Novel Agents for the Treatment of Type2 Diabetes

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Agenda

- Case presentation
- Why should diabetes be controlled?
- Pathophysiology of T2DM
- T2DM New Agents
- CVOTS for GLP-1 Agonists & SGLT-2 Inhibitors
- Co- Formulation of Insulins
- 2023 ADA Guideline

Introducing a Case

- A 68-year-old woman with 12-year history of type 2 diabetes is referred to you. She takes Atorvastatin 40 mg, metformin 2000 mg and gliclazide MR 60 mg daily. She respects the diet recommended by the nutritionist.
- She has peripheral neuropathy.
- She has a history of acute MI during a couple of months ago and also a hospitalization due to decompensated HF
- She claims that in the past, with increasing gliclazide dose, several hypoglycemic episodes had occurred. She fears hypoglycemia because she lives alone.
- BMI: 35.5 kg/m^2

Case presentation continued

- Laboratory tests:
- FBS: 180 mg/dl
- HbA1c: 9.2%
- Cr: 1.2 mg/dl (eGFR ~ 50 ml/min)
- LDL: 120 mg/dl
- TG: 250 mg/dl

- Which therapeutic approach would you recommend to her?

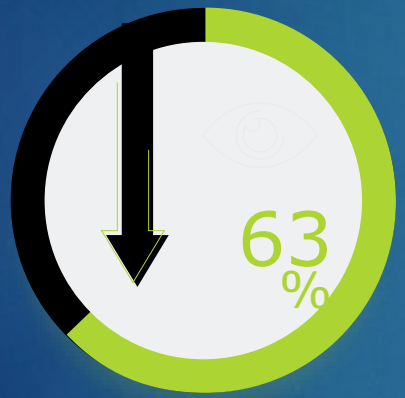
- A) Add Basal insulin+ Atorvastatin 80
- B) Add Liraglutide+ Rosuvastatin 40
- C) Add Pioglitazone 15 + Rosuvastatin 40
- D) Add Sitagliptin 100 mg + Fenofibrate 100 mg + Atorvastatin 40 mg
- E) Add Empagliflozin 10 mg + Rosuvastatin 40 mg + Semaglutide SC

Good glycaemic control prevents or delays long-term complications of diabetes

The Diabetes Control and Complications Trial (**DCCT**) in people with **T1D**

Intensive† vs conventional‡ glycaemic control
reduced the risk of diabetes-associated complications

RISK OF
RETINOPATHY[1]



RISK OF
ALBUMINURIA[1]

RISK OF
CLINICAL NEUROPATHY[1]

†External insulin pump or ≥3 daily insulin injections vs ‡1–2 daily insulin injections.
Abbreviations: CGM, continuous glucose monitoring; HbA1c, glycated haemoglobin; T1D, type 1 diabetes.
References: 1. The DCCT Research Group. N Engl J Med 1993;329(14):977-86.

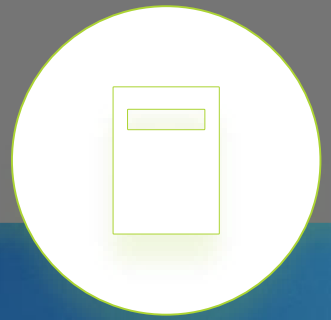
Good glycaemic control prevents or delays microvascular complications, and reduces cardiovascular and diabetes-related mortality

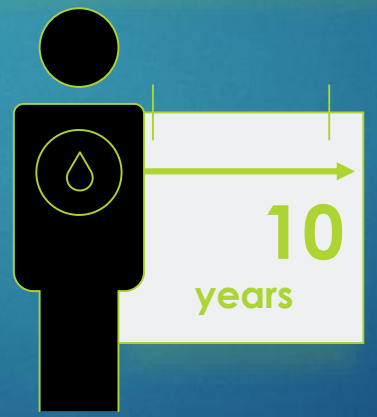
The landmark **UKPDS** study in people with **T2D** demonstrated that **each 1% reduction in HbA_{1c}** is associated with a…

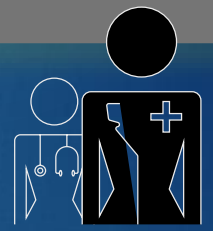
37% …reduced risk of **microvascular complications**[1]

21% …reduced risk of **diabetes-related mortality**[1]

14% …reduced risk of **myocardial infarction**[1]







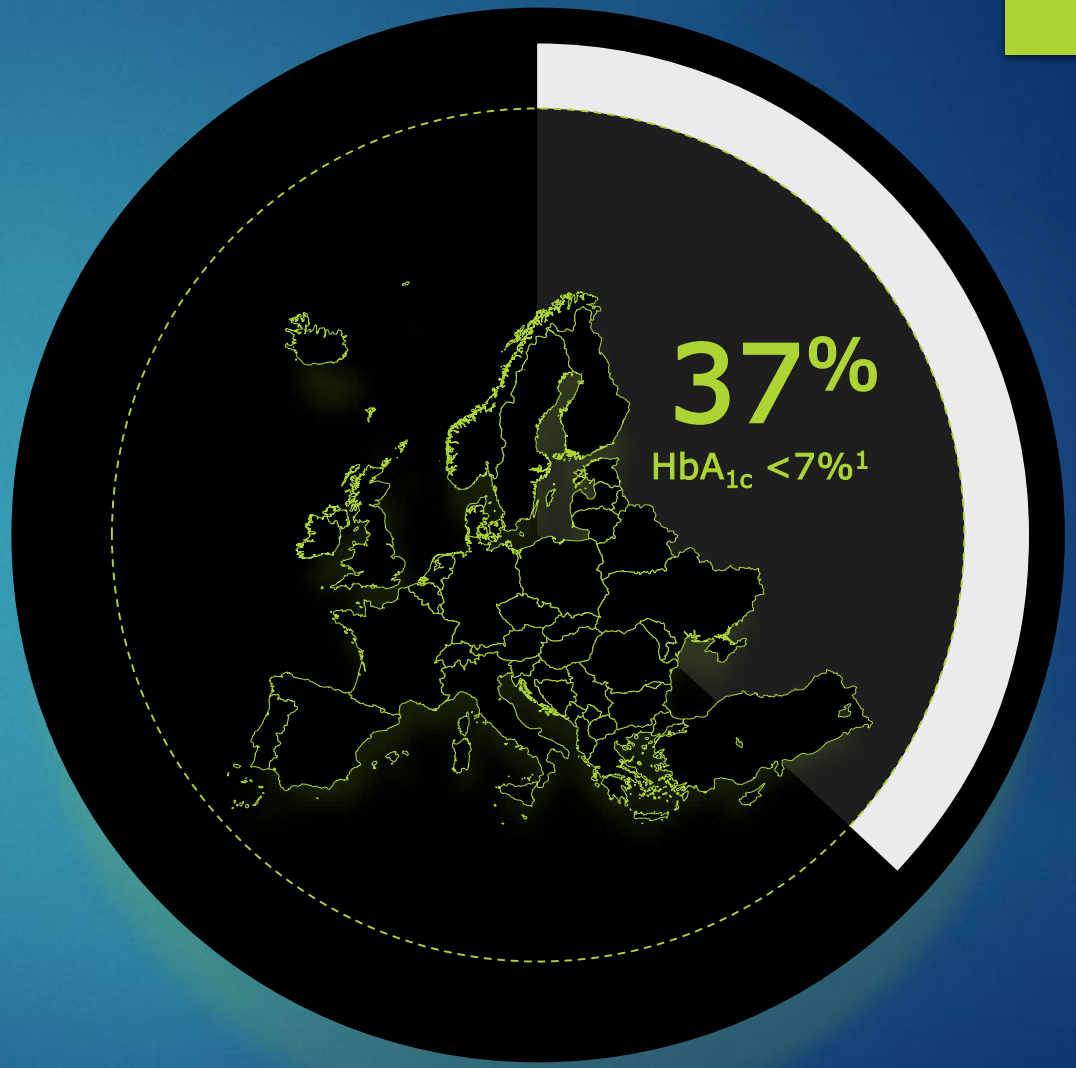
Benefits of an intensive treatment strategy in people with T2D are **sustained for up to 10 years**[2]

Abbreviations: HbA_{1c}, glycated haemoglobin; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study

References: 1. Stratton et al. BMJ 2000;321(7258):405-12. **2.** Holman et al. NEJM 2008;359(15):1577-89.

The burden of inadequate glycaemic control in diabetes is a challenge

Of people with
T2DM across Europe,
37% have
HbA_{1c}<7%[1]
(range: 26% in the Netherlands to 52% in Turkey)



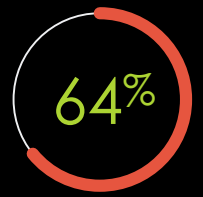
Abbreviations: HbA_{1c}, glycated haemoglobin; T2D, type 2 diabetes

References: **1**. de Pablos-Velasco et al. Clin Endocrinol 2014;80(1):47-56.

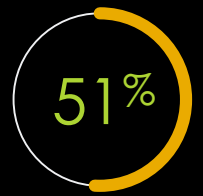
Even a 1 year delay in treatment intensification is associated with an increased risk of diabetes-related complications in people with T2D

A 1-year delay in treatment intensification in people with T2D with HbA_{1c} ≥7% is associated with a

INCREASED RISK OF **myocardial infarction** (HR 1.67, 95% CI 1.39–2.01)[1]



INCREASED RISK OF **heart failure** (HR 1.64, 95% CI 1.40–1.91)[1]



INCREASED RISK OF **stroke** (HR 1.51, 95% CI 1.25–1.83)[1]

….compared with those with **HbA_{1c} <7%**[1†]

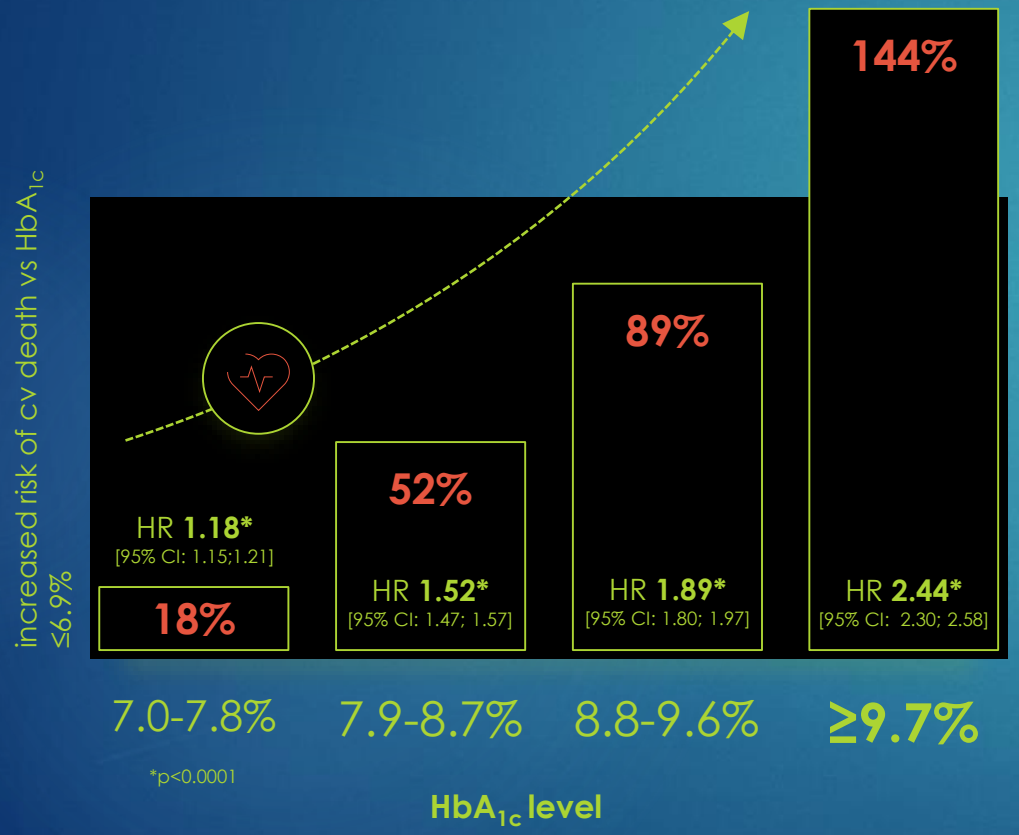
†Median study follow-up 5.3 years.

Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; T2D, type 2 diabetes.

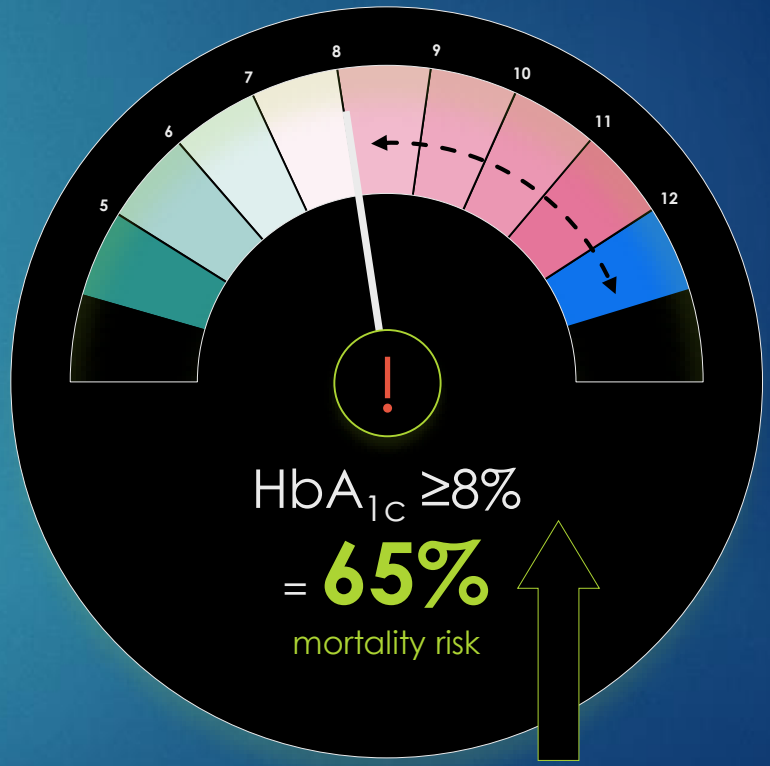
References: 1. Paul et al. Cardiovascular Diabetology 2015;14:100.

Worsening glycaemic control in people with diabetes is associated with an increased cardiovascular mortality risk

Worsening glycaemic control (HbA_{1c} >6.9%) in people with T2D (across all age categories) is associated with an **increasing risk of cardiovascular death** compared with people with T2D with HbA_{1c} ≤6.9%[1]:



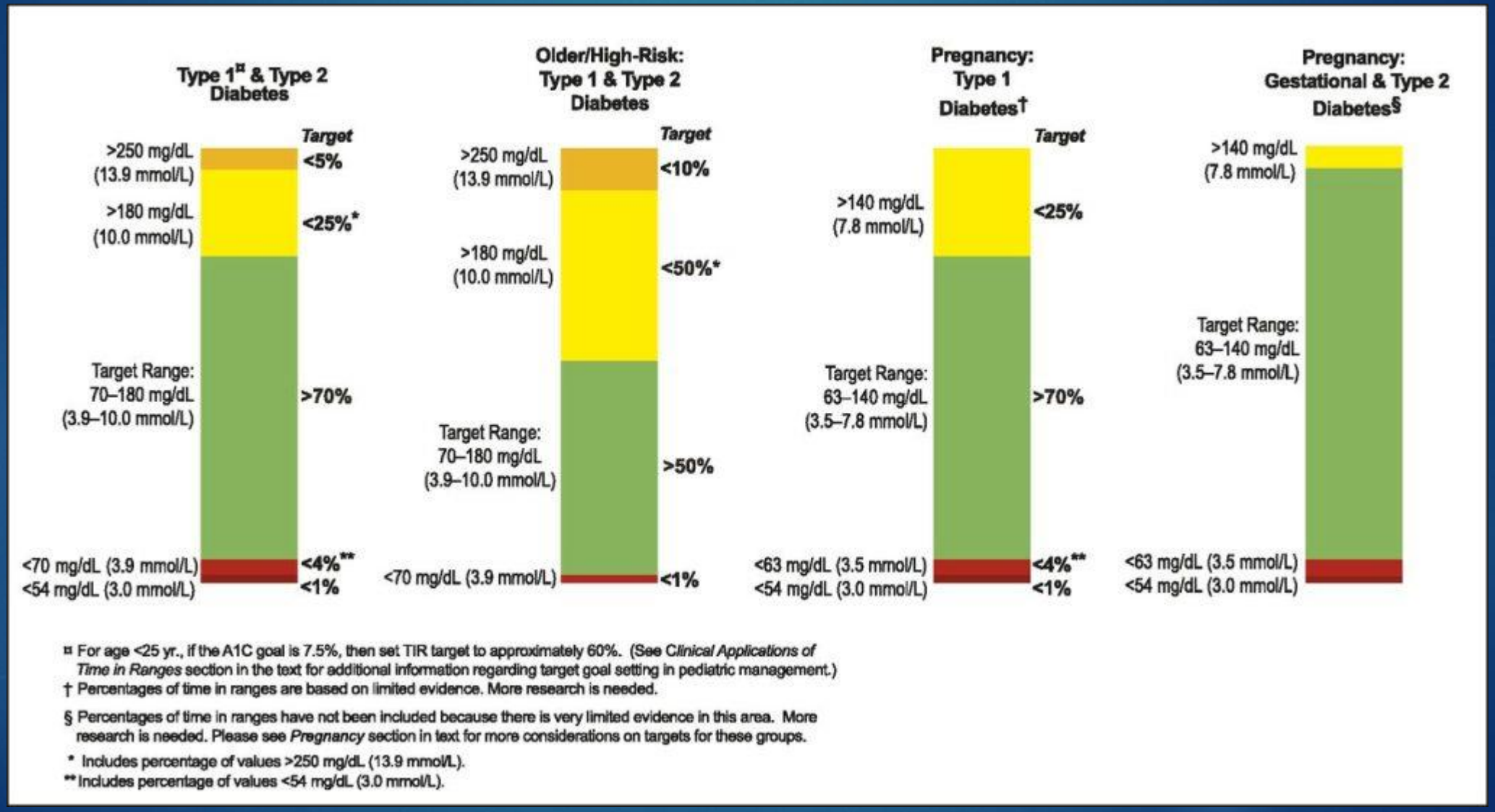
In people with diabetes, **HbA_{1c} ≥8%** is associated with a **65% increased risk** of **all-cause mortality**, compared with HbA_{1c} <6%[2]



Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; T2D, type 2 diabetes.

References: **1**. Tancredi et al. NEJM 2015 Oct 29;373(18):1720-32. **2**. Nelson et al. Diabetes Care. 2010 Nov;33(11):2360-4.

Time in Range



¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)

† Percentages of time in ranges are based on limited evidence. More research is needed.

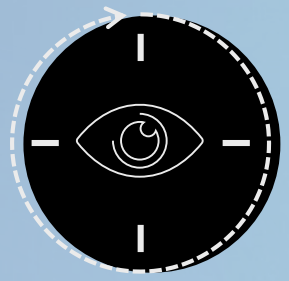
§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.

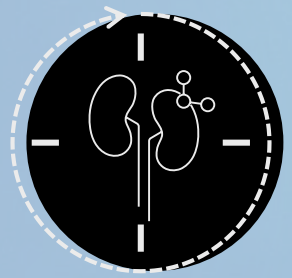
* Includes percentage of values >250 mg/dL (13.9 mmol/L).

** Includes percentage of values <54 mg/dL (3.0 mmol/L).

Lower TIR may be associated with an increased risk of microvascular complications[1]

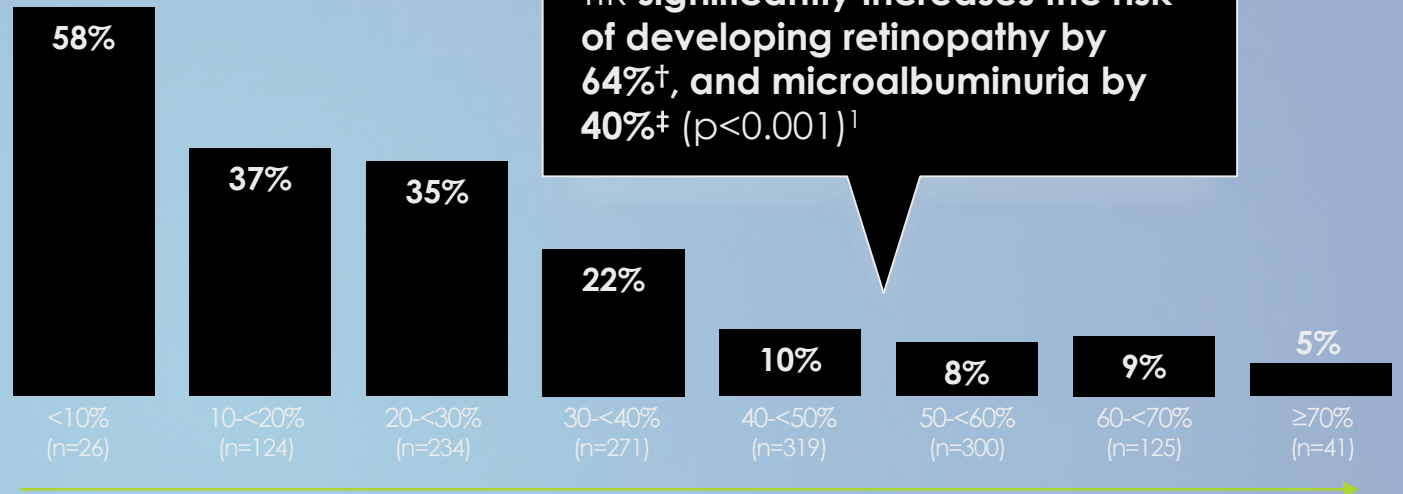
TIR may be a new **predictor of long-term diabetes complications**



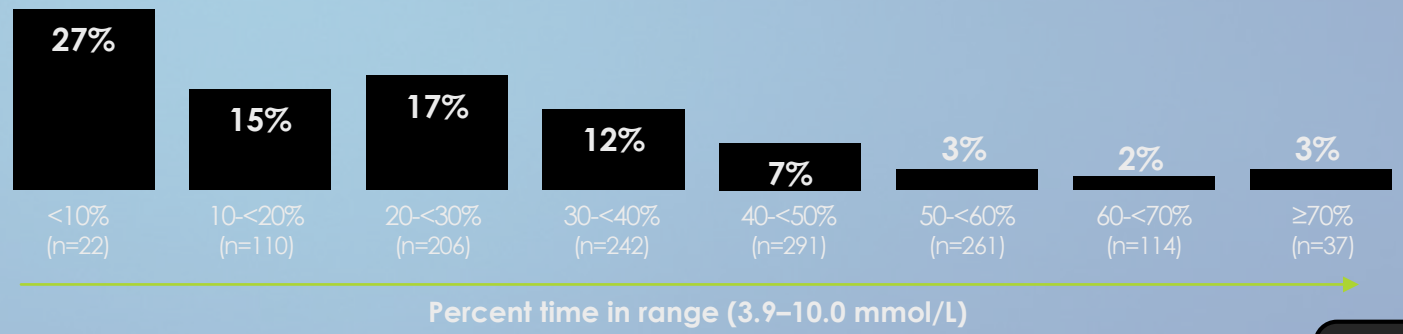


Each 10 percentage point lower TIR **significantly increases the risk of developing retinopathy by 64%†, and microalbuminuria by 40%‡** (p<0.001)[1]

Frequency of **retinopathy**[1]



