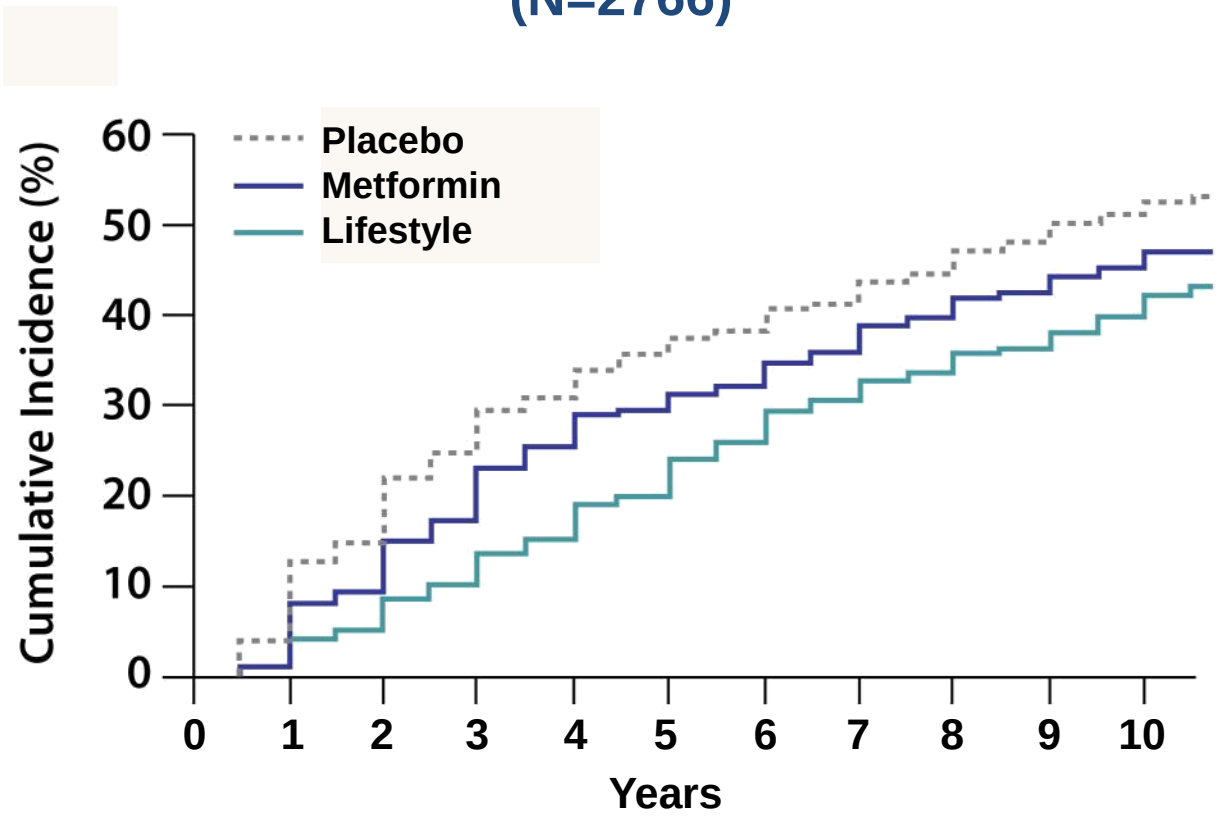
58% decreased risk with lifestyle modification
31% decreased risk with metformin



*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.

10-Year Incidence of T2D

DPP Outcomes Study (N=2766)

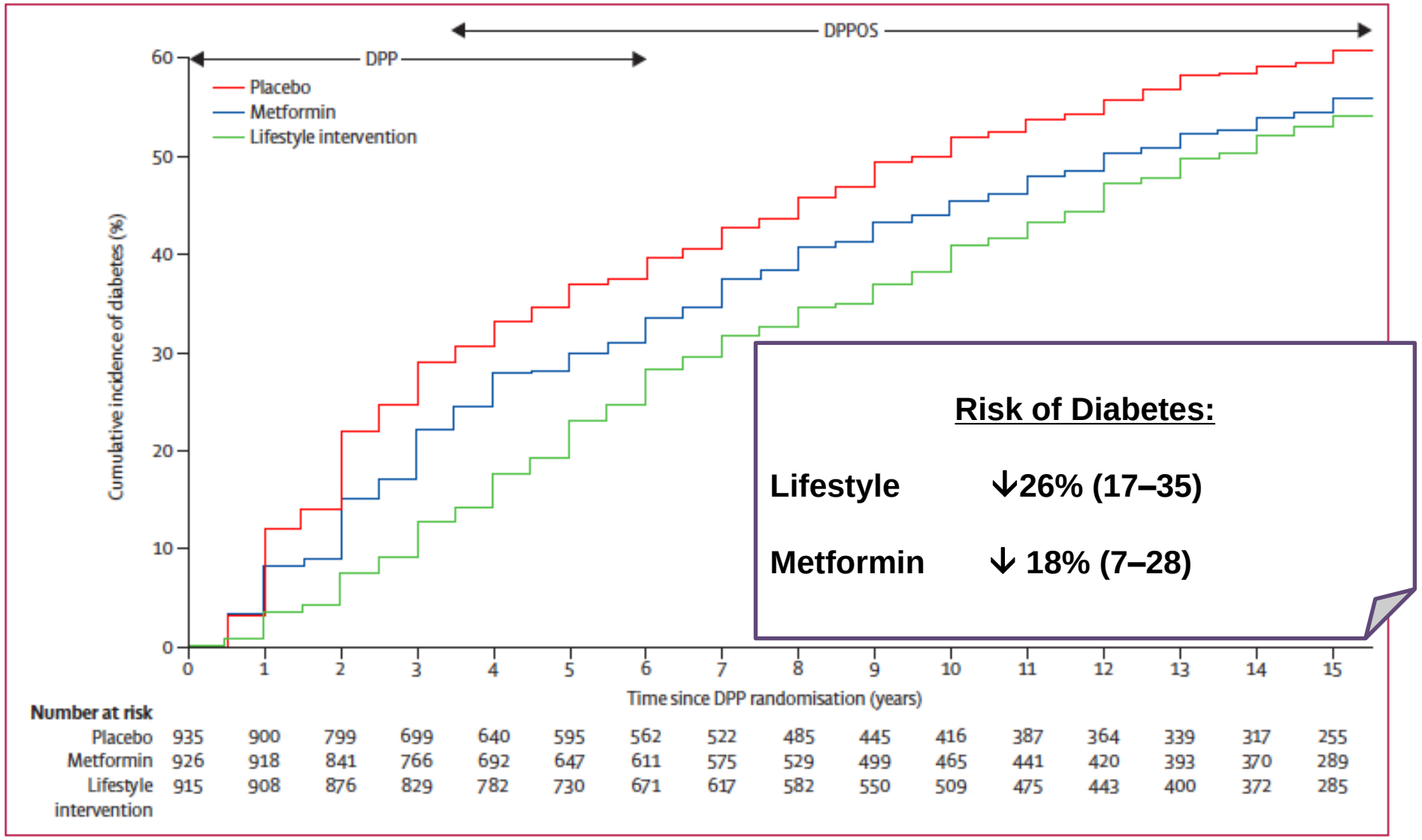


DPP, Diabetes Prevention Program; T2D, type 2 diabetes.

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

DPPOS

Follow-up after 15 years showed a continued benefit in the original lifestyle intervention and metformin groups

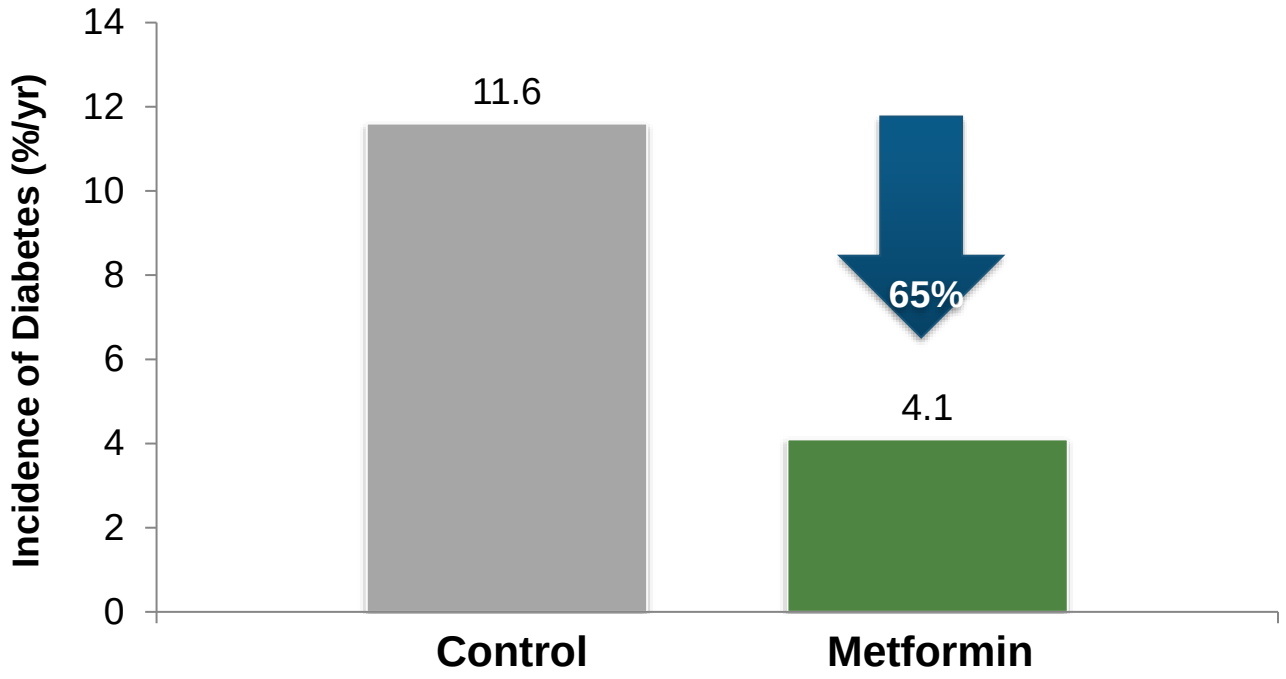
With long-term reductions in diabetes development of 27 and 18 %, respectively

compared with the original placebo group (cumulative incidence of diabetes 55, 56, and 62 % in the lifestyle, metformin, and placebo groups, respectively).

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

The Chinese Prevention Study

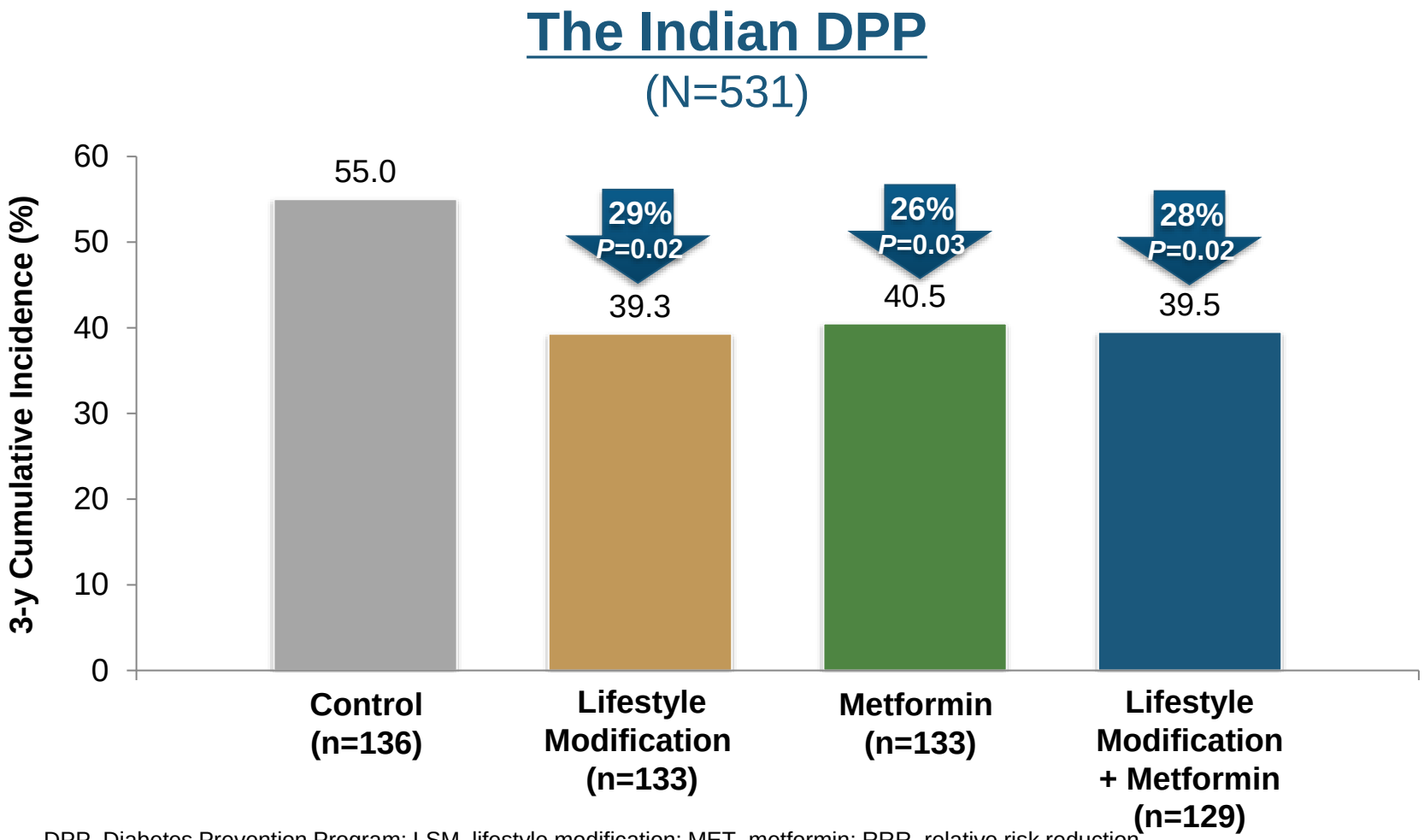
(N=321)



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



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

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

- In the DPP, metformin was as effective as lifestyle modification in participants with BMI > 35 kg/m2 and in younger participants aged 25–44 years.

Metformin role

Metformin was particularly effective in individuals who:

1- were younger (<60 years of age)

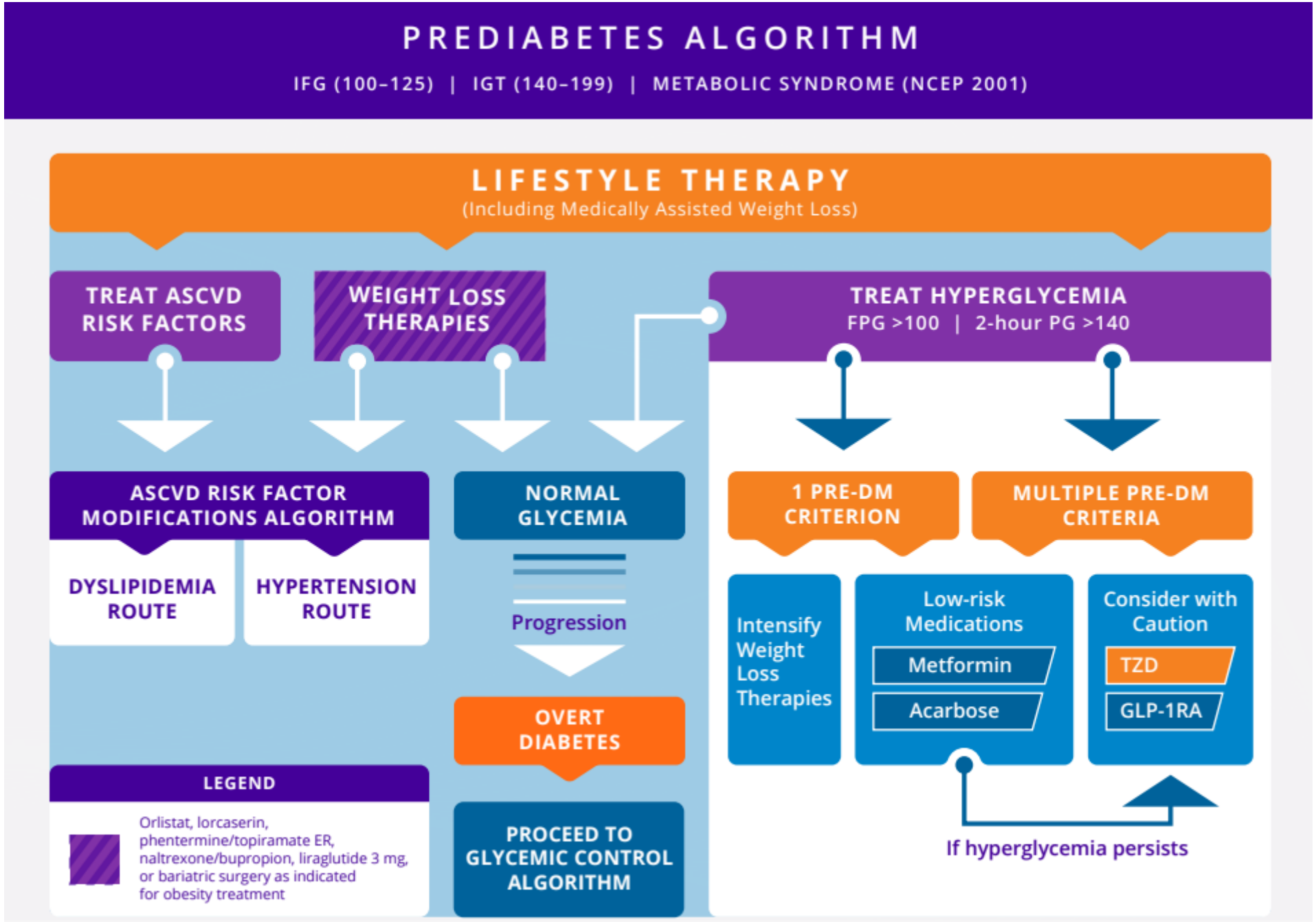
2- with class II obesity (BMI >35 kg/m^2),

3- and at highest risk for developing diabetes

Cost-effectiveness analysis

A cost-effectiveness analysis using data from the DPP (three years) and the DPPOS (seven years) showed that lifestyle intervention was cost effective compared with placebo.

