
بسم الله الرحمن الرحیم

Diabetes mellitus

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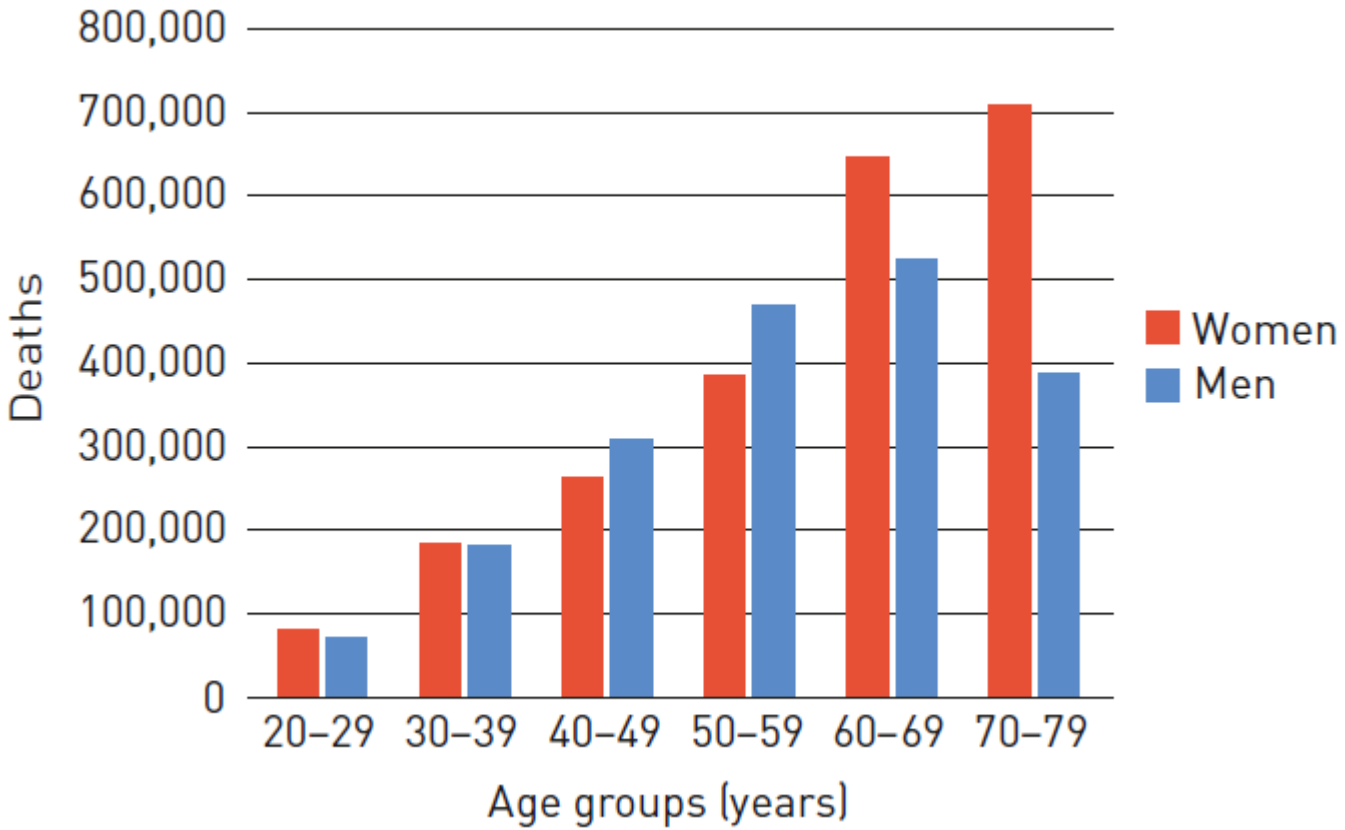
Diabetes Facts

Worldwide toll of diabetes.

Diabetes is one of the **fastest growing health challenges** of the 21st century, with the number of adults living with diabetes having more than tripled over the past 20 years

The latest edition of the *IDF* shows that **463 million adults** are currently living with diabetes

Number of deaths due to diabetes in adults (20–79 years) by age and sex in 2019

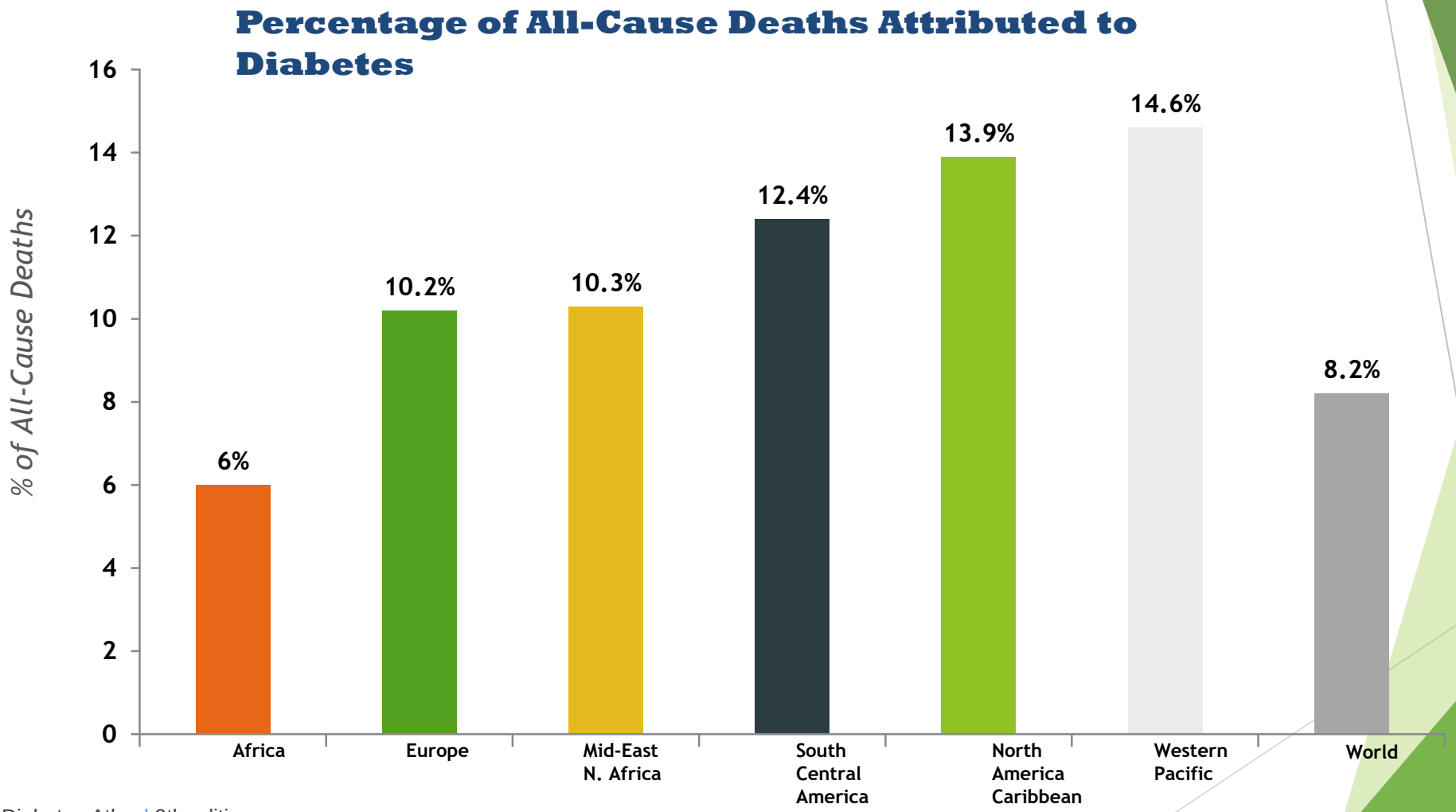


Every **8 seconds** a person dies from diabetes

(5 million annually)

IDF Diabetes Atlas | 9th edition

Diabetes is a Leading Cause of Death Worldwide accounting for 8.2% 0f global all-cause mortality



IDF Diabetes Atlas | 9th edition

Classification

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune ß-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. Type 2 diabetes (due to a progressive loss of ß-cell insulin secretion frequently on the background of insulin resistance)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

Age profile of diabetes

Working age

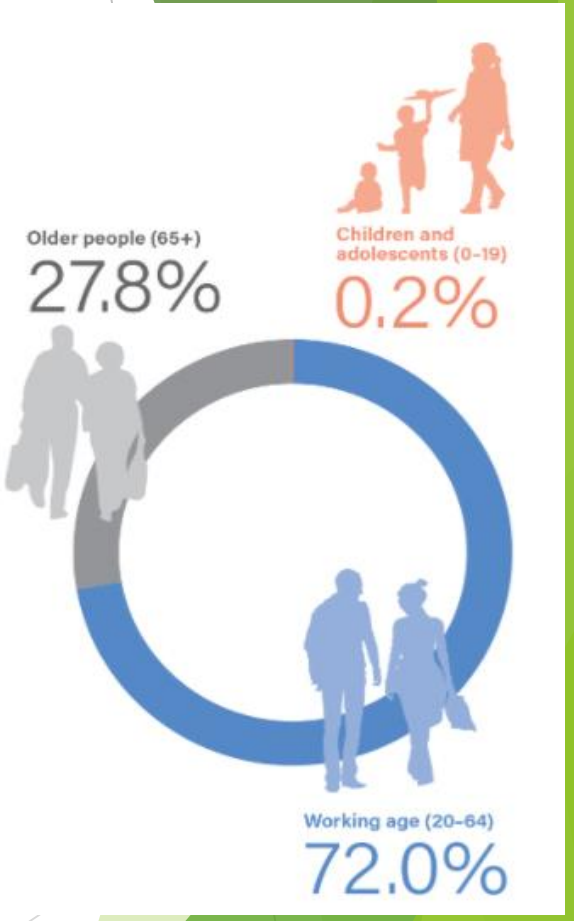
Three in four people living with diabetes (٣٥٢ million people) are of working age (i.e. between ٢٠ and ٦٤ years old).

