Joke Marlier

Dienst Endocrinologie

“Wat is nieuw en relevant voor de huisarts in de aanpak van diabetes mellitus type 2?

Avondcolloquium – 22 september 2021

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Diabetes, kidney and heart: an inherent trio

Epidemiology, pathophysiology & consequences

Treatment modalities

Conclusion & future prospects

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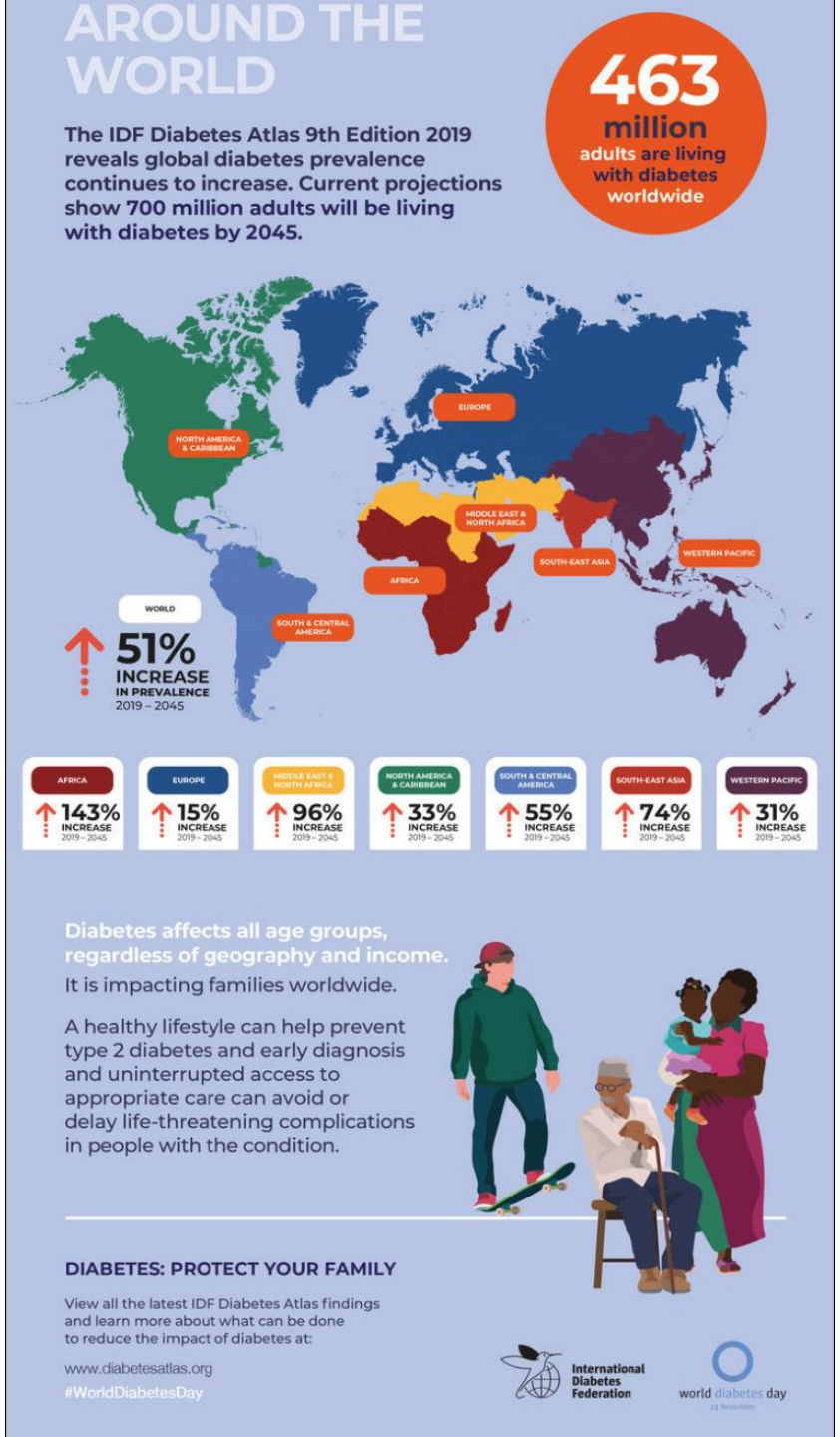
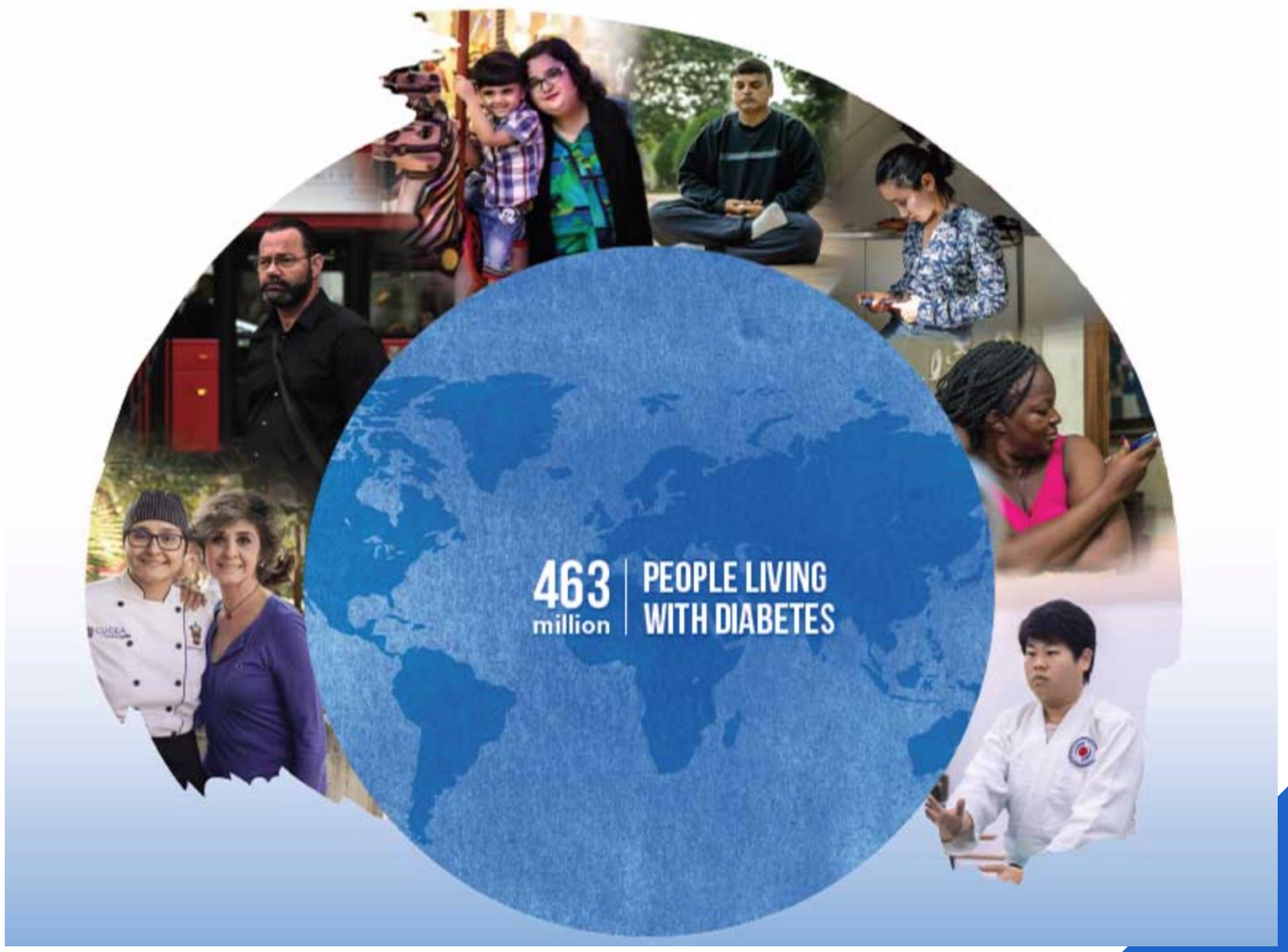
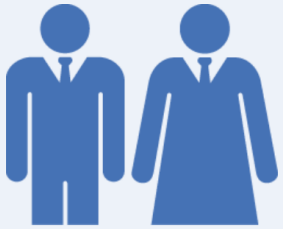
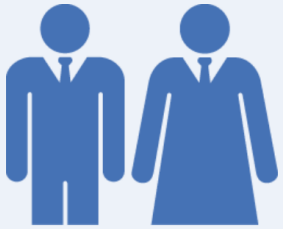
Epidemiology, pathophysiology & consequences







1 in 11 adults (20-79 years) have diabetes (463 million people)



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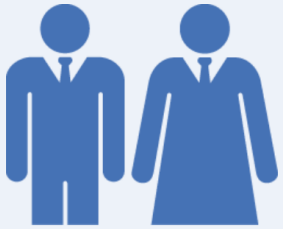

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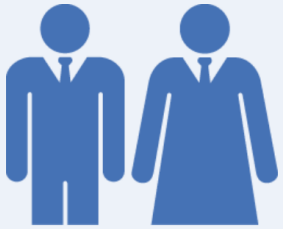

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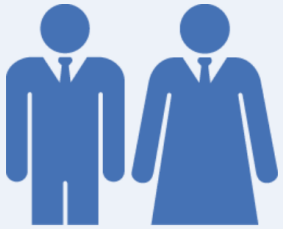

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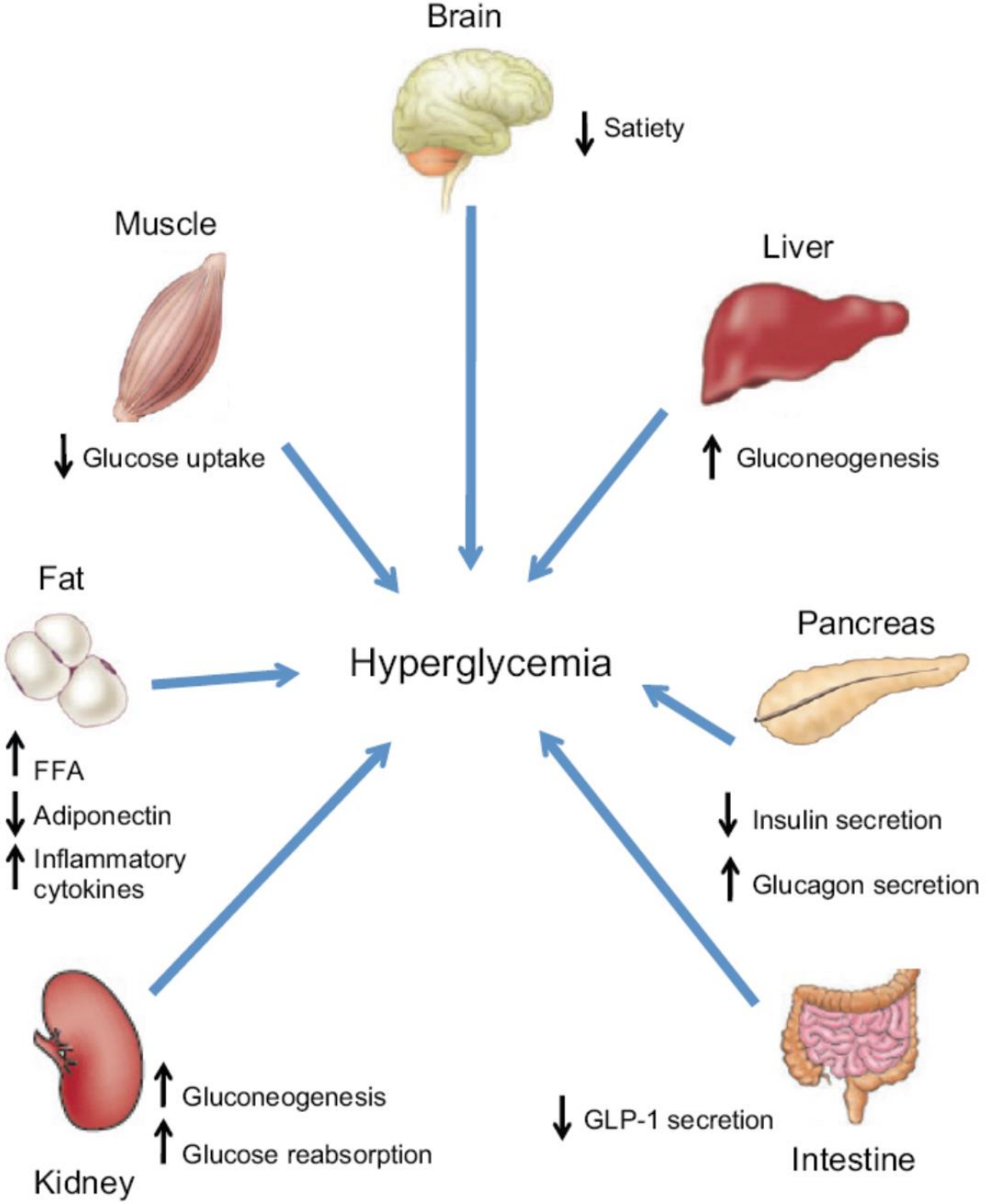
1 in 13 adults (20-79 years) have impaired glucose tolerance (374 million people)

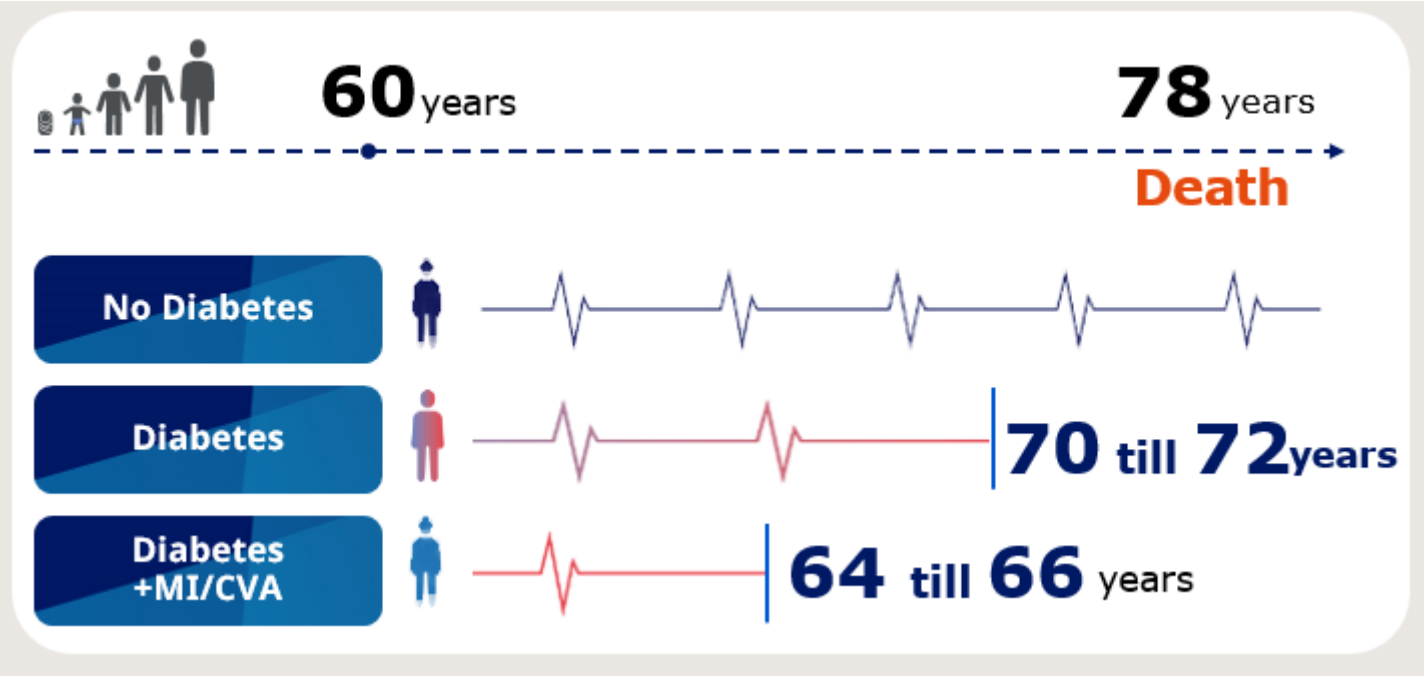
Epidemiology, **pathophysiology** & consequences

- T2DM is a cluster of metabolic distrubances who share
  - Insulin resistance, eventually leading to hyperglycemia
  - Development of chronic micro –and macrovascular complications
  - Often coincides with other important CV risk factors (dyslipidemia, arterial hypertension, obesity,…)

- Major causes are:
  - Sedentarism and unhealthy eating pattern leading to overweight and obesity
  - Important genetic contribution
  - Other factors: chronic inflammation, drug, pollution


Brain
Satiety
Muscle
Glucose uptake
Liver
Gluconeogenesis
Fat
FFA
Adiponectin
Inflammatory cytokines
Hyperglycemia
Pancreas
Insulin secretion
Glucagon secretion
Kidney
Gluconeogenesis
Glucose reabsorption
GLP-1 secretion
Intestine

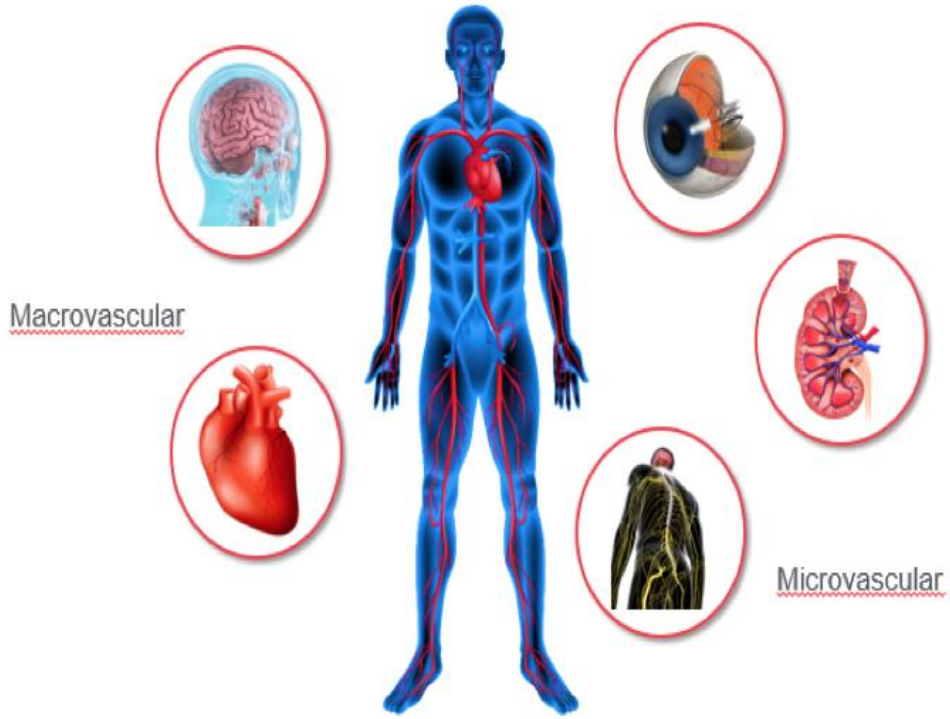
Having type 2 diabetes significantly impacts the life expectancy of your patient



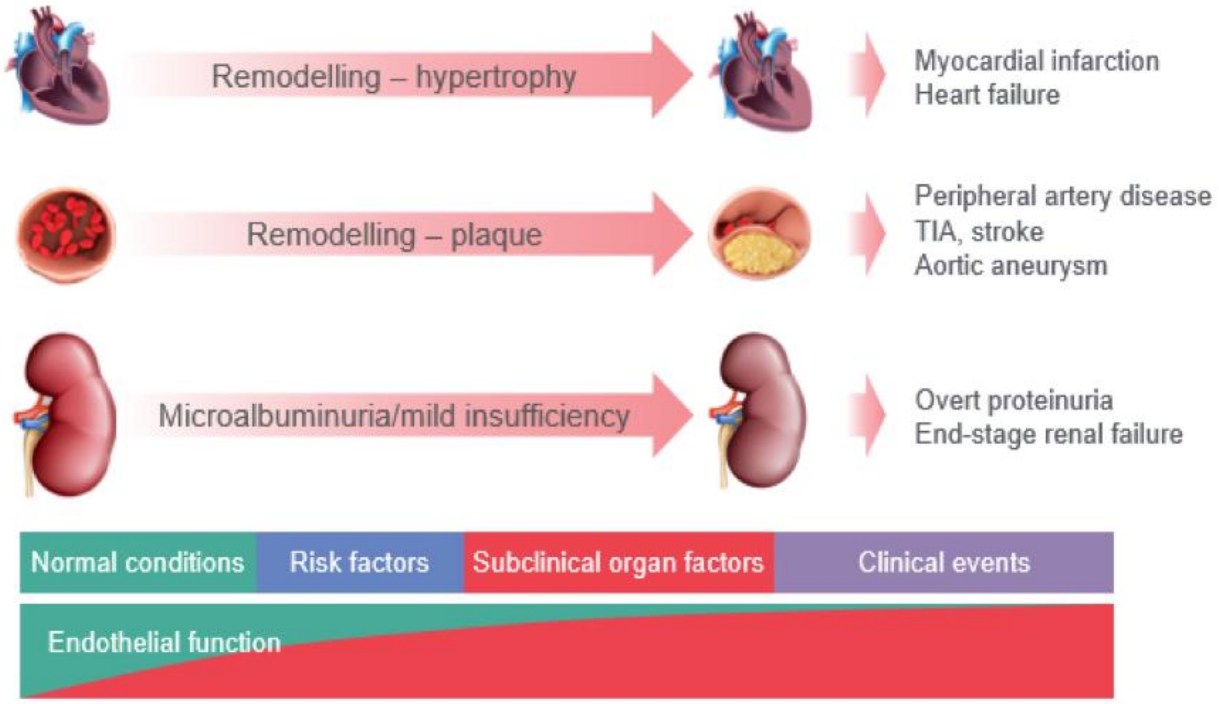
CVA, CEREBROVASCULAR ACCIDENT; MI, MYOCARDIAL INFARCTION.
ADAPTED FROM: THE EMERGING RISK FACTORS COLLABORATION. *JAMA*. 2015;314:52–60.