Moreover, metformin was actually cost-saving.



National Institute for Health and Care Excellence (NICE)

In the UK, NICE guidelines suggest metformin for patients with:

1- Elevated FPG (FPG; 100 to 125 mg/dL or A1C (6 to 6.5 % who are unable to participate in lifestyle interventions

2- or in whom FPG or A1C values deteriorate despite participation in a lifestyle intervention program.

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

Choice of drug therapy

For selected patients :

- (age <60 years and/or BMI ≥35 kg/m^2, women with a history of GDM) with IGT, IFG, or A1C of 5.7 to 6.4 % , in whom lifestyle interventions fail to improve glycemic indices

- Metformin is suggested for diabetes prevention (850 mg once daily for one month; if tolerating, increase to 850 mg twice daily).

Choice of drug therapy

- Metformin has been approved for prevention in several countries internationally but remains off-label for prevention in the US

Cochrane Library

Cochrane Database of Systematic Reviews

Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus (Review)

Madsen KS, Chi Y, Metzendorf MI, Richter B, Hemmingsen B

Meta-analysis of RCT on Metformin

- A meta-analysis of randomized trials of metformin for the prevention of diabetes in high-risk individuals showed that metformin decreased new-onset diabetes compared with **standard diet and exercise**, with or without placebo (141 versus 281 per 1000, risk ratio [RR] 0.5, 95% CI 0.38-0.65).

- Madsen KS, Chi Y, Metzendorf MI, et al. Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. Cochrane Database Syst Rev 2019; 12:CD008558.

Meta-analysis of RCT on Metformin

Metformin

Metformin did not reduce the development of type 2 diabetes compared with **intensive diet and exercise** (133 versus 167 per 1000 in the intensive intervention group, RR 0.80, 95% CI 0.47-1.37).

There were insufficient data to address patient important outcomes, such as micro- and macrovascular outcomes and mortality.

The DPP trial

- In the largest trial in the meta-analysis, the DPP, metformin reduced the rate of progression to diabetes **compared with placebo** (22 versus 29 % at an average follow-up of three years [in the intensive lifestyle arm, the incidence of diabetes was 14 %).

- **Metformin** was effective in males and females and in all ethnic groups but was **relatively ineffective in older patients** and in those who were less overweight.

Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393.

Delay or prevention?

- There has been concern that the diabetes prevention benefit of metformin might represent a delaying of the development of diabetes rather than true prevention since follow-up OGTT in most studies was done while patients were still taking the medication.

- In one follow-up study of 1274 subjects in the DPP metformin group (who had not developed diabetes), follow-up OGTTs after stopping metformin (on average 11 days) showed that approximately 75 % of the metformin benefit persisted.

Diabetes Prevention Program Research Group. Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program. Diabetes Care 2003; 26:977.

Delay or prevention?

Although the authors suggested that this finding is consistent with prevention, **longer drug-free trials are needed to firmly draw this conclusion.**

- Patients treated with metformin require at least annual monitoring (A1C or fasting glucose).

Second case study

35 - year - old overweight lady with history of GDM in previous labor 5 years ago

BP =120/75 mmHg

FBS = 122 mg/dl

Repeated 2 days later =117 mg/dl

Ch=220 mg/dl

LDL= 130 mg/dl

HDL= 49 mg/dl

Triglyceride=200 mg/dl

HbA1c= 6.15 %

ORIGINAL ARTICLE

Endocrine Care

Prevention of Diabetes in Women with a History of Gestational Diabetes: Effects of Metformin and Lifestyle Interventions

Robert E. Ratner, Costas A. Christophi, Boyd E. Metzger, Dana Dabelea, Peter H. Bennett, Xavier Pi-Sunyer, Sarah Fowler, Steven E. Kahn, and The Diabetes Prevention Program Research Group*

(J Clin Endocrinol Metab 93: 4774–4779, 2008)

Patients

- A total of 2190 women were randomized into the DPP and provided information for past history of GDM.
- This analysis addressed the differences between
- **350** women providing a past history of GDM
- **1416** women with a previous live birth but no history of GDM.

Results

placebo

Whereas entering the study with similar glucose levels, women with a history of GDM randomized to placebo had a crude incidence rate of diabetes 71% higher than that of women without such a history.

intervention

Among women reporting a history of GDM, both intensive lifestyle and metformin therapy reduced the incidence of diabetes by approximately 50% compared with the placebo group

Whereas this reduction was 49 and 14%, respectively in parous women without GDM.

Results

These data suggest that metformin may be more effective in women with a GDM history as compared with those without.

Conclusions

Progression to diabetes is more common in women with a history of GDM compared with those without GDM history despite equivalent degrees of IGT at baseline.

Both intensive lifestyle and metformin are highly effective in delaying or preventing diabetes in women with IGT and a history of GDM

Weight change without history of GDM

Weight change with a history of GDM

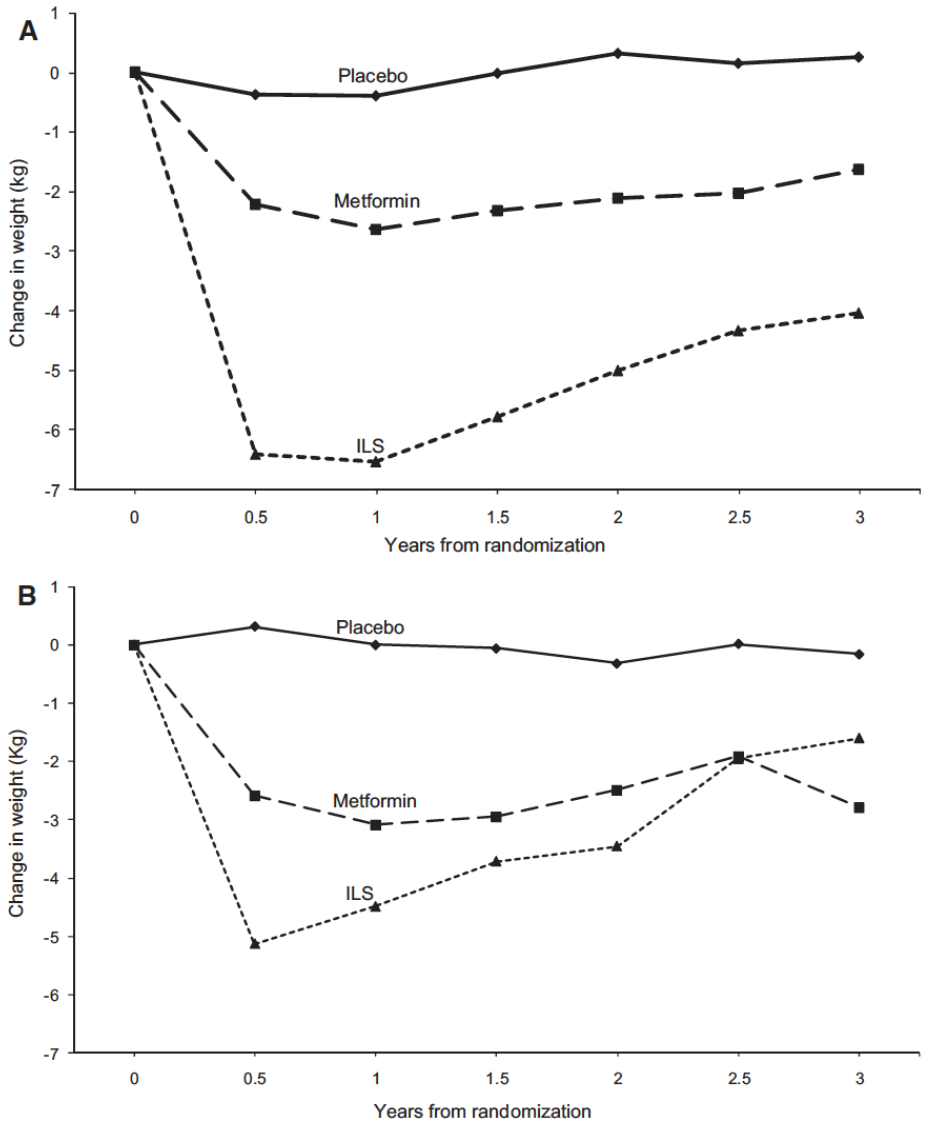


FIG. 3. Change in weight during DPP by randomized treatment group. *Panel A*, Women without a history of GDM; *Panel B*, women with a history of GDM.

Metformin in GDM

- Metformin was most effective in reducing the risk of diabetes in younger people with obesity, and particularly in women with a history of gestational diabetes .

- Metformin is relatively inexpensive and has no long-term, serious side effects.

- Ratner RE, Christophi CA, Metzger BE, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008; 93:4774.

Metformin in GDM

In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk.

Both interventions remained highly effective during a 10-year follow-up period.

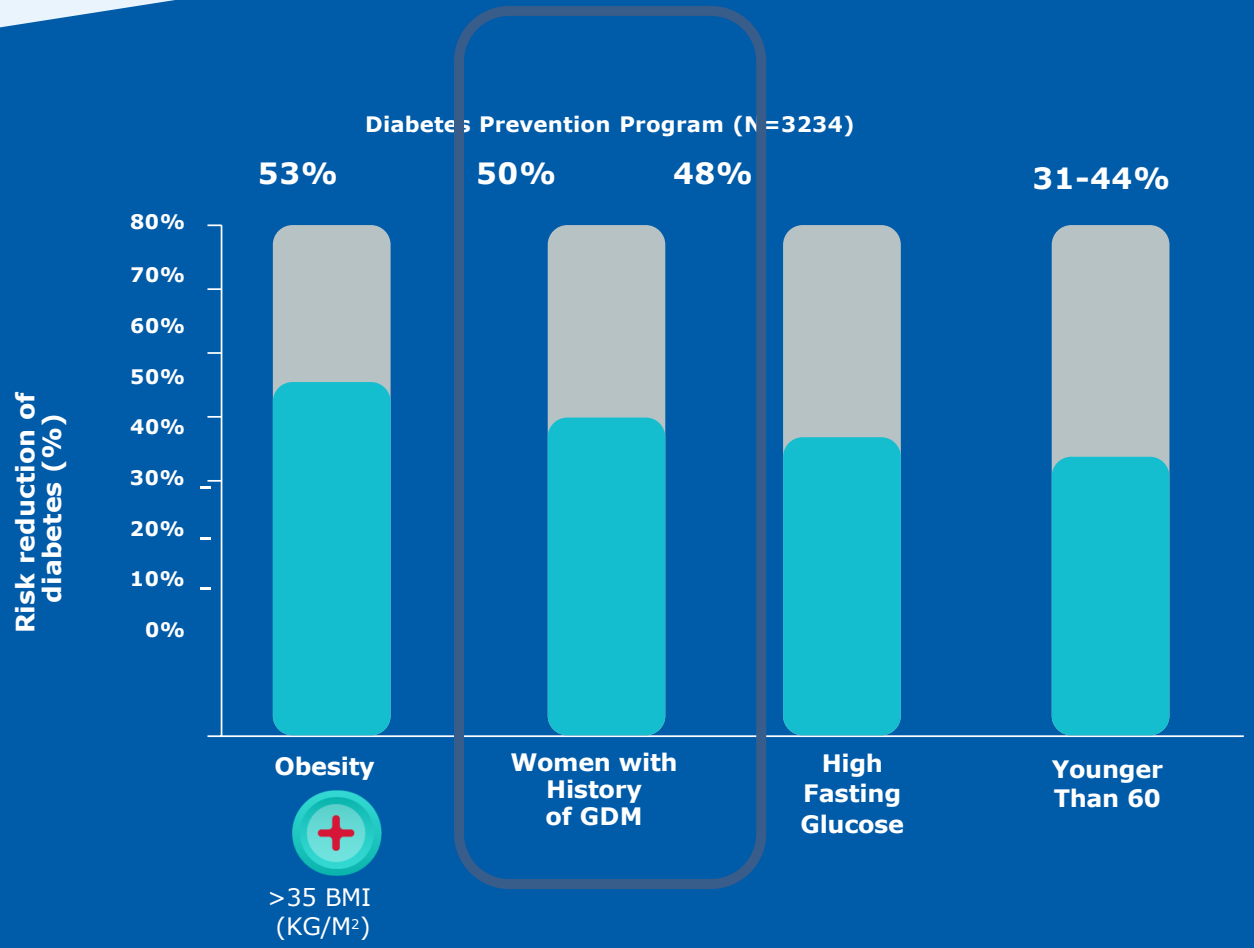
History of GDM

- In contrast to the findings in the entire DPP cohort (lifestyle intervention more effective than metformin therapy)

- Metformin and lifestyle intervention were similarly effective in reducing the incidence of diabetes in women with a history of gestational diabetes.

