

# Cardiovascular risk in type 2 diabetes : time for action

**Satellite Symposium Novo Nordisk**

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CHU UCL Namur*



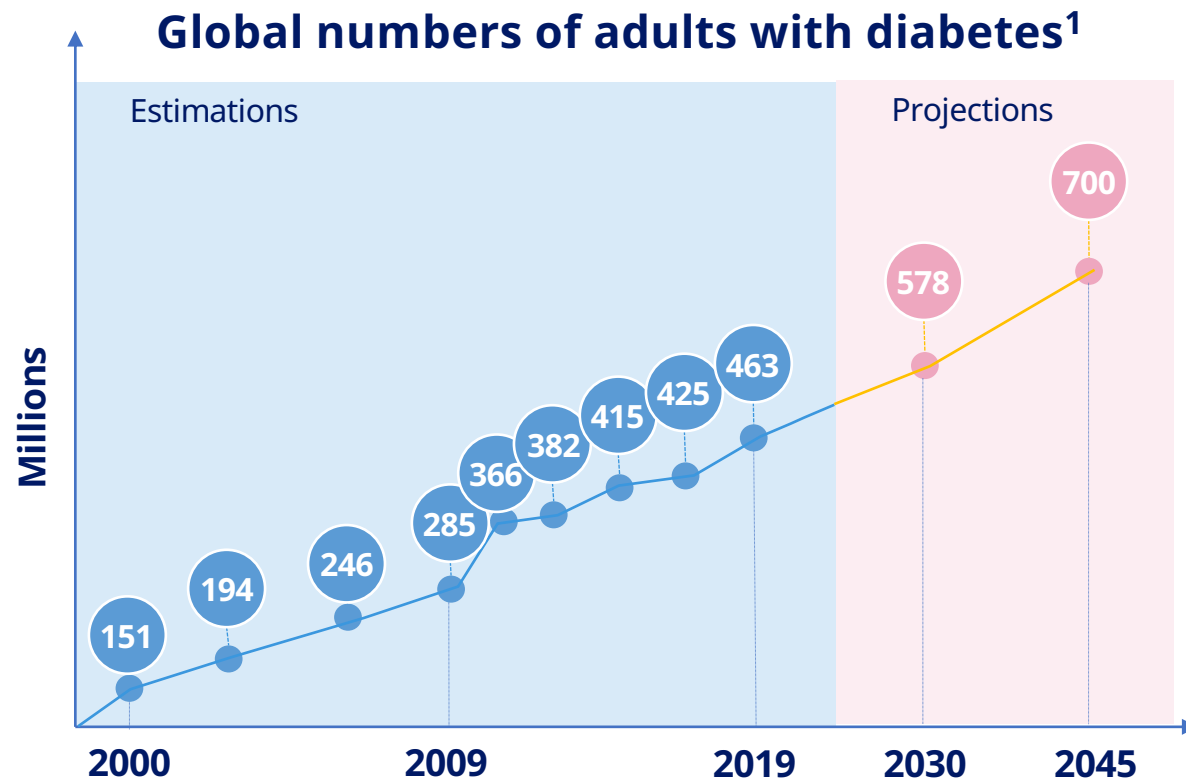


# Disclosure

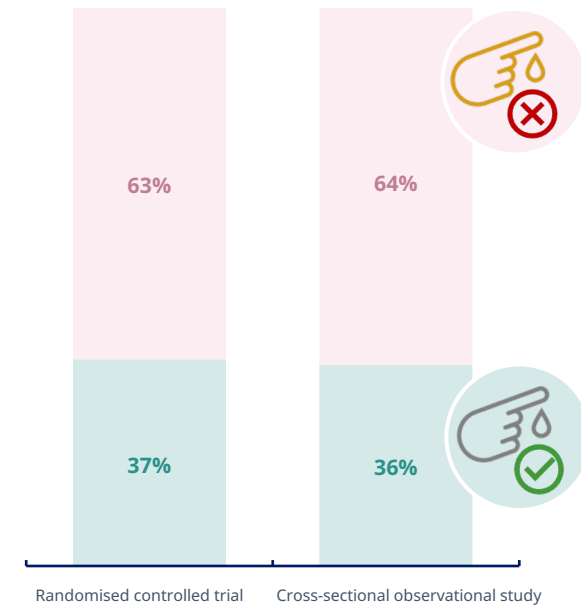
Consulting fees and/or honoraria for delivering lectures and for consultancy/advisory board (payments to CHU UCL Namur) from Novonordisk, Sanofi, Daiichi-Sankyo, Novartis, Servier, Johnson&Johnson, Astra-Zeneca



# The global diabetes burden is increasing and remains largely uncontrolled despite current treatments



**>60% of people with T2D have poor glucose control (HbA<sub>1c</sub> ≥7%) according to a meta-analysis<sup>2</sup>**



T2D, type 2 diabetes; HbA<sub>1c</sub>, glycated haemoglobin

1. International Diabetes Federation, Diabetes Atlas 9th edition 2019. Available at: <https://diabetesatlas.org/en/>. Accessed October 2021; 2. Mannucci E et al. J Endocrinol Invest 2014;37:477-95.



