

Type 2 Diabetes Management and focus on Multifactorial Intervention

Introduction

- The burden of Type 2 diabetes (T2D) is increasing exponentially in the world with an alarming rise in developing countries.

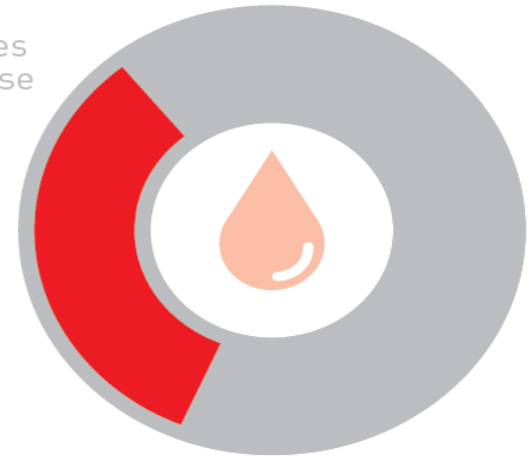
DIABETES IS
ON THE RISE



422 MILLION
adults have diabetes

3.7 MILLION
deaths due to diabetes
and high blood glucose

1.5 MILLION
deaths caused
by diabetes



THAT'S **1** PERSON IN **11**



Introduction

- The burden of Type 2 diabetes (T2D) is increasing exponentially in the world with an alarming rise in developing countries.

Types of diabetes

Type 1 diabetes (or insulin dependent)

Caused by the destruction of insulin-producing cells, resulting in the body producing little, or no insulin.¹

78,000

Number of children developing type 1 diabetes, globally, every year²



Type 2 diabetes

Caused by insulin resistance and relative deficiency, where insulin produced by the body is not used effectively.³



Almost half of all people with type 2 diabetes are not aware that they have it⁴

Type 2 diabetes accounts for 85%-95% of all diabetes in high-income countries⁵

80%

of type 2 diabetes cases are believed to be preventable by changing diet and levels of physical activity⁶



Diabetes Burden

Number of people with diabetes worldwide:

1 in 12



People with diabetes who do not know they have it:

1 in 2



**DIABETES:
A GLOBAL
VIEW**

FACTS & STATS

Lives lost globally from diabetes:

one every 7 seconds

OR

almost 5 million annually

Where 77% of people with diabetes live:

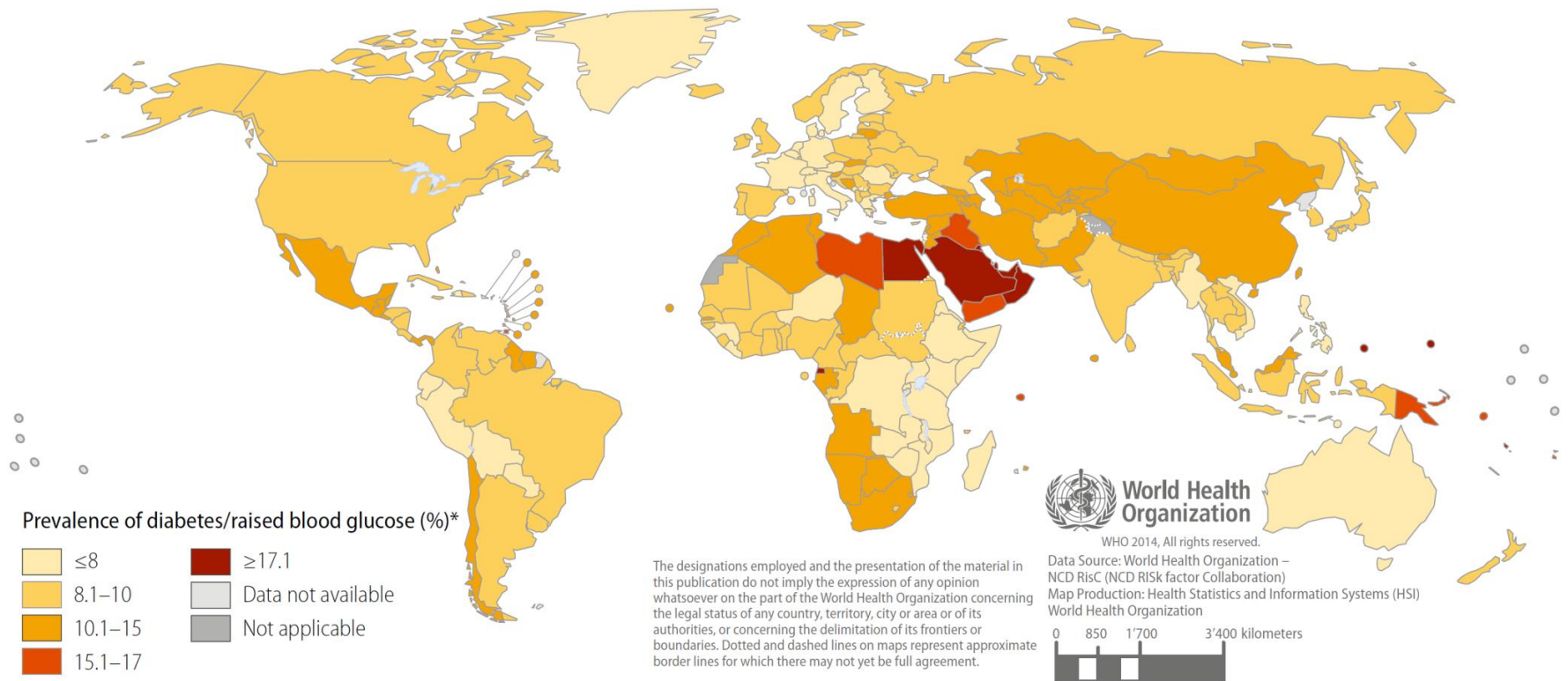
77%

Low & middle-income countries

Diabetes in India

- India is one of the epicentres of the global diabetes mellitus pandemic.
- India has about 90 million diabetic patients, and the disease leads to the enormous burden on the health care systems of the country
- In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively.