- Ratner RE, Christophi CA, Metzger BE, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008; 93:4774

Effectiveness of Metformin for Diabetes Prevention in Patient Subgroups[1,2]



References:

1. Knowler et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The new England journal of medicine*, 346, 2002.

2. Aroda, V. et al. Metformin and Type 2 Diabetes Prevention. *Diabetes Spectr*. 2018 Nov; 31(4): 336–342.

Pharmacologic interventions

Metformin therapy for the prevention of type 2 diabetes should be considered in adults at high risk of T2DM

as typified by the DPP

Especially those aged 25– 59 years with BMI > 35 kg/m2

Higher fasting plasma glucose (e.g., >110 mg/dL), and

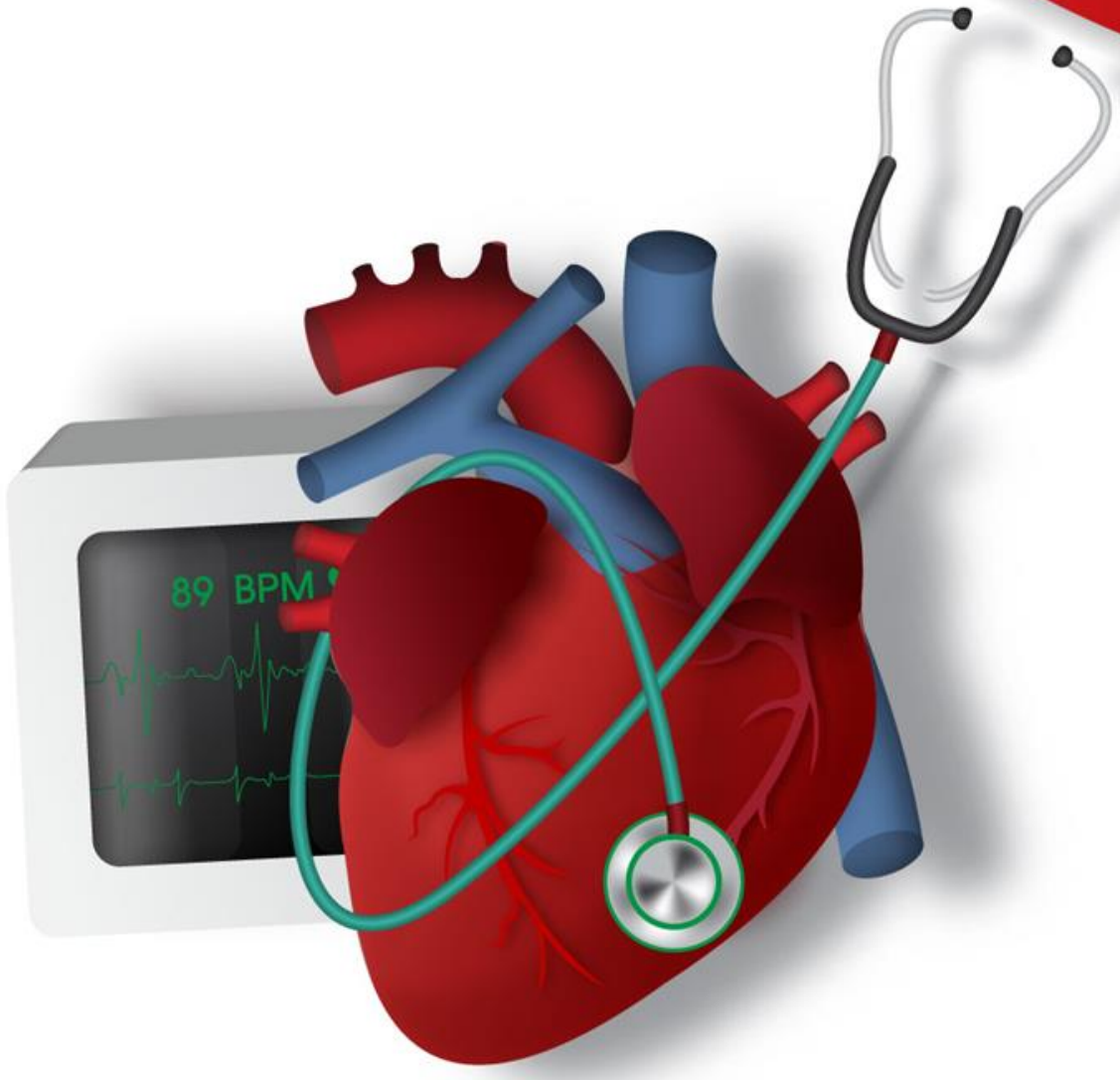
Higher A1C (e.g., > 6.0%), and

Individuals with prior GDM. A

Measurement of vitamin B12

- 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

Metformin & Heart



UKPDS

Randomized, interventional study, overweight patients
15 SITES in UK

Median treatment duration 10.7 years

- **N=411, Diet**
- **N=342, Metformin**
- N=277, Glibenclamide
- N=409, Insulin
- N=265, Chlorpropamide

Primary endpoints

- Time to first occurrence of
  - any diabetes-related clinical complication
  - diabetes-related death
  - all-cause mortality

Secondary endpoints

- Myocardial infarction
- Stroke
- Amputation/death due to PVD
- Microvascular complications

Source: UKPDS 33: Lancet, 1998, 352: 837-53.

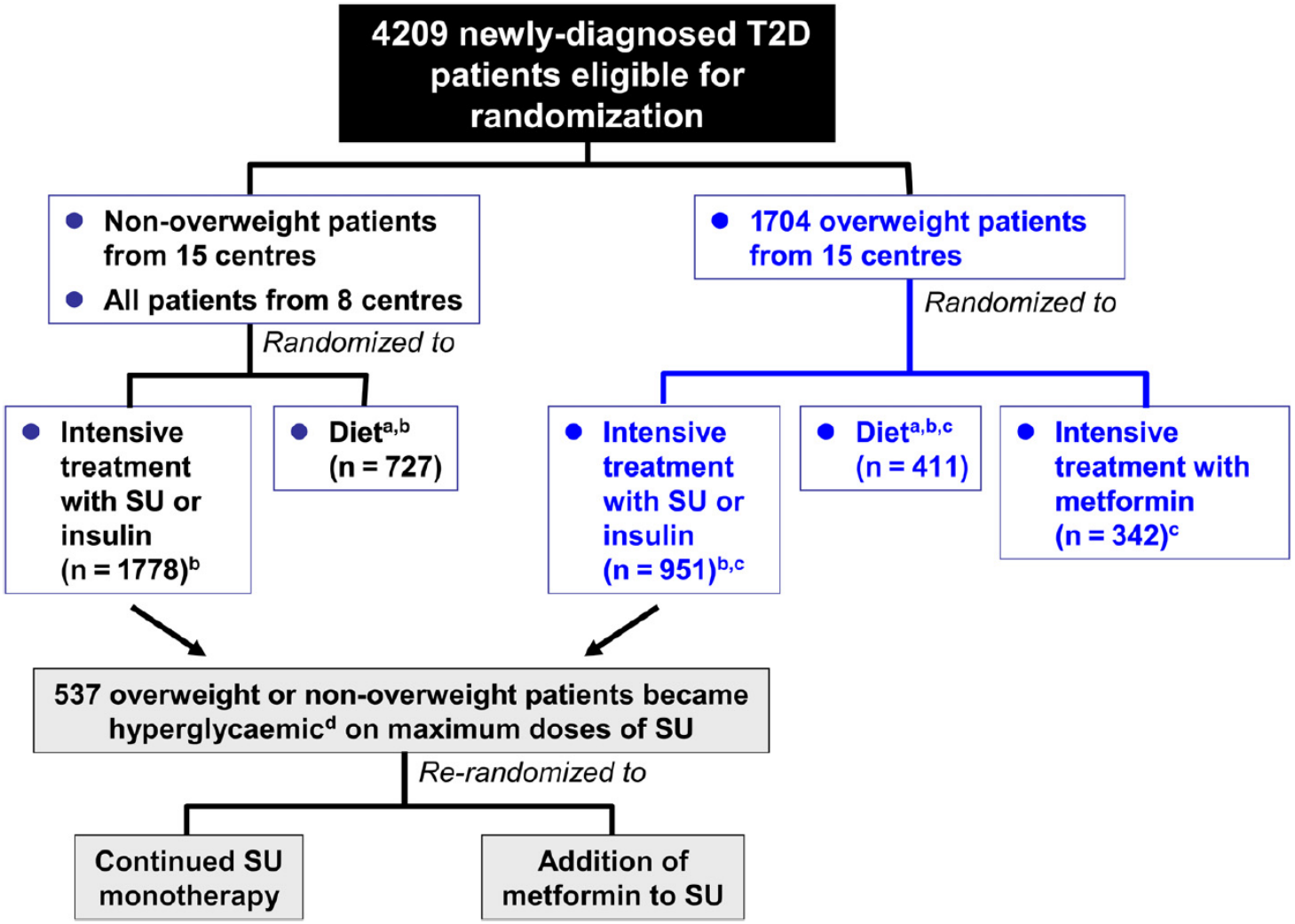


FIGURE 1 Summary of randomized allocation of patients to treatment in the UK Prospective diabetes study. SU, sulphonylurea; T2D, type 2 diabetes. [a]Conventional treatment policy in the UKPDS. [b]These patients were included in the main trial analysis (UKPDS 33). [c]UKPDS 34. [d]Defined as fasting plasma glucose 6.1–15 mmol/L (110–270 mg/dL) without symptoms of hyperglycaemia. Adapted from references[7,8] with permission from Elsevier

UKPDS

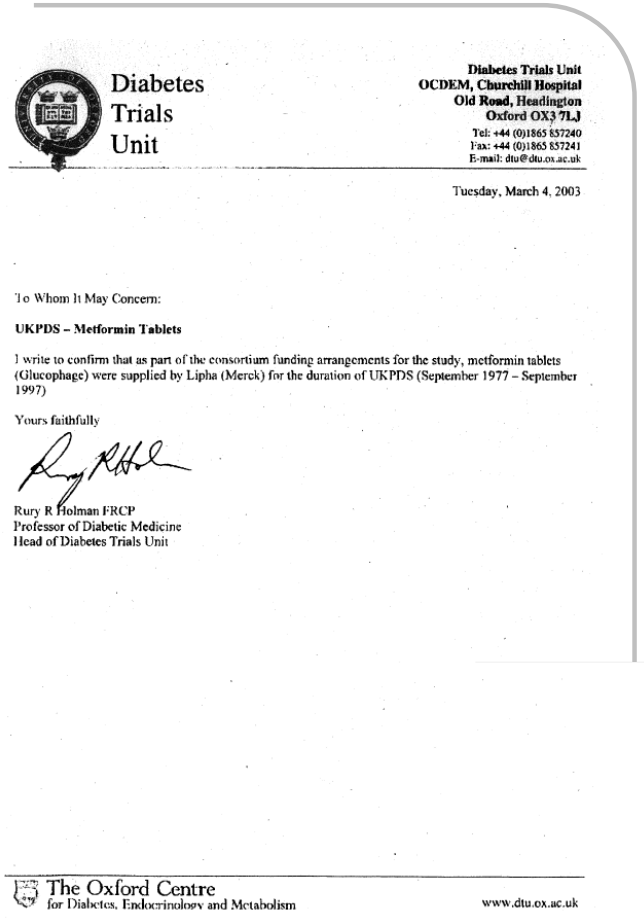
Randomized, interventional study, overweight patients
15 SITES in UK

Median treatment duration 10.7 years

N=411, Diet

N=342, Glucophage®

Clinical endpoint versus diet	Metformin
Any diabetes related complication	**↓ 32% (p=0.002)**
Diabetes–related deaths	**↓ 42% (p=0.017)**
All-cause mortality	**↓ 36% (p=0.011)**
Myocardial infarction	**↓ 39% (p=0.01)**
Stroke	↓ 41% (p=0.13)
Amputation/death due to PVD	↓ 26% (p=0.62)
Microvascular complications	↓ 29% (p=0.19)



Diabetes Trials Unit

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Tuesday, March 4, 2003

To Whom It May Concern:

UKPDS – Metformin Tablets

I write to confirm that as part of the consortium funding arrangements for the study, metformin tablets (Glucophage) were supplied by Lipha (Merck) for the duration of UKPDS (September 1977 – September 1997)

Yours faithfully

Rury R Holman FRCP
Professor of Diabetic Medicine
Head of Diabetes Trials Unit

The Oxford Centre for Diabetes, Endocrinology and Metabolism
www.dtu.ox.ac.uk

Source: UKPDS 34: Lancet, 1998, 352:854-65.

UKPDS – legacy effect

Post-trial monitoring for 10 years
15 SITES in UK

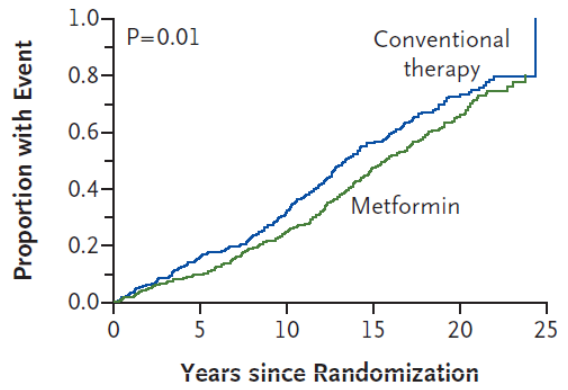
Median monitoring duration 10 years

N=309, conventional therapy

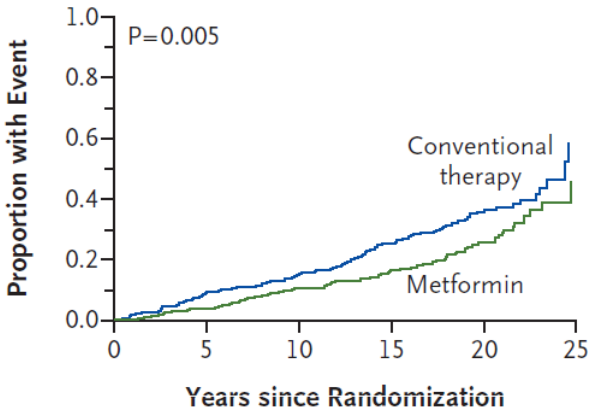
N=279, intensive Glucophage® therapy

Clinical endpoint versus conventional	Metformin
Any diabetes related complication	**↓ 21% (p=0.01)**
Diabetes–related deaths	**↓ 30% (p=0.01)**
All-cause mortality	**↓ 27% (p=0.002)**
Myocardial infarction	**↓ 33% (p=0.005)**
Stroke	↓ 20% (p=0.35)
Amputation/death due to PVD	↓ 37% (p=0.19)
Microvascular complications	↓ 16% (p=0.31)

Any diabetes-related complication



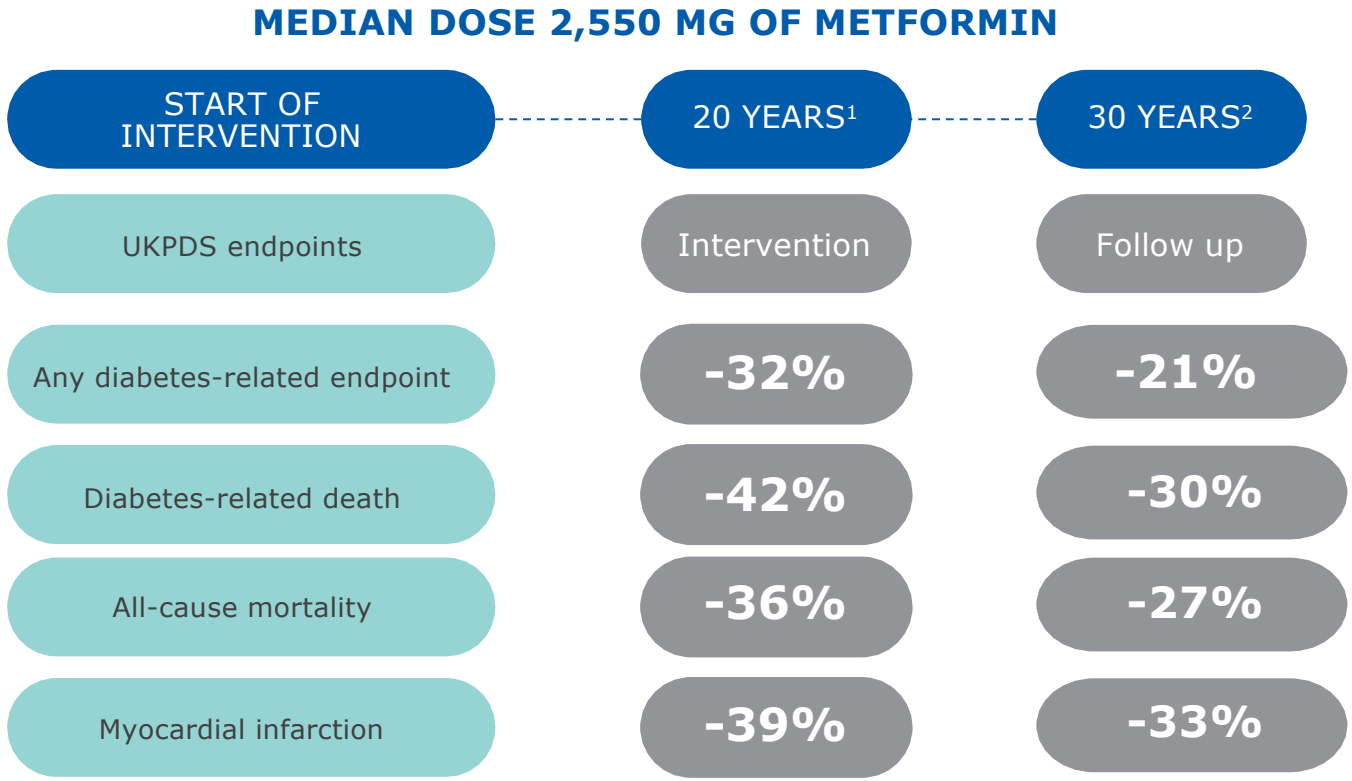
Myocardial infarction



Benefits of intensive treatment with Glucophage® persisted despite the early loss of within-trial differences in glycated hemoglobin levels between the intensive- therapy group and the conventional-therapy group — the so-called legacy effect.