Epidemiology, pathophysiology & **consequences**

T2D is a major and independent risk factor for both microvascular and macrovascular complications[1]



Endothelial dysfunction is common to microvascular and macrovascular events[2]



CV disease can occur **10–15 years earlier** in patients with diabetes compared with those without diabetes[1,2]

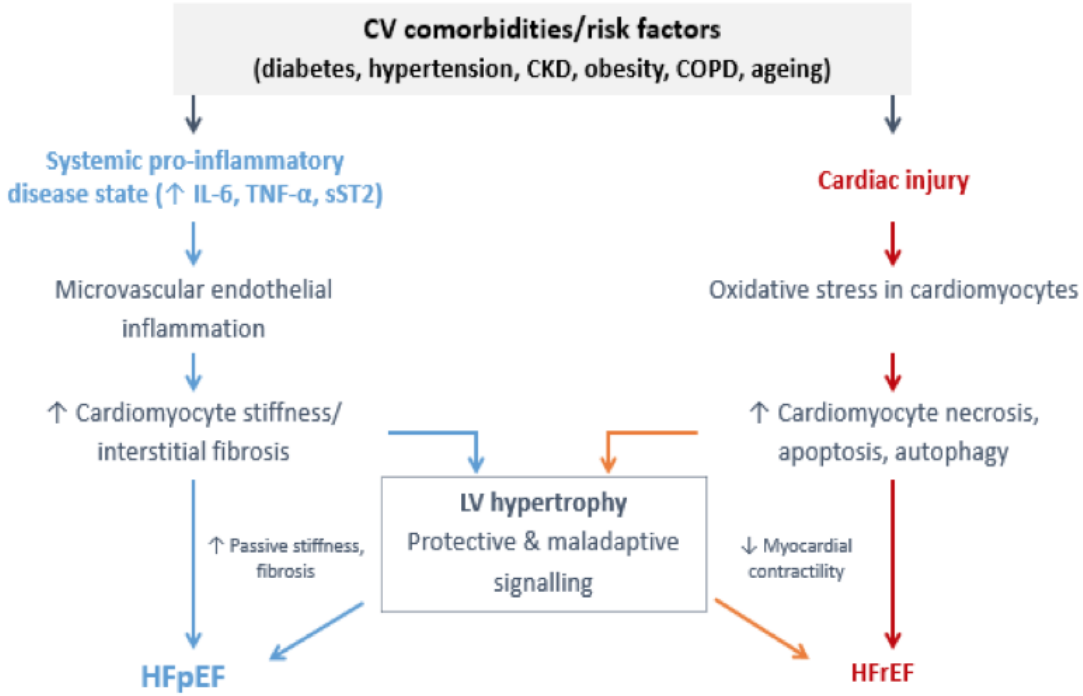
Most patients with T2D **die from CV disease**[3]

1. Malmberg K *et al. Circulation* 2000;102:1014; 2. Booth GL *et al. Lancet* 2006;368:29; 3. Morrish NJ *et al. Diabetologia* 2001;44(Suppl. 2):S14

Diabetes is an important risk factor for heart failure. People with diabetes have a 2-to 5-fold higher risk of developing heart failure[1]

Risk factors for heart failure[2]

Heart failure is associated with multiple risk factors[3]

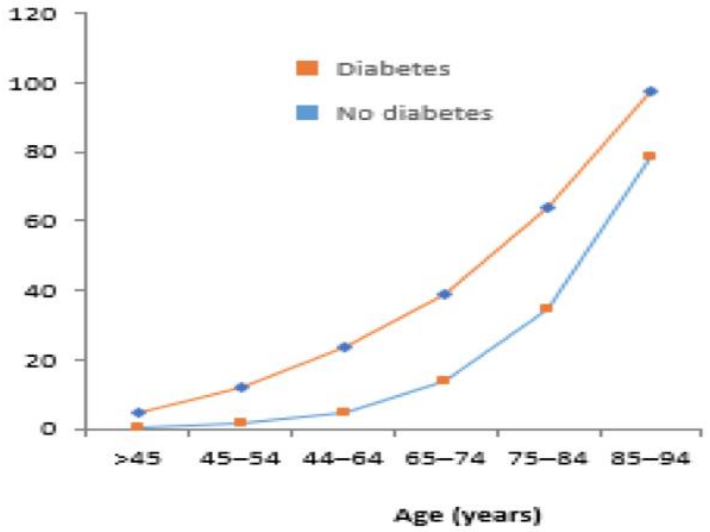


Diabetes confers 60–80% greater probability of CV death and all-cause mortality in those with established HF[4,5]

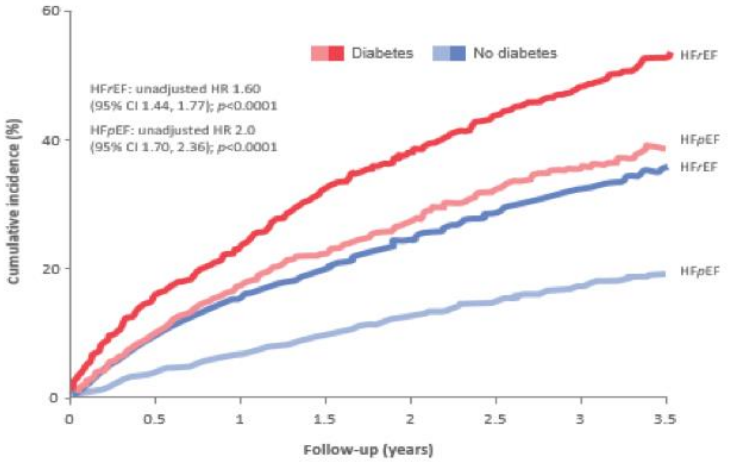
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IL, interleukin, LV, left ventricular; TNF, tumor necrosis factor

Age-associated incidence of heart failure increase in patients with diabetes

HF incidence by age group[1]



CV death or HHF in patients with or without diabetes based on ejection fraction[2]



HRs refer to the risk of CV death or HHF in patients with diabetes versus non-diabetes

CV, cardiovascular; EF, ejection fraction; HHF, hospitalisations for heart failure HF, heart failure; rEF, reduced ejection fraction

Development of CV/renal complications in newly diagnosed T2D

- 153,403 patients with **newly diagnosed T2D**
  - Identified between 1998 and 2015 through **Danish** nationwide registers
  - **Free of diagnoses** of cardiovascular and renal disease at inclusion

New diagnosis T2D without CV/renal disease

Follow-up for a median of 9.7 years

62% develops 1 complication
25% develops 2 complications
13% develops 3 complications

	% of patients developing this complication within 5 years	5-year risk ratio of death associated with this complication*	Decrease in lifespan (months) within 5 years associated with this complication*
Heart failure	1.6%	3 (2.9–3.1)	11.7 (11.6-11.8)
Ischemic heart disease	8.2%	1.3 (1.3-1.4)	1.6 (1.5-1.7)
Stroke	3.1%	2.2 (2.1-2.2)	6.4 (6.3-6.5)
Chronic kidney disease	2.2%	1.7 (1.7-1.8)	4.4 (4.3-4.6)
Peripheral artery disease	2.1%	2.3 (2.3-2.4)	6.9 (.8-7.0)

* Compared to patients without complications of CV/renal diseases

Zareini B et al. Circ Cardiovasc Qual Outcomes 2020;13(7):e006260

Risk factors for CVD – non modifiable risk factors

Age
- Significantly higher risk in men >45 years and women >55 years

Sex
- Men are at a higher risk than women of the same age
- Higher risk in women post menopause

Family history
- People with parents or siblings with a history of premature development of cardiovascular disease

Ethnicity
- African Americans are at a higher risk than Europeans

Modifiable risk factors

Hypertension

- Major risk factor for cardiovascular disease

Dyslipidaemia

- Abnormal lipid profile consisting of high levels of total cholesterol, triglycerides and LDL-C and/or low levels of HDL-C

Obesity

- Causes insulin resistance

Hyperglycaemia

- Increases the risk of early development of cardiovascular diseases

Physical inactivity

- Increases the risk of heart disease and stroke by 50%

Unhealthy diet

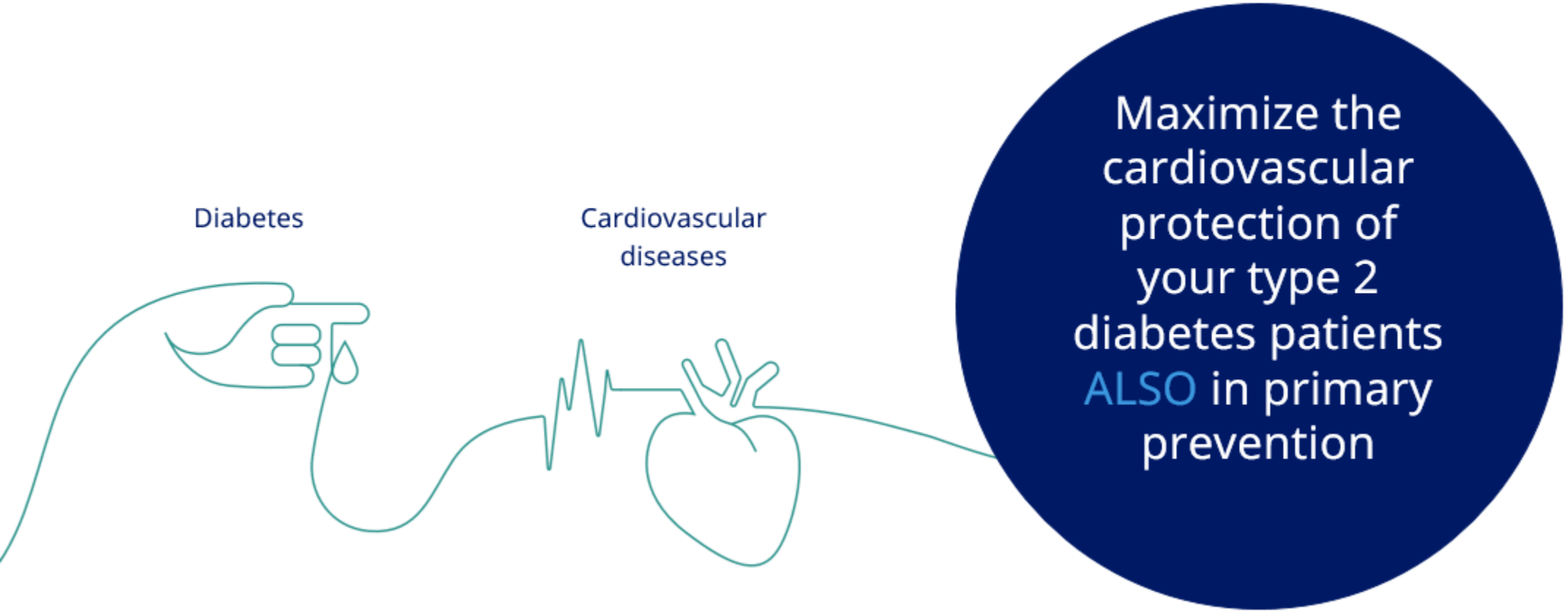
- Diet rich in saturated fats increases the risk of heart disease and stroke

Cigarette smoking

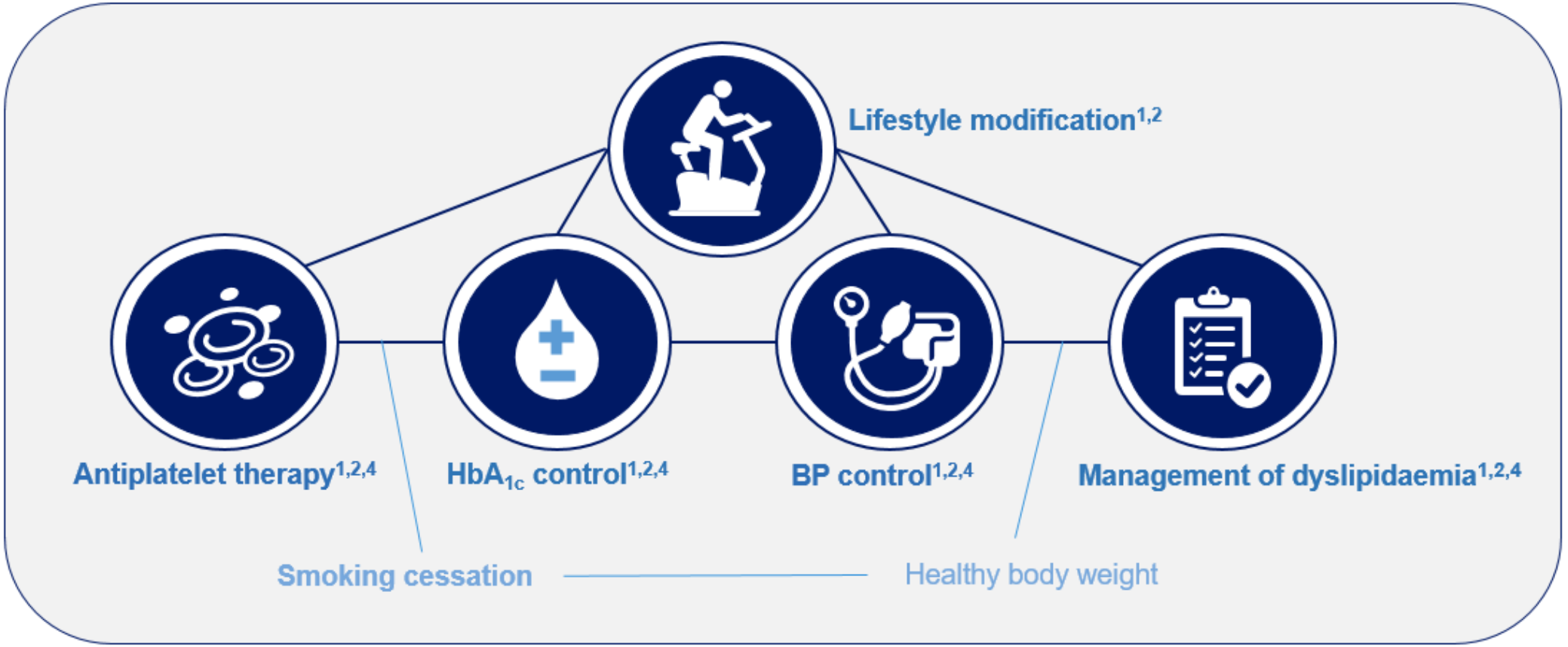
- Increases the risk of heart disease and stroke

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Tackling the CV risk in every type 2 diabetes patient



The CV risk approach is multifactorial and individualized[1-4]



 CV, CARDIOVASCULAR; HBA_{1C}, GLYCOSYLATED HAEMOGLOBIN; BP, BLOOD PRESSURE

1. AMERICAN DIABETES ASSOCIATION. *DIABETES CARE* 2018;41(SUPPL 1):S86–S104; 2. PIEPOLI MF ET AL. *EUR HEART J* 2016;37:2315–2381; 3. RYDÉN L ET AL. *EUR HEART J* 2013;34:3035–3087; 4. COSENTINO F ET AL. *EUR HEART J* 2019;00:1–69

Guidelines recognise the presence of diabetes as a major CV risk factor

EUROPEAN SOCIETY OF CARDIOLOGY®

Very high risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularisation and other arterial revascularisation procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima-media thickness of the carotid artery • **Diabetes with target organ damage, e.g. proteinuria or with a major risk factor, e.g. smoking or marked hypercholesterolaemia or marked hypertension** • Severe CKD (GFR <30 ml/min/1.73 m^2) • A calculated SCORE ≥10%
High risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/l (>310 mg/dl) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg • **Most other people with diabetes (with the exception of young people with T1D and without major risk factors that may be at low or moderate risk)** • Moderate CKD (GFR 30–59 ml/min/1.73 m^2) • A calculated SCORE ≥5% and <10%
Moderate risk	SCORE is ≥1 and <5% at 10 years. Many middle-aged subjects belong to this category
Low risk	SCORE <1%

Very high risk

Diabetes with target organ damage or with a major risk factor

High risk

Most other patients with diabetes

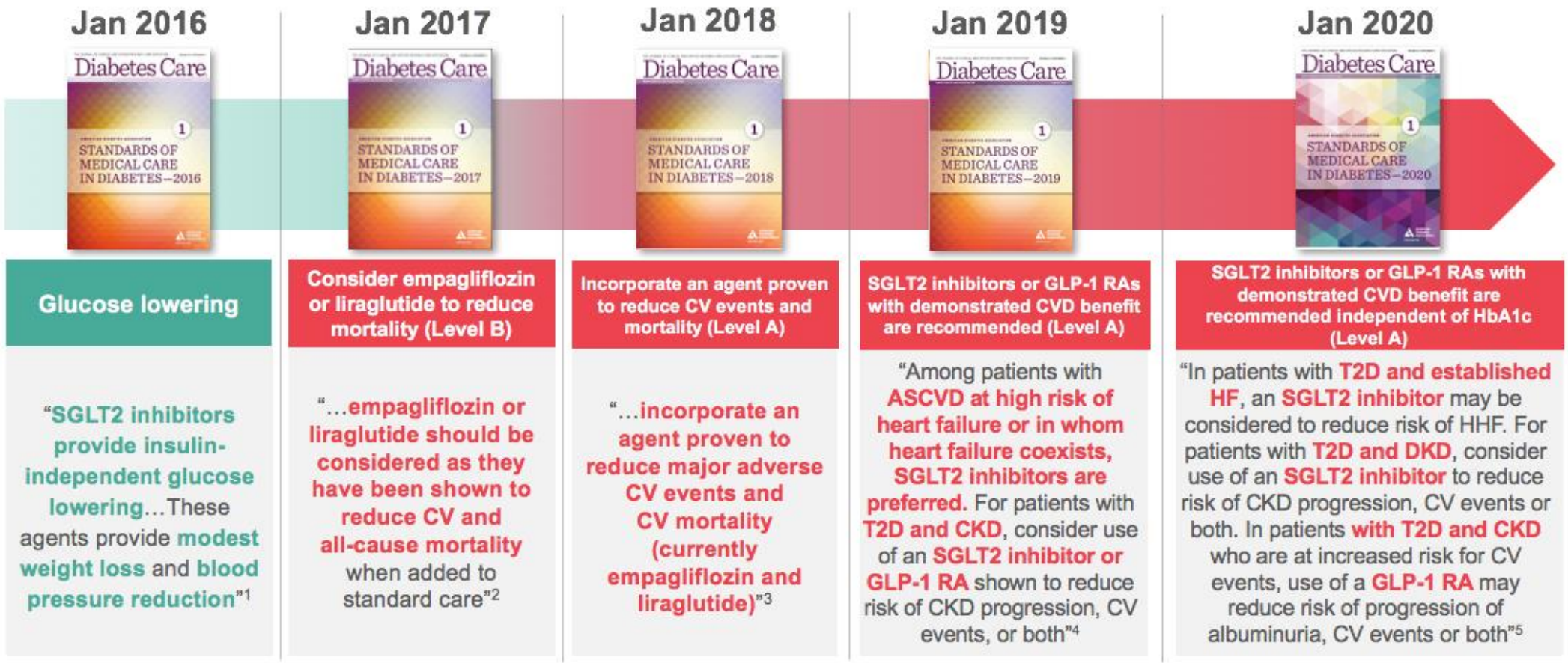
ACS, acute coronary syndrome; AMI, acute myocardial infarction; BP, blood pressure; CVD, cardiovascular disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; PAD, peripheral artery disease; SCORE, systematic coronary risk estimation; TIA, transient ischaemic attack; T1D, type 1 diabetes

Piepoli MF *et al. Eur Heart J* 2016;37:2315

Diabetes is a major CV risk factor
ESC Guidelines on diabetes, pre-diabetes and CV diseases – 2019

The classification of CV risk levels in patients with diabetes and pre-diabetes	
Very high risk	Patients with diabetes **and** established CV disease **Or** other target organ damage† **Or** three or more major risk factors‡ **Or** early-onset T1DM of long duration (>20 years)
High risk	Patients with diabetes duration of ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with diabetes duration <10 years, without other risk factors

ADA guidelines have evolved to recommend SGLT2 inhibitors and GLP-1 RAs with proven CV and kidney benefits



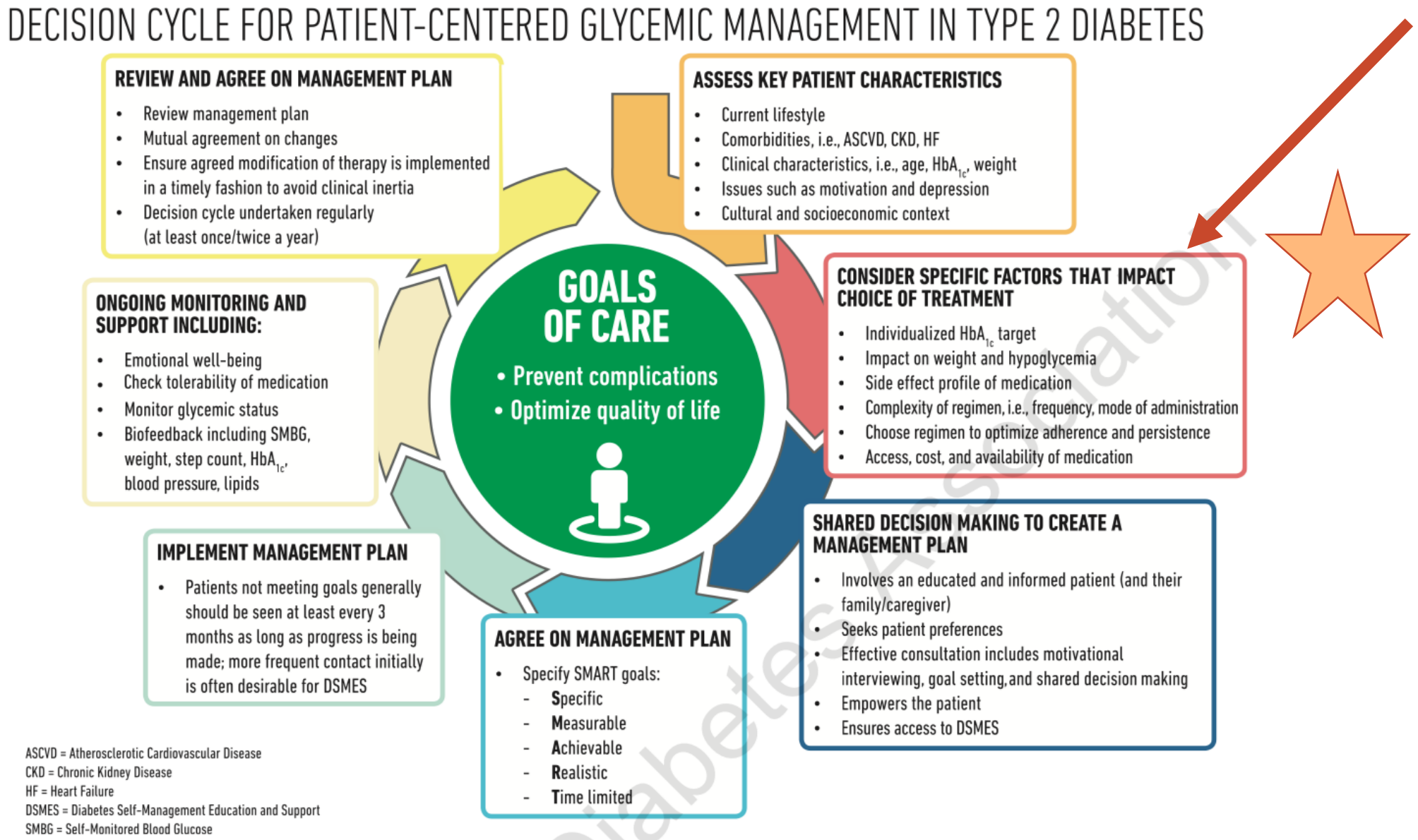


Figure 4.1—Decision cycle for patient-centered glycemic management in type 2 diabetes. Reprinted from Davies et al. (99).