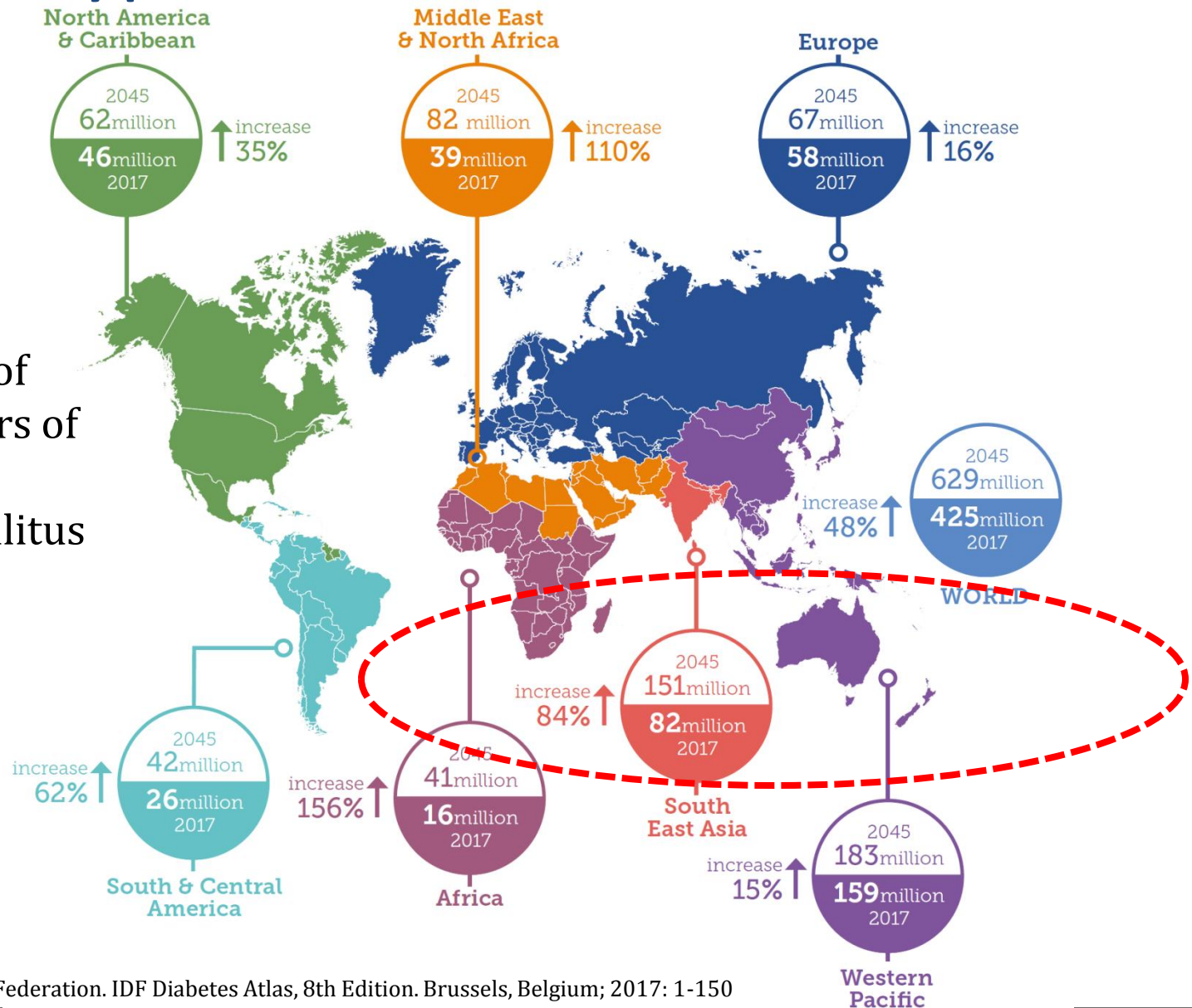
Diabetes in India



* Defined as fasting blood glucose ≥ 7 mmol/l or on medication for raised blood glucose or with a history of diagnosis of diabetes.

Type II Diabetes Mellitus

- India is one of the epicenters of the global diabetes mellitus pandemic.



Mortality due to diabetes

Adults who died from diabetes, HIV/AIDS, tuberculosis, and malaria



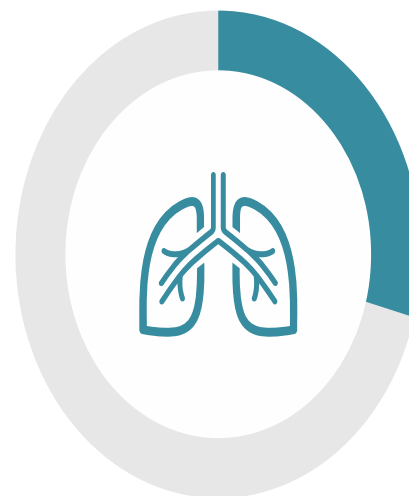
5.0 million

from diabetes
2015
IDF



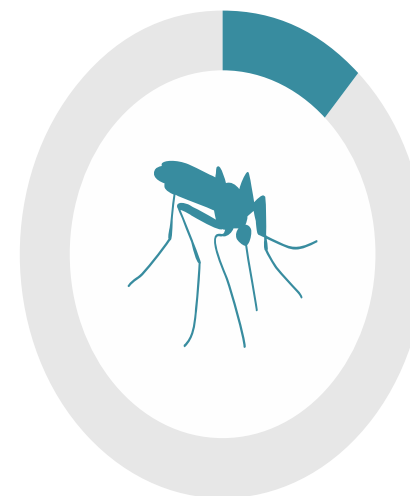
1.5 million

from HIV/AIDS
2013
WHO Global Health
Observatory Data
Repository 2013



1.5 million

from tuberculosis
2013
WHO Global Health
Observatory Data
Repository 2013



0.6 million

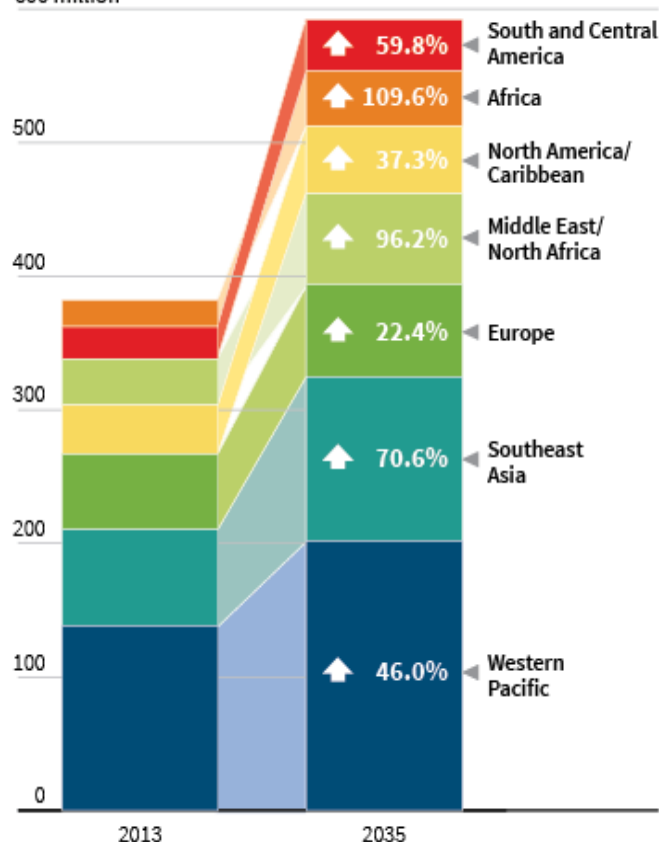
from malaria
2013
WHO Global Health
Observatory Data
Repository 2013

Trends in diabetes burden

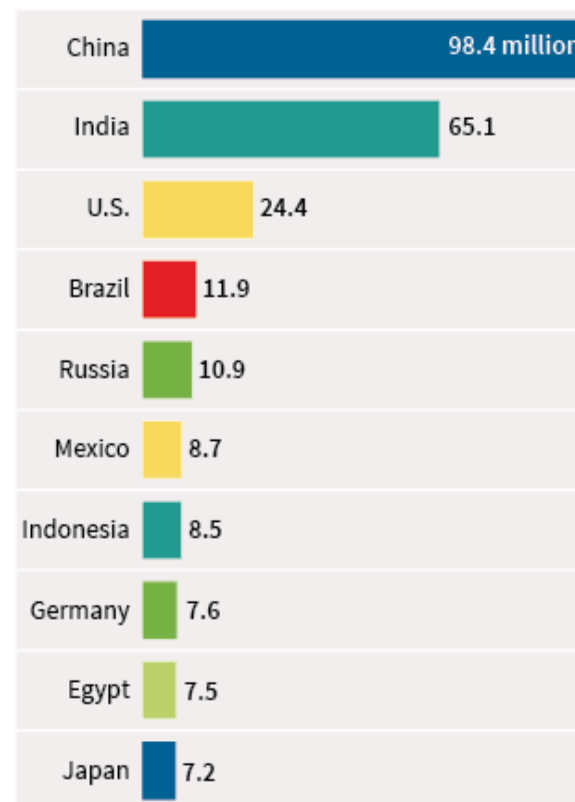
World diabetes cases expected to jump 55 percent by 2035