Source: UKPDS 34: Lancet, 1998, 352:854-65.

UK Prospective Diabetes Study: Intensive Glucose Control with Metformin & Cardiovascular Outcomes[1,2]



References:
1. UKPDS Group. *Lancet*. 1998 Sep 12;352(9131):854-65.
2. Holeman, R. *N Engl J Med* 2008; 359:1577-1589.

Prediabetes and CVD risk

- People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia,

and are at increased risk for cardiovascular disease.

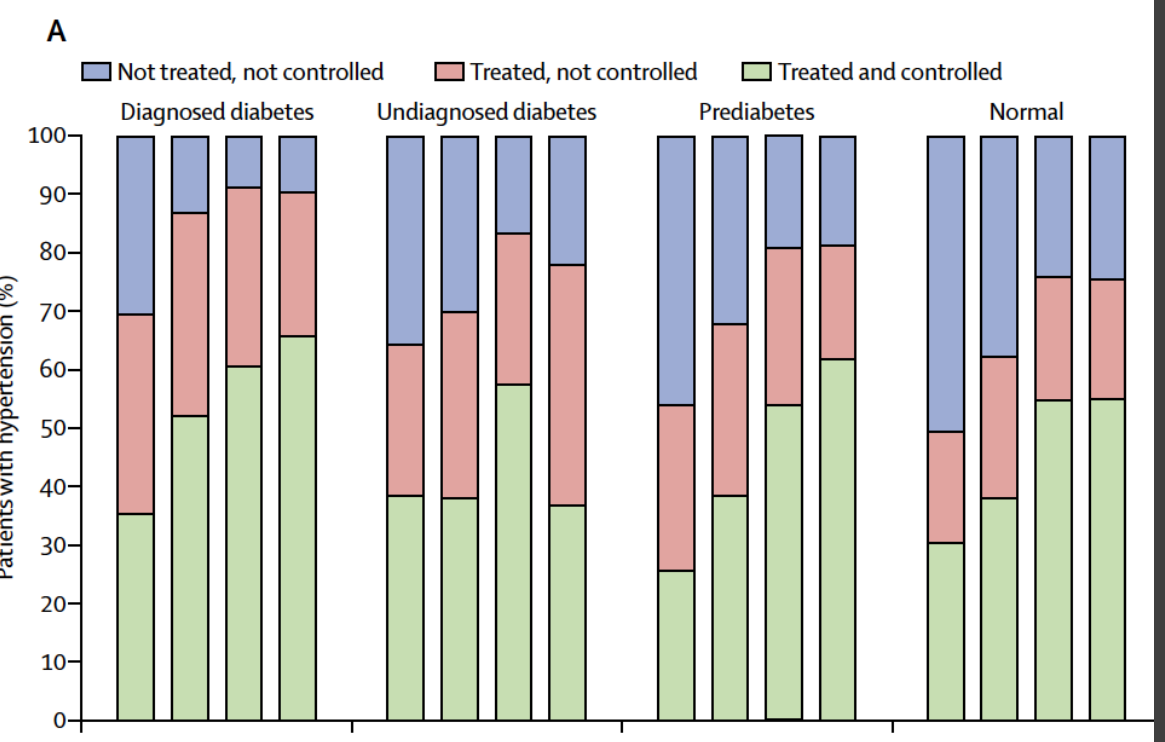
- Pan Y, Chen W, Wang Y. Prediabetes and outcome of ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2019;28:683–692
- Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality:

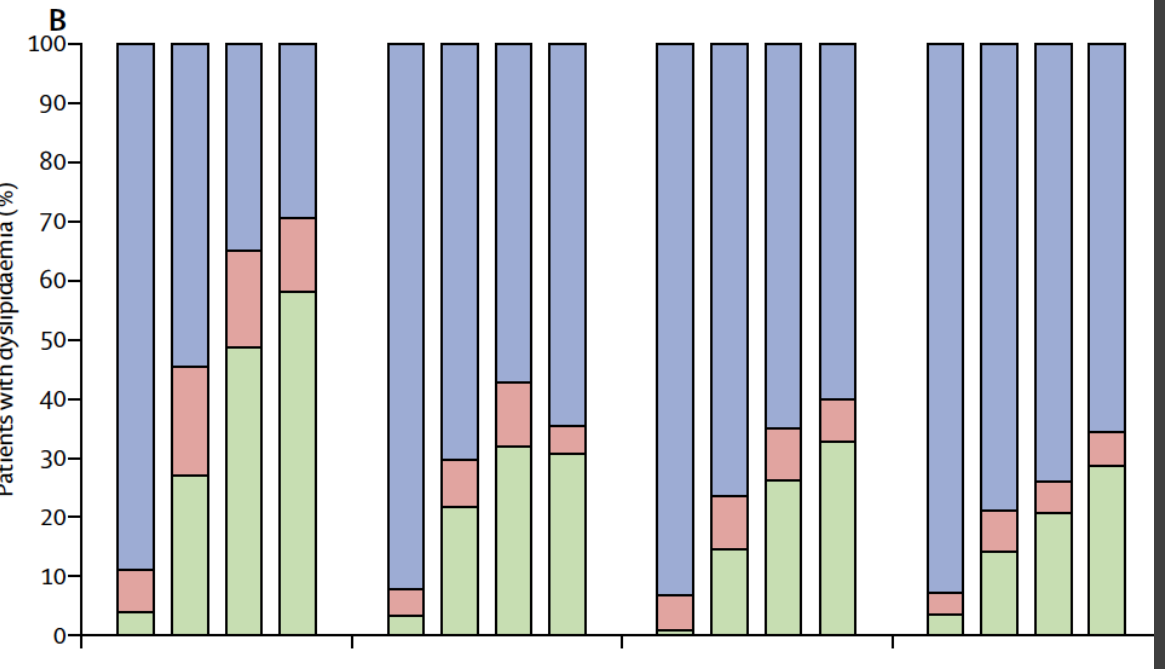
ARTICLES | VOLUME 6, ISSUE 5, P392-403, MAY 2018

Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988–2014

Mohammed K Ali, MD • Kai McKeever Bullard, PhD • Sharon Saydah, PhD • Giuseppina Imperatore, MD • Edward W Gregg, PhD

Published: February 27, 2018 • DOI: https://doi.org/10.1016/S2213-8587(18)30027-5 •





In the USA

- 1- More than a third of adults with IFG or increased HbA1c had hypertension
- 2-More than half had dyslipidemia
- 3- More than a quarter smoked
- 4- about 11% had some form of CKD
- 6% reported a previous MI or stroke

- 7- The mean 10-year risk of a cardiovascular event was about 6%.

RESEARCH ARTICLE | VOLUME 28, ISSUE 3, P683-692, MARCH 2019

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Prediabetes and Outcome of Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Meta-analysis

Yuesong Pan, PhD • Weiqi Chen, MD, PhD • Yongjun Wang, MD

Published: November 26, 2018 • DOI: https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.11.008

Prediabetes & stroke

- Prediabetes was at increased risk of stroke compared with normal glucose metabolism (HR: 1.42, P = 003).
- Poor outcome was also more frequent in patients with prediabetes compared with normal glucose metabolism (odds ratio: 1.33, 1P =.002), while mortality was not significant (HR: 1.69, P =.14).
- There was no evidence of statistical heterogeneity among the included studies for stroke and poor outcome, but for mortality.

Conclusions

Prediabetes was associated with an increased risk of new stroke and poor outcome, compared with normal glucose metabolism among patients with ischemic stroke or TIA.

Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis

Yuli Huang,[1] Xiaoyan Cai,[2] Weiyi Mai,[3] Meijun Li,[1,4] Yunzhao Hu[1]

Result

- 53 prospective cohort studies with 1 611 339 individuals were included for analysis.
- The median follow-up duration was 9.5 years.

Result

- Compared with normoglycemia, prediabetes was associated with an increased risk of

- Composite cardiovascular disease (relative risk 1.13, 1.26, and 1.30 for IFG-ADA, IFG-WHO, and IGT, respectively)
- Coronary heart disease (1.10, 1.18, and 1.20, respectively)
- Stroke (1.06, 1.17, and 1.20, respectively)
- All cause mortality (1.13, 1.13 and 1.32)

- Increases in HbA1c to 5.7 to 6.4 % or 42-47 mmol/mol were both associated with an
- Increased risk of composite cardiovascular disease (1.21 and 1.25, respectively)
- Coronary heart disease (1.15 and 1.28, respectively)
- But not with an increased risk of stroke and all cause mortality.

Conclusions

- Prediabetes, defined as IGT , IFG, or raised HbA1c, was associated with an increased risk of CVD
- The health risk might be increased in people with a fasting glucose concentration as low as 100 mg/dL or HbA1c of 5.7%

Lifestyle interventions & cardiovascular risk factors

- The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown:

- A reduction in cardiovascular risk factors
- And the need for medications used to treat these cardiovascular risk factors.

Lifestyle interventions & cardiovascular risk factors

- In longer-term follow-up, lifestyle interventions for diabetes prevention also prevented the development of microvascular complications among women enrolled in the DPPOS and in the study population enrolled in the China Da Qing Diabetes Prevention Outcome Study.

- The lifestyle intervention in the latter study was also efficacious in preventing cardiovascular disease and mortality at 23 and 30 years of follow-up.

Prediabetes & risk factor management

Treatment goals and therapies for hypertension and dyslipidemia in the primary prevention of cardiovascular disease for people with prediabetes **should be based on their level of cardiovascular risk.**

Pioglitazone in IRIS trial

- The IRIS (Insulin Resistance Intervention after Stroke) trial was a dedicated study of people with a recent (<6 months) stroke or TIA, without diabetes but with insulin resistance, as defined by a HOMA index of > 3.0, evaluating (target dose of 45 mg daily) compared with placebo.

IRIS trial

At 4.8 years, the risk of stroke or MI, as well as the risk of diabetes, was lower within the pioglitazone group than with placebo,

though risks of weight gain, edema, and fracture were higher in the pioglitazone treatment group.

Lower doses may mitigate the adverse effects, though further study is needed to confirm the benefit at lower doses .

Prevention or Delay of Type 2 Diabetes and Associated Comorbidities

Overall Recommendation

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

Lifestyle Behavior Change for Diabetes Prevention

- Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by 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

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

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

Pharmacologic Interventions

- 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 DPP, 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 GDM. A

Third case study

65 - year - old obese man with a history of HTN , HLP and CABG 4 years ago

BP =145/95 mmHg

FBS = 118 mg/dl

Repeated 2 days later =123 mg/dl

Ch=245 mg/dl

LDL= 151 mg/dl

HDL= 30 mg/dl

Triglyceride=320 mg/dl

HbA1c= 6. 35%

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Review

Metformin and the heart: Update on mechanisms of cardiovascular protection with special reference to comorbid type 2 diabetes and heart failure

Guntram Schernthaner [a,*], Kerstin Brand [b], Clifford J. Bailey [c]

Table 1

Randomised, controlled cardiovascular outcomes trials that evaluated metformin in populations with type 2 diabetes.

a) UK Prospective Diabetes Study (UKPDS): 753 overweight (>120% ideal weight) people with newly diagnosed type 2 diabetes randomised to metformin (n = 342) or to diet intervention (n = 411).

Outcome	Randomised phase (median 10.7 y) [4]		10 y post-trial follow-up [7]	
	RR (95% CI)[a]	p[a]	RR (95% CI)[a]	p[a]
Any diabetes-related endpoint	0.68 (0.53, 0.87)	0.0023	0.79 (0.66 to 0.95)	0.01
Myocardial infarction	0.61 (0.41, 0.89)	0.01	0.67 (0.51 to 0.89)	0.005
Diabetes-related death	0.58 (0.37, 0.91)	0.017	0.70 (0.53 to 0.92)	0.01
All-cause death	0.64 (0.45, 0.91)	0.011	0.73 (0.59 to 0.89)	0.002
Stroke, peripheral vascular disease, microvascular disease	No significant reduction associated with metformin vs. control (diet) for any of these endpoints			

SPREAD-DIMCAD Trial showed a significant reduction in a cardiovascular composite for metformin compared with a sulfonylurea after 5 years of randomized treatment[1]

Aim

To evaluate the different effects of glipizide and metformin on the major cardiovascular events and mortality among type 2 diabetic patients with a history of coronary artery disease.

Study design

304 type 2 diabetes patients with coronary artery disease randomised to metformin 1500 mg/day or glipizide 30 mg/ day; median follow-up 5 years.

Outcome

Outcome	RR (95% CI)[a]	*p*[a]
Primary cardiovascular composite[b]	**0.54 (0.30 to 0.90)**	**0.026**

Overview

- Prospective, randomized, double-blind, placebo-controlled trial.

a HRs and *p* values are for metformin vs. non-metformin control, as specified (values <1 favour metformin). b Non-fatal myocardial infarction or stroke, revascularisation, cardiovascular death or all-cause death). c Myocardial infarction; heart failure; prespecified ECG changes; acute coronary syndrome; diabetic foot; stroke; transient ischemic attack; peripheral arterial disease; peripheral arterial reconstruction; percutaneous transluminal coronary angioplasty (PTCA); coronary artery bypass graft (CABG); nontraumatic amputation; sudden death; progression of retinopathy, nephropathy, or neuropathy; death by any other cause; myocardial infarction, stroke, PTCA, CABG, cardiovascular death, all-cause death. HR: hazard ratio; RR: relative risk. d Microvascular and microvascular components of the primary endpoint. Adapted from ref. [1].

SPREAD-DIMCAD - Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease

[1] - Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, Zhou Z, Tang W, Zhao J, Cui L, Zou D, Wang D, Li H, Liu C, Wu G, Shen J, Zhu D, Wang W, Shen W, Ning G; SPREAD-DIMCAD Investigators. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013 May;36(5):1304-11. doi: 10.2337/dc12-0719. Epub 2012 Dec 10. PMID: 23230096; PMCID: PMC3631843.

HOME Trial concluded that the primary endpoint (a mixture of macrovascular and microvascular endpoints) was not affected significantly, although there was a significant reduction in the secondary macrovascular composite[1]

Aim

To investigate the effects of metformin in patients with T2D intensively treated with insulin on the quality of the metabolic control of diabetes.

Study design

c) Kooy et al, metformin versus placebo in insulin-treated people with diabetes: 390 insulin-treated type 2 diabetes patients with diabetes duration >13 years were randomised to additional metformin (up to 2550 mg/day)

Outcome

Outcome	RR (95% CI)[a]	*p*[a]
Primary composite[c]	0.92 (0.72 to 1.18)	*p* = 0.33
Cardiovascular composite[d]	0.60 (0.40 to 0.92)	0.04
Microvascular composite[d]	1.04 (0.75 to 1.44)	*p* = 0.43

Overview

- It is hypothesized that patients with T2D treated with insulin, metformin, compared with placebo, would have sustained beneficial metabolic effects, even at the same level of glycemic control, and thus decrease cardiovascular disease.
- Follow up period – 4.3 years

a HRs and *p* values are for metformin vs. non-metformin control, as specified (values <1 favour metformin). b Non-fatal myocardial infarction or stroke, revascularisation, cardiovascular death or all-cause death). c Myocardial infarction; heart failure; prespecified ECG changes; acute coronary syndrome; diabetic foot; stroke; transient ischemic attack; peripheral arterial disease; peripheral arterial reconstruction; percutaneous transluminal coronary angioplasty (PTCA); coronary artery bypass graft (CABG); nontraumatic amputation; sudden death; progression of retinopathy, nephropathy, or neuropathy; death by any other cause; myocardial infarction, stroke, PTCA, CABG, cardiovascular death, all-cause death. HR: hazard ratio; RR: relative risk. d Microvascular and microvascular components of the primary endpoint. Adapted from ref. [1].

[1] - Kooy A, de Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, Stehouwer CD. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med. 2009 Mar 23;169(6):616-25. doi: 10.1001/archinternmed.2009.20. PMID: 19307526.

b) Hong et al, metformin versus glipizide [8]: 304 type 2 diabetes patients with coronary artery disease randomised to metformin 1500 mg/day or glipizide 30 mg/day; median follow-up 5 years.

