Diabetes Management Guideline 2022

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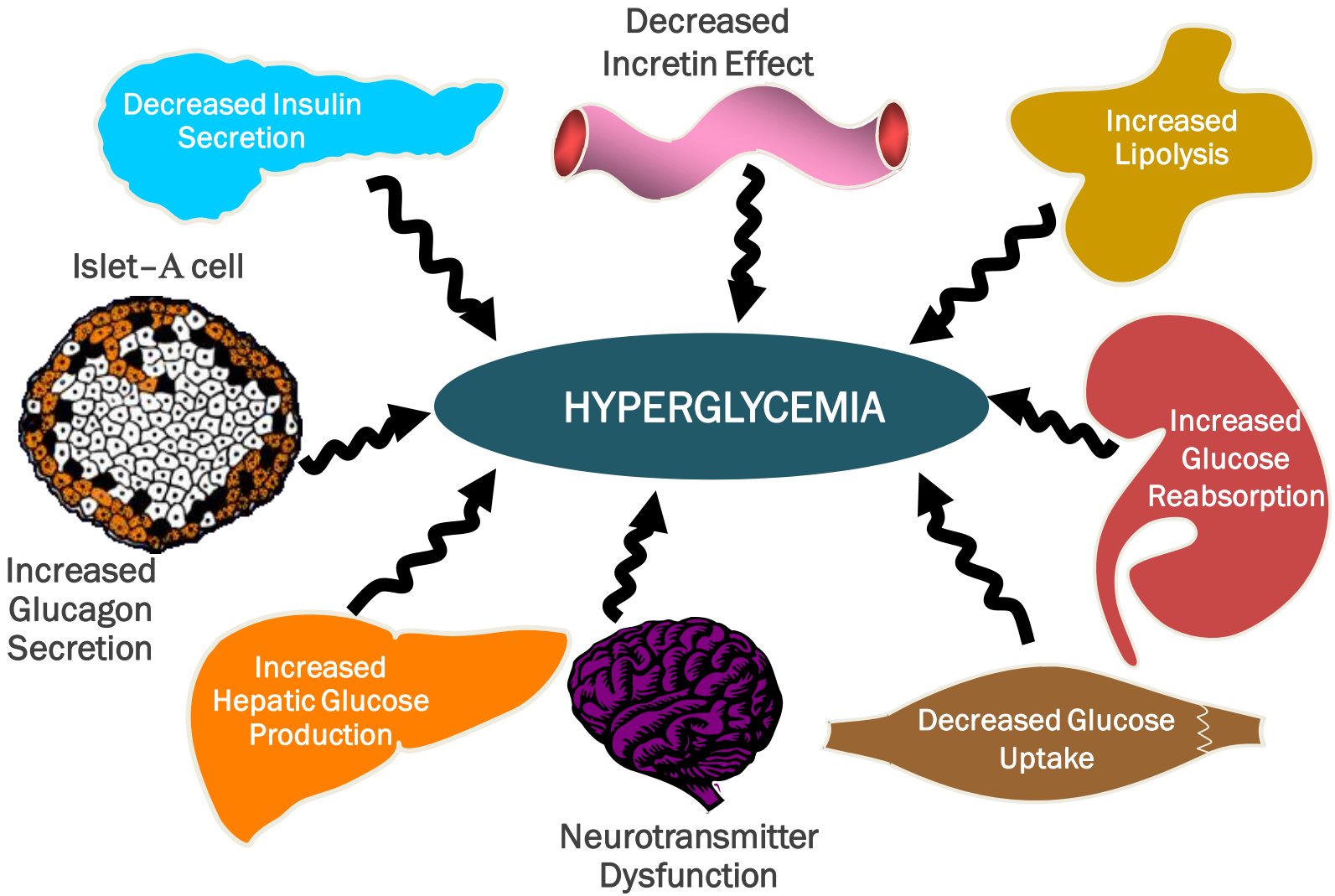
Presentation Outlines

- Lowering blood glucose levels in patients with diabetes mellitus is a too simplistic goal. The key component being how to lower blood sugar and how much.
- Cardiovascular disease is the leading cause of mortality and morbidity among diabetic patients.
- Lower Cardiovascular Risk with Diabetic Drugs: A Paradigm Shift from Glucocentricity to Cardio Protectiveness
- Key new additions in the 2019 guidelines
- ADA Standard of care 2022
- FDA (Food and Drug Administration) and European medicine agency (EMA) made it mandatory to have CVOT (Cardiovascular outcome trial) as an integral part of drug approval process.

Ominous Octet



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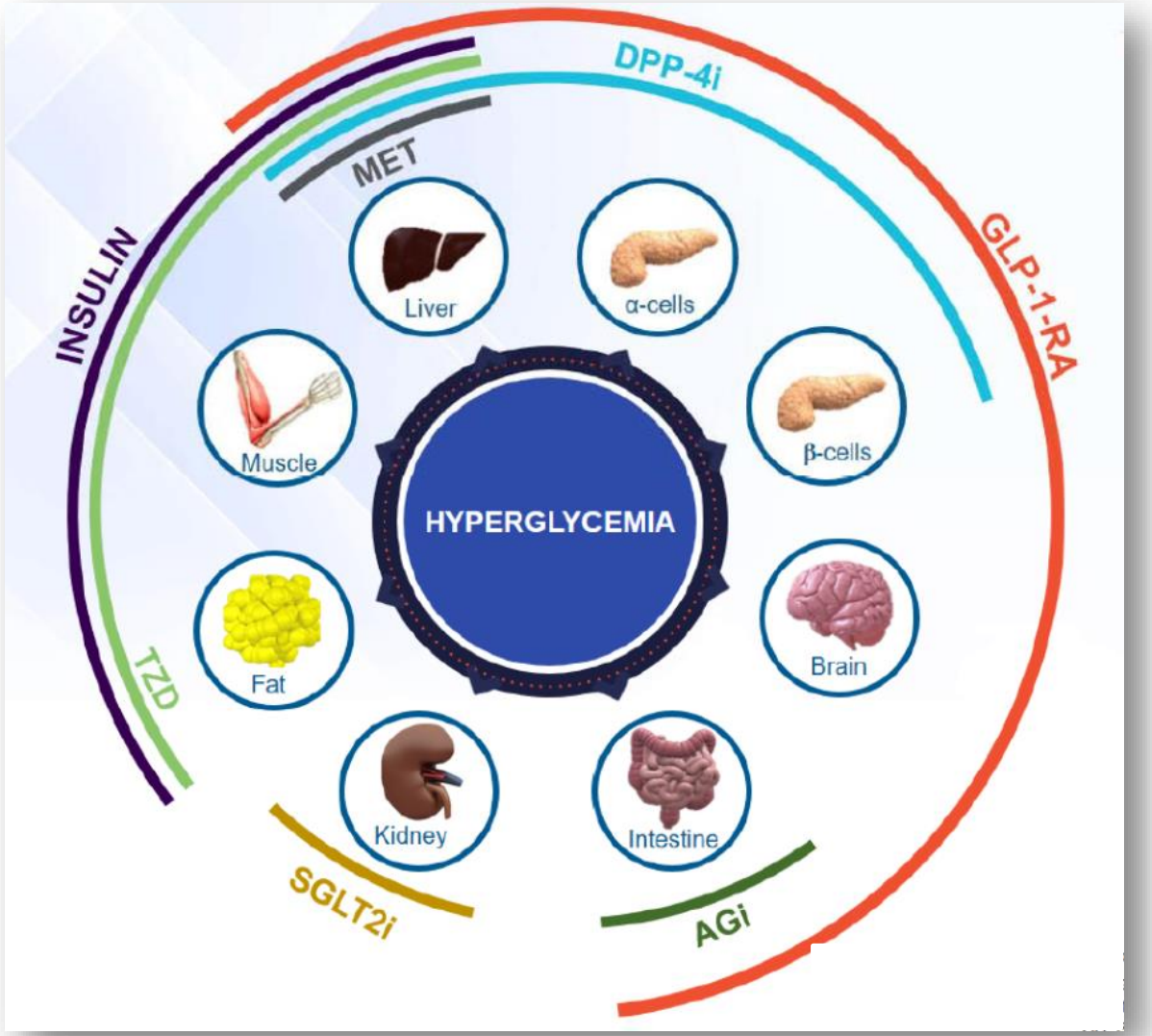
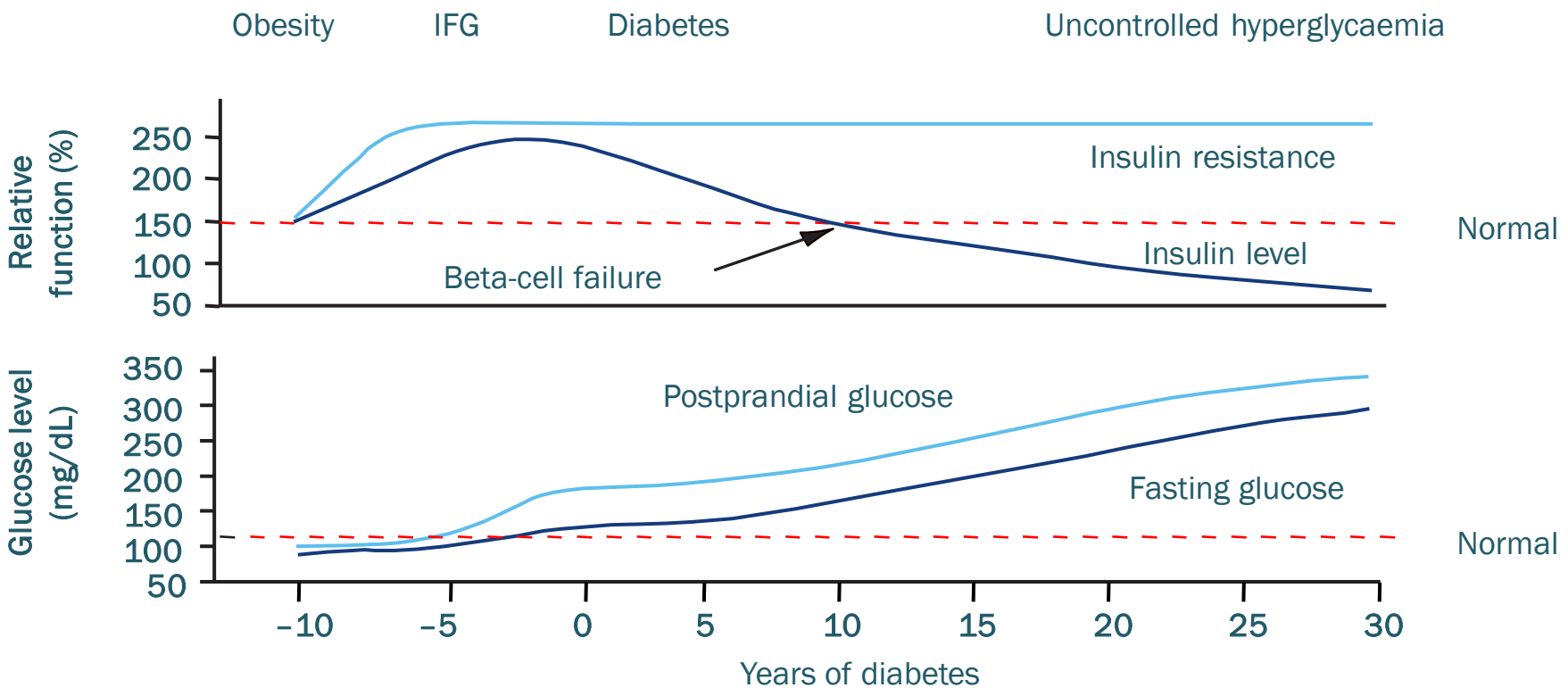
Consider Therapies Targeting Different Pathophysiologic Abnormalities

- MET
- INSULIN
- GLP-1 RA
- SGLT2i
- DPP-4i
- TZD
- AGi



1. Ferrannini E, et al. Eur Heart J. 2015;36:2288-96. 2. ADA. Diabetes Care. 2017;40(Suppl 1):S1-135

Natural History: Insulin Secretion and Blood Glucose Control

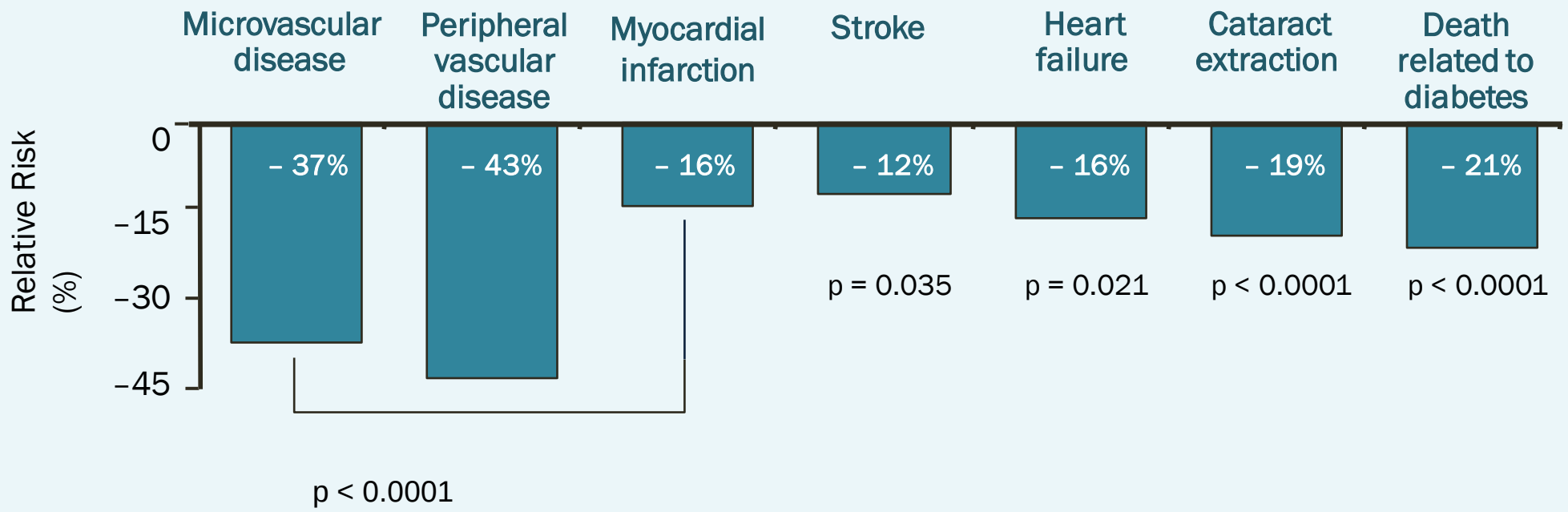


IFG, impaired fasting glucose

Adapted from Bergenstal et al. In: Degroot & Jameson (eds). Endocrinology 2001;821–35

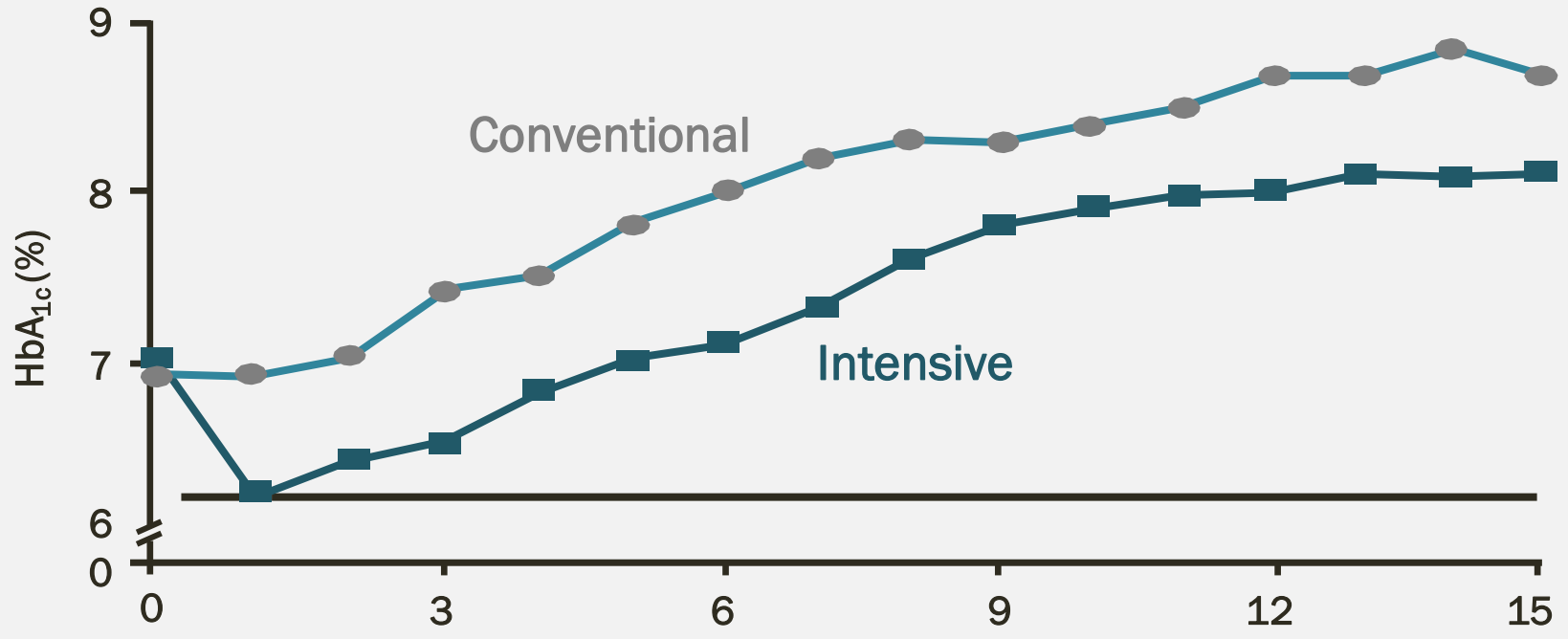
Effective control of DM reduces risk of complications – UKPDS 35

1% decrease in HbA_{1c} correlates with reduction in risk of :-



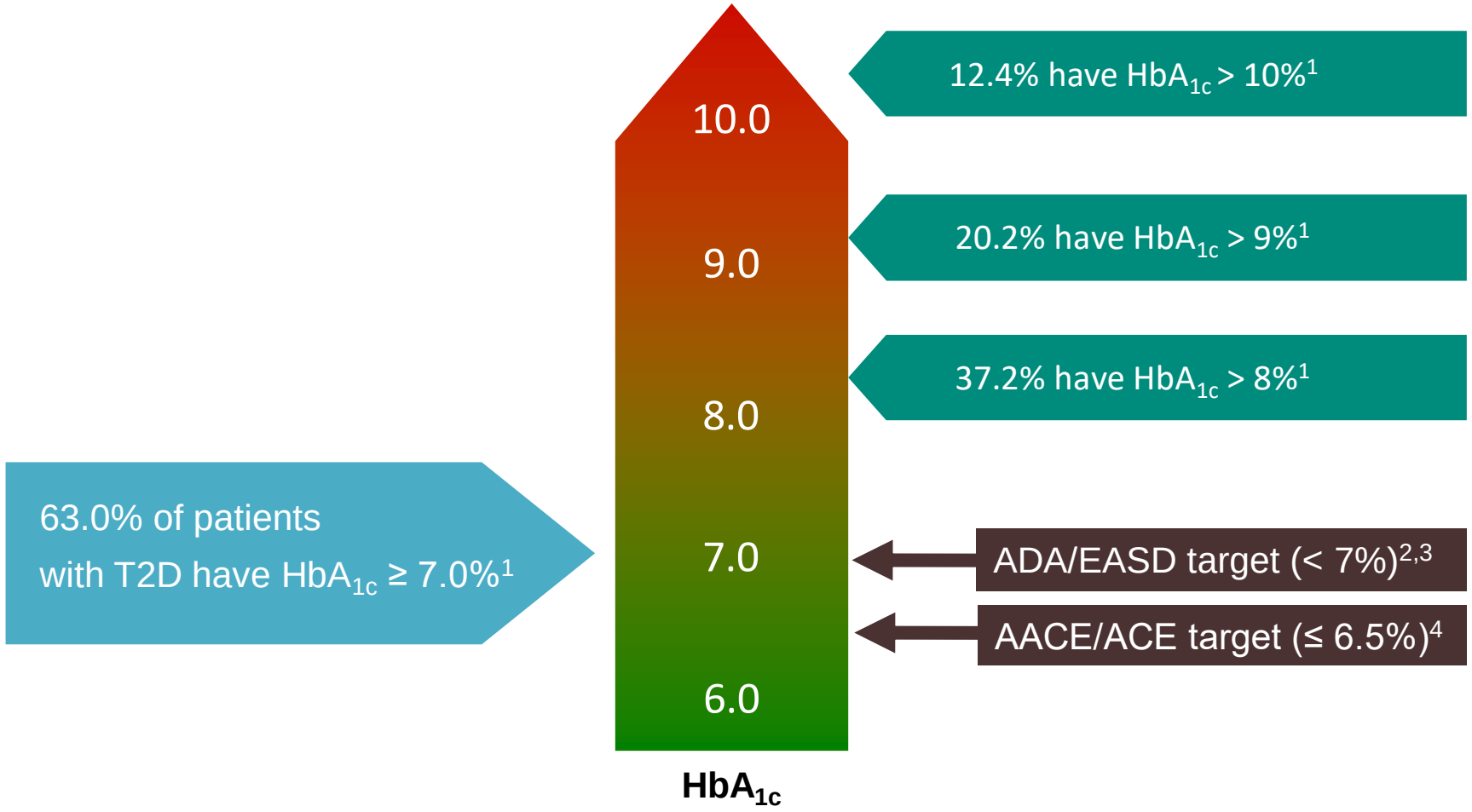
Stratton IM, et al. *BMJ*. 2000;321:405-412

UKPDS: Progressive decline in glycemic control irrespective of treatment regime



UKPDS, 1998

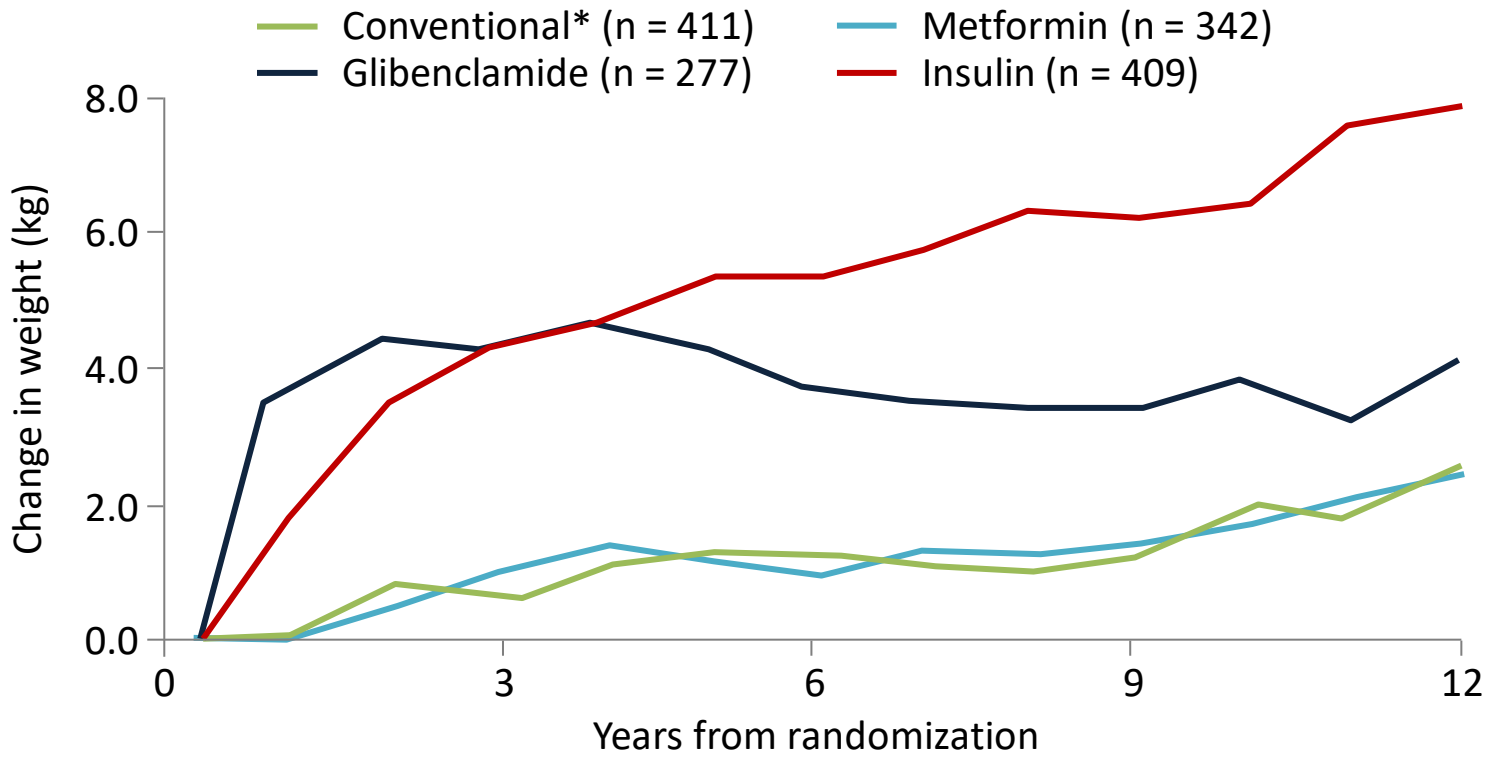
The majority of patients with T2D remain above glycaemic goals



AACE, American Association of Clinical Endocrinologists;
ACE, American College of Endocrinology; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; HbA_{1c}, glycosylated haemoglobin; T2D, Type 2 Diabetes. 1. Saydah SH, et al. JAMA. 2004;291:335–342; 2. ADA. Diabetes Care. 2013;36:S11–S66;
3. Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364–1379;
4. AACE/ACE. *Endocr Pract*. 2009;15:540–559.