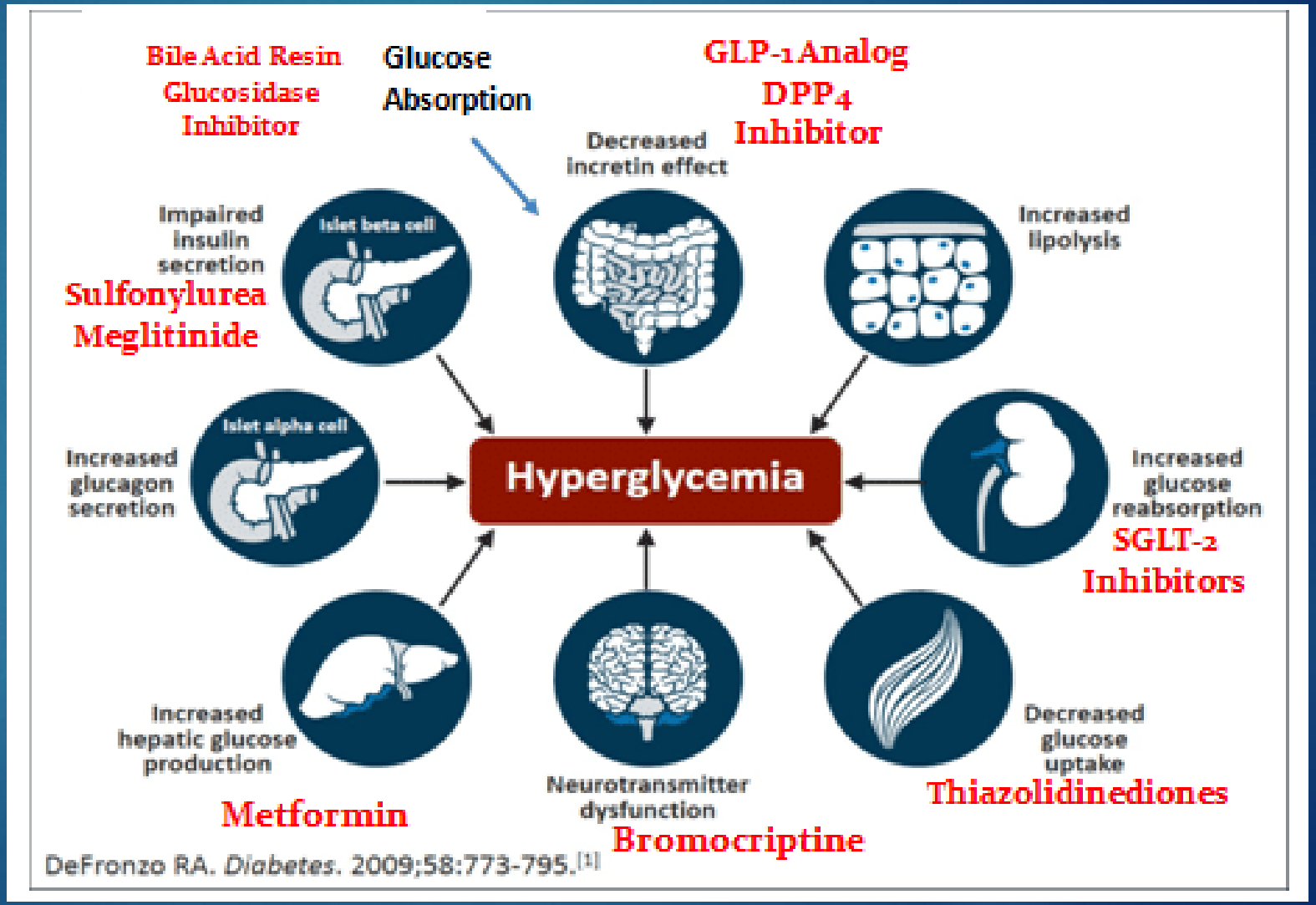
Frequency of **microalbuminuria**[1]



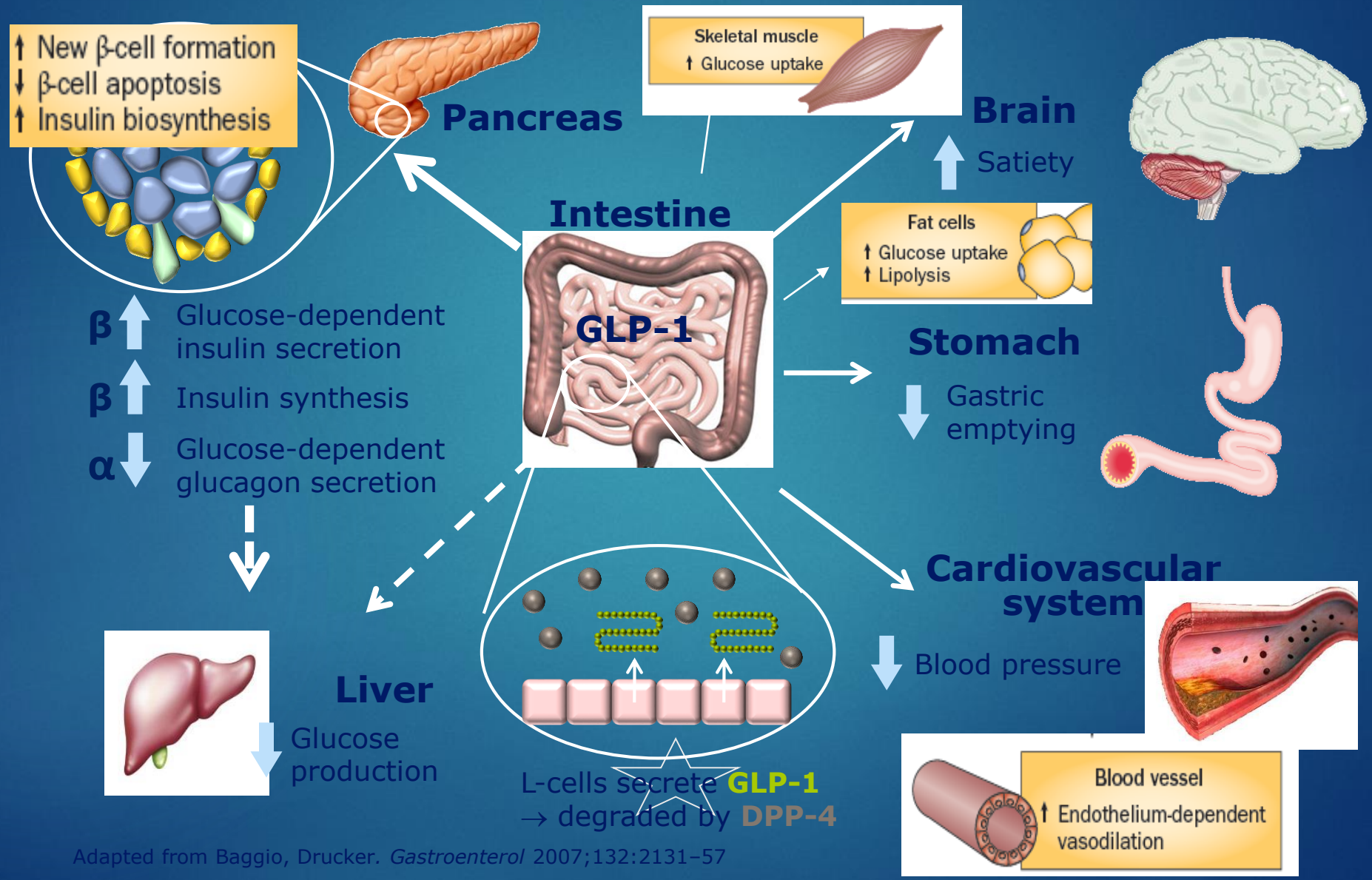
TIR

†95% CI: 51, 78. ‡95% CI: 25, 56.
Abbreviations: CI, confidence interval; TIR, time in range.
References: 1. Beck et al. Diabetes Care 2019;42(3):400-405.

Pathophysiology of T2DM

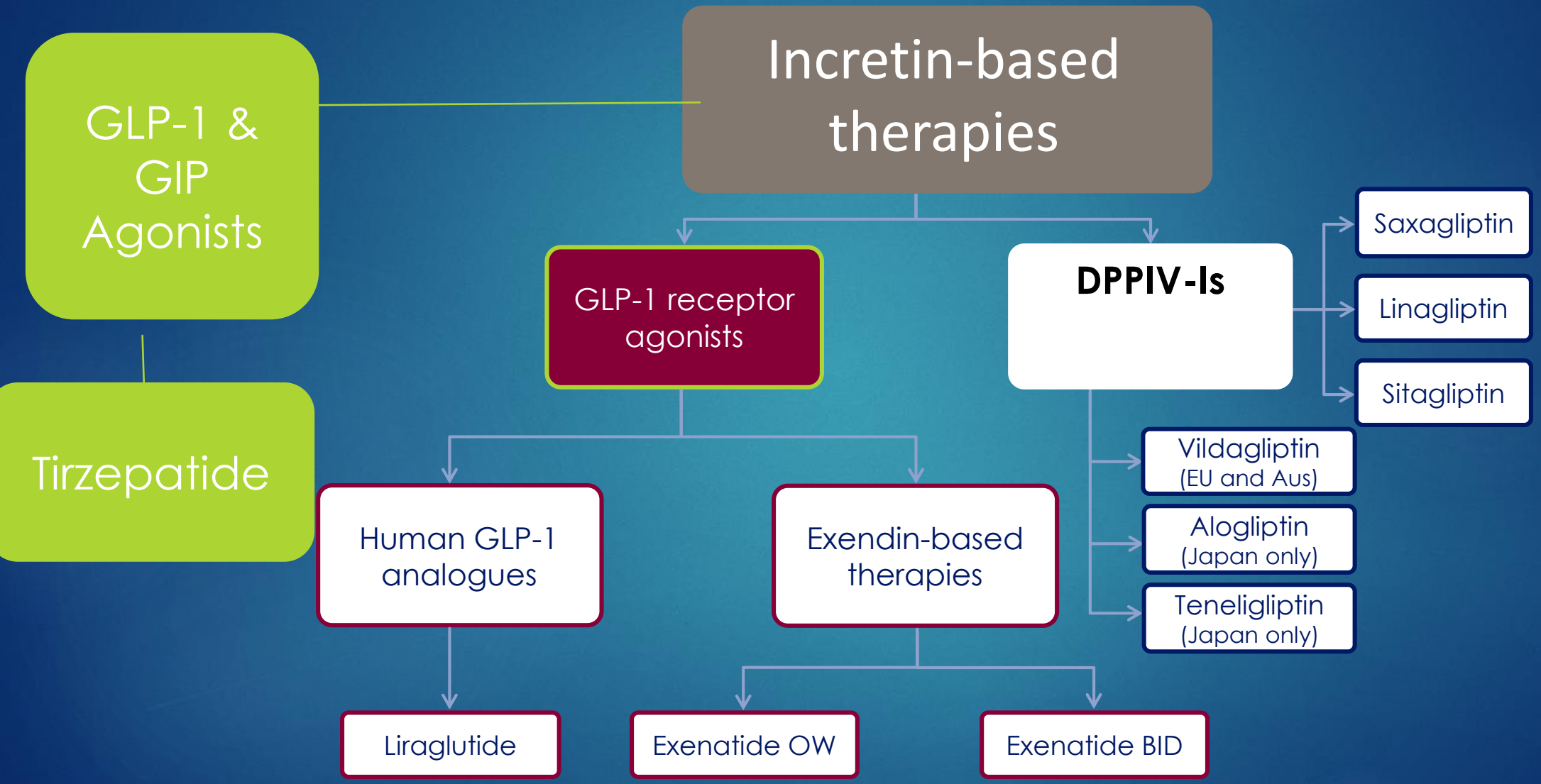


Glucagon-like peptide 1(GLP-1): an Incretin Hormone



Adapted from Baggio, Drucker. *Gastroenterol* 2007;132:2131–57

Incretin-Based Therapies



Aus, Australia; EU, Europe

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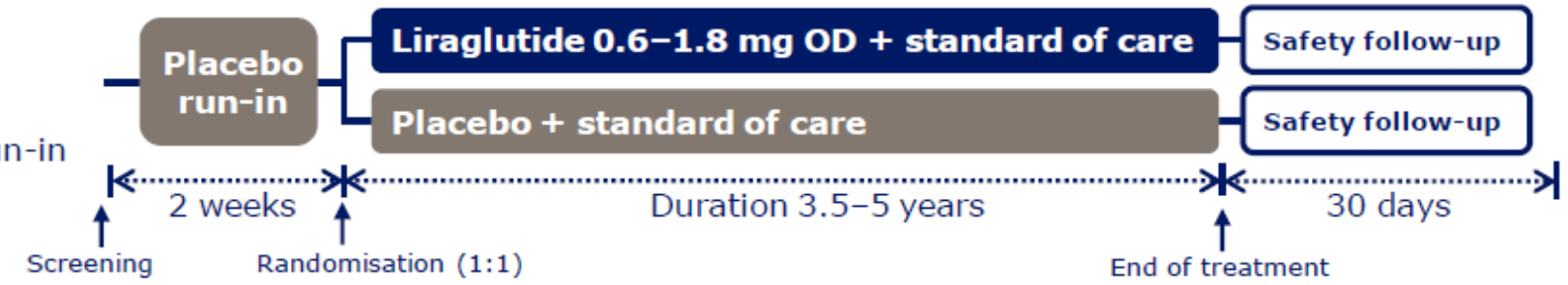
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