Current and projected cases of diabetes by region

600 million



Top 10 countries by number of people with diabetes in 2013, ages 20 to 79

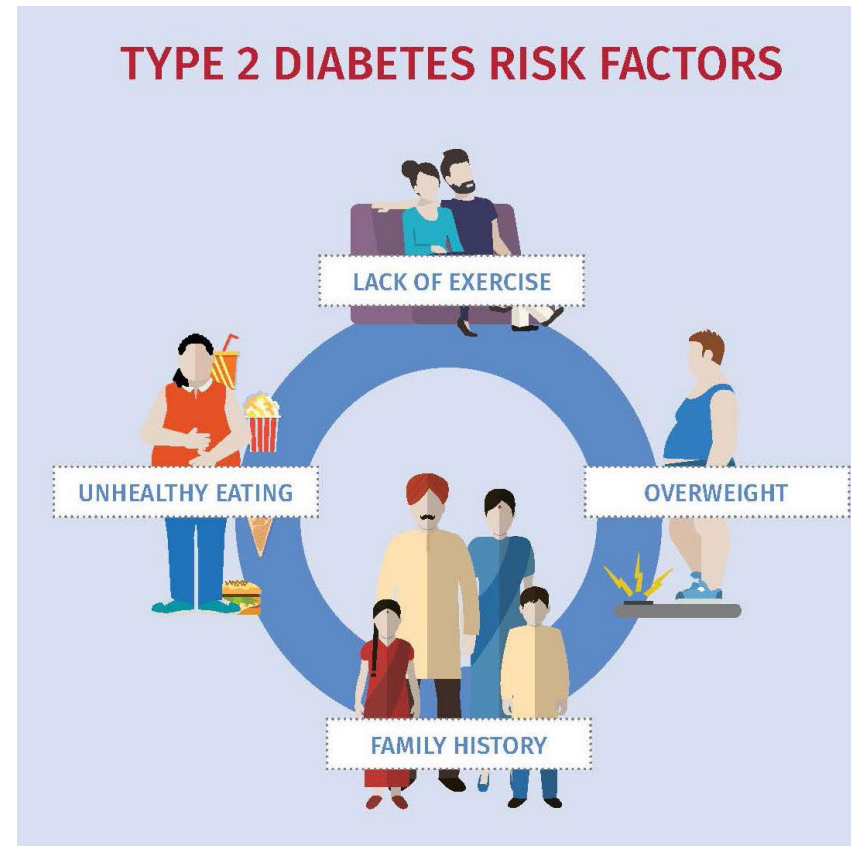


Source: International Diabetes Federation

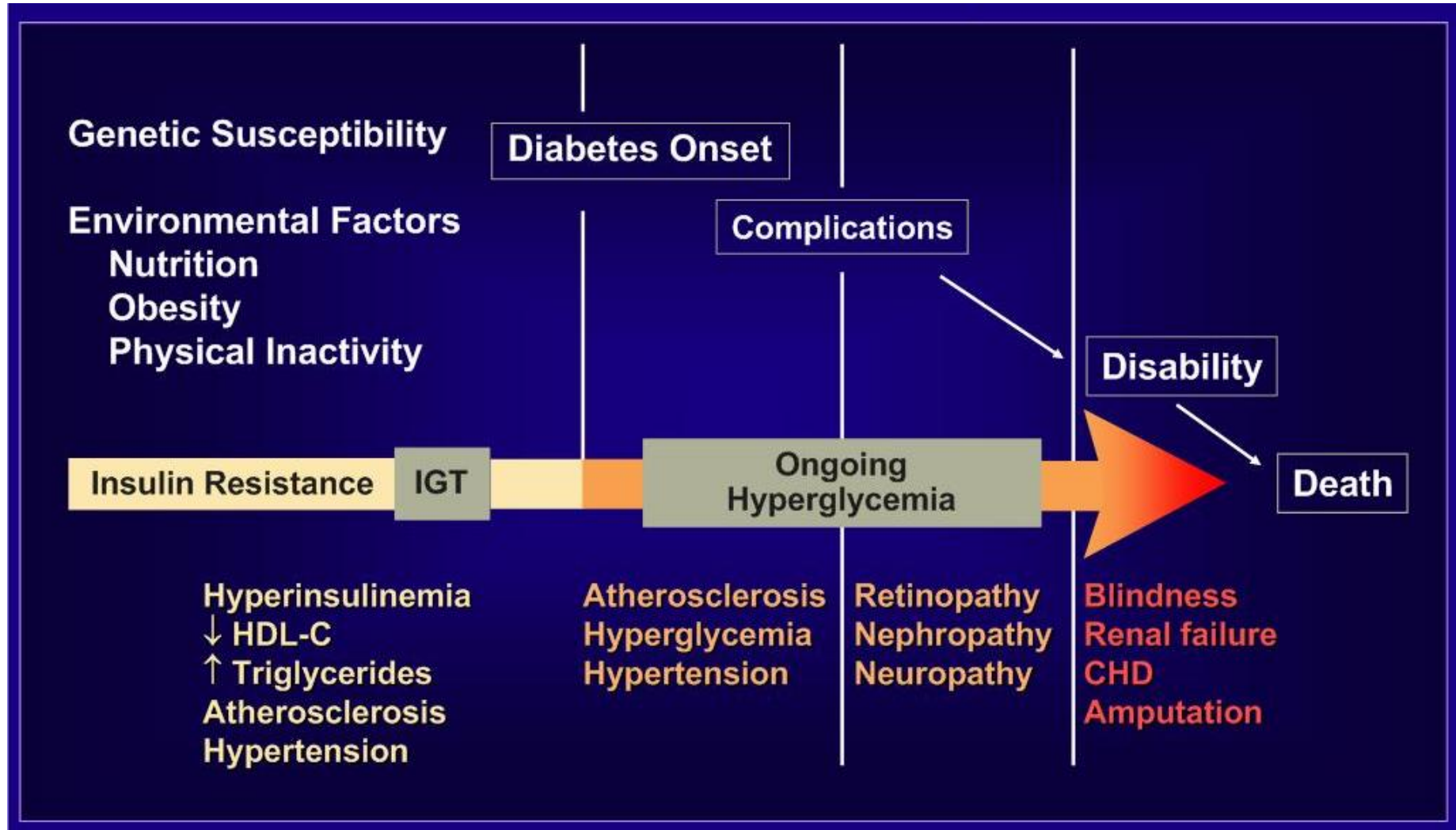
S. Culp, 12/11/2013

Diabetes: Risk Factors

- Family history of diabetes
- Overweight
- Unhealthy diet
- Physical inactivity
- Increasing age
- High blood pressure
- Ethnicity
- Impaired glucose tolerance
- History of gestational diabetes
- Poor nutrition during pregnancy