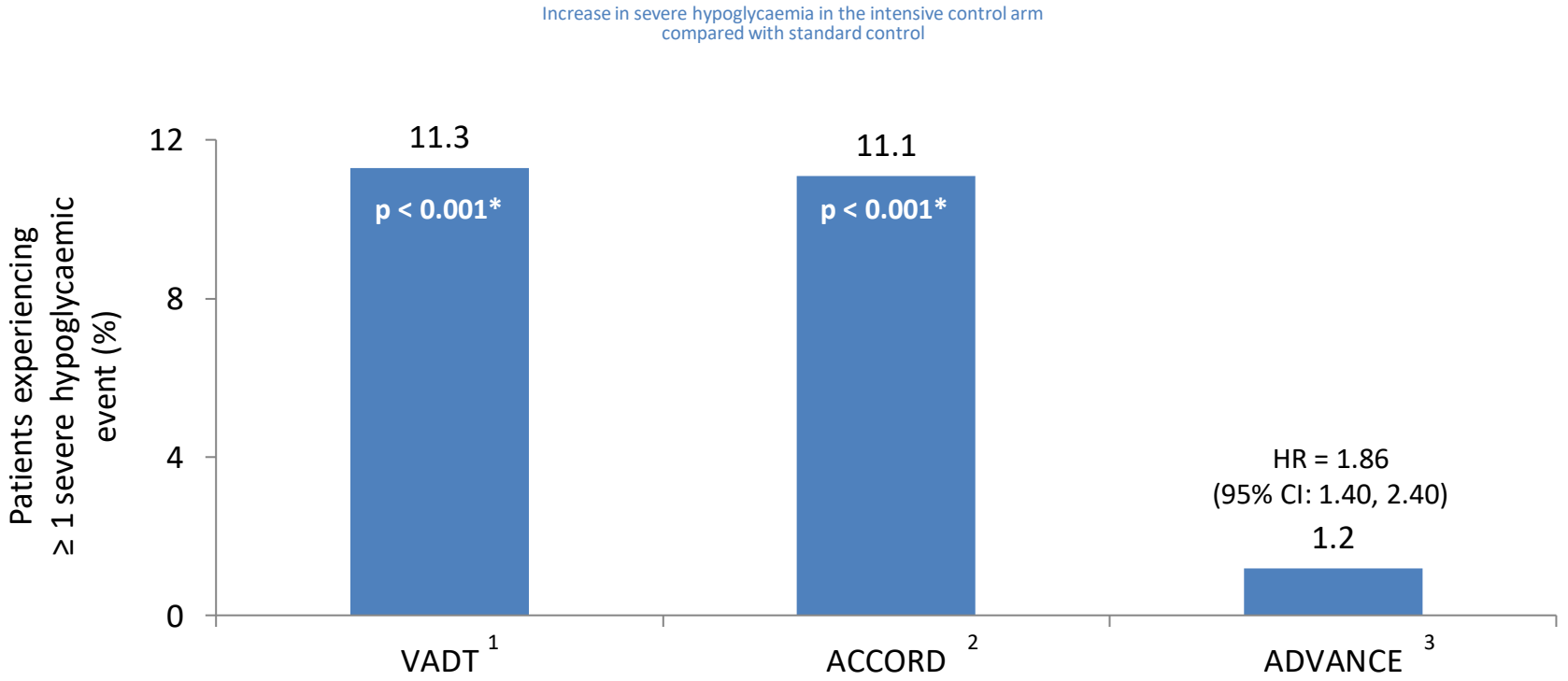
Some therapy options for T2D are associated with weight gain

UK Prospective Diabetes Study 34



T2D, Type 2 Diabetes. *Diet initially then sulphonylureas, insulin and/or metformin if fasting plasma glucose > 15 mmol/L. UK Prospective Diabetes Study 34. *Lancet*. 1998;352:854–865.

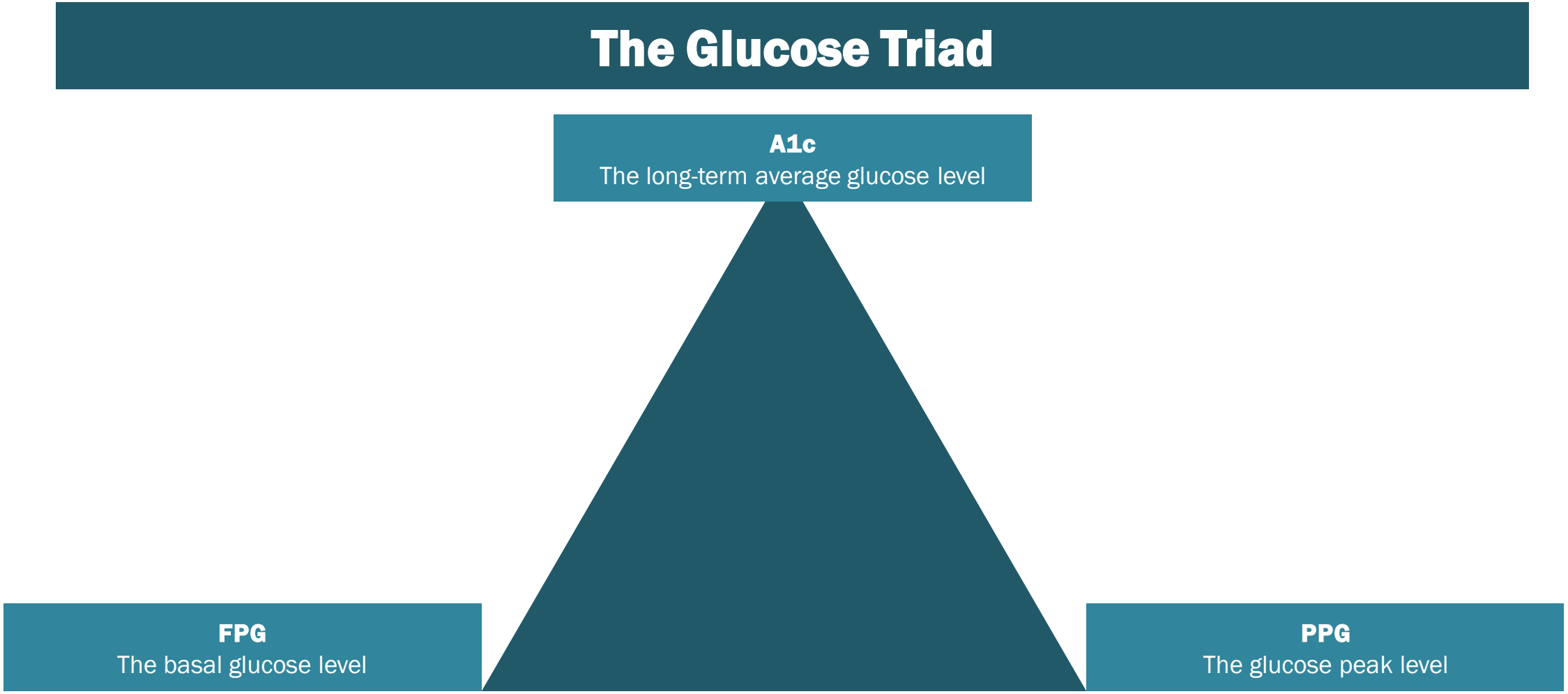
Low HbA_{1c} targets may be associated with a high risk of severe hypoglycaemia



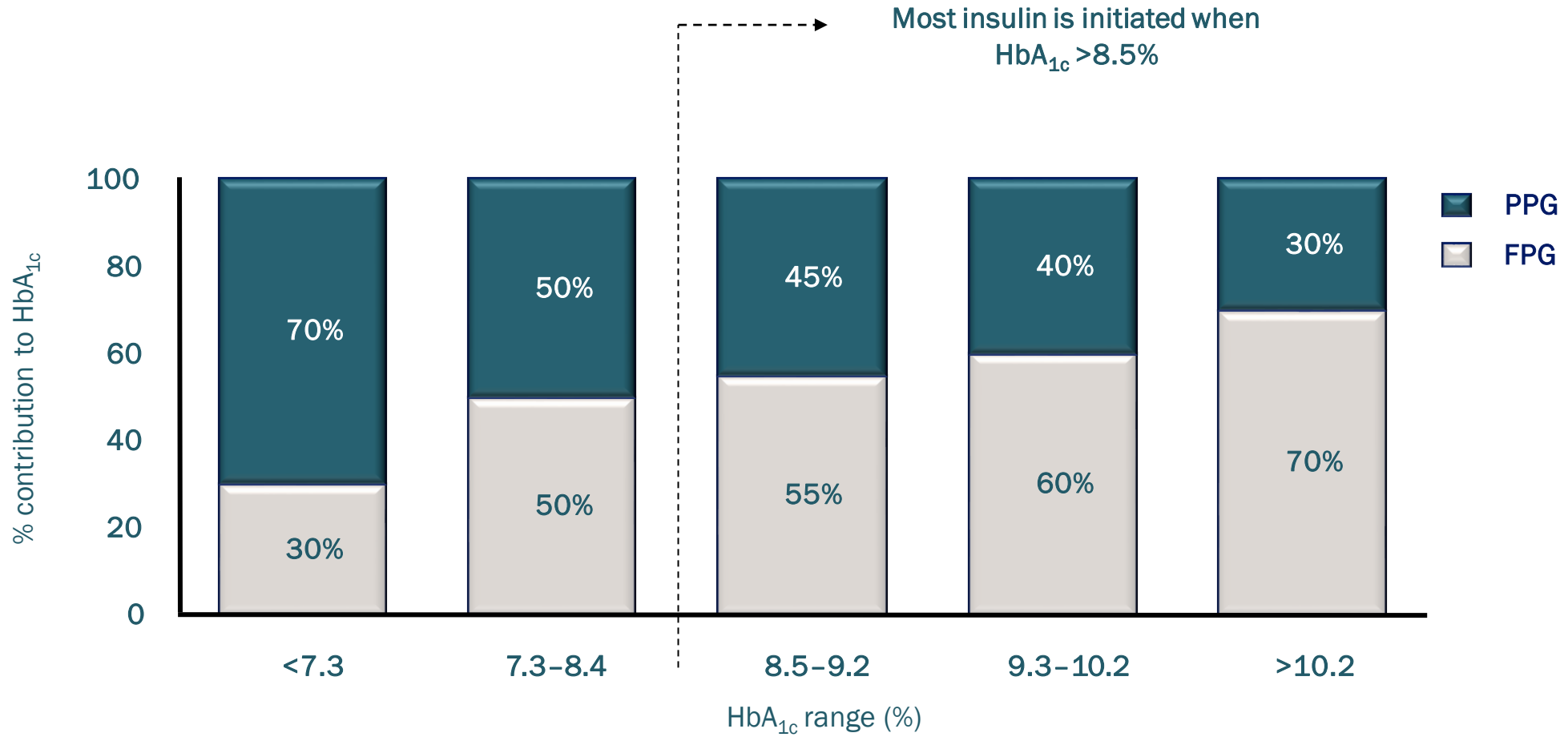
Definitions of severe hypoglycaemia	
VADT	Severe change in consciousness, including loss of consciousness
ACCORD	Requiring assistance of another person and plasma glucose < 2.8 mmol/L or symptoms that promptly resolved with oral carbohydrate, intravenous glucose, or glucagon
ADVANCE	Requiring assistance of another person and plasma glucose < 2.8 mmol/L

CI, confidence interval; HbA_{1c}, glycosylated haemoglobin; HR, hazard ratio.
*Comparison between intensive control vs standard control. 1. Skyler JS, et al. *J Am Coll Cardiol*. 2009;53:298–304; 2. ACCORD study Group. *N Engl J Med*. 2008;358:2545–2559; 3. ADVANCE Study Group. *N Engl J Med*. 2008;358:2560–2572.

For Optimal Diabetes Management, We Should Target: FPG & PPG

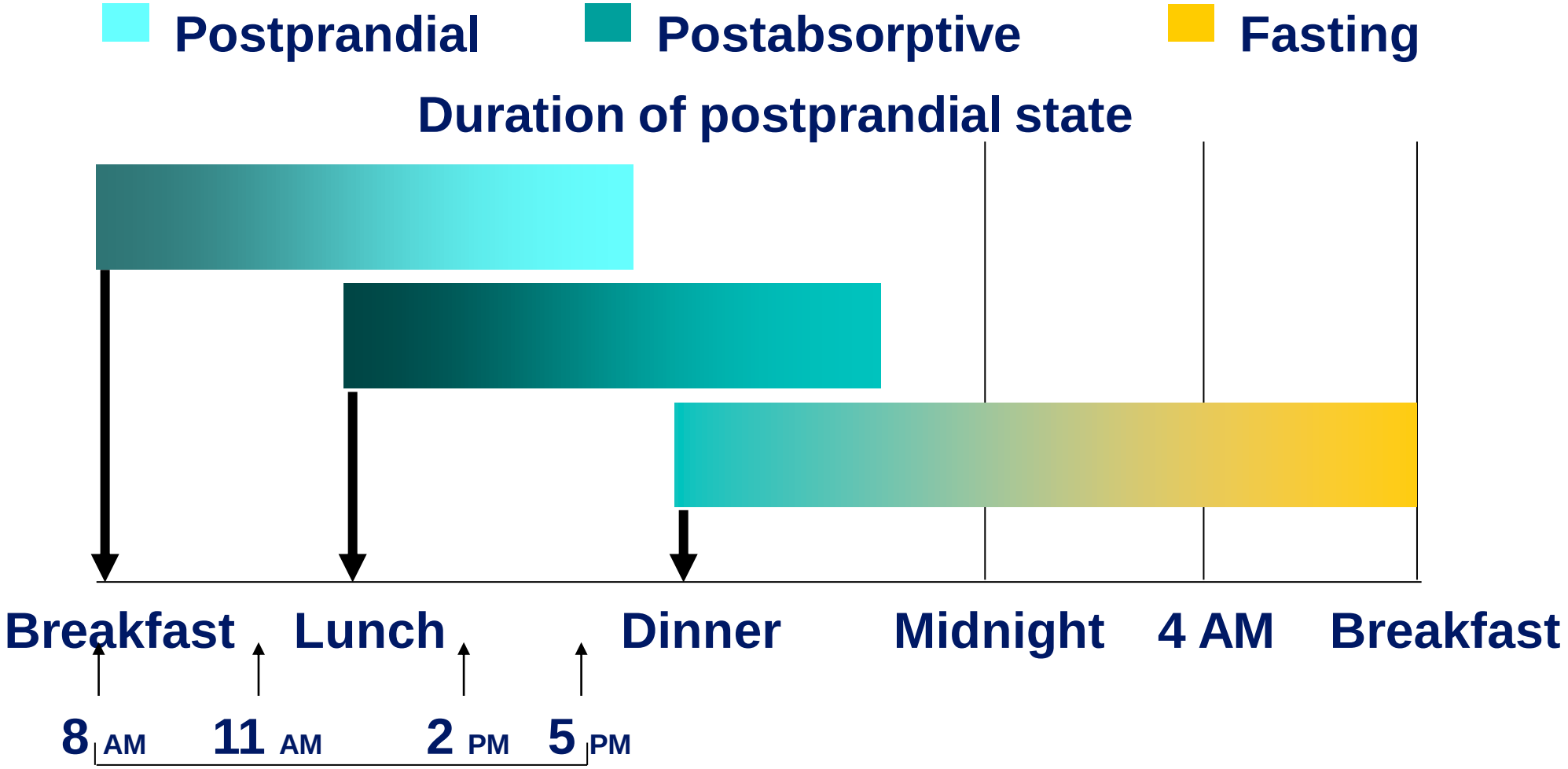


To normalize blood glucose, both FPG and PPG must be reduced



Adapted from Monnier L et al. Diabetes Care 2003;26:881–5

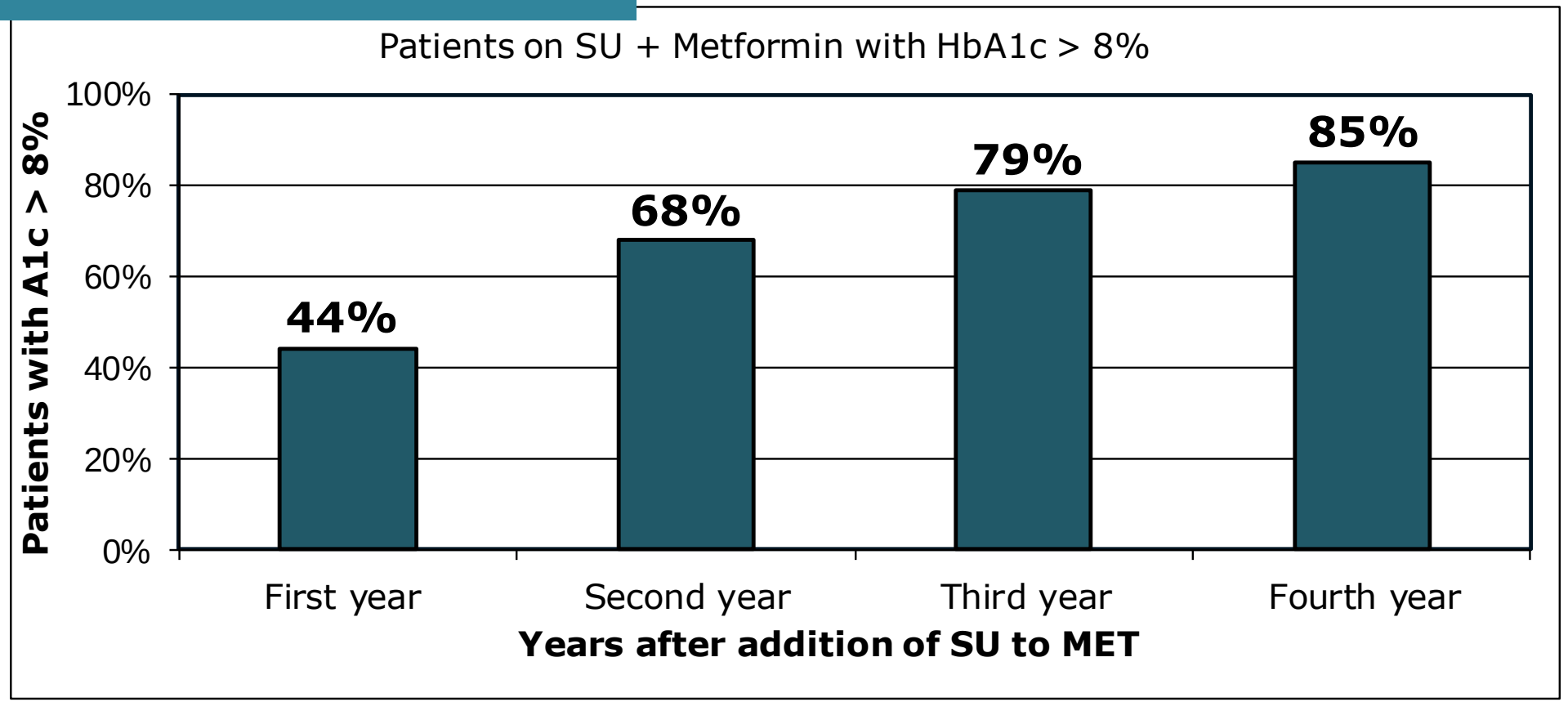
Patients With Type 2 DM may spend more than 12 Hours per day in the P.P. State



Adapted from Monnier L. *Eur J Clin Invest.* 2000;30(suppl 2):3-11.

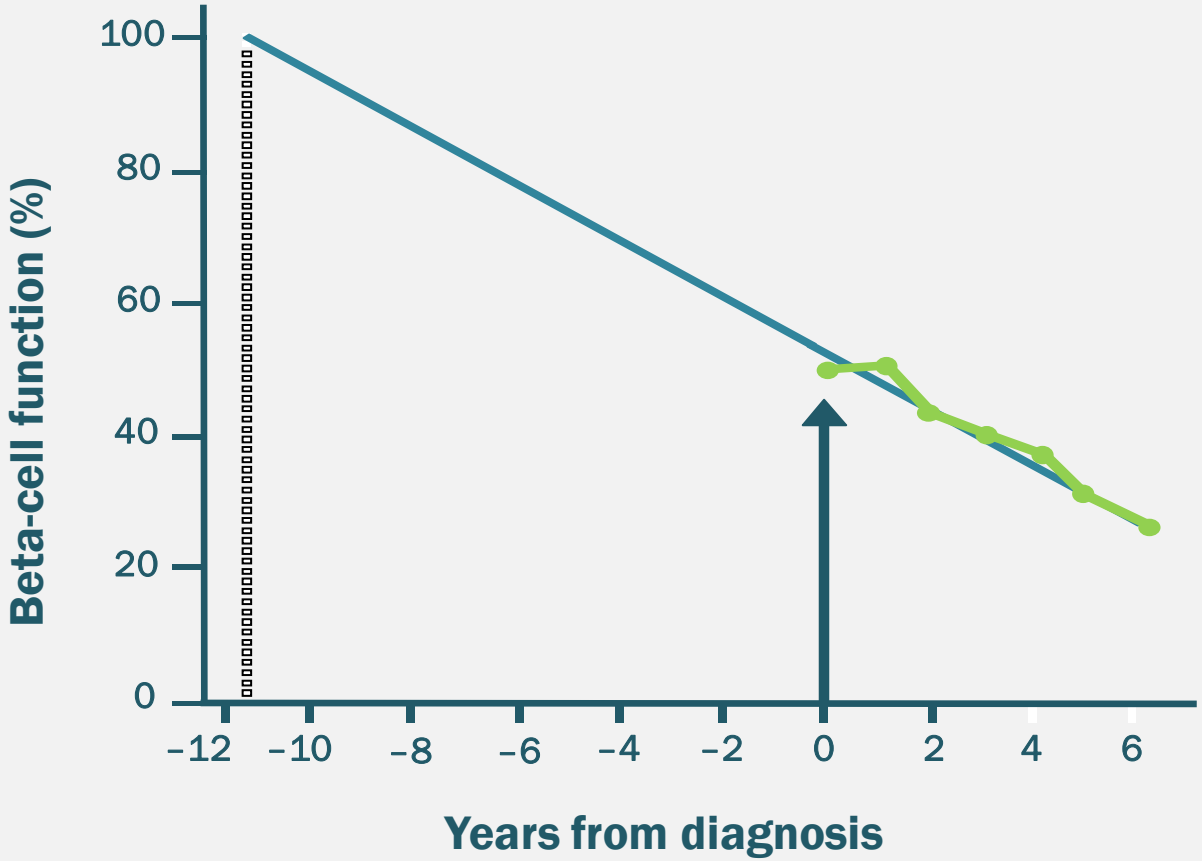
Not only OAD Mono-therapy fails but also combination OADs

2220 patients with T2DM treated with MET + SU

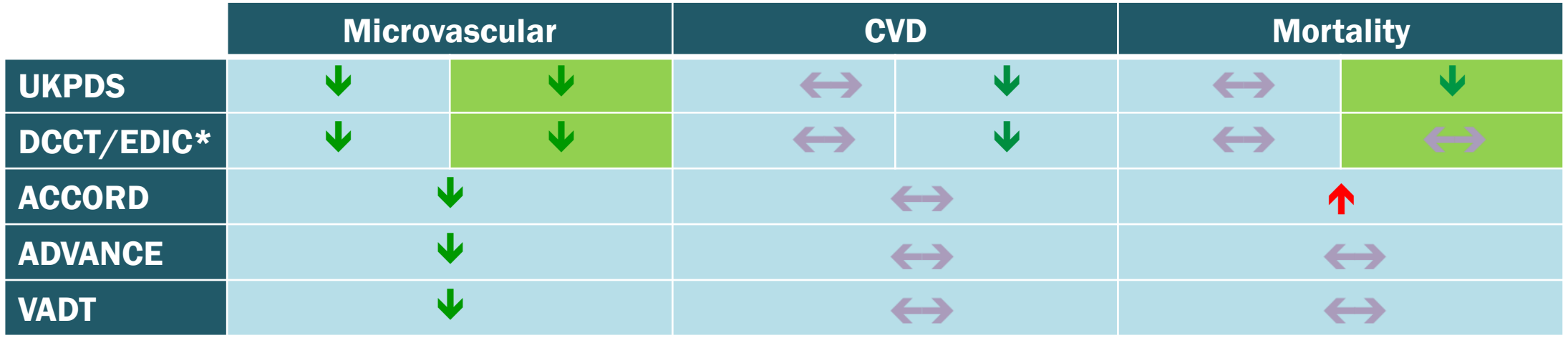


Cook *et al. Diabetes Care* 2005; 28:995-1000

Progressive loss of beta-cell function in the UKPDS



Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials



*In type 1 diabetes
CVD, cardiovascular disease

Adapted from Kendall *et al*. © International Diabetes Center 2009

UKPDS Group. *Lancet* 1998;352:854–65; Holman *et al. N Engl J Med*. 2008;359:1577–89; DCCT Research Group. *N Engl J Med* 1993;329;977–86; Nathan *et al. N Engl J Med* 2005;353:2643–53; Gerstein *et al. N Engl J Med* 2008;358:2545–59; Patel *et al. N Engl J Med* 2008;358:2560–72; Duckworth *et al. N Engl J Med* 2009;360:129–39 (erratum in *N Engl J Med*. 2009;361:1028); Moritz. *N Engl J Med* 2009;361:1024–5

IDF Guidelines

	If not at target (generally HbA_{1c} <7%)	Alternative approach
First line	Metformin	SU α-glucosidase inhibitor
Second line	SU	Metformin a-glucosidase inhibitor DPP-4i TZD
Third line	**Basal insulin** **Premix insulin** α-glucosidase inhibitor DPP-4i TZD	GLP-1 agonist
Fourth line	**Premix insulin** **Basal insulin** **Basal–bolus insulin**	

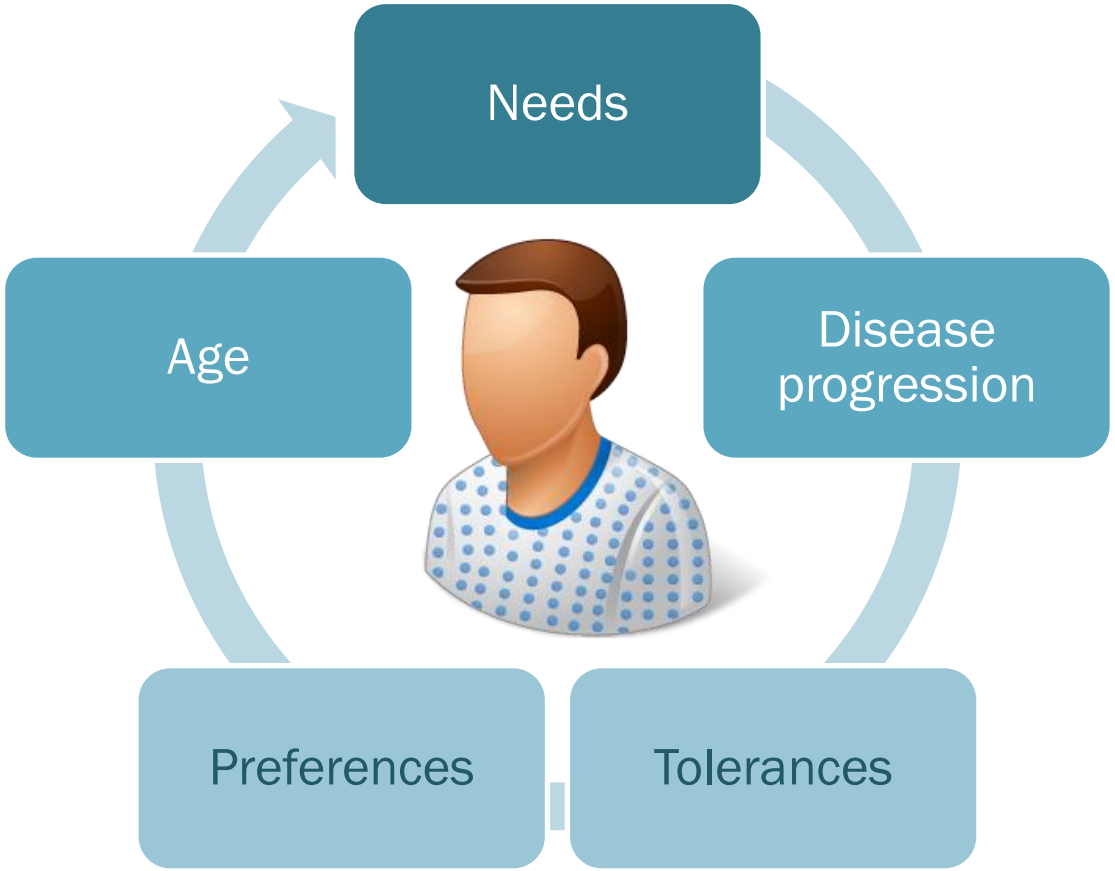
Recent updates to treatment guidelines

- *Advise people with diabetes that maintaining HbA_{1c} below 7.0% [53 mmol/mol] minimises the risk of developing complications*
- *If starting insulin, add basal insulin or use premix insulin*