Older people

In ٢٠١٩, the estimated number of people over ٦٥ years of age with diabetes is ١١١ million. One in five adults in this age group is estimated to have diabetes

Children and adolescents

An estimated ١.١ million children and adolescents (aged under ٢٠) have type ١ diabetes. There is some evidence that type ٢ diabetes among children and adolescents is increasing in some counties



T1D & T2D

Type 1

- Usually <30 years but not always.
- Usually lean weight
- Males > Females
- Onset sudden
- Always symptomatic
- Thirst/polyuria / nocturia
- Weight loss
- Prone to ketosis
- Diagnosis - chronic high blood glucose
- INSULIN mandatory
- Otherwise normally healthy

Type 2

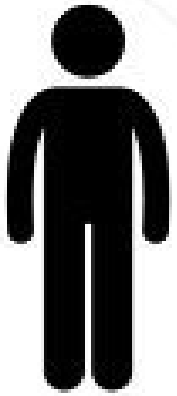
- Previously >30 but now seen in adolescents.
- Mostly overweight or obese
- Males = Females
- Onset usually slow
- May be asymptomatic
- Maybe some weight loss
- Not prone to ketosis
- Diagnosis often at routine screening
- Recurrent infections
- Emergency admission – Heart Attack, stroke
- Co-existing health problems often present, hypertension

Diabetes

Diabetes – a hormonal disease

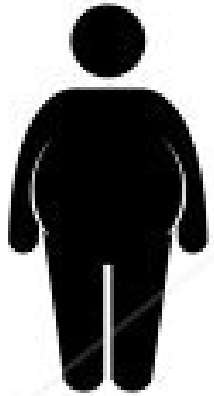
- Diabetes is a chronic disease that occurs when the pancreas is no longer able to make insulin, or when the body cannot make good use of the insulin it produces
- An absolute or relative lack of insulin leaves too much glucose in the bloodstream

Type 1 diabetes



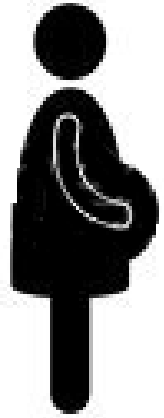
- **Absolute** lack of insulin
- Autoimmune or idiopathic
- Usually children

Type 2 diabetes



- Insulin **resistance** (relative lack of insulin)
- β-cell dysfunction
- Lifestyle factors
- Usually adults

Gestational diabetes



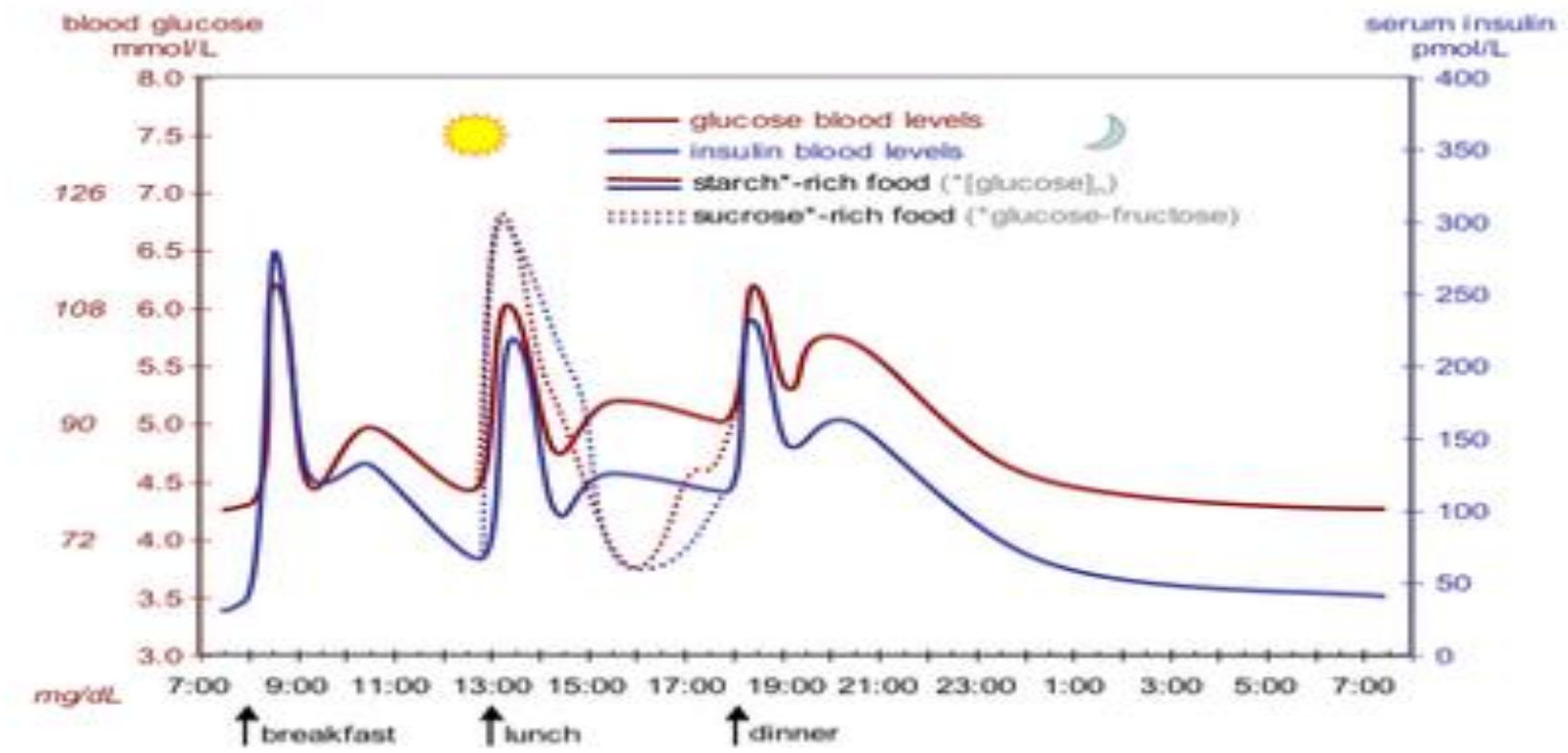
- Insulin **resistance** (relative lack of insulin)
- Starting during pregnancy
- Risk to mother and child

- The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003:26:S5

Diabetes – a hormonal disease

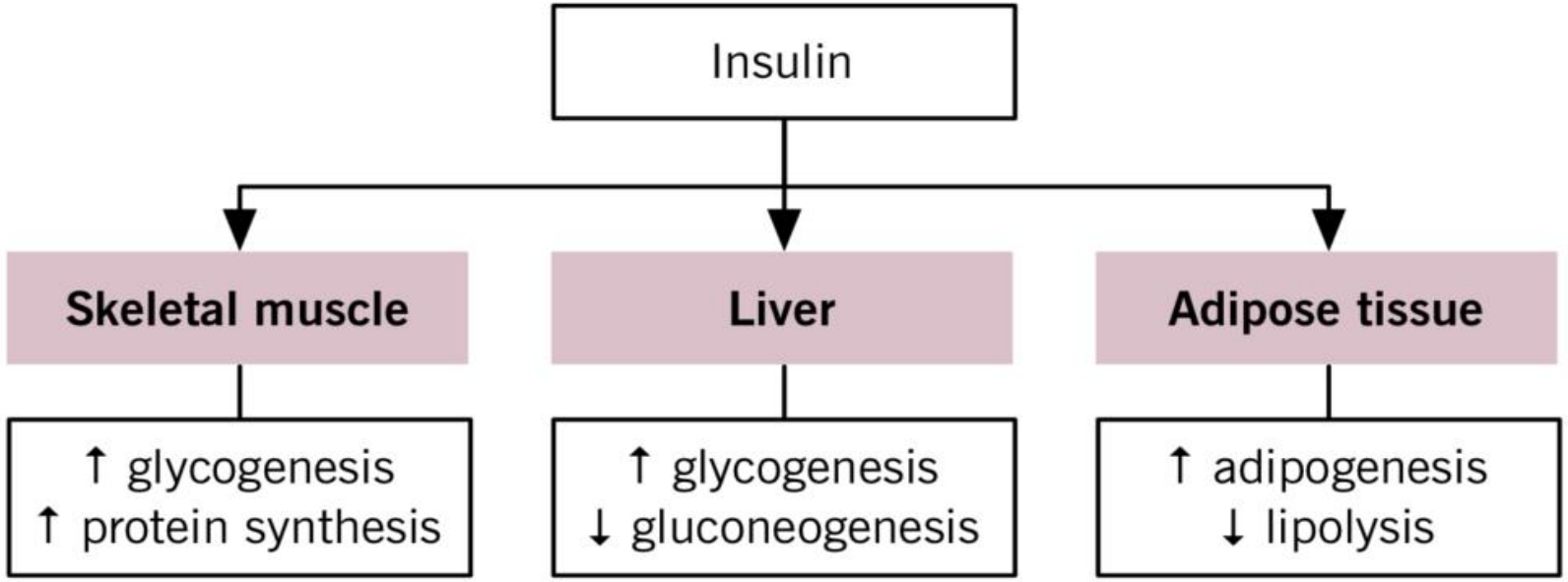
- Body glycemic status is tightly controlled by two pancreatic hormones, insulin and glucagon