Outcome	RR (95% CI)[a]	p[a]
Primary cardiovascular composite[b]	0.54 (0.30 to 0.90)	0.026

c) Kooy et al, metformin versus placebo in insulin-treated people with diabetes [9]: 390 insulin-treated type 2 diabetes patients with diabetes duration >13 years were randomised to additional metformin (up to 2550 mg/day) or placebo for median 4.3 y

Outcome	RR (95% CI)[a]	p[a]
Primary composite[c]	0.92 (0.72 to 1.18)	$p = 0.33$
Cardiovascular composite[d]	0.60 (0.40 to 0.92)	0.04
Microvascular composite[d]	1.04 (0.75 to 1.44)	$p = 0.43$

Observational studies

- A recent comprehensive meta-analysis that included 701,843 people with type 2 diabetes who had received metformin and 1,160,254 controls noted reduced risks of mortality (OR 0.44) or adverse cardiovascular outcomes (OR 0.73) for metformin versus no metformin.

Cardiovascular risk following metformin treatment in patients with type 2 diabetes mellitus: results from meta-analysis. Diabetes Res Clin Pract 2020 Feb;160:108001.

Observational studies

- A meta-analysis from 2019 that included data from >1 million subjects with type 2 diabetes and coronary artery disease reported similar results .

- Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. Cardiovasc Diabetol 2019;18:96.

Observational studies

- A database study of 4030 patients with type 2 diabetes with incident MI showed that receipt of metformin at hospital admission was associated with an increased risk of major adverse cardiovascular events (MACE) in survivors after discharge.

- Metformin use and cardiovascular outcomes after acute myocardial infarction in patients with type 2 diabetes: a cohort study. Cardiovasc Diabetol 2019;18:168

Observational studies

- Accordingly, metformin may be harmful in the setting of acute myocardial ischemia, consistent with its contraindications.
- However, the risk of subsequent MACE was reduced in patients who received metformin after the period of acute ischemia.

Metformin treatment in people with type 2 diabetes and HF

- Metformin can be prescribed for patients with stable HF, but is contraindicated for patients with decompensated HF

Metformin treatment in people with type 2 diabetes and HF

- **A meta-analysis of 9 observational studies** included 34,504 patients with type 2 diabetes and HF (6624 were receiving metformin).

- Compared with non-metformin controls (mostly sulfonylurea), metformin was associated with reduced risk of mortality (relative risk 0.80 [0.74, 0.87], $p < 0.001$).

- Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. Circ Heart Fail 2013;6: 395–402.

Metformin treatment in people with type 2 diabetes and HF

- Findings were similar in a meta-analysis of 11 observational studies (*N* = 35,950 with diabetes and HF), where treatment with versus without metformin was associated with a 22% reduction in mortality (HR 0.78 [0.71, 0.87], *p* = 0.003]).

Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med 2017;166:191–200.

Metformin treatment in people with type 2 diabetes and HF

- Risk reductions became non-significant in two studies in patients with severely reduced left ventricular ejection fraction (LVEF <30% or <40%) or in two studies in patients with comorbid chronic kidney disease (CKD), but there was no adverse safety signal in these sub-populations

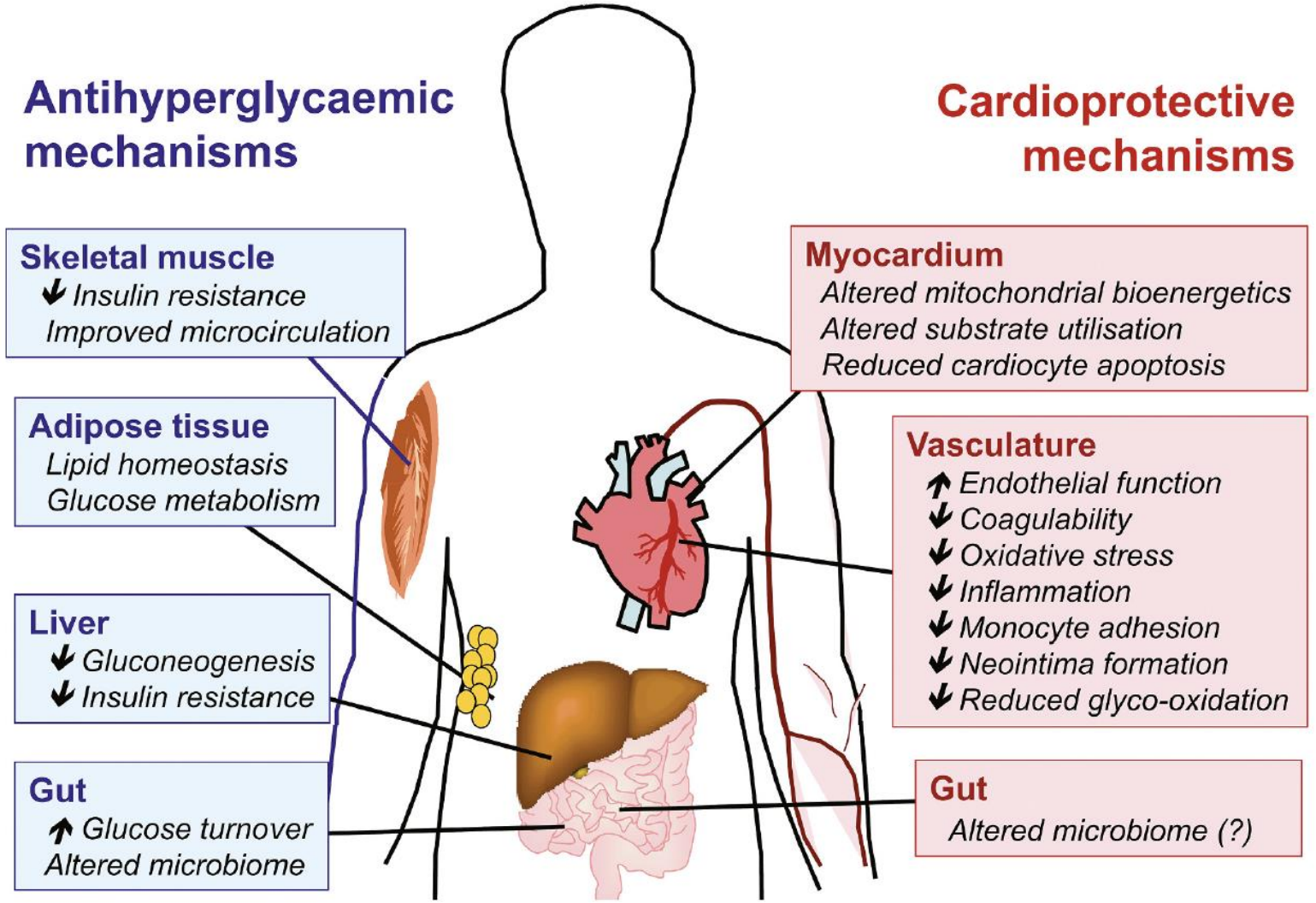

Fig. 1. Overview of mechanisms for the antihyperglycaemic and cardioprotective mechanisms for metformin that have been presented in the literature.

- The potential to improve myocardial function in chronic HF is perhaps the next chapter in metformin's long story, and the results of the DANHEART study are awaited with great interest.

- HFpEF, in particular, is regarded increasingly as a hitherto under recognized cardiovascular complication of diabetes and is associated with a severely adverse prognosis.

- Papp Z, Radovits T, Paulus WJ, Hamdani N, Seferovi´c PM. Molecular and pathophysiological links between heart failure with preserved ejection fraction and type 2 diabetes mellitus. Eur J Heart Fail 2018;20:1649–52.

The EMPEROR Preserved trial

- The EMPEROR Preserved trial recently identified a SGLT2 inhibitor as the first pharmacologic intervention to improve hard clinical outcomes in this population

- The suggestion of improved outcomes in metformin-treated patients with HFpEF from a meta-analysis and retrospective studies, described above, merits further study.

- Halabi A, Sen J, Huynh Q, Marwick TH. Metformin treatment in heart failure with preserved ejection fraction: a systematic review and meta-regression analysis. Cardiovasc Diabetol 2020;19:124.

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Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes (VA-IMPACT)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02915198

Recruitment Status : Not yet recruiting
First Posted : September 26, 2016
Last Update Posted : January 13, 2023

See **Contacts and Locations**

View this study on Beta.ClinicalTrials.gov

VA-IMPACT trial

- Elsewhere, VA-IMPACT (Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular Outcomes; NCT02915198) is a large (>7000 participants) multicenter, prospective, randomized, double blind, secondary prevention study to investigate whether metformin reduces mortality and cardiovascular morbidity in **people with pre-diabetes and established atherosclerotic cardiovascular disease.**

VA-IMPACT trial

- The primary outcome of this trial is the time to first occurrence of death, non-fatal myocardial infarction or stroke, hospitalization for unstable angina with evidence of acute myocardial ischemia, or coronary revascularization driven by acute or progressive symptoms.

- Recruitment to this trial is on temporary hold during the coronavirus pandemic: it was due to complete late 2024 but will now be later.

LIMIT trial

- Several other studies are assessing related conditions, including LIMIT (NCT04500756) in abdominal aortic aneurism.

Ongoing SMARTEST study

- The ongoing SMARTEST study (NCT03982381) will be the first head-to-head comparison between metformin and an SGLT2 inhibitor in an extended rage of cardiovascular outcomes, and this study is also due for 2024.

Ongoing studies

- These ongoing studies will extend the clinical database on metformin with respect to effects on clinical cardiovascular outcomes and will clarify the extent to which metformin protects the cardiovascular system in people with type 2 diabetes.

Prevention of Vascular Disease and Mortality

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

Prevention of Vascular Disease and Mortality

- 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.

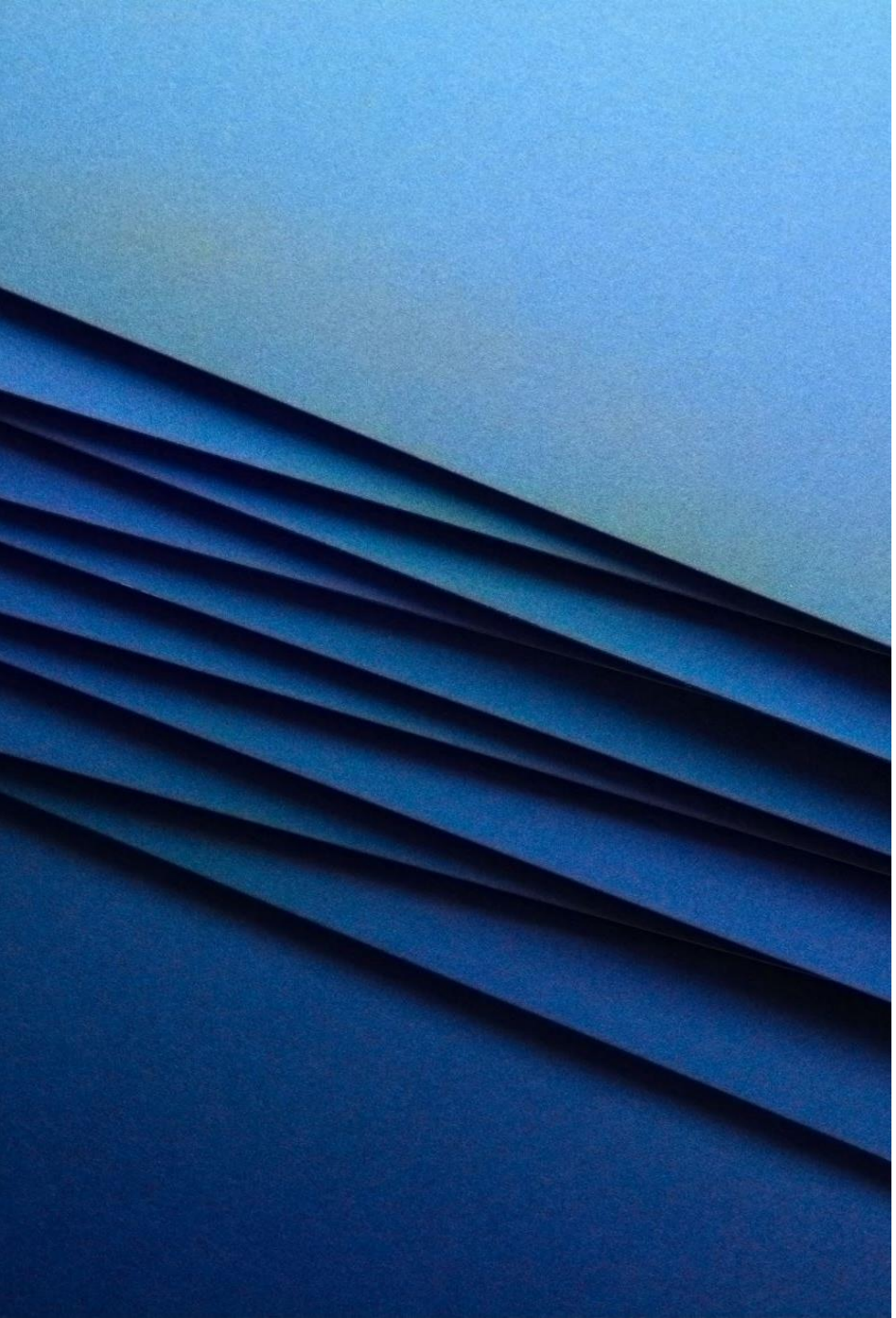
- It is not recommended that statins be discontinued. B

Prevention of Vascular Disease and Mortality

- 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.

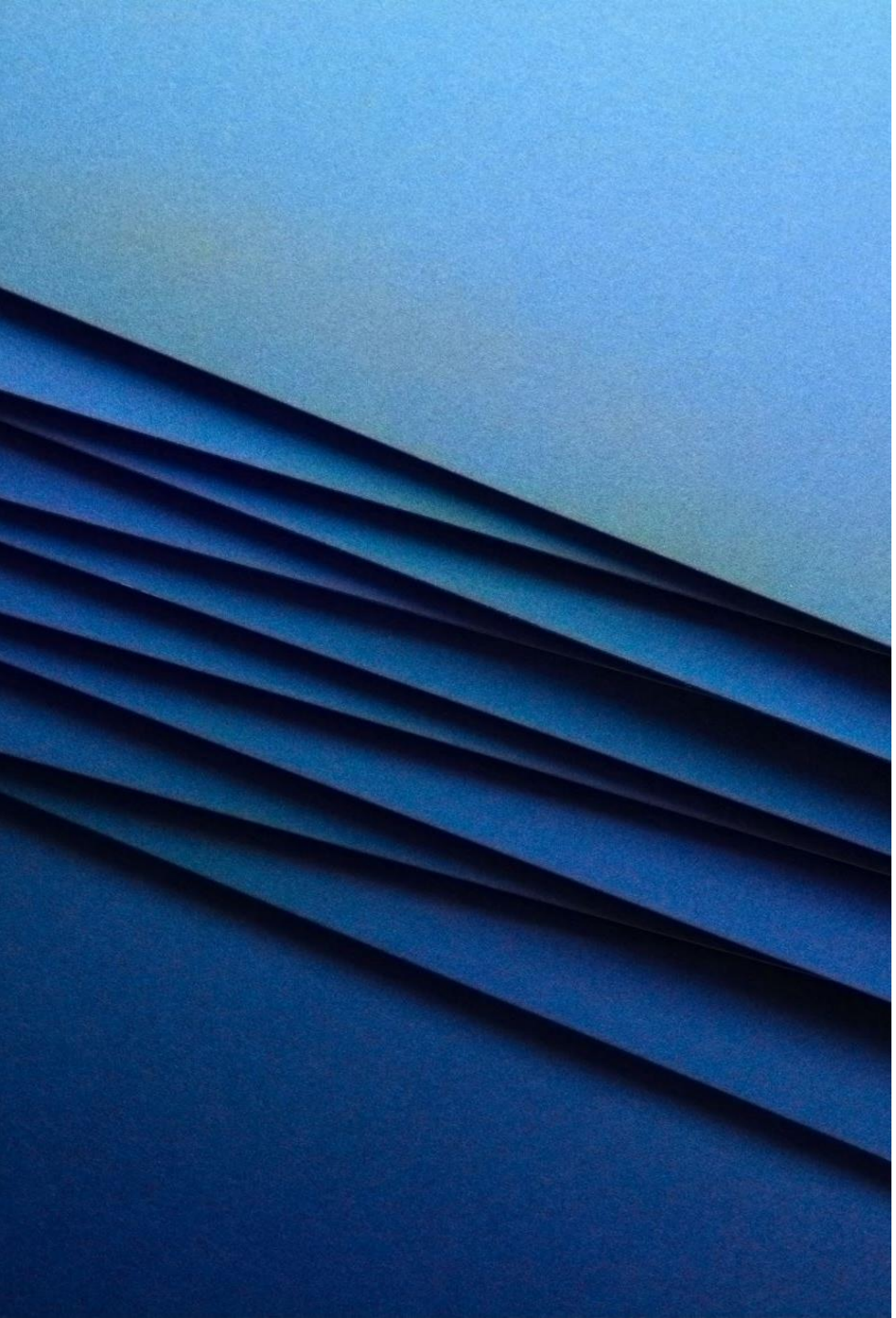
- A Lower doses may mitigate the risk of adverse effects. C



Patient-Centered Care Goals

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

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



Patient-Centered Care Goals

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., FBS=110–125 mg/dL, 2-h post-challenge glucose 173–199 mg/dL, A1C ≥6.0%)

and individuals with a history of GDM. A

Pharmacologic approach to the patients with type 2 diabetes

Case study

A 48 – years- old overweight lady diagnosed with T2 DM for 6 months ago.