Adapted from the IDF treatment algorithm for people with type 2 diabetes. www.idf.org/treatment-algorithm-people-type-2-diabetes

ADA/EASD: Patient Centered Approach

- Metformin
- SGLT-2 inhibitors
- Dopamine-2 agonists
- Amylin mimetics
- α-glucosidase inhibitors
- Insulin

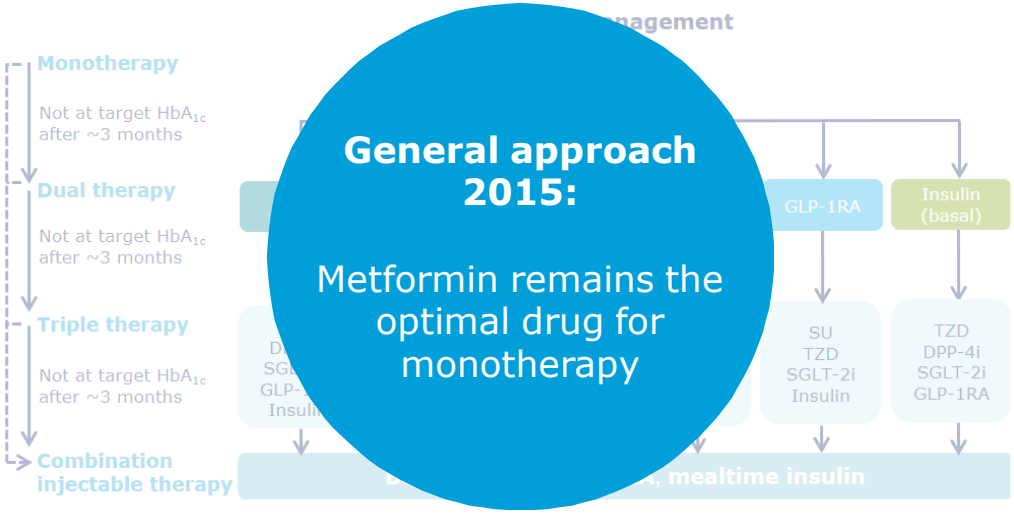


- SUs
- Glinides
- GLP-1 RAs
- DPP-4is
- TZDs
- Bile acid sequestrants

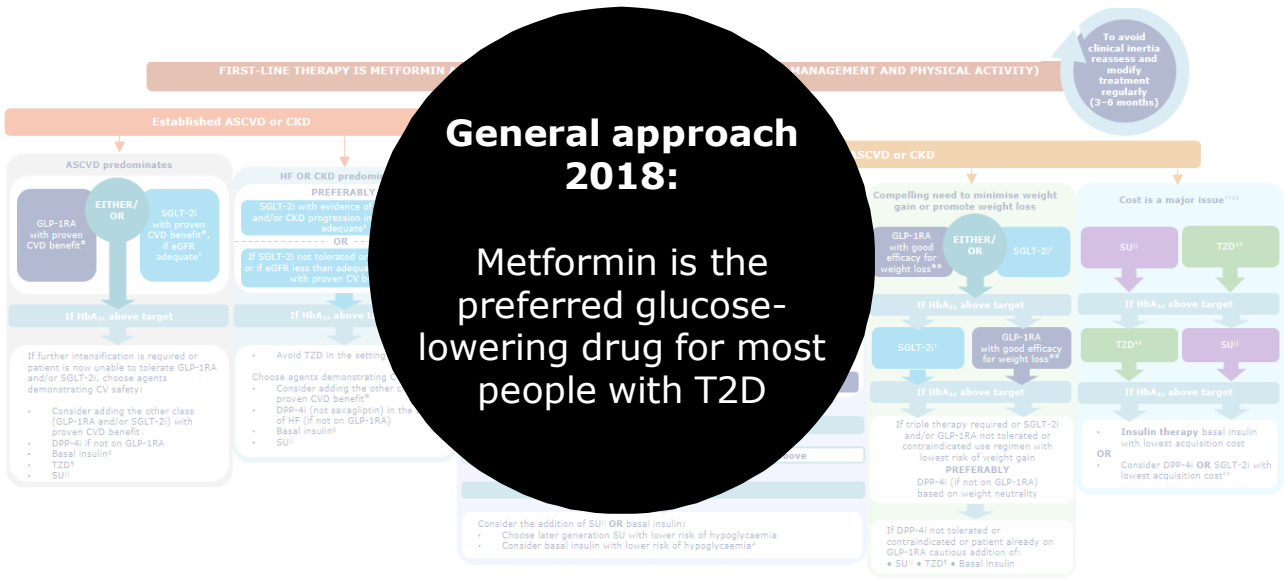
First-line glucose-lowering medication for T2D

What are the changes?

2015

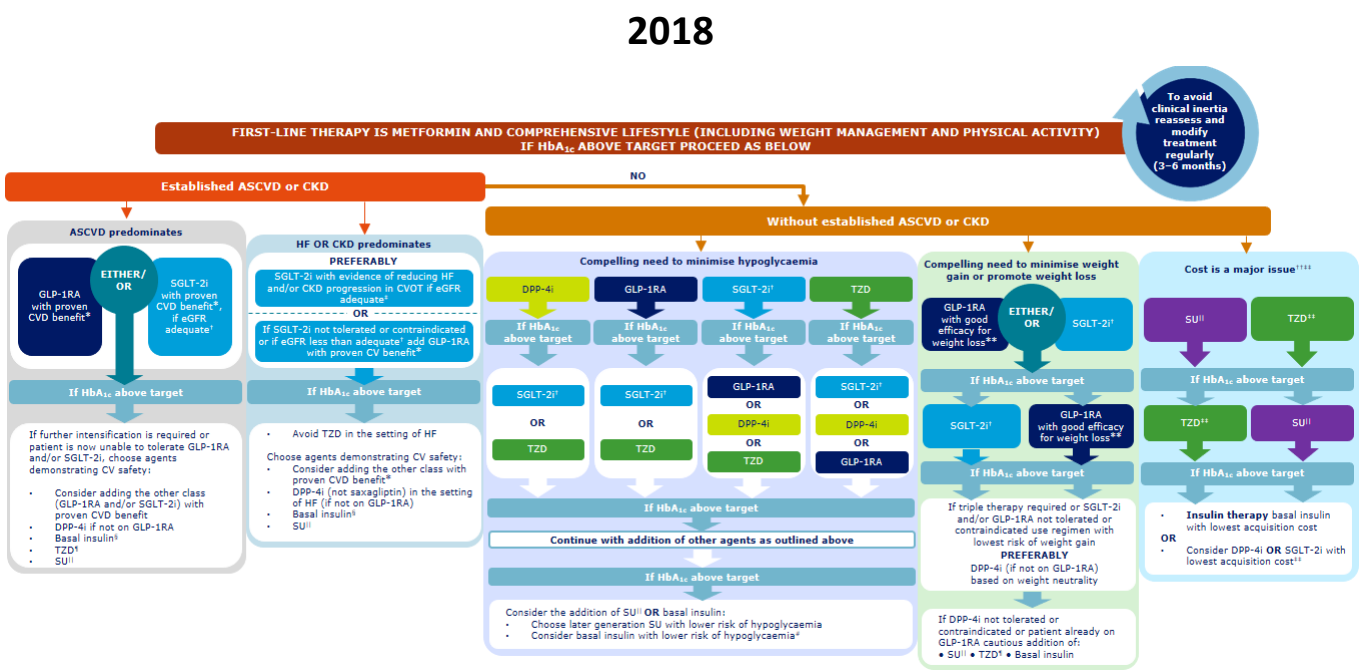


2018



T2D, type 2 diabetes

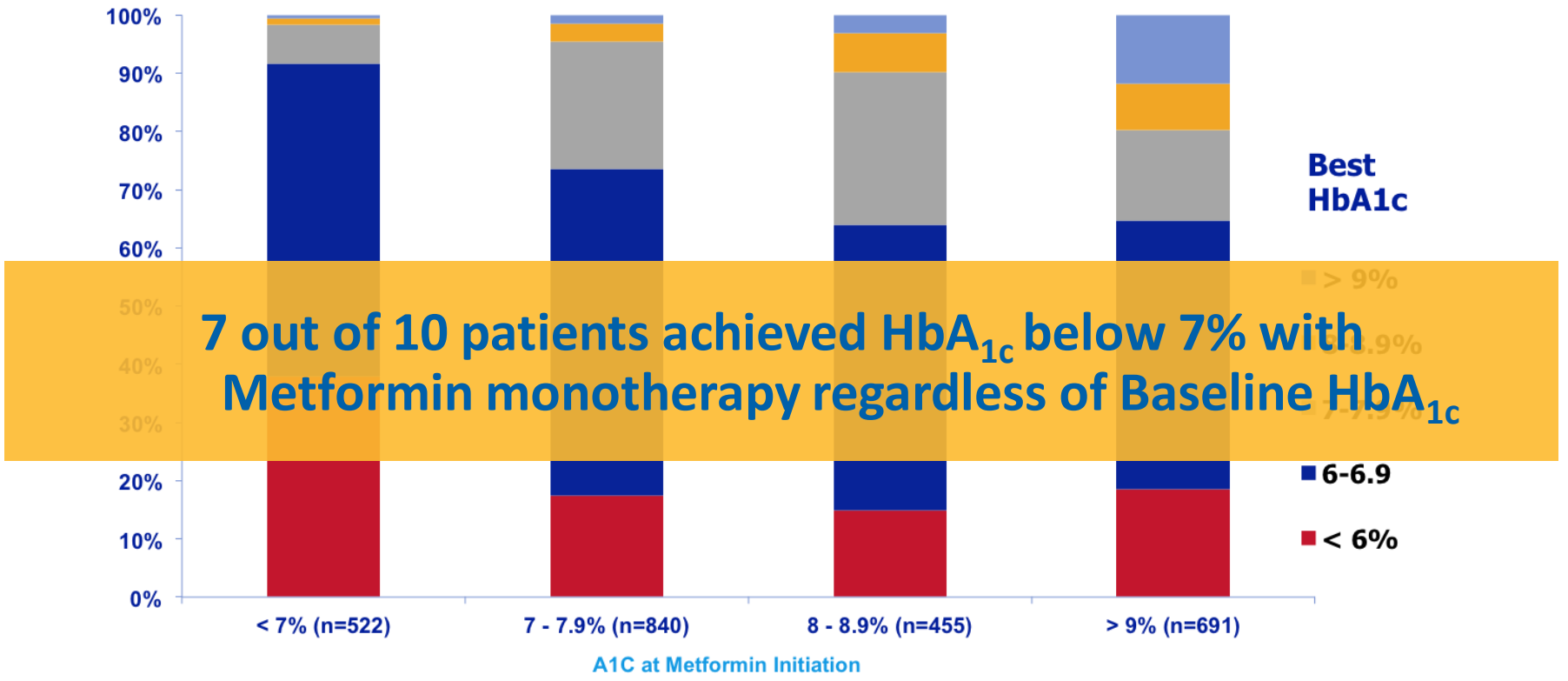
First-line glucose-lowering medication for T2D



- **Metformin**, on top of lifestyle intervention, remains as the recommended first line glucose-lowering medication for patients with T2D

T2D, type 2 diabetes

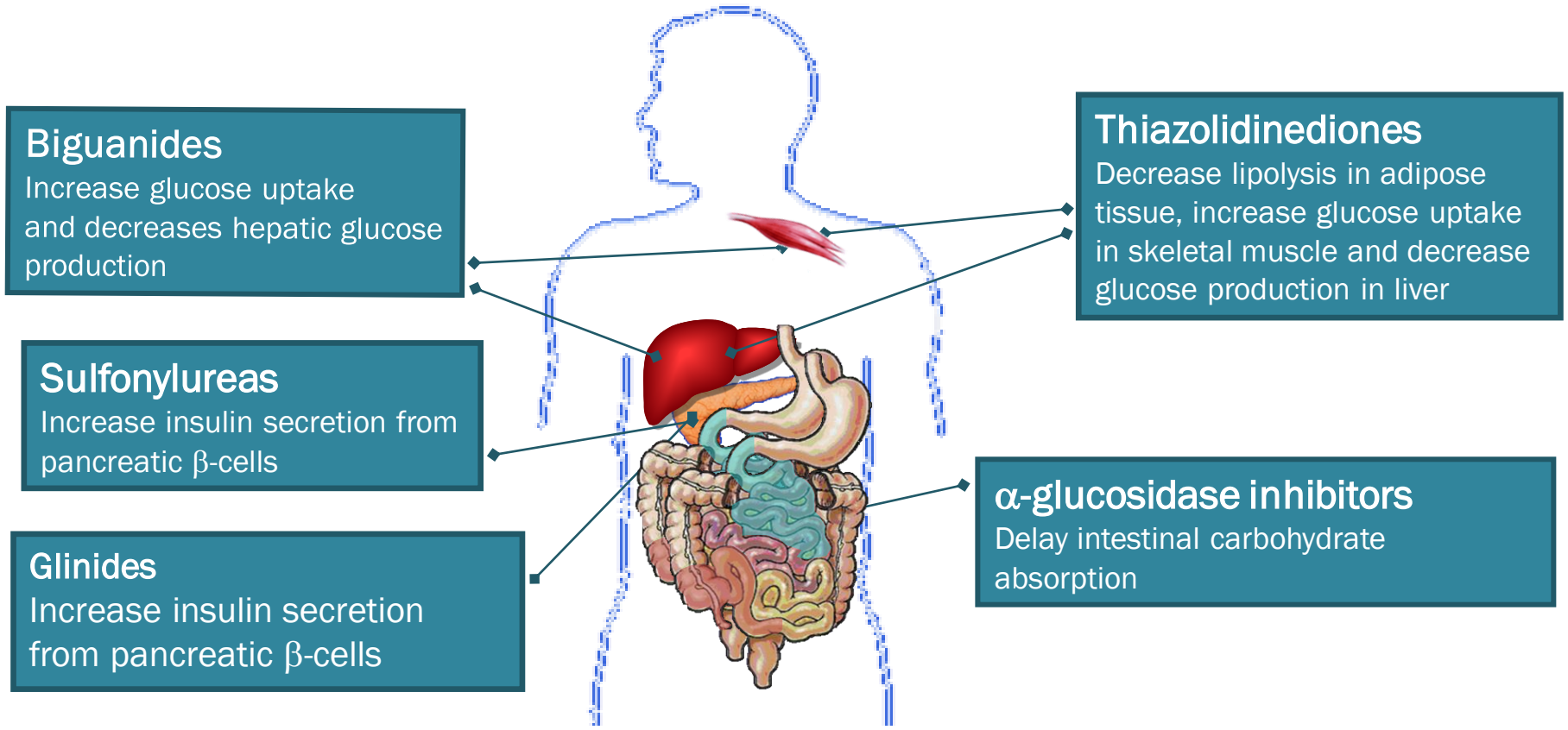
High Response rate with new patients



7 out of 10 patients achieved HbA_{1c} below 7% with Metformin monotherapy regardless of Baseline HbA_{1c}

Reference: Adapted from Nichols et al. Curr Med Res Opin 2010;26:2127-2135.

Pharmacologic Targets of Current Drugs Used in the Treatment of T2DM



Adapted from Cheng AY, Fantus IG. *CMAJ*. 2005; 172: 213–226.Ahrén B, Foley JE. *Int J Clin Pract 2008*; 62: 8-14.

Pharmacologic Targets of Current Drugs Used in the Treatment of T2DM

SGLT2 Inhibitors
Inhibit glucose reabsorption in the renal proximal tubule Resultant glucosuria leads to a decline in plasma glucose

DPP-4 inhibitors
Prolong GLP-1 action leading to improved pancreatic islet glucose sensing, increase glucose uptake

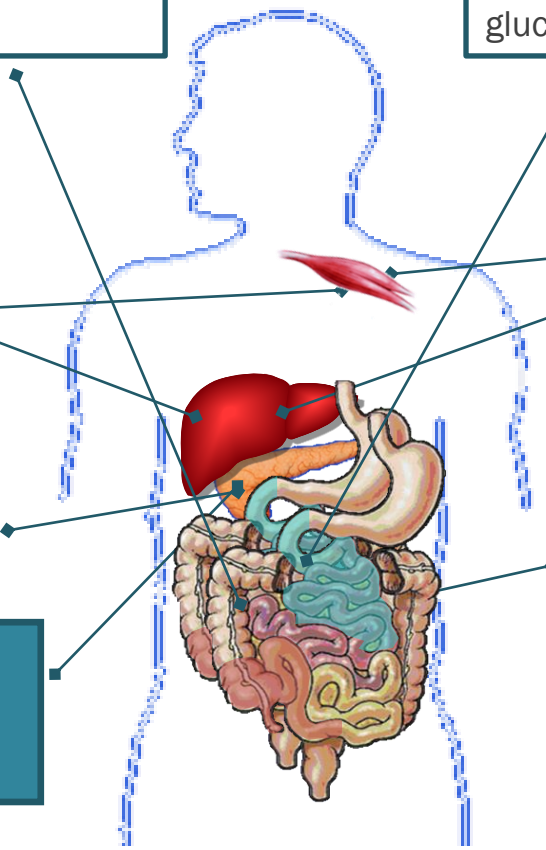
Biguanides
Increase glucose uptake and decreases hepatic glucose production

Thiazolidinediones
Decrease lipolysis in adipose tissue, increase glucose uptake in skeletal muscle and decrease glucose production in liver

Sulfonylureas
Increase insulin secretion from pancreatic β-cells

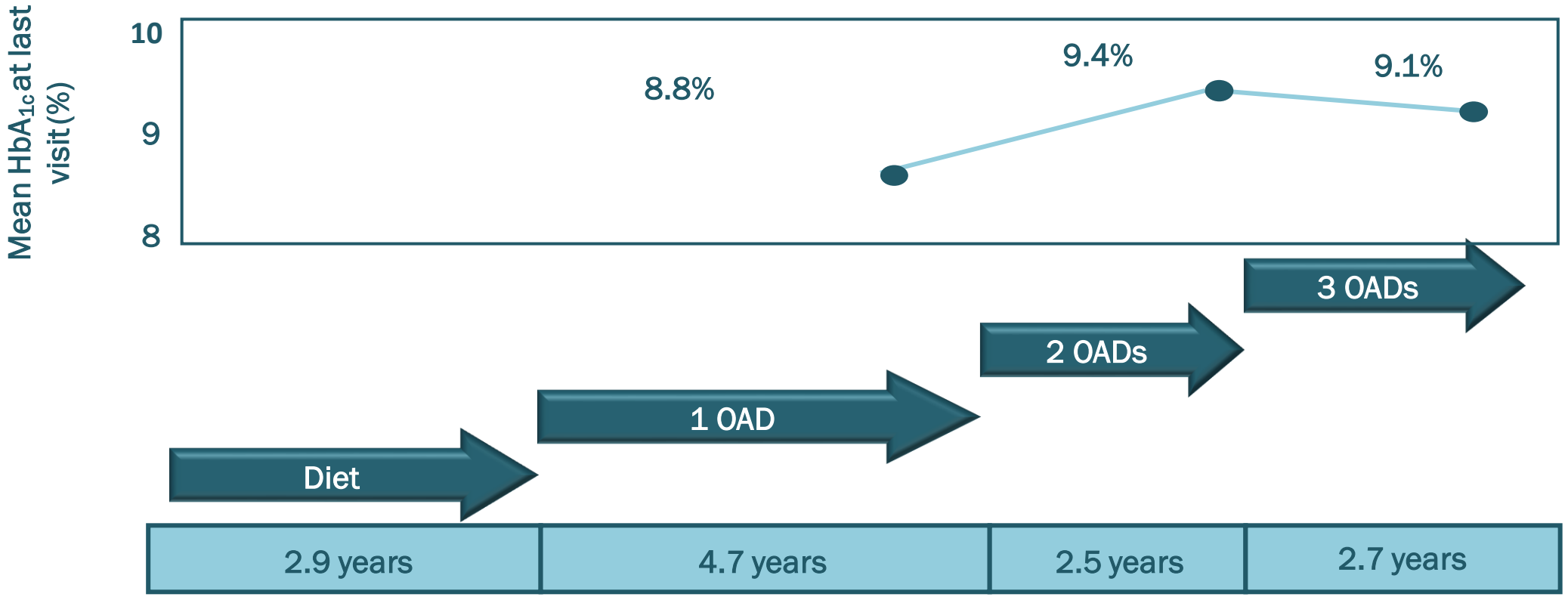
α-glucosidase inhibitors
Delay intestinal carbohydrate absorption

Glinides
Increase insulin secretion from pancreatic β-cells

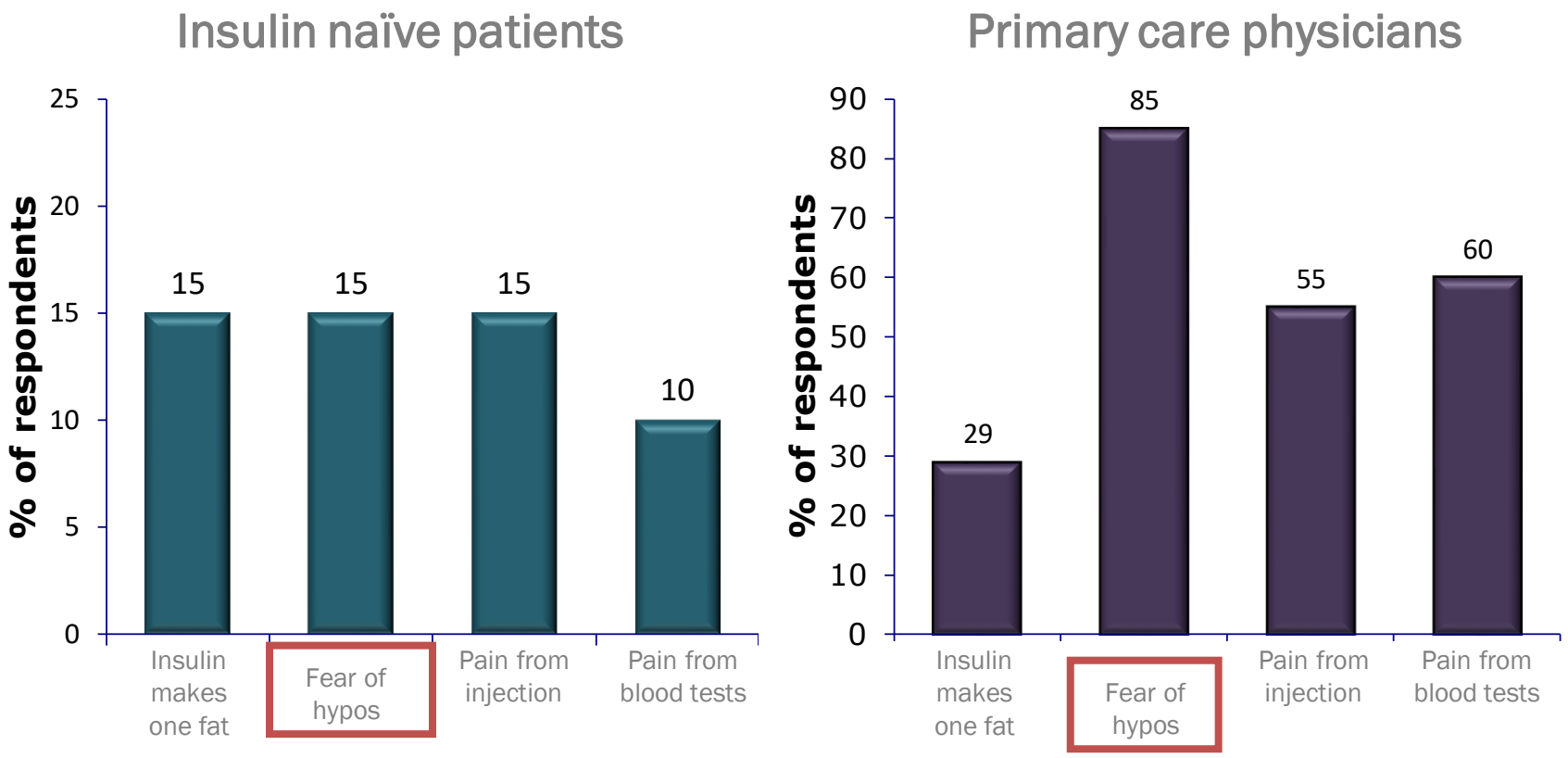


Adapted from Cheng AY, Fantus IG. *CMAJ*. 2005; 172: 213–226.Ahrén B, Foley JE. *Int J Clin Pract 2008*; 62: 8-14.

Insulin use is often delayed, despite poor glycemic control



Common reasons for clinical intertia



* Percentage of patients/physicians interviewed who provided this as a reason for not starting insulin

Nakar et al. J Diabetes Complications 2007;21:220–6

Diabetes Care 1

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies,[1,2] David A. D'Alessio,[3] Judith Fradkin,[4] Walter N. Kernan,[5] Chantal Mathieu,[6] Geltrude Mingrone,[7,8] Peter Rossing,[9,10] Apostolos Tsapas,[11] Deborah J. Wexler,[12,13] and John B. Buse[14]

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M.J.D. and J.B.B. were co-chairs for the Consensus Statement Writing Group. D.A.D'A., J.F., W.N.K., and D.J.W. were the writing group members for the American Diabetes Association. C.M., G.M., P.R., and A.T. were writing group members for the European Association for the Study of Diabetes.

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CONSENSUS REPORT

Diabetologia
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CONSENSUS REPORT

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)

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Abstract
The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the prior position statements, published in 2012 and 2015, on the management of type 2 diabetes in adults. A systematic evaluation of the literature since 2014 informed new recommendations. These include additional focus on lifestyle management and diabetes self-management education and support. For those with obesity, efforts targeting weight loss, including lifestyle, medication and surgical interventions, are recommended. With regards to medication management, for patients with clinical cardiovascular disease, a sodium–glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended. For patients with chronic kidney disease or clinical heart failure and atherosclerotic cardiovascular disease, an SGLT2 inhibitor with proven benefit is recommended. GLP-1 receptor agonists are generally recommended as the first injectable medication.

Keywords Cardiovascular disease · Chronic kidney disease · Costs · Glucose-lowering therapy · Guidelines · Heart failure · Hypoglycaemia · Patient-centred care · Type 2 diabetes mellitus · Weight management

Abbreviations

ARR	Absolute risk reduction
ASCVD	Atherosclerotic cardiovascular disease
CANVAS	Canagliflozin Cardiovascular Assessment Study
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trial
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase-4
DPP-4i	Dipeptidyl peptidase-4 inhibitor
DSMES	Diabetes self-management education and support
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
ESRD	End-stage renal disease
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HF	Heart failure
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of of Cardiovascular Outcomes Results
MACE	Major adverse cardiac events
MI	Myocardial infarction
MNT	Medical nutrition therapy
RCT	Randomised clinical trial
SGLT2	Sodium–glucose cotransporter-2

M. J. Davies and J. B. Buse were co-chairs for the Consensus Statement Writing Group. D. A. D'Alessio, J. Fradkin, W. N. Kernan and D. J. Wexler were the writing group members for the ADA. C. Mathieu, G. Mingrone, P. Rossing and A. Tsapas were writing group members for the EASD.