How to treat T2DM in 2021?

ESC/EASD recommendations for the management of blood pressure in patients with diabetes and pre-diabetes

Recommendations	Class[a]	Level[b]
Treatment targets		
Antihypertensive drug treatment is recommended for people with DM when office BP is >140/90 mmHg.[155,178–180]	I	A
It is recommended that patients with hypertension and DM are treated in an individualized manner. The BP goal is to target SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years), the SBP goal is to a range of 130 - 139 mmHg.[155,159,160,181–183]	I	A
It is recommended that target DBP is targeted to <80 mmHg, but not <70 mmHg.[160]	I	C
An on-treatment SBP of <130 mmHg may be considered in patients at particularly high risk of a cerebrovascular event, such as those with a history of stroke.[154–157,173]	IIb	C
Treatment and evaluation		
Lifestyle changes [weight loss if overweight, physical activity, alcohol restriction, sodium restriction, and increased consumption of fruits (e.g. 2–3 servings), vegetables (e.g. 2–3 servings), and low-fat dairy products] are recommended in patients with DM and pre-DM with hypertension.[161–163,166]	I	A
A RAAS blocker (ACEI or ARB) is recommended in the treatment of hypertension in patient with DM, particularly in the presence of microalbuminuria, albuminuria, proteinuria, or LV hypertrophy.[167–170]	I	A
It is recommended that treatment is initiated with a combination of a RAAS blocker with a calcium channel blocker or thiazide/thiazide-like diuretic.[167–171]	I	A
In patients with IFG or IGT, RAAS blockers should be preferred to beta-blockers or diuretics to reduce the risk of new-onset DM.[173–175]	IIa	A
The effects of GLP1-RAs and SGLT2 inhibitors on BP should be considered.	IIa	C
Home BP self-monitoring should be considered in patients with DM on antihypertensive treatments to check that their BP is appropriately controlled.[184]	IIa	C
24 h ABPM should be considered to assess abnormal 24 h BP patterns and adjust antihypertensive treatment.[185]	IIa	C

ABPM = ambulatory blood pressure monitoring; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; DBP = diastolic blood pressure; DM = diabetes mellitus; GLP1-RA = glucagon-like peptide-1 receptor agonist; IFG = impaired fasting glycaemia; IGT = impaired glucose tolerance; LV = left ventricular; RAAS = renin–angiotensin–aldosterone system; SBP = systolic blood pressure; SGLT2 = sodium-glucose co-transporter 2.

[a]Class of recommendation.

[b]Level of evidence.

ESC/EASD recommendations for the management of dyslipidaemia in patients with diabetes and pre-diabetes

Recommendations	Class[a]	Level[b]
Targets		
In patients with T2DM at moderate CV risk,[c] an LDL-C target of <2.5 mmol/L (<100 mg/dL) is recommended.[210–212]	I	A
In patients with T2DM at high CV risk,[c] an LDL-C target of <1.8 mmol/L (<70 mg/dL) or an LDL-C reduction of at least 50% is recommended.[d] [210–212]	I	A
In patients with T2DM at very high CV risk,[c] an LDL-C target of <1.4 mmol/L (<55 mg/dL) or an LDL-C reduction of at least 50% is recommended.[d] [200,201,210]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV-risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV-risk patients, is recommended.[d,213,214]	I	B
Treatment		
Statins are recommended as the first-choice lipid-lowering treatment in patients with DM and high LDL-C levels: administration of statins is defined based on the CV risk profile of the patient[c] and the recommended LDL-C (or non-HDL-C) target levels.[187]	I	A
If the target LDL-C is not reached, combination therapy with ezetimibe is recommended.[200,201]	I	B
In patients at very high CV risk, with persistent high LDL-C despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance, a PCSK9 inhibitor is recommended.[203–206]	I	A
Lifestyle intervention (with a focus on weight reduction, and decreased consumption of fast-absorbed carbohydrates and alcohol) and fibrates should be considered in patients with low HDL-C and high triglyceride levels.[191,207]	IIa	B
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
Statins should be considered in patients with T1DM at high CV risk,[c] irrespective of the baseline LDL-C level.[187,215]	IIa	A
Statins may be considered in asymptomatic patients with T1DM beyond the age of 30 years.	IIb	C
Statins are not recommended in women of childbearing potential.[189,190]	III	A

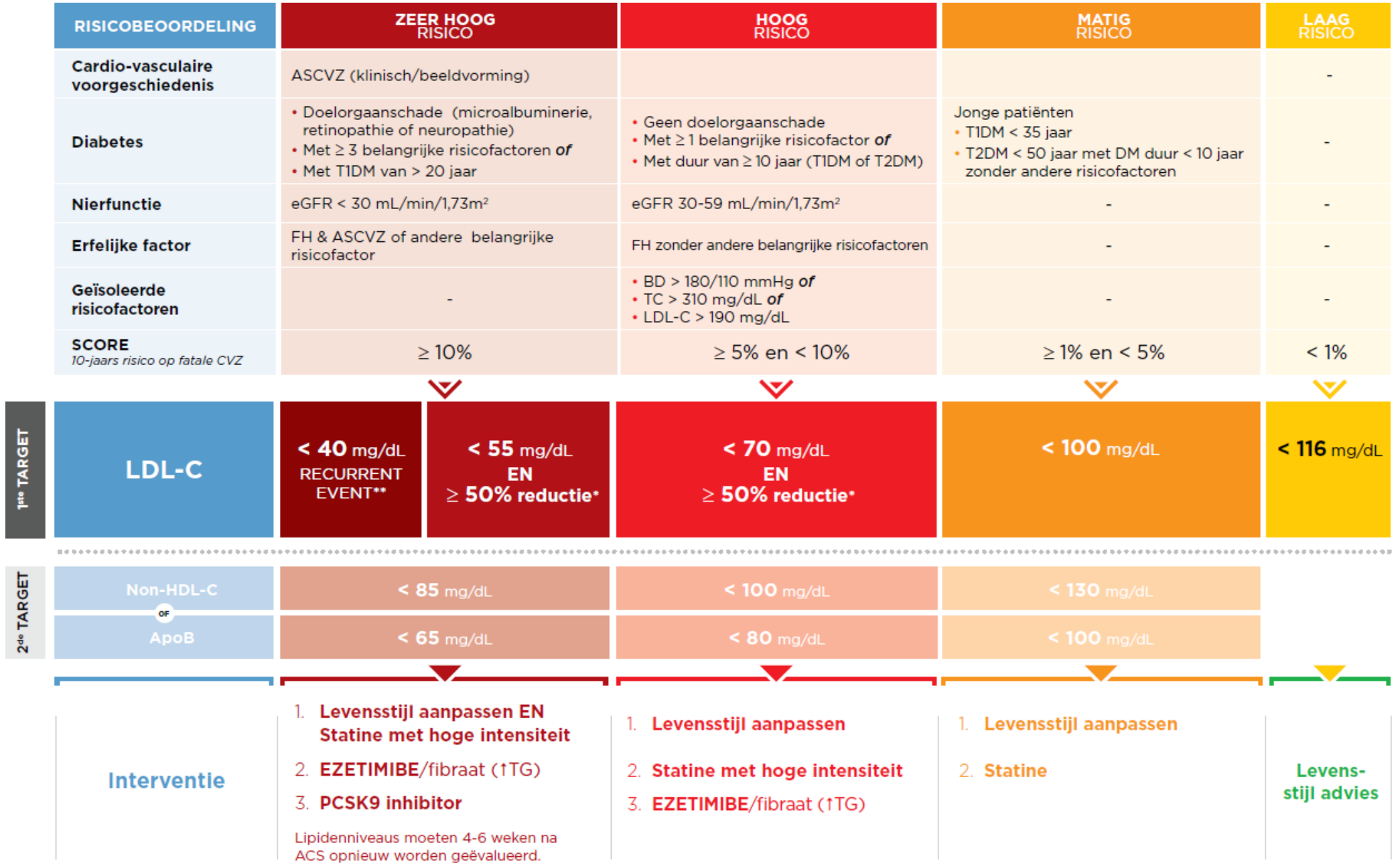
CV = cardiovascular; DM = diabetes mellitus; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

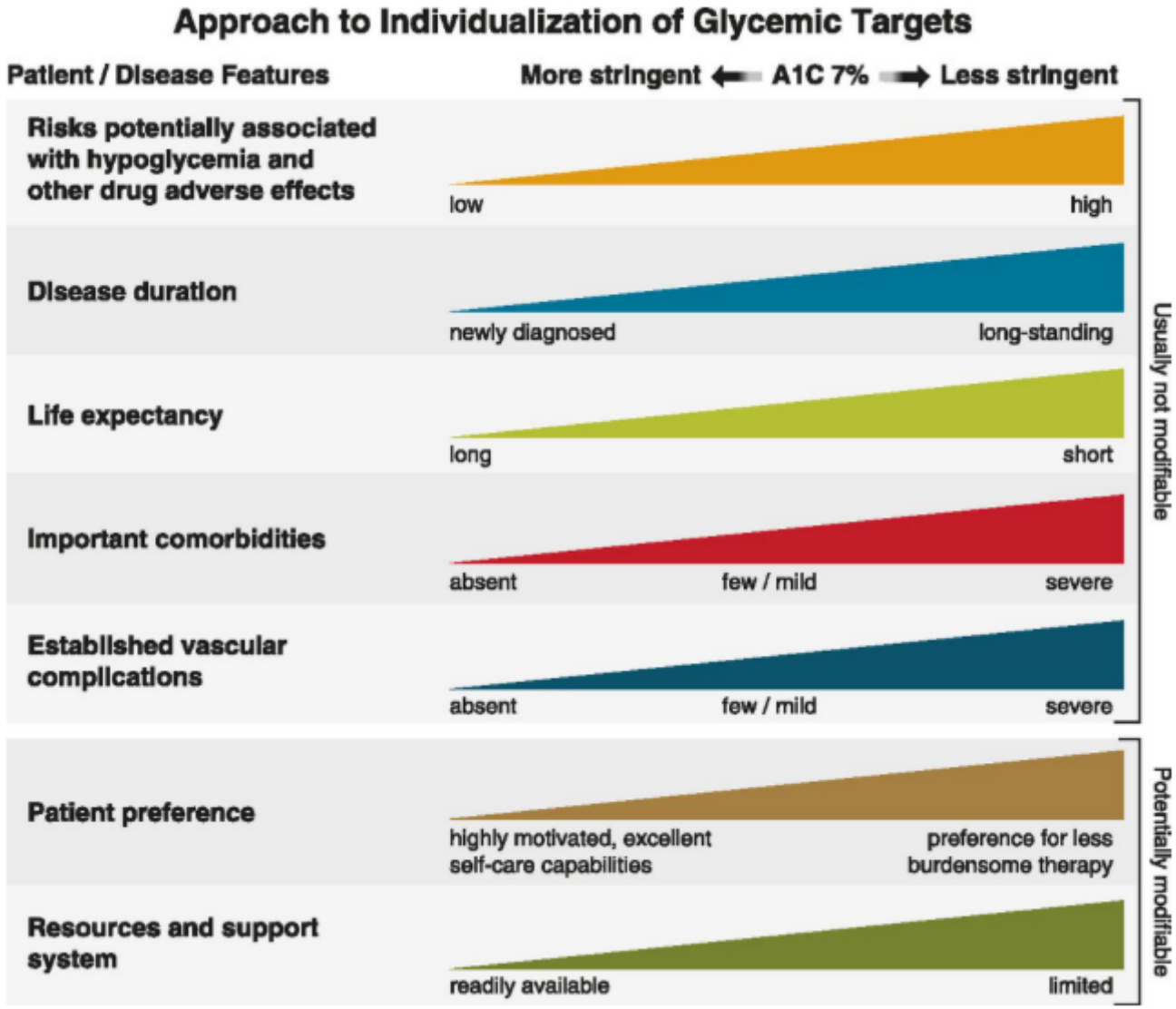
[c]See *Table 7*.

[d]See the 2019 ESC/EAS Guidelines for the management of dyslipidaemias for non-HDL-C and apolipoprotein B targets.



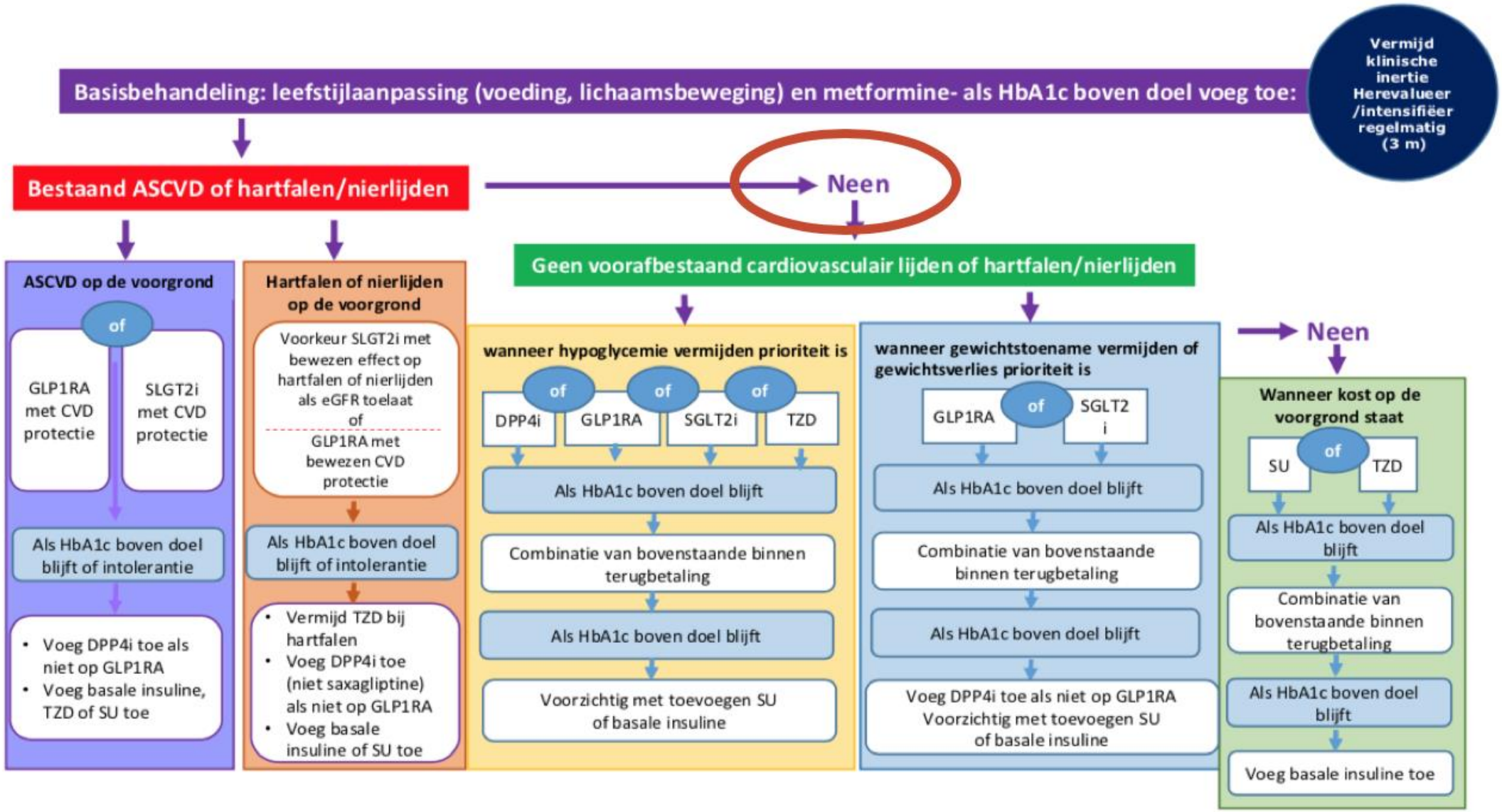
DESCAMPS OS. ET AL . LOUVAIN MED 2020 SEPTEMBRE ; 139 (07) : 396-404

Individualization of glycaemic targets



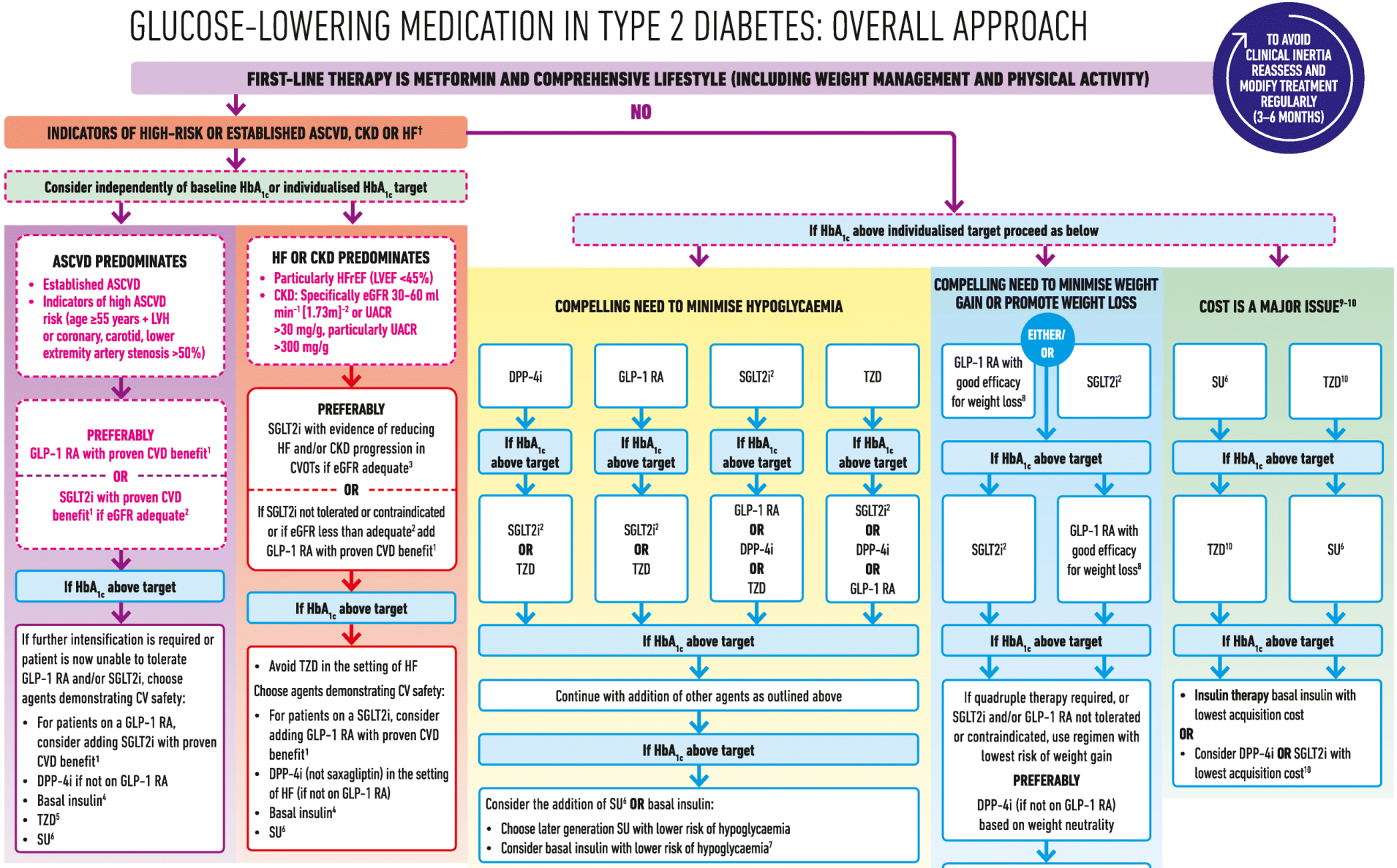
ADA STANDARDS OF MEDICAL CARE IN DIABETES. DIABETES CARE 2021 JAN; 44(SUPPLEMENT 1): S73-S84.