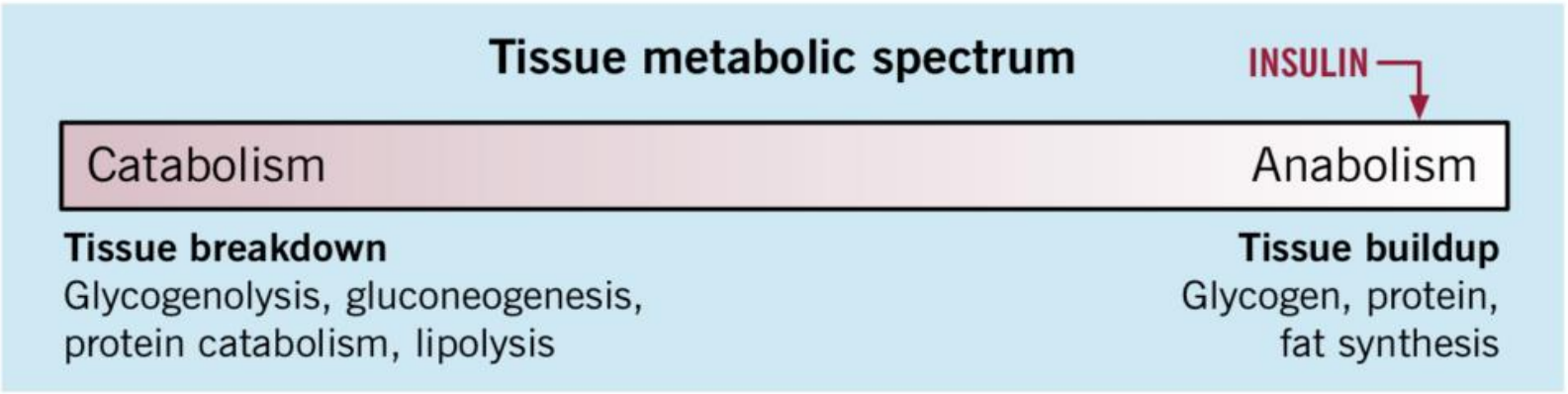
  - Insulin keeps blood glucose in a tight, healthy range in the bloodstream



Diabetes – a hormonal disease

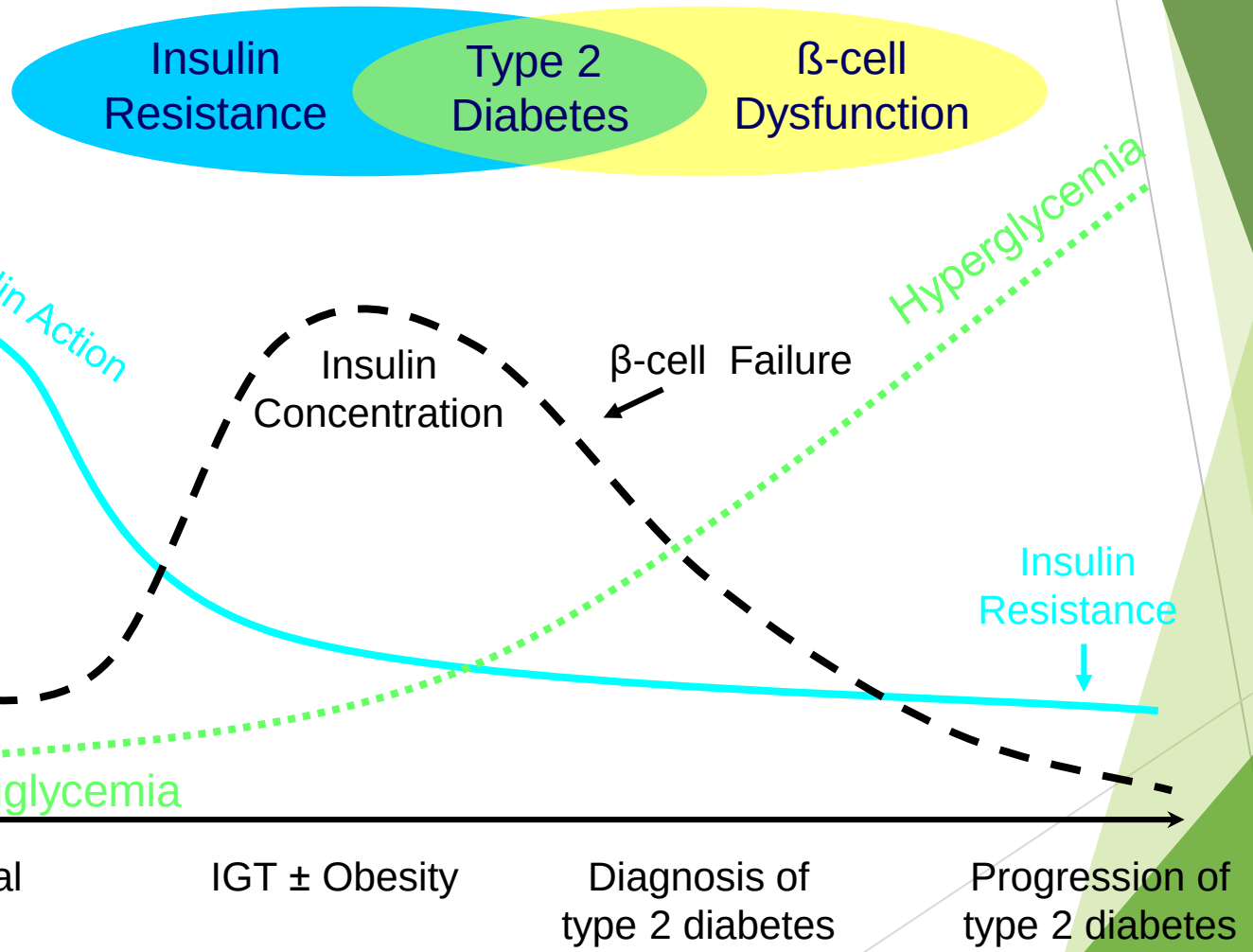
Insulin is an anabolic hormone





http://www.pathophys.org/hyperglycemic-emergencies-diabetic-ketoacidosis-and-hyperosmolar-hyperglycemia-state/dm-anabolicinsulin/