This article is being simultaneously published in *Diabetes Care* and *Diabetologia* by the American Diabetes Association and the European Association for the Study of Diabetes.

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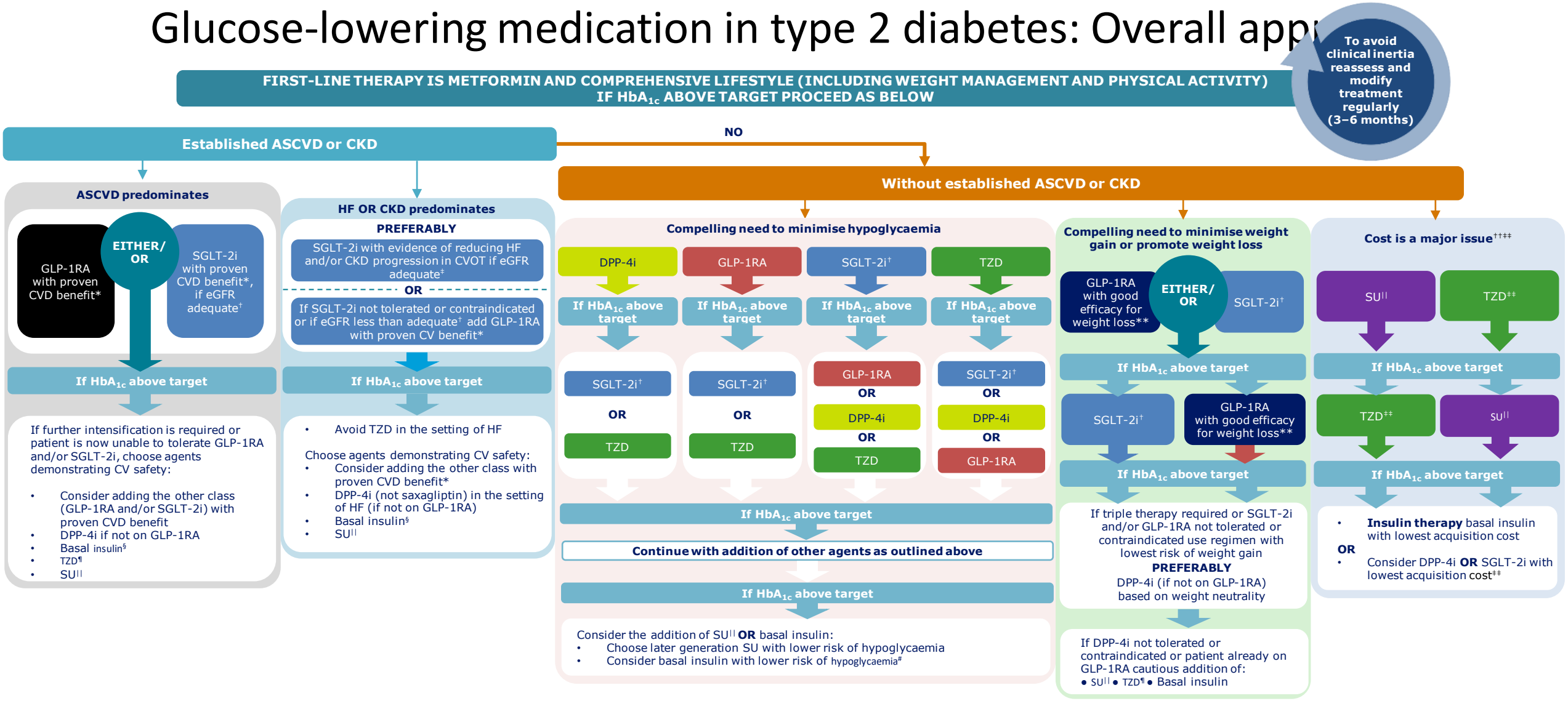
Extended author information available on the last page of the article

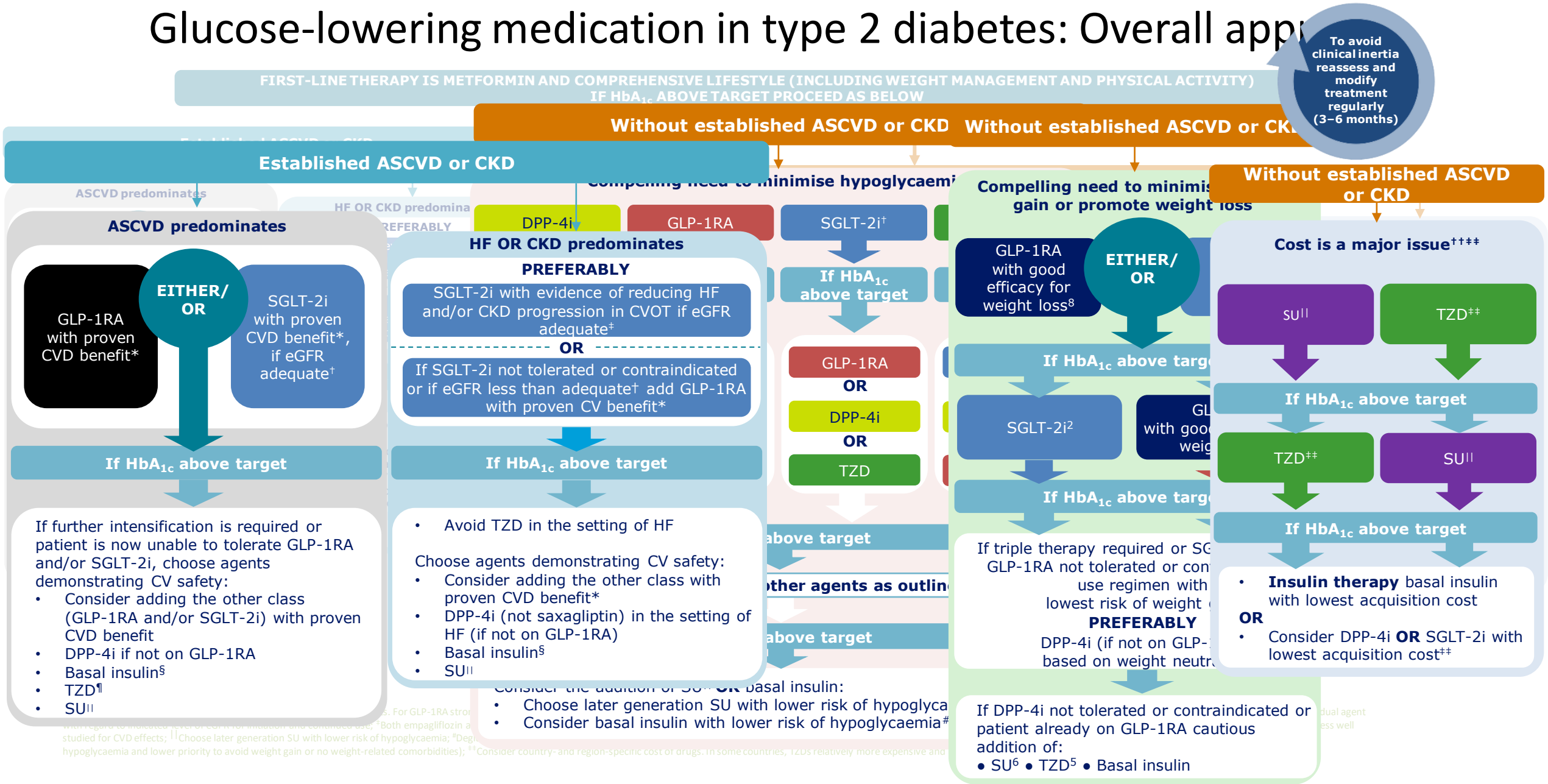
DA/EASD 2018 Consensus Report

Glucose-lowering medication in type 2 diabetes: Overall appr



*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated though less well studied for CVD effects; ||Choose later generation SU with lower risk of hypoglycaemia; #Degludec / glargine U300<glargine U100 / detemir<NPH insulin; **Semaglutide>liraglutide>dulaglutide>exenatide>lixisenatide; ††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); ‡‡Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

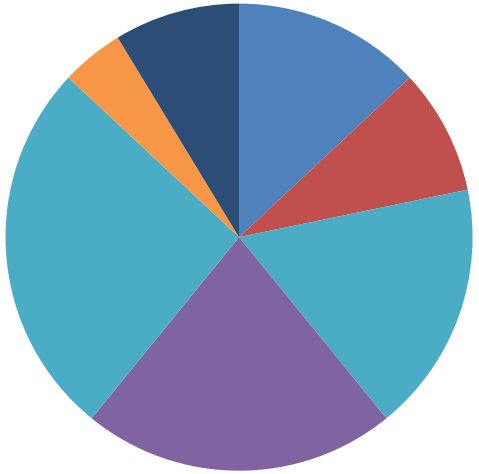
Glucose-lowering medication in type 2 diabetes: Overall appr



Question

Which factor would you consider most when selecting a new antihyperglycaemic treatment

- Efficacy
- Cost
- Weight
- Hypoglycaemia risk
- Other side effects



Live Polling Results

Intensification Options Based on American Diabetes Association Guidelines

Add a Third OAM or Consider an Injectable

TRIPLE THERAPY

Lifestyle therapy **+ metformin + SU +**

	TZD	DPP-4i	SGLT2i	GLP-1 RA	Insulin (basal)
Efficacy	high	intermediate	intermediate	high	highest
Hypo risk	low risk	low risk	low risk	low risk	high risk
Weight	gain	neutral	loss	loss	gain
Side effects	oedema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycaemia
Cost	low	high	high	high	high

According to the American Diabetes Association's treatment guidelines, if our patient is not to target after 3 months of dual therapy with metformin and an SU, it may be time to consider adding an additional therapy to this patient's treatment

fxs = bone fractures; GI = gastrointestinal; GU = genito-urinary; HF = heart failure.

American Diabetes Association. Standards of medical care in diabetes-2017; *Diabetes Care*. 2017;40(suppl 1):S1-S135.

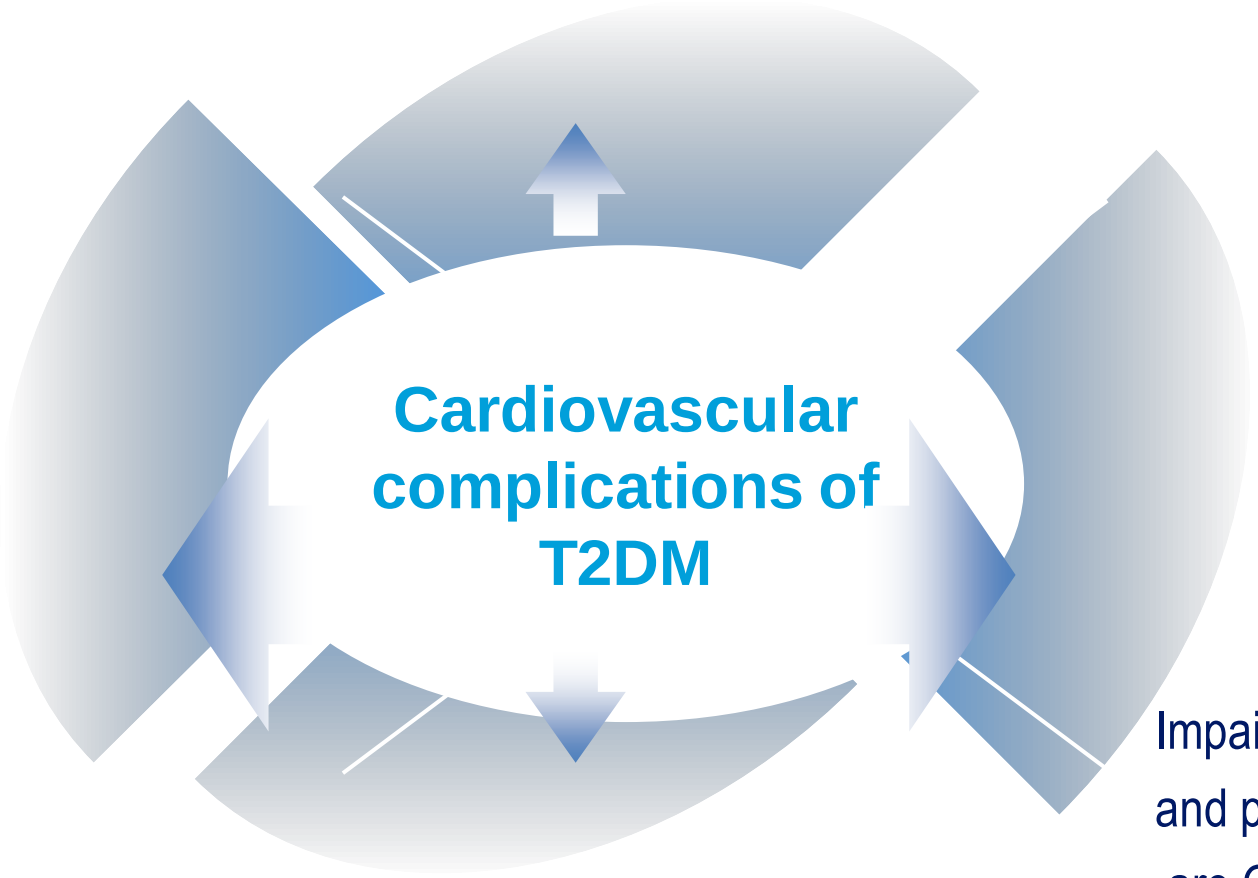
From Optimizing glycemia to

CVD Protection.

Cardiovascular disease and diabetes

~65% of deaths are due to CV disease

Coronary heart disease deaths ↑2- to 4-fold



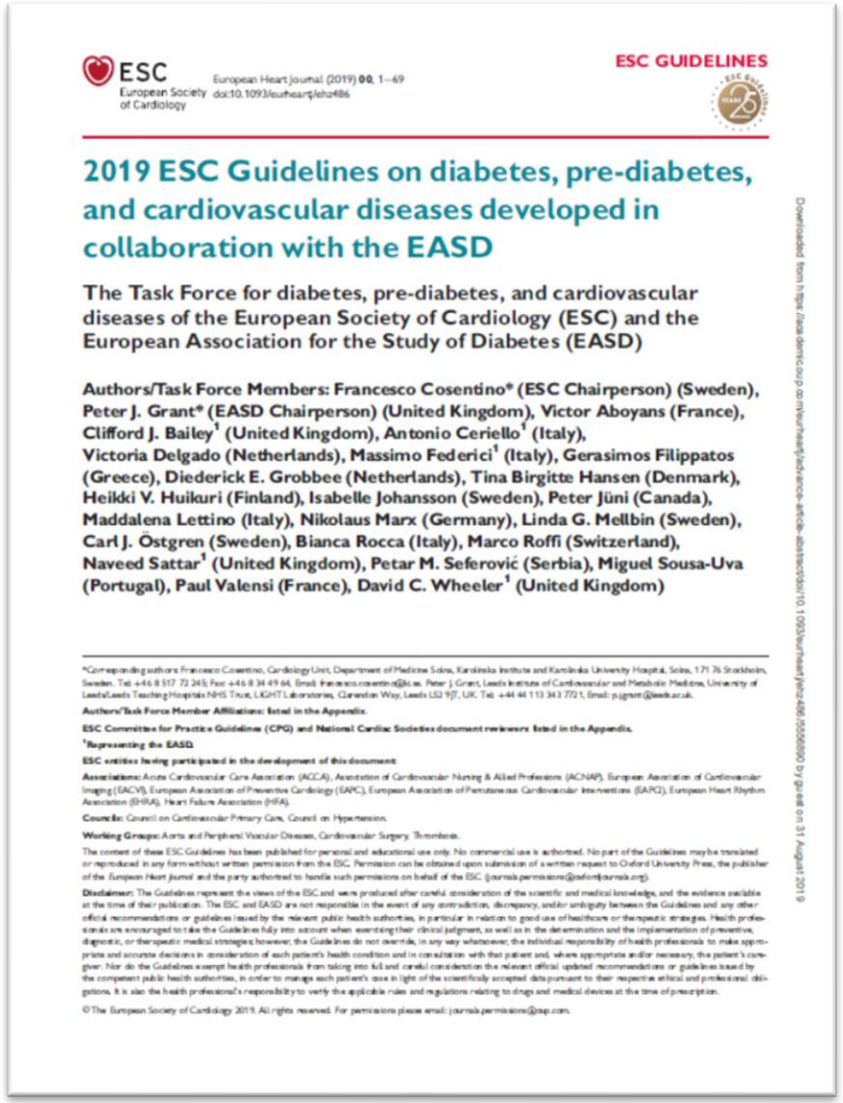
Stroke risk ↑2- to 4-fold

Heart failure ↑2- to 5-fold

Impaired glucose tolerance (IGT) and postprandial hyperglycemia are CV risk factors

Funagata Diabetes Study;
Honolulu Heart Program;
DECODE Study;
Rancho Bernardo Study

Bell DSH. *Diabetes Care*. 2003;26:2433-41.
Centers for Disease Control (CDC). www.cdc.gov.



ESC European Society of Cardiology

European Heart Journal (2019) 00, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

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)

Authors/Task Force Members: Francesco Cosentino* (ESC Chairperson) (Sweden), Peter J. Grant* (EASD Chairperson) (United Kingdom), Victor Aboyans (France), Clifford J. Bailey[1] (United Kingdom), Antonio Ceriello[1] (Italy), Victoria Delgado (Netherlands), Massimo Federici[1] (Italy), Gerasimos Filippatos (Greece), Diederick E. Grobbee (Netherlands), Tina Birgitte Hansen (Denmark), Heikki V. Huikuri (Finland), Isabelle Johansson (Sweden), Peter Jüni (Canada), Maddalena Lettino (Italy), Nikolaus Marx (Germany), Linda G. Mellbin (Sweden), Carl J. Östgren (Sweden), Bianca Rocca (Italy), Marco Roffi (Switzerland), Naveed Sattar[1] (United Kingdom), Petar M. Seferović (Serbia), Miguel Sousa-Uva (Portugal), Paul Valensi (France), David C. Wheeler[1] (United Kingdom)

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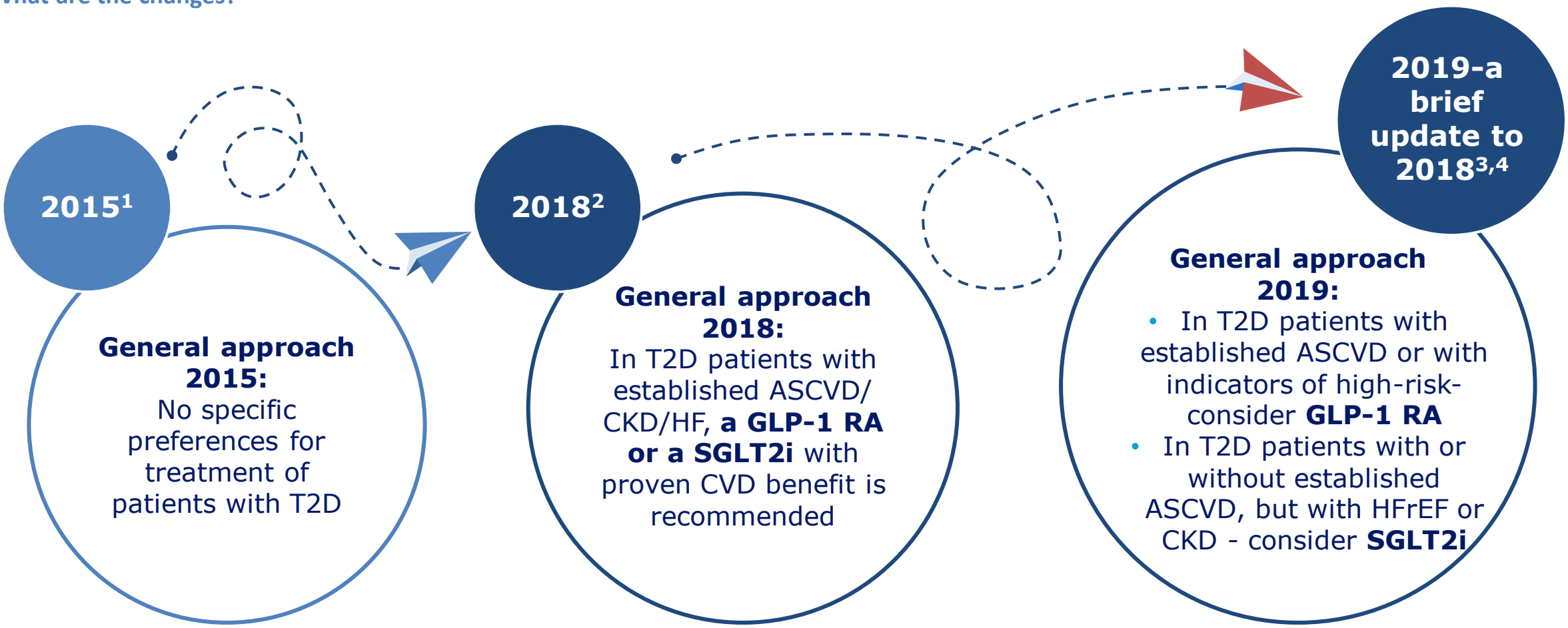
2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

EASD, European Association of the Study of Diabetes; ESC, European Society of Cardiology

Cosentino F et al. *Eur Heart J* 2019;00:1–69

Evolution of ADA/EASD guidelines for T2D

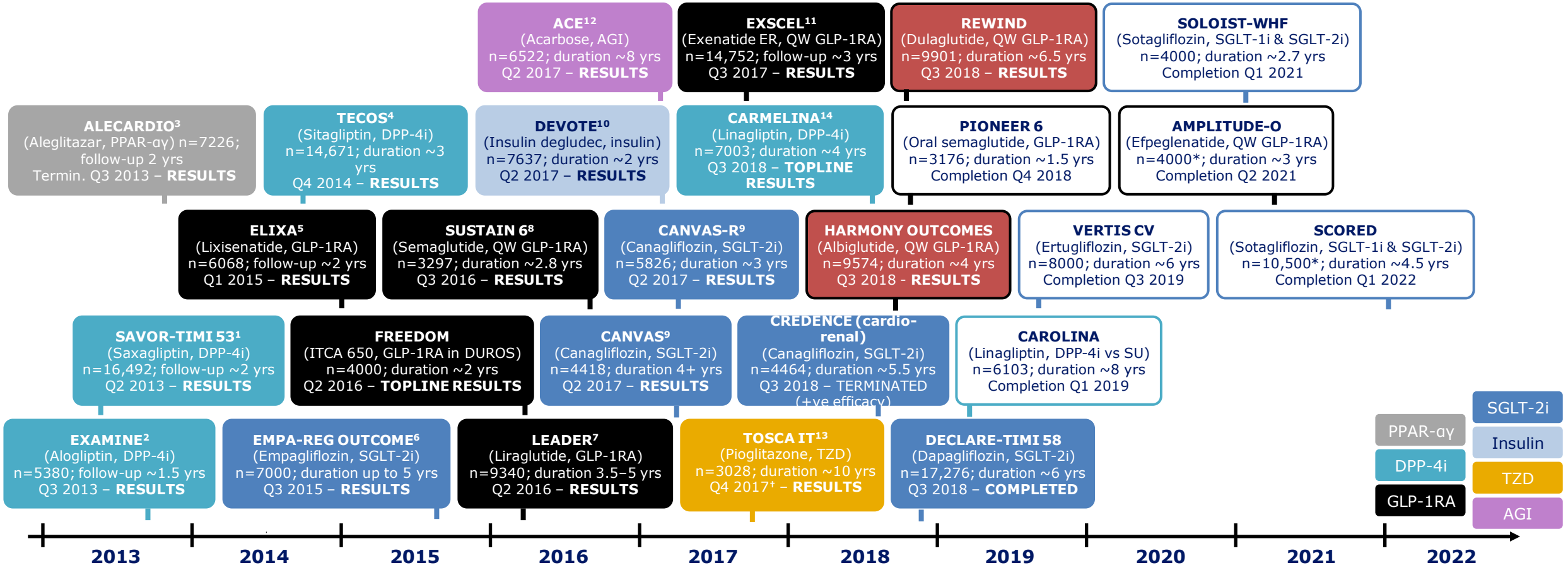
What are the changes?