LEADER: Study design

9340 patients

- Double blinded
- 2-week placebo run-in



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

Primary and key secondary outcomes

Primary outcome	**Time to first MACE composed of** • CV death • Non-fatal MI • Non-fatal stroke
Key secondary outcomes	**Time to first occurrence of** • Expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, unstable angina pectoris requiring hospitalisation, or hospitalisation for heart failure) • All-cause death • Each individual component of expanded composite CV outcome

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

3MACE: 13% Reduced

All cause Mortality: 15%
CVD Death : 22%

Liraglutide dosing

- To improve gastrointestinal tolerability, the starting posology is 0.6 mg liraglutide daily

*Some patients are expected to benefit from an increase in dose from 1.2 to 1.8 mg and, based on clinical response, after at least 1 week, the dose can be increased to 1.8 mg to further improve glycaemic control. Daily doses higher than 1.8 mg are not recommended

1. Novo Nordisk. Liraglutide SPC. July 2011

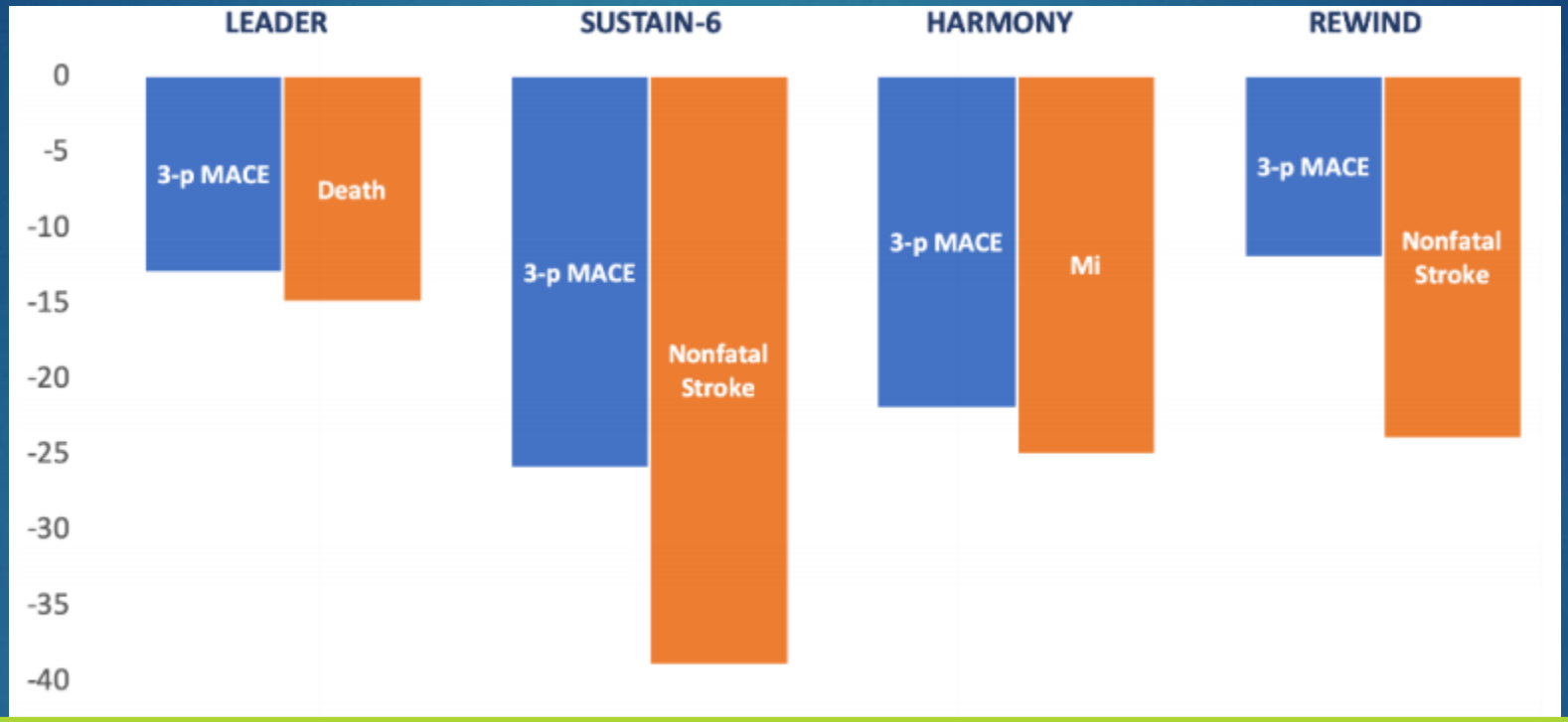
Summary of baseline characteristics and primary composite cardiovascular outcomes of the completed CVOTs for GLP-1 RA

GLP-1 RA: Study name	No. of patients	Median follow-up (years)	% with CV disease*	% of statin use	Baseline age	Baseline HgA1c	Baseline BMI	Primary composite CV outcome HR (95% CI)	P value
Lixisenatide: ELIXA	6068	2.1	100%	93%	60.3	7.7%	30.1	1.02 (0.89 to 1.17)	0.81
Liraglutide: LEADER	9340	3.8	81%	72%	64.3	8.7%	32.5	0.87 (0.78 to 0.97)	0.01
Semaglutide: SUSTAIN-6	3297	2.1	60%	73%	64.6	8.7%	32.8	0.74 (0.58 to 0.95)	0.02
Exenatide QW: EXSCEL	14752	3.2	73.1%	74%	62.0	8.0%	31.8	0.91 (0.83 to 1.00)	0.06
Albiglutide: Harmony	9463	1.6	100%	84%	64.1	8.7%	32.3	0.78 (0.68 to 0.90)	0.0006
Dulaglutide: REWIND	9901	5.4	31.5%	66%	66.2	7.2%	32.3	0.88 (0.79 to 0.99)	0.026
Oral semaglutide: PIONEER 6	3183	1.3	84.7%	85%	66.0	8.2%	32.3	0.79 (0.57 to 1.11)	0.17

*Remaining participants with cardiovascular risk factors.
BMI, body mass index;CV, cardiovascular; HgA1c, glycated haemoglobin.

Postgrad Med J 2020;96:156–161

GLP-1RA RCT studies with known beneficial cardiovascular endpoints



Liraglutide, Semaglutide SC, Albiglutide, Dulaglutide

1. J. Clin. Med. 2020, 9, 947

Key GLP-1RA RCTs with cardiovascular endpoint

Drug (Ref)	Trial	*n*	Studied Population	Mean Duration	Composite Primary CV Endpoint	Result HR (95% CI; *p*)	Individual Primary CV Endpoint	Result HR (95% CI; *p*)
Lixisenatide [45]	ELIXA	6068	T2D and acute coronary syndrome	25 m	3P-MACE	Neutral	None	Neutral
Exenatide [46]	EXSCEL	14,752	T2D with or without CVD	3.2 y	3P-MACE	Neutral	None	Neutral
Liraglutide [19,47]	LEADER	9340	T2D and high CV risk	3.8 y	3P-MACE	0.87 (0.78–0.97; $p < 0.001$)	Death from any cause	0.85 (0.74–0.97; $p = 0.02$)
Semaglutide [20] (sc)	SUSTAIN-6	3297	T2D 50 y or more with established CVD, CHF or CKD G3 or higher or >60 y w/CV risk factor	2.1 y	3P-MACE	0.74 (0.58–0.95; $p = 0.02$)	Nonfatal stroke	0.61 (0.38–0.99; $p = 0.04$)
Albiglutide [48]	HARMONY	9469	T2D and CVD or CV risk factors	3.8 y	3P-MACE	0.78 (0.68–0.90; $p = 0.0006$)	Fatal or nonfatal myocardial infarction	0.75 (0.61–0.90, $p = 0.003$)
Dulaglutide [28]	REWIND	9901	T2D and CVD or CV risk factors	5.4 y	3P-MACE	0.88 (0.79–0.99; $p = 0.026$)	Nonfatal Stroke	0.76 (0.61–0.95; $p = 0.017$)
Semaglutide [49] (oral)	PIONEER-6	3183	T2D and CVD or CV risk factors	15.9 m	3P-MACE	Neutral	None	Neutral
Exenatide [22]	FREEDOM-CVO	4000	T2D and CV disease	UK	UK	UK	UK	UK

T2D, type 2 diabetes mellitus; CVD, Cardiovascular disease; 3P-MACE, 3-point MACE (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke); SC; subcutaneous, UK, unknown; y, years; m, Month; RCTs: randomized clinical trial.

3P-MACE 13-26%

Non-Fatal Stroke 39%

1. J. Clin. Med. 2020, 9, 947

Key GLP-1RA RCTs with kidney endpoints

Drugs	Trials	% *n* eGFR < 60	Composite Kidney Endpoint	Results	Individual Kidney Endpoint	Result HR (95% CI; *p*)
Lixisenatide [45]	ELIXA	23	NA	NA	New onset macroalbuminuria	0.808 (0.660–0.991; $p = 0.0404$)
Exenatide [46]	EXSCEL	17	40% reduction in eGFR loss, onset of dialysis or transplantation, renal death and onset of macroalbuminuria	0.85 (0.73–0.98; $p = 0.027$)	None	Neutral
Liraglutide [19,47]	LEADER	23	New onset macroalbuminuria, sustained serum creatinine duplication, initiation of renal replacement therapy or renal death	0.78 (0.67–0.92; $p = 0.003$)	New onset macroalbuminuria	0.74 (0.37–0.77; $p = 0.001$)
Semaglutide [20] (sc)	SUSTAIN-6	28.5	New onset macroalbuminuria, doubling serum creatinine reaching an eGFR <45 mL/min/1.73 m^2, initiation of renal replacement therapy or renal death	0.64 (0.46–0.88; $p = 0.005$)	Persistent macroalbuminuria	0.54 (0.60–0.91; $p = 0.0$
Albiglutide [48]	HARMONY	11	UK	UK	UK	UK
Dulaglutide [28]	REWIND	22	New onset macroalbuminuria, sustained decreased of eGFR <30% or the initiation of renal replacement therapy	0.85 (0.77–0.93, $p = 0.0004$)	New onset macroalbuminuria; Sustained decline in eGFR of ≥40%; Sustained decline in eGFR of ≥50%	0.77 (0.68–0.87; $p < 0.0001$); 0.70 (0.57–0.85; $p = 0.0004$); 0.74 (0.66–0.84; $p < 0.0001$)
Semaglutide [49] (oral)	PIONEER-6	27	UK	UK	UK	UK
Exenatide [22]	FREEDOM-CVO	UK	UK	UK	UK	UK

NA, not apply; SC; subcutaneous; UK, unknown; RCTs: randomized clinical trial.