# Atherosclerotic cardiovascular disease is a burden in T2D

## Atherosclerosis<sup>1</sup>

The formation of 'fibro-fatty' lesions in the artery wall

Primary cause of most CVD



Myocardial infarction

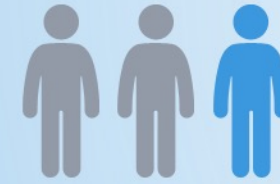


Stroke



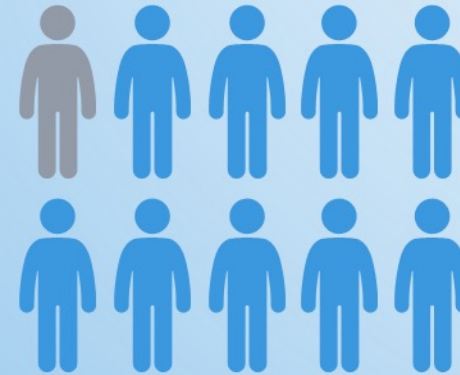
Peripheral artery disease

CVD accounts for around half of all deaths in T2D<sup>2</sup>



Nearly 1 in 3 people with T2D have CVD<sup>2,3</sup>

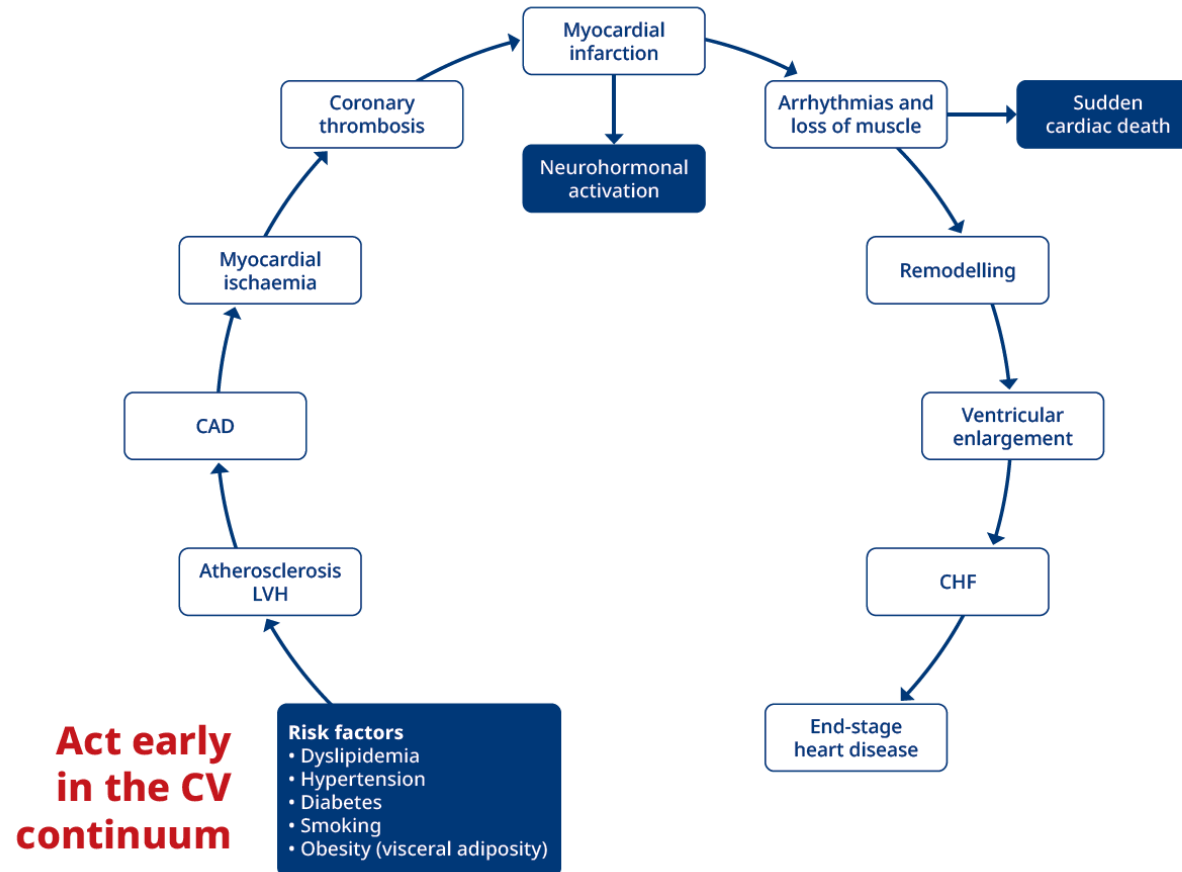
of those with established CVD



9 out of 10 have ASCVD<sup>2,3</sup>

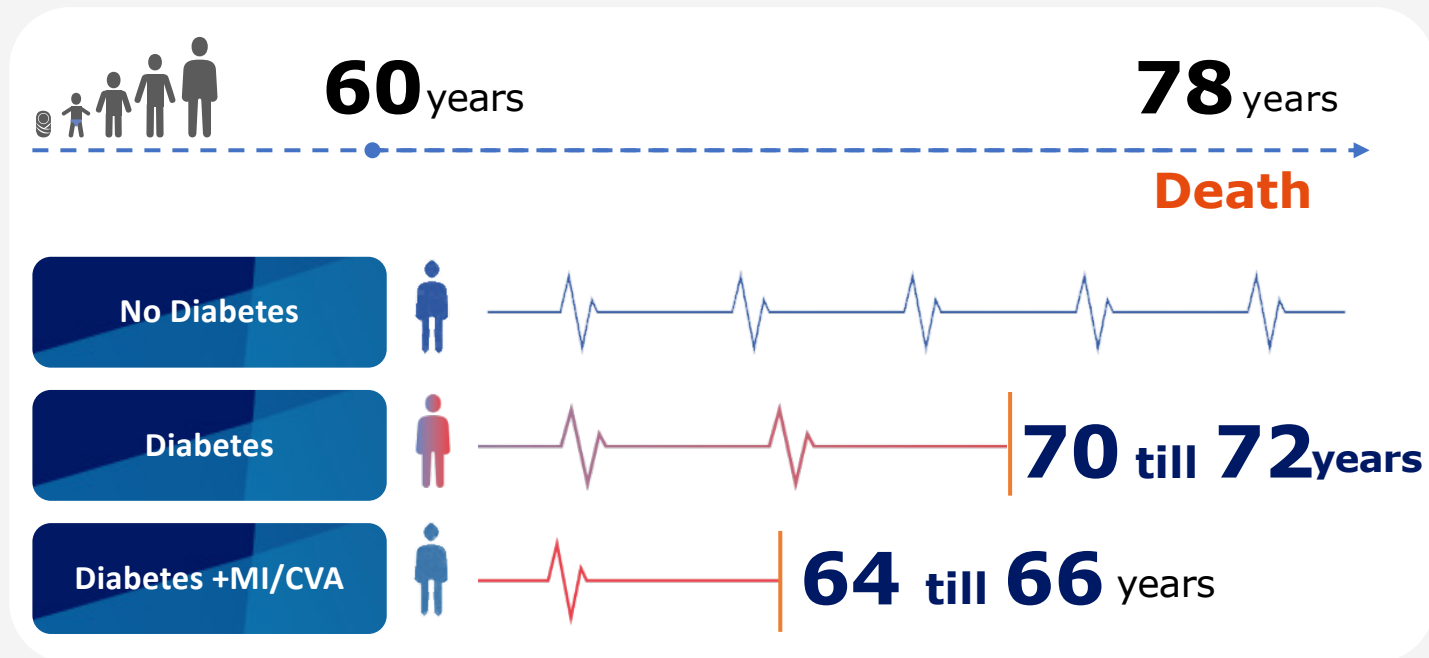


# The various stages of the CV continuum





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





## Mortality risk and CV disease are increased with diabetes\*



Hazard ratio for  
all-cause mortality:  
**1.80**

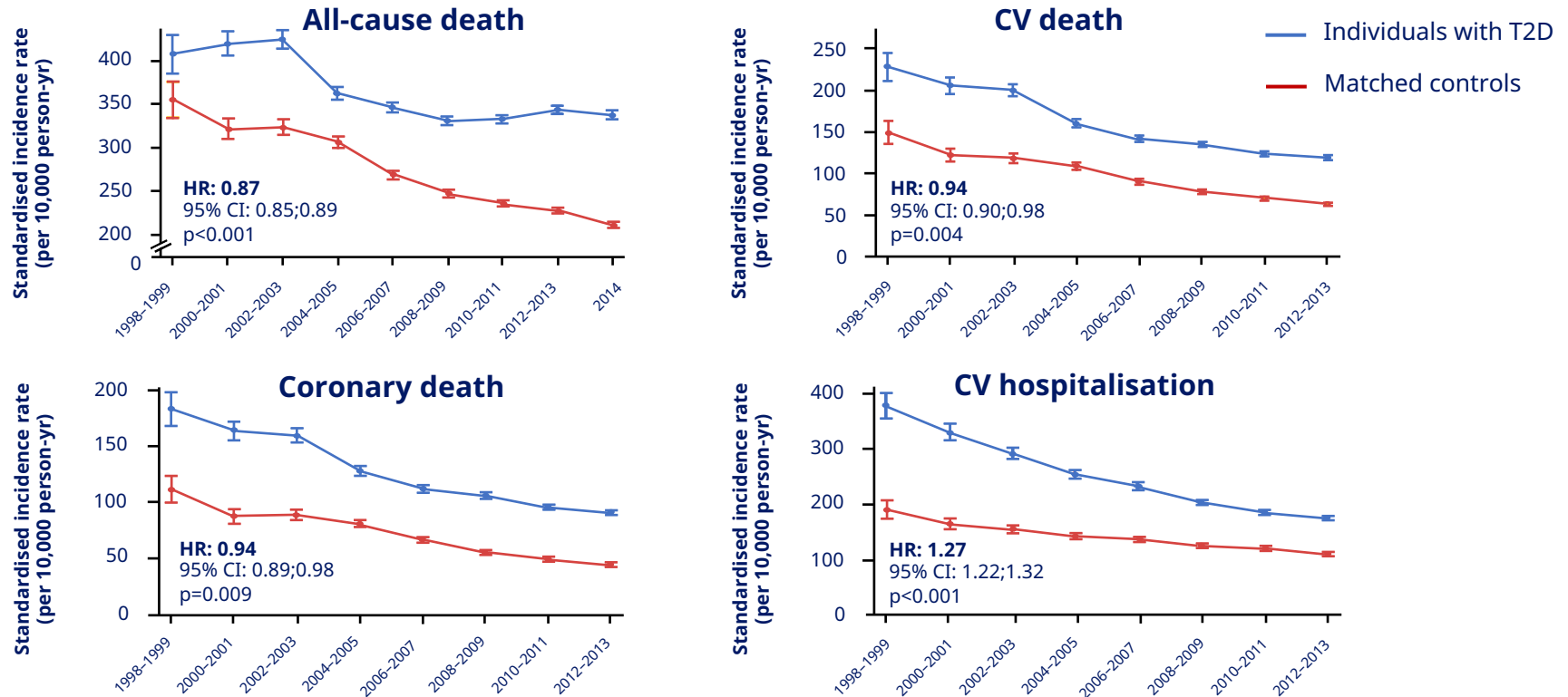


Hazard ratio for  
CV death:  
**2.32**

\*Mortality risk associated with diabetes vs no diabetes (n=820,900).  
CV, cardiovascular.  
Rao Kondapally Seshasai S et al. N Engl J Med 2011;364:829–41.



# Individuals with T2D are at increased risk of CVD vs those without CVD



Although CV death rate is declining in general, the difference in CV death between individuals with and without T2D is still evident

Data are mean ± 95% CI; HR (95% CI) are patients with T2D vs matched controls.  
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; yr, years.  
Rawshani A et al. N Engl J Med 2017;376:1407-18.

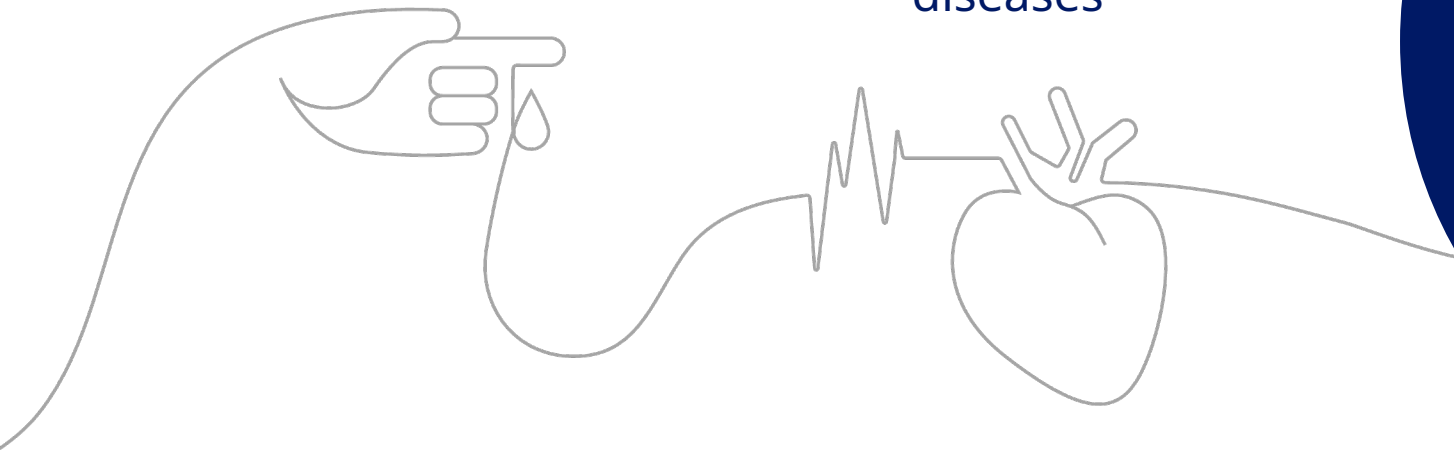




## Tackling the CV risk in every type 2 diabetes patient

Diabetes

Cardiovascular  
diseases



Maximize the  
cardiovascular  
protection of  
your type 2 diabetes  
patients  
**ALSO** in primary  
prevention



## PATIENT PROFILE | GEORGE



### Summary

- Male, 56
- Works as an accountant
- Likes to play golf twice a month but recently needs to take more breaks per round
- Comes for a check-up as he wants to discuss his concerns about recent weight gains
- Understands his blood results and starts to worry that his general health is deteriorating – would like to hear further treatment options
- Is starting to worry given his family history for cardiovascular events



### Patient Characteristics

CV Risk : **High** <sup>1</sup>



HbA1c	<b>8.2</b>	Blood pressure (mmHg)	<b>140/90</b>
BMI	<b>31.5</b>	LDL level (mg/dl)	<b>160</b>
		Triglycerides (mg/dl)	<b>180</b>

- 6 years since T2D diagnosis
- Smoker
- No existing CVD



### Medical History

- Takes maxim dosage of **daily metformin** along with a **DPP-4i**
- Follows a treatment for his blood pressure (ACE inhibitor) and cholesterol (Statins)
- Father died from a stroke at 65
- No chronic kidney disease

“

I'm worrying about my weight and health; it seems to go for the worst. My father had a stroke, so I want to really be on top of my diabetes to stop its progression before it's too late.