Glucoseverlagende medicatie bij type 2 diabetes: globale aanpak



ADA-EASD GUIDELINE. MATHIEU C, ET AL. VTD 2018

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



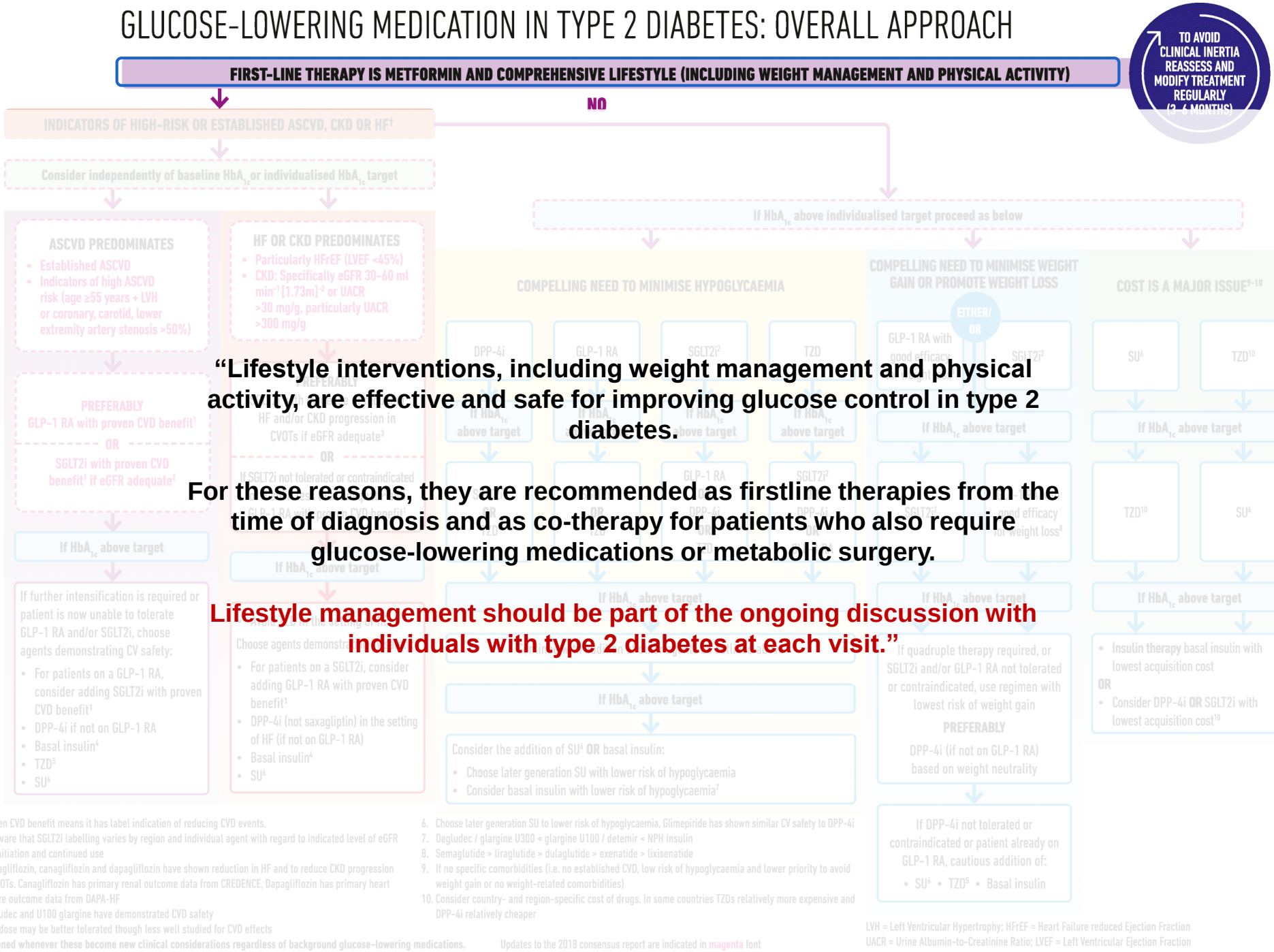
1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE, Dapagliflozin has primary heart failure outcome data from DAPA-HF
4. Degludec and 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 to lower risk of hypoglycaemia, Glimepiride has shown similar CV safety to DPP-4i
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 hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† **Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.**

Updates to the 2018 consensus report are indicated in magenta font

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Buse JB et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetologia. 2020;63(2):221-228



“Lifestyle interventions, including weight management and physical activity, are effective and safe for improving glucose control in type 2 diabetes.

For these reasons, they are recommended as firstline therapies from the time of diagnosis and as co-therapy for patients who also require glucose-lowering medications or metabolic surgery.

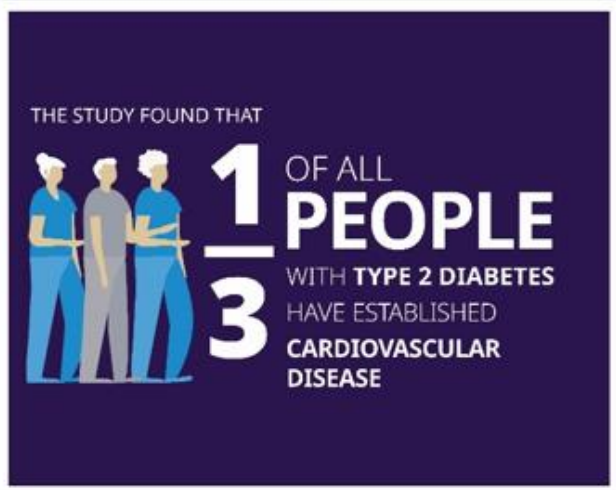
Lifestyle management should be part of the ongoing discussion with individuals with type 2 diabetes at each visit.”

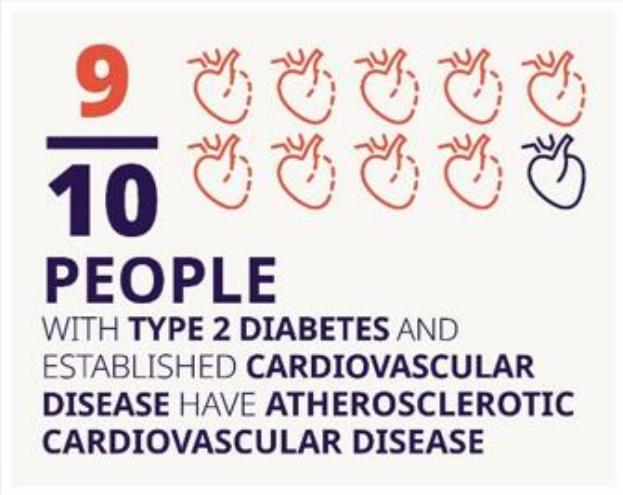
Buse JB et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetologia. 2020;63(2):221-228

Fysieke activiteit -- ADA guidelines 2021

- Most adults with diabetes mellitus should engage **in 150 min or more of moderate- to vigorous-intensity aerobic acivity per week, spread over at least 3 days/week**, with no more than 2 consecutive days without activity.
- Adults and particularly those with type 2 diabetes, should **decrease the amount of time spent in daily sedentary behavior.**
- **Prolonged sitting should be interrupted every 30 min for blood glucose benefits**.
- **Flexibility training and balance training** are recommended 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance.
- Examples include walking, yoga, housework, gardening, swimming, and dancing.

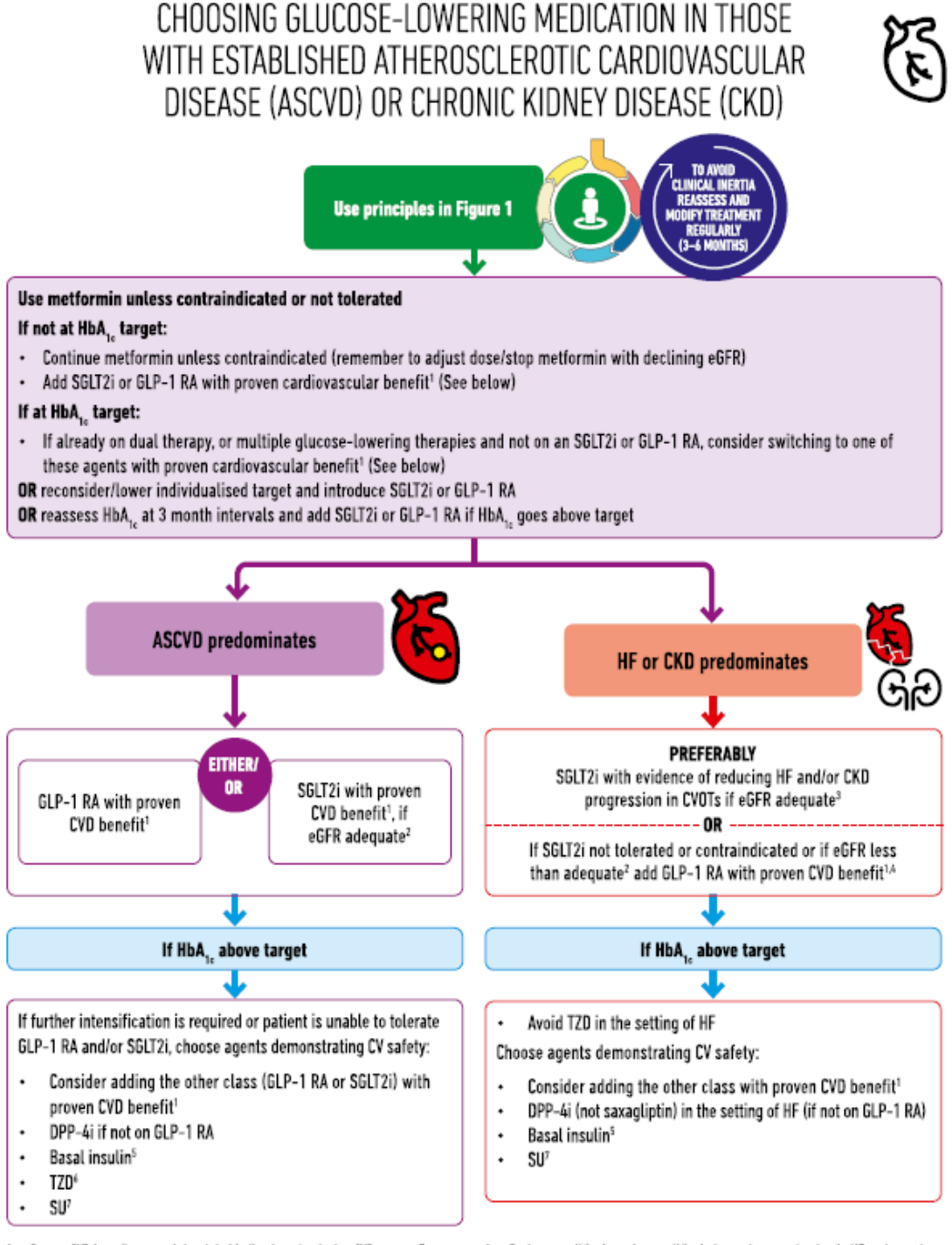
The CAPTURE study highlights that while the prevalence of ASCVD within the T2D population is high, the vast majority are not being managed with treatments that are proven to reduce the risk of life-altering cardiovascular events



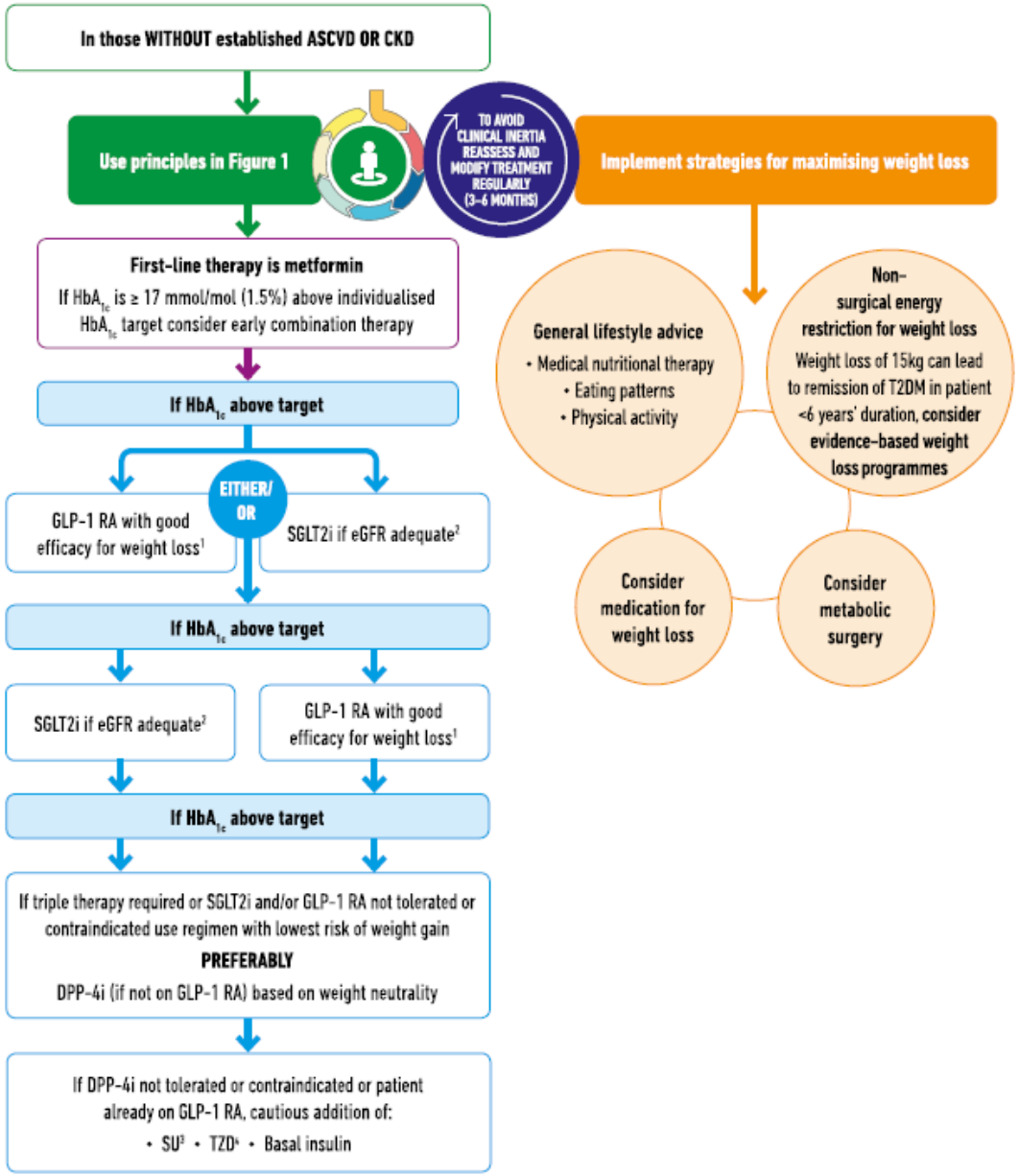


MOSENZON O, ALGUWAIHES A, ARENAS LEON J.L., ET AL. CAPTURE: A CROSS-SECTIONAL STUDY OF THE CONTEMPORARY (2019) PREVALENCE OF CARDIOVASCULAR DISEASE IN ADULTS WITH TYPE 2 DIABETES ACROSS 13 COUNTRIES. ABSTRACT 158. PRESENTED AT THE 56TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION OF THE STUDY OF DIABETES, MACROVASCULAR COMPLICATIONS AND BEYOND, 10:15 CEST ON 24 SEPTEMBER 2020

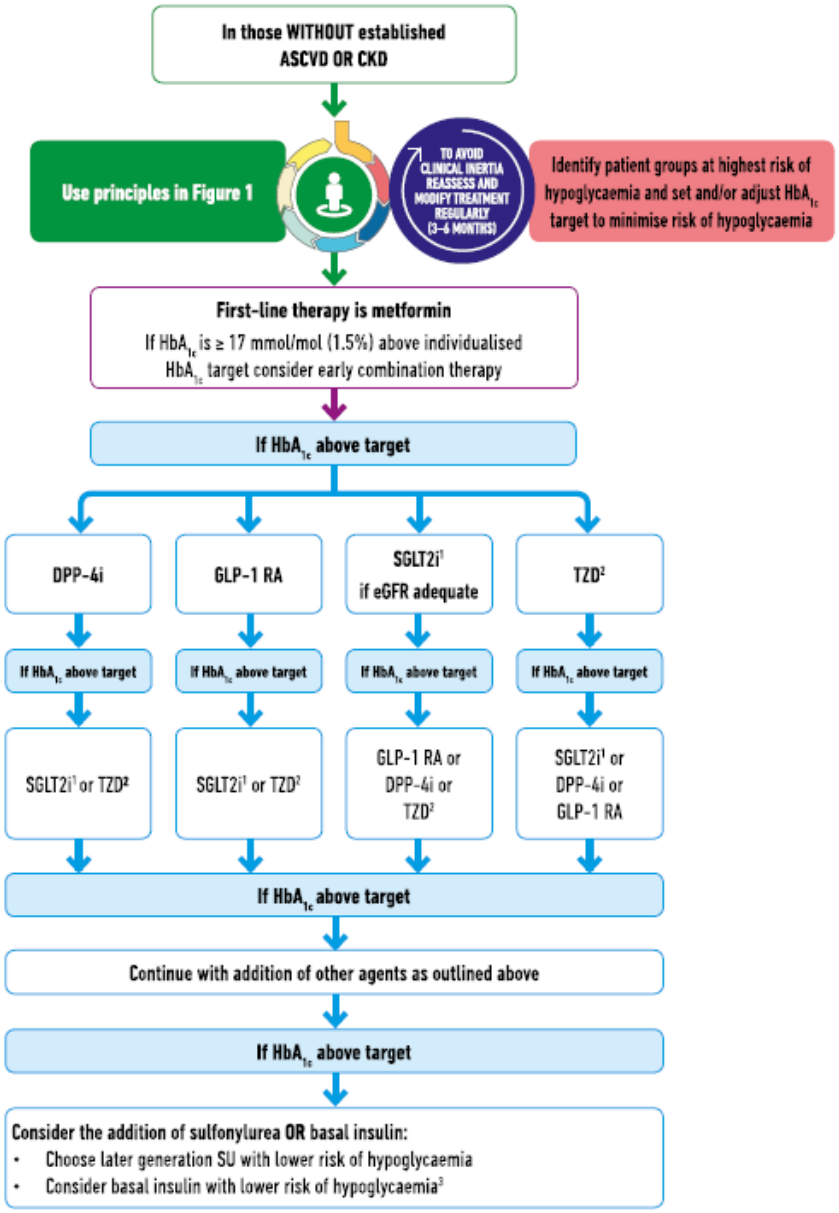
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



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

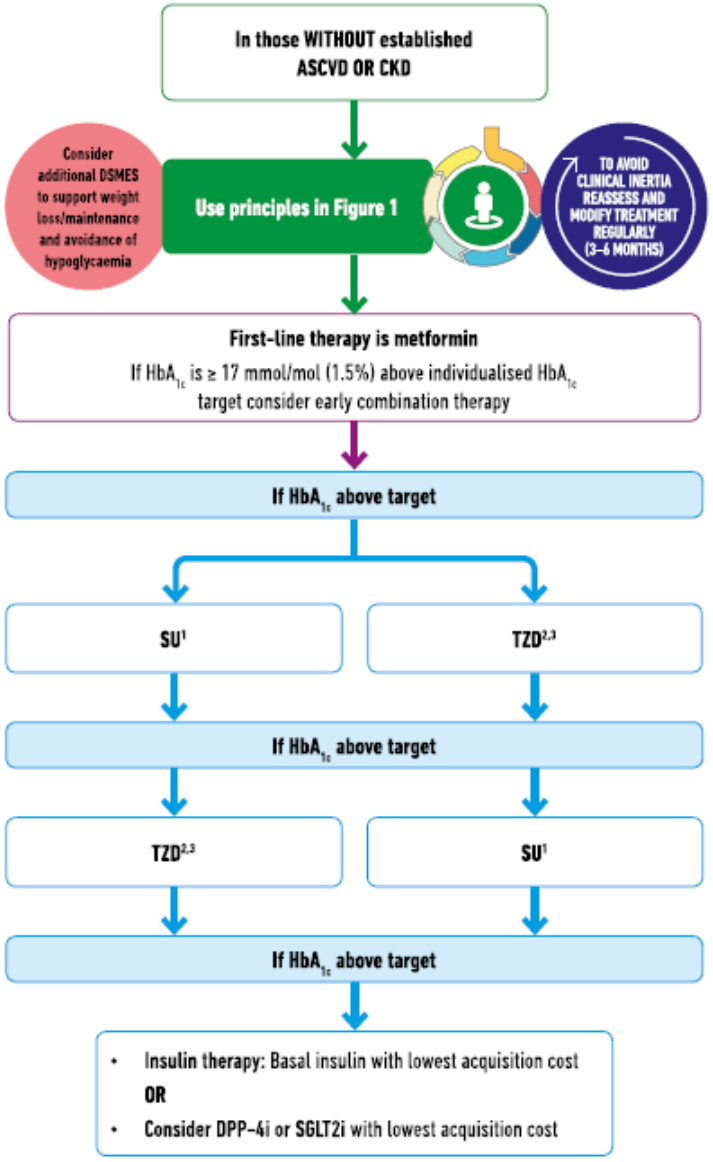


CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



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

CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE



How to treat T2DM in 2021?
What in common practice…

- Metformine
- Sulfonylureum
- Glinide
- Glitazone
- Gliptine = DPP4-inhitor
- Gliflozine = SGLT2-inhibitor
- GLP-1 analoog
- Insuline

- … and combinations

How to treat T2DM in 2021?
-- Are TZDs, SU or insulin so bad?