ADA, American diabetes association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; EASD, European association for the study of diabetes; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SGLT2i, sodium-glucose cotransporter-2 inhibitor

1. Inzucchi SE et al. Diabetologia 2015;58:429–442 ; 2. Davies MJ et al. Diabetologia 2018;61:2461-2498; 3 Buse JB et al. Diabetologia 2019;doi:10.1007/s00125-019-05039-w; 4. Diabetes Care; 2019:dci190066

Contemporary CVOTs in diabetes



*Estimated enrolment; †Stopped early after a median follow-up of 57.4 months following futility analysis

Trials with filled boxes are completed. Trials with a white background are ongoing

AGI, alpha-glucosidase inhibitor; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; ER, extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist; ITCA 650, continuous subcutaneous delivery of exenatide; PPAR-αγ, peroxisome proliferator-activated receptors-α and γ; QW, once weekly; SGLT-1i, sodium-glucose co-transporter 1 inhibitor; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

1. Scirica BM et al. *N Engl J Med* 2013;369:1317–1326; 2. White WB et al. *N Engl J Med* 2013;369:1327–1335; 3. Lincoff AM et al. *JAMA* 2014;311:1515–1525;
4. Green JB et al. *N Engl J Med* 2015;16;373:232–242; 5. Pfeffer MA et al. *N Engl J Med* 2015;373:2247–2257; 6. Zinman B et al. *N Engl J Med*. 2015;373:2117–2287; 7. Marso SP et al. *N Engl J Med* 2016;375:311–322; 8. Marso SP et al. *N Engl J Med* 2016;375:1834–1844; 9. Neal B et al. *N Engl J Med* 2017;377:644–657; 10. Marso SP et al. *N Engl J Med* 2017;377:723–732; 11. Holman RR et al. *N Engl J Med*. 2017;377:1228–1239; 12. Holman RR et al. *Lancet Diabetes Endocrinol* 2017;5:877–886; 13. Vaccaro O et al. *Lancet Diabetes Endocrinol* 2017;5:887–897; 14. Rosenstock J et al. *Cardiovasc Diabetol* 2018;17:39. doi: 10.1186/s12933-018-0682-3 [epub ahead of print]. ClinicalTrials.gov. Accessed 24 July 2018

Key new recommendations in the 2019 guidelines

Key new additions to the 2019 ESC guidelines

Glucose-lowering treatment

Empagliflozin, **canagliflozin** or **dapagliflozin** are recommended in patients with T2D and CVD, or at very high/high CV risk, to reduce CV events

Empagliflozin is recommended in patients with T2D and CVD to reduce the risk of death

Liraglutide, **semaglutide** or **dulaglutide** are recommended in patients with T2D and CVD, or very high/high CV risk, to reduce CV events

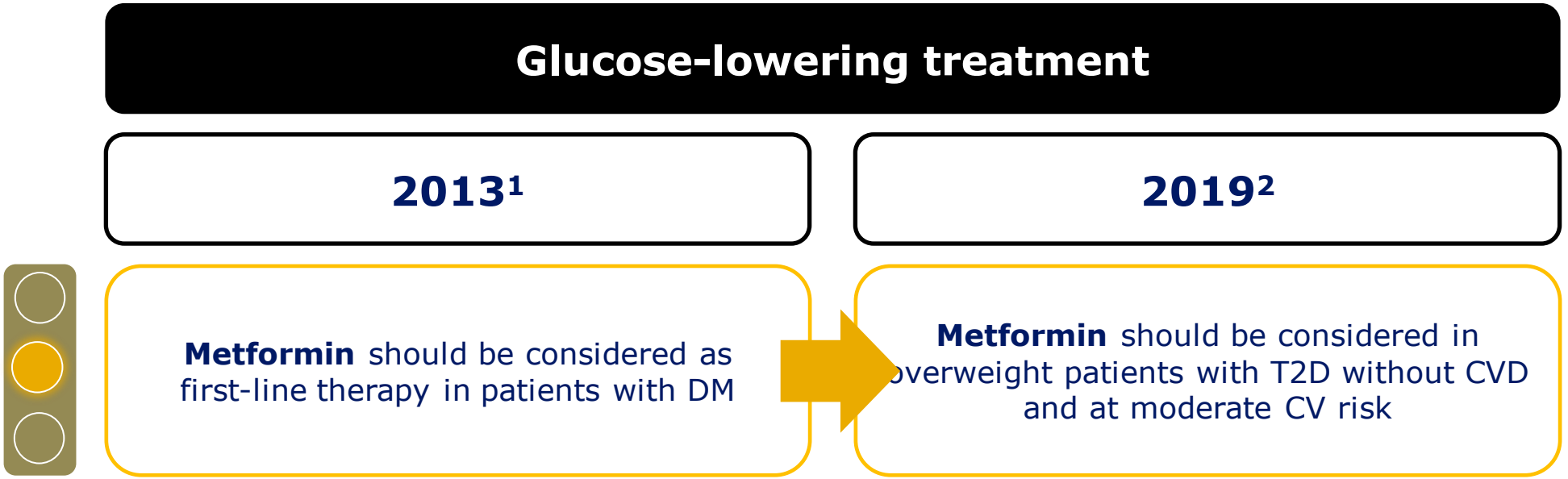
Liraglutide is recommended in patients with T2D and CVD, or at very high/high CV risk, to reduce the risk of death

Saxagliptin is not recommended in patients with T2D and a high risk of HF

CV, cardiovascular; CVD, cardiovascular disease; ESC, European Society of Cardiology; HF, heart failure; T2D, type 2 diabetes

Cosentino F et al. *Eur Heart J* 2019;00:1–69

Key change to the 2019 ESC guidelines since 2013



CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; ESC, European Society of Cardiology; T2D, type 2 diabetes

1. Ryden L et al. *Eur Heart J* 2013;34:3035–3087; 2. Cosentino F et al. *Eur Heart J* 2019;00:1–69

Cardiovascular risk assessment in patients with diabetes and pre-diabetes

The 2016 European guidelines on CVD prevention in clinical practice established clear CV risk categories

Diabetes is a major CV risk factor

Risk estimation charts were used to calculate individual SCORE risk

Low- to moderate-risk persons (SCORE <5%)	**Should be offered lifestyle advice to maintain their low- to moderate-risk status**	Low risk: SCORE <1% Moderate risk: SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category
High-risk persons (SCORE ≥5% and <10%)	**Qualify for intensive lifestyle advice and may be candidates for drug treatment**	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 DM (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)
Very-high-risk persons (SCORE ≥10%)	**Drug treatment is more frequently required**	Documented CVD, clinical or unequivocal on imaging. Unequivocally documented CVD on imaging includes 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. DM with target organ damage such as 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)

BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; SCORE, Systematic Coronary Risk Estimation; T1D, type 1 diabetes

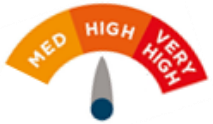
Piepoli MF et al. *Eur Heart J* 2016;37:2315–2381

CV risk categories in patients with diabetes in the new 2019 ESC guidelines

The 2019 ESC guidelines[1a] build upon the SCORE risk from the 2016 European Guidelines on CVD prevention in clinical practice[2] to stratify CV risk in patients with diabetes and pre-diabetes

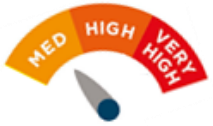
Very high risk

Patients with DM **and** established CVD
or other target organ damage[b]
or three or more major risk factors[c]
or early onset T1D of long duration (>20 years)



High risk

Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor



Moderate risk

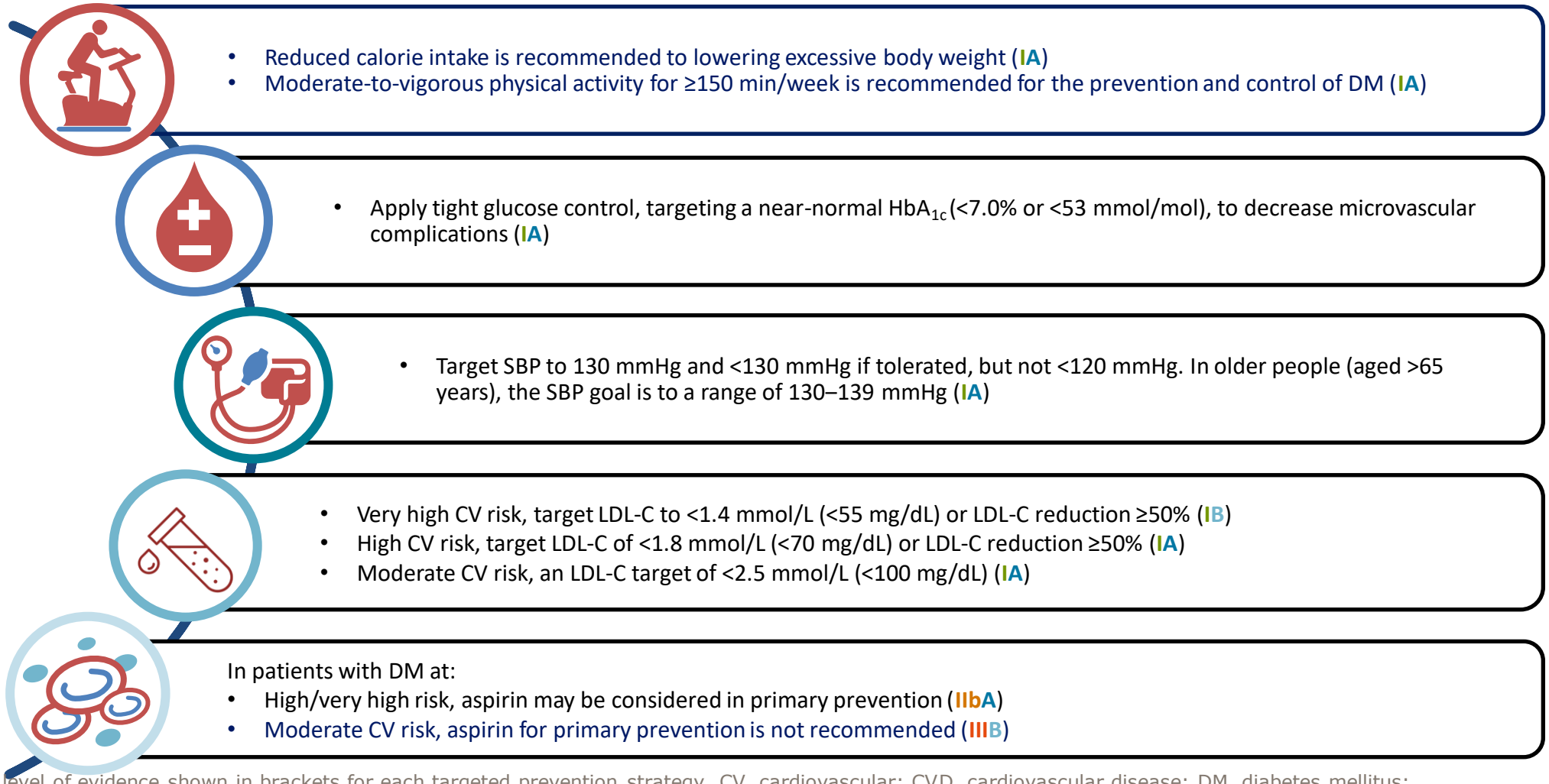
Young patients (T1D aged <35 years or T2D aged <50 years) with DM duration <10 years, without other risk factors

[a]Modified from the 2016 European guidelines on cardiovascular disease prevention in clinical practice[2]
[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy or retinopathy
[c]Age, hypertension, dyslipidaemia, smoking, obesity
CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; SCORE, Systematic Coronary Risk Estimation; T1D, type 1 diabetes; T2D, type 2 diabetes

1. Cosentino F et al. *Eur Heart J* 2019;00:1–69; 2. Piepoli MF et al. *Eur Heart J* 2016;37:2315–2381

Prevention of cardiovascular disease in patients with diabetes and pre-diabetes

Targeted preventions strategies to reduce CVD in patients with diabetes and pre-diabetes

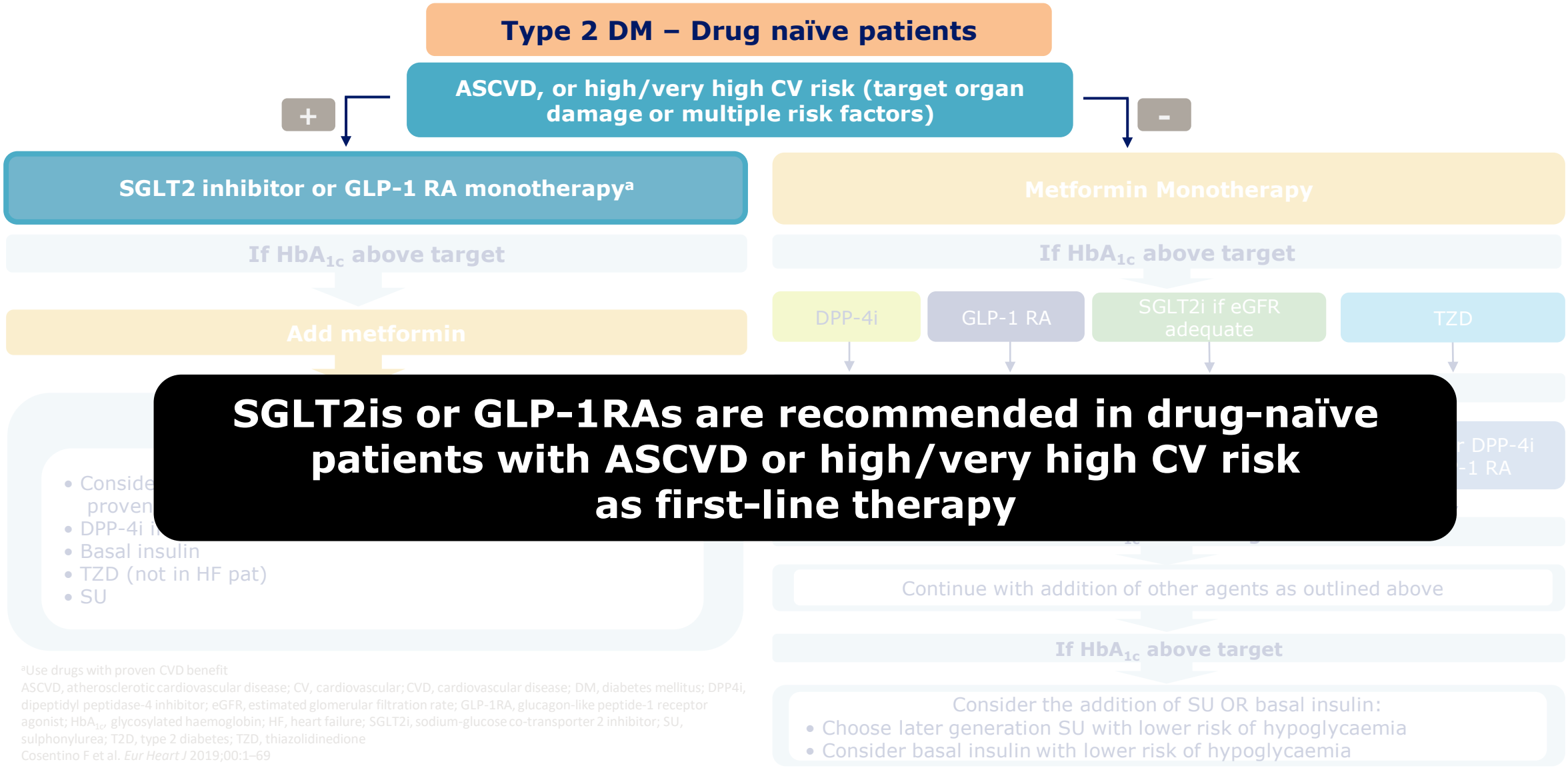


Class of recommendation and level of evidence shown in brackets for each targeted prevention strategy. CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HbA_{1c}, glycosylated haemoglobin; LDL-C, low density lipoprotein-cholesterol; SBP, systolic blood pressure; T2D, type 2 diabetes

Cosentino F et al. *Eur Heart J* 2019;00:1–69

Glucose-lowering treatment for patients with diabetes

Recommended treatment pathway in drug-naïve patients

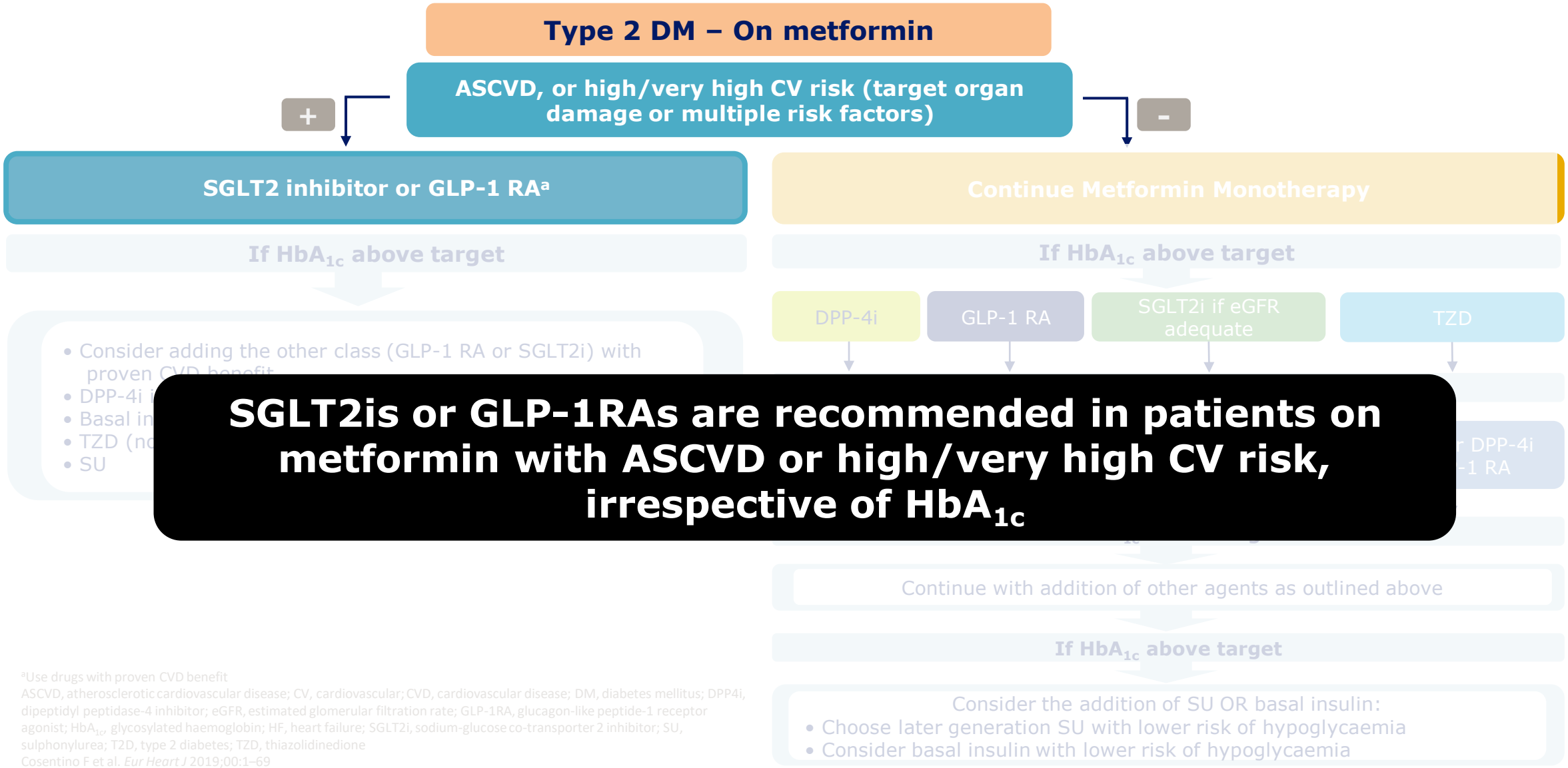


[a]Use drugs with proven CVD benefit

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; HF, heart failure; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione

Cosentino F et al. *Eur Heart J* 2019;00:1–69

Recommended treatment pathway in patients on metformin



[a]Use drugs with proven CVD benefit

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; HF, heart failure; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione

Cosentino F et al. *Eur Heart J* 2019;00:1–69

Recommendations for glucose-lowering treatment for patients with diabetes

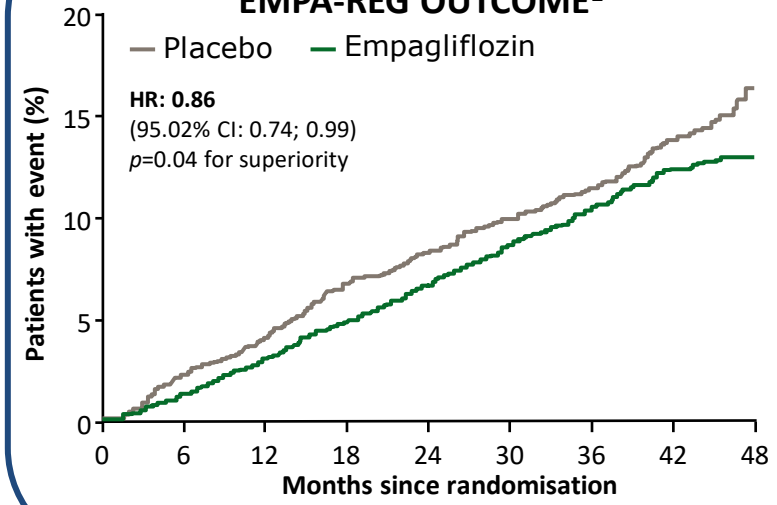
I	Recommended or is indicated	A	Multiple RCTs and meta-analyses
IIa	Should be considered	B	Single RCTs or large non-randomised studies
IIb	May be considered	C	Expert opinion, small/retrospective studies, registries
III	Is not recommended		

SGLT2 inhibitors

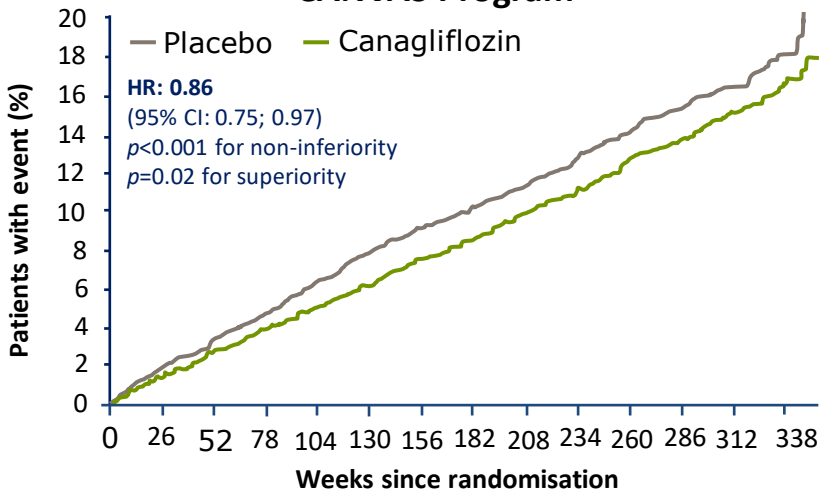
Recommendations	Class of recommendations	Level of evidence
Empagliflozin, **canagliflozin** or **dapagliflozin** are recommended in patients with T2D and CVD, or at very high/high CV risk, to reduce CV events	I	A

3-point MACE: CV death, non-fatal MI or non-fatal stroke

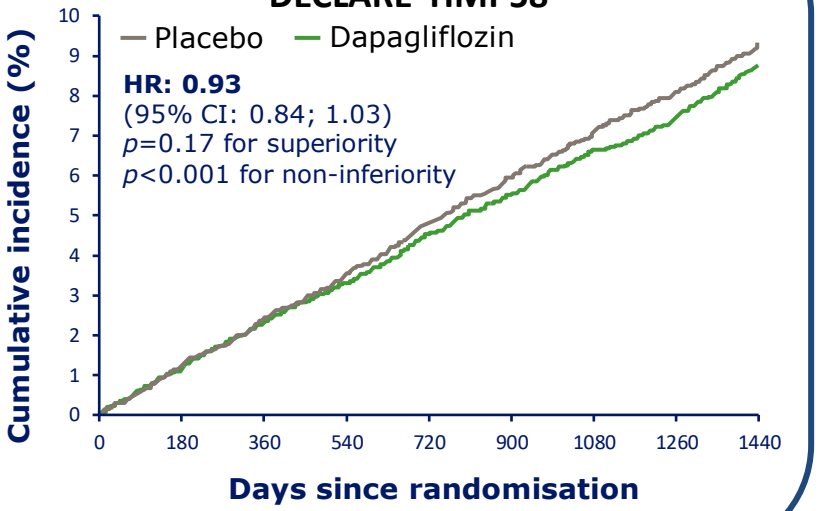
EMPA-REG OUTCOME[1]



CANVAS Program[2]



DECLARE-TIMI 58[3]



CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

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

Recommendations for glucose-lowering treatment for patients with diabetes

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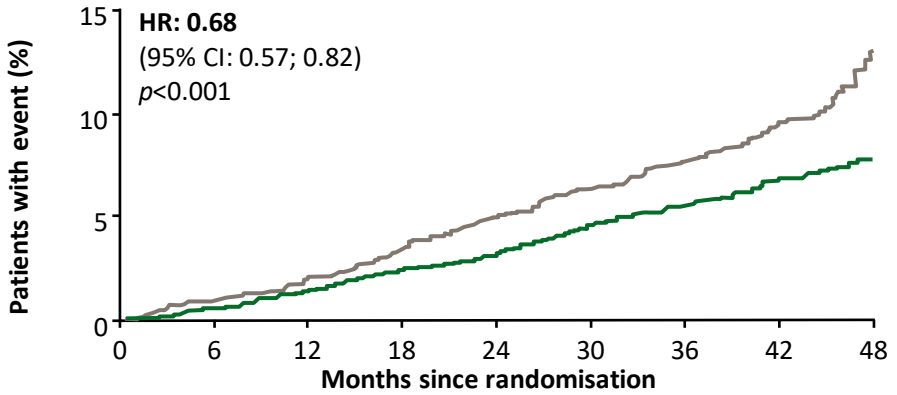
IIa	Should be considered	B	Single RCTs or large non-randomised studies
IIb	May be considered	C	Expert opinion, small/retrospective studies, registries
III	Is not recommended		

SGLT2 inhibitors

Recommendations	Class of recommendations	Level of evidence
Empagliflozin, **canagliflozin** or **dapagliflozin** are recommended in patients with T2D and CVD, or at very high/high CV risk, to reduce CV events	I	A
Empagliflozin is recommended in patients with T2D and CVD to reduce the risk of death	I	B

EMPA-REG OUTCOME: All-cause mortality



CI, confidence interval; HR, hazard ratio
Zinman B et al. *N Engl J Med* 2015;373:2117–2128

CV, cardiovascular; CVD, cardiovascular disease; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes
Cosentino F et al. *Eur Heart J* 2019;00:1–69

Recommendations for glucose-lowering treatment for patients with diabetes

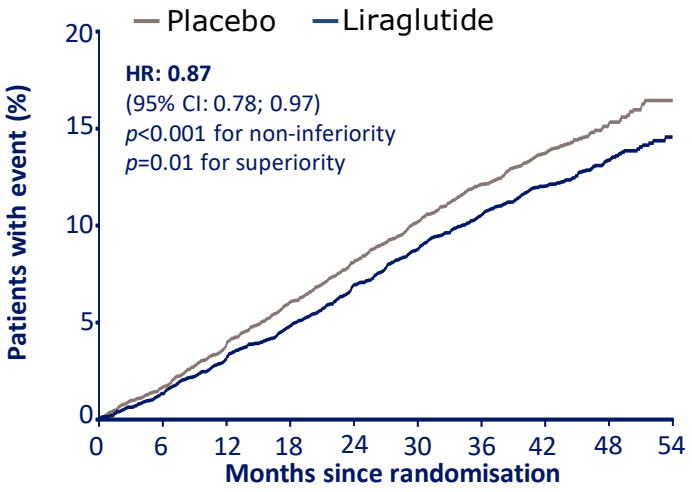
I	Recommended or is indicated	A	Multiple RCTs and meta-analyses
IIa	Should be considered	B	Single RCTs or large non-randomised studies
IIb	May be considered	C	Expert opinion, small/retrospective studies, registries
III	Is not recommended		

GLP-1RAs

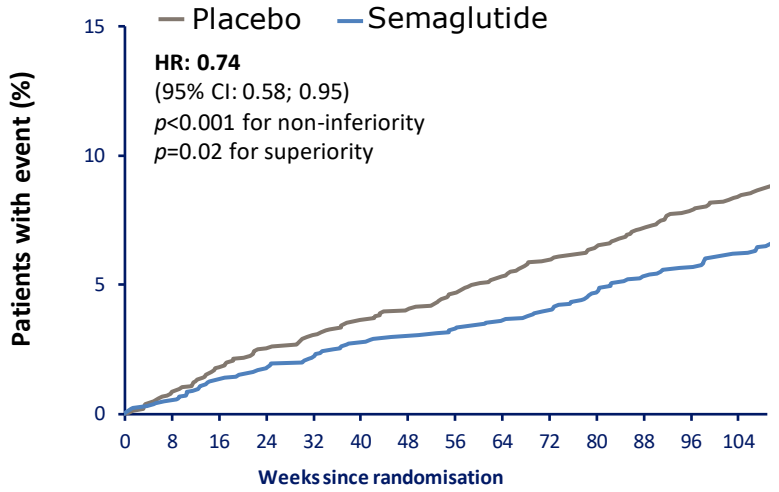
Recommendations	Class of recommendations	Level of evidence
Liraglutide, **semaglutide** or **dulaglutide** are recommended in patients with T2D and CVD, or at very high/high CV risk, to reduce CV events	I	A