Her BMI =28, she is otherwise healthy, advised for lifestyle modification

Her most recent HbA1c is 7.5%

Lipid profile was normal, e GFR= 80 ml/min

Normotensive

What is the best next step treatment ?

Best next step?

- Metformin plus sitagliptin
- Gliclazide
- Metformin
- Empagliflozin

Best next step?

- Metformin plus sitagliptin
- Gliclazide
- Metformin
- Empagliflozin

Pharmacologic Therapy for Adults With Type 2 Diabetes
First step

Healthy lifestyle behaviors

a) Diabetes self-management education and support

b) Avoidance of clinical inertia

c) Social determinants of health

should be considered in the glucose-lowering management of type 2 diabetes.

Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. A

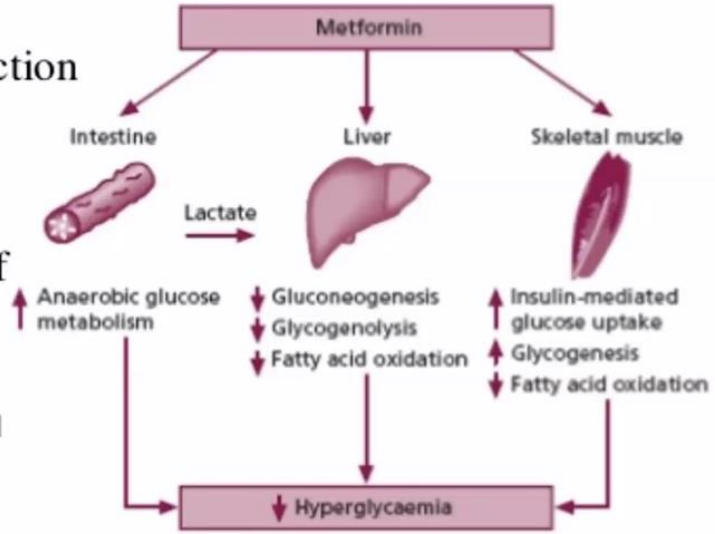
Metformin

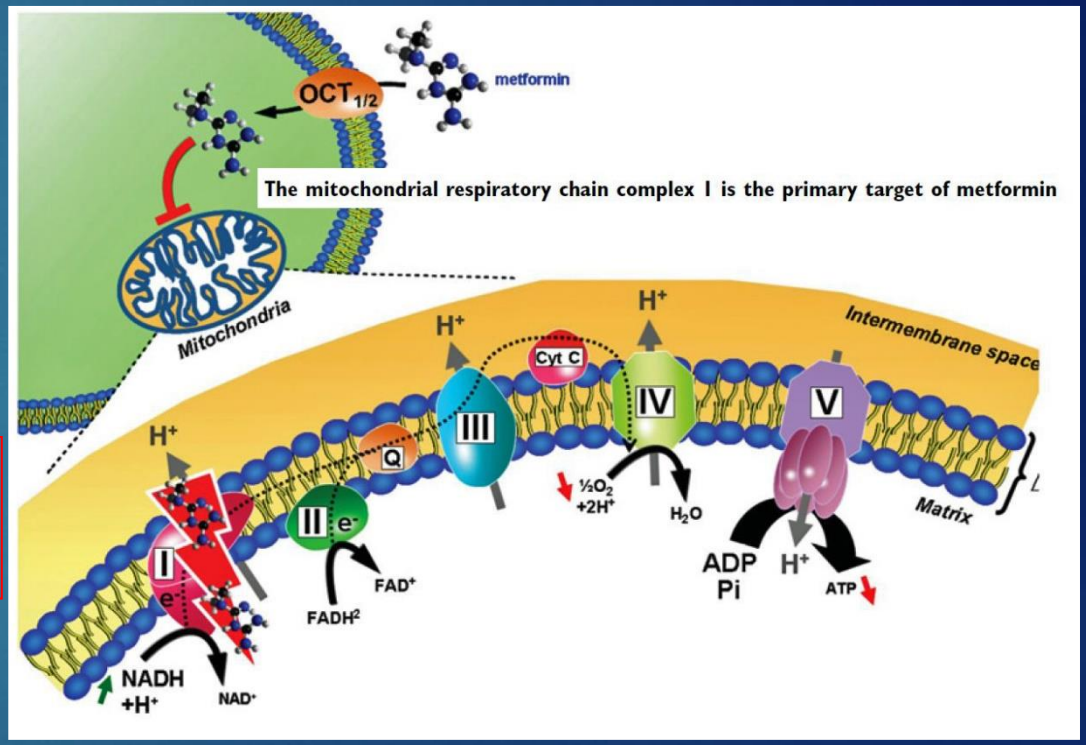
	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 ml/min per 1.73 m^2	Oral	Low

Traditionally recommended as first-line glucose-lowering therapy for type 2 diabetes, because of its high efficacy in lowering HbA_{1c}, minimal hypoglycemia risk when used as monotherapy, potential for some modest weight loss, good safety profile, low cost

MECHANISM OF ACTION

- Decrease hepatic glucose production through a mild inhibition of the mitochondrial respiratory-chain complex 1.[2]
- Decrease intestinal absorption of glucose
- anti-oxidative properties of metformin on endothelial cells[2]

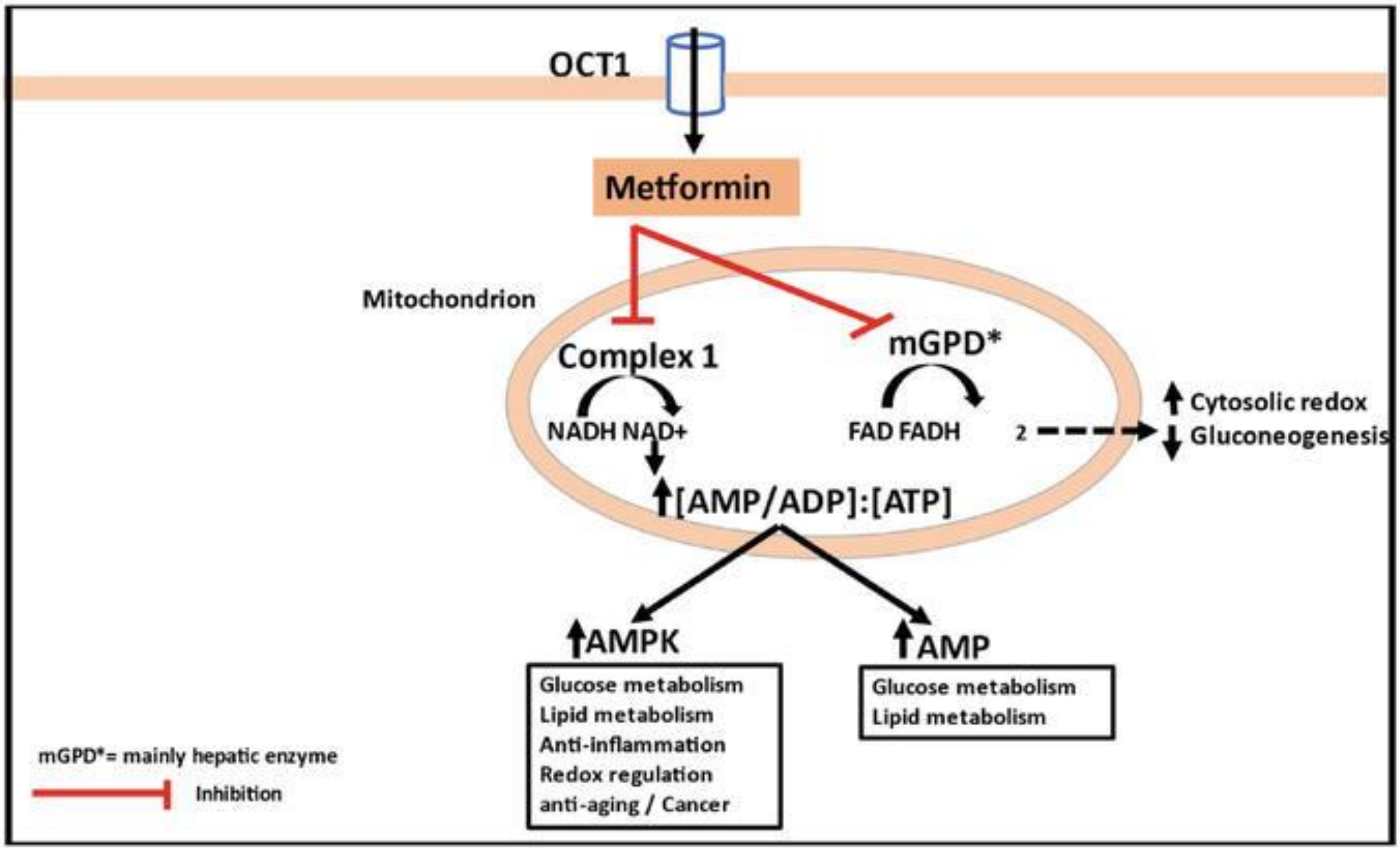




Metformin inhibits this complex

The consequence of *inhibition of the respiratory chain complex I by* metformin is a transient reduction in cellular energy status.

AMPK activation


OCT1
Metformin
Mitochondrion
Complex 1
mGPD*
NADH NAD+
FAD FADH
2
Cytosolic redox
Gluconeogenesis
[AMP/ADP]:[ATP]
AMPK
AMP
Glucose metabolism
Lipid metabolism
Anti-inflammation
Redox regulation
anti-aging / Cancer
Glucose metabolism
Lipid metabolism
mGPD*= mainly hepatic enzyme
Inhibition

Diabetes and CKD

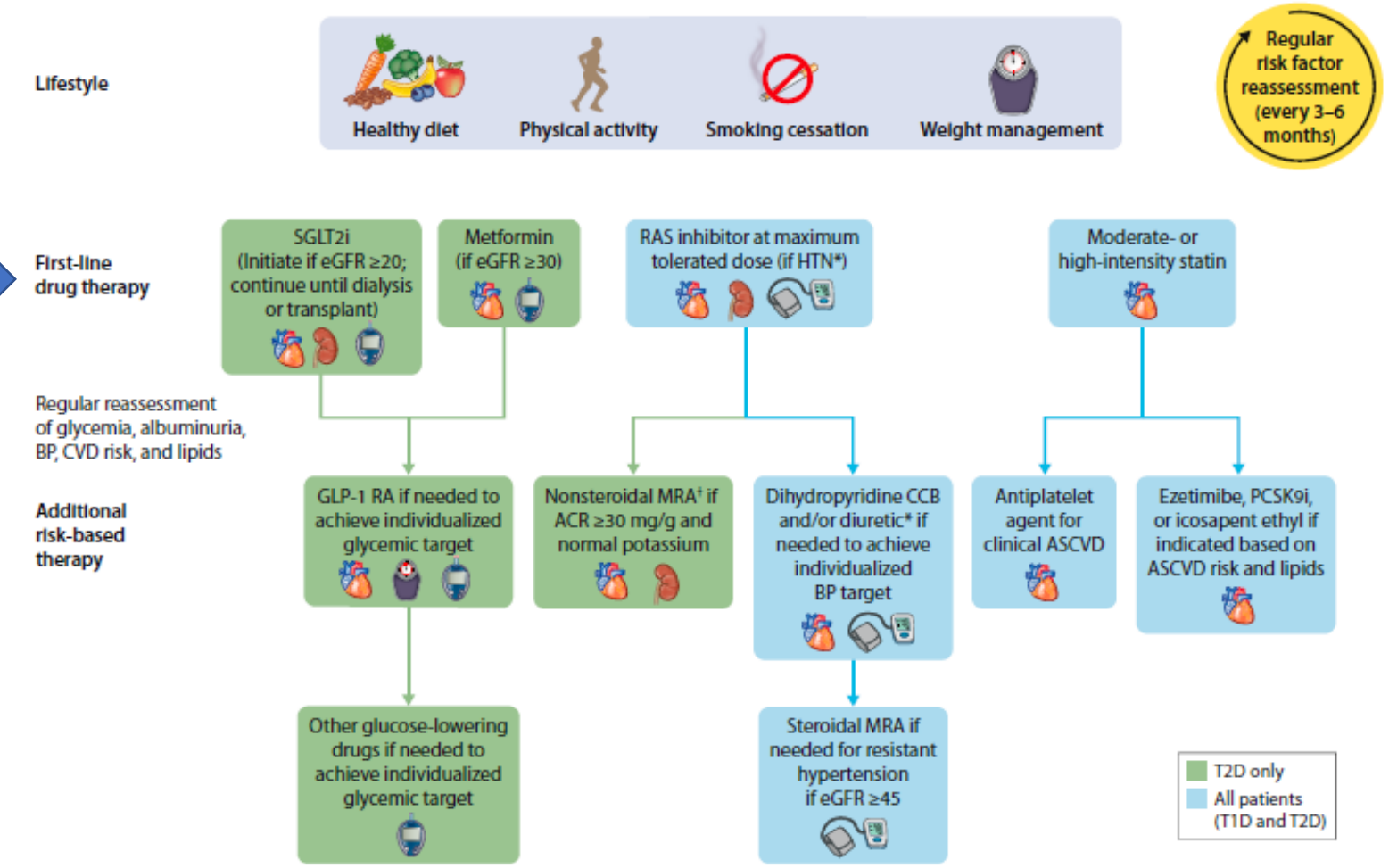


Figure 3—Holistic approach for improving outcomes in patients with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, GLP-1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.

Table 2—Considerations for selecting glucose-lowering agents in patients with T2D and CKD (2,17)

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

[a]Benefit supported by primary and secondary outcome data. [b]Benefit supported by secondary outcome data. [c]Benefit or risk is agent specific. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2.

Table 3—Key monitoring and risk mitigation strategies for preferred glucose-lowering agents

Medication	Consideration	Monitoring and/or risk mitigation strategies
Metformin	Metformin-associated lactic acidosis	• Monitor eGFR with increasing frequency as eGFR falls to <60 mL/min/1.73 m^2 • Adjust metformin dose as appropriate per eGFR (see Table 4) • Consider dose reduction in the presence of conditions that predispose patients to hypoperfusion and hypoxemia for eGFR 45–59 mL/min/1.73 m^2 • Discontinue for eGFR <30 mL/min/1.73 m^2 • Institute a sick day protocol
	B_{12} malabsorption	• Monitor patients for vitamin B_{12} deficiency when treated with metformin for >4 years
SGLT2i	Genital mycotic infections	• Counsel on genital hygiene
	Volume depletion	• Monitor for hypovolemia and consider proactive dose reduction of diuretics in patients at high risk • Hold SGLT2i during illness
	Diabetic ketoacidosis	• Educate about signs/symptoms to facilitate early recognition • Monitor blood or urine ketones in the case of very high risk • Institute a sick day protocol • Maintain at least low-dose insulin in insulin-requiring individuals
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate
GLP-1 receptor agonists	Nausea/vomiting/diarrhea	• Educate on tolerability and symptom recognition • Start at lowest recommended dose and titrate slowly
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
SGLT2 inhibitors*			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily†	Initiation not recommended with eGFR <25 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily‡		Initiation not recommended with eGFR <20 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m²		

Pharmacologic Therapy for Adults With Type 2 Diabetes

In adults with type 2 diabetes and

1- Established/high risk of ASCVD

2- Heart failure

3- and/or CKD

the treatment regimen should include **agents that reduce cardiorenal risk**. A

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

- Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. E

- Weight management is an impactful component of glucose-lowering management in type 2 diabetes.