- Thiazolidinediones
  - Only pioglitazone available
    - + : insulin sensitizing, maybe(?) useful in NAFLD
    - - : might cause mild weight gain, fluid retention, fractures
- Sulfonylurea
  - Old workhorses; considered CV safe
    - + : experience, price
  - - : hypoglycemia’s, weight gain

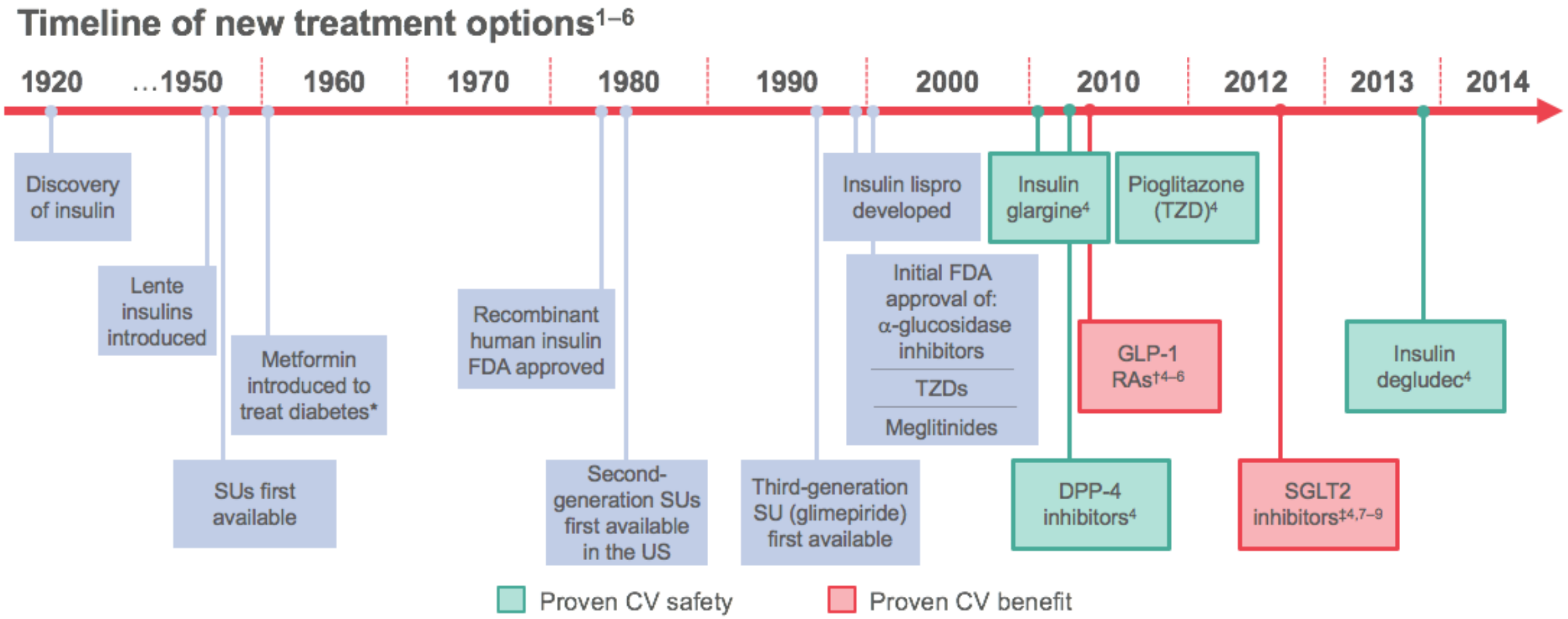
How to treat T2DM in 2021?
Are TZDs, SU or insulin so bad?!

- Insulin
  - Old workhorses; considered CV safe
    - + : experience, universally effective
    - - : hypoglycemia’s, weight gain, injections
- Variable cost
- ~~Probably~~ For sure the drug with the most impact in the history of endocrinology!

➔ There’s a whole arsenal to treat patients with T2DM

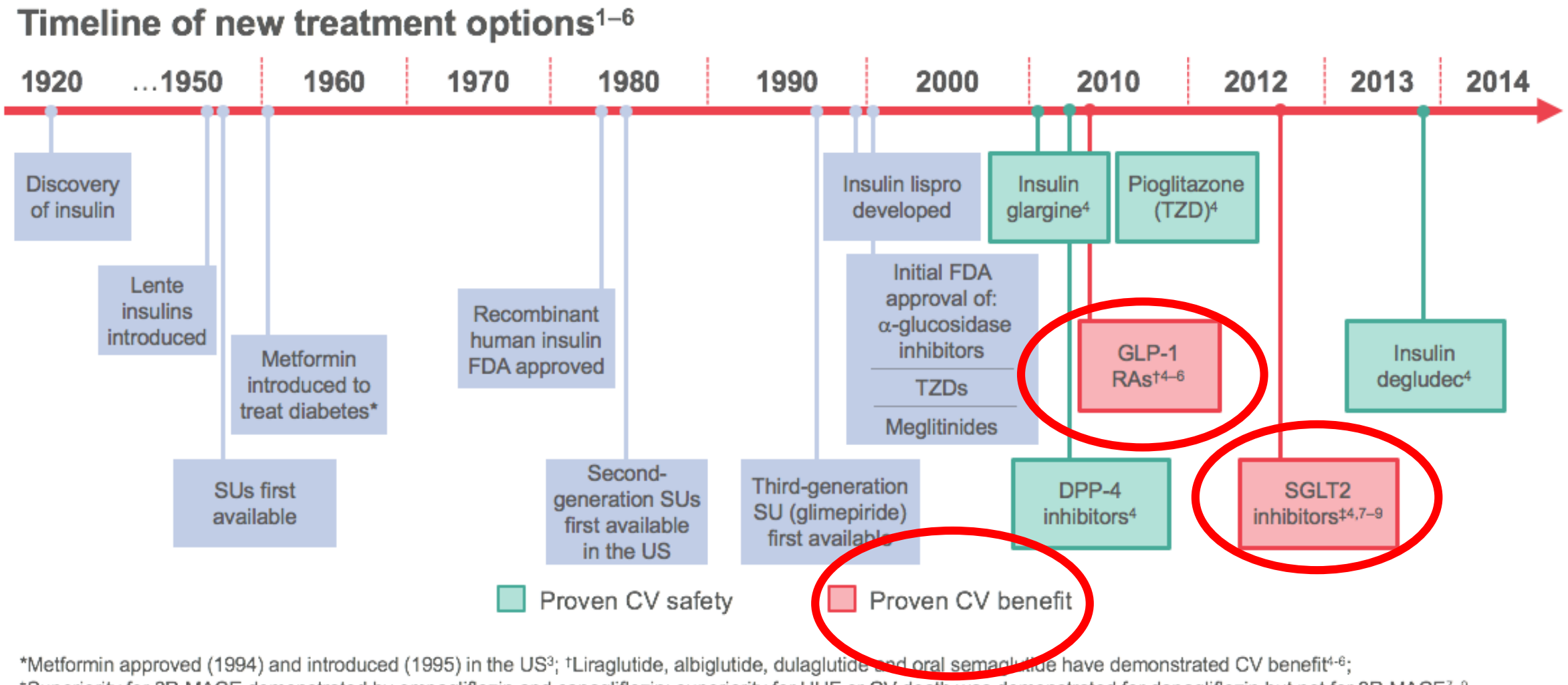
- Early diagnosis & treatment of T2DM still a major challenge!
- Impact of lifestyle interventions not to be underestimated
- 1st line: Metformin! Metformin! Metformin!
- 2nd line: you can choose
  - CV- and renal benefits of SGLT2-inhibitors and GLP-1 analogs
  - Cost is always an issue → SU’s, DPP4-inhibitors, and insulin wisely
- T2DM is a progressive disease: multidrug treatment will probably be needed

Some glucose-lowering therapies now show CV benefit as well as CV safety



*Metformin approved (1994) and introduced (1995) in the US[3]; †Liraglutide, albiglutide, dulaglutide and oral semaglutide have demonstrated CV benefit[4-6]; ‡Superiority for 3P-MACE demonstrated by empagliflozin and canagliflozin; superiority for HHF or CV death was demonstrated for dapagliflozin but not for 3P-MACE[7–9]
HHF, hospitalisation for heart failure
See slide notes for full list of references

Some glucose-lowering therapies now show CV benefit as well as CV safety



*Metformin approved (1994) and introduced (1995) in the US[3]; †Liraglutide, albiglutide, dulaglutide and oral semaglutide have demonstrated CV benefit[4-6];
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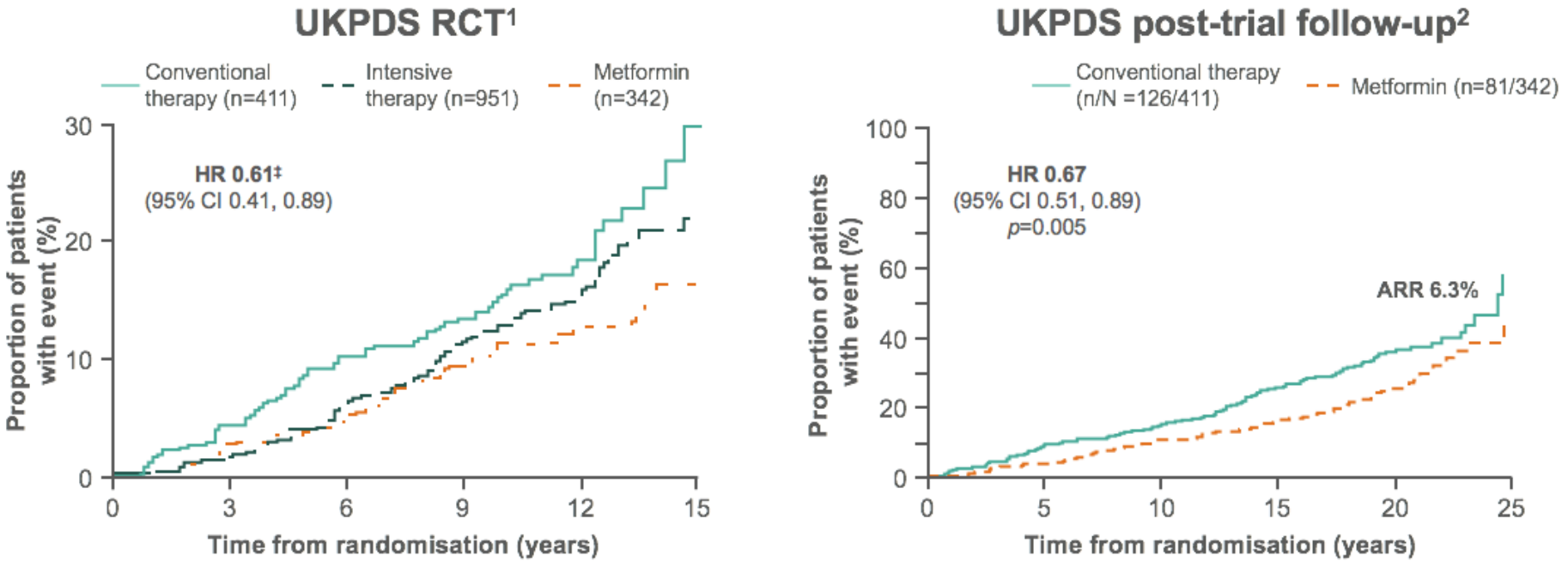
HHF, hospitalisation for heart failure
See slide notes for full list of references

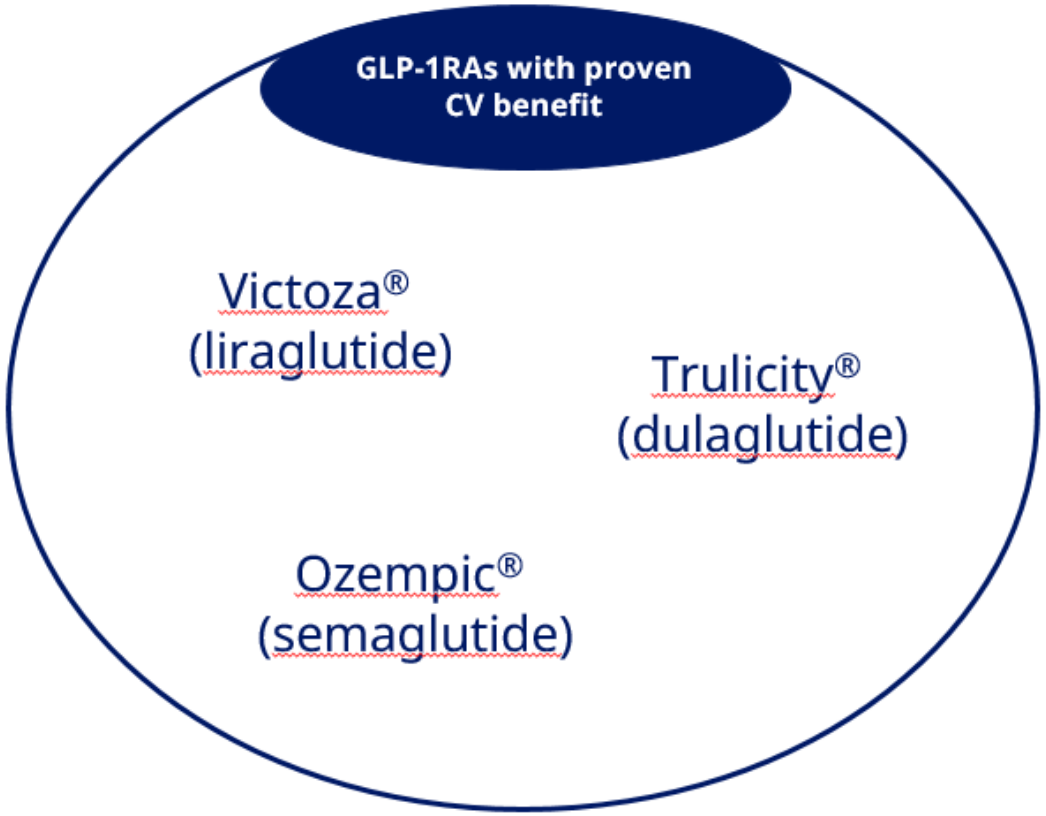
Results from UKPDS 34 show some evidence of CV benefit with metformin

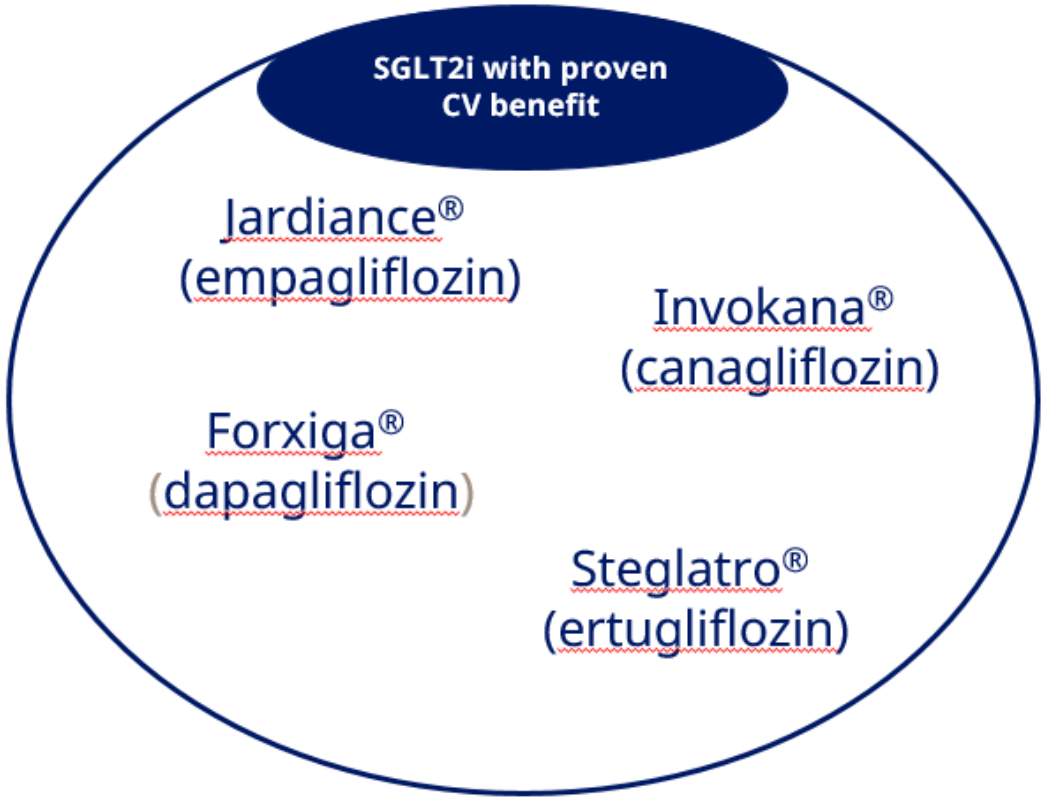
A reduced risk of MI with metformin versus conventional therapy* was maintained at long-term follow-up in overweight† patients with T2D[1,2]



*Conventional therapy was mainly diet alone; †>120% ideal body weight; ‡Metformin vs conventional therapy
ARR, absolute risk reduction; RCT, randomised controlled trial
1. UKPDS 34. *Lancet* 1998;352:854; 2. Holman RR *et al. N Engl J Med* 2008;359:1577

Overview of antidiabetic drugs with proven CV benefit on the Belgian market

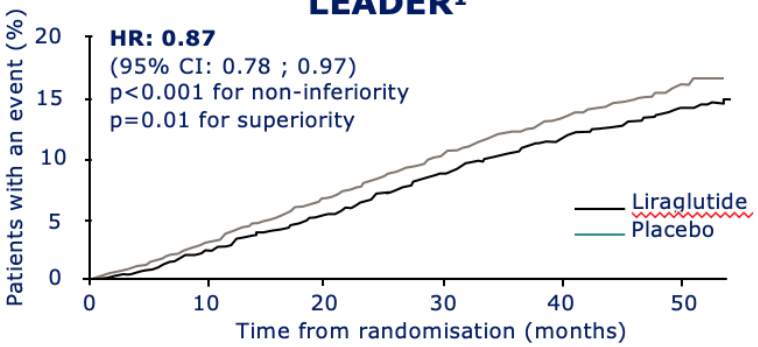




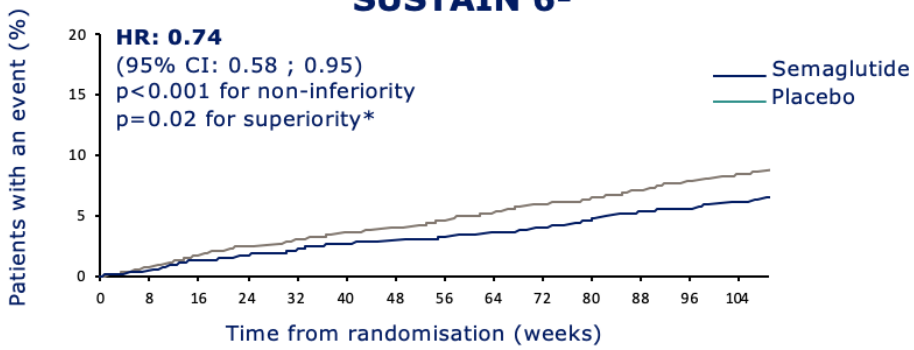
Human GLP-1 analogue CVOTs: primary MACE outcomes

CV death, non-fatal MI or non-fatal ischaemic stroke

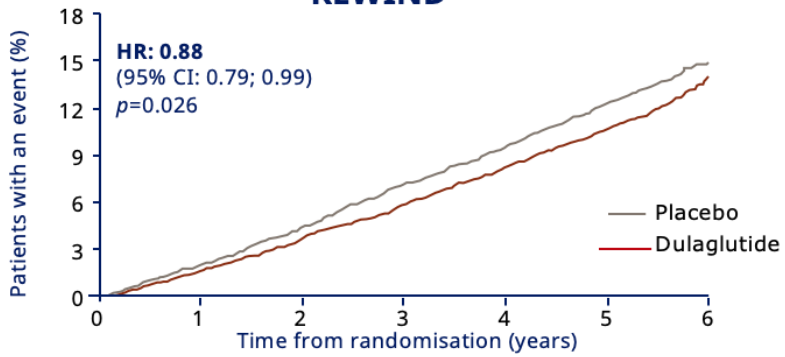
LEADER[1]



SUSTAIN 6[2]



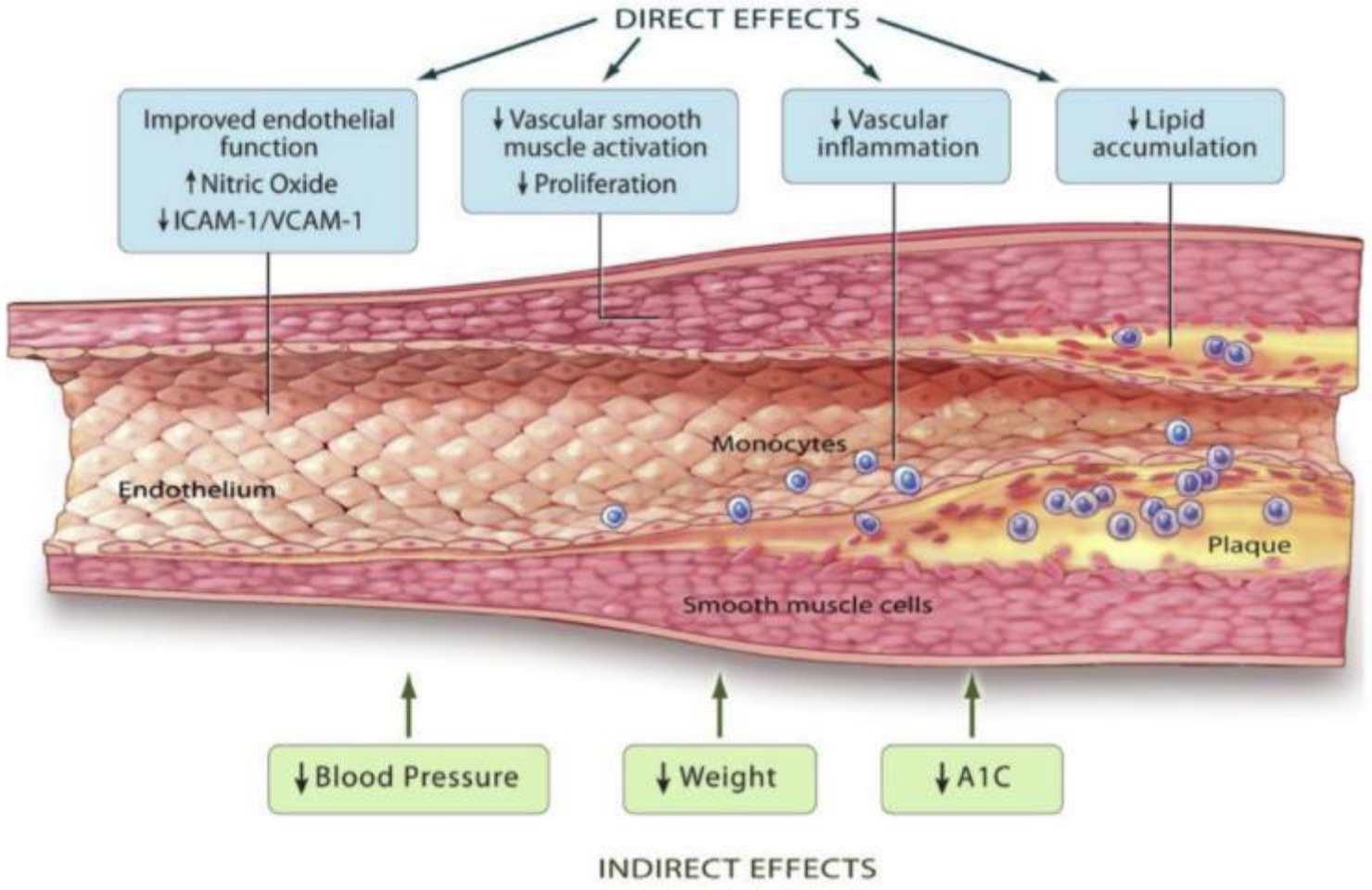
REWIND[3]