Complications of Diabetes



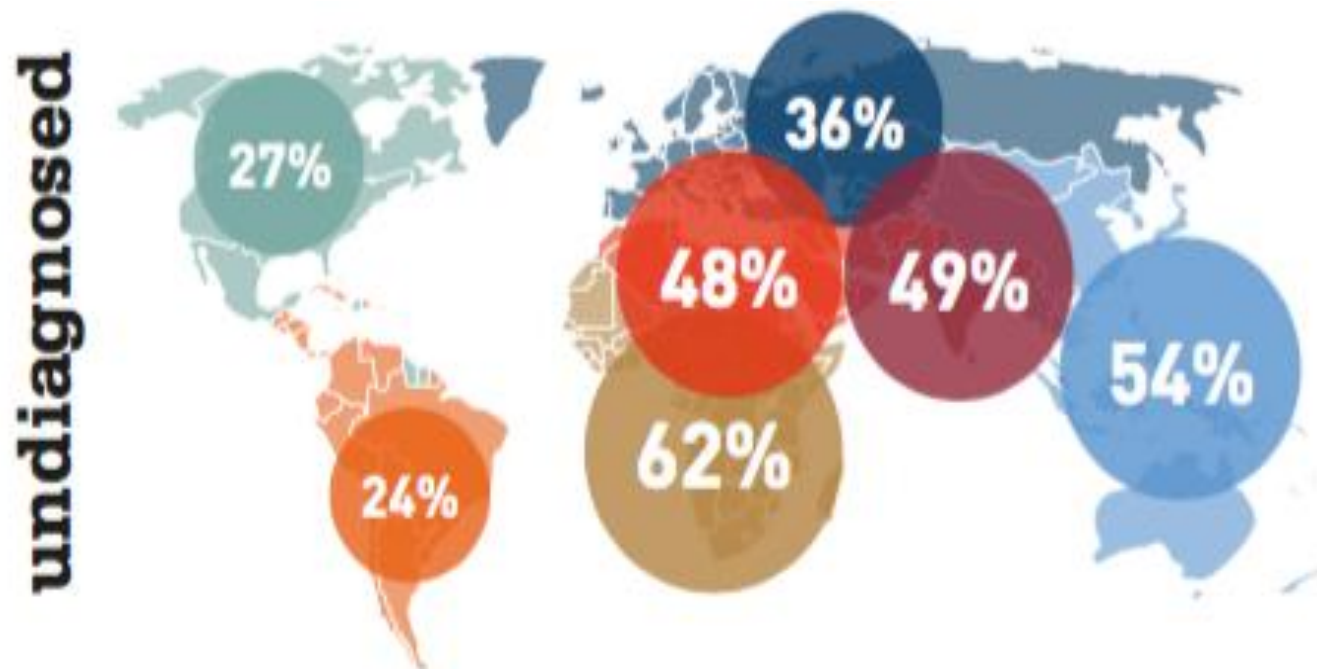
1. <http://www.idf.org/membership/sea/india>

2. http://www.searo.who.int/india/mediacentre/events/world_health_day/brief_note_on_diabetes_in_india-6april.pdf

Managing Diabetes

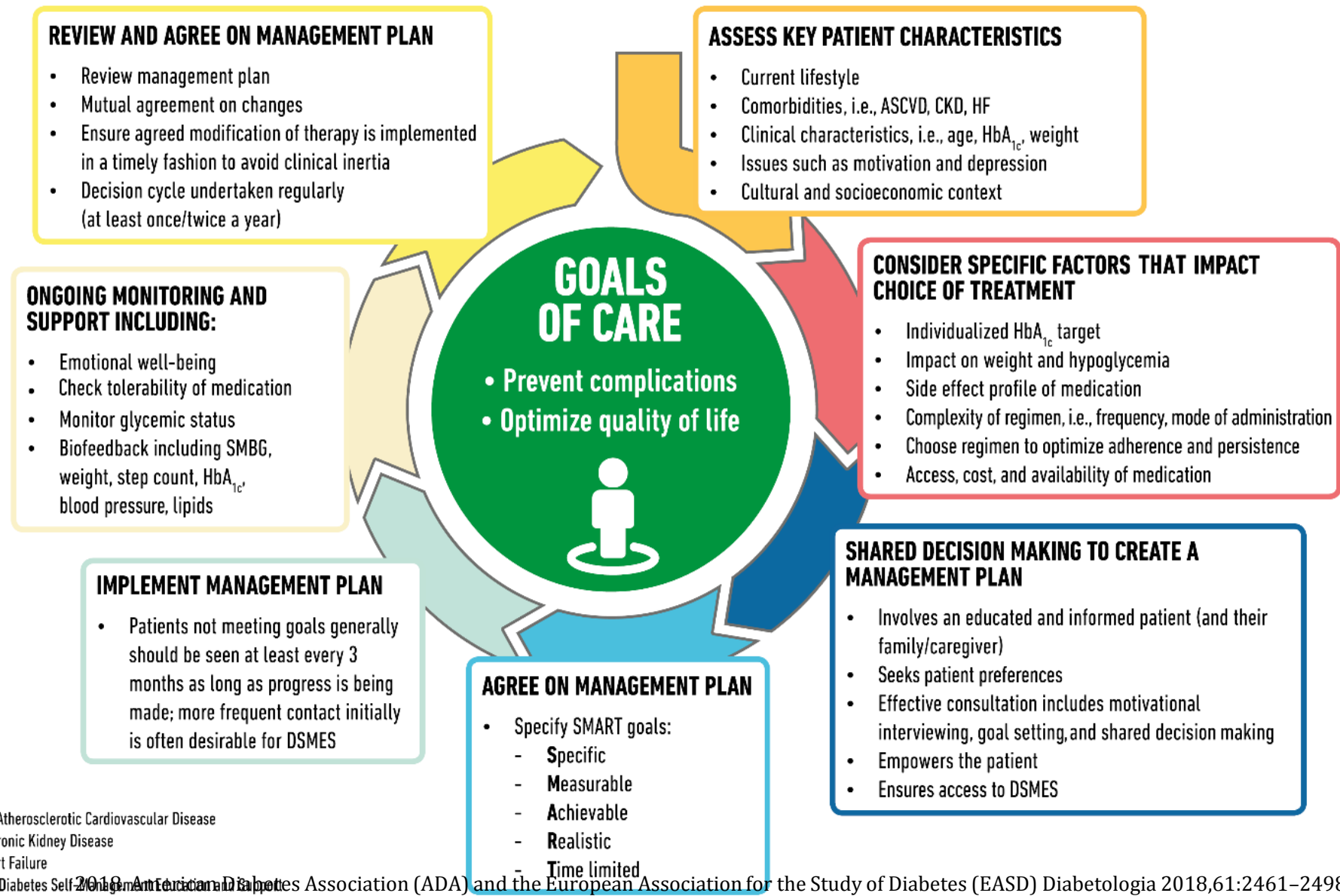
The human and economic costs of diabetes could be significantly reduced by investing in prevention, particularly early detection, in order to avoid the onset of diabetic complications

At least 50% of all people with diabetes are unaware of their condition



Diabetes Management

Decision cycle for patient-centered glycemic management in type 2 diabetes



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

**FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW**

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

**EITHER/
OR**

GLP-1 RA with proven CVD benefit¹

SGLT2i with proven CVD benefit¹, if eGFR adequate²

If HbA_{1c} above target

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

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin⁴
- TZD⁵
- SU⁶

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate³ add GLP-1 RA with proven CVD benefit¹

If HbA_{1c} above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
- Consider adding the other class with proven CVD benefit¹
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin⁴
- SU⁶

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i

GLP-1 RA

SGLT2i⁷

TZD

If HbA_{1c} above target

If HbA_{1c} above target

If HbA_{1c} above target

If HbA_{1c} above target

SGLT2i⁷
OR
TZD

SGLT2i⁷
OR
TZD

GLP-1 RA
OR
DPP-4i
OR
TZD

SGLT2i⁷
OR
DPP-4i
OR
GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU⁶ **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia⁷

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

**EITHER/
OR**

GLP-1 RA with good efficacy for weight loss⁸

SGLT2i⁷

If HbA_{1c} above target

SGLT2i⁷

GLP-1 RA with good efficacy for weight loss⁸

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

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

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
• SU⁶ • TZD⁵ • Basal insulin

COST IS A MAJOR ISSUE⁹⁻¹⁰

SU⁶

TZD¹⁰

If HbA_{1c} above target

TZD¹⁰

SU⁶

If HbA_{1c} above target

- Insulin therapy basal insulin with lowest acquisition cost
- OR**
- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost¹⁰

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.