22%
26%

36%
46%

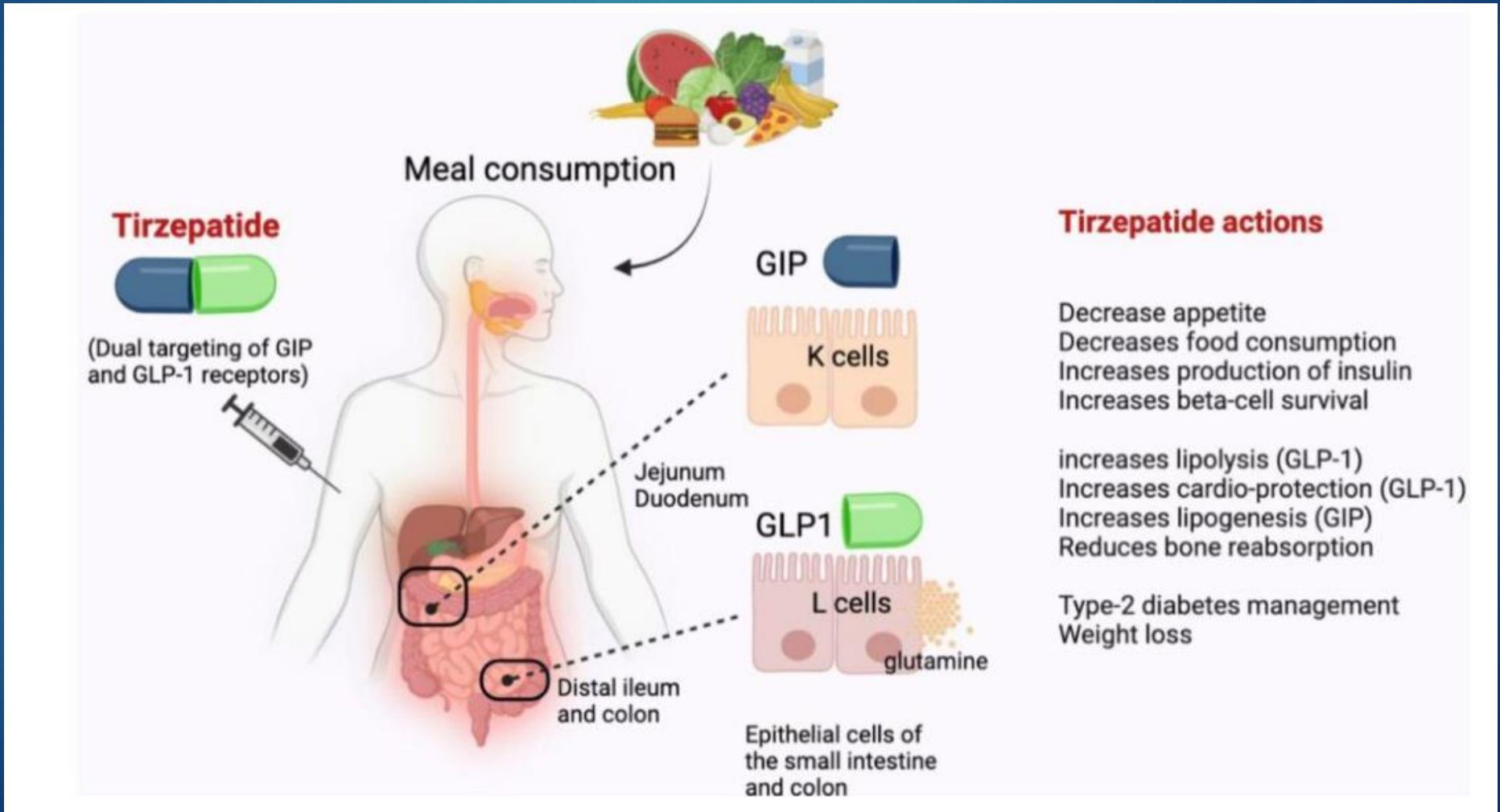
1. J. Clin. Med. 2020, 9, 947

Summary of CVOTs with GLP-1 Agonists

GLP-1 RA	MACE	CV Death	Stroke	Kidney Combined Outcomes	Total Mortality	Trial Duration (yrs)
LEADER Liraglutid	**0.87** (0.78, 0.99) **NNT 53**	**0.78** (0.66, 0.93) **NNT 77**	**0.86** (0.71 1.06)	**0.54** (0.67, 0.82) **NNT 67**	**0.85** (0.74, 0.97) **NNT 71**	3.8
SUSTAIN Semaglutid	**0.74** (0.58, 0.95) **NNT 30**	**0.98** (0.65 1.48)	**0.61** (0.38 0.99) **NNT 91**	**0.64** (0.47, 0.77) **NNT 43**	**1.05** (0.74, 1.50)	2.1
REWIND Dulaglutid	**0.88** (0.79, 0.99) **NNT 71**	**0.91** (0.78 1.06)	**0.76** (0.62 0.94) **NNT 111**	**0.85** (0.77, 0.93) **NNT 40**	**0.90** (0.80 1.01)	5.4
PIONEER **Oral** Semaglutid	**0.79** (0.57, 1.11)	**0.49** (0.27, 0.92) **NNT 100**	**0.74** (0.35 1.57)	**nk**	**0.51** (0.31, 0.84) **NNT 71**	1.3

Swiss Medical Weekly 2023

GLP1-GIP Recepetor Agonist, Mechanism of action of Tirzepatide



SURMOUNT-2 Study

Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

W Timothy Garvey, Juan P Frias, Ania M Jastreboff, Carel W le Roux, Naveed Sattar, Diego Aizenberg, Huzhang Mao, Shuyu Zhang, Nadia N Ahmad, Mathijs C Bunck, Imane Benabbad, Xiaotian M Zhang, for the SURMOUNT-2 investigators

Summary

Background Weight reduction is essential for improving health outcomes in people with obesity and type 2 diabetes. We assessed the efficacy and safety of tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, versus placebo, for weight management in people living with obesity and type 2 diabetes.

Methods This phase 3, double-blind, randomised, placebo-controlled trial was conducted in seven countries. Adults (aged ≥18 years) with a body-mass index (BMI) of 27 kg/m² or higher and glycated haemoglobin (HbA_{1c}) of 7–10% (53–86 mmol/mol) were randomly assigned (1:1:1), using a computer-generated random sequence via a validated interactive web-response system, to receive either once-weekly, subcutaneous tirzepatide (10 mg or 15 mg) or placebo for 72 weeks. All participants, investigators, and the sponsor were masked to treatment assignment. Coprimary endpoints were the percent change in bodyweight from baseline and bodyweight reduction of 5% or higher. The treatment-regimen estimand assessed effects regardless of treatment discontinuation or initiation of antihyperglycaemic rescue therapy. Efficacy and safety endpoints were analysed with data from all randomly assigned participants (intention-to-treat population). This trial is registered with ClinicalTrials.gov, NCT04657003.

Findings Between March 29, 2021, and April 10, 2023, of 1514 adults assessed for eligibility, 938 (mean age 54·2 years [SD 10·6], 476 [51%] were female, 710 [76%] were White, and 561 [60%] were Hispanic or Latino) were randomly assigned and received at least one dose of tirzepatide 10 mg (n=312), tirzepatide 15 mg (n=311), or placebo (n=315). Baseline mean bodyweight was 100·7 kg (SD 21·1), BMI 36·1 kg/m² (SD 6·6), and HbA_{1c} 8·02% (SD 0·89; 64·1 mmol/mol [SD 9·7]). Least-squares mean change in bodyweight at week 72 with tirzepatide 10 mg and 15 mg was –12·8% (SE 0·6) and –14·7% (0·5), respectively, and –3·2% (0·5) with placebo, resulting in estimated treatment differences versus placebo of –9·6% percentage points (95% CI –11·1 to –8·1) with tirzepatide 10 mg and –11·6% percentage points (–13·0 to –10·1) with tirzepatide 15 mg (all p<0·0001). More participants treated with tirzepatide versus placebo met bodyweight reduction thresholds of 5% or higher (79–83% *vs* 32%). The most frequent adverse events with tirzepatide were gastrointestinal-

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See Online/Comment https://doi.org/10.1016/S0140-6736(23)01292-8

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RCT, Placebo-controlled, double-blind, multicenter

Total number : 938

72 weeks follow up

Mean patients age: 54.2 y/o

BMI>27 & HbA1C 7-10%

Principal Findings

- The coprimary outcomes at 72 weeks were determined separately for tirzepatide 10 mg and 15 mg vs. placebo:

(the percentage change in BW from baseline & the percentage of participants achieving >5% BW reduction at 72 weeks)

- Coprimary outcome 1, percent change in body weight: -**12.8% and -14.7%** vs. -3.2%, $p < 0.0001$ for both
- Coprimary outcome 2, percentage with weight reduction ≥5%: **79% and 83%** vs. 32%, $p < 0.0001$ for both

Secondary outcomes for tirzepatide 10 mg & 15 mg vs. placebo:

- **Percentage with weight reduction ≥15%**: 40% and 48% vs. 3%, $p < 0.0001$ for both
- Change in HbA1c: -2.07% and -2.08% vs. -0.51%, $p < 0.0001$ for both
- Mean change in body weight: -12.9 kg and -14.8 kg vs. -3.2 kg, $p < 0.0001$ for both
- Mean change in BMI: -4.9 kg/m2 and -5.7 kg/m2 vs. -1.2 kg/m2, $p < 0.0001$ for both
- Follow-up HbA1c <7%: 87% and 84% vs. 36%, $p < 0.0001$ for both
- **Follow-up HbA1c <5.7%**: 46% and 49% vs. 4%, $p < 0.0001$ for both

Secondary outcomes for pooled Tirzepatide group vs. placebo:

- Mean change in systolic blood pressure (SBP): -6.3 mm Hg vs. -1.2 mm Hg, $p < 0.0001$
- Percent change in fasting triglycerides: -27.2% vs. -3.3%, $p < 0.0001$
- Percent change in non–high-density lipoprotein cholesterol: -5.9% vs. -3.7%, $p < 0.0001$

Safety outcomes for Tirzepatide 10 mg & 15 mg vs. placebo

- Discontinuation of study drug: 4% and 7% vs. 4%
- Nausea, vomiting, or diarrhea: 51% and 57% vs. 18%
- Confirmed pancreatitis: 0 and 1% (n = 2) vs. <1% (n = 1)
- Hypoglycemia <54 mg/dL: 4% and 5% vs. 1%

Conclusion

- The SURMOUNT-2 trial demonstrates both more frequent clinically significant weight loss (≥5% body weight) and increased magnitude of weight loss with the use of once-weekly tirzepatide in patients with obesity and T2DM.

- Additionally, tirzepatide was associated with a meaningful reduction in HbA1c, with **normalization to nondiabetic levels in nearly half of the tirzepatide groups.**