”



# Most patients with type 2 diabetes are at high to very high risk of CV events

Patients with type 2 diabetes mellitus	
Patients with type 1 DM above 40 years of age may also be classified according to these criteria	<p>Patients with well controlled short-standing DM (e.g. &lt;10 years), no evidence of TOD and no additional ASCVD risk factors</p> <p><b>Moderate-risk</b></p>
	<p>Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria.</p> <p><b>High-risk</b></p>
	<p>Patients with DM with established ASCVD and/or severe TOD:<sup>87, 93-95</sup></p> <ul style="list-style-type: none"> <li>• eGFR &lt;45 mL/min/1.73 m<sup>2</sup> irrespective of albuminuria</li> <li>• eGFR 45-59 mL/min/1.73 m<sup>2</sup> and microalbuminuria (ACR 30 -300 mg/g)</li> <li>• Proteinuria (ACR &gt;300 mg/g)</li> <li>• Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)</li> </ul> <p><b>Very high-risk</b></p>

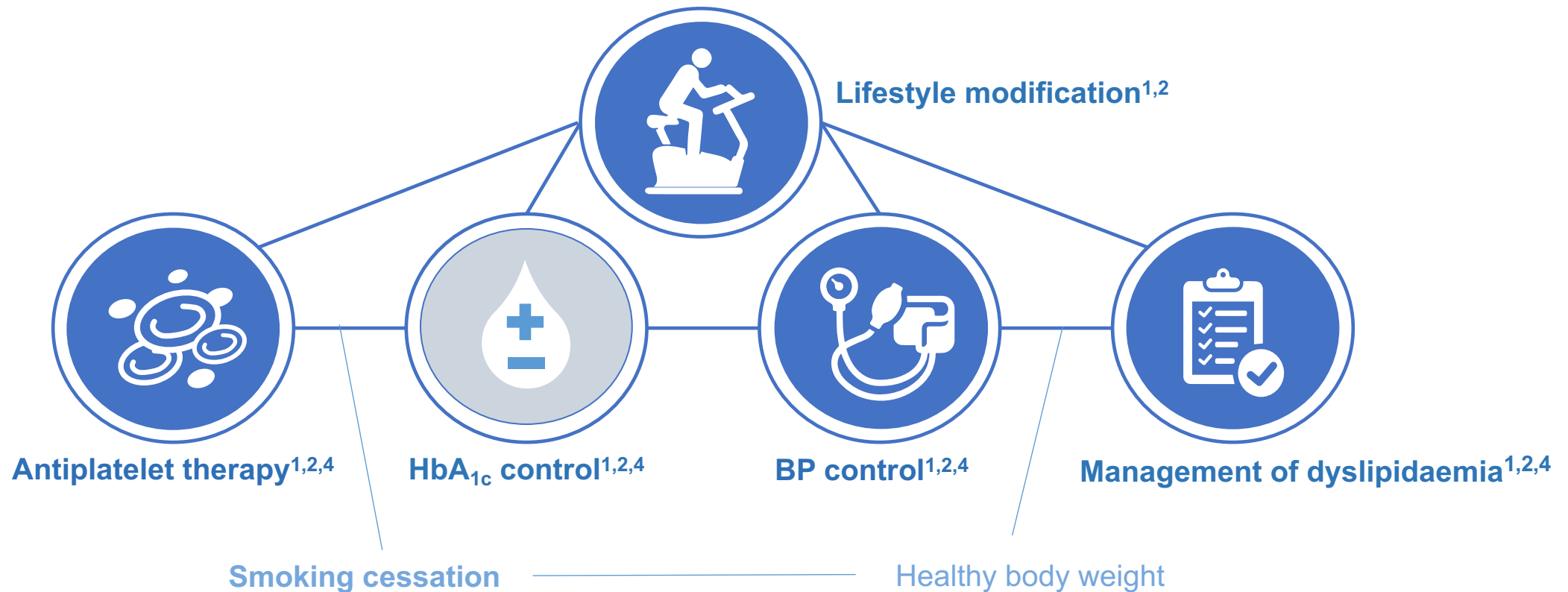
Risk factors George :

- Age = 56 years
- BMI = 31.5 kg/m<sup>2</sup>
- Hypertension
- Dyslipidemia
- HbA1c = 8.2%





# The CV risk approach in a type 2 diabetes patient such as George is multifactorial and individualized<sup>1-4</sup>

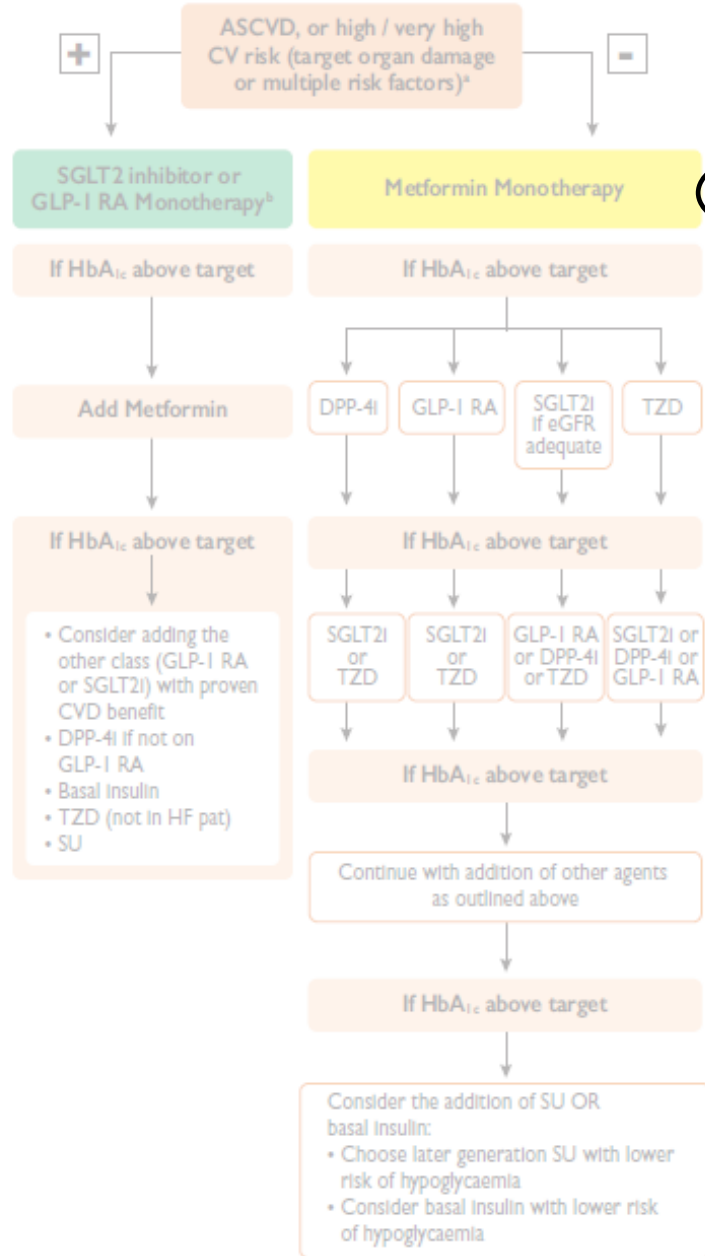


CV, cardiovascular; HbA<sub>1c</sub>, glycosylated haemoglobin; BP, blood pressure