*SUPERIORITY WAS NOT PRESPECIFIED. CI, CONFIDENCE INTERVAL; CV, CARDIOVASCULAR; CVOT, CARDIOVASCULAR OUTCOME TRIAL; GLP-1RA, GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST; HR, HAZARD RATIO; MACE: MAJOR ADVERSE CARDIOVASCULAR EVENTS; MI, MYOCARDIAL INFARCTION

1. MARSO SP ET AL. *N ENGL J MED* 2016;375:311–322; 2. MARSO SP ET AL. *N ENGL J MED* 2016;375:1834–1844; 3. GERSTEIN HC ET AL. LANCET 2019;394:121–130

Mechanisms whereby GLP-1 analogues modify the risk of cardiovascular outcomes

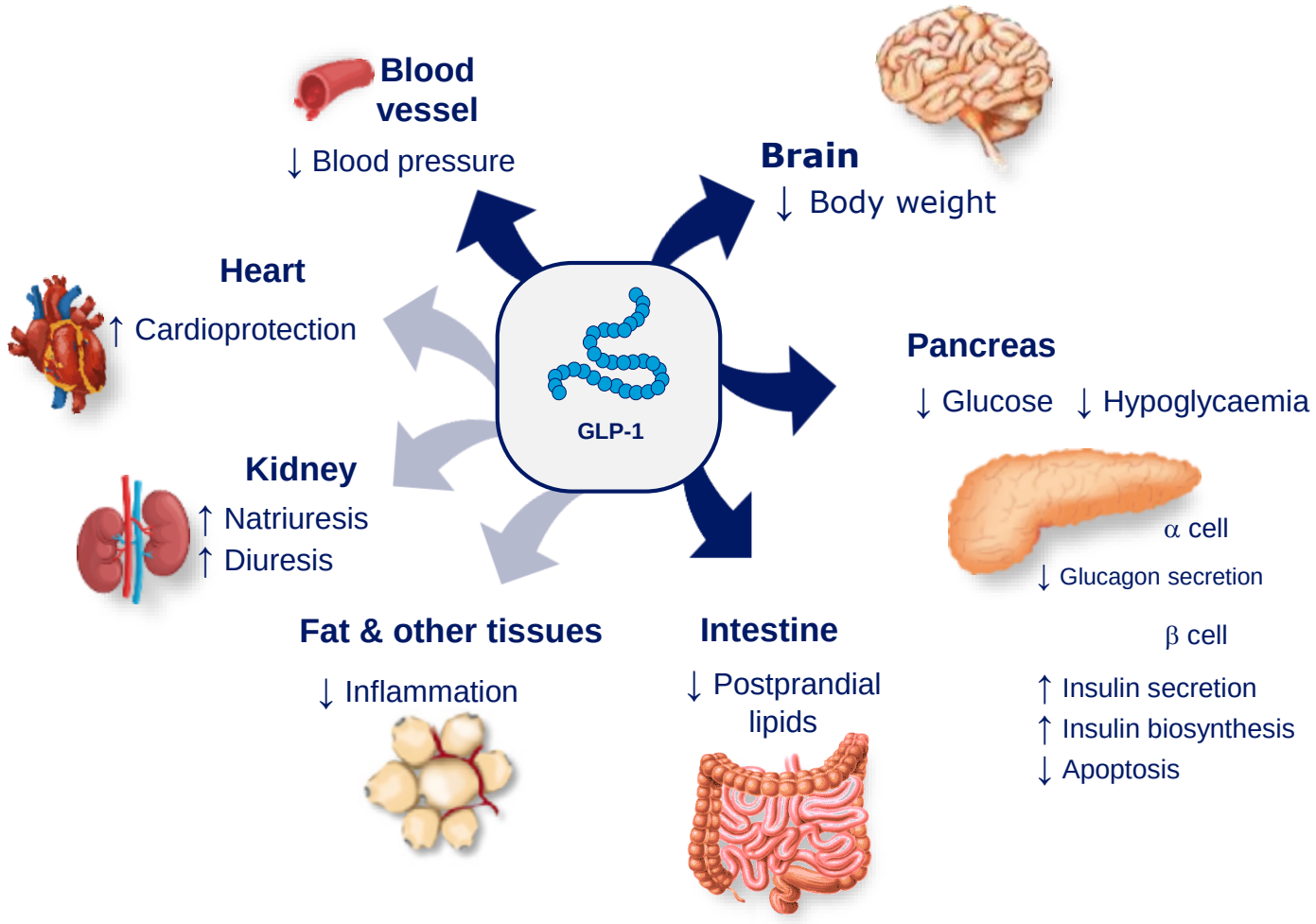


Impact on atherosclerotic / ischemic events

Adapted from: Sharma A, Verma S. *Can J Diabetes*. 2020;44(1):93-102
A1C, glycated hemoglobin; ICAM-1, intercellular adhesionmolecule 1; VCAM-1, vascular cell adhesion molecule 1

Pleiotropic actions of GLP-1 analogues

Effects on metabolic CV risk factors

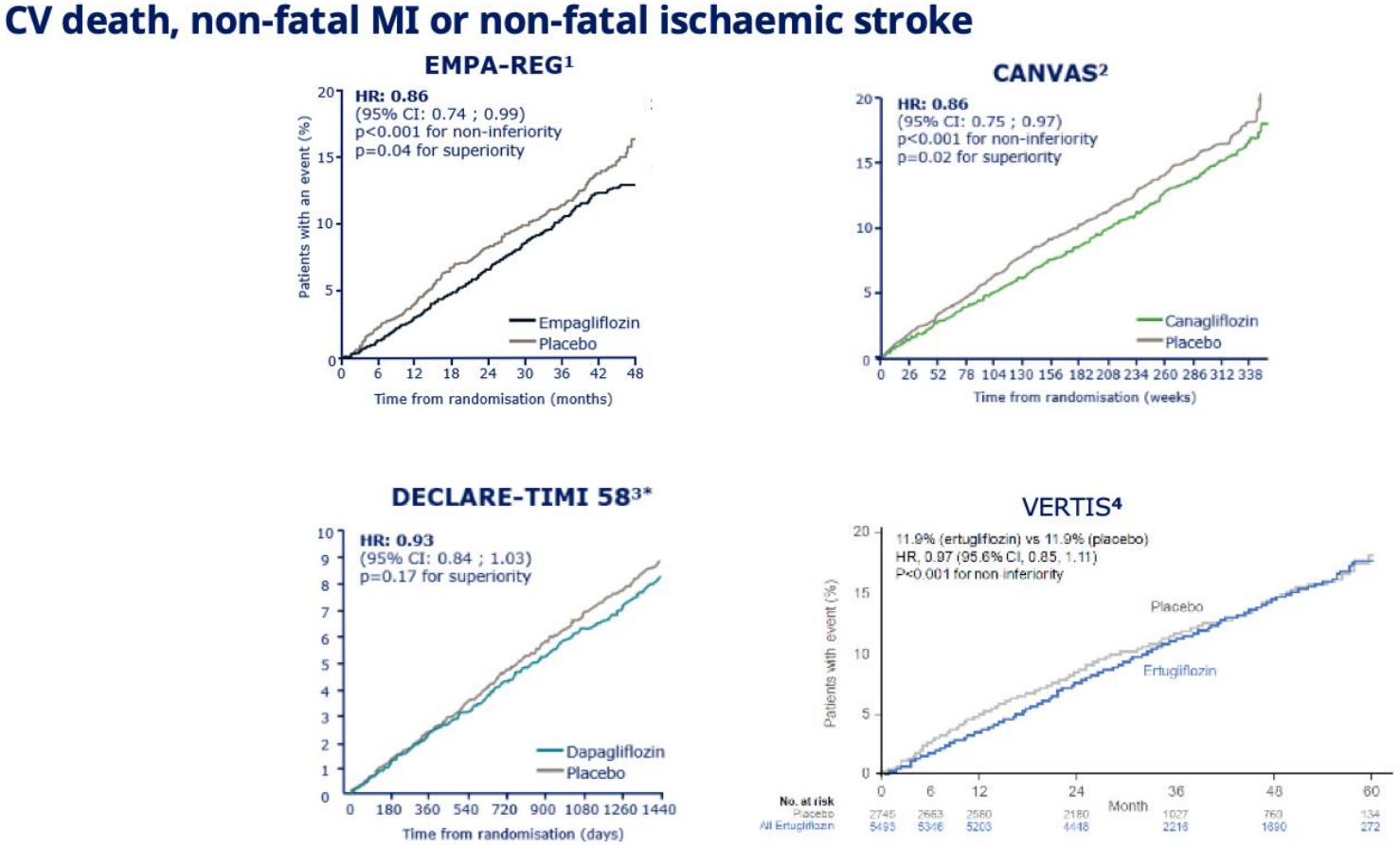


- ↓ Weight
- ↓ Glucose
- ↓ Hypertension
- ↓ Dyslipidaemia

CV, cardiovascular. Dark blue arrows indicate main MoA of GLP-1 analogues.
Adapted from: Drucker DJ. *Cell Metab* 2016;24:15–30

SGLT-2 inhibitor CVOTs: primary MACE outcomes

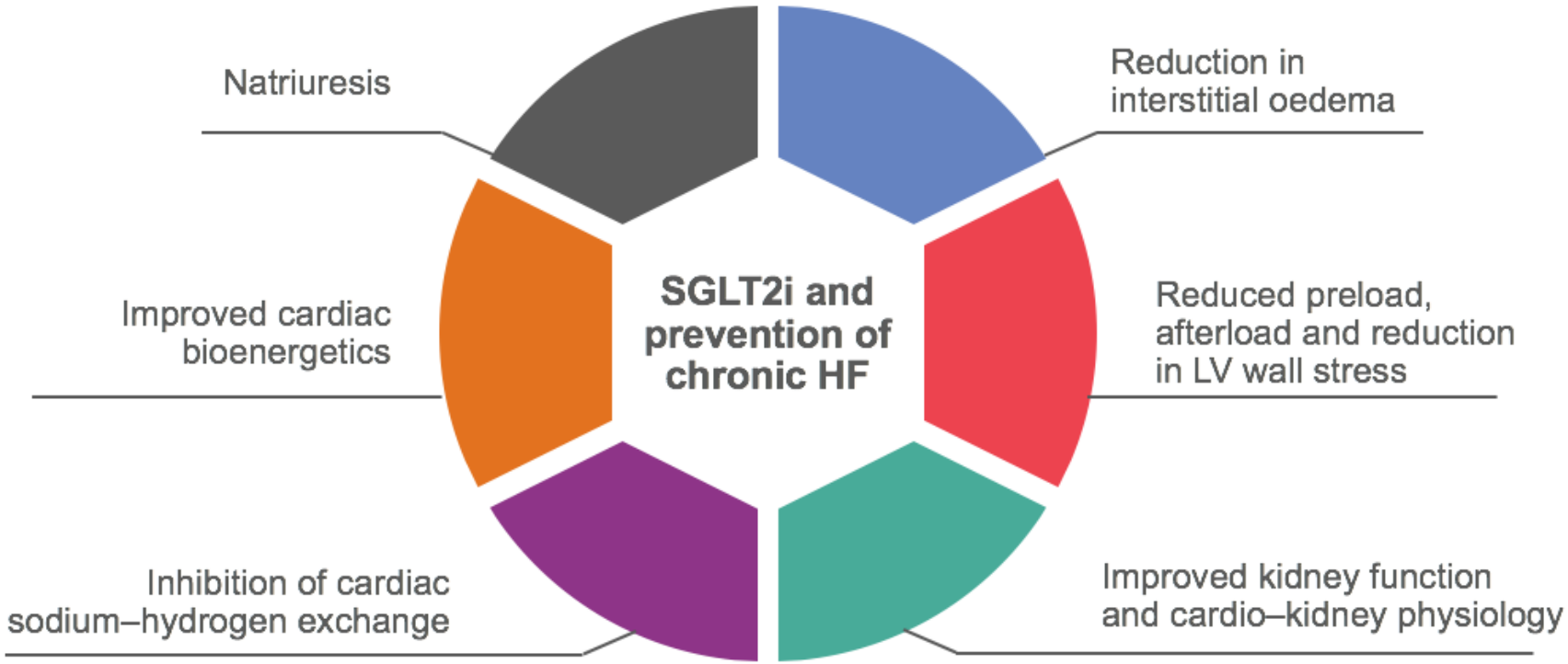
CV death, non-fatal MI or non-fatal ischaemic stroke



*THE PRIMARY COMPOSITE OUTCOME INCLUDED FATAL AND NON-FATAL STROKE AND MI. CI, CONFIDENCE INTERVAL; CV, CARDIOVASCULAR; CVOT, CARDIOVASCULAR OUTCOMES TRIAL; HR, HAZARD RATIO; MACE, MAJOR ADVERSE CARDIOVASCULAR EVENT; MI, MYOCARDIAL INFARCTION; SGLT-2, SODIUM–GLUCOSE CO-TRANSPORTER-2

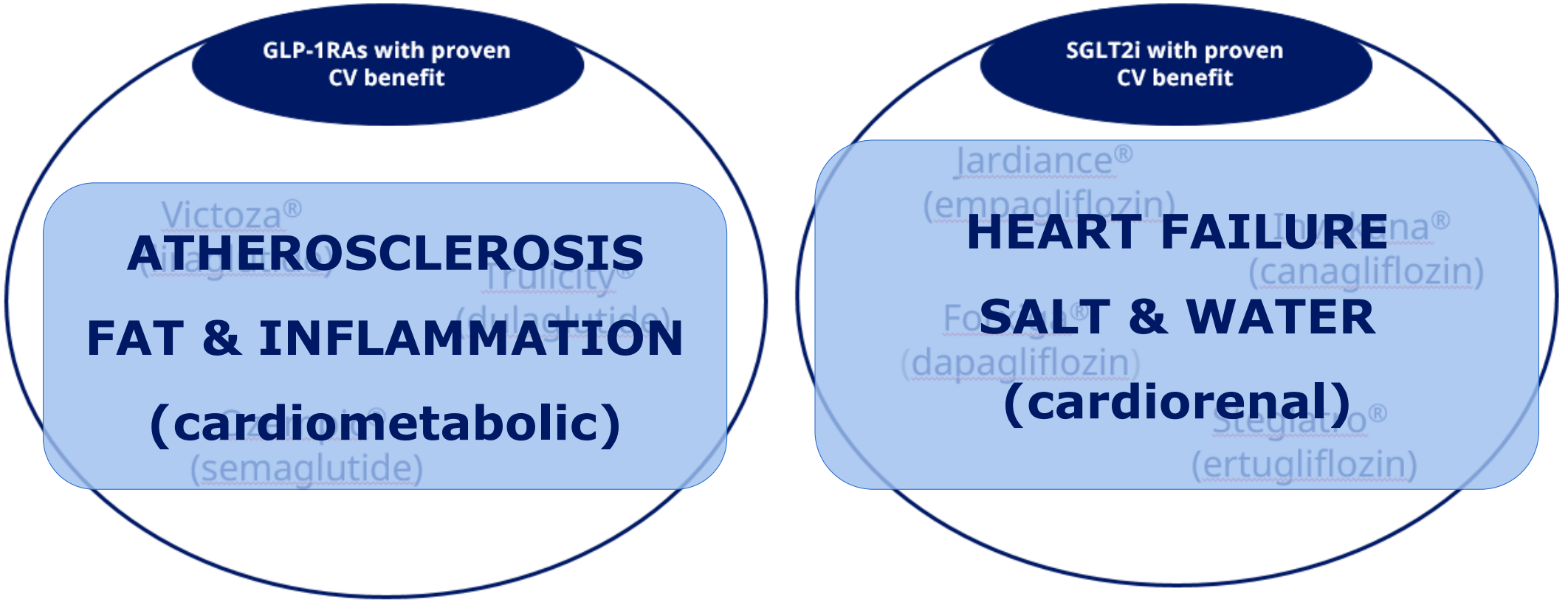
1. ZINMAN B ET AL. *N ENGL J MED* 2015;373:2117–2128; 2. NEAL B ET AL. *N ENGL J MED* 2017;377:644–657; 3. WIVIOTT SD ET AL. *N ENGL J MED* 2019;380:347–357; 4. CANNON CP ET AL. *N ENGL J MED* 2020 DOI: 10.1056/NEJMOA2004967

Many potential mechanisms may contribute to the beneficial effects on heart failure seen with SGLT2 inhibitors



HF, heart failure; LV, left ventricular; SGLT2i, sodium-glucose co-transporter-2 inhibitor
Farkouh ME & Verma S. *J Am Coll Cardiol* 2018;71:2505

Overview of antidiabetic drugs with proven CV benefit on the Belgian market

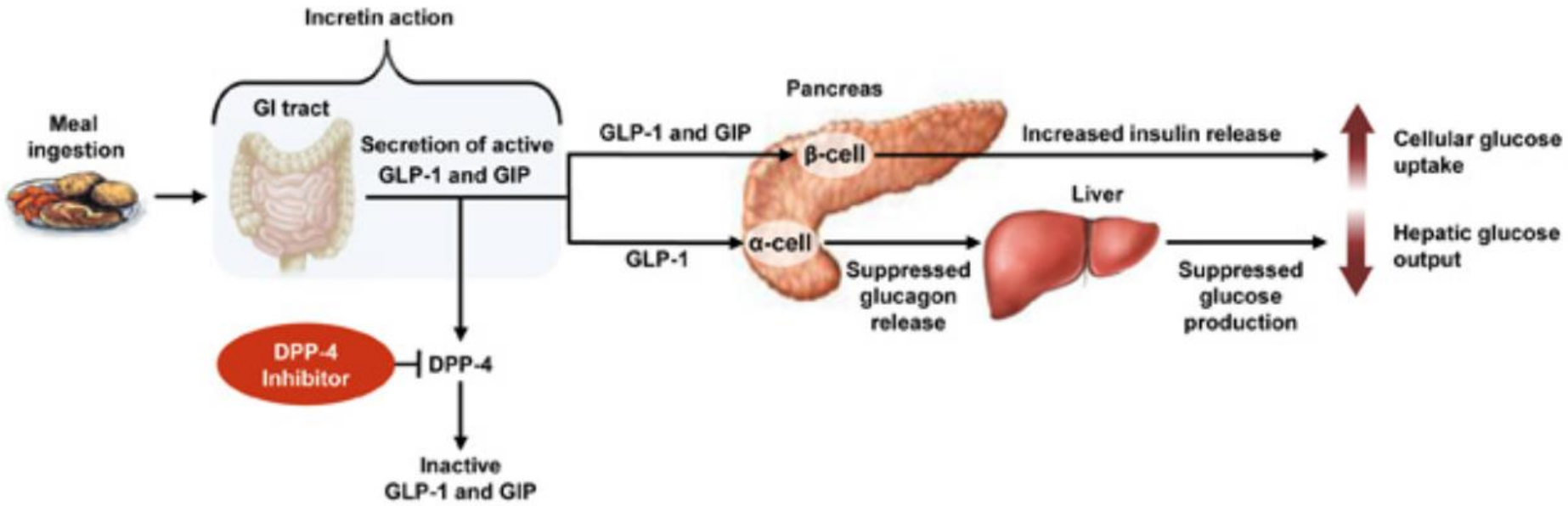


GLP1-analogen vs. SGLT2-inhibitoren

GLP-1RA **(Liragluitde, Semaglutide, Dulaglutide)**	**SGLT-2i** **(Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin)**
Adult T2D, ≥3 months on metformin, HbA1c >7.5%	Adult T2D, ≥3 months on metformin, HbA1c 7-9%
BMI ≥30 kg/m^2	No BMI restriction
eGFR >15 mL/min/1.73m^2	eGFR >60 mL/min/1.73m^2
MoA: anti-atherosclerotic, anti-inflammatory, anti-thrombotic effects	MoA: haemodynamic effect, heart metabolism, direct effects of the heart
Caution in patients with pancreatitis, gastric surgery, or gastroparesis; risk of hypoglycemia if added to SU or insulin Major side effects: GI intolerance	Caution in patients at higher risk for diabetic ketoacidosis; risk of hypoglycemia if added to SU or insulin. Major side effects: lower urinary tract infections; hypovolemia (in elderly patients, if added to diuretics)
Injection	Oral

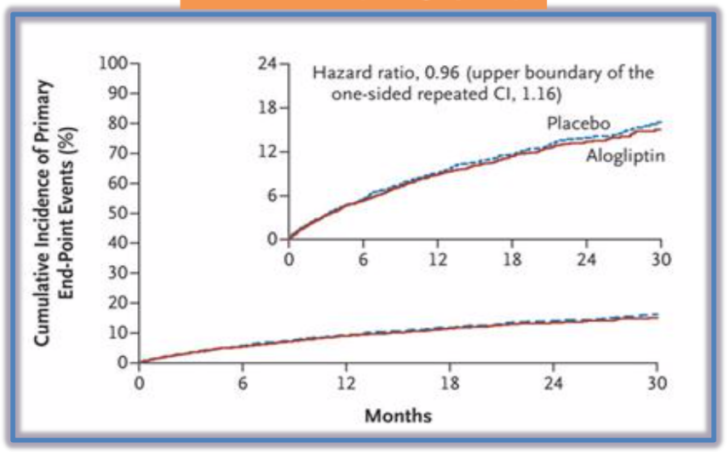
DPP4-inhibitoren (gliptines)

- Insulinesynthese ↑
- Glucagonsecretie ↓
- Glucose afhankelijke insulinesecretie ↑
- Maaglediging ↓
- Eetlust ↓