Type 2 Diabetes – a glucotoxic disease



- De Fronzo Diabetes Care 1992; 15: 318-68

EARLY AND INTENSIVE APPROACH TO T2DM MANAGEMENT

At diagnosis of T2DM:50% of patients already have complications

Up to 50% of β-cell function has already been lost

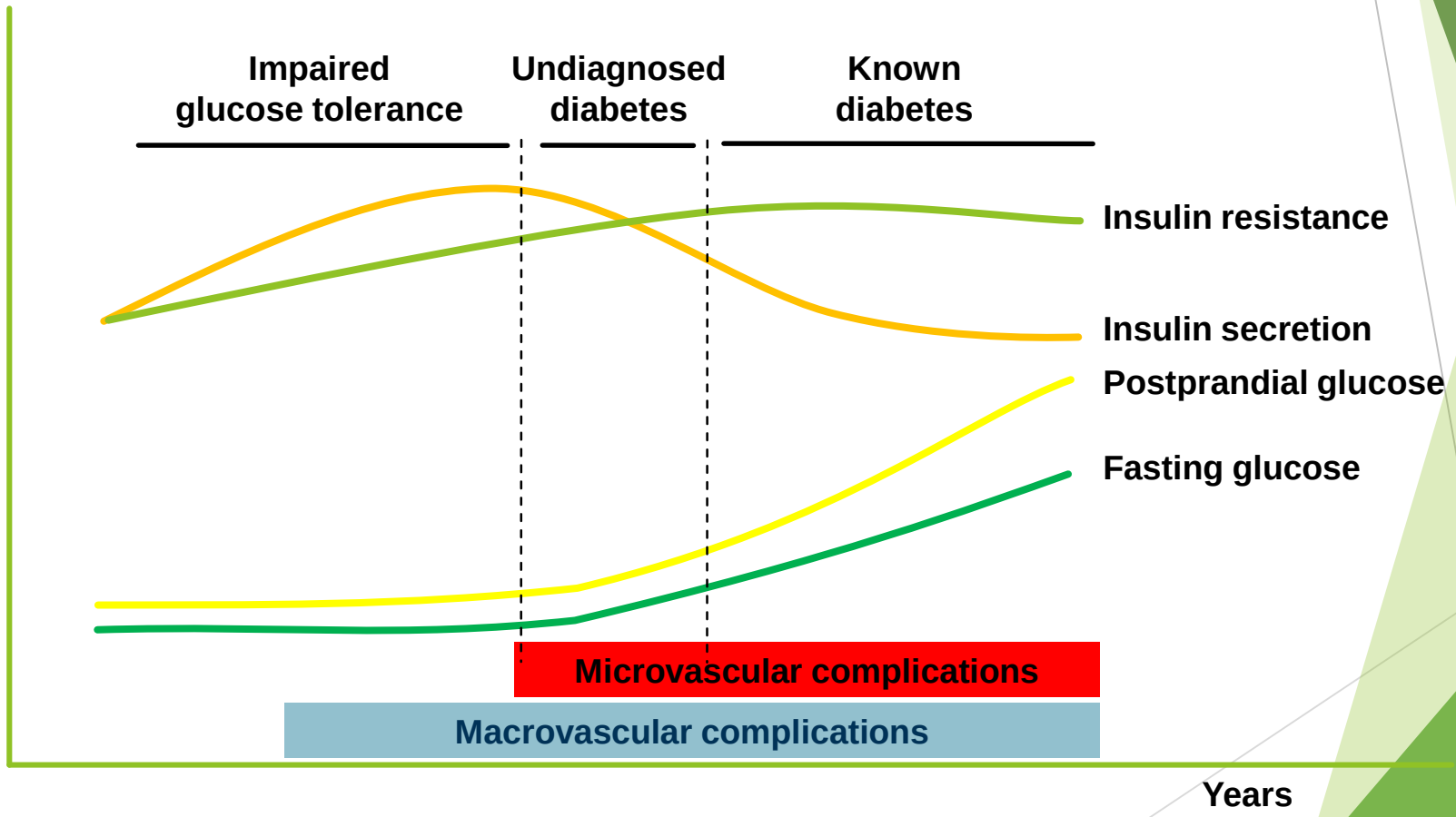


Table 2.2—Criteria for the diagnosis of diabetes

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

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

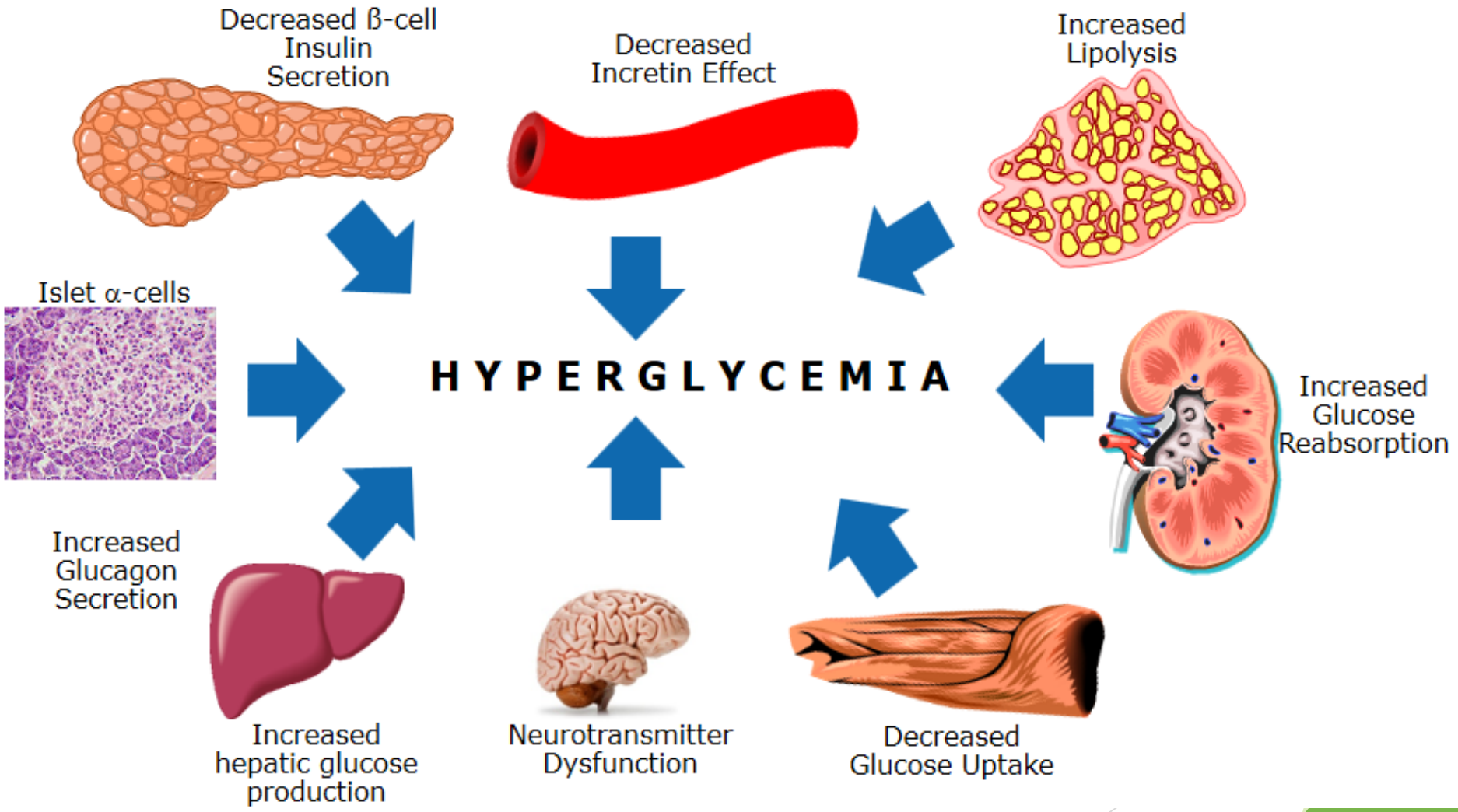
Diabetes – a hormonal disease

- Body glycemic status is tightly controlled by two pancreatic hormones, insulin and glucagon
  - Insulin keeps blood glucose in a tight, healthy range in the bloodstream

	Fasting Plasma Glucose		Oral Glucose Tolerance Test		HbA1c
	mg/dl	mmol/l	mg/dl	mmol/l	%
healthy	<100	<=5.5	<140	<7.8	<=5.6
Prediabetes	100-125	5.6-6.9	140-199	7.8-11.0	5.7-6.4
Type 2 diabetes	≥ 126	≥7.0	≥200	≥11.1	≥6.5

Standards of medical care in Diabetes ,ADA 2021

Type 2 diabetes – the ominous octet



Diabetes increases the risk of health complications

- Half of the 463 million adults living with diabetes today are unaware that they are therefore at high risk of developing serious diabetes-related complications.

- Globally, 8,2 -11.3% of deaths are due to diabetes. Almost half of these deaths are in people under 60 years of age.

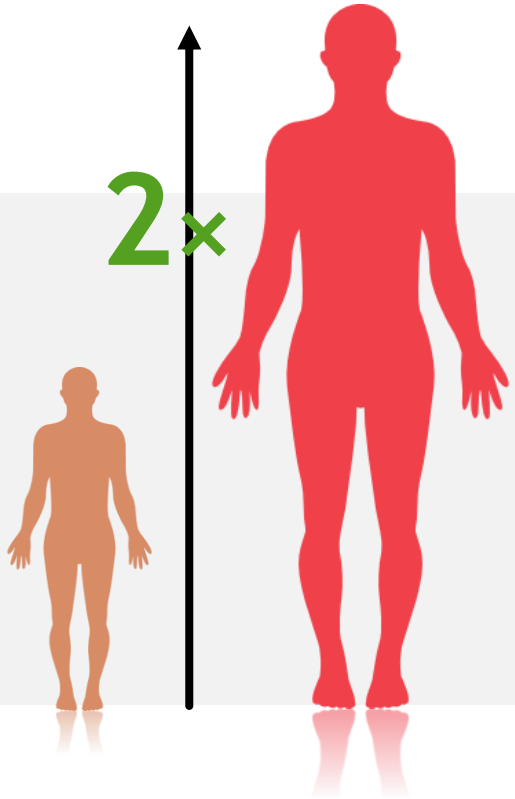
❑ Acute diabetes complications

Are common in type 1 diabetes and can also occur, when certain medications are used, in type 2 and other forms of diabetes. These can lead to permanent illness or even death.