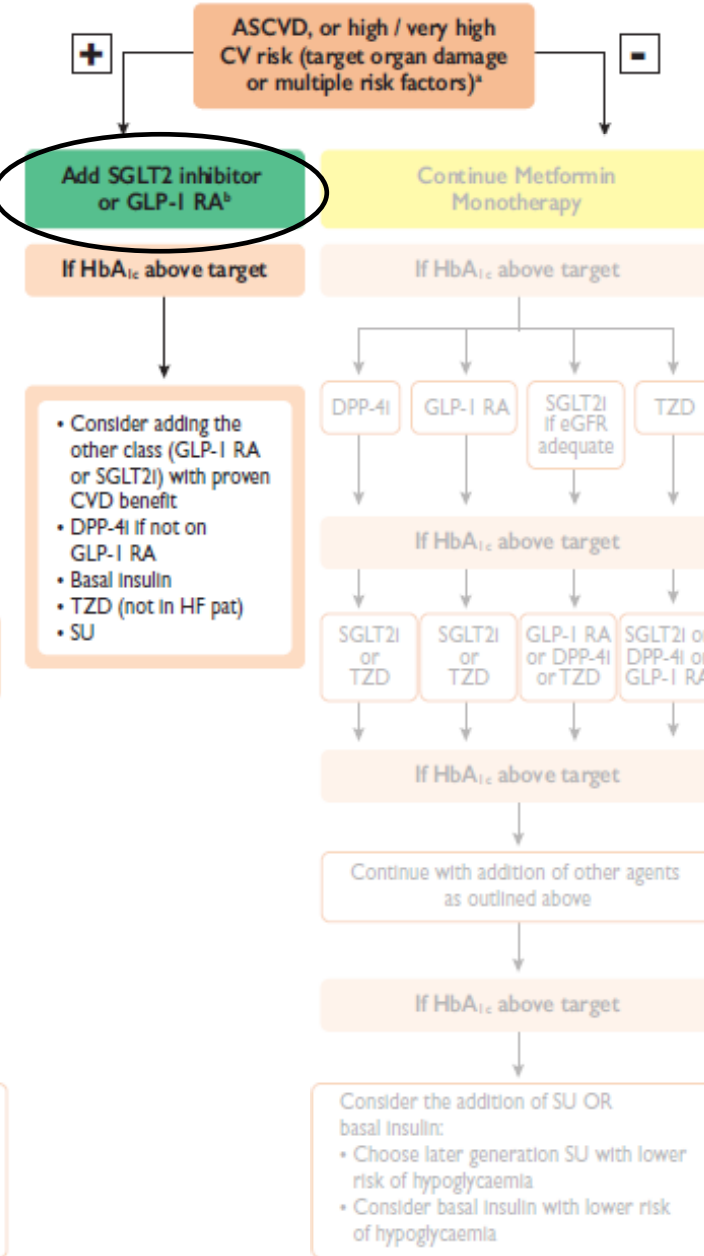
1. American Diabetes Association. *Diabetes Care* 2018;41(Suppl 1):S86–S104; 2. Piepoli MF et al. *Eur Heart J* 2016;37:2315–2381; 3. Rydén L et al. *Eur Heart J* 2013;34:3035–3087; 4. Cosentino F et al. *Eur Heart J* 2019;00:1–69



### A Type 2 DM - Drug naïve patients



### B Type 2 DM - On metformin



## 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

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Councils: Council on Cardiovascular Primary Care, Council on Hypertension.

Working Groups: Aorta and Peripheral Vascular Diseases, Cardiovascular Surgery, Thrombosis.

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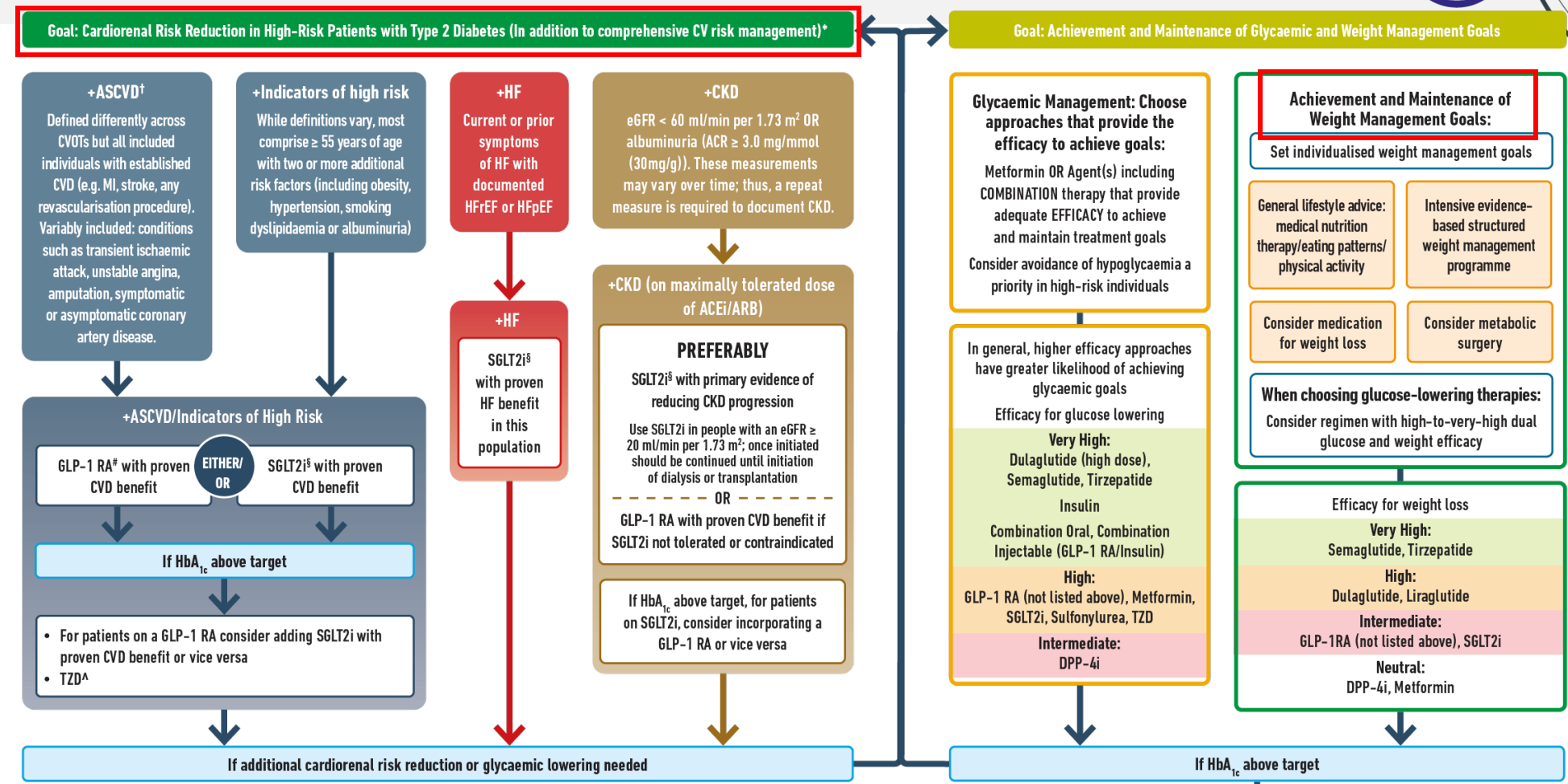
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**The 2019 ESC guidelines reflect a move towards a more individualised, evidence-based approach to patient management, driven by CVOTs in the diabetes field**

## FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

TO AVOID THERAPEUTIC INERTIA, REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)



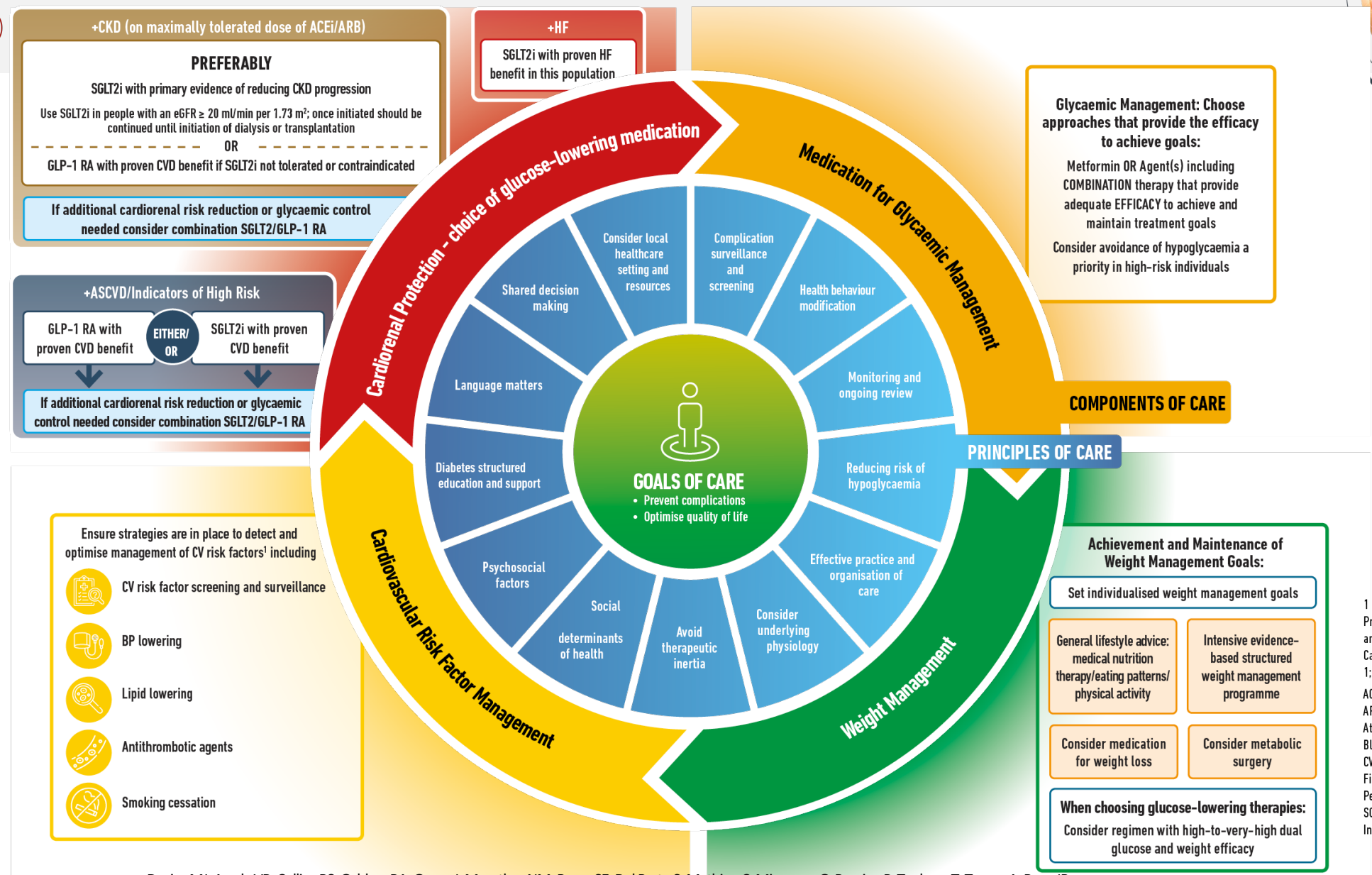
ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; TZD, Type 2 Diabetes; TZD, Thiazolidinedione.