3-point MACE: CV death, non-fatal MI or non-fatal stroke

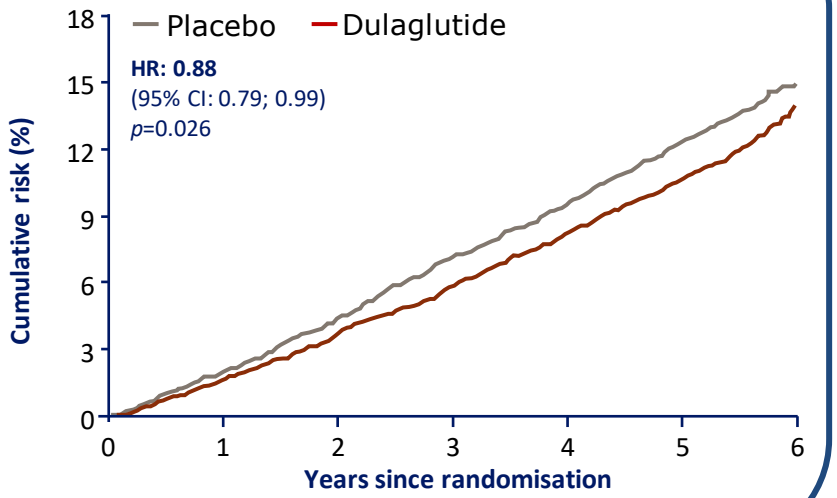
LEADER[1]



SUSTAIN 6[2]



REWIND[3]



CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

1. Marso SP et al. *N Eng 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

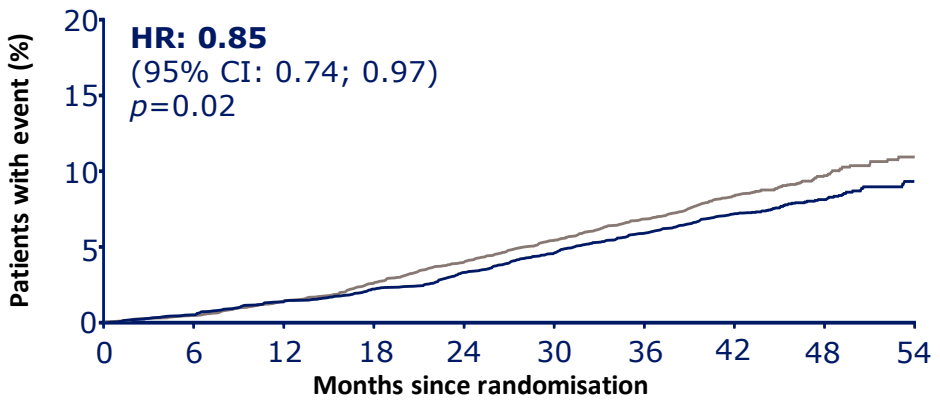
Cosentino F et al. *Eur Heart J* 2019;00:1–69

Recommendations for glucose-lowering treatment for patients with diabetes

I	Recommended or is indicated	A	Multiple RCTs and meta-analyses
IIa	Should be considered	B	Single RCTs or large non-randomised studies
IIb	May be considered	C	Expert opinion, small/retrospective studies, registries
III	Is not recommended		

GLP-1RAs

Recommendations	Class of recommendations	Level of evidence
Liraglutide, **semaglutide**, or **dulaglutide** are recommended in patients with T2D and CVD, or at very high/high CV risk, to reduce CV events	I	A
Liraglutide is recommended in patients with T2D and CVD, or at very high/high CV risk, to reduce the risk of death	I	B



CI, confidence interval; HR, hazard ratio
Marso SP et al. *N Eng J Med* 2016;375:311–322

CV, cardiovascular; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes
Cosentino F et al. *Eur Heart J* 2019;00:1–69

Recommendations for glucose-lowering treatment for patients with diabetes

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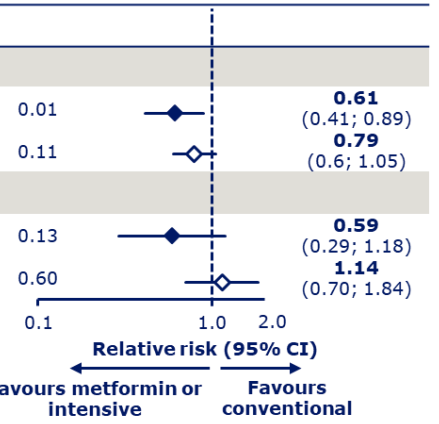
IIa	Should be considered	B	Single RCTs or large non-randomised studies
IIb	May be considered	C	Expert opinion, small/retrospective studies, registries
III	Is not recommended		

Biguanides

Recommendations	Class of recommendations	Level of evidence
Metformin should be considered in overweight patients with T2D without CVD and at moderate CV risk	IIa	C

UKPDS

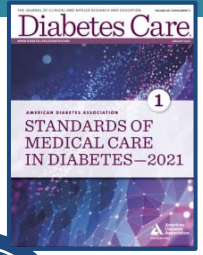
Subgroup	*p* for metformin vs intensive	Patients with aggregate endpoints		Absolute risk (events per 1000 patient-years)		Log-rank 2p	RR (95% CI)
		Metformin or intensive	Conventional	Metformin or intensive	Conventional		
Myocardial infarction	*p*=0.12						
Metformin		89	73	11.0	18.0	0.01	**0.61** (0.41; 0.89)
Intensive		139	73	14.4	18.0	0.11	**0.79** (0.6; 1.05)
Stroke	*p*=0.032						
Metformin		12	23	3.3	5.5	0.13	**0.59** (0.29; 1.18)
Intensive		60	23	6.2	5.5	0.60	**1.14** (0.70; 1.84)



N=753

CI, confidence interval; RR, relative risk
UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854–865

CV, cardiovascular; CVD, cardiovascular disease; T2D, type 2 diabetes
Cosentino F et al. *Eur Heart J* 2019;00:1–69



2021 ADA: Glucose-lowering medication in T2D

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD OR HF†

NO

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

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

+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)

GLP-1 RA with proven CVD benefit[1] — Either/OR — 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 m^2) and thus at increased risk of cardiovascular events

GLP-1 RA with proven CVD benefit[1] — Either/OR — SGLT2i with proven CVD benefit[1,7]

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

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

• SU[4] • TZD[2] • Basal insulin

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

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. More details mentioned in 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

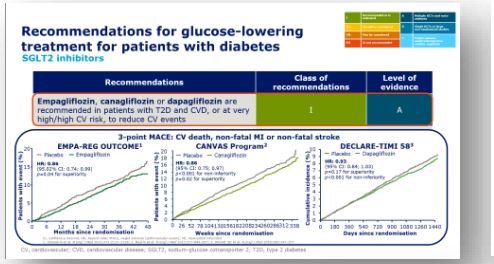
†Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications. *Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy. A1C, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione

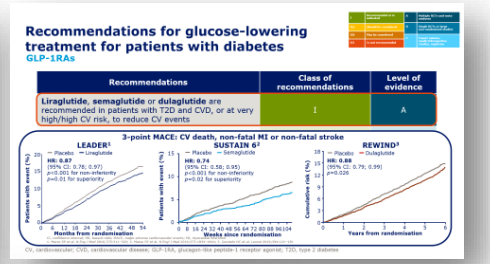
Figure 9.1 Adapted from American Diabetes Association. Diabetes Care 2021 Jan; 44(Supplement 1):S116 https://doi.org/10.2337/dc21-S009
ADA, American Diabetes Association; CV, cardiovascular; DKD, Diabetes kidney disease; NPH, Neutral Protamine Hagedorn
American Diabetes Association. Diabetes Care 2021 Jan; 44(Supplement 1):S116 https://doi.org/10.2337/dc21-S009;

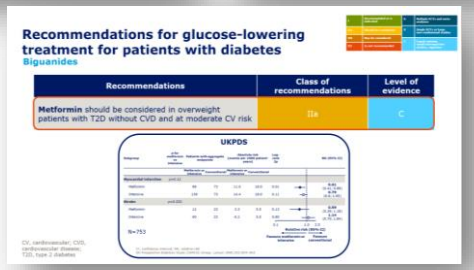
Summary

2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases in collaboration with the EASD

- The new guidelines provide guidance on the management and prevention of CVD in subjects with, and at risk of developing, diabetes in light of new data
- Recent CVOTs show CV benefits from newer glucose-lowering drugs in patients with CVD or very high/high CV risk
  - Specifically, **GLP1-RAs** or **SGLT2is** are recommended for the treatment of patients with T2D with CVD or a high/very high risk as first-line therapy who are drug-naïve
  - For patients previously treated with metformin, the addition of a **GLP-1RA** or **SGLT2i** is recommended irrespective of HbA_{1c}
  - **Metformin** should be considered in overweight patients with T2D without CVD and at moderate CV risk
- Treatment to reduce CV events should be prioritised based on the presence of CVD and CV risk







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

CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DM, diabetes mellitus; EASD, European Association of the Study of Diabetes; ESC, European Society of Cardiology; GLP-1RA, glucagon-like peptide receptor agonist; HbA_{1c}, glycosylated haemoglobin; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.
Cosentino F et al. *Eur Heart J* 2019;00:1–69

Standards of Medical Care in Diabetes—2022

ADA Standards of Care – A Living Document.

- Beginning with the 2018 ADA Standards of Medical Care in Diabetes, the Standards document became a “living” document where notable updates are incorporated into the Standards
- Living Standards Updates Available at: http://care.diabetesjournals.org/living-standards

Table of Contents.

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Why do we need National Diabetes Guidelines?

Management of Type 2 Diabetes Mellitus in Adults in the UAE

The need for up-to-date guidelines	• **Existing diabetes management guidelines for the UAE were last produced in 2009 and 2012.** • **Since that time, important evidence has emerged, with extensive implications for clinical practice.**
Updates in 2020	• **The 2020 guidelines are based on an expert panel's collective analysis, evaluation and opinion on the available clinical evidence, and thus represents expert opinion only.**
Expert panel	• **The writing group for the 2020 guidelines consisted of 21 experts.**
Presented and published	• **The 2020 consensus report was presented at the 10th Emirates Diabetes and Endocrine Congress on 26 February 2020, with simultaneous publication in the *Dubai Diabetes and Endocrine Journal.***

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Burden of Diabetes in the UAE

- The reported diabetes prevalence rate in the UAE of 16.3% (for the 20-79 years age-group)[1] is based on a survey in 1999-2000.
- Few studies on diabetes prevalence in the UAE since.
- Recently reported prevalence rates: 17.6% for diabetes and 27.1% for pre-diabetes (Weqaya, Abu Dhabi, 2012)[2]; and 25.1% (Northern Emirates, 2018)[3].
- Diabetes prevalence for expatriates in UAE was 19.1%, of whom 64.2% were previously undiagnosed[4].

References:

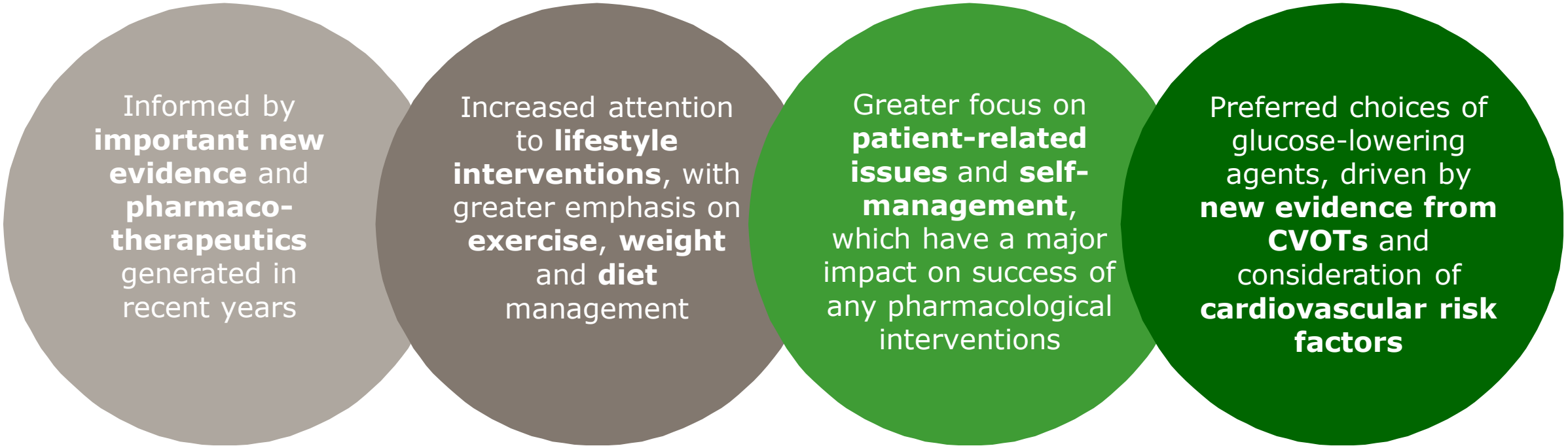
[1]International Diabetes Federation. IDF DIABETES ATLAS 9th edition 2019. 2019; https://www.diabetesatlas.org/en/resources.

[2]Hajat C, Harrison O, Al Siksek Z, Weqaya: a population-wide cardiovascular screening program in Abu Dhabi, United Arab Emirates. *Am J Public Health* 2012 102: 909-914.

[3]Sulaiman N, Mahmoud I, Hussein A, Elbadawi S, Abusnana S*, et al.*, Diabetes risk score in the United Arab Emirates: a screening tool for the early detection of type 2 diabetes mellitus. *BMJ Open Diabetes Res Care* 2018 6: e000489.

[4]Sulaiman N, Albadawi S, Abusnana S, Mairghani M, Hussein A*, et al.*, High prevalence of diabetes among migrants in the United Arab Emirates using a cross-sectional survey. *Sci Rep* 2018 8: 6862.

The 2020 Guidelines



The goal is to improve the standard of care for people with diabetes in the UAE, through increased awareness of these management practices.

Abbreviation: CVOT, cardiovascular outcomes trial

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Screening and Monitoring for Type 2 Diabetes

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Screening for diabetes or pre-diabetes

- We recommend that the ADA screening criteria[1] be adopted but starting at **a lower age of 30 years**.
- Adults of any age who are overweight or obese with **≥1 additional risk factor**.
- For persons with normal test results, repeat testing at least once every 3 years (unless conditions changed), or 6-monthly if the person is diagnosed with pre-diabetes.

Reference: [1]American Diabetes Association, 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020 43: S14-s31

Additional risk factors

- Adults of any age who are overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 for Asian descent) with **≥1 additional risk factor**:
    - First-degree relative with diabetes.
    - Pre-diabetes i.e. HbA1c ≥5.7%, IGT, or IFG on previous testing.
    - Low levels of high-density lipoprotein (HDL) cholesterol (<35 mg/dL [<0.90 mmol/L]) and/or high triglyceride levels (>250 mg/dL [>1.70 mmol/L]).
    - Hypertension (blood pressure ≥140/90 mm Hg or on treatment for hypertension).
    - Physical inactivity.
    - High-risk ethnic groups.
    - History of cardiovascular disease (CVD).
    - Polycystic ovary syndrome.
    - History of gestational diabetes (GDM).
    - Other conditions associated with insulin resistance, e.g. severe obesity or acanthosis nigricans.

Abbreviations: HbA1c - Glycated haemoglobin, IFG - Impaired fasting glucose , IGT - Impaired glucose tolerance.

Criteria for a diagnosis of diabetes

Diagnostic Test	Diabetes	Pre-diabetes
FPG*	≥126 mg/dL (7.0 mmol/L)**	100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OGTT†	≥200 mg/dL (11.1 mmol/L)	140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
HbA1c‡	≥6.5% (48.0 mmol/mol)	5.7-6.4% (39.0-47.0 mmol/mol)
RBG in symptomatic individuals§	>200 mg/dL (11.1 mmol/L)	-

- **HbA1c** is most preferred: Convenient as it does not require fasting and is not affected by illness or stress at the time of testing.

*FPG: Fasting is defined as no caloric intake for at least 8 hours.
†OGTT: The test should be performed as described in the WHO guidelines[8], using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.
‡HbA1c = glycated haemoglobin. A1C assay should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay. A1C may not be appropriate for diagnosis of diabetes in conditions where red cell turnover is abnormal (please see Table 2).
§RBG can only be used for diagnosis of diabetes in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis.
**In the absence of unequivocal hyperglycaemia, diagnosis of diabetes requires two abnormal test results from the same sample or in two separate test samples.
Abbreviations: ADA - American Diabetes Association; FPG - fasting blood glucose; HbA1c – glycated haemoglobin; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; OGTT - 2-hour fasting glucose during a 75g oral glucose tolerance test; RBG - random blood glucose; WHO - World Health Organization.

Reference: American Diabetes Association, 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020 43: S14-s31

Limitations of HbA1c test

Inappropriately low HbA1c	Inappropriately high HbA1c	Either high or low HbA1c
Acute or chronic blood loss	Renal failure (uraemia)	Certain haemoglobinopathies
Haemoglobinopathies: • Sickle cell • Thalassemia • Elliptocytosis	Low red cell turnover: • Vitamin B12 deficiency • Iron deficiency	Foetal haemoglobin
Blood transfusion	Alcohol	Methaemoglobin
Haemolysis, including G6PD deficiency	Hyperbilirubinaemia	Assay interference
Drugs: • Iron therapy • Vitamin B12 supplements • Erythropoietin • Antiretrovirals, ribavirin • Dapsone • Aspirin (low dose) • Vitamin C • Vitamin E	Drugs: • High dose aspirin • Chronic opiate use	
Chronic liver disease	Splenectomy	
Hypertriglyceridaemia	Aplastic anaemia	
Pregnancy	Lead poisoning	
Reticulocytosis		
Rheumatoid Arthritis		

Management of Pre-diabetes

Strategy for prevention of diabetes

Screening for diabetes

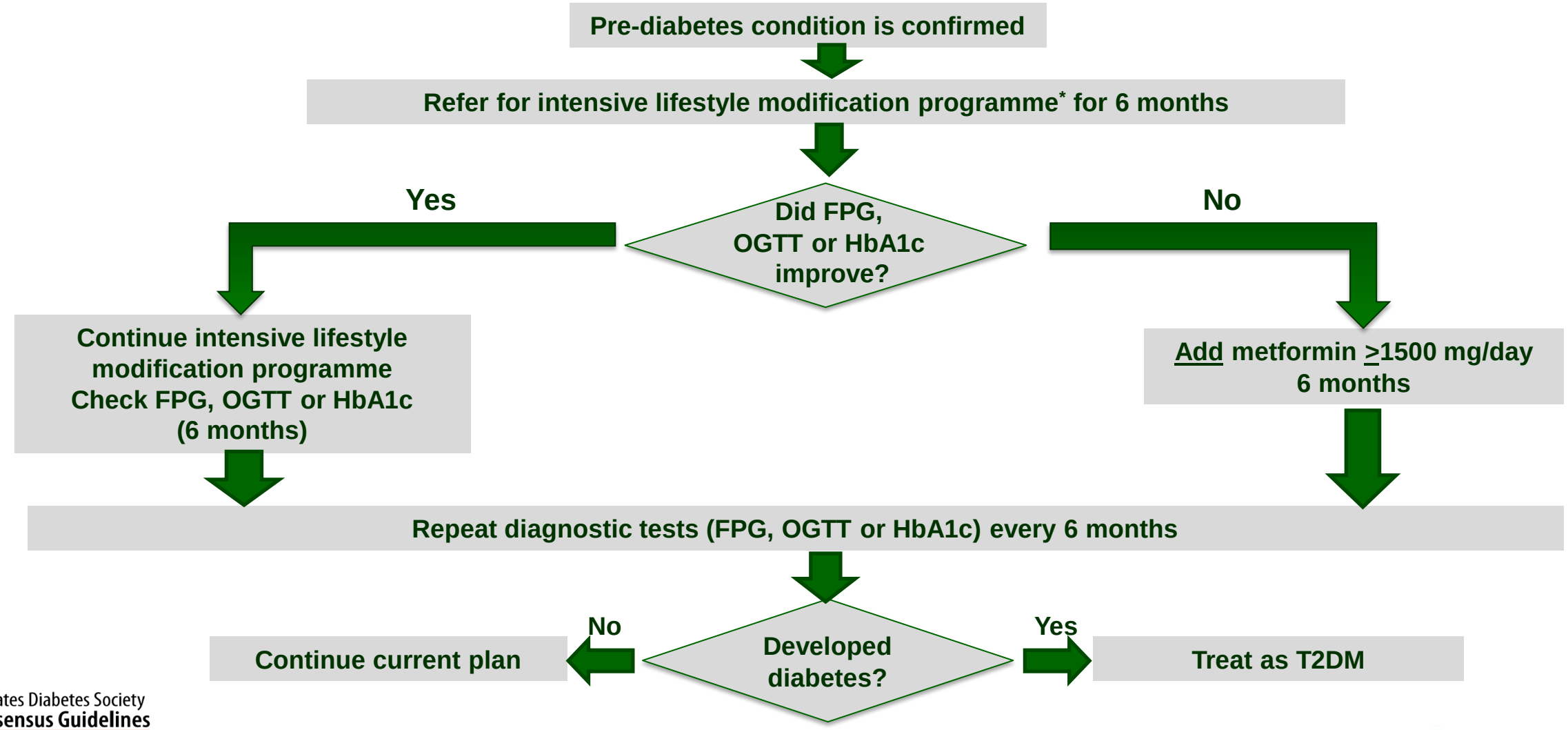
- Identify individuals for preventive measures

Treatment of pre-diabetes

- A **comprehensive lifestyle modification programme** that includes weight management, medical nutrition therapy, exercise and smoking cessation.
- Pharmacologic therapy for pre-diabetes for whom lifestyle modification failed or is not sustainable.

Reference: American Diabetes Association, 3. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020 43: S32-s36.

Treatment algorithm for pre-diabetes



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*The target is to achieve and maintain 5-10% loss of initial body weight and increase moderate-intensity physical activity (such as brisk walking) to at least 150min/week.
Abbreviations: FPG - fasting blood glucose; HbA1c – glycated haemoglobin; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; OGTT - 2-hour fasting glucose during a 75g oral glucose tolerance test; T2DM – Type 2 diabetes mellitus

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Lifestyle modification: Pre-diabetes

- **Weight management**
  - A weight loss of ≥5% is needed to produce beneficial outcomes in glycemic control, lipids and blood pressure[1]
- **Exercise**
  - >150 minutes/week, over ≥3 days/week, with no more than 2 consecutive days without exercise[2]
- **Dietary therapy**
  - A dietary pattern of healthful foods rather than specific nutrients, allows greater flexibility and personal preference improves long-term adherence[3]
- **Smoking cessation**
  - Smoking is a predictor of incident T2DM[4]

References:
[1]Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, et al., Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001 344: 1343-1350.
[2]Grontved A, Rimm EB, Willett WC, Andersen LB, Hu FB, A prospective study of weight training and risk of type 2 diabetes mellitus in men. Arch Intern Med 2012 172: 1306-1312.
[3]Mozaffarian D, Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. Circulation 2016 133: 187-225.
[4]Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL, Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. Ann Intern Med 2010 152: 10-17.

Management of Hyperglycaemia in Type 2 Diabetes

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Structured education programme

When should the programme be offered:	The programme must aim to:	Curriculum should contain:
• At and around the time of diagnosis. • Annually thereafter for reinforcement and review. • When complicating factors occur. • During transition of care. • At intensification of treatment (e.g. introduction of injectable therapy, change from basal to intensive insulin)	• Have specific aims and learning objectives. • Suit the needs of the person (individualised). • Have a documented, structured curriculum that is theory-driven, evidence-based and resource-effective; together with supporting materials (leaflets). • Have specific aims and learning objectives. • Support the person and their family members and caregivers in developing attitudes, beliefs, knowledge and skills to self-manage his/her diabetes. • Be quality assured, and reviewed by trained, competent and independent assessors who can measure the programme against its objectives; ensure consistency, and audit its outcomes regularly.	• Diabetes pathophysiology and treatment options. • Healthy eating. • Physical activity. • Medication and its usage. • Monitoring and using patient-generated health data. • Preventing, detecting, and treating acute and chronic complications of diabetes. • Coping with psychosocial issues and concerns. • Problem solving. • Social aspects such as fasting, driving and travelling for patients on insulin.

References:
National Institute for Health and Care Excellence (NICE). Section 1.2 Patient education. 2015; https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations - patient-education-2.
Beck J, Greenwood DA, Blanton L, Bollinger ST, Butcher MK, *et al.*, 2017 National Standards for Diabetes Self-Management Education and Support. *Diabetes Care* 2017 40: 1409-1419.

Glucose monitoring

- Self-monitoring of blood glucose:
  - To evaluate response to therapy and assess whether glycaemic targets are being safely achieved.
  - To guide therapy including diet, exercise and medication (particularly in titrating prandial insulin doses); and prevent hypoglycaemia.
  - Frequency and timing of monitoring depends on the specific needs and goals of the patient
  - To inform patients on basal insulin dose adjustments to achieve blood glucose targets.

- Education and support should be provided on initiation and during the annual assessment thereafter
  - Include a review of self-monitoring skills, equipment used, quality and frequency of testing, interpretation of blood glucose results and action taken.

Lifestyle modification: patients with diabetes

- **Weight management**
  - A weight loss of ≥5% is needed to produce beneficial outcomes in glycemic control, lipids and blood pressure[1]
- **Exercise**
  - **Patients with diabetes should be encouraged to embark on >150 minutes of moderate aerobic exercise in addition to 2-3 sessions of resistance exercise weekly[2,3].**
- **Dietary therapy**
  - **Medical nutrition therapy guidance throughout the course of a structured weight management plan is strongly recommended[4].**
- **Smoking cessation**

References:
[1]Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H*, et al.*, Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001 344: 1343-1350.
[2]Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW*, et al.*, Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care* 2016 39: 2065-2079.
[3]Sigal RJ, Armstrong MJ, Bacon SL, Boule NG, Dasgupta K*, et al.*, Physical Activity and Diabetes. *Can J Diabetes* 2018 42 Suppl 1: S54-s63.
[4]Razaz JM, Rahmani J, Varkaneh HK, Thompson J, Clark C*, et al.*, The health effects of medical nutrition therapy by dietitians in patients with diabetes: A systematic review and meta-analysis: Nutrition therapy and diabetes. *Prim Care Diabetes* 2019 13: 399-408

Initial and Follow-up Assessment of Patients with Diabetes

Periodic assessment for patients with diabetes

- A comprehensive set of periodic assessment checklists for patients with diabetes is provided (Appendix B of guidelines):
  - Diabetes medical evaluation by history.
  - Diabetes medical evaluation by physical examination.
  - Diabetes medical evaluation by laboratory tests.