❑ Chronic complications of diabetes

May already be present in people with type 2 diabetes by the time they are diagnosed. They can also appear soon after the onset of type 1 diabetes. Early detection and appropriate treatment are essential to prevent disability and death.

Diabetes greatly increases the risk of CV disease

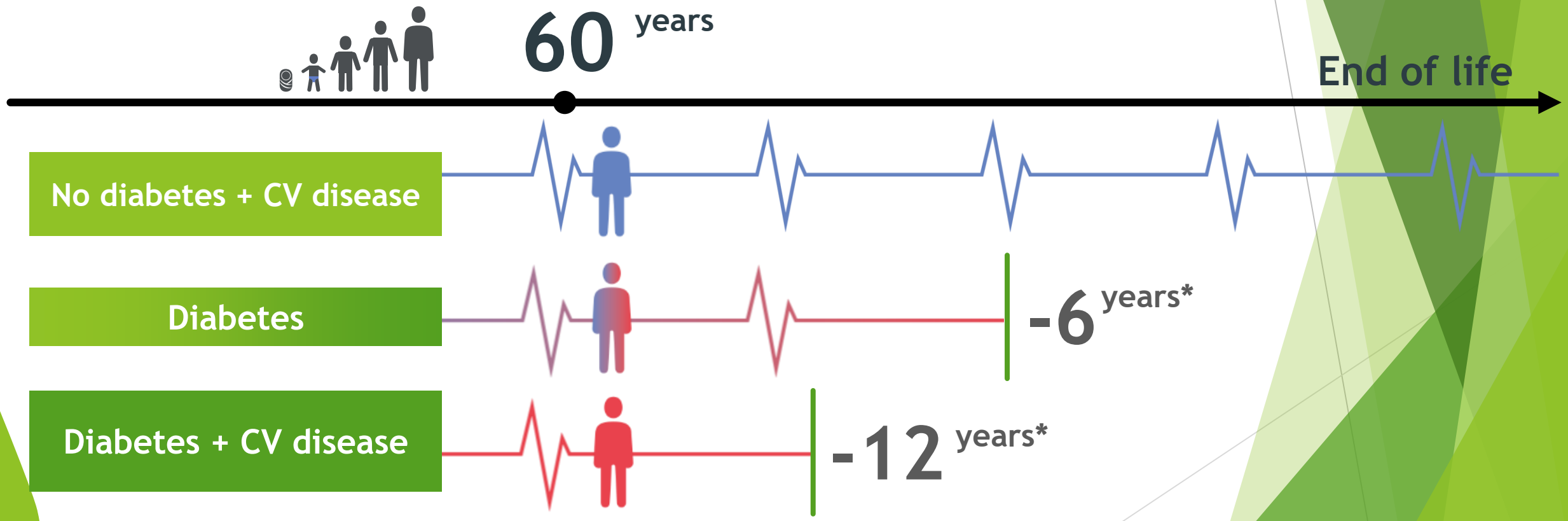


Patients with T2D have twice the risk of CV disease compared with the general population

CV, cardiovascular; T2D, type 2 diabetes
Sarwar N *et al. Lancet* 2010;375:2215

Life expectancy is reduced by ~12 years in patients with diabetes and CV disease

A 60-year-old patient with diabetes and CV disease dies, on average, 12 years earlier than a person without diabetes and CV disease



In this case, CV disease is represented by MI or stroke
*Average for men and women
CV, cardiovascular, MI, myocardial infarction
The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52

Metformin & Diabetes first line or Not?

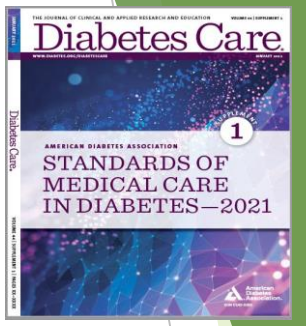
History of Metformin in DM2

- history is linked to Galega officinalis , found to be rich in guanidine, which, in 1918, was shown to lower blood glucose
- Guanidine derivatives, (not metformin) were used to treat diabetes in the 1920s and 1930s but were discontinued due to toxicity and the increased availability of insulin
- Metformin was rediscovered in the search for antimalarial agents in the 1940s and, during clinical tests, proved useful to treat influenza when it sometimes lowered blood glucose.
- French physician Jean Sterne, who first reported the use of metformin to treat diabetes in 1957. However, metformin received limited attention as it was less potent than other glucose-lowering biguanides (phenformin and buformin), which were generally discontinued in the late 1970s due to high risk of lactic acidosis
- After intensive scrutiny metformin was introduced first line in USA in 1995
- Long-term cardiovascular benefits of metformin were identified by the UK Prospective Diabetes Study (UKPDS) in 1998, providing a new rationale to adopt metformin as initial therapy to manage hyperglycaemia in type 2 diabetes

Metformin & Diabetes

- Reduces hepatic glucose production and improves peripheral glucose utilization slightly
- Metformin reduces fasting plasma glucose (FPG) and insulin levels, improves the lipid profile, and promotes modest weight loss
- An extended-release form is available and may have fewer GI side effects (diarrhea, anorexia, nausea, metallic taste)
- Initial dose should be low and then escalated every 1–2 weeks based on SMBG measurements to a maximally tolerated dose of 2000 mg daily
- Long-term use is associated with reduced micro- and probably macro vascular complications

Pharmacologic Therapy for Type 2 Diabetes



Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A

Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. 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% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. E

Prevention or Delay of Type 2 Diabetes

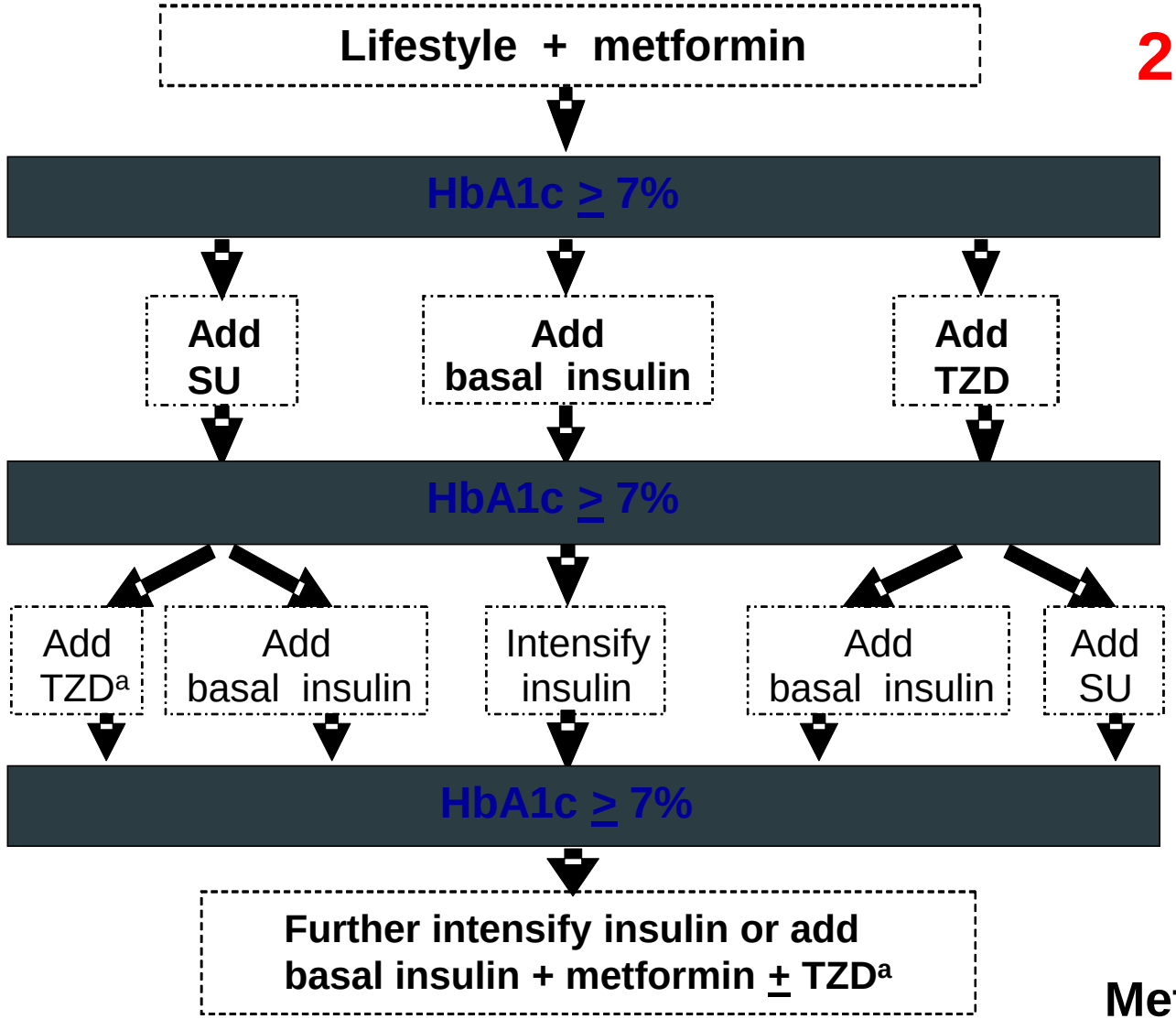
Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m2, those aged,60 years, and women with prior gestational diabetes mellitus. A