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

**Identify barriers to goals:**

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g. diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact on achievement of goals

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT



Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; <https://doi.org/10.2337/dci22-0034>. Diabetologia 2022; <https://doi.org/10.1007/s00125-022-05787-2>.

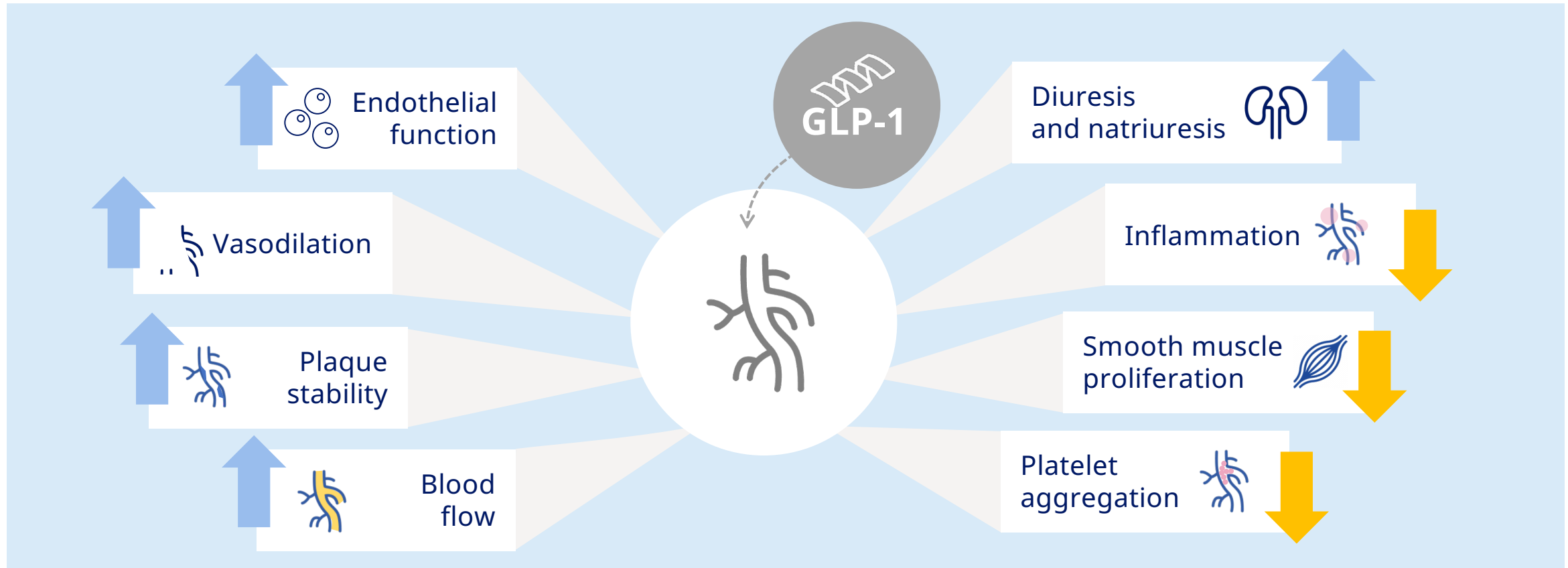
1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144-74.

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



# Effects of semaglutide on cardiovascular system

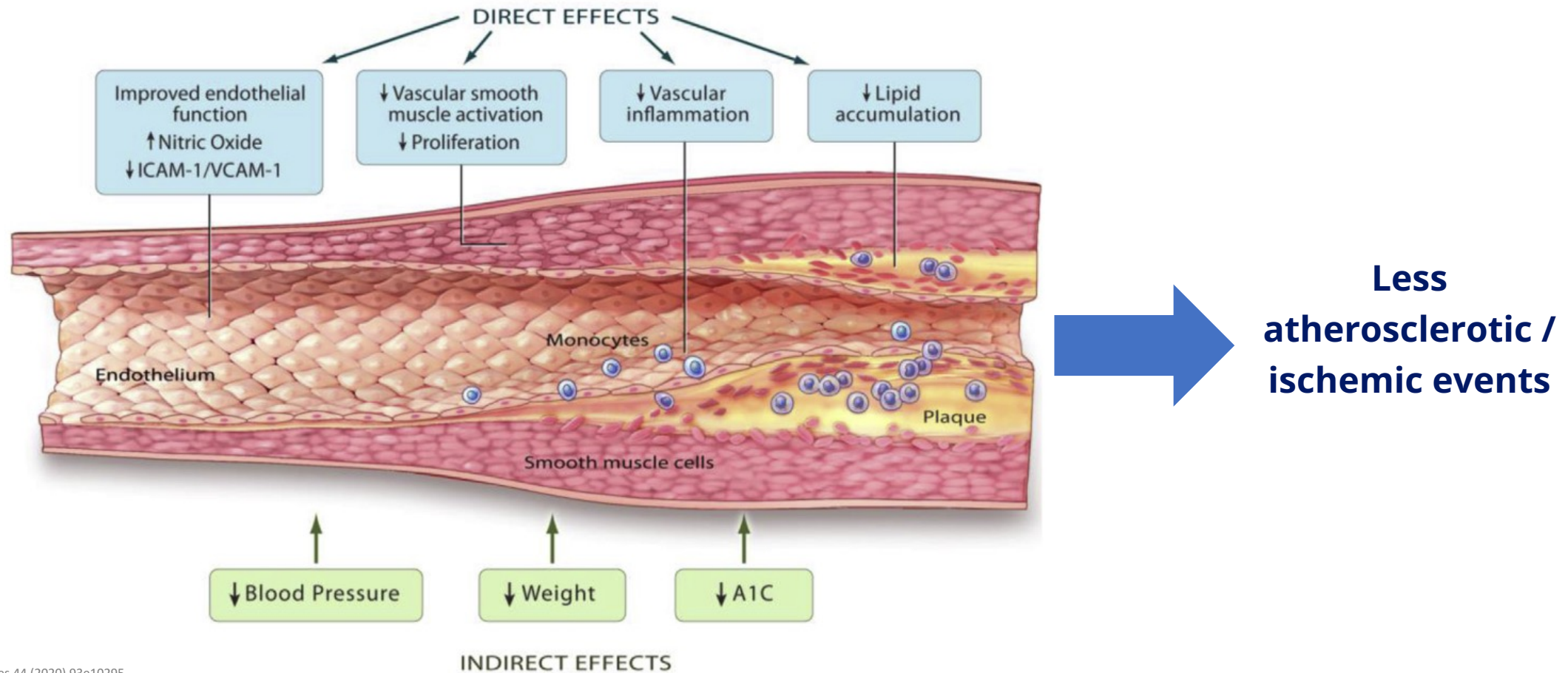
Potential mechanisms for beneficial effect of GLP-1 on cardiovascular risk factors







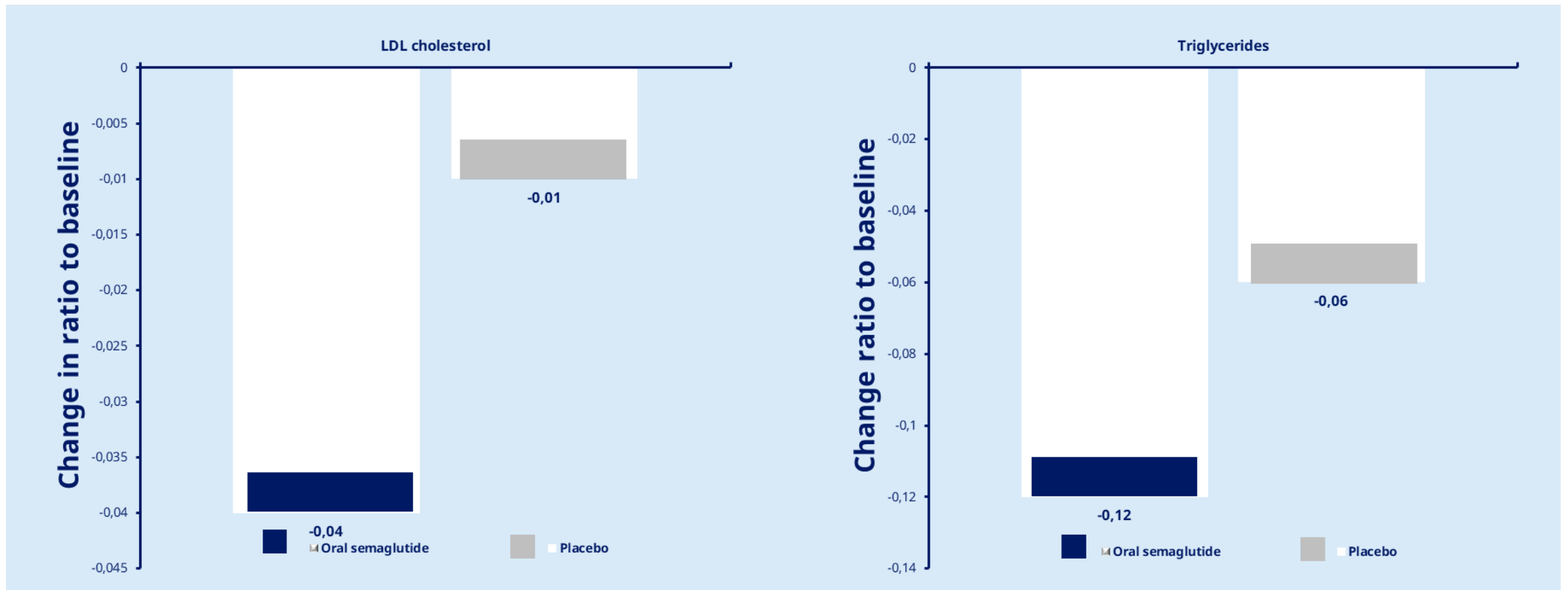
# Mechanisms whereby GLP-1 analogues modify the risk of cardiovascular outcomes