References:
[1]National Institute for Health and Care Excellence (NICE). Section 1.2 Patient education. 2015; https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations - patient-education-2.
[2]American Diabetes Association, 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020 43: S37-s47
[3]Beck J, Greenwood DA, Blanton L, Bollinger ST, Butcher MK, *et al.*, 2017 National Standards for Diabetes Self-Management Education and Support. *Diabetes Care* 2017 40: 1409-1419.
[4]Diabetes Australia. General practice management of type 2 diabetes 2016–18 2019; https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/management-of-type-2-diabetes.
[5]International Diabetes Federation IDF Clinical Practice Recommendations for Managing Type 2 Diabetes in Primary Care 2019 https://www.idf.org/e-library/guidelines/128-idf-clinical-practice-recommendations-for-managing-type-2-diabetes-in-primary-care.html
[6]The Royal Australian College of General Practitioners. General practice management of type 2 diabetes: 2016–18. East Melbourne, Vic: RACGP, 2016. Available at www.racgp.org.au/your-practice/guidelines/diabetes.
[7]Driskell OJ, Holland D, Waldron JL, Ford C, Scargill JJ, Heald A, et al. Reduced testing frequency for glycated hemoglobin, HbA1c, is associated with deteriorating diabetes control. Diabetes Care. 2014 Oct;37(10):2731-7.

Diabetes medical evaluation by history

	Factors	Initial visit	Periodic visits	Annual visit
Diabetes	Hypoglycaemia symptoms	√	√	√
	Hyperglycaemia symptoms	√	√	√
	Hospitalization	√	√	√
Comorbidities	Dyslipidemia	√	√	√
	Hypertension	√	√	√
	Neuropathy: Peripheral Autonomic Mononeuritis	√ √ √	√	√ √ √
	Visual impairment	√		√
	Depression/anxiety	√		√
	Haemoglobinopathies	√		
	Thyroid disorder	√		√
	Infections	√	√	√
	Cancer	√		√

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Diabetes medical evaluation by history

	Factors	Initial visit	Periodic visits	Annual visit
Lifestyle	Work status	√		√
	Smoking status	√	√	√
	Alcohol	√		√
	Physical activity	√	√	√
	Eating patterns/disorder	√	√	√
	Sleep pattern	√		√
Medications	Compliance	√	√	√
	Side effects	√	√	√
	Alternative therapies	√	√	√
	Vaccinations: Pneumococcus	√		
	Influenza	√		√
	Hepatitis B	√		
Self-care	Glucose monitoring	√	√	√
	Independency	√		√
	Accessibility to healthcare	√		√
	Support at home	√		√
	Personal hygiene/oral health	√		√

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Diabetes medical evaluation by physical examination

Physical Examination	Target procedure or value	Initial visit	Periodic visits	Annual visit
Vitals				
Weight/BMI	<28 kg/m², for BMI 28-35 kg/m², aim for 5-10% weight loss. BMI 30 to <40 kg/m², consider bariatric surgery if weight loss is unsuccessful with lifestyle and medication. BMI > 40, advise to have bariatric surgery if weight loss is unsuccessful with lifestyle modification and medication.	√	√	√
Blood Pressure (BP) **Orthostatic BP**	<140/90 mmHg, <130/80 in patients with high risk of CVD[1]	√ √	√	√ √

Abbreviations: BMI - body mass index; ECG, electrocardiogram
*Digital fundus examination is the preferred method. Refer to specialist every 2 years if no retinopathy and more frequently as necessary
†10-g monofilament test should be performed with at least one other assessment (pinprick, temperature or vibration)[3].
‡An Ankle Brachial Pressure Index (ABI) should be performed on a patient with diabetes who is >50 years of age; or in under 50 years of age and has other PAD risk factors (e.g. smoking, HTN, lipids); or a duration of diabetes of >10 years. The ABI should be repeated in 5 years if normal[2,4].

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Diabetes medical evaluation by physical examination

Physical Examination	Target procedure or value	Initial visit	Periodic visits	Annual visit
Complications				
Skin exam	Look for injection sites, evidence of lipodystrophy, or more frequently if applicable.	√		√
Fundus examination*		√		√
Foot exam for evidence of neuropathy, PAD, deformity or infection	• Inspection (skin integrity, callous, ulcers, gangrene, and toe nails)[2].	√	√	√
	• Palpation of peripheral pulses.	√	√	√
	• Vibration testing.	√	√	√
	• Sensitivity with 10g monofilament†.	√	√	√
	• Ankle Brachial Pressure Index‡.	√		
Systemic				
Cardiovascular	• Auscultation of carotid, heart and lung bases • ECG • 2D echo if symptoms or signs of heart failure	√ √ √		√ √ √
Abdomen	Liver	√		√
Lower limbs	Look for oedema, lipodystrophy	√		√

Abbreviations: 2D - 2-dimensional; ABI - Ankle Brachial Pressure Index, PAD - Peripheral vascular disease.
*Digital fundus examination is the preferred method. Refer to specialist every 2 years if no retinopathy and more frequently as necessary
†10-g monofilament test should be performed with at least one other assessment (pinprick, temperature or vibration)[3].
‡An Ankle Brachial Pressure Index (ABI) should be performed on a patient with diabetes who is >50 years of age; or in under 50 years of age and has other PAD risk factors (e.g. smoking, HTN, lipids); or a duration of diabetes of >10 years. The ABI should be repeated in 5 years if normal[2,4].

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Diabetes medical evaluation by laboratory tests

Test	Target	Initial visit	Periodic visits	Annual visit
Glycaemia				
Blood Glucose Levels	FPG 5-7 mmol/L (90 – 126 mg/dL) RBG 7-10 mmol/L (126 – 180 mg/dL)*	√	√	√
HbA1c†	≤7% (53 mmol/mol) - individual 6.5-7.5% (48-58 mmol/mol)in majority of patients*	√	√	√
Lipid profile‡				
• **Total Cholesterol**	< 4.0 mmol/L (<160 mg/dL)	√		√
• **LDL**		√		√
• **Very high risk**	< 1.4 mmol/L (<55 mg/dL)			
• **High risk**	< 1.8 mmol/L (<70 mg/dL)			
• **Moderate risk**	< 2.6 mmol/L (<100 mg/dL)			
• **Low risk**	< 3.0 mmol/L (<116 mg/dL)			
• **Triglycerides**	< 2.0 mmol/L (<80 mg/dL)	√		√

Abbreviations: HbA1c - hemoglobin HbA1c; FPG - fasting blood glucose; LDL - low-density lipoproteins; HDL - high-density lipoproteins; RBG - random blood glucose.

*Less stringent targets between 7.5% and 8.0% (58 to 64 mmol/mol) can be recommended for elderly, patients with short life expectancy, recurrent hypoglycaemia, and hypoglycaemia unawareness[5,6].
†The recommended frequency of HbA1c testing is 2-4 times per year[7].
‡The recommended frequency of lipids testing is 1-3 times per year. Patients without dyslipidemia and not on lipid lowing agents, testing can be less frequent.
**LDL target is based of the ESC/EASD risk categorisation mentioned in Fig 2.
§ eGFR and liver function tests can be done more frequently based on the condition of the patient upon initiation or dose modification of medications.

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Diabetes medical evaluation by laboratory tests

Test	Target	Initial visit	Periodic visits	Annual visit
Kidney function				
• **Electrolytes** • **eGFR§**	eGFR >60ml/min/1.73m^2	√ √	√	√ √
• **Urine albumin: Creatinine Ratio**	< 3.5 mg/mmol in women < 2.5 mg/mmol in men	√		√
Other tests				
Liver function tests		√		√
Vitamin B12	For patients on metformin.	√		√

Abbreviations: HbA1c - hemoglobin HbA1c; FPG - fasting blood glucose; LDL - low-density lipoproteins; HDL - high-density lipoproteins; eGFR - estimated glomerular filtration rate; RBG - random blood glucose.

*Less stringent targets between 7.5% and 8.0% (58 to 64 mmol/mol) can be recommended for elderly, patients with short life expectancy, recurrent hypoglycaemia, and hypoglycaemia unawareness[5,6].
†The recommended frequency of HbA1c testing is 2-4 times per year[7].
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**LDL target is based of the ESC/EAS risk categorisation mentioned in Fig 2.
§eGFR and liver function tests can be done more frequently based on the condition of the patient upon initiation or dose modification of medications.

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Pharmacotherapy for T2DM: Overview

Emirates Diabetes Society
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Risk-based pharmacotherapy

- We recommend risk-based pharmacotherapy for patients with diabetes (based on cardiovascular, renal, hypoglycaemia and weight risks)[1,2]
- This risk is usually related to the age of the patient, duration of diabetes and the presence of one or multiple CVD risk factors[3]
- We present treatment algorithms based on cardiovascular risk (adapted from the ESC/EASD guidelines[1]) and information on anti-diabetic medications

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Abbreviations: CVD - cardiovascular disease. EASD - European Society for the Study of Diabetes, ESC - European Society of Cardiology.

References:
[1]Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, *et al.*, 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2019.
[2]American Diabetes Association, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020 43: S98-s110.
[3]Rawshani A, Sattar N, Franzen S, Rawshani A, Hattersley AT, *et al.*, Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet* 2018 392: 477-486.

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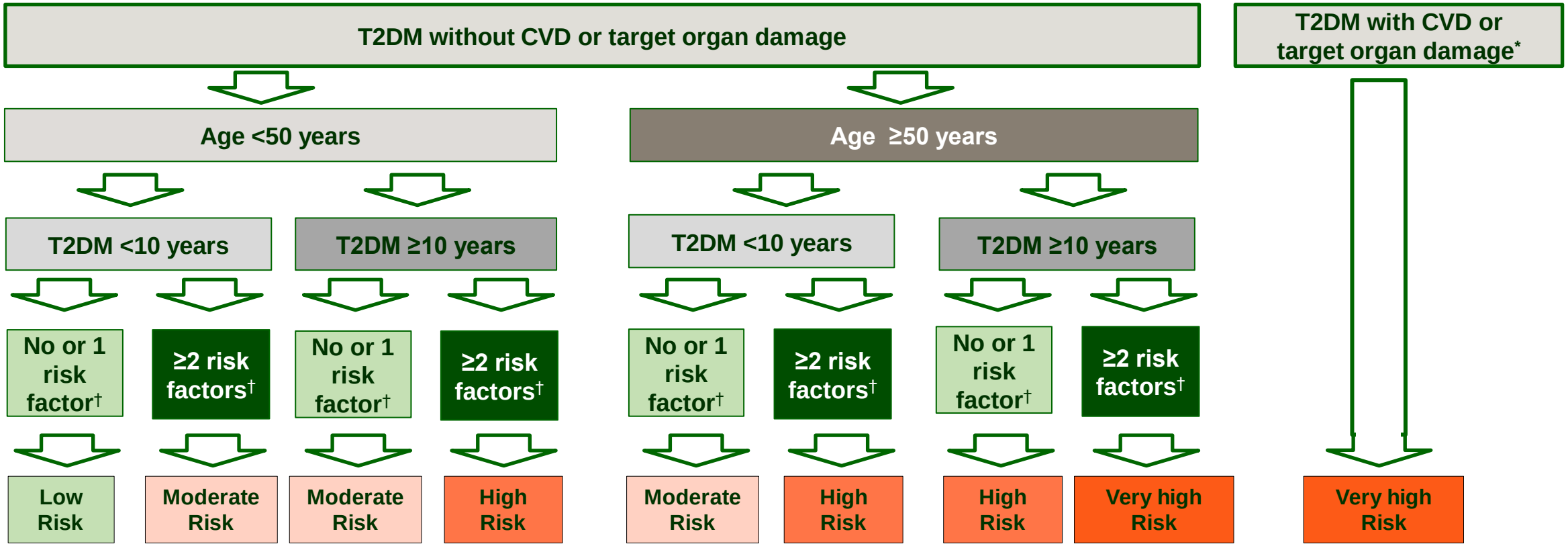
Cardiovascular risk categorisation



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*Proteinuria, renal impairment defined as eGFR <60 mL/min/1.73 m^2, left ventriclular hypertrophy, or retinopathy.
†Age, hypertension, dyslipidemia, smoking, obesity.
Abbreviations: CVD - cardiovascular disease; T2DM – Type 2 diabetes mellitus.
Reference: Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A*, et al.*, 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2019.

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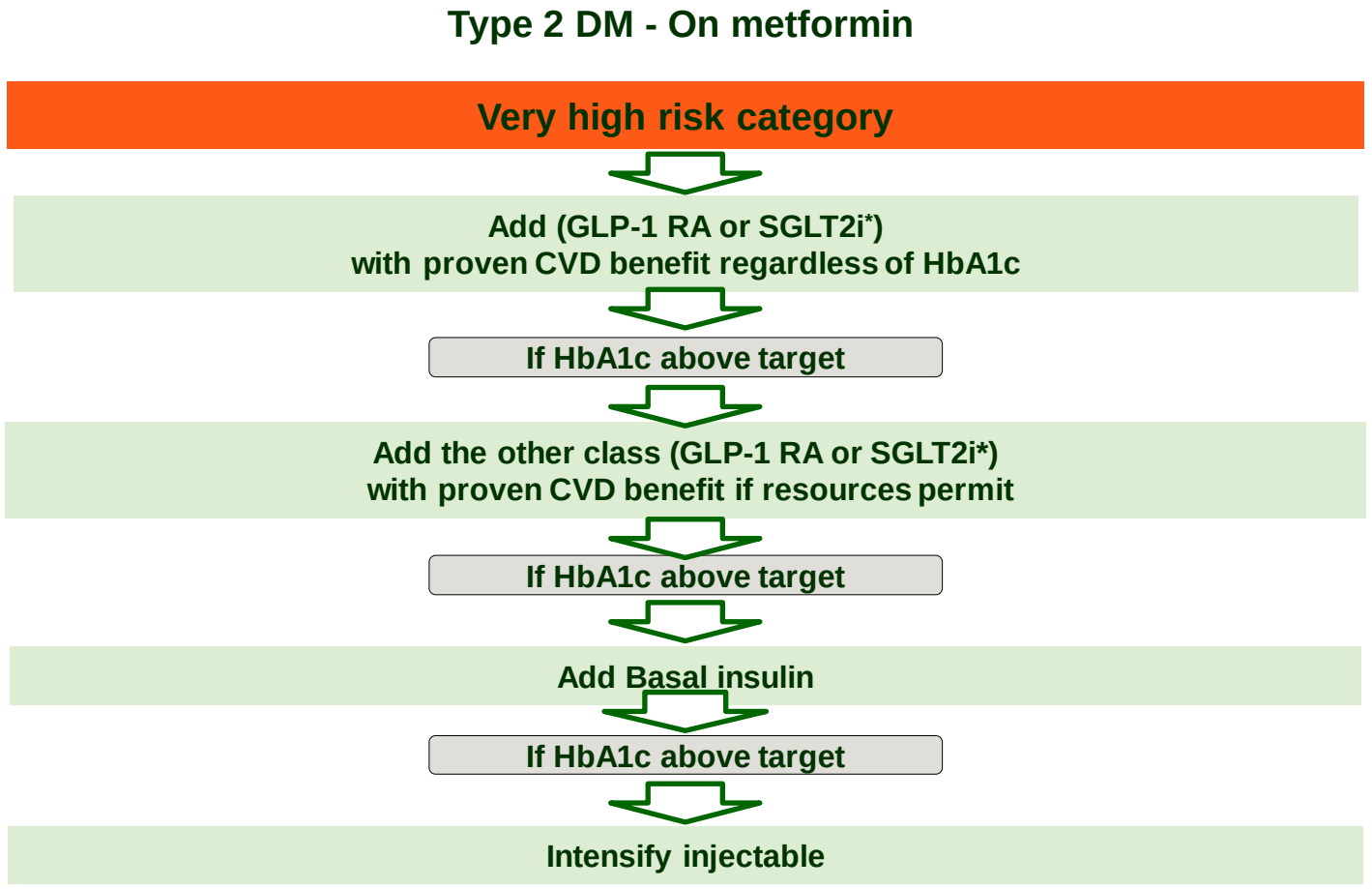
Cardiovascular risk categorisation

Cardiovascular risk category	Treatment considerations
Very high risk	Drugs with cardiovascular and/or renal benefits are preferred as a second choice of treatment after metformin regardless of the level of glycaemic control for those who are considered as very high risk for CVD.
High risk	For patients who are considered at high risk, our recommendations have taken into consideration not only the benefit of the drugs for patients with multiple CVD risk factors, but also the limited evidence for these drugs (small number of studies) and their cost-effectiveness (patients may not have the ability to afford these expensive medications).
Moderate risk	For patients with moderate and low risk of CVD, the choice of drug therapy for those not well-controlled on metformin will also depend on other associated factors such as the glycaemic effectiveness of the drug, risk of hypoglycaemia, the impact of the drug on body weight and its cost.
Low risk	See Moderate risk above.

Abbreviations: CVD - cardiovascular disease

Very high risk category



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*SGLT2i is the preferred option in people with heart failure or impaired renal function.
Abbreviations: BMI – body mass index; GLP-1 RA - glucagon-like peptide 1 receptor agonists; HbA1c – glycated haemoglobin; SGLT2i - sodium–glucose cotransporter 2 inhibitors.
Reference: 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019.

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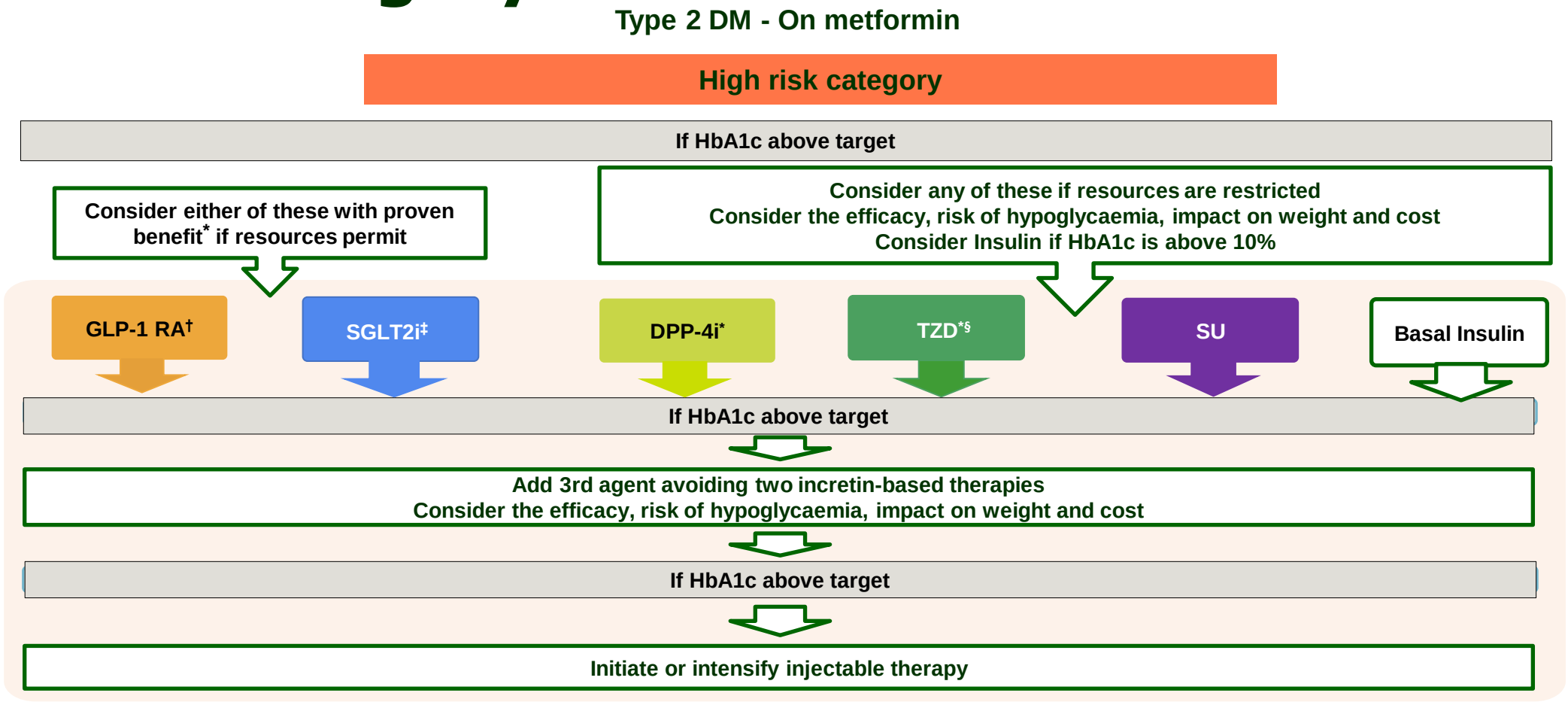
High risk category



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*Avoid pioglitazone, saxagliptin and alogliptin in congestive heart failure.
†GLP1-RA, can be used in patients with eGFR >30 mL/min, dulaglutide can be used up to eGFR >15mL/min. Avoid semaglutide in patients with retinopathy.
‡SGLT2i is the preferred option in people with heart failure or impaired renal function. SGLT2i can be used in eGFR >45. Avoid using SGLT2i in patients with aortic stenosis and eGFR<45ml/min.
§Metformin (where eGFR >30 mL/min) and pioglitazone are safe in CKD and can be used interchangeably.
Abbreviations: BMI – body mass index; DPP-4i - dipeptidyl peptidase 4 inhibitors; GLP-1 RAs - glucagon-like peptide 1 receptor agonists; HbA1c – glycated haemoglobin; SGLT2i - sodium–glucose cotransporter 2 inhibitors; SU - sulfonylureas; TZD – thiazolidinediones.
Reference: 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019.

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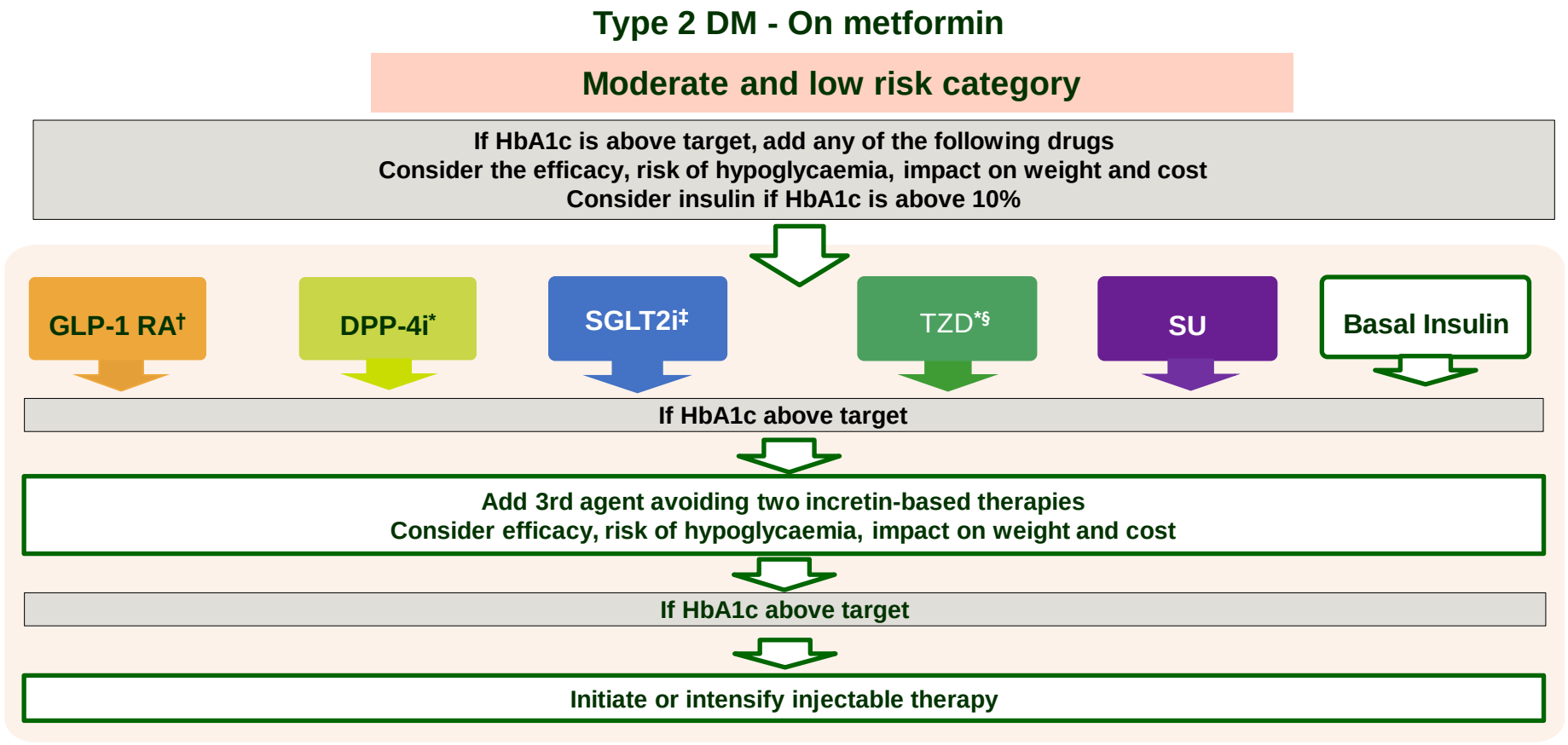
Moderate and low risk category



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*Avoid pioglitazone, saxagliptin and alogliptin in congestive heart failure.
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‡SGLT2i is the preferred option in people with heart failure or impaired renal function. SGLT2i can be used in eGFR >45. Avoid using SGLT2i in patients with aortic stenosis and eGFR<45ml/min.
§Metformin (where eGFR >30 mL/min) and pioglitazone are safe in CKD and can be used interchangeably.
Abbreviations: BMI – body mass index; DPP-4i - dipeptidyl peptidase 4 inhibitors; GLP-1 RAs - glucagon-like peptide 1 receptor agonists; HbA1c – glycated haemoglobin; SGLT2i - sodium–glucose cotransporter 2 inhibitors; SU - sulfonylureas; TZD – thiazolidinediones.
Reference: 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019.