- The glucose-lowering treatment regimen should consider approaches that support weight management goals A

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. A

Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. A

The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10%) or blood glucose levels (≥300mg/dL) are very high. E

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

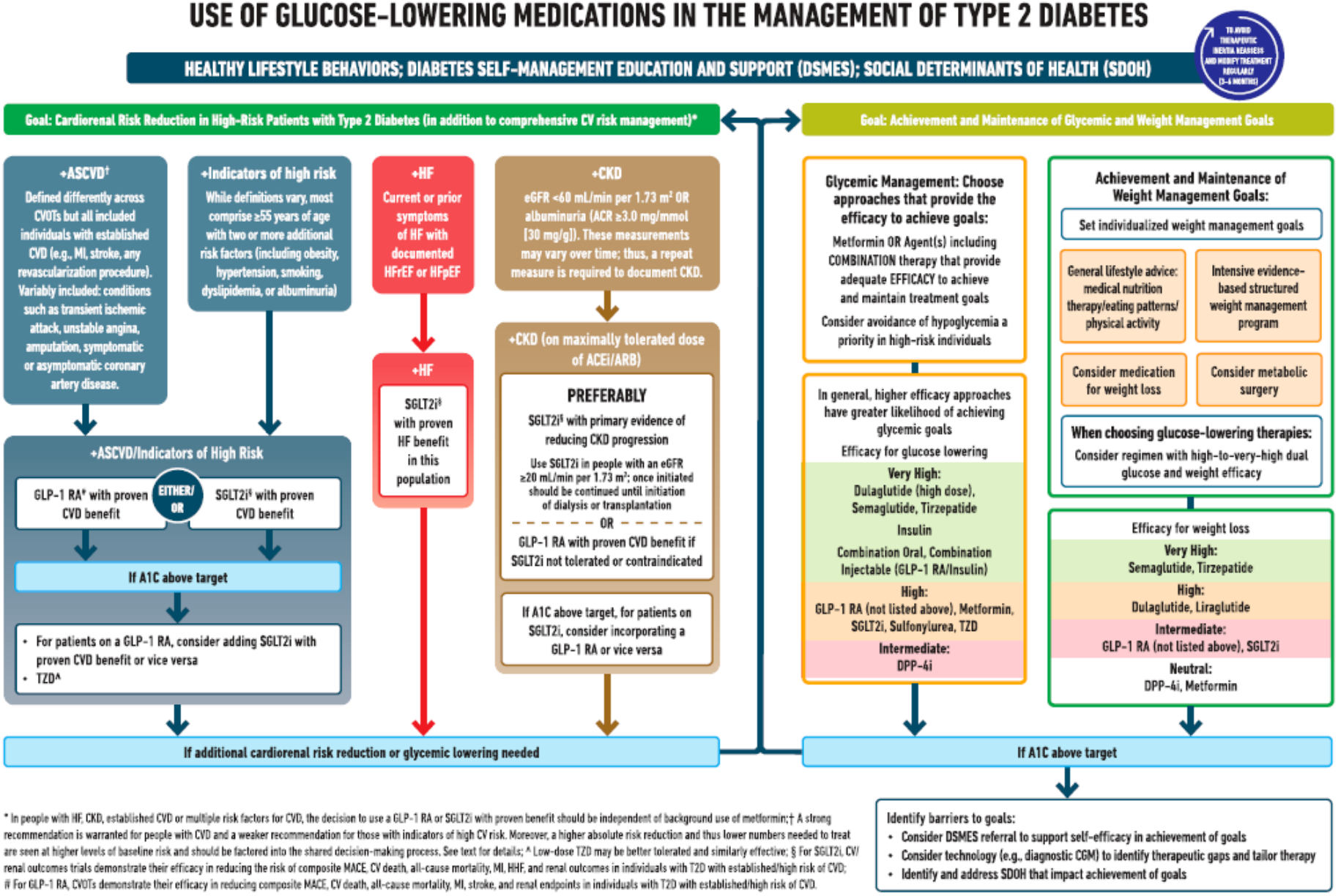
- A person-centered approach should guide the choice of pharmacologic agents.

- Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. **E**

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

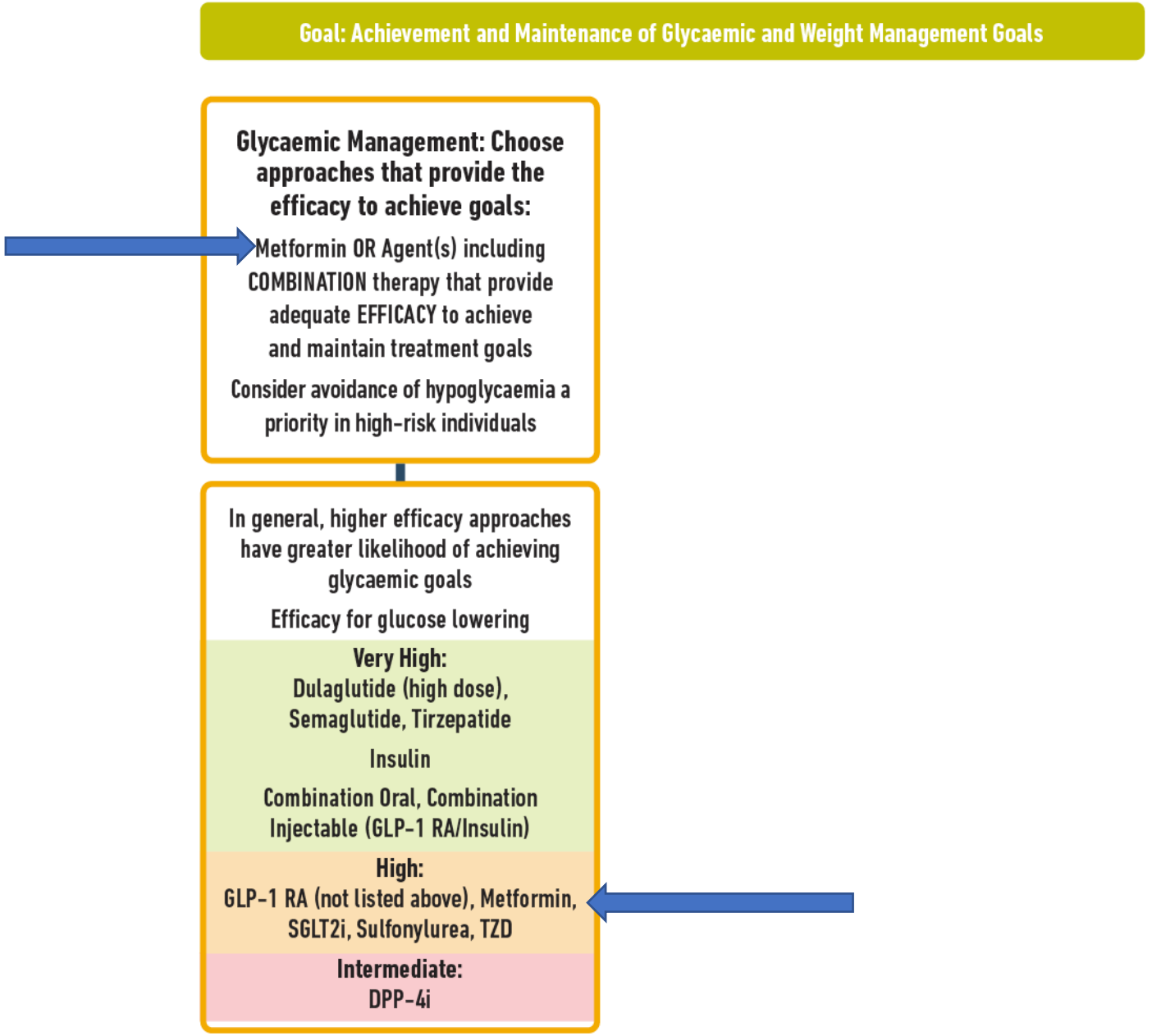
- Among individuals with type 2 diabetes who have
- established ASCVD
- indicators of high cardiovascular risk
- established kidney disease
- heart failure
- a SGLT2 inhibitor and/or GLP-1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. **A**

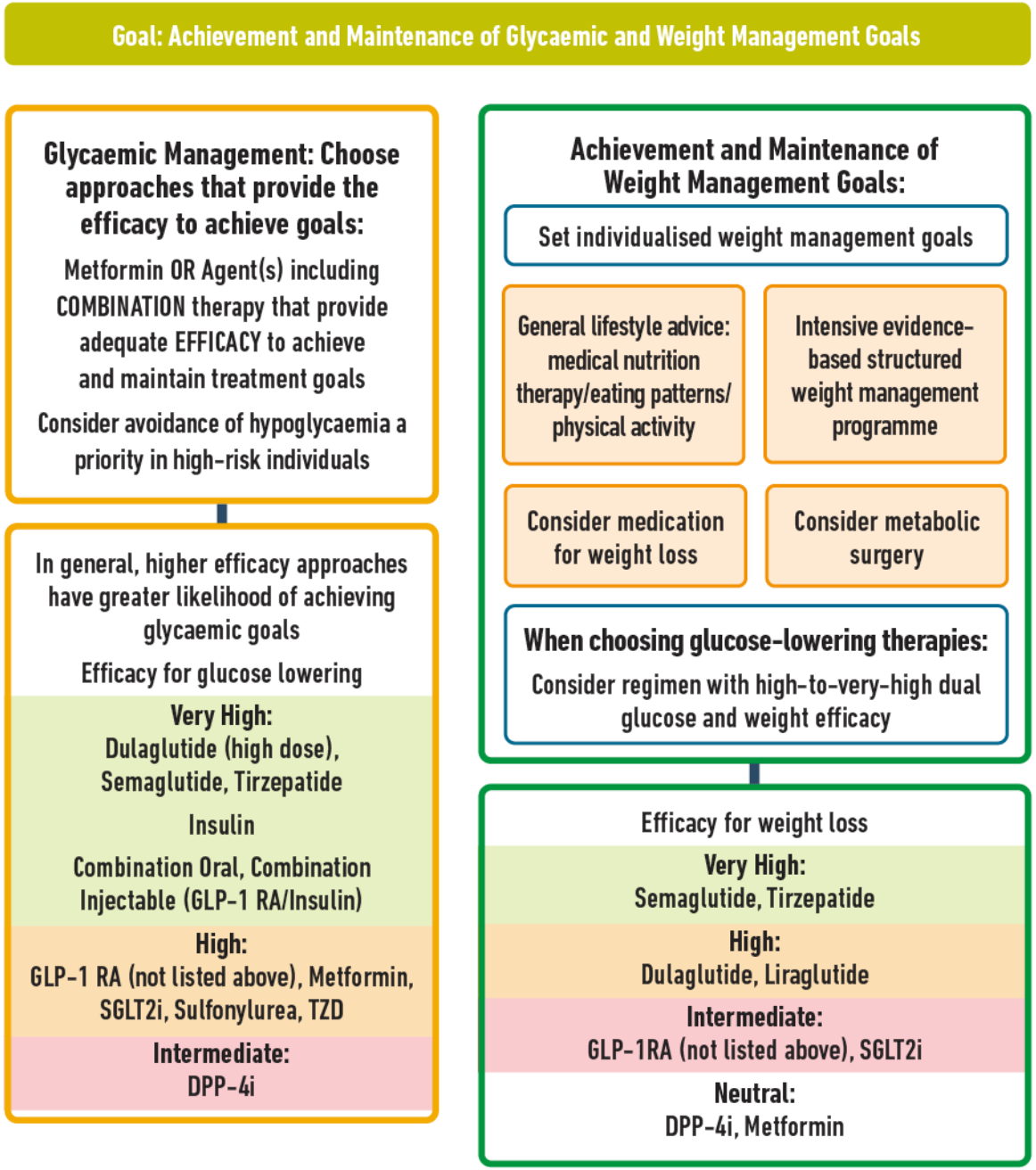
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Diabetes Care 2023;46(Suppl. 1):S140-S157


Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals
Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of hypoglycaemia a priority in high-risk individuals
In general, higher efficacy approaches have greater likelihood of achieving glycaemic goals
Efficacy for glucose lowering
Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
Intermediate:
DPP-4i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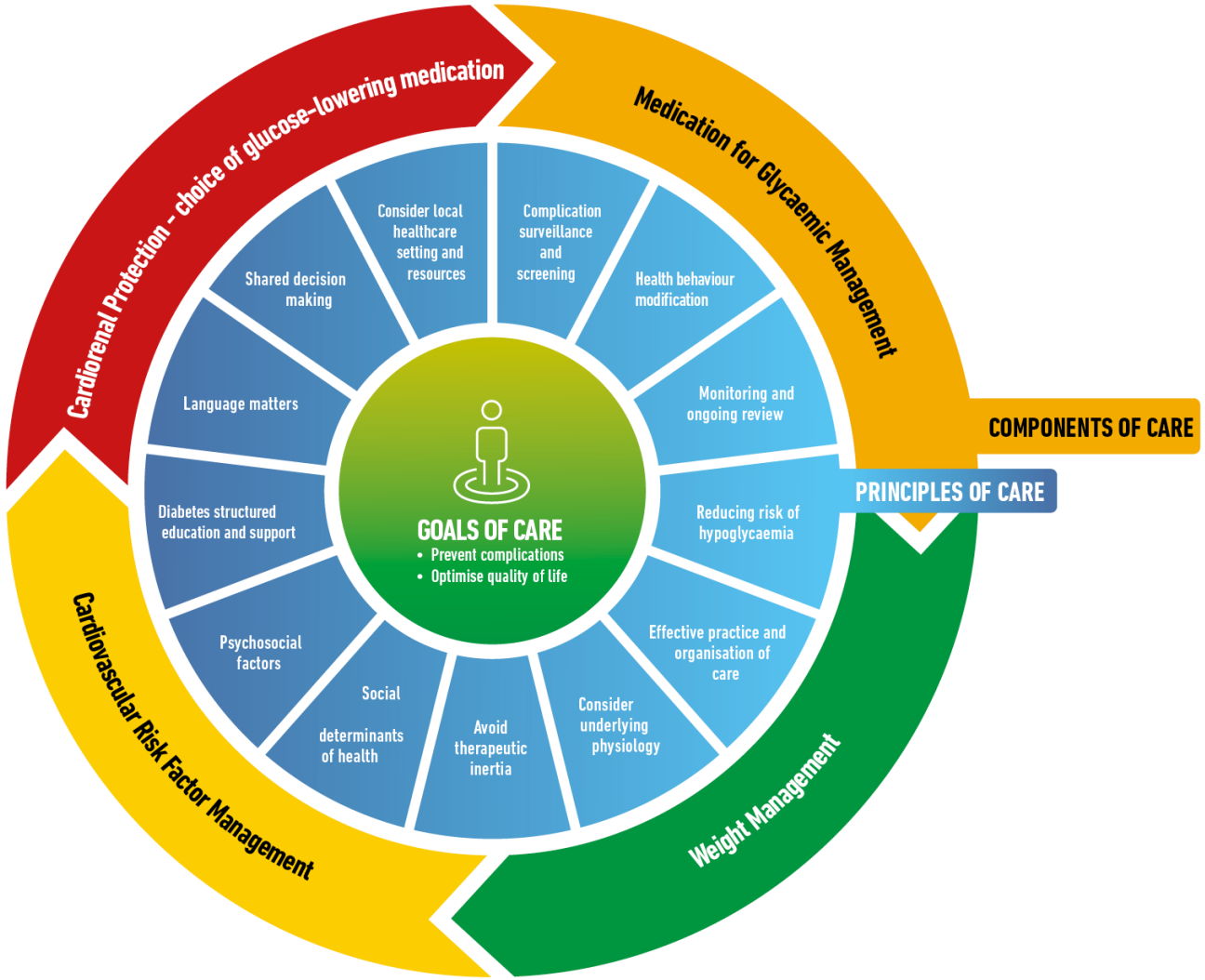
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
Intermediate:
DPP-4i
Achievement and Maintenance of Weight Management Goals:
Set individualised weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity
Intensive evidence-based structured weight management programme
Consider medication for weight loss
Consider metabolic surgery
When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy
Efficacy for weight loss
Very High:
Semaglutide, Tirzepatide
High:
Dulaglutide, Liraglutide
Intermediate:
GLP-1RA (not listed above), SGLT2i
Neutral:
DPP-4i, Metformin