The NEW ENGLAND JOURNAL of MEDICINE

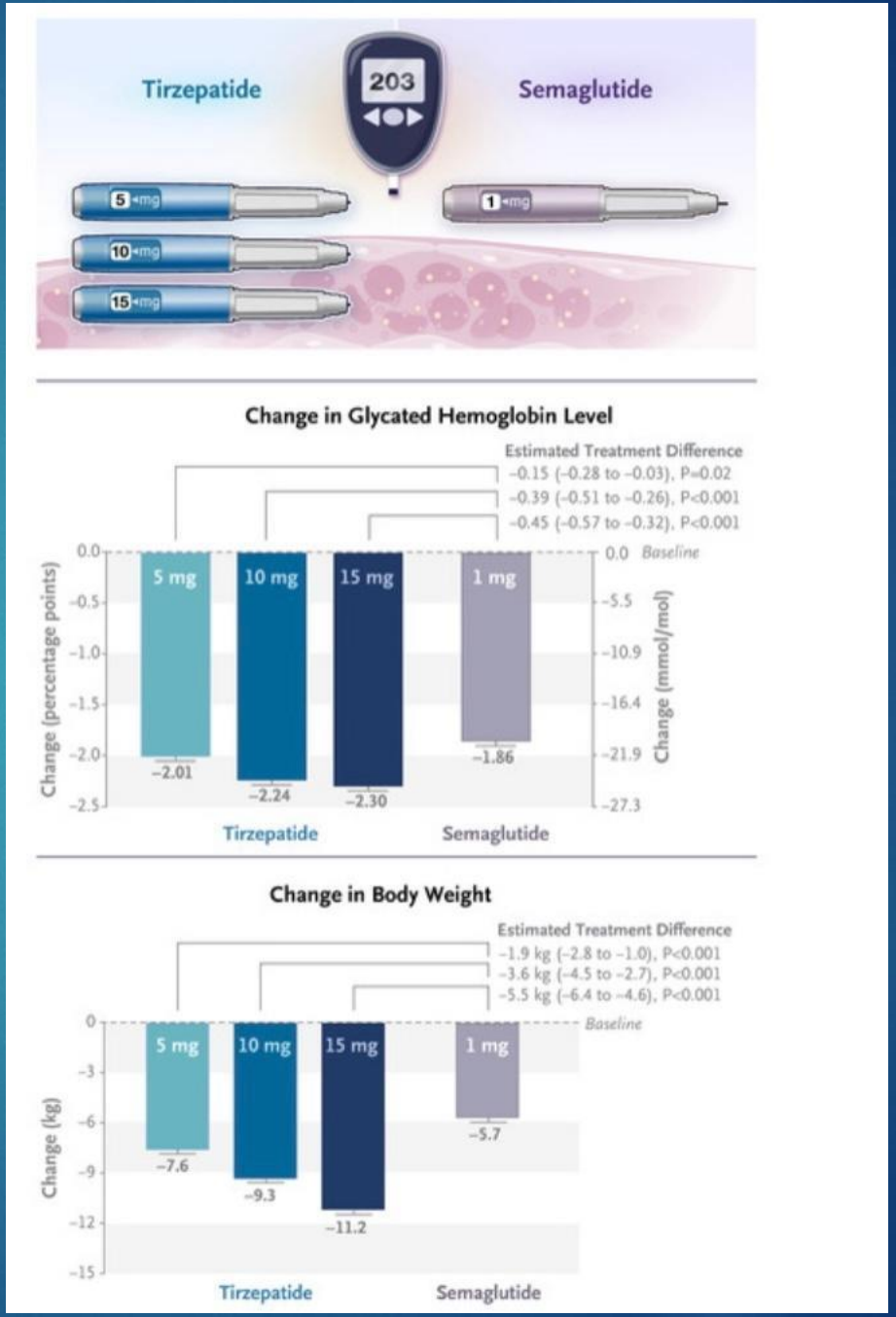
ORIGINAL ARTICLE

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

Juan P. Frías, M.D., Melanie J. Davies, M.D., Julio Rosenstock, M.D., Federico C. Pérez Manghi, M.D., Laura Fernández Landó, M.D., Brandon K. Bergman, Pharm.D., Bing Liu, Ph.D., Xuewei Cui, Ph.D., and Katelyn Brown, Pharm.D., for the SURPASS-2 Investigators*

ABSTRACT

Tirzepatide is superior to Semaglutide in reducing HbA1C in adults with T2 DM

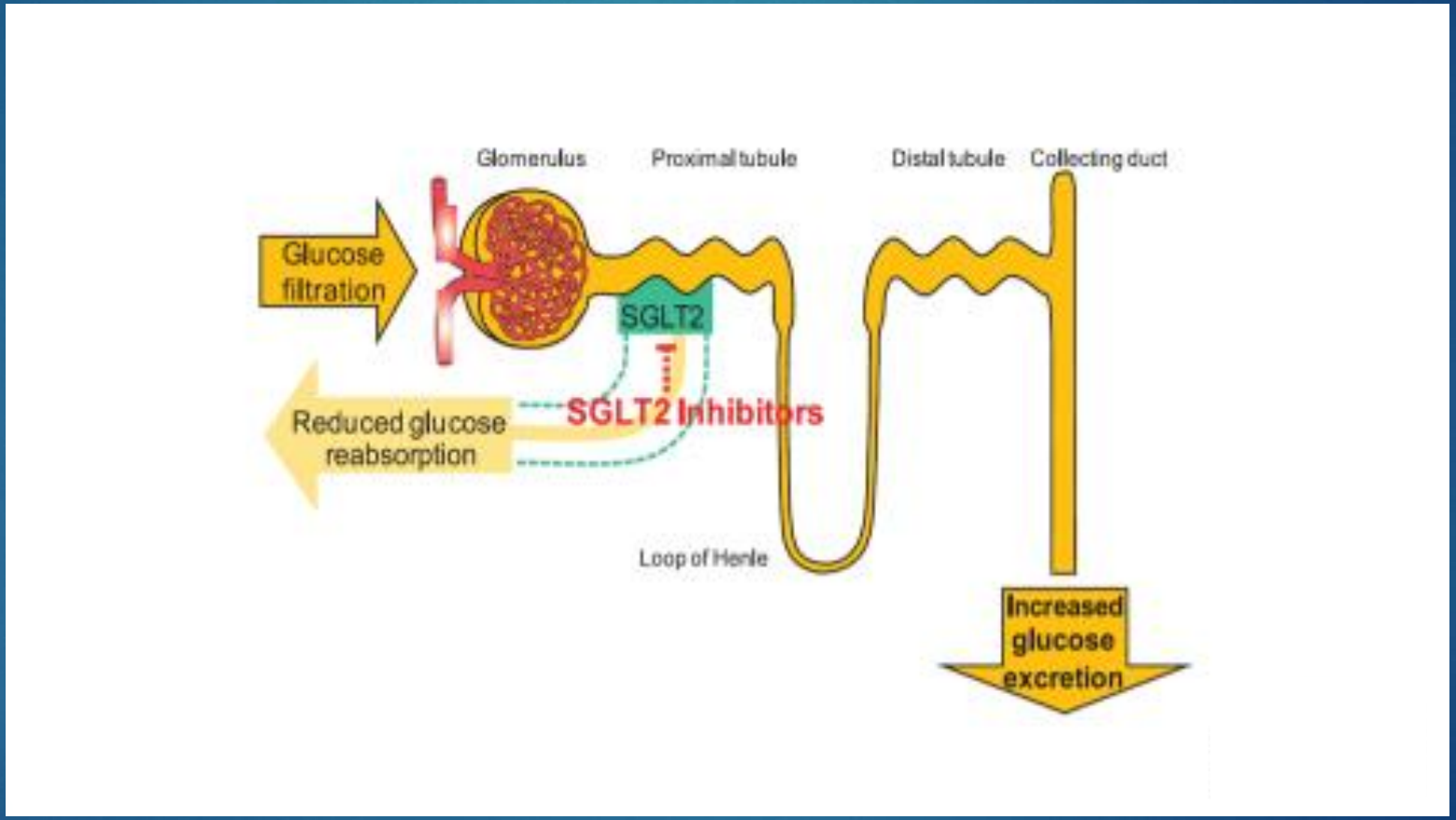


Pen injection devices for GLP-1 receptor agonists and fixed-dose combinations of GLP-1 receptor agonists with basal insulin preparations

	GLP-1 receptor agonists								GLP-1 receptor agonist/ basal insulin fixed-dose combinations	
Pen devices for injection										
Drug name: Generic Commercial	Exenatide b.i.d. Byetta®	Lixisenatide Lyxumia®	Liraglutide Victoza®	Exenatide once weekly, Bydureon® (original)	Bydureon® BCise (improved)	Dulalgutide Trulicity®	Albiglutide Eperzan®, Tanzeum®	Semaglutide Ozempic®	IdegLira Xultophy®	iGlarLixi Soliqua®
Pen for single or multiple use?	multiple	multiple	multiple	single	single	single	single	multiple	multiple	multiple
Pen for pre-determined single dose/ variable dosing	single	single	variable (0.6, 1.2, or 1.8 mg)	single	single	single	single	single	variable, for titration	variable, for titration
Pen devices available (maximum dose)	5 or 10 µg	10 or 20 µg	1.8 mg	2 mg	2 mg	0.75 or 1.5 mg	30 or 50 mg	0.25, 0.5 or 1.0 mg	Up to 1.8 mg (plus insulin *degludec* up to 50 IU)	Up to 20 µg (plus insulin *glargine* up to 60 IU)
Resuspension before injection necessary?	no	no	no	yes	No, but thorrough mixing	no	yes	no	no	no

European Journal of Endocrinology (2019) 181, R211–R234

SGLT2 Inhibitors



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

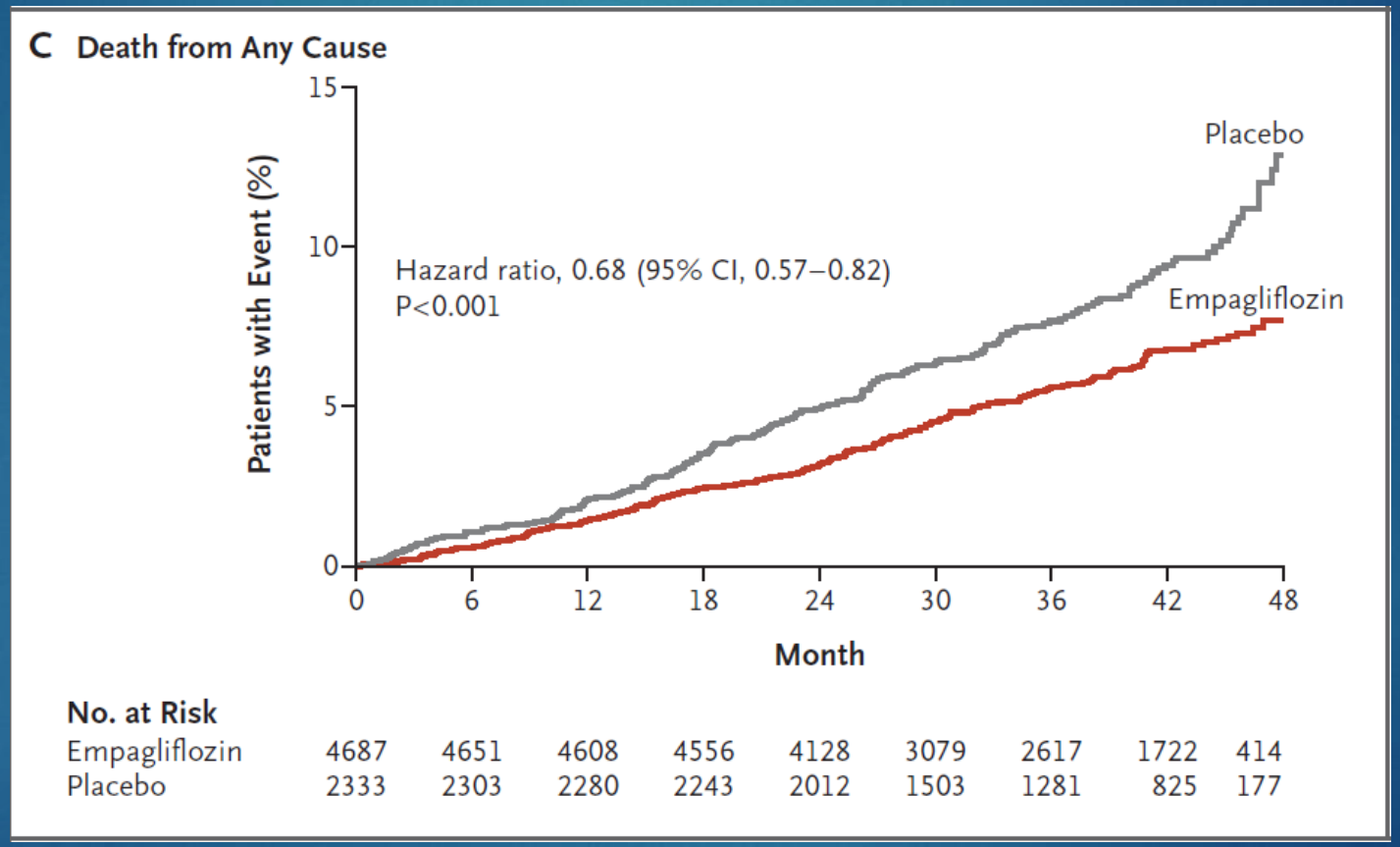
NEJM. 2015 Sep 17

7020 diabetic patients were treated over a median follow up of 3.1 years:

- Reduced the composite outcome of MI, Stroke, cardiovascular death by 14%
- Reduced cardiovascular death by 38%
- Reduced HF by 35%
- Reduced all cause mortality by 32%