# Effects of semaglutide on cardiovascular system

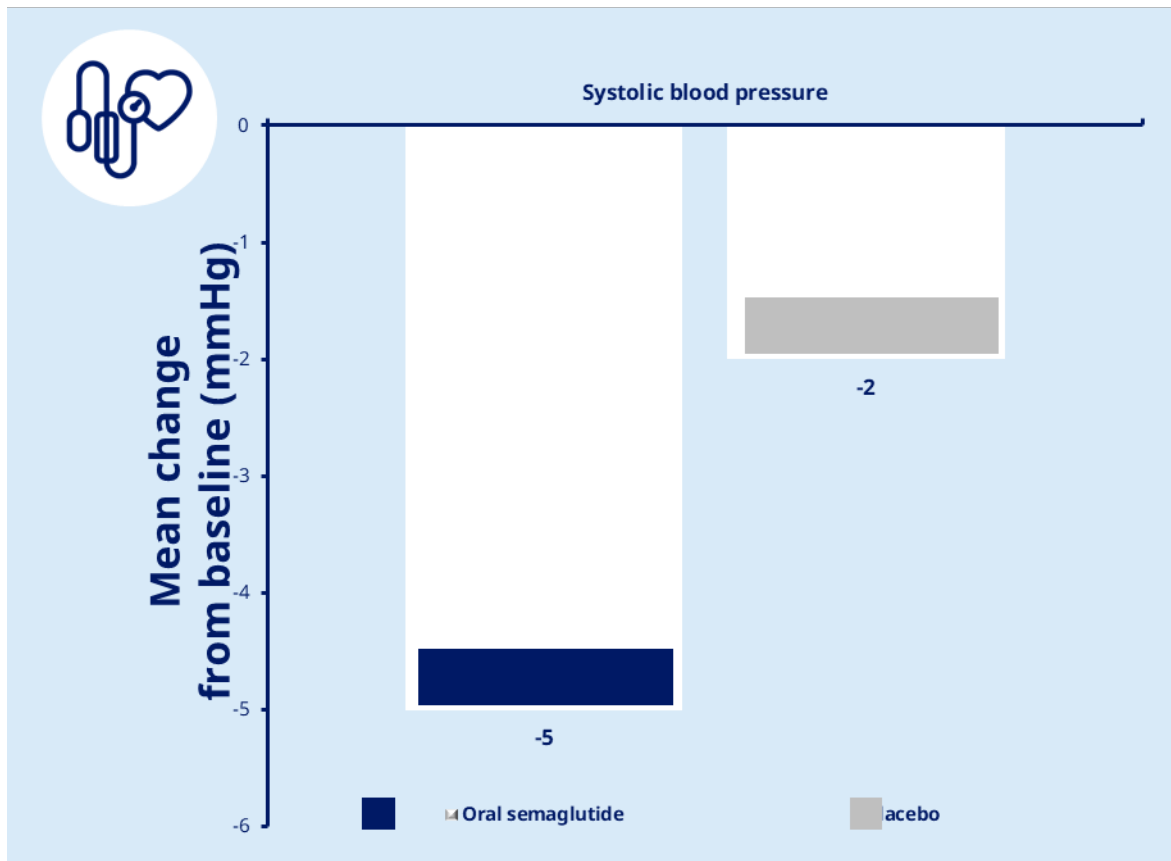
Oral semaglutide improves **blood lipids**





# Effects of semaglutide on cardiovascular system

Oral semaglutide reduces **systolic blood pressure**



Each 10 mmHg decrease in mean systolic blood pressure is associated with reductions in risk in people with T2D



**11%** for any complication related to diabetes



**16%** for deaths related to diabetes



**11%** for myocardial infarction

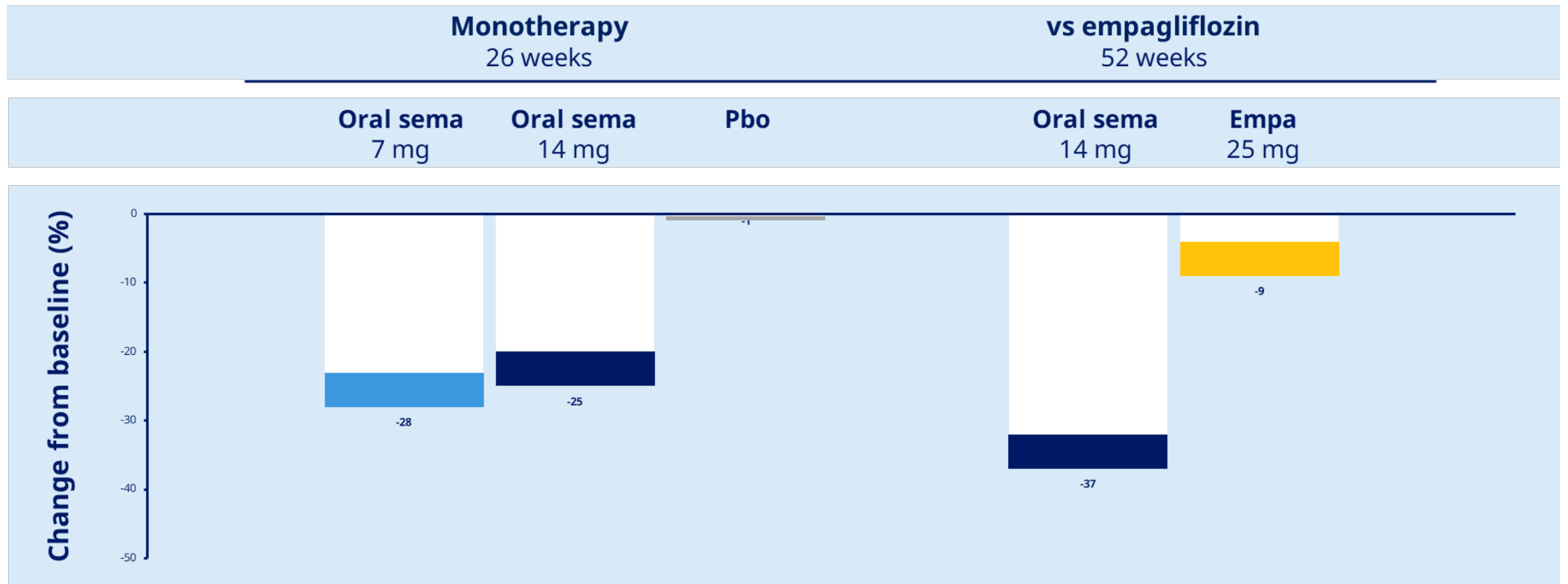


**10%** for microvascular complications



# Effects of semaglutide on cardiovascular system

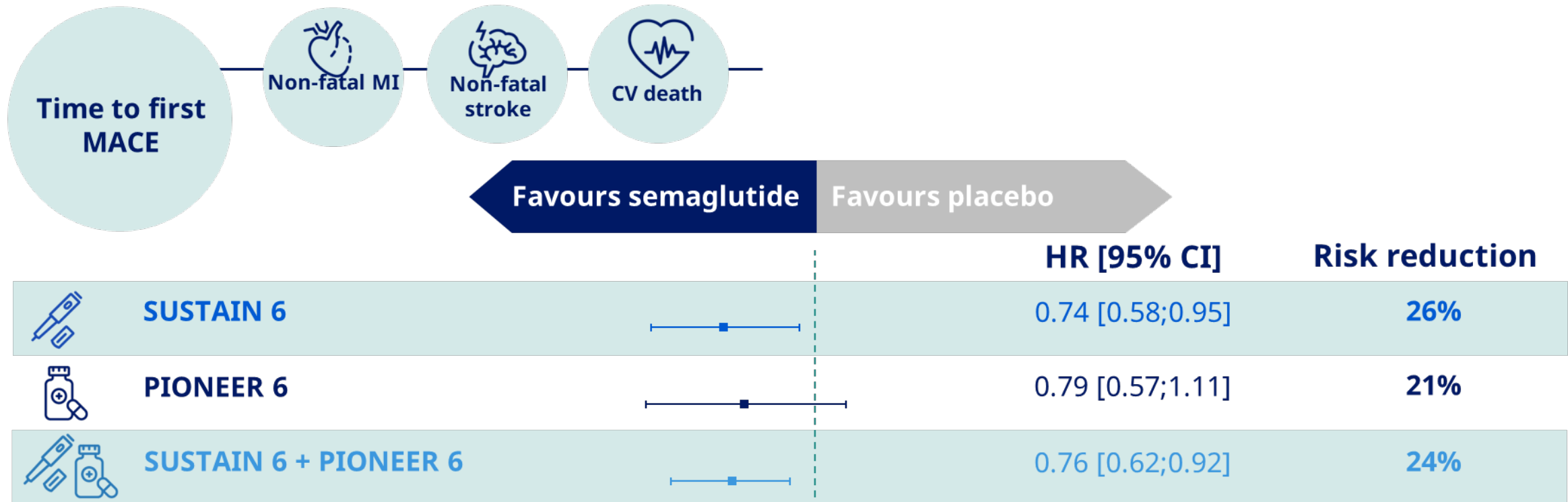
Semaglutide reduced **inflammation marker hsCRP** levels vs comparators