2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use

3. Both empagliflozin and canagliflozin have demonstrated reduction in HF and CKD progression in CVOTs

4. Degludec or U100 glargine have demonstrated CVD safety

5. Low dose may be better tolerated though less well studied for CVD effects

6. Choose later generation SU with lower risk of hypoglycemia

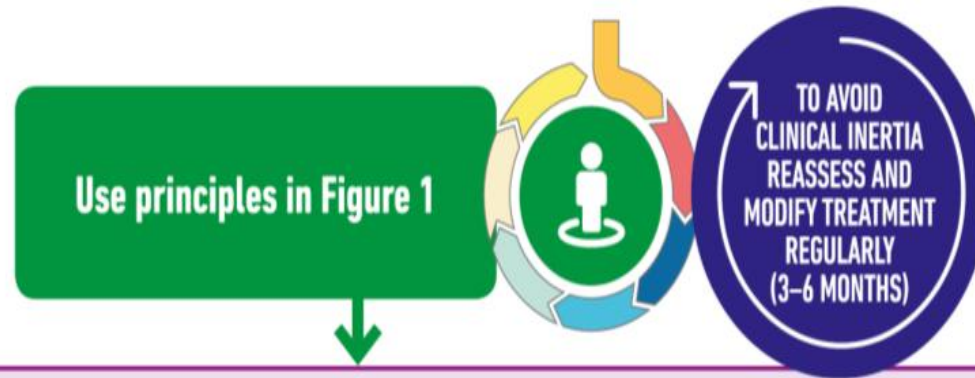
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower

10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit¹ (see below)

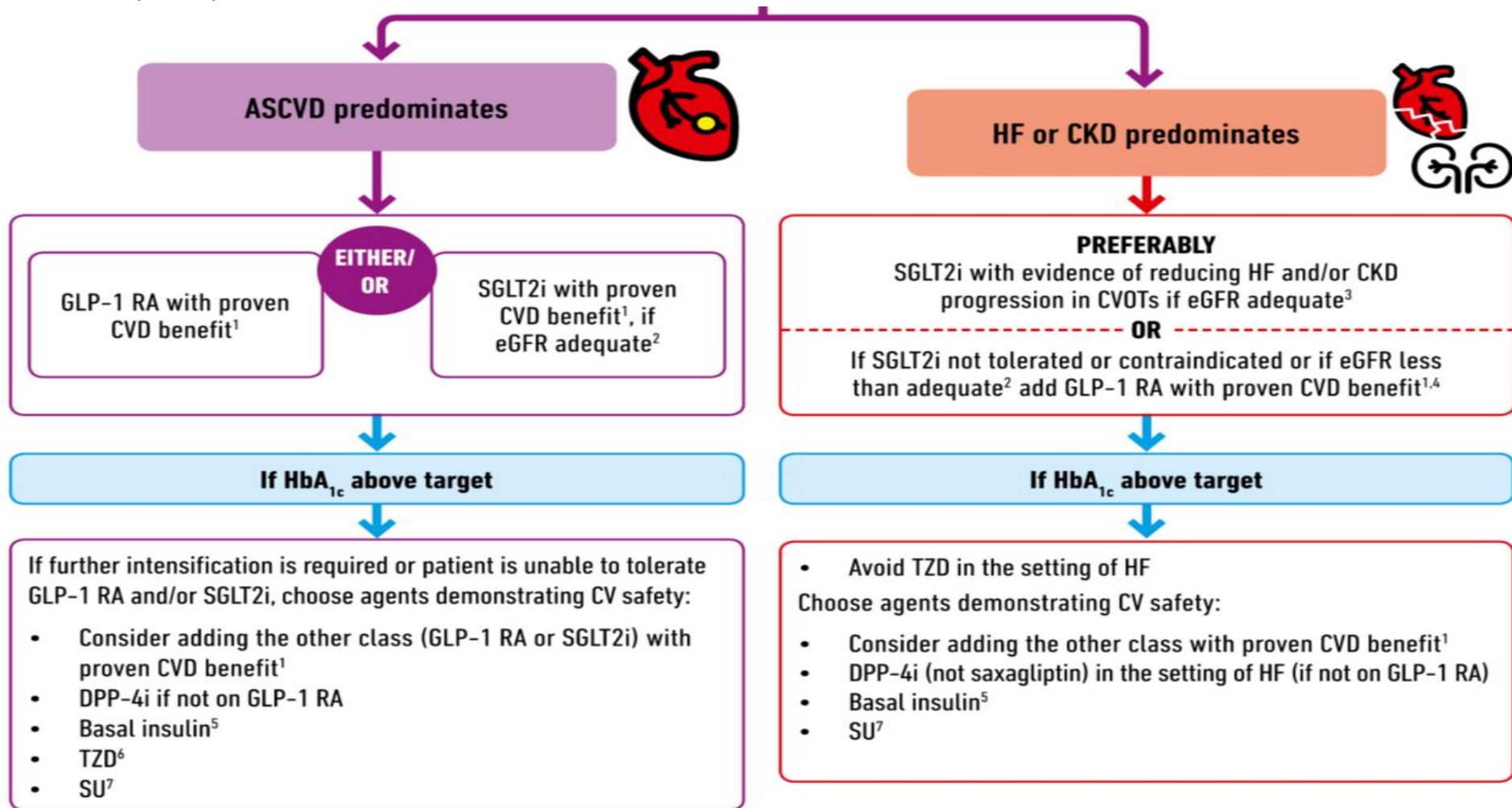
If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit¹ (see below)

OR reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

Choosing glucose-lowering medication in those with established ASCVD, HF, and CKD



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have been shown to reduce HF and CKD progression in CVOTs

4. Caution with GLP-1 RA in ESRD
5. Degludec or U100 glargine have demonstrated CVD safety
6. Low dose may be better tolerated though less well studied for CVD effects
7. Choose later generation SU to lower risk of hypoglycemia

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



In those **WITHOUT** established ASCVD OR CKD

Use principles in Figure 1



TO AVOID
CLINICAL INERTIA
REASSESS AND
MODIFY TREATMENT
REGULARLY
(3–6 MONTHS)

Implement strategies for maximizing weight loss

First-line therapy is metformin

If HbA_{1c} is ≥ 17 mmol/mol (1.5%) above individualized HbA_{1c} target consider early combination therapy

If HbA_{1c} above target

**EITHER/
OR**

GLP-1 RA with good
efficacy for weight loss¹

SGLT2i if eGFR adequate²

If HbA_{1c} above target

SGLT2i if eGFR adequate²

GLP-1 RA with good
efficacy for weight loss

General lifestyle advice

- Medical nutritional therapy
- Eating patterns
- Physical activity

**Non-surgical energy
restriction for weight loss**

Weight loss of 15 kg can lead to remission of T2DM in patient <6 years' duration, consider evidence-based weight loss programs

**Consider
medication for
weight loss**

**Consider
metabolic
surgery**

Choosing glucose-lowering medication if compelling need to minimize weight gain or promote weight loss