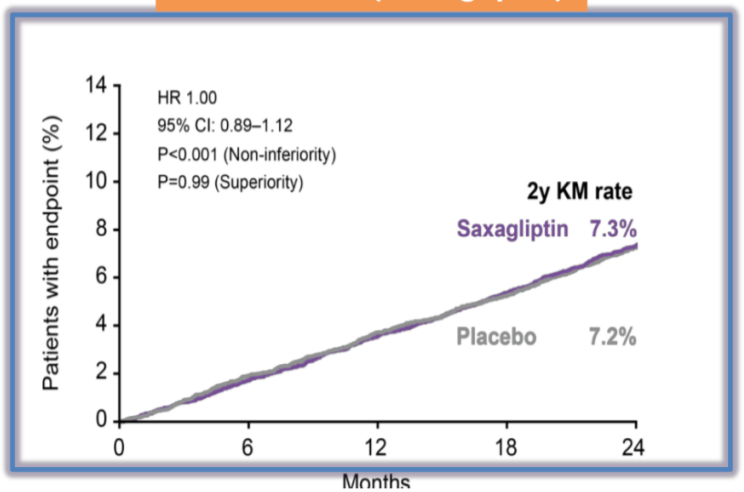


DPPA-inhitor and CV risk: safe

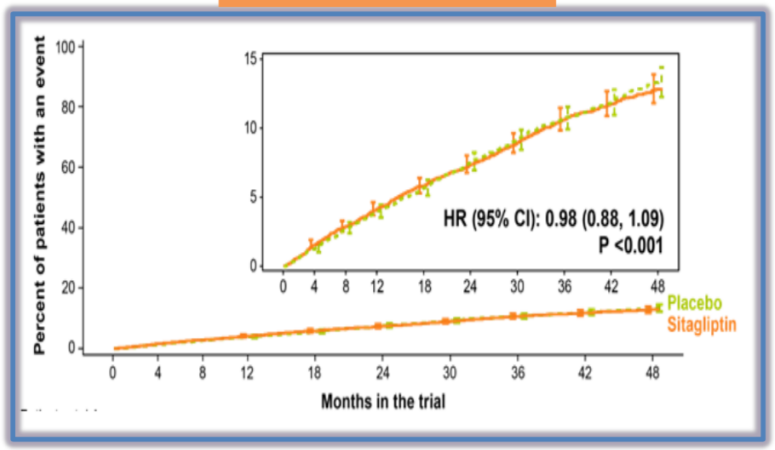
EXAMINE (Alogliptin)



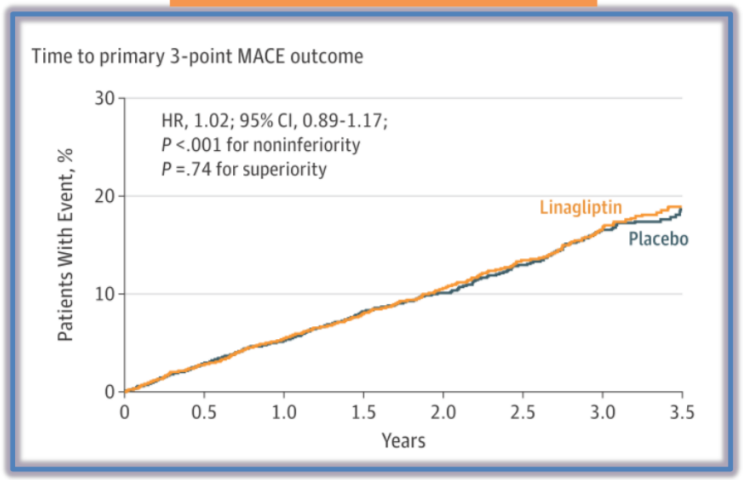
SAVOR-TIMI (Saxagliptin)



TECOS (Sitagliptin)

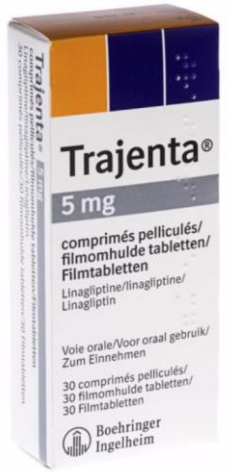


CARMELINA (Linagliptin)



White NEJM 2013. Scirica NEJM 2013. Green NEJM 2015, Rosenstock JAMA 2018

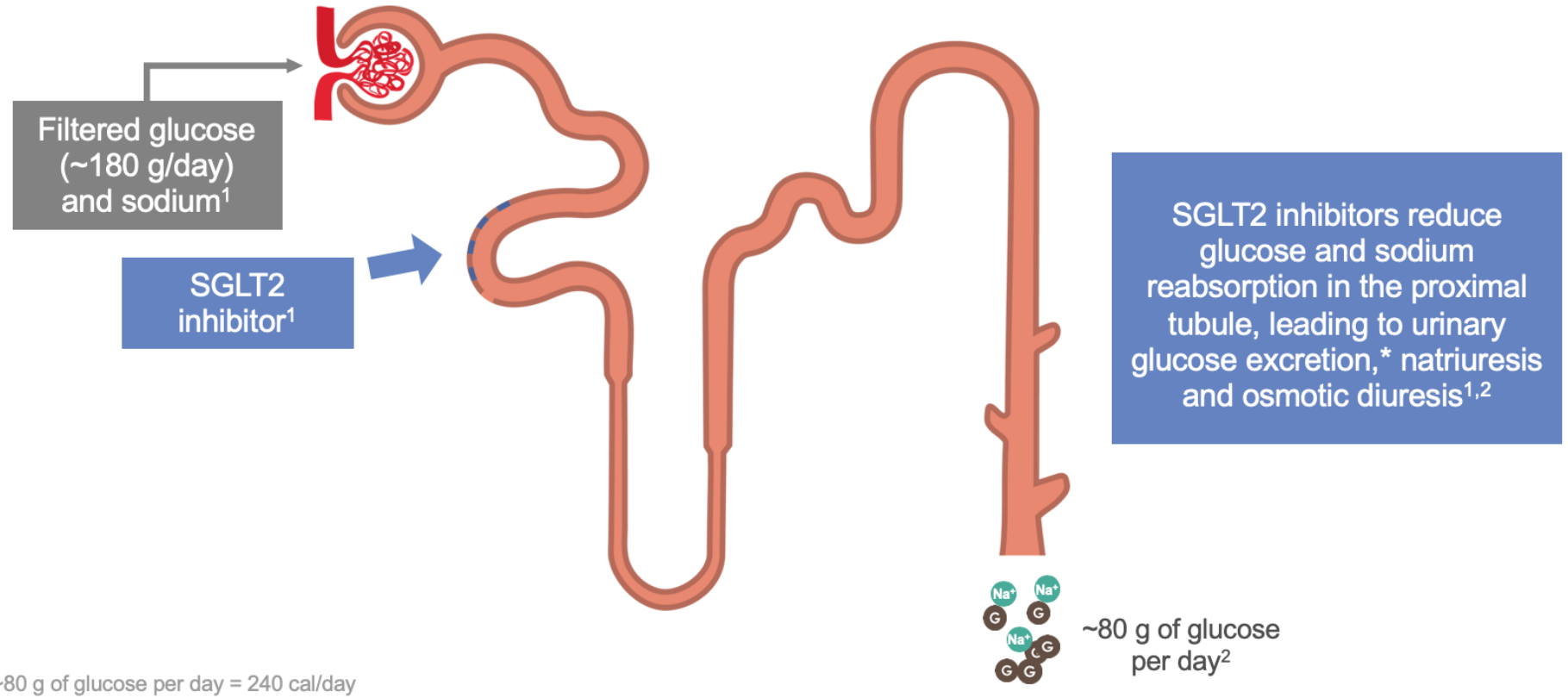
		+ metformine
- alogliptine:	Vipidia®	Vipdomet®
- linagliptine:	Trajenta®	Jentadueto®
- saxagliptine:	Onglyza®	Komboglyze®
- sitagliptine:	Januvia®	Janumet®
- vildagliptine:	Galvus®	Eucreas®



MDRD (ml/min)	sitagliptine Januvia®	vildagliptine Galvus®	saxagliptine Onglyza®	linagliptine Trajenta®	alogliptine Vipidia®
> 50	1 x 100 mg	2 x 50 mg	1 x 5 mg	1 x 5 mg	1 x 25 mg
30 tot 50	1 x 50 mg	1 x 50 mg	1 x 2,5 mg	1 x 5 mg	1 x 12.5 mg
< 30	1 x 25 mg	1 x 50 mg	1 x 2,5 mg	1 x 5 mg	1 x 6.25 mg

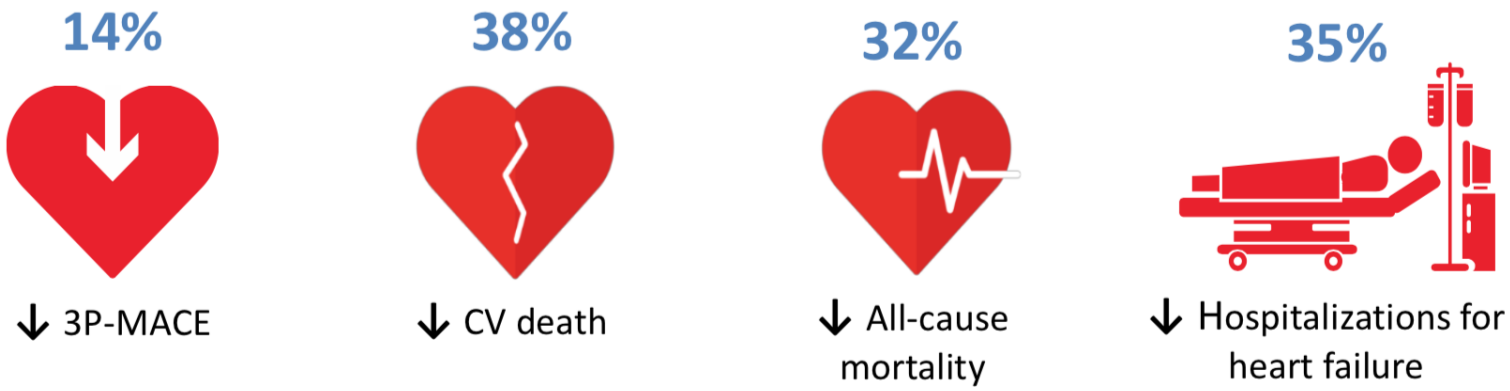
SGLT2-inhibitoren (gliflozines)

- Glucosurie ↑
- Natriurese ↑
- Osmotische diurese ↑



*Loss of ~80 g of glucose per day = 240 cal/day
SGLT2, sodium-glucose co-transporter-2

SGLT2-inhibitoren outcome (EMPA-reg)



Zinman B, et al. N Engl J Med 2015;373:2117-28.

Combinatiepreparaten + metformine

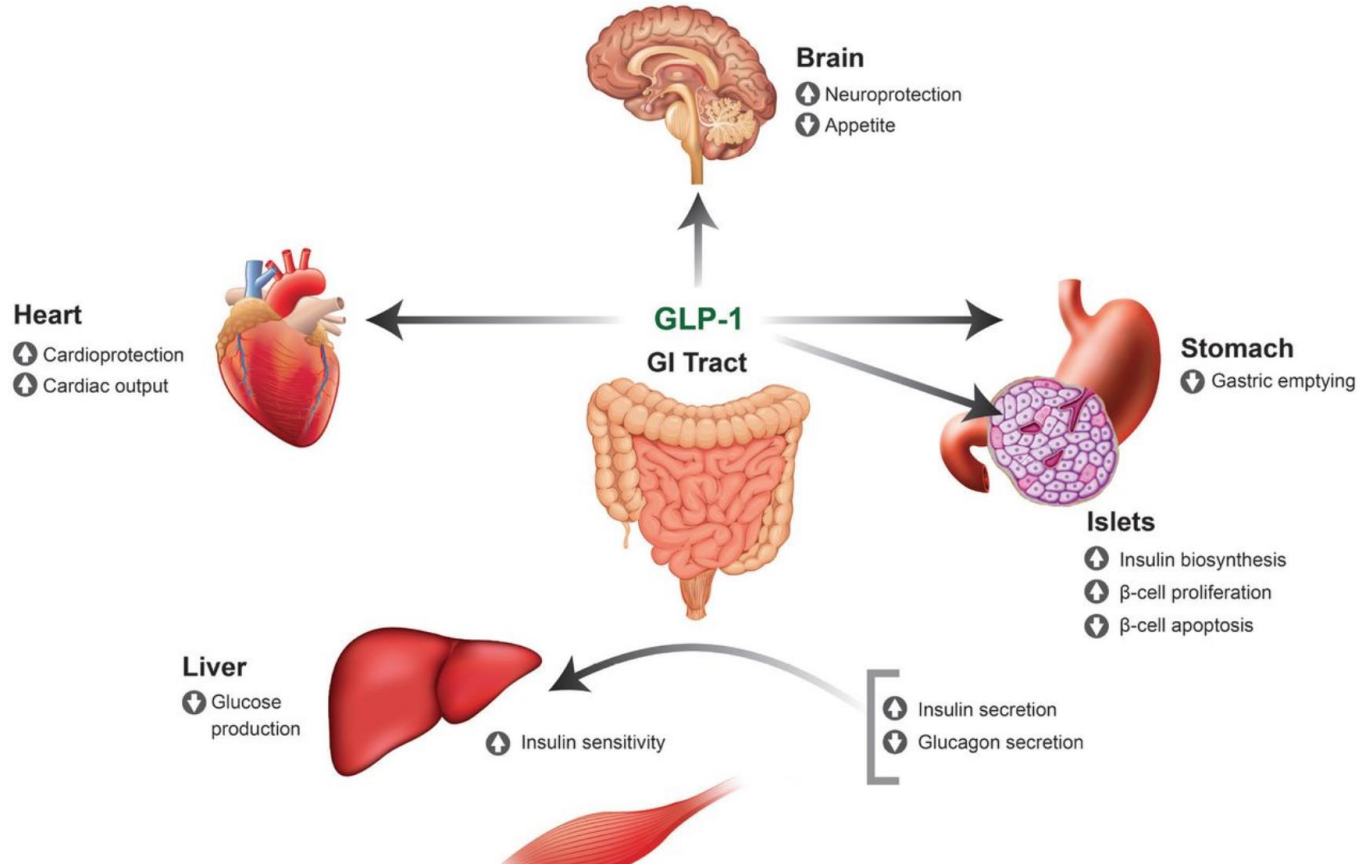
- Canagliflozine	Invokana®	Vokanamet®
- Dapagliflozine	Forxiga®	~~Xigduo~~®
- Empagliflozine	Jardiance®	Synjardy®
- Etrugliflozine	Steglatro®	Segluromet®

The ACC Expert Consensus Decision Pathway: guidance for the use of SGLT2 inhibitors with proven CV benefit in patients with T2D and ASCVD

- If HbA1c is well controlled at baseline, or there is a known history of frequent hypoglycaemic events
  - reduce the sulphonylurea dose by 50% / basal insulin dose by 20% when starting therapy
- avoid hypovolaemia: if needed reduce thiazide or loop diuretic
- educate patients regarding the symptoms of low blood pressure (light headedness, orthostasis, weakness)
- instruct patients to closely monitor glucose at home for the first 4 weeks of therapy
- educate patients regarding symptoms of DKA (nausea, vomiting, weakness)
  - **DKA can occur even if blood glucose readings are in the 150–250 mg/dl range**
  - if a patient experiences DKA-like symptoms, he or she should be instructed to seek medical attention
- educate patients on foot care and follow-up foot pulse examination (particularly those on canagliflozin)
- monitor kidney function
- educate patients on the potential for genital mycotic infections

Als pillen niet meer helpen… GLP1-analoog

- Insulinesynthese ↑
- Glucose afhankelijke Insulinesecreti⌢ ↑
- Glucagonsecretie ↓
- Maaglediging ↓
- Eetlust ↓



GLP1-analoog ↔ basaal insuline

- Zelfde effect op A1c
- Minder hypoglycemie
- beter effect op gewicht
- Gemakkelijker in gebruik
- Meer neveneffecten (gastro-intestinaal)

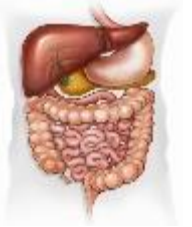
Verschillende GLP1- analogen en combinaties

- Exenatide	Byetta	2xdd
- Liraglutide	Victoza	1xdd
- Lixisenatide	Lyxumia	1xdd
~~- Exenatide LA~~	~~Bydureon~~	~~1x/w~~
- Dulaglutide	Trulicity	1x/w
- Semaglutide	Ozempic	1x/w

- Liraglutide + degludec	Xultophy	1xdd
~~- Lixisenatide + glargine~~	~~Suliqua~~	~~1xdd~~

GLP1-analogen	exenatide Byetta®	exenatide microsferen Bydurion®	liraglutide Victoza®	lixisenatide Lyxumia®	dulaglutide Trulicity®
frequentie	2 x dagelijks	1 x wekelijks	1 x dagelijks	1 x dagelijks	1 x wekelijks
timing	60-30 min voor ontbijt en avondmaal	onafhankelijk van maaltijd	onafhankelijk van maaltijd	60-30 min voor maaltijd die meeste glycemie verhoging geeft	onafhankelijk van maaltijd
startdosis (eerste 14d)	2 x 5 microg /d	2 mg /wk	0.6 mg /d	10 microg /d	1.5 mg /wk (0.75 mg /wk als hoog bejaard)
onderhoudsdosis	2 x 10 microg /d	2 mg /wk	1,2 mg	20 microg /d	1.5 mg /wk (0.75 mg /wk als hoog bejaard)
maximale dosis	2 x 10 microg /d	2 mg /wk	1.8 mg*	20 microg /d	1.5 mg /wk
MDRD < 50 ml/min	2 x 5 microg /d	niet gebruiken	0,6 mg /d	10 microg /d	1.5 mg /wk
MDRD < 30 ml/min	niet gebruiken	niet gebruiken	niet gebruiken	niet gebruiken	niet gebruiken
apparaat	wegwerppen, aparte pen voor 5 en 10 microg	wegwerppen of kit, poeder (reconstitutie nodig)	wegwerppen, één pen voor alle dosissen	wegwerppen, aparte pen voor 10 en 20 microg	wegwerppen, aparte pen voor 0.75 en 1.5 mg, poeder

How to overcome nausea



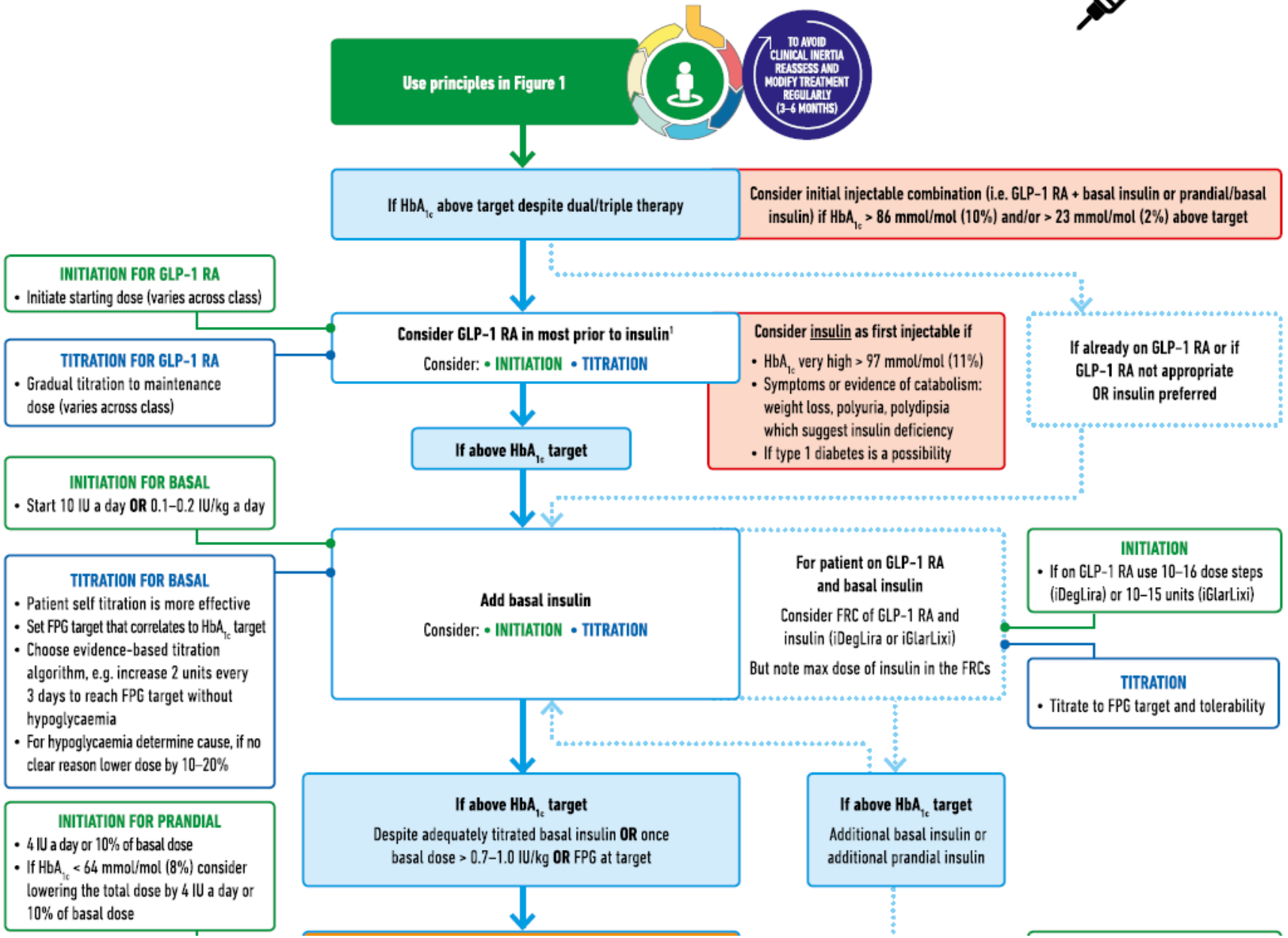
- **Gastrointestinal (GI) side effects**, including nausea, diarrhoea, and vomiting, are the most common side effects with GLP-1 analogues[1,3]
  - Nausea, diarrhea, and vomiting occurred in ± 20%, 14%, and 10% of the T2D patients treated with semaglutide in clinical trials[2,3]
- These gastrointestinal side effects usually occur **early**, tend to be **transient**, and can often be **mitigated by gradual dose titration**[3,4]
- GI complaints were the leading reason for discontinuation of a GLP-1 analogue, with 3–8% of patients discontinuing GLP-1RA therapy compared with 1% on placebo[2,3]
- Certain **dietary guidelines** could be considered to reduce GI side effects[4]:
  - Take **several small meals** throughout the day and eat slowly.
  - Eat the meal at room temperature.
  - **Drink water** frequently and regularly throughout the day.
  - Avoid odors that make you sick and foods that are very greasy, sweetened, or seasoned.