# Effects of semaglutide on cardiovascular system

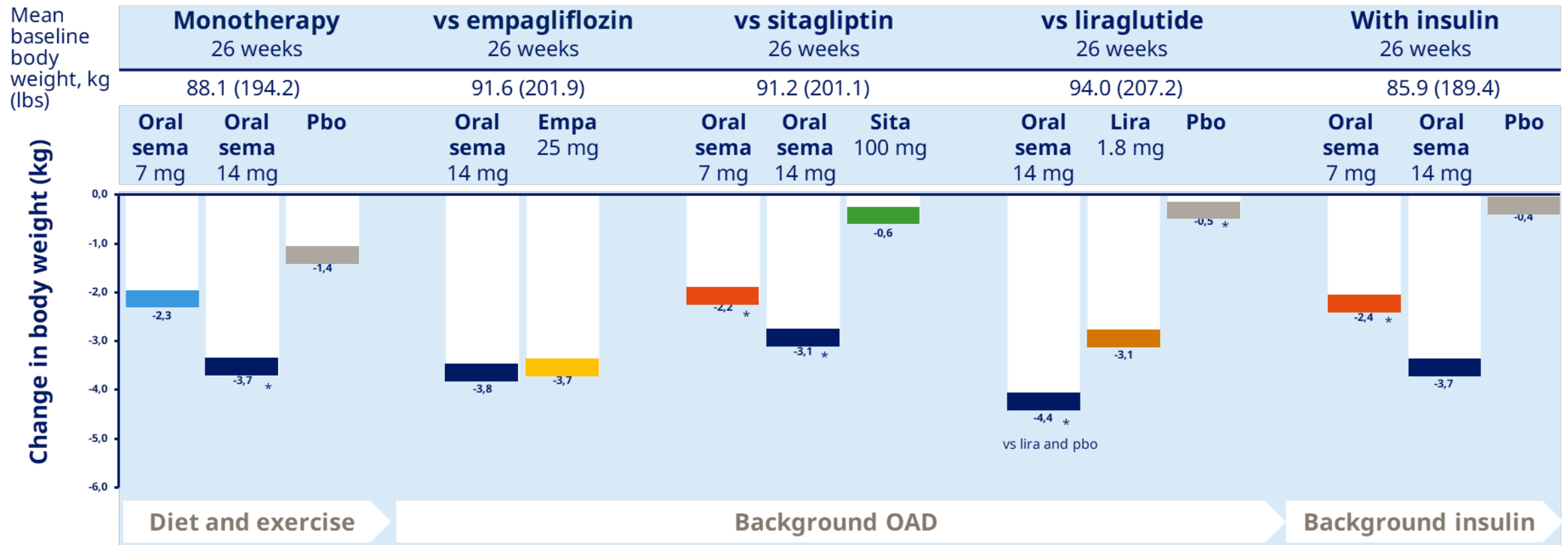
Semaglutide reduced time to first occurrence of **MACE** when compared with placebo in dedicated cardiovascular outcome studies





# Change in body weight with oral semaglutide

## The PIONEER programme



Results for semaglutide 3 mg are not shown, as this is not a treatment dose

\*Statistically significantly greater compared with placebo or active comparator. Treatment policy estimand.

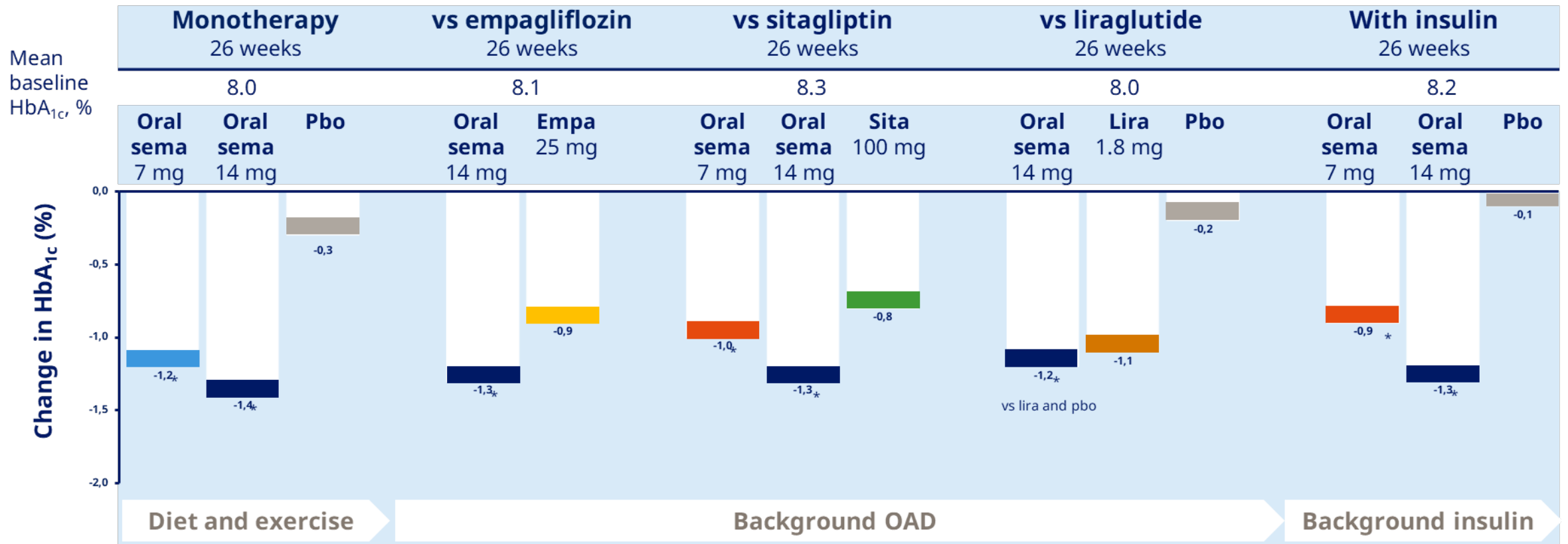
Empa, empagliflozin; Lira, liraglutide; OAD, oral antidiabetes drug; Pbo, placebo; Sema, semaglutide; Sita, sitagliptin.

Aroda VR et al. Diabetes Care 2019;42:1724-32; Rodbard HW et al. Diabetes Care 2019;42:2272-81; Rosenstock J et al. JAMA 2019;321:1466-80; Pratley R et al. Lancet 2019;394:39-50; Zinman B et al. Diabetes Care 2019;42:2262-71.



# Change in HbA1c with oral semaglutide

## The PIONEER programme



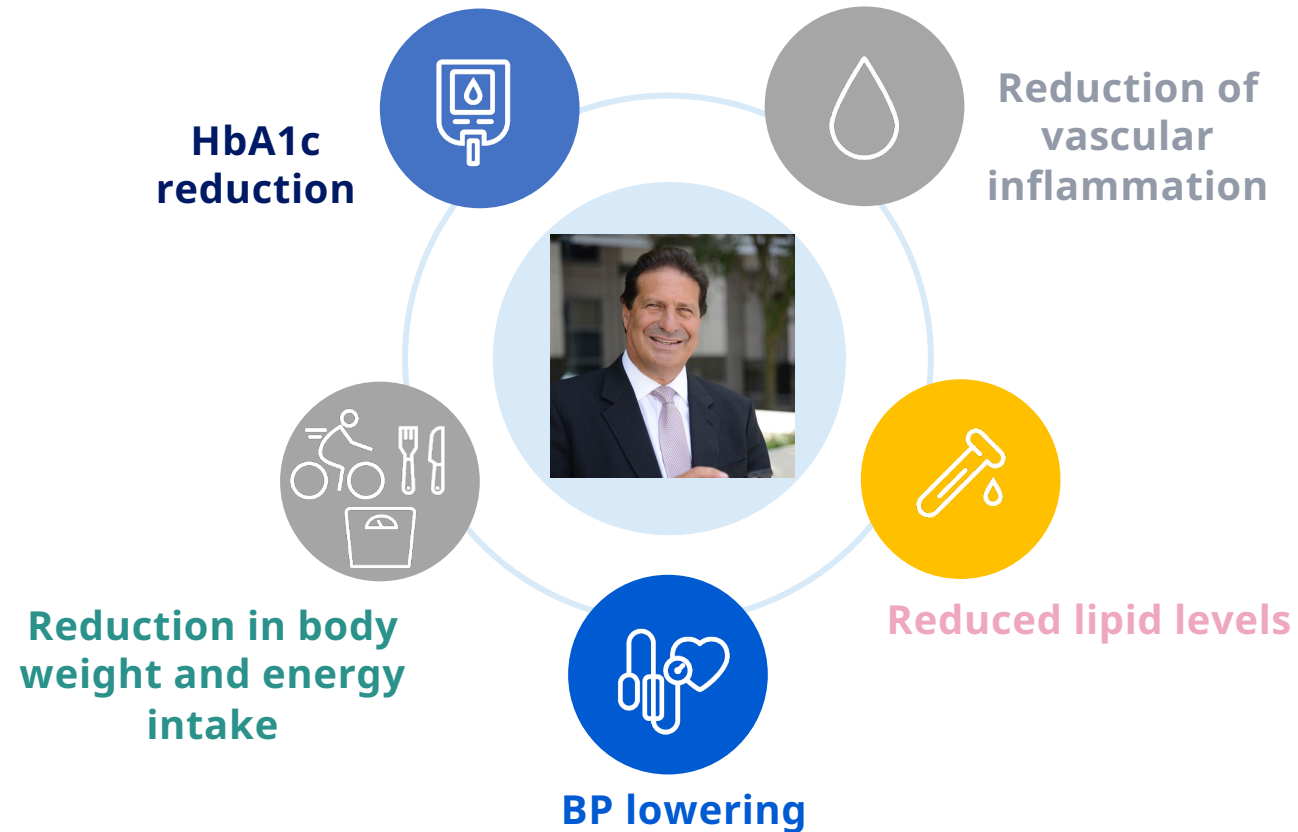
Results for semaglutide 3 mg are not shown, as this is not a treatment dose