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

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

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

• SU³ • TZD⁴ • Basal insulin

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA



In those **WITHOUT** established
ASCVD OR CKD

Use principles in Figure 1



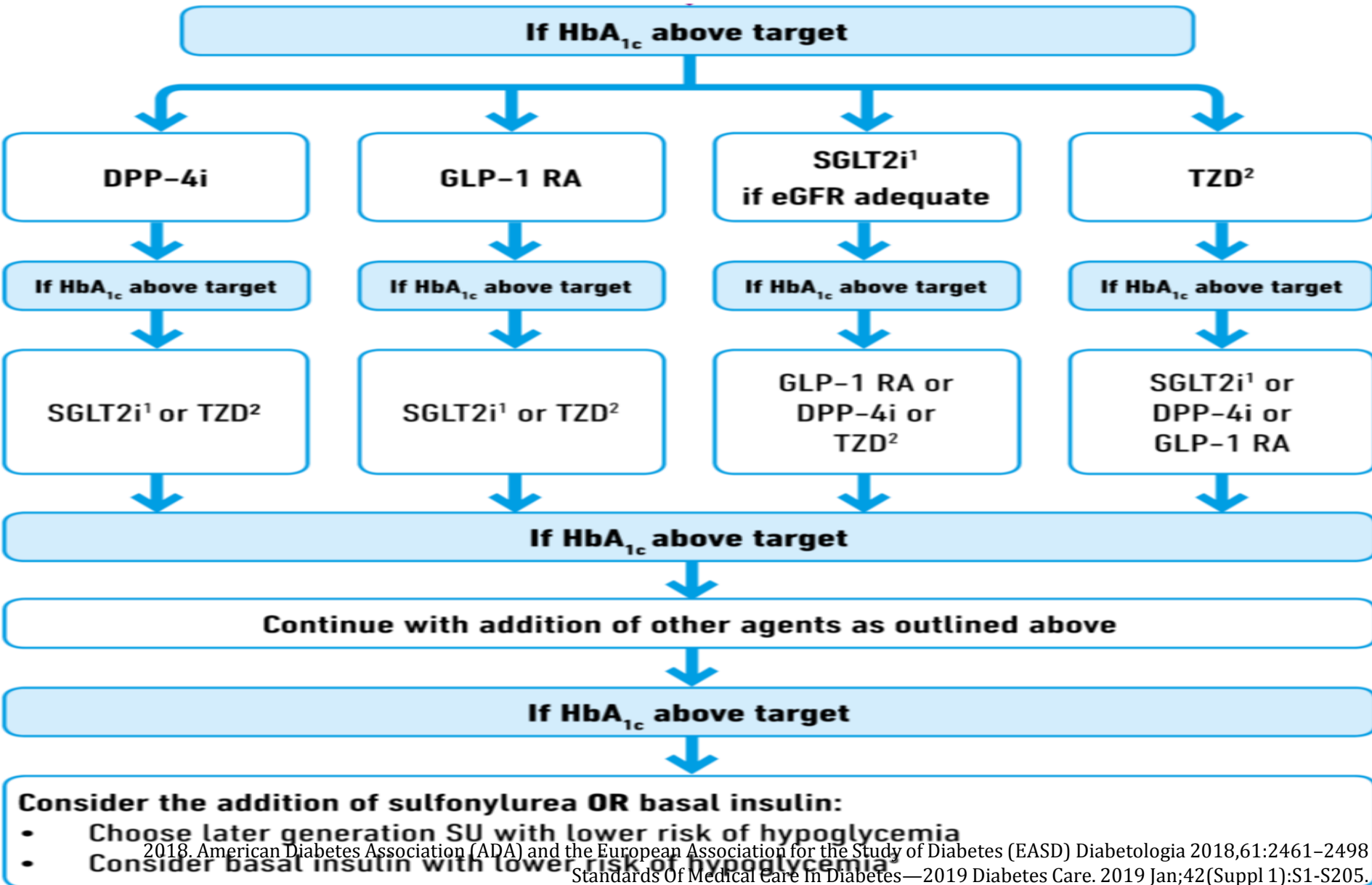
TO AVOID
CLINICAL INERTIA
REASSESS AND
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REGULARLY
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Identify patient groups at highest risk of hypoglycemia and set and/or adjust HbA_{1c} target to minimize risk of hypoglycemia

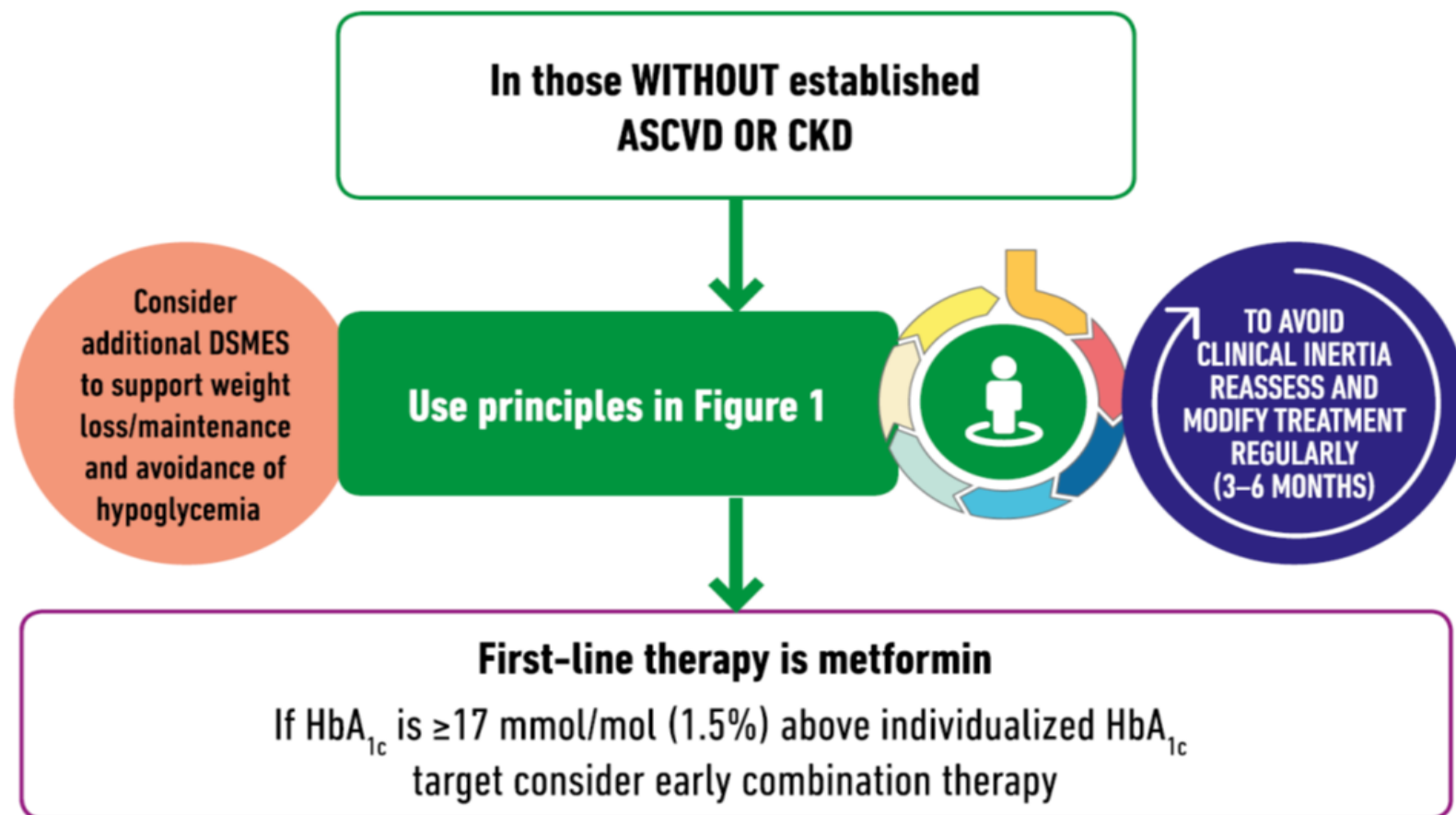
First-line therapy is metformin

If HbA_{1c} is ≥ 17 mmol/mol (1.5%) above individualized HbA_{1c} target consider early combination therapy

Choosing glucose-lowering medication if compelling need to minimize hypoglycemia



CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE

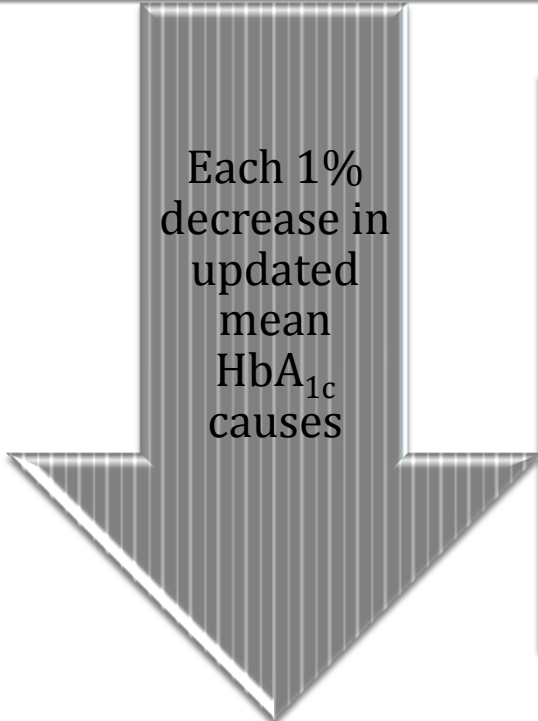


Multifactorial Intervention

- Type 2 diabetes mellitus is associated with a high rate of complications related to cardiovascular disease and diabetic nephropathy, retinopathy, and neuropathy
- The rate of death among patients with type 2 diabetes is approximately twice as high as that among persons without the disorder
- However, trials of interventions for single risk factors have shown efficacy in reducing the development and progression of complications