All cause mortality

NNT=39



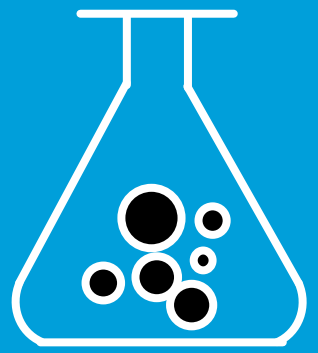
Summary of CVOTs with SGLT-2 Inhibitors

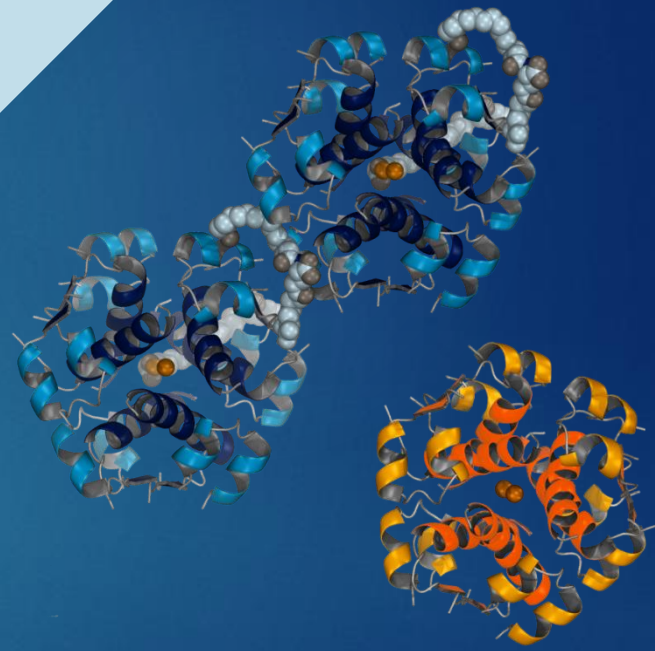
Risk Reduction (95% CI) SGLT-2 inhibitors	MACE	CV Death	Heart Failure	Kidney Combined Outcomes	Total Mortality	Trial Duration (yrs)
EMPA-REG Empagliflozin	**0.86** (0.74, 0.99) **NNT 63**	**0.62** (0.49, 0.77) **NNT 45**	**0.65** (0.50,0.85) **NNT 71**	**0.54** (0.40, 0.75) **NNT 71**	**0.68** (0.57, 0.82) **NNT 38**	3.1
CANVAS/R Canagliflozin	**0.86** (0.75, 0.97) **NNT 94**	**0.87** (0.72 1.06)	**0.67** (0.52 0.87) **NNT 86**	**0.60** (0.47, 0.77) **NNT 83**	**0.87** (0.74, 1.01)	3.4
DECLARE-TIMI Dapagliflozin	**0.93** (0.84, 1.03)	**0.98** (0.82 1.17)	**0.73** (0.61 0.88) **NNT 125**	**0.53** (0.43, 0.66) **NNT 40**	**0.93** (0.82 1.04)	4.2
VERTIS CV Ertugliflozin	**0.97** (0.85, 1.11)	**0.92** (0.77, 1.11)	**0.70** (0.54 0.90) **NNT 91**	**0.81** (0.64, 1.03)	**0.93** (0.80, 1.08)	3.5

Swiss Medical Weekly 2023

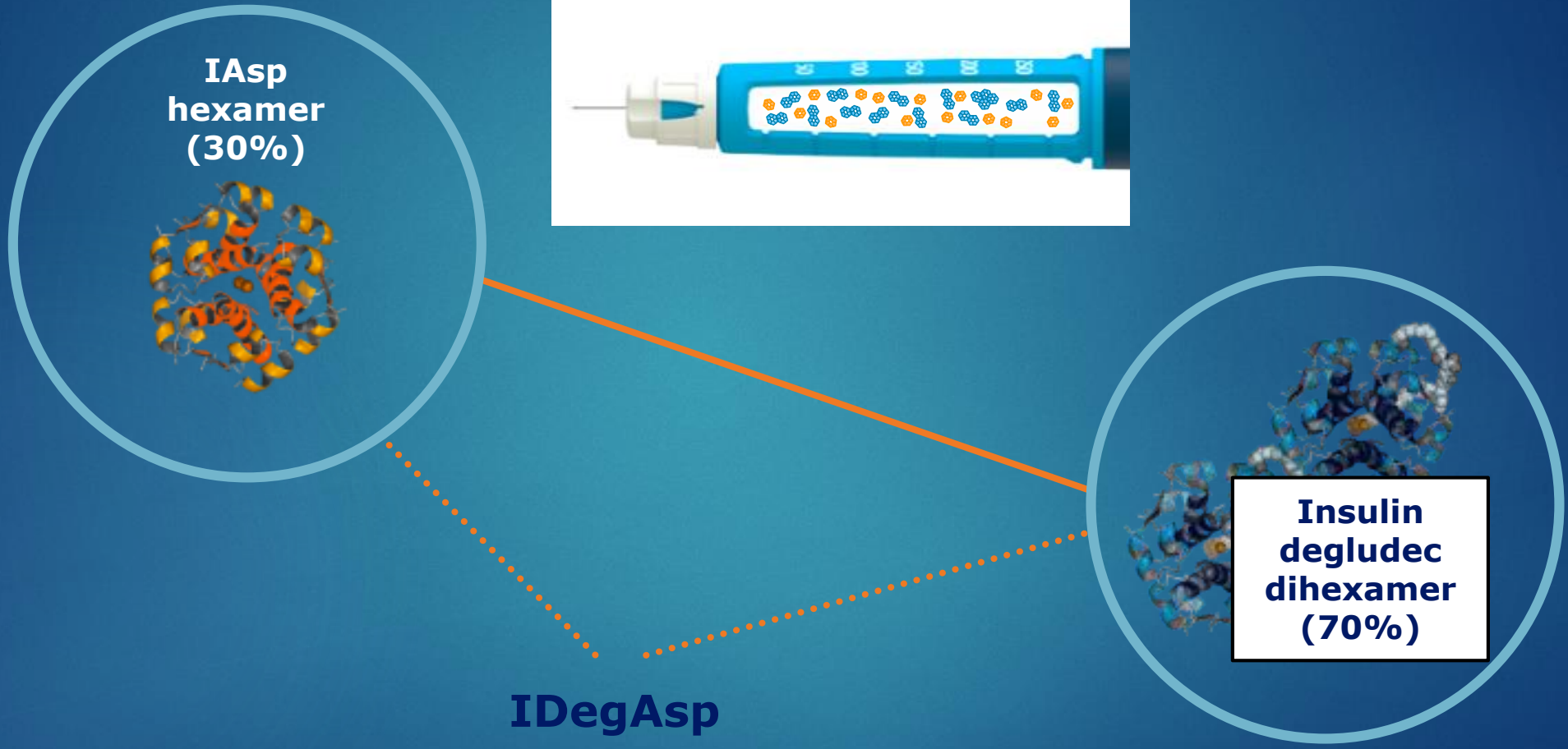
Co-Formulation of Insulins

The IDegAsp co-formulation





Co-formulation of insulin degludec with insulin aspart (IAsp)

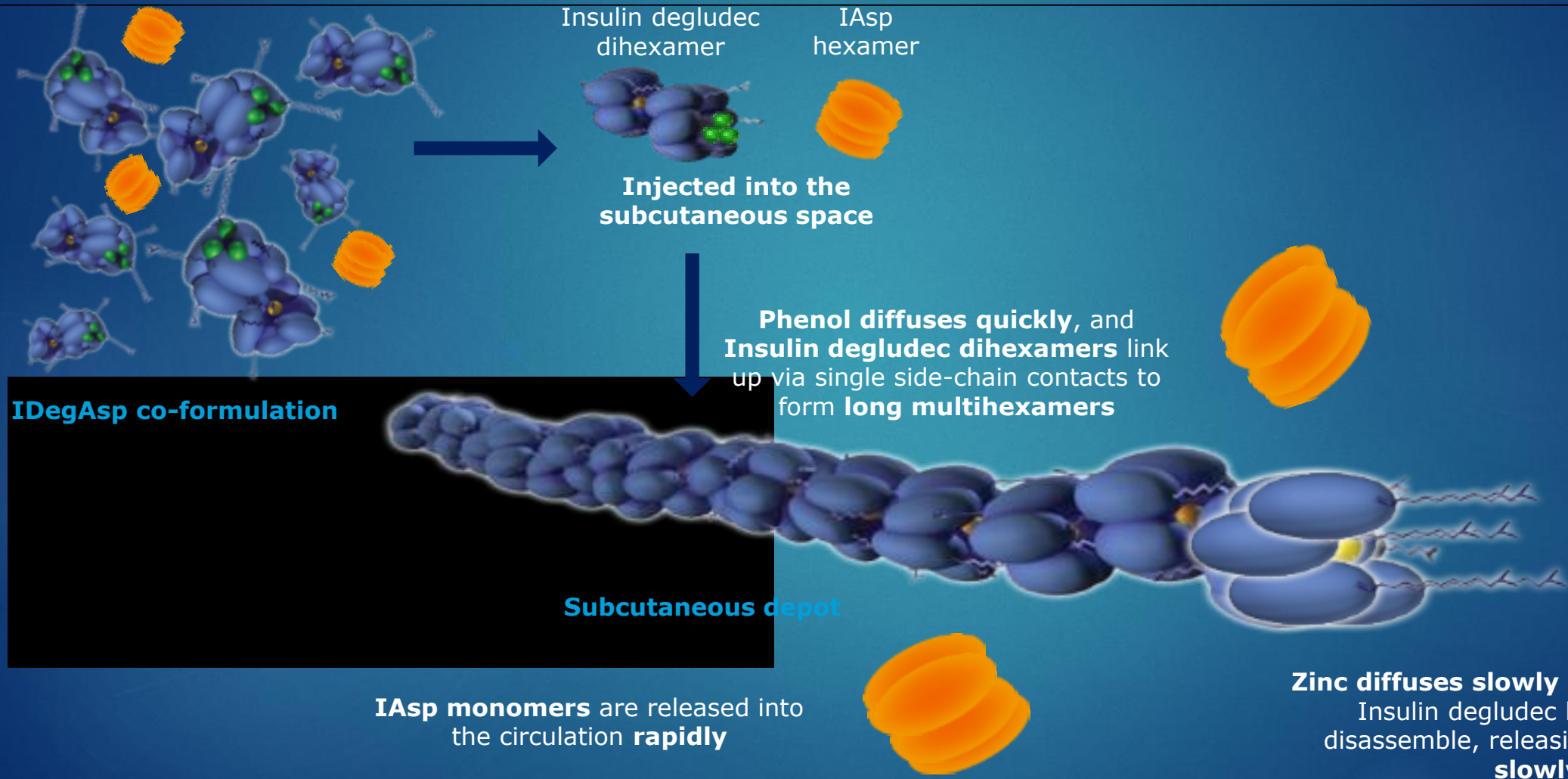


IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart

IDegAsp

Mode of protraction at steady state

[Phenol; Zn^{2+}]