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

	MECHANISM OF ACTION	EXAMPLES[a]	HBA_{1c} REDUCTION (%)[b]	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Oral						
Biguanides[c*]	↓ Hepatic glucose production	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency	Renal insufficiency (see text for GFR <45 mL/min), CHF, radiographic contrast studies, hospitalized patients, acidosis
α-Glucosidase inhibitors[c**]	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
Dipeptidyl peptidase IV inhibitors[c***]	Prolong endogenous GLP-1 action; ↑ Insulin, ↓ glucagon	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia	Angioedema/ urticarial and immune-mediated dermatologic effects	Reduced dose with renal disease
Insulin secretagogues: Sulfonylureas[c*]	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease
Insulin secretagogues: Nonsulfonylureas[c***]	↑ Insulin secretion	Mitiglinide nateglinide, repaglinide	0.5–1.0	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver disease

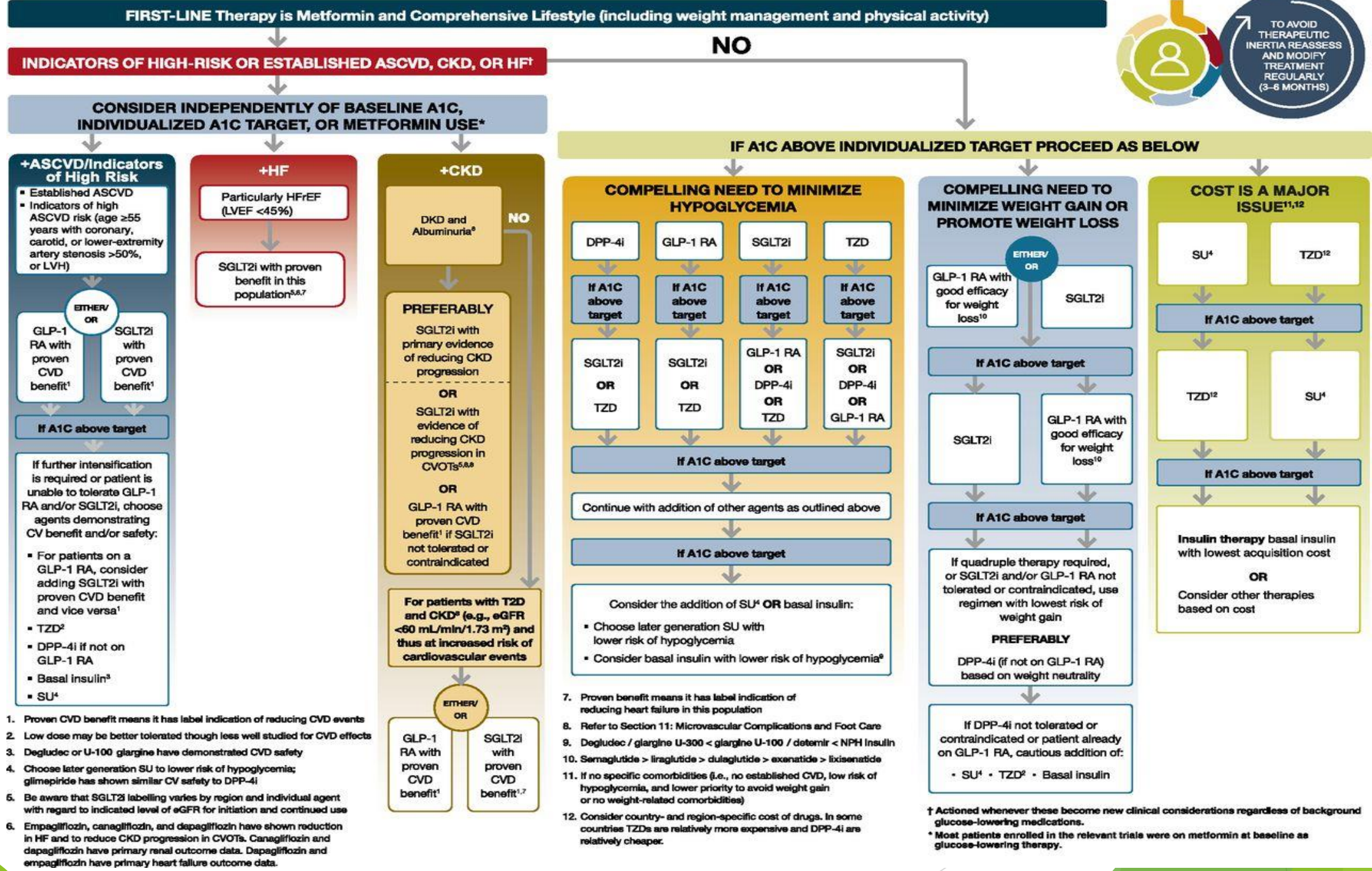
ADA-EASD Consensus Algorithm for T2DM

2006



Metformin

Nathan. Diabetes Care 2006; 29: 1963-1972



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Diabetes Care 2021; 44(Suppl. 1):S111-S124.

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i	TZD
If A1C above target	If A1C above target	If A1C above target	If A1C above target
SGLT2i **OR** TZD	SGLT2i **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i **OR** DPP-4i **OR** GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[9]

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss[10]	**EITHER/ OR**	SGLT2i

If A1C above target

SGLT2i	GLP-1 RA with good efficacy for weight loss[10]

If A1C above target

If quadruple 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

COST IS A MAJOR ISSUE[11,12]

SU[4]	TZD[12]

If A1C above target

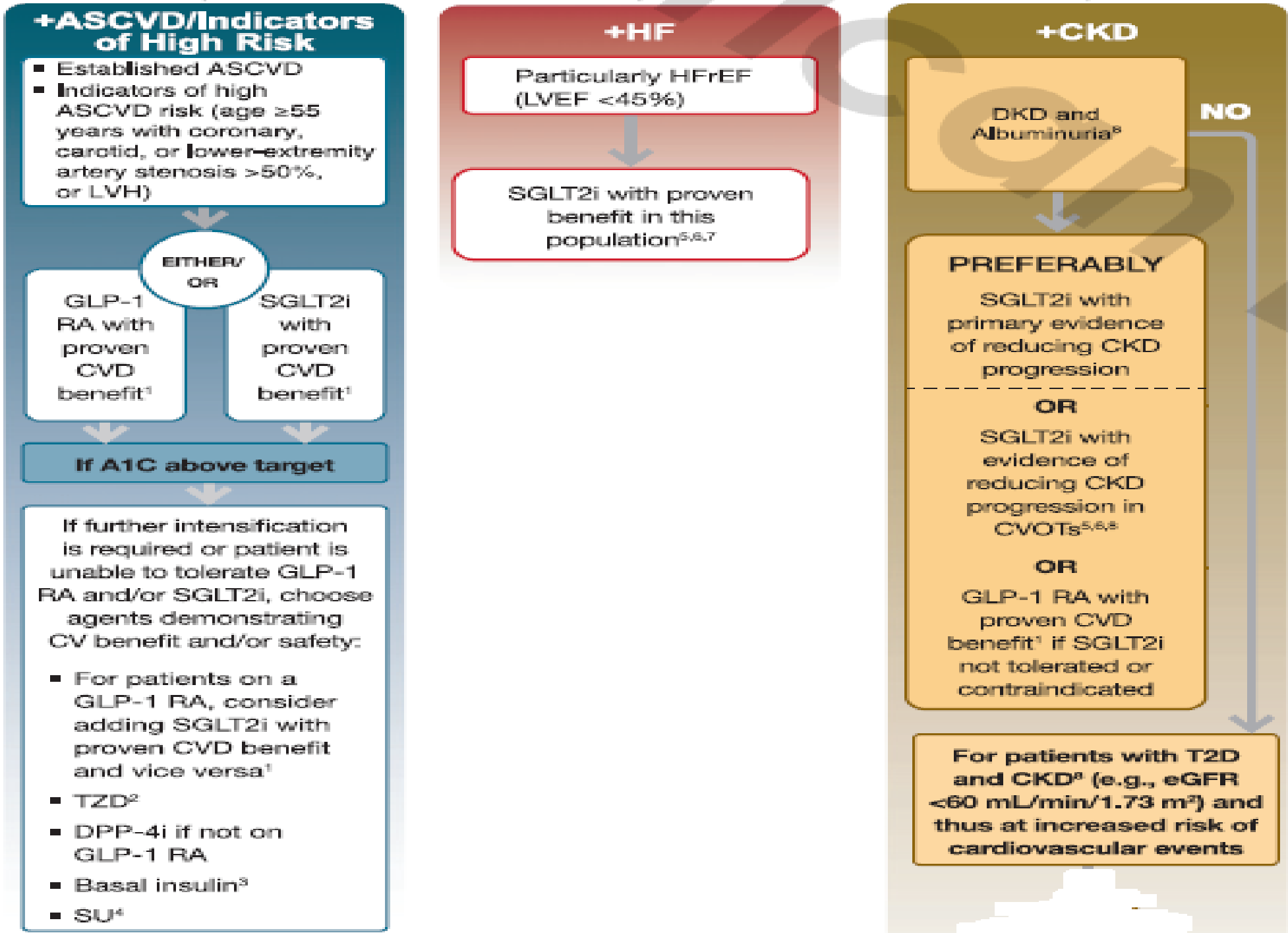
TZD[12]	SU[4]