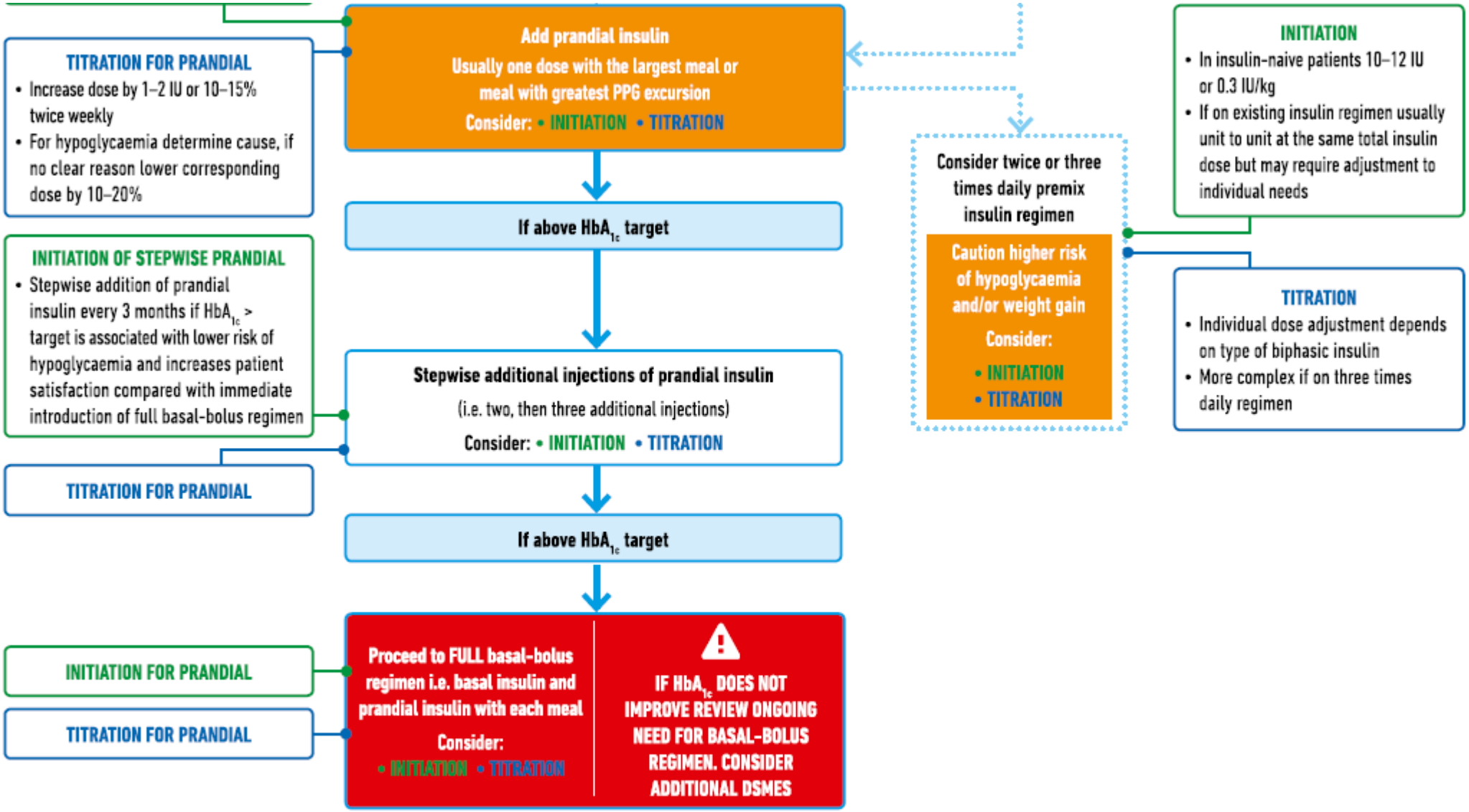
GI: gastrointestinal; GLP-1RA: glucagon-like peptide 1 receptor agonist; T2D: type 2 diabetes

1. Ozempic® Summary of Product Characteristics October 2020; 2. Pratley RE et al. *Lancet Diabetes Endocrinol* 2018;6:275–86; 3. Aroda VR et al. Diabetes Metab. 2019;45(5):409-418; 4. Honigberg MC et al. JAMA Cardiol. 2020 Jun 17. doi: 10.1001/jamacardio.2020.1966

What if all this is not enough?

INTENSIFYING TO INJECTABLE THERAPIES

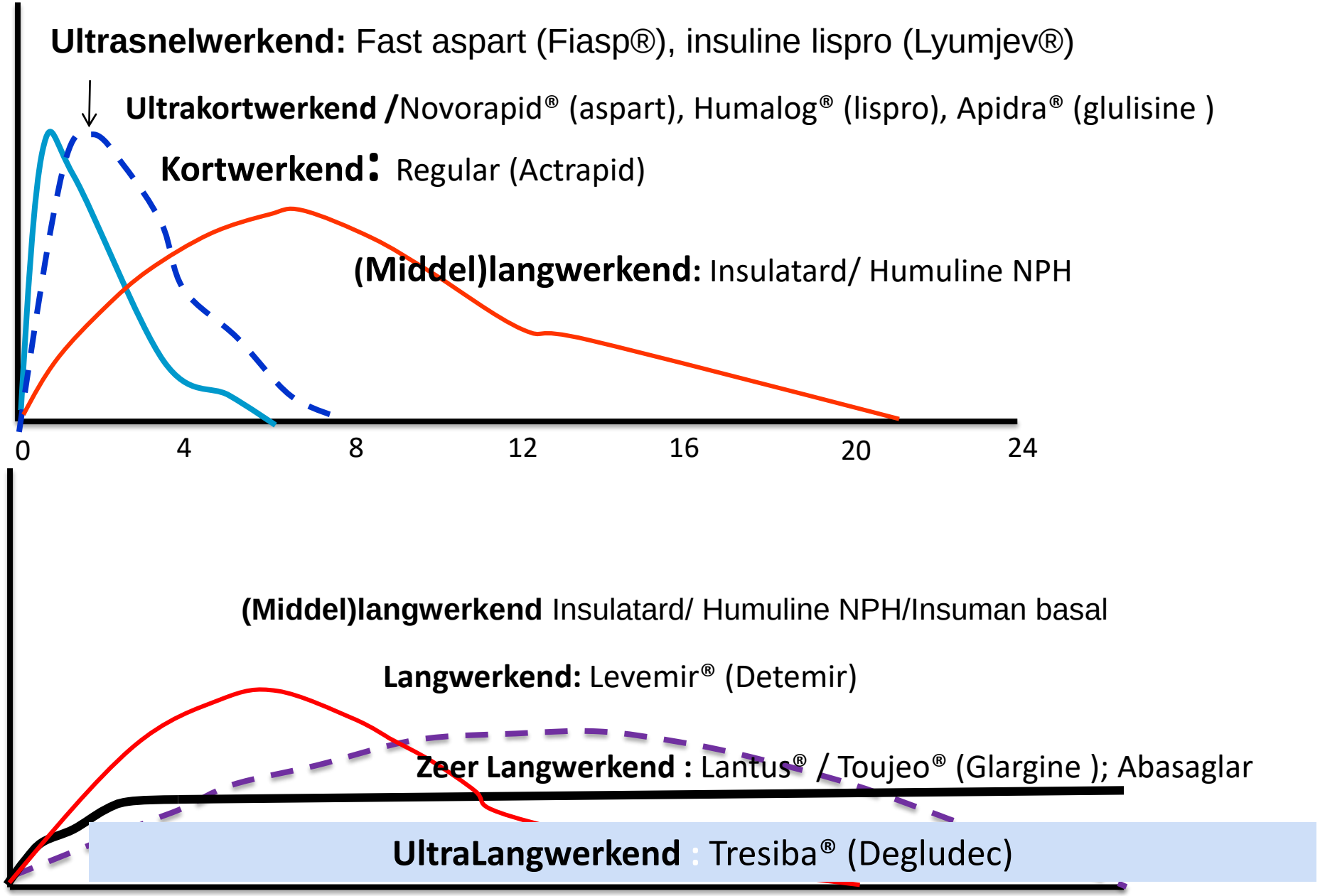




1. Consider choice of GLP-1 RA considering: patient preference, HbA_{1c} lowering, weight-lowering effect or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit

FPG = Fasting Plasma Glucose
FRC = Fixed Ratio Combination
PPG = Post Prandial Glucose

INSULINE


Ultrasnelwerkend: Fast aspart (Fiasp®), insuline lispro (Lyumjev®)
Ultrakortwerkend /Novorapid® (aspart), Humalog® (lispro), Apidra® (glulisine)
Kortwerkend: Regular (Actrapid)
(Middel)langwerkend: Insulatard/ Humuline NPH
0
4
8
12
16
20
24
(Middel)langwerkend Insulatard/ Humuline NPH/Insuman basal
Langwerkend: Levemir® (Detemir)
Zeer Langwerkend : Lantus® / Toujeo® (Glargine); Abasaglar
UltraLangwerkend : Tresiba® (Degludec)

	Merknaam	Begineffect	Piekeffect	Duur
1. Ultrasnelle insuline		20 minuten	1,5 u	4-5 u
Insuline Aspart	Novorapid® Fiasp®	Meest snelwerkend, samen met Lyumjev		
Insuline Lispro	Humalog® Lyumjev®			
Insuline Glulisine	Apidra®	Werkt iets sneller dan Aspart		
2. Snelwerkende insuline		30 minuten	2-3 u	6-8 u
Humaan, biosynthetisch	Actrapid®			
	Humuline Regular® Insuman rapid®			
3. Intermediair werkende insuline		1,5 u	2-8 u	18-20 u
Humaan, biosynthetisch	Humuline NPH®			
	Insulatard® Insuman basal®			
4.Traagwerkende insuline		4 u	18-24u	
Insuline Detemir	Levemir®			
Insuline Glargine Insuline Degludec	Lantus® Toujeo® Abasaglar® Tresiba®			

Future prospectives

- New pharmacologic developments:
  - Implantable GLP-1 analogs (6-24 months)
  - Oral GLP-1 analogs (semaglutide) and higher doses
  - Dual-agonist peptides (tirzepatide); SGLT1/2-inhibitors
  - ...
- New indications for (old) drugs
  - Metformin in prevention of non-diabetic CKD progression
  - SGLT2-inhibitors in heart failure and CKD
  - GLP1-analogs for obesity

CASUS 1

General profile

- Man, 59 years old
- T2D since 2016
- Arterial hypertension
- Dyslipidemia
- Obesity
- Active smoker

Clinical examination

- BMI 31.5 kg/m^2
- Waist 145 cm
- Blood pressure 146/89 mmHg

Lab parameters

- HbA1c 7.6%
- Cholesterol 218 mg/dl
- LDL-C 102 mg/dl
- HDL-C 35 mg/dl
- Triglycerides 194 mg/dl
- eGFR 85 ml/min/1.73 m^2

Current treatment

- Metformin: 850 mg 3x/day
- Bisoprolol 5 mg 1x/day
- Pantoprazole 20 mg 1x/day
- Simvastatin 20 mg 1x/day

ESC/EASD recommendations for the management of blood pressure in patients with diabetes and pre-diabetes

Recommendations	Class[a]	Level[b]
Treatment targets		
Antihypertensive drug treatment is recommended for people with DM when office BP is >140/90 mmHg.[155,178–180]	I	A
It is recommended that patients with hypertension and DM are treated in an individualized manner. The BP goal is to target SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years), the SBP goal is to a range of 130 - 139 mmHg.[155,159,160,181–183]	I	A
It is recommended that target DBP is targeted to <80 mmHg, but not <70 mmHg.[160]	I	C
An on-treatment SBP of <130 mmHg may be considered in patients at particularly high risk of a cerebrovascular event, such as those with a history of stroke.[154–157,173]	IIb	C
Treatment and evaluation		
Lifestyle changes [weight loss if overweight, physical activity, alcohol restriction, sodium restriction, and increased consumption of fruits (e.g. 2–3 servings), vegetables (e.g. 2–3 servings), and low-fat dairy products] are recommended in patients with DM and pre-DM with hypertension.[161–163,166]	I	A
A RAAS blocker (ACEI or ARB) is recommended in the treatment of hypertension in patient with DM, particularly in the presence of microalbuminuria, albuminuria, proteinuria, or LV hypertrophy.[167–170]	I	A
It is recommended that treatment is initiated with a combination of a RAAS blocker with a calcium channel blocker or thiazide/thiazide-like diuretic.[167–171]	I	A
In patients with IFG or IGT, RAAS blockers should be preferred to beta-blockers or diuretics to reduce the risk of new-onset DM.[173–175]	IIa	A
The effects of GLP1-RAs and SGLT2 inhibitors on BP should be considered.	IIa	C
Home BP self-monitoring should be considered in patients with DM on antihypertensive treatments to check that their BP is appropriately controlled.[184]	IIa	C
24 h ABPM should be considered to assess abnormal 24 h BP patterns and adjust antihypertensive treatment.[185]	IIa	C

ABPM = ambulatory blood pressure monitoring; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; DBP = diastolic blood pressure; DM = diabetes mellitus; GLP1-RA = glucagon-like peptide-1 receptor agonist; IFG = impaired fasting glycaemia; IGT = impaired glucose tolerance; LV = left ventricular; RAAS = renin–angiotensin–aldosterone system; SBP = systolic blood pressure; SGLT2 = sodium-glucose co-transporter 2.

[a]Class of recommendation.

[b]Level of evidence.

ESC/EASD recommendations for the management of dyslipidaemia in patients with diabetes and pre-diabetes

Recommendations	Class[a]	Level[b]
Targets		
In patients with T2DM at moderate CV risk,[c] an LDL-C target of <2.5 mmol/L (<100 mg/dL) is recommended.[210–212]	I	A
In patients with T2DM at high CV risk,[c] an LDL-C target of <1.8 mmol/L (<70 mg/dL) or an LDL-C reduction of at least 50% is recommended.[d] [210–212]	I	A
In patients with T2DM at very high CV risk,[c] an LDL-C target of <1.4 mmol/L (<55 mg/dL) or an LDL-C reduction of at least 50% is recommended.[d] [200,201,210]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV-risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV-risk patients, is recommended.[d,213,214]	I	B
Treatment		
Statins are recommended as the first-choice lipid-lowering treatment in patients with DM and high LDL-C levels: administration of statins is defined based on the CV risk profile of the patient[c] and the recommended LDL-C (or non-HDL-C) target levels.[187]	I	A
If the target LDL-C is not reached, combination therapy with ezetimibe is recommended.[200,201]	I	B
In patients at very high CV risk, with persistent high LDL-C despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance, a PCSK9 inhibitor is recommended.[203–206]	I	A
Lifestyle intervention (with a focus on weight reduction, and decreased consumption of fast-absorbed carbohydrates and alcohol) and fibrates should be considered in patients with low HDL-C and high triglyceride levels.[191,207]	IIa	B
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
Statins should be considered in patients with T1DM at high CV risk,[c] irrespective of the baseline LDL-C level.[187,215]	IIa	A
Statins may be considered in asymptomatic patients with T1DM beyond the age of 30 years.	IIb	C
Statins are not recommended in women of childbearing potential.[189,190]	III	A

CV = cardiovascular; DM = diabetes mellitus; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

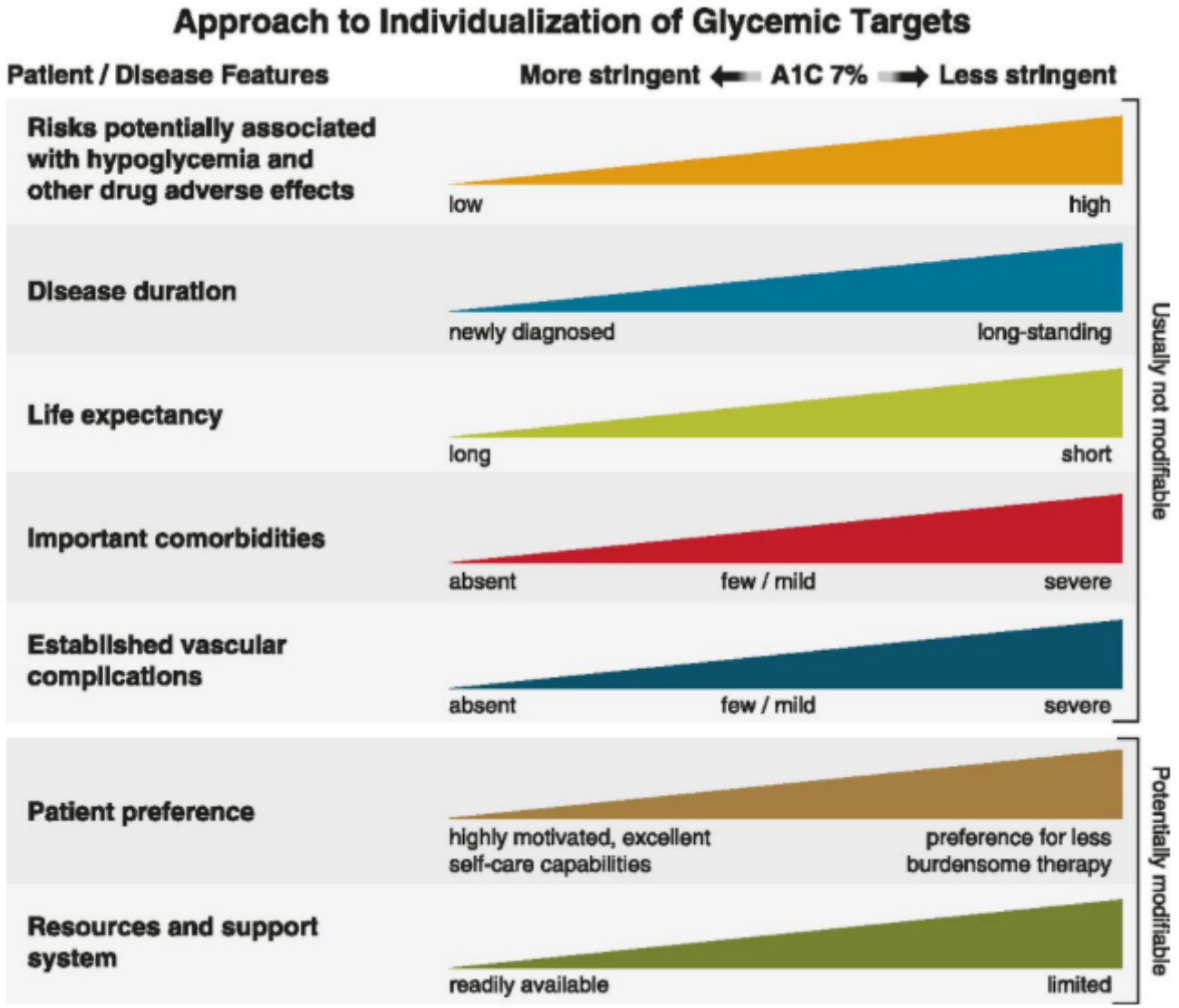
[c]See *Table 7*.

[d]See the 2019 ESC/EAS Guidelines for the management of dyslipidaemias for non-HDL-C and apolipoprotein B targets.

RISICOBEOORDELING	ZEER HOOG RISICO	HOOG RISICO	MATIG RISICO	LAAG RISICO
Cardio-vasculaire voorgeschiedenis	ASCVZ (klinisch/beeldvorming)			-
Diabetes	• Doelorgaanschade (microalbuminerie, retinopathie of neuropathie) • Met ≥ 3 belangrijke risicofactoren ***of*** • Met T1DM van > 20 jaar	• Geen doelorgaanschade • Met ≥ 1 belangrijke risicofactor ***of*** • Met duur van ≥ 10 jaar (T1DM of T2DM)	Jonge patiënten • T1DM < 35 jaar • T2DM < 50 jaar met DM duur < 10 jaar zonder andere risicofactoren	-
Nierfunctie	eGFR < 30 mL/min/1,73m²	eGFR 30-59 mL/min/1,73m²	-	-
Erfelijke factor	FH & ASCVZ of andere belangrijke risicofactor	FH zonder andere belangrijke risicofactoren	-	-
Geïsoleerde risicofactoren	-	• BD > 180/110 mmHg ***of*** • TC > 310 mg/dL ***of*** • LDL-C > 190 mg/dL	-	-
SCORE *10-jaars risico op fatale CVZ*	≥ 10%	≥ 5% en < 10%	≥ 1% en < 5%	< 1%
1ste TARGET **LDL-C**	**< 40** mg/dL RECURRENT EVENT**	**< 55** mg/dL **EN ≥ 50% reductie***	**< 70** mg/dL **EN ≥ 50% reductie***	**< 100** mg/dL	**< 116** mg/dL
2de TARGET Non-HDL-C	**< 85** mg/dL	**< 100** mg/dL	**< 130** mg/dL	
OF ApoB	**< 65** mg/dL	**< 80** mg/dL	**< 100** mg/dL	
Interventie	1. **Levensstijl aanpassen EN Statine met hoge intensiteit** 2. **EZETIMIBE**/fibraat (↑TG) 3. **PCSK9 inhibitor** Lipidenniveaus moeten 4-6 weken na ACS opnieuw worden geëvalueerd.	1. **Levensstijl aanpassen** 2. **Statine met hoge intensiteit** 3. **EZETIMIBE**/fibraat (↑TG)	1. **Levensstijl aanpassen** 2. **Statine**	**Levens-stijl advies**

DESCAMPS OS. ET AL . LOUVAIN MED 2020 SEPTEMBRE ; 139 (07) : 396-404

Individualization of glycaemic targets



ADA STANDARDS OF MEDICAL CARE IN DIABETES. DIABETES CARE 2021 JAN; 44(SUPPLEMENT 1): S73-S84.

CASUS 2

General profile

- Man, 63 years old
- T2D since 7 years
- Myocardial infarction, 14 months ago
- Excellent recovery after PCI
- Smoker

Clinical examination

- Length 1.72 m
- Weight 90 kg
- BMI 30.4 kg/m^2
- Blood pressure 150/76 mmHg

Lab parameters

- HbA1c 8.2%
- LDL-C 77 mg/dl
- HDL-C 55 mg/dl
- Triglycerides 155 mg/dl
- eGFR 75 ml/min/1.73 m^2

Current treatment

- Metformin: 850 mg 3x/day
- Bisoprolol 5 mg, Lisinopril 20 mg
- Acetylsalicylic acid 80 mg
- Simvastatin 20 mg

Dank voor jullie aandacht

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