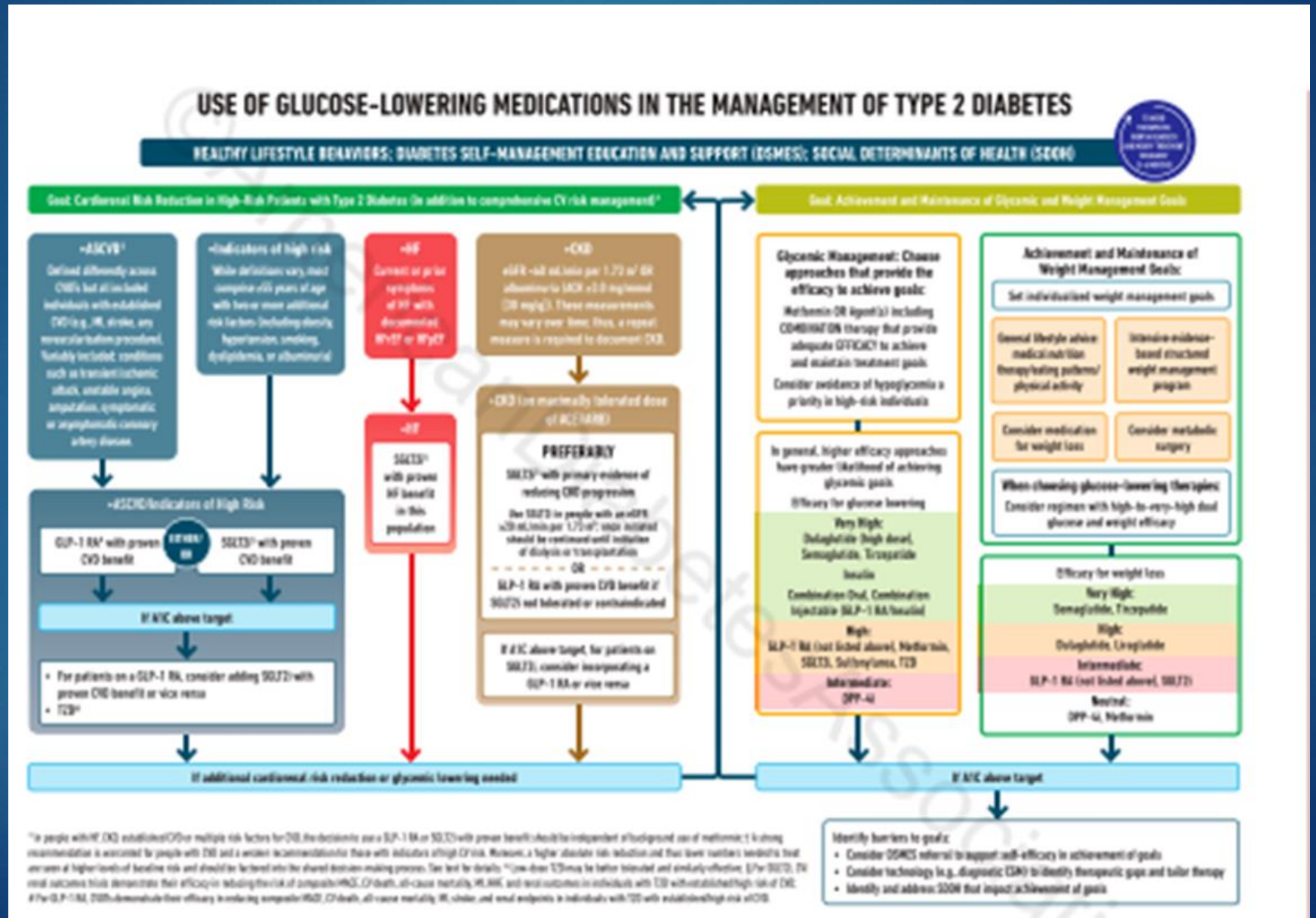


IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; Zn, zinc

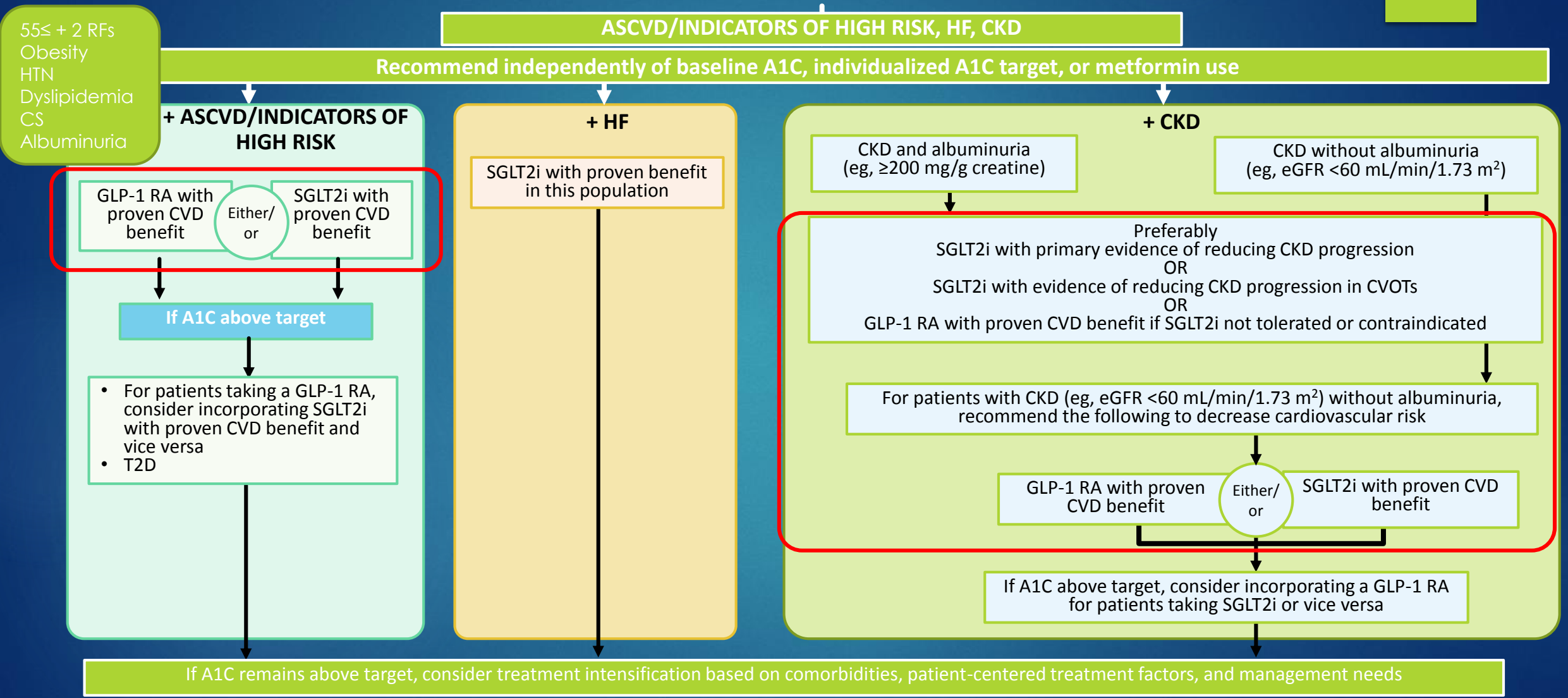
Jonassen *et al. Pharm Res* 2012;29:2104–14

Insulin+ GLP1Agonists Glargine+ Lixisenatide

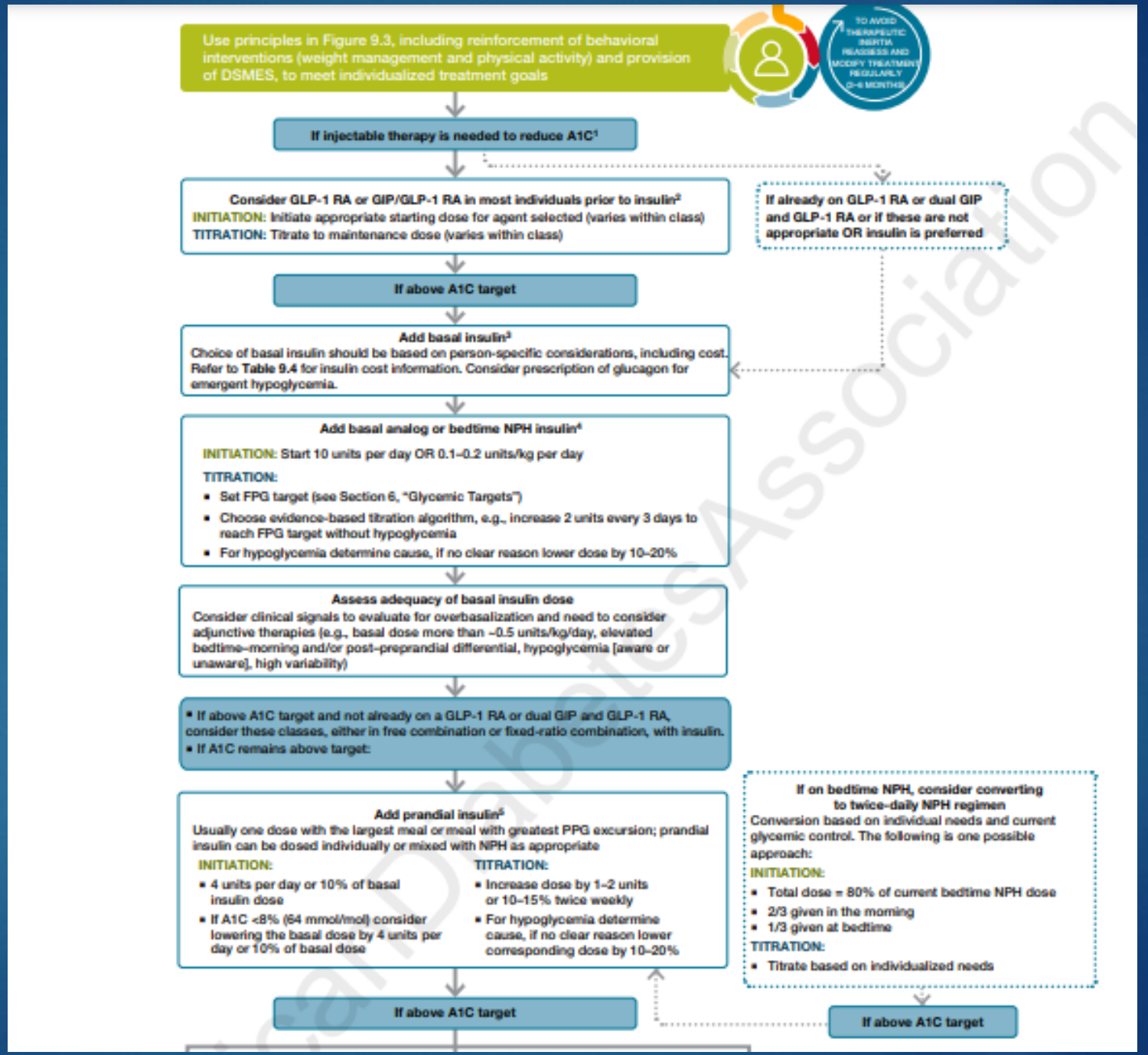
ADA Guideline 2023



2023 ADA Standards of Medical Care for Diabetes



ElSayed. Diabetes Care. 2023;46:S140.


Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES, to meet individualized treatment goals
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA or GIP/GLP-1 RA in most individuals prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)
If already on GLP-1 RA or dual GIP and GLP-1 RA or if these are not appropriate OR insulin is preferred
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on person-specific considerations, including cost. Refer to Table 9.4 for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.
Add basal analog or bedtime NPH insulin[4]
INITIATION: Start 10 units per day OR 0.1–0.2 units/kg per day
TITRATION:
Set FPG target (see Section 6, "Glycemic Targets")
Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10–20%
Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime–morning and/or post–preprandial differential, hypoglycemia [aware or unaware], high variability)
If above A1C target and not already on a GLP-1 RA or dual GIP and GLP-1 RA, consider these classes, either in free combination or fixed-ratio combination, with insulin.
If A1C remains above target:
Add prandial insulin[5]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
INITIATION:
4 units per day or 10% of basal insulin dose
If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 units per day or 10% of basal dose
TITRATION:
Increase dose by 1–2 units or 10–15% twice weekly
For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10–20%
If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:
INITIATION:
Total dose = 80% of current bedtime NPH dose
2/3 given in the morning
1/3 given at bedtime
TITRATION:
Titrate based on individualized needs
If above A1C target
If above A1C target

The Case

- A 68-year-old woman with 12-year history of type 2 diabetes is referred to you. She takes metformin 2000 mg and gliclazide MR 60 mg daily. She respects the diet recommended by the nutritionist.
- She has peripheral neuropathy.
- She has a history of acute MI during a couple of months ago and also a hospitalization due to decompensated HF
- She claims that in the past, with increasing gliclazide dose, several hypoglycemic episodes had occurred. She fears hypoglycemia because she lives alone.
- BMI: 35.5 kg/m^2

Case presentation

- Laboratory tests:
- FBS: 180 mg/dl
- HbA1c: 9.2%
- Cr: 1.2 mg/dl (eGFR ~ 50 ml/min)
- LDL: 120 mg/dl
- TG: 250

- Which therapeutic approach would you recommend to her?

- A) Add Basal insulin+ Atorvastatin 80
- B) Add Liraglutide+ Rosuvastatin 40
- C) Add Pioglitazone 15 + Rosuvastatin 40
- D) Add Sitagliptin 100 mg+ Fenofibrate 100 mg+ Arorvastatin 40 mg
- E) Add Empagliflozin 10 mg+ Rosuvastatin 40+ Semaglutide SC

Thank you