Results from UKPDS Study

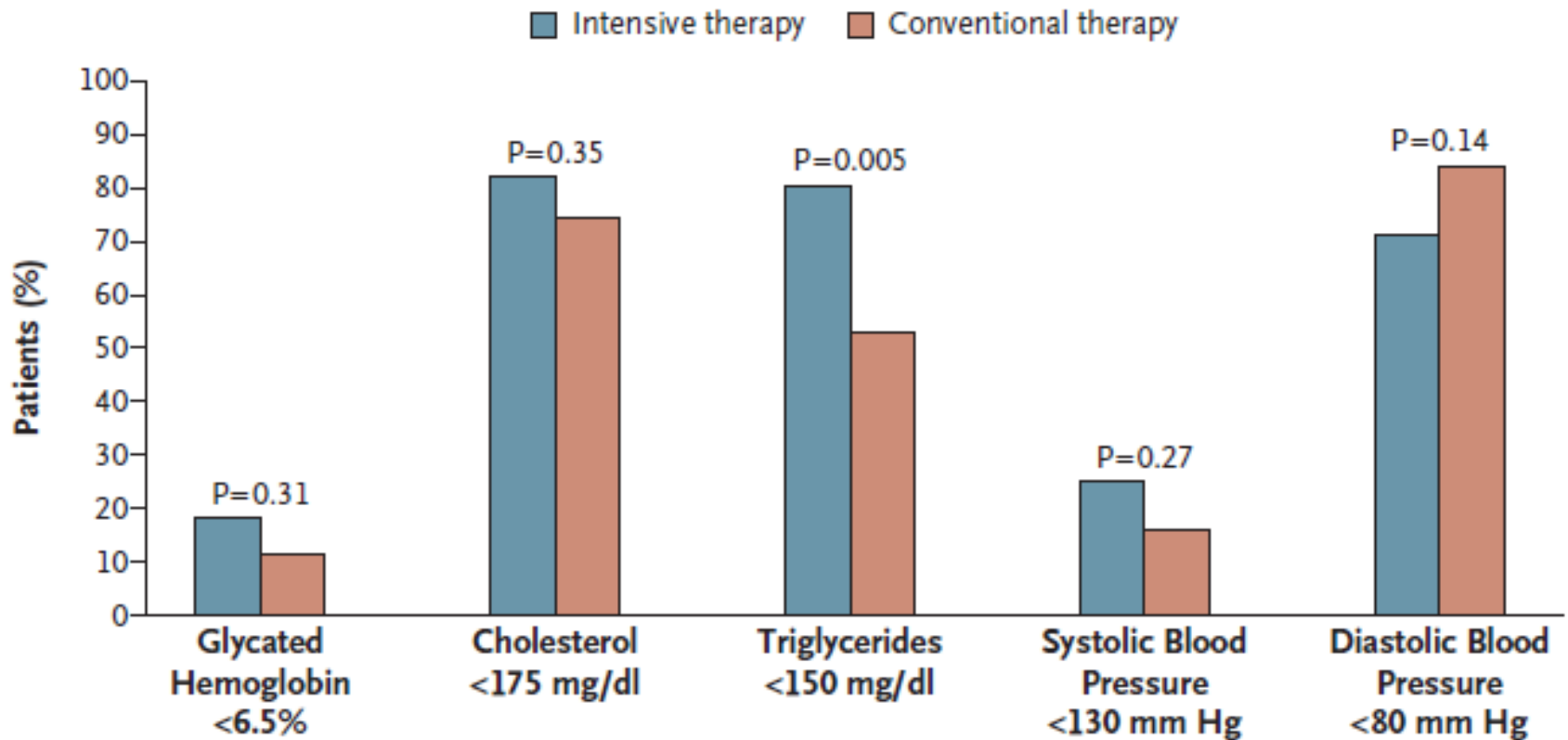
UK Prospective Diabetes Study assessed the association between micro and macro vascular complications and glycemia in 4585 white, Asian Indian, and Afro-Caribbean patients from 23 hospital based clinics



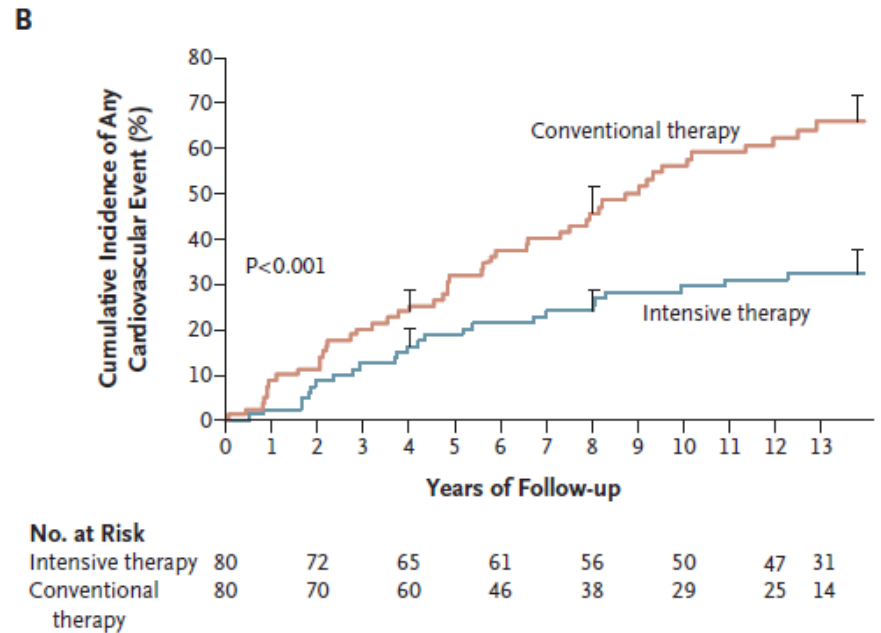
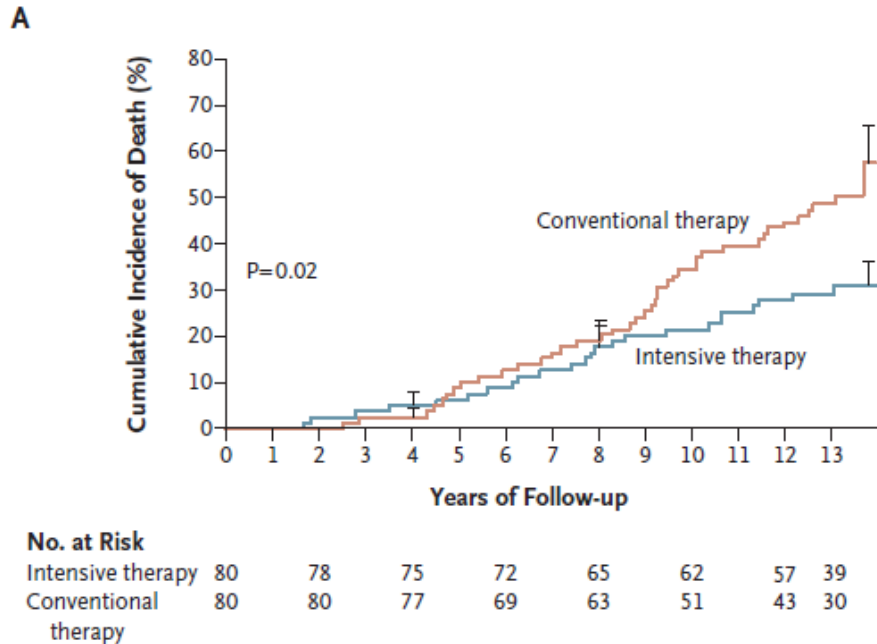
Each 1% decrease in updated mean HbA_{1c} causes