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT



1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT

Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycaemia a priority in high-risk individuals

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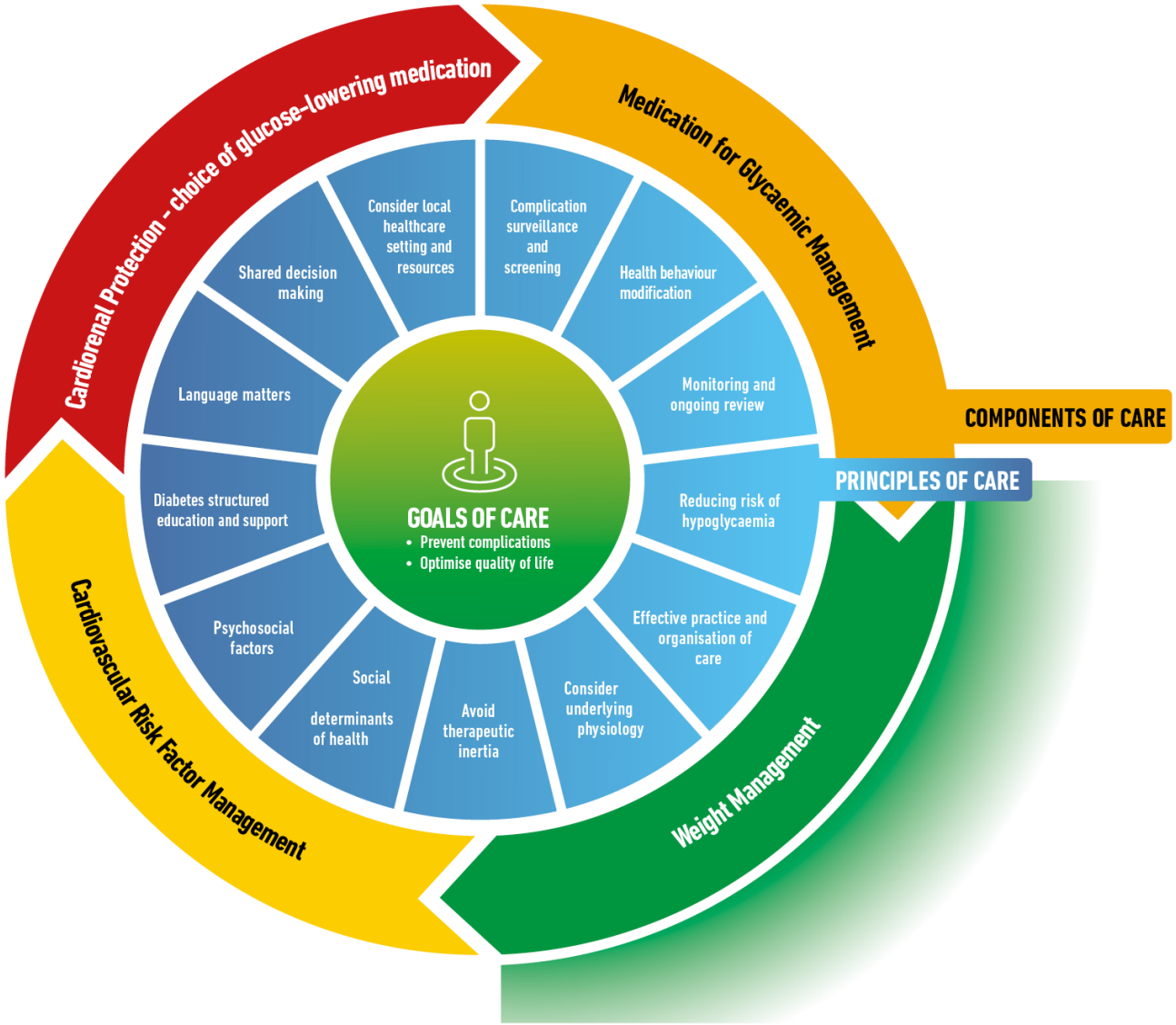

Achievement and Maintenance of Weight Management Goals:

Set individualised weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management programme

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

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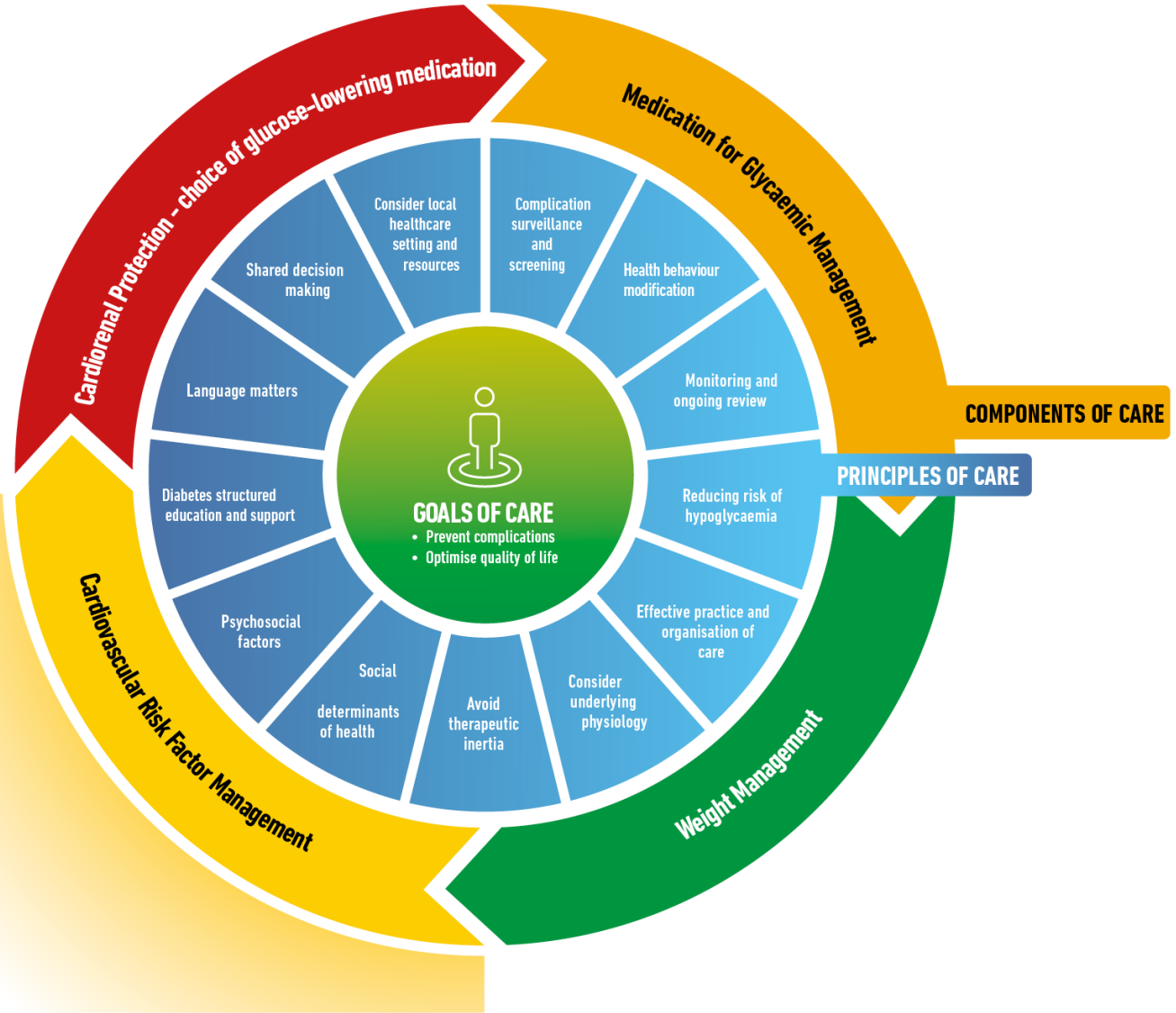

Ensure strategies are in place to detect and optimise management of CV risk factors[1] including

- CV risk factor screening and surveillance
- BP lowering
- Lipid lowering
- Antithrombotic agents
- Smoking cessation

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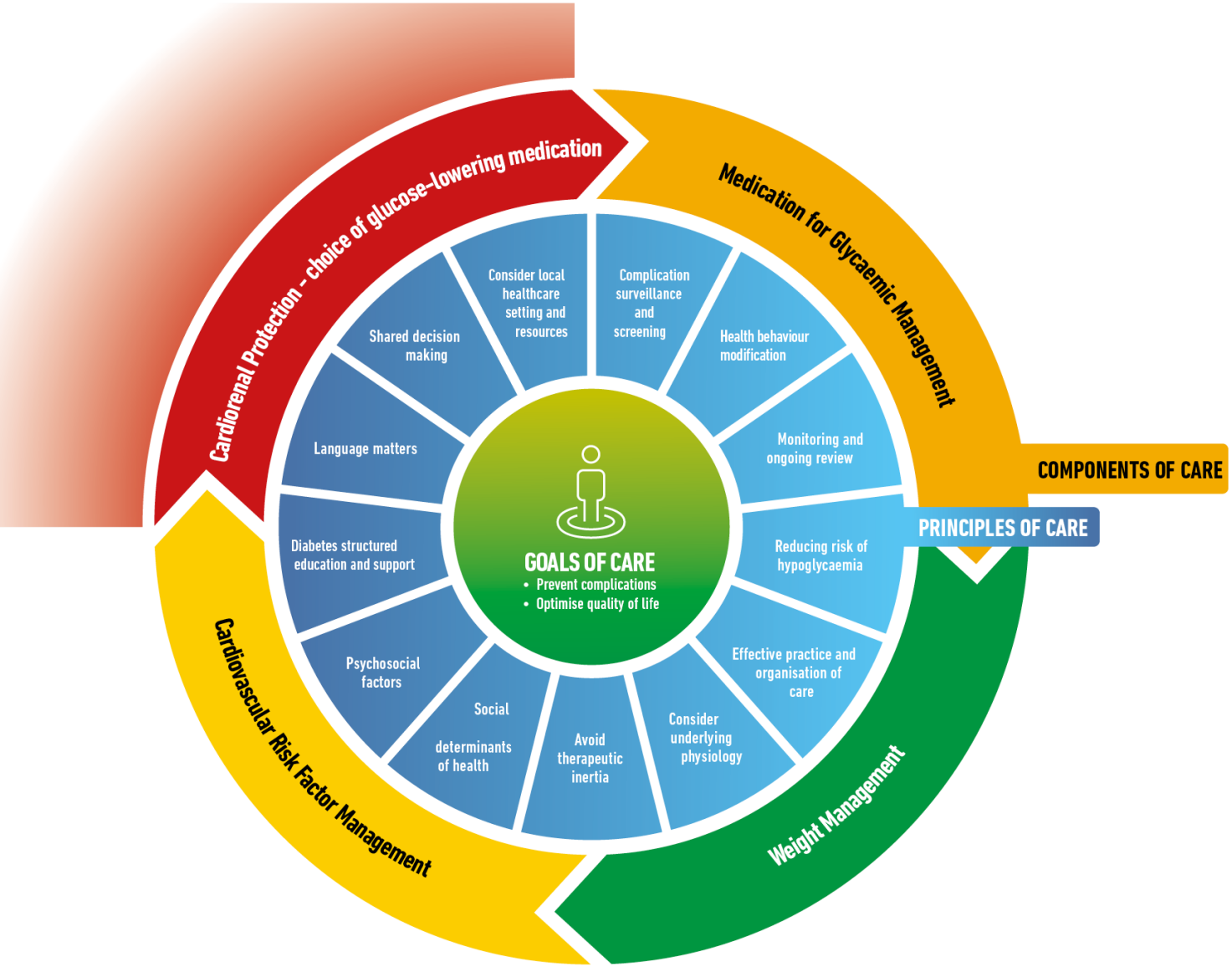

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

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

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+ASCVD/Indicators of High Risk

GLP-1 RA with proven CVD benefit — EITHER/OR — SGLT2i with proven CVD benefit

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+HF

SGLT2i with proven HF benefit in this population

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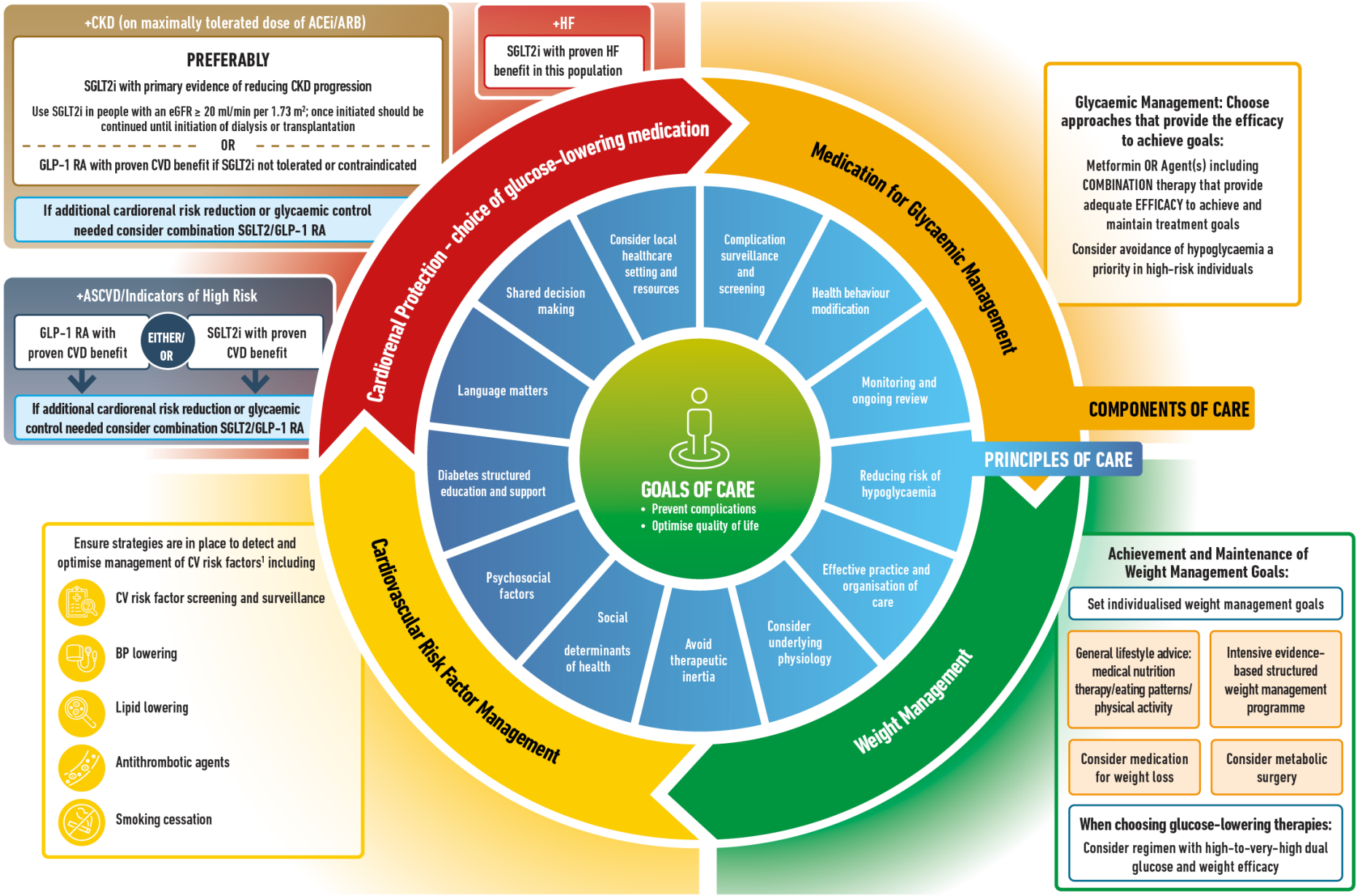

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The last but not the least

As we stand today, we have evidence for cardiovascular protection with metformin, including from randomized trials, many observational studies, and substantial experimental data.

However, the nature of the clinical trial evidence has been overtaken by the new constellation of outcomes trials that were designed to address questions of clinical safety that were formulated long after the randomized evaluations of metformin were conducted.

Interpreting the current evidence base for metformin is undoubtedly a challenging task, but no less important for that.