If A1C above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost


+ASCVD/Indicators of High Risk
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
If A1C above target
If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa[1]
TZD[2]
DPP-4i if not on GLP-1 RA
Basal insulin[3]
SU[4]
+HF
Particularly HFrEF (LVEF <45%)
SGLT2i with proven benefit in this population[5,6,7]
+CKD
DKD and Albuminuria[8]
NO
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs[5,6,8]
OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated
For patients with T2D and CKD[8] (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events

Similarities over 15 years (2006 and 2021)

Metformin remains the Number 1 and core therapy in Guidelines today

Universal support across International guidelines

but European Society of Cardiology recommend newer agents for ASCVD and CKD in T2DM

CLINICAL TRIALS

New CVOTs - % Patients on background dosing with metformin

	SGLT-2 inhibitors			GLP-1 receptor antagonists							DPP-4 inhibitors			
Trial →	DECLARE	EMPA-REG	CANVAS	ELIXA	LEADER	SUSTAIN	PIONEER	EXCEL	HARMONY	REWIND	SAVOR	EXAMINE	TECOS	CARME-LINA
	Dapagliflozin	Empagliflozin	Canagliflozin	Lixisenatide	Liraglutide	Semaglutide subcut	Semaglutide oral	Exenatide	Albiglutide	Dulaglutide	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin
Number of patients	17,276	7,000	10,142	6,076	9,340	3,299	3,182	14,752	9,463	9,901	18,206	5,380	14,724	6,980
Follow-up (years)	6	3.1	3.6	2.1	3.8	2.1	1.3							
												29	30	31.3
			65	100	~81	~83	35	73	100	31	78	100	100	57
Metformin background (%)	80	74	70-80	66	76	73	77	76	73	81	67	66	82	54

4 in 5 PATIENTS WORLDWIDE are on METFORMIN in 2020

80% 74% 75% 66% 76% 73% 77% 76% 73% 81% 67% 66% 82% 54%

ACE (acarbose): Lancet Diab Endocrin 2017; 5: 877–86
CANVAS (canaglifozin): N Engl J Med 2017;377:644-57
CARMELINA (linagliptin): JAMA. 2019;321(1):69-79
DECLARE-TIMI 58 (dapagliflozin): DOI: 10.1056/NEJMoa1812389
ELIXA lixisenatide): N Engl J Med 2015;373:2247-57
EMPA-REG (empaglifozin): N Engl J Med 2015;373:2117-28.
EXAMINE (Alogliptin): N Engl J Med 2013;369:1327-35
EXCEL (Exenatide): N Engl J Med 2017;377:1228-39
HARMONY (albiglutide): Lancet 2018; 392: 1519–29
LEADER (Liraglutide):N Engl J Med 2016;375:311-22.
REWIND (dulaglutide): Lancet 2019; 394: 121–30
PIONEER (semaglutide): N Engl J Med 2019;381:841-51
SAVOR-TIMI (Saxagliptin): N Engl J Med 2013;369:1317-26
SUSTAIN-6 (semaglutide):N Engl J Med 2016; 375:1834-1844
TECOS (Sitagliptin): N Engl J Med 2015;373:232-42
White JB Diabetes, Obesity and Metabolism17: 395–402, 2015
UKDS 34: Lancet. 1998;352:854-65
UKPDS 33 Lancet.1998; 352:837-53

ADA Standards of Medical Care 2021

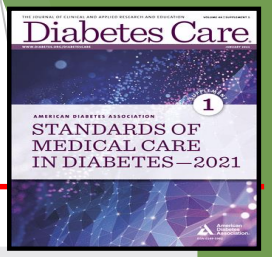


Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin		No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m²	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors						High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion,
GLP-1 RAs	High									
DPP-4 inhibitors	Intermediate									
Thiazolidinediones	High									▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin: Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin: Analogs						High	SQ			

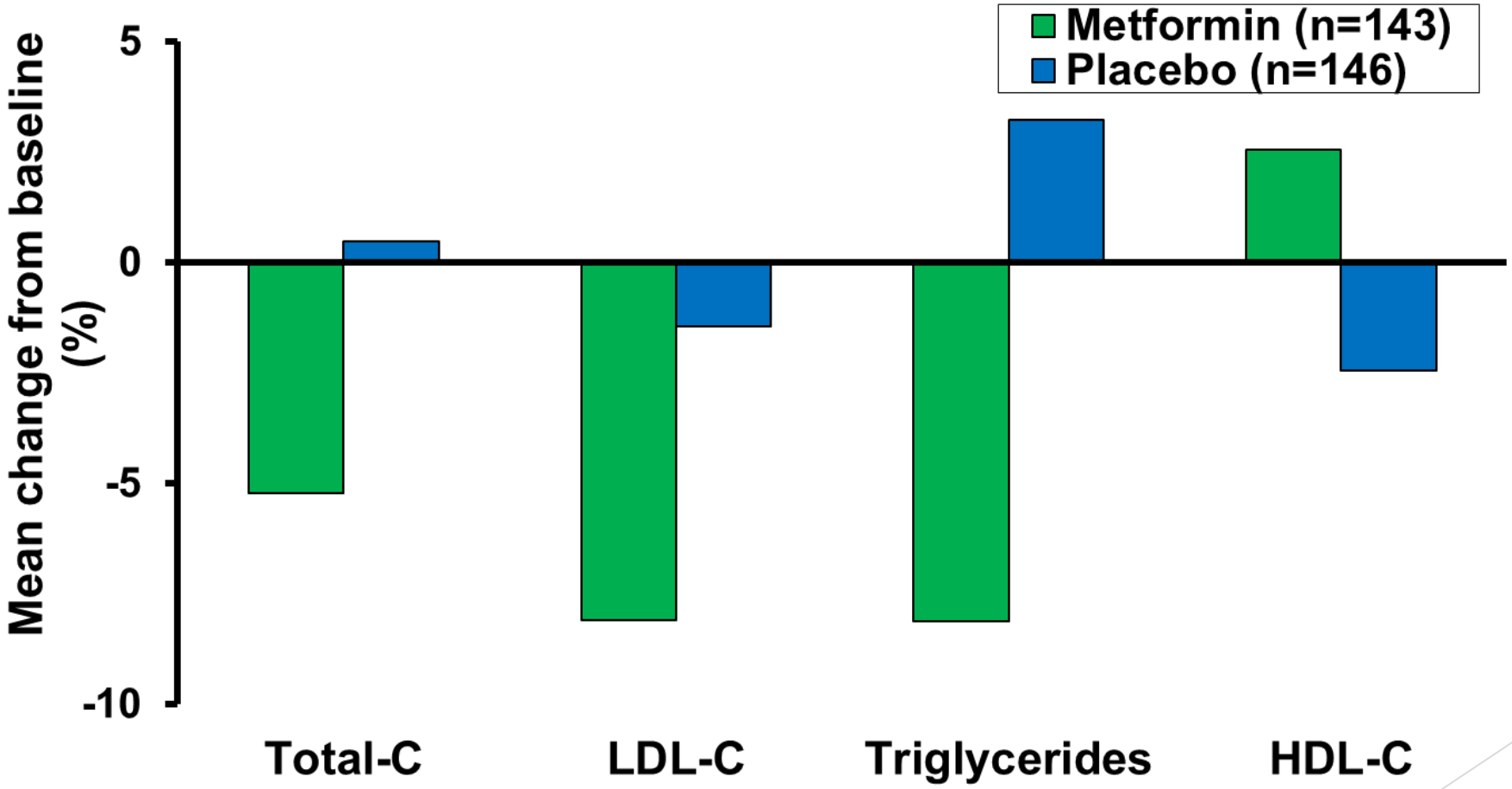
*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. ‡FDA-approved for heart failure indication; §FDA-approved for CKD indication. CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.