- 21% reduction in any end point related to diabetes ($p < 0.0001$),
- 21% reduction in deaths related to diabetes ($p < 0.0001$)
- 14% reduction in myocardial infarction ($p < 0.0001$)
- 37% reduction in microvascular complications ($p < 0.0001$)

Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes



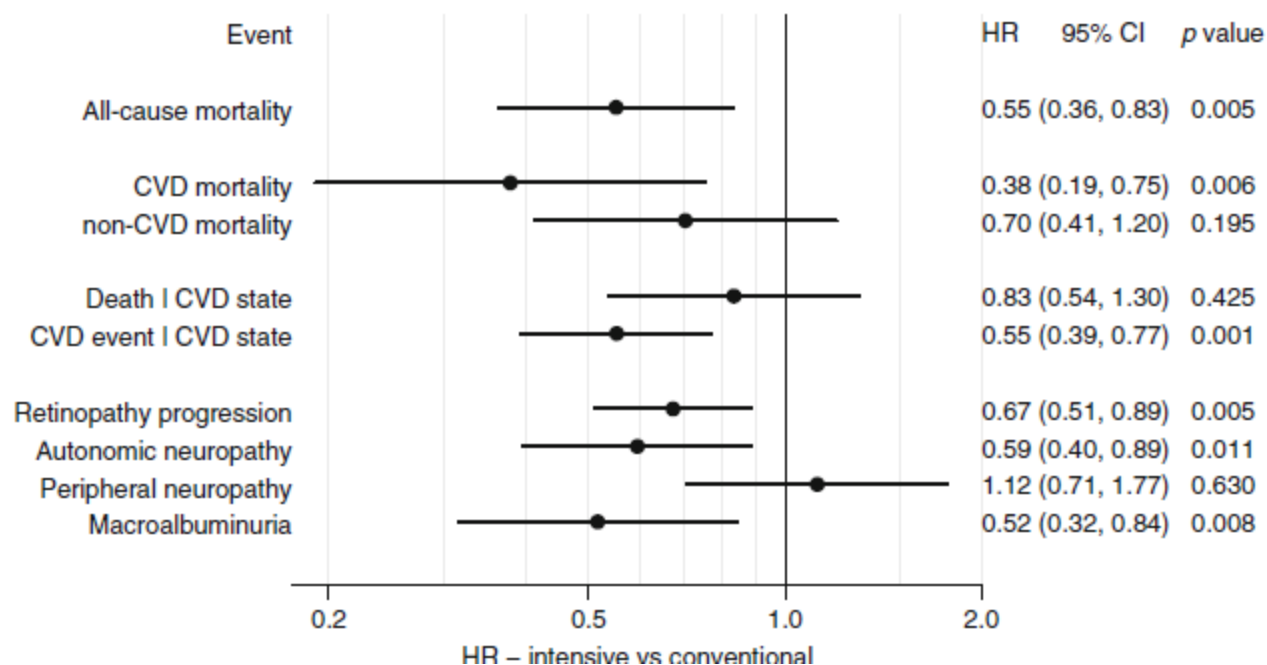
Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes



Kaplan-Meier Estimates of the Risk of Death from Any Cause and from Cardiovascular Causes and the Number of Cardiovascular Events, According to Treatment Group.

21 years follow-up on the Steno-2 trial

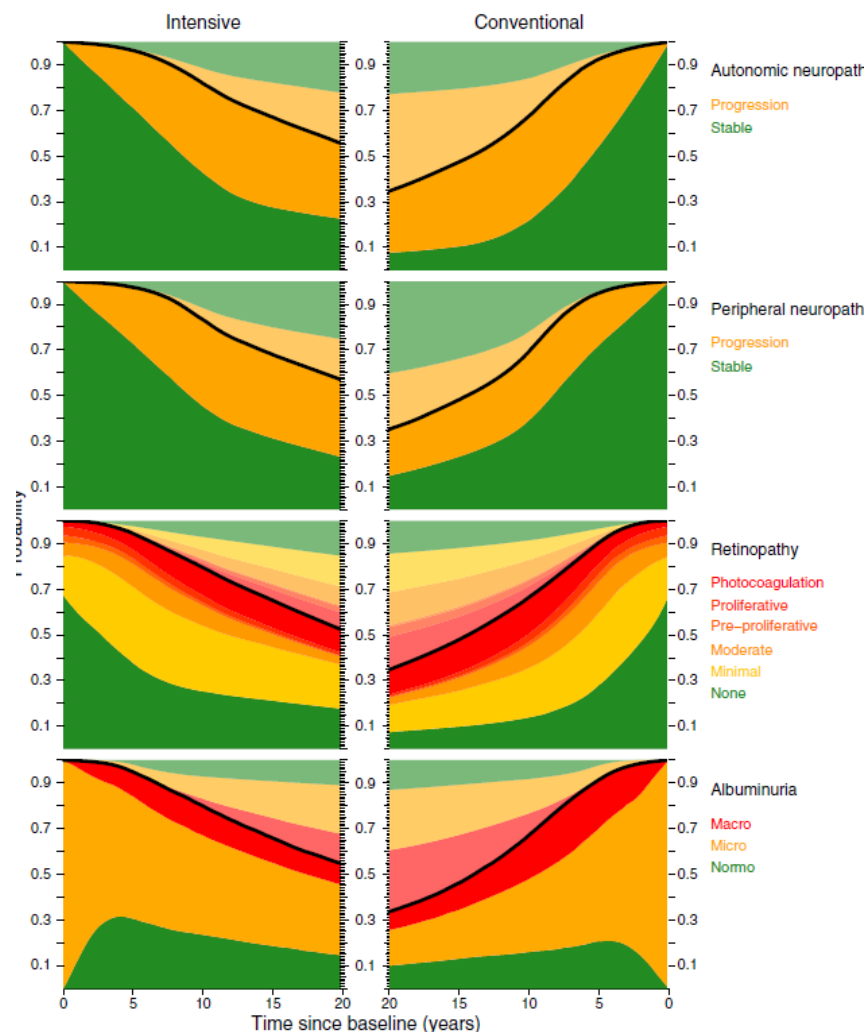
- Forest plot of the HR (95% CI) for secondary and tertiary endpoints.
- Significant risk reductions for all-cause mortality, CVD mortality, CVD events and progression of retinopathy, autonomic neuropathy and macroalbuminuria in intensive group



21 years follow-up on the Steno-2 trial

Progression of microvascular complications

- Progression of retinopathy was decreased by 33% in the intensive-therapy group.
- Blindness in at least one eye was reduced in the intensive-therapy group with an HR of 0.47 (95% CI 0.23, 0.98, $p = 0.044$).
- Autonomic neuropathy was decreased by 41% in the intensive-therapy group.
- Progression to diabetic nephropathy (macroalbuminuria) was reduced by 48% in the intensive-therapy group.



Conclusion

- Preventing diabetes is of enormous value for any nation particularly in the developing world because of the high cost of treating diabetes and its complication.
- The need of the hour is to develop pragmatic, cost effective strategies for primary prevention to extend the benefits to the population at large.
- The significance of early, intensified risk factor control in patients with complicated type 2 diabetes to be emphasized.

Thank You