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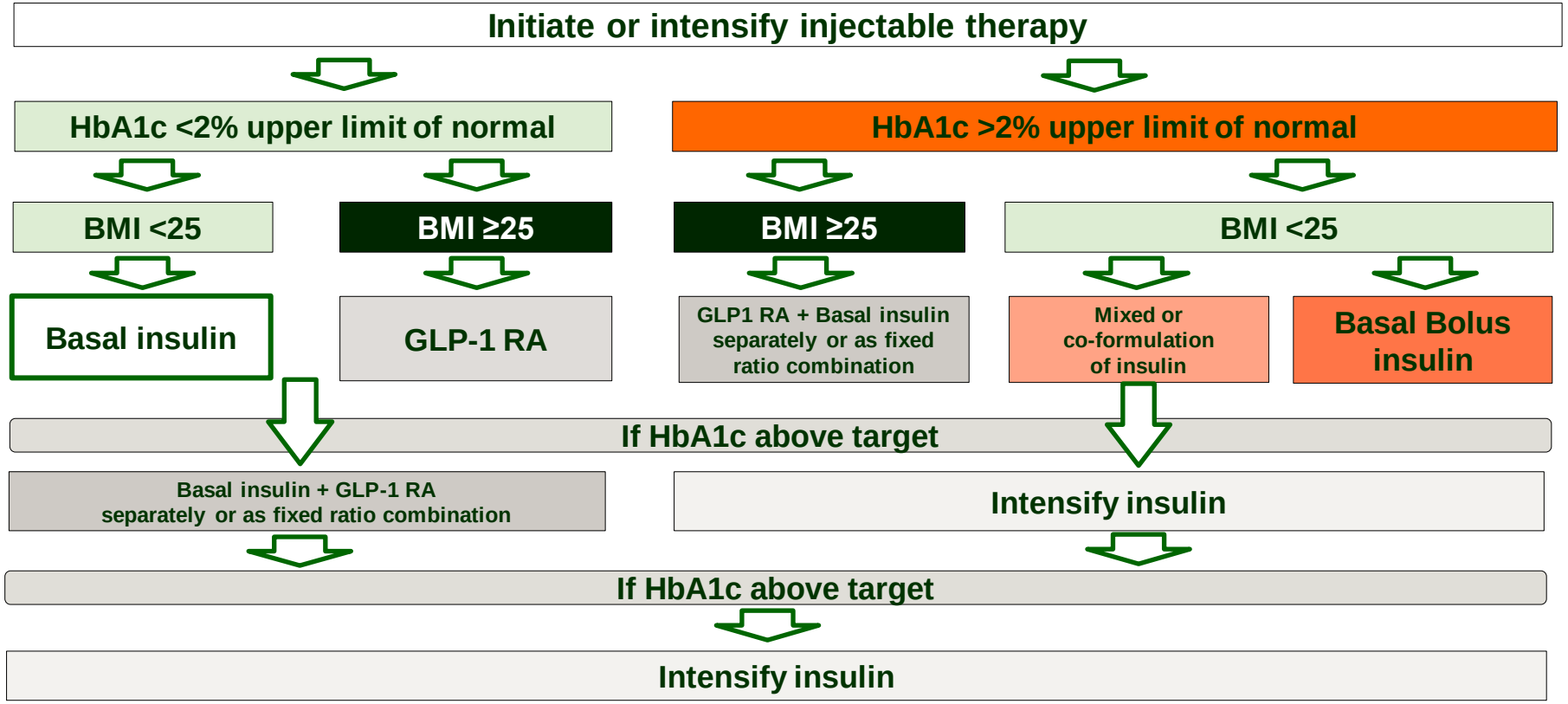
Initiate or intensify injectable therapy



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Abbreviations: BMI – body mass index; GLP-1 RAs - glucagon-like peptide 1 receptor agonists; HbA1c – glycated haemoglobin
Reference: 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019.

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Summary:
Key Recommendations

Key Recommendations

- We recommend that the American Diabetes Association screening criteria be adopted but starting at **a lower age of 30 years**. (Section 4)
- For persons with normal test results, repeat testing at least once every 3 years (unless conditions changed), or 6-monthly if the person is diagnosed with pre-diabetes. (Section 4.2)
- Patients with pre-diabetes should be provided with a **comprehensive lifestyle modification programme** that includes weight management, medical nutrition therapy, exercise and smoking cessation. (Section 5.1.2, Fig 1)
- **Structured education for diabetes self-management** should be an integral part of diabetes care and offered to all adults diagnosed with T2DM and/or their family members or caregivers (as appropriate). (Section 6.1, Table 3)

Key Recommendations

- Patients with diabetes should be encouraged to embark on **>150 minutes of moderate aerobic exercise** in addition to **2-3 sessions of resistance exercise weekly**. (Section 6.3.1)
- **Medical nutrition therapy guidance** throughout the course of a **structured weight management plan** is strongly recommended. (Section 6.3.2)
- We recommend **risk-based pharmacotherapy** for patients with diabetes (based on cardiovascular, renal, hypoglycaemia and weight risks). (Section 6.4.1, Fig 2-6, Appendix C)
- A comprehensive set of checklists for periodic assessment of patients with diabetes is provided. (Section 7, Appendix B)

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Summary: Approach for Use of Antihyperglycaemic Medications in T2D Management[1,2]

Healthy lifestyle behaviours; diabetes self-management education and support; social determinants of health

To avoid therapeutic inertia, re-assess and modify treatment regularly (3-6 months)

Goal

To reduce cardiorenal risk in high-risk people with T2D (in addition to comprehensive CV risk management)[a]

+ASCVD[b]

CVOTs included participants with established CVD (e.g., MI, stroke or any revascularisation procedure), but the definition of ASCVD differed between them. Variably included were TIA, unstable angina, amputation, symptomatic or asymptomatic CAD.

+High-risk indicators

Definition of ASCVD may vary across CVOTs; however, most patients are ≥55 years of age with ≥2 additional risk factors (including obesity, hypertension, smoking dyslipidaemia or albuminuria)

+ASCVD/High-risk indicators

GLP-1 RA[c] with proven CVD benefit

Either/ Or

SGLT-2i[d] with proven CVD benefit

If HbA1c above target levels

- Consider the addition of SGLT-2i with proven CVD benefit or vice versa in people using GLP-1 RA
- TZD[e]

+HF

HF symptoms, currently or earlier, with documented HFrEF or HFpEF

+HF

SGLT-2i[d] with proven HF benefit

+CKD

eGFR <60 mL/min/1.73 m^2 or albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may differ over time, needing a repeat measure to document CKD

+CKD (on MTD of ACEi/ARB)

SGLT-2i[d] with primary evidence of reducing CKD progression

Use SGLT-2i in people with eGFR ≥20 mL/min/1.73 m^2; once initiated, continue until initiation of dialysis or transplantation

Or

GLP-1 RA with proven CVD benefit if SGLT-2i not tolerated or contraindicated

If HbA1c above target levels, for people on SGLT-2i, consider including a GLP-1 RA or vice versa

If additional reduction of cardiorenal risk or lowering of glycaemia required

Goal

To achieve and maintain glycaemic and weight management goals

Managing glycaemia: Choose approaches that provide the efficacy to achieve goals:

Metformin **or** medicines including **combination** treatment that provide adequate **efficacy** to achieve and maintain treatment goals

In high-risk individuals, consider avoidance of hypoglycaemia a priority

Generally, higher efficacy approaches have increased the possibility to achieve glycaemic goals

Efficacy for lowering glucose levels

Very High

Dulaglutide (high dose), semaglutide, tirzepatide
Insulin

Combination oral, combination injectable (GLP-1 RA/insulin)

High

GLP-1 RA (not listed above), metformin, SGLT-2i, sulphonylurea, TZD

Intermediate

DPP-4i

Achieving and maintaining weight management goals:

Setting individualised weight management goals

- Lifestyle advice: MNT/ healthy eating patterns/ physical activity
- Intensive evidence-based structured weight management programme
- Weight-loss medication to be considered
- Metabolic surgery to be considered

When choosing antihyperglycaemic medications: Consider regimen with high-to-very-high dual glucose and weight efficacies

Efficacy for weight loss

Very High

Semaglutide, tirzepatide

High

Dulaglutide, liraglutide

Intermediate

GLP-1RA (not listed above), SGLT-2i

Neutral

DPP-4i, metformin

If HbA1c above target levels

Identify barriers:

- Consider DSMES referral to support self-efficacy in goal achievement
- Identify and address social determinants of health that affect goal achievement
- Consider technology (e.g., diagnostic CGM) to identify therapeutic lacuna and individualise therapy

Note: Explanation for footnote indicators and abbreviations are available in the speaker notes.

1. Data from Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.
2. Data from Davies MJ, et al. *Diabetologia*. 2022;65(12):1925-1966.

Case Study

Patient Journey Over a Period of 1 Year & 6 Months

Mr. Adam is a 49-year-old male who was brought to GP by his son with symptoms of weakness on little exertion everyday, increased thirst and burning of both feet occasionally.

Mr. Adam – Presented to the GP (Family Physician)

Presenting complaint	Weakness on little exertion everyday Increased thirst Burning of both feet occasionally
Medical history	No history of hypertension/diabetes mellitus/cardiovascular disease, no smoking
Family history	Father: Type 2 diabetes mellitus Mother: Hypertension
Current medication	Multivitamin capsules (occasionally)

Mr. Adam – Presented to the GP (Family Physician)

Physical examinations and investigations	Temperature: 36.8^{0}C Pulse: 78/min Blood pressure: 130/84 mmHg Acanthosis nigricans on the back of the neck BMI: 25.9 kg/m^{2} Random plasma glucose: 275 mg/dL HbA1c: 6.9% LDL-C: 98 mg/dL, HDL-C: 34 mg/dL, TG: 156 mg/dL, Total cholesterol: 123 mg/dL Electrocardiogram: Normal
Diagnosis	Type 2 diabetes mellitus
Management	Metformin 500 mg bid with meal Atorvastatin 10 mg qd Telmisartan 20 mg qd Continue Multivitamin capsules

Mr. Adam's Case Study – Management Considerations

If you were Adam's general practitioner, what would you advise?

Please select all that apply:

1. Increase the dose of Metformin
2. Switch to an alternative glucose-lowering medication
3. Encourage weight loss with diet and exercise suggestions
4. Stop antihypertensive therapy
5. Add an additional lipid-lowering agent

Mr. Adam's Case Study– Management Considerations

1. Increase the dose of Metformin
   - Increasing the dose of metformin is **not recommended** because the recommended starting dose of Metformin is 500 mg orally twice a day or 850 mg once a day given with meals and higher doses initially may cause gastrointestinal intolerance.

2. Switch to an alternative glucose-lowering medication
   - Metformin should be considered in overweight patients (BMI: 25 to <30 kg/m^2) with type 2 diabetes mellitus without CVD and at moderate CV risk. So, no alternate glucose-lowering medication is suggested.

Mr. Adam's Case Study– Management Considerations

3. Encourage weight loss with diet and exercise suggestions
   - Because diabetes increases Adam's CV risk, therefore close monitoring and control of CV risk factors are crucial.
   - Dietary (reduction of calorie intake) and appropriate exercise (moderate-to-vigorous, ≥150 min/week, combined aerobic and resistance training) suggestions should be reinforced. A minimum weight loss of 5% is recommended.

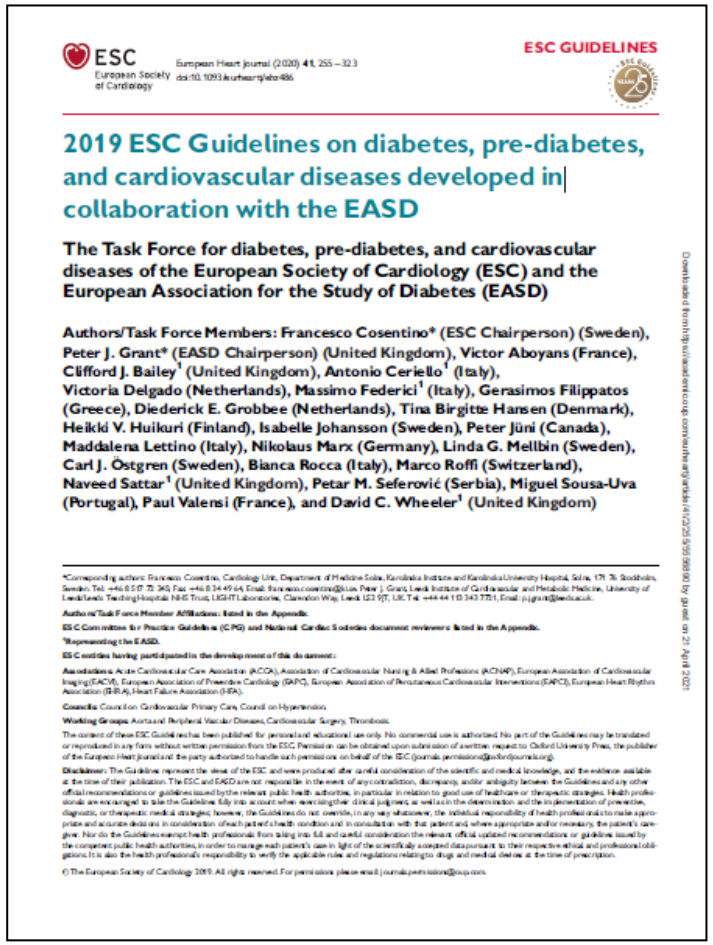
4. Stop antihypertensive therapy
   - SBP is already 130 mmHg. The patient should limit sodium consumption to 2,300 mg/day.

5. Add an additional lipid-lowering agent
   - Adding another lipid-lowering agent is not recommended rather therapy should be discontinued because in patients with type 2 diabetes mellitus at moderate CV risk, an LDL-C target is <100 mg/dL; Adam is at the LDL-C target of <100 mg/dL.

Mr. Adam's Case Study – Factors Indicating Moderate CV Risk

- Adam, a 49-year-old male, is a known case of type 2 diabetes mellitus (aged <50 years) with diabetes mellitus duration of<10 years without other risk factors (smoking/hypertension/dyslipidaemia/obesity/major microvascular or macrovascular disorder).
- Therefore, the patient falls in moderate CV risk category.

The ESC/EASD 2019 Guidelines: Diabetes and CV Risk



ESC European Society of Cardiology

European Heart Journal (2020) 41, 255–323
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

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)

Authors/Task Force Members: Francesco Cosentino* (ESC Chairperson) (Sweden), Peter J. Grant* (EASD Chairperson) (United Kingdom), Victor Aboyans (France), Clifford J. Bailey[1] (United Kingdom), Antonio Ceriello[1] (Italy), Victoria Delgado (Netherlands), Massimo Federici[1] (Italy), Gerasimos Filippatos (Greece), Diederick E. Grobbee (Netherlands), Tina Birgitte Hansen (Denmark), Heikki V. Huikuri (Finland), Isabelle Johansson (Sweden), Peter Jüni (Canada), Maddalena Lettino (Italy), Nikolaus Marx (Germany), Linda G. Mellbin (Sweden), Carl J. Östgren (Sweden), Bianca Rocca (Italy), Marco Roffi (Switzerland), Naveed Sattar[1] (United Kingdom), Petar M. Seferović (Serbia), Miguel Sousa-Uva (Portugal), Paul Valensi (France), and David C. Wheeler[1] (United Kingdom)

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- CV risk categories in people with diabetes[1]

Category	Risk factors
Very high risk	Patients with DM **and** established cardiovascular 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 DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (aged <35 years with T1DM or aged <50 years with T2DM) with DM duration of <10 years without other risk factors

DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; CV, cardiovascular.
*Proteinuria, renal impairment defined as eGFR <30 ml/min/1.73 m^2, left ventricular hypertrophy or retinopathy.
**Age, hypertension, dyslipidaemia, smoking, obesity.

Mr. Adam 6 months later…

Reason for visiting HCP	Follow-up
Present complaints/ status	Weakness subsided slowly, thirst only in moderation, frequent urination (6–7 times during the daytime and once in the night-time) Burning of both feet still persists Bloating of stomach occasionally after meal
Medical history	Type 2 diabetes mellitus detected 6 months ago
Current medication	Metformin 500 mg bid with meal Atorvastatin 10 mg qd Telmisartan 20 mg qd Multivitamin capsules qd

Mr. Adam's Case Study – Clinical Examination and Investigations

Physical examination	You examine Adam and note the following: • Temperature: 37^{0}C • Pulse: 76/min • Blood pressure: 128/80 mmHg • Acanthosis nigricans on the back of the neck: Present • BMI: 26.3 kg/m^2 You ask Adam some questions about his symptoms: • Is weakness predominantly present when fasting? • Tell me more about recent occurrence of burning sensation of feet • Is there any burning during urination?
Blood test results	FPG: 178 mg/dL PPG: 299 mg/dL HbA1c: 7.6% LDL-C: 89 mg/dL, HDL-C: 38 mg/dL, TG: 160 mg/dL, Total cholesterol: 129 mg/dL eGFR: 57 mL/min/1.73 m^2 UACR: 33 mg/g

Mr. Adam's Case Study – Management Considerations

What are your recommendations for Adam's case management?

Please select all that apply:

1. Increase the dose of Metformin
2. Add another glucose-lowering medication
3. Stop antihypertensive therapy
4. Add medical agent for neuropathic complaints (burning pain in feet)

Mr. Adam's Case Study– Management Considerations

✗ 1. Increase the dose of Metformin

- Increasing the dose of metformin is not recommended as Adam is facing gastrointestinal intolerance (bloating of stomach). Indeed initiating SR preparation or switching to another insulin sensitiser with no gastrointestinal upset is preferred.
- **Pioglitazone is preferred** to reduce insulin resistance (as Adam has acanthosis nigricans, a sign of insulin resistance). Also, Adam has no contraindication for the drug Pioglitazone (No CHF or fluid retention). Pioglitazone decreases fasting and postprandial plasma glucose levels by improving the sensitivity of liver and peripheral (muscle) tissue to insulin.

✓ 2. Add second glucose-lowering medication

- Adam shall require second glucose-lowering medication, which is weight neutral with CV and renal benefits. Empagliflozin 10 mg qd is preferred over SU & DPP4i as a second agent. It will help Adam to lose weight along with providing CV and renal benefits.

Mr. Adam's Case Study– Management Considerations

3. Stop antihypertensive therapy
   - BP is normal. Advise to limit sodium consumption to 2,300 mg/day and avoid oily food.

4. Add medical agent for neuropathic complaints (burning pain in feet)
   - Pregabalin (75 mg) SR on an empty stomach before breakfast is recommended.

Mr. Adam 6 Months Later…

Reason for visiting HCP	Follow-up
Present complaints/ status	Feeling energetic with almost negligible burning of feet Urination (4–6 times during daytime) with occasional burning No bloating of stomach Occasional palpitations in the chest
Medical history	Type 2 diabetes mellitus for 1 year
Current medication	Metformin 500 mg bid with meals Pioglitazone 15 mg qd with meal Empagliflozin 10 mg qd Pregabalin 75 mg SR qd on empty stomach before breakfast Methylcobalamin 1500 mcg qd at night

Mr. Adam's Case Study – Clinical Examination and Investigations

Physical examination	You examine the patient and note the following: • Temperature: 37^0C • Pulse: 92/min • Blood pressure: 126/82 mmHg • Acanthosis nigricans on the back of the neck: Present • BMI: 26.1 kg/m^2 • Electrocardiogram: Normal You ask some questions to the patient about his symptoms: • The frequency and severity of palpitations and whether palpitations appear at rest or at exertion You advise the patient to maintain hygiene of genital area after urination. Provide him with information on the symptoms of urinary tract infections and inform him to seek medical advice if such symptoms occur.
Blood test results	FPG: 122 mg/dL PPG: 180 mg/dL HbA1c: 7.2% LDL-C: 110 mg/dL, HDL-C: 35 mg/dL, TG: 200 mg/dL, Total cholesterol: 187 mg/dL eGFR: 49 mL/min/1.73 m^2 UACR: 31 mg/g
Advise (Rx)	Continue the medication until the next follow-up after 6 months

Initial ‘dip’ in eGFR on SGLT2i [EMPA-REG OUTCOME Trial]

- The study population included 7,020 treated participants with T2DM, established CV disease and eGFR ≥30 ml/min per 1.73 m^2.
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  mg or 25
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  observat
- Empagli
  of treatr
  time poi
  eGFR re
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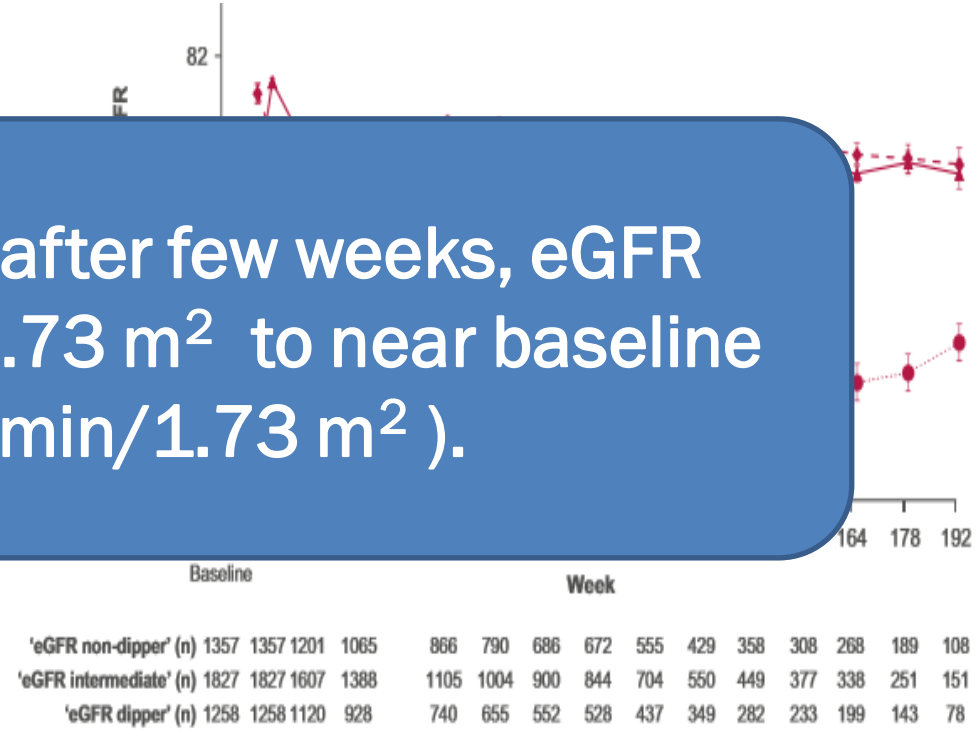
  eGFR. The adjusted estimates of annual decreases in eGFR were 0.19 + 0.11 ml/min/1.73 m^2 in the empagliflozin group and 1.67 + 0.13 ml/min/1.73 m^2 (significantly greater decrease) in the placebo group.
- **SGLT2 inhibitors induce an early, reversible reduction in GFR and can preserve GFR in the long-term in type 2 diabetic patients.[1,2]**

In this patient on follow-up after few weeks, eGFR increased from 49 ml/min/1.73 m^2 to near baseline value of 57 (55 ml/min/1.73 m^2).



eGFR over time per ‘eGFR dipping‘ category in empagliflozin-treated participants[1]

Mr. Adam's Case Study – Management Considerations

What are your priorities for Adam's long-term management?

Please select all that apply:

1. Maintaining blood glucose control
2. Reducing CV risk and preserving kidney function
3. Controlling BP to a target of ≤130/80 mmHg

Mr. Adam's Case Study – Management Considerations

1. Maintain blood glucose control
   - Continue to monitor blood glucose levels to reduce the CV risk.

2. Reduce CV risk and preserve kidney function
   - Regularly monitor glucose and BP to reduce CV risk and measure eGFR and UACR (≥3 measurements annually) to assess any further kidney function decline.

3. Control BP to a target of ≤130/80 mmHg
   - Target BP of 130/80 mmHg needs to be established.

Review of the ESC/EASD Guidelines and Management of DM with CV Risk

Blood pressure targets	Individualised blood pressure targets are recommended. Lower SBP to 130 mmHg and, <130 mmHg if tolerated, but not <120 mmHg. In older people (>65 years), target SBP to a range of 130–139 mmHg. Lower DBP to <80 mmHg but not <70 mmHg.
Lipid targets	In patients with T2DM at moderate CV risk, an LDL-C target of <100 mg/dL (<2.6 mmol/L) is recommended.
Glucose-lowering treatment	Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk. To reduce CV events: **Empagliflozin, canagliflozin, dapagliflozin**, liraglutide, semaglutide and dulaglutide are recommended in patients with T2DM and CVD or at very high/high CV risk. To reduce the risk of death: **Empagliflozin** is recommended in patients with T2DM and CVD. Liraglutide is recommended in patients with T2DM and CVD or at very high/high CV risk. Saxagliptin is not recommended in patients with T2DM and a high risk of HF. **Empagliflozin, canagliflozin, and dapagliflozin** are recommended to lower the risk of HF hospitalisation. **SGLT2 inhibitors are recommended to reduce the progression of diabetic kidney disease.**

The ESC/EASD 2019 Guidelines: Diabetes and CV Risk

Summary of treatment targets for the management of patients with diabetes

Risk factor	Target
BP	• Target systolic blood pressure 130 mmHg for most adults, <130 mmHg if tolerated, but not <120 mmHg • Less-stringent targets, systolic blood pressure 130–139 in older patients (aged >65 years)
Glycaemic control: HbA1c	• HbA1c target for most adults is <7.0% (<53 mmol/mol) • More-stringent HbA1c goal of <6.5% (48 mmol/mol) may be suggested on a personalised basis if this can be achieved without significant hypoglycaemia or other adverse effects of treatment • Less-stringent HbA1c goals of <8% (64 mmol/mol) or <9% (75 mmol/mol) may be adequate for elderly patients
Lipid profile: LDL-C	• In patients with diabetes mellitus at very high cardiovascular risk,[a] target LDL-C to <1.4 mmol/L (<55 mg/dL) • In patients with diabetes mellitus at high cardiovascular risk,[b] target LDL-C to <1.8 mmol/L (<70 mg/dL) • In patients with diabetes mellitus at moderate cardiovascular risk,[c] aim for an LDL-C target of <2.6 mmol/L (<100 mg/dL)
Platelet inhibition	In patients with diabetes mellitus at high/very high cardiovascular risk
Smoking	Cessation obligatory
Physical activity	Moderate-to-vigorous, ≥150 min/week, combined aerobic and resistance training
Weight	Aim for weight stabilisation in overweight or obese patients with diabetes mellitus based on calorie balance Aim for weight reduction in subjects with IGT to prevent the development of diabetes mellitus
Dietary habits	Reduction of caloric intake is recommended in obese patients with type 2 diabetes mellitus to lower body weight; there is no ideal percentage of calories from carbohydrates, proteins and fats for all individuals with diabetes mellitus

Moderate risk: Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years without other risk factors. *European Heart Journal*. 2020 Jan 7;41(2):255–323.

Thank You!

Mr. Samer

A 70--year-old patient with type 2 diabetes and is being treated for prostate cancer with an androgen inhibitor. His fasting blood glucose remains between 140 mg/dL (7.8mmol/dl) and 180 mg/dL (10 mmol/L)despite treatment with a sulfonylurea and basal insulin. His HbA_{1c} is usually between 8.1% and 8.9%. He also takes digoxin for mild heart failure and once-daily furosemide. His Serum Creatinine is 1.0 mg/dl

He tends to stay outside all day working on his car or talking to neighbours, and he forgets to drink liquids,.

He has episodes during which he becomes confused, and when testing his blood glucose, it will be all the way down to 40 mg/dL (2.2 mmol/L). His wife does a finger stick and then treats it.

Patient profile Clinical implications

- Age: 70 years
- GFR: 74ml/min/1.73m2
- Stays out all day
- Doesn’t drink liquids
- FBG: 140mg/dl-180mg/dl
- Hb1AC: 8.1-8.9%

Medication history:

- Metformin
- SU’s
- Insulin
- Androgen inhibitor
- Digoxin .Furosemide

- Elderly
- Moderate renal impairment
- Doesn’t urinate frequently
- Dehydrated easily
- Not well controlled

Disease history

- Diabetic
- History of hypoglycemia

- Prostate cancer
- Heart failure

What is your A1C target for Samer?

- A) A1C < 6.5%?
- B) A1C < 7.0%?
- C) A1C < 7.5%?
- D) A1C < 8.0%

What is the CV risk level of the patient?

a) Low risk
b) Medium risk
c) High risk

Risk Factors

- Diabetic
- Heart failure
- Elderly

What are the lifestyle modifications that need to be done?

a) Diet ?
b) Exercise?
c) Patient Education?
d) All of the above ?

Best treatment option for the patient

a) Add on DPP4i to SU and insulin
b) Add on Empagliflozin to SU and insulin
c) Change the regimen to Empagliflozin+ Metformin + adjust insulin dose
d) Change to Dapagliflozin + Metformin + adjusted insulin dose
e) Other combination