METFORMIN

EFFICACY - High
Hypos - No
Wt change - Neutral/modest loss
CV Benefits - Potential benefit in ASCVD
COST - Low

Diabetes Care 2021 43 Supplement 1st Jan

Metformin effect on lipid parameters in dyslipidemic T2DM patients



DeFronzo RA & Goodman AM. NEJM 1995;333:541-9;
Després JP. Diabetes Metab 2003:6S53-61

Metformin's beneficial effects support its use in overweight and lean T2DM patients

After 24 weeks of metformin treatment, improvements in clinical parameters were significant, and comparable, in overweight and lean newly-diagnosed Chinese patients

	Lean, n=31 (BMI < 25 kg/m^2)		Overweight, n=37 (25 kg/m^2 < BMI < 30 kg/m^2)		
	Baseline	At 24 weeks	Baseline	At 24 weeks	p
HbA1c (%)	7.9 ± 0.2	6.3 ± 0.1*	8.1 ± 0.3	6.3 ± 0.1*	0.538
FPG (mmol/L)	8.6 ± 0.3	6.7 ± 0.3*	8.4 ± 0.4	6.4 ± 0.2*	0.602
Body weight (kg)	62.5 ± 1.4	60.0 ± 1.6*	72.6 ± 1.3	70.5 ± 1.4*	0.740
Waist circumference (cm)	87.7 ± 1.6	86.7 ± 2.2	95.8 ± 1.4	93.9 ± 1.0*	0.336

p values for treatment difference between metformin-treated lean and overweight subgroups; * p<0.05 from baseline

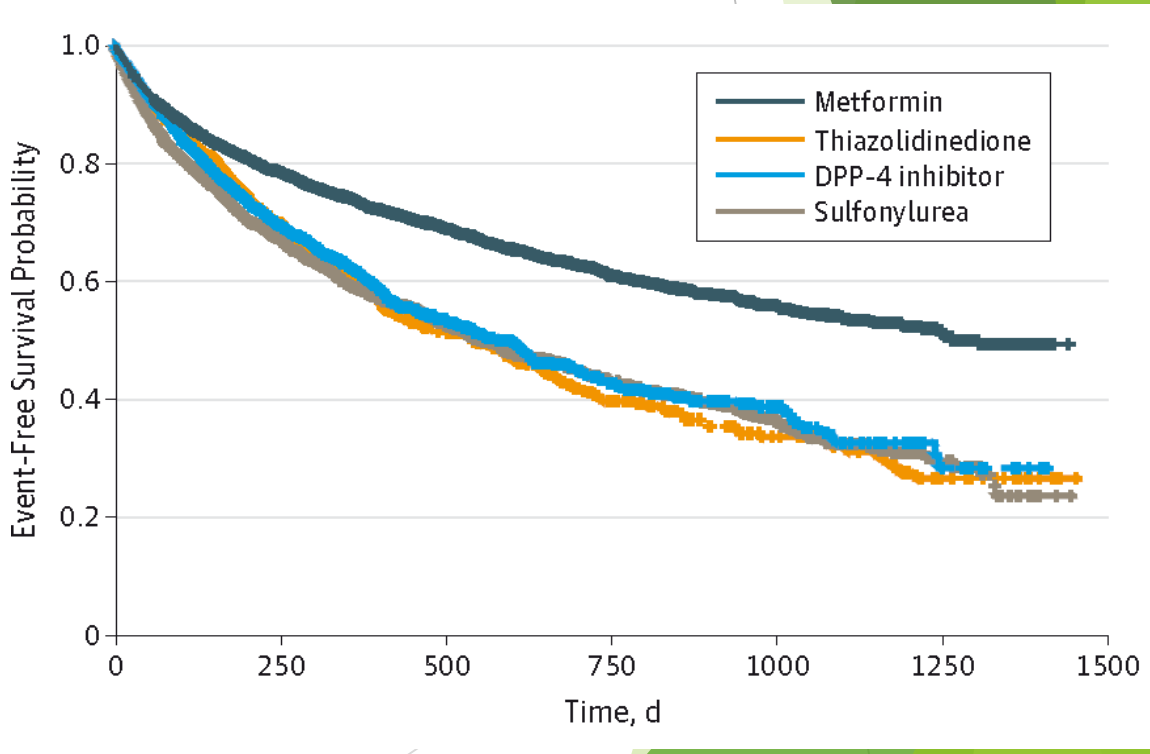
Increases in insulin sensitivity and ß-cell function were also significant and comparable after 24 weeks in the two groups

Bi Y, et al. Diabetes Metab Res Rev 2013;29:664–72

Metformin treatment initiation significantly delays the need for treatment intensification

compared to other oral antihyperglycemic

- Patients beginning therapy with SUs, DPP-4-i's, and TZDs instead of metformin were significantly more likely to need treatment intensification (addition of or substitution with anther oral agent or insulin)
  - If not used as initial treatment, metformin was chosen as addition for >40% of patients, suggesting that there was no contraindication
  - Other agents offered no compensatory benefits over metformin on adverse events



Berkowitz SA, et al. JAMA Intern Med.2014.5294

Therapeutic Advances in Endocrinology and Metabolism *Review*

Should metformin remain the first-line therapy for treatment of type 2 diabetes?

Chelsea Baker, Cimmaron Retzik-Stahr, Vatsala Singh, Renee Plomondon, Victoria Anderson and Neda Rasouli

Ther Adv Endocrinol Metab

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DOI: 10.1177/2042018820980225

Metformin & Diabetes: first line or Not?

- Metformin monotherapy has been shown to decrease mean HbA1c by 1.3%, compared with a 0.4% increase in the placebo group after 29 weeks.
- The (UKPDS) not only found a greater improvement in glycemic control in patients taking metformin compared with the conventional treatment arm but also showed that metformin therapy resulted in a reduction in hypoglycemic events and weight gain compared with sulfonylureas and insulin
- Comparing monotherapy of rosiglitazone, metformin, and glyburide in patients with newly-diagnosed diabetes, reported that 36% of subjects in the metformin group achieved an A1c
- The ADA still recommends metformin as first-line therapy while considering GLP-1 RAs and SGLT-2 inhibitors independently of baseline HbA1c in high risk patients.
- Alternatively, the EASD recently recommended considering GLP-1 RAs and SGLT-2 inhibitors as the first line for patients who have certain comorbidities, such as cardiovascular and renal disease

Metformin & Diabetes: first line or Not?

- The use of metformin as first line therapy for type 2 diabetes has been supported by a comprehensive systematic review and meta-analysis, given its relative safety and its beneficial effects on HbA1c
- Body weight was reduced or maintained with metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors, the study found, and it was increased with sulphonylureas, thiazolidinediones, and insulin
-
- The authors said that all of the diabetes medicines had specific side effects and that newer drugs were not necessarily safer than the older ones

Rojas and Gomes *Diabetology & Metabolic Syndrome* 2013, **5**:6
http://www.dmsjournal.com/content/5/1/6

DIABETOLOGY & METABOLIC SYNDROME

REVIEW Open Access

Metformin: an old but still the best treatment for type 2 diabetes

Lilian Beatriz Aguayo Rojas* and Marilia Brito Gomes*

- All noninsulin antidiabetic drugs when added to maximal metformin therapy are associated with similar HbA1c reduction but with varying degrees of weight gain and hypoglycemia risk.

- In 1980, Scambato et al. reported that, in a 3-year observational study of 310 patients with ischaemic cardiomyopathy, patients treated with metformin had reduced rates of re-infarction, occurrence of angina pectoris, acute coronary events other than acute myocardial infarction, and death in patients.1

1-Sgambato S, Varricchio M, Tesauro P, Passariello N, Carbone L: Use of metformin in ischemic cardiopathy. Clin Ther 1980, 94:77–85

Metformin & Diabetes

- The addition of metformin to adults with type 1 diabetes caused small reductions in body weight and lipid levels but did not improve A1C
- Metformin should be started at the time type 2 diabetes is diagnosed unless there are contraindications; for many patients this will be monotherapy in combination with lifestyle modifications
- Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death
- Metformin is available in an immediate-release form for twice daily dosing or as an extended-release form that can be given once daily

Metformin & Diabetes

- Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality
- The researchers, from Johns Hopkins University School of Medicine found moderate evidence that metformin monotherapy was associated with a lower risk of cardiovascular mortality than sulfonylurea monotherapy
- The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea
- These can be mitigated by gradual dose titration
- The drug is cleared by renal filtration

Metformin & Diabetes

- Very high circulating levels have been associated with lactic acidosis
- the FDA has revised the label for metformin to reflect its safety in patients with eGFR 30 mL/min/1.73 m2
- A recent randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy
- This is compatible with a recent report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12

CONTRAINDICATIONS

- Any form of acidosis
- Unstable congestive heart failure (CHF)
- liver disease
- Severe hypoxemia
- Metformin may be safe at a GFR >30 mL/min, with a reduced dose when the GFR is <45 mL/min

Metformin should be discontinued in:

- hospitalized patients
- patients who can take nothing orally
- receiving radiographic contrast material

Management of Gestational Diabetes Mellitus

- Lifestyle behavior change is an essential management of gestational diabetes mellitus and may suffice for the treatment of many women.A
- Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus. Metformin and glyburide should not be used as first-line agents, as both cross the placenta to the fetus. A
- Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data
- Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester. A