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Empa, empagliflozin; Lira, liraglutide; OAD, oral antidiabetes drug; Pbo, placebo; Sema, semaglutide; Sita, sitagliptin.

Aroda VR et al. Diabetes Care 2019;42:1724-32; Rodbard HW et al. Diabetes Care 2019;42:2272-81; Rosenstock J et al. JAMA 2019;321:1466-80; Pratley R et al. Lancet 2019;394:39-50; Zinman B et al. Diabetes Care 2019;42:2262-71.



# Improving the cardiometabolic risk profile of George with semaglutide



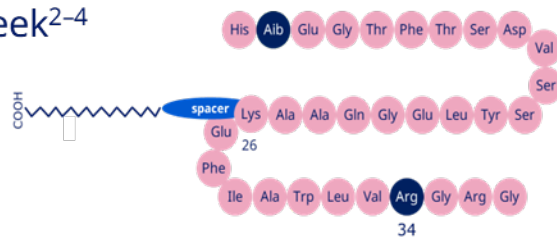




# Oral semaglutide (Rybelsus®)

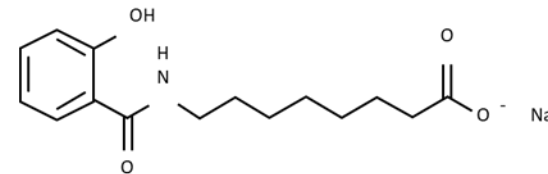
## Semaglutide

- 94% homology to human GLP-1<sup>1</sup>
- t<sub>1/2</sub> of approximately 1 week<sup>2-4</sup>
- Amino acid substitution protects against DPP-4 degradation<sup>1</sup>



## SNAC (Sodium N-(8-(2-hydroxybenzoyl) Amino) Caprylate)

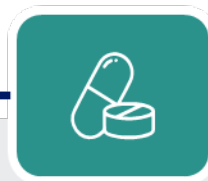
- SNAC causes a local increase of pH that protects against proteolytic degradation and facilitates absorption across the gastric epithelium<sup>5</sup>



- Absorption enhancer
- Increase bioavailability of oral administration<sup>5</sup>



Once-weekly s.c. semaglutide



Once-daily oral semaglutide

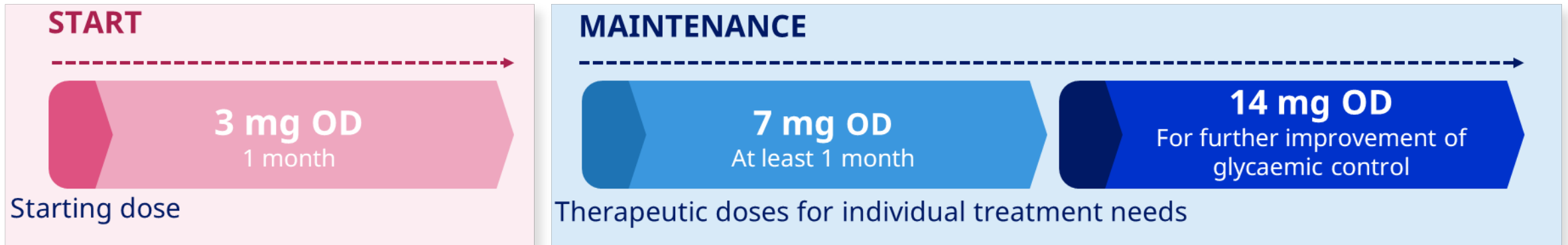
Effective reductions in HbA<sub>1c</sub>, bodyweight and CV risk factors<sup>6-11</sup>





# Practical use of oral semaglutide (Rybelsus®)

Dose escalation is recommended to mitigate gastrointestinal adverse events



## Additional strategies for mitigation of gastrointestinal adverse events



Educate and set the expectations for patients



Decrease food intake and avoid fatty meals

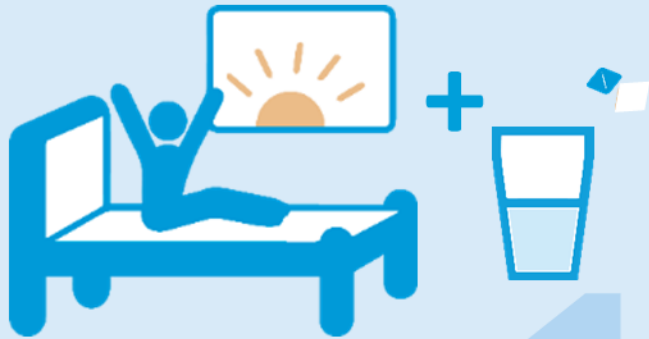


Keep a food diary to identify foods that worsen nausea



## Dosing instructions for oral semaglutide (Rybelsus®)

Wake up fasting and take your semaglutide tablet with up to half a glass of water (approximately 120 mL/4 fl oz)



1

Wait at least **30 minutes** before eating, drinking or taking any other oral medication



2

Have your first meal and drink of the day and take any other medications you need

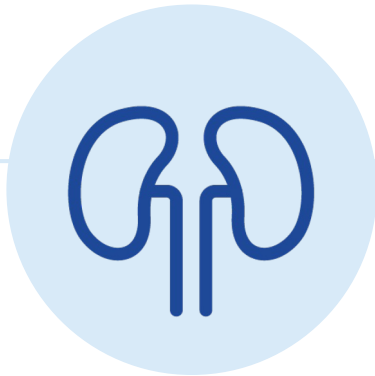


3

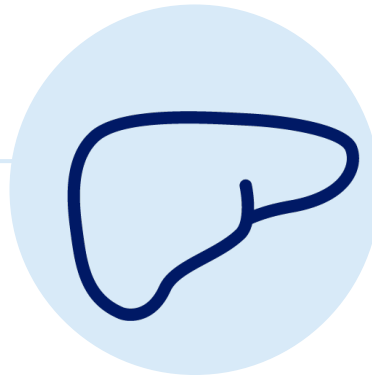


## Practical use of oral semaglutide (Rybelsus®)

No dose adjustment of oral semaglutide is required in special populations



Patients with mild,  
moderate, or severe  
renal impairment<sup>a</sup>



Patients with hepatic  
impairment<sup>b</sup>

65+

Elderly patients<sup>c</sup>



# Reimbursement of GLP-1 analogues in Belgium

## Voor uw type 2 diabetespatiënten

- Onvoldoende gecontroleerd ( $HbA_{1c} > 7,5\%$ )  
*EN*
- Met een body mass index (BMI)  $\geq 30 \text{ kg/m}^2$   
*EN*
- Voorafgaande behandeling gedurende minstens 3 maanden met **tenminste** metformine

In het zorgtraject



Zonder attest

Buiten het zorgtraject



Met attest:

- 1<sup>ste</sup> Aanvraag voor 12 maanden
- 2<sup>de</sup> Aanvraag voor 12 maanden  $HbA_{1c} < 7\%$  of een daling van  $\geq 1\%$

**Het is niet nodig** een nieuwe aanvraag in te dienen bij aanpassing van de dosis.

## Pour vos patients diabétiques de type 2

- Insuffisamment contrôlés ( $HbA_{1c} > 7,5\%$ )  
*ET*
- Avec un indice de masse corporel (IMC)  $\geq 30 \text{ kg/m}^2$   
*ET*
- Sous un traitement préalable d'au moins 3 mois sous au **minimum** de la metformine

Dans le trajet de soin



Sans attestation

Hors trajet de soin



Avec attestation :

- 1<sup>ère</sup> demande pour 1 an
- Prolongation pour 1 an si l' $HbA_{1c} < 7\%$  ou en cas de diminution de  $\geq 1\%$

**Il n'est pas nécessaire** d'introduire une nouvelle demande en cas de changement de dosage.



# Rybelsus® : the opportunity for an early treatment with a GLP-1 RA in T2D patients



Benefits on  
cardiometabolic risk  
factors<sup>1-2</sup>



Reduction in body  
weight and energy  
intake<sup>3,4</sup>



Significant HbA<sub>1c</sub>  
reduction superior to all  
comparators<sup>3</sup>

CARDIO  
SCOPIE

**THANK YOU**

