Practical prescribing guide for SGLT2 inhibitors and GLP agonists

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Summary

1. Treatment aims – DM2
2. New guidelines - EASD and ADA

3. **SGLT2 inhibitors**
   - Mechanism of action
   - Evidence / data
   - Save prescribing
   - Clinical case
   - Questions

4. **GLP1 agonists**
   - Mechanism of action
   - Save prescribing
   - Evidence / data
   - Clinical cases
   - Questions

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/ OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target			
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia[7]

COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/ OR

- GLP-1 RA with good efficacy for weight loss[8]
- SGLT2i[2]

If HbA_{1c} above target

SGLT2i[2]	GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} above target

If triple 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[6]
- TZD[5]
- Basal insulin

COST IS A MAJOR ISSUE[9–10]

SU[6]	TZD[10]
If HbA_{1c} above target	
TZD[10]	SU[6]

If HbA_{1c} above target

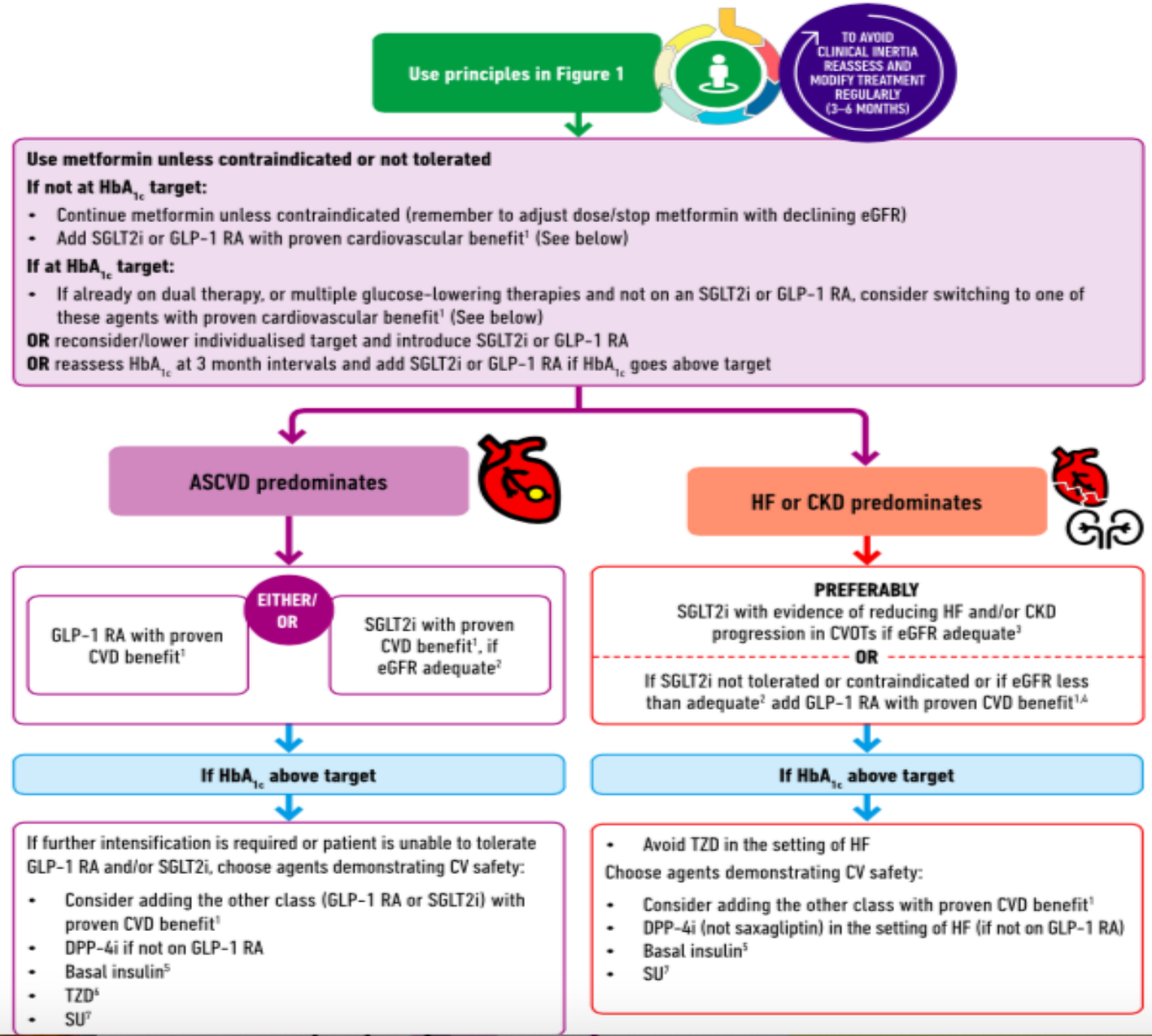
- **Insulin therapy** basal insulin with lowest acquisition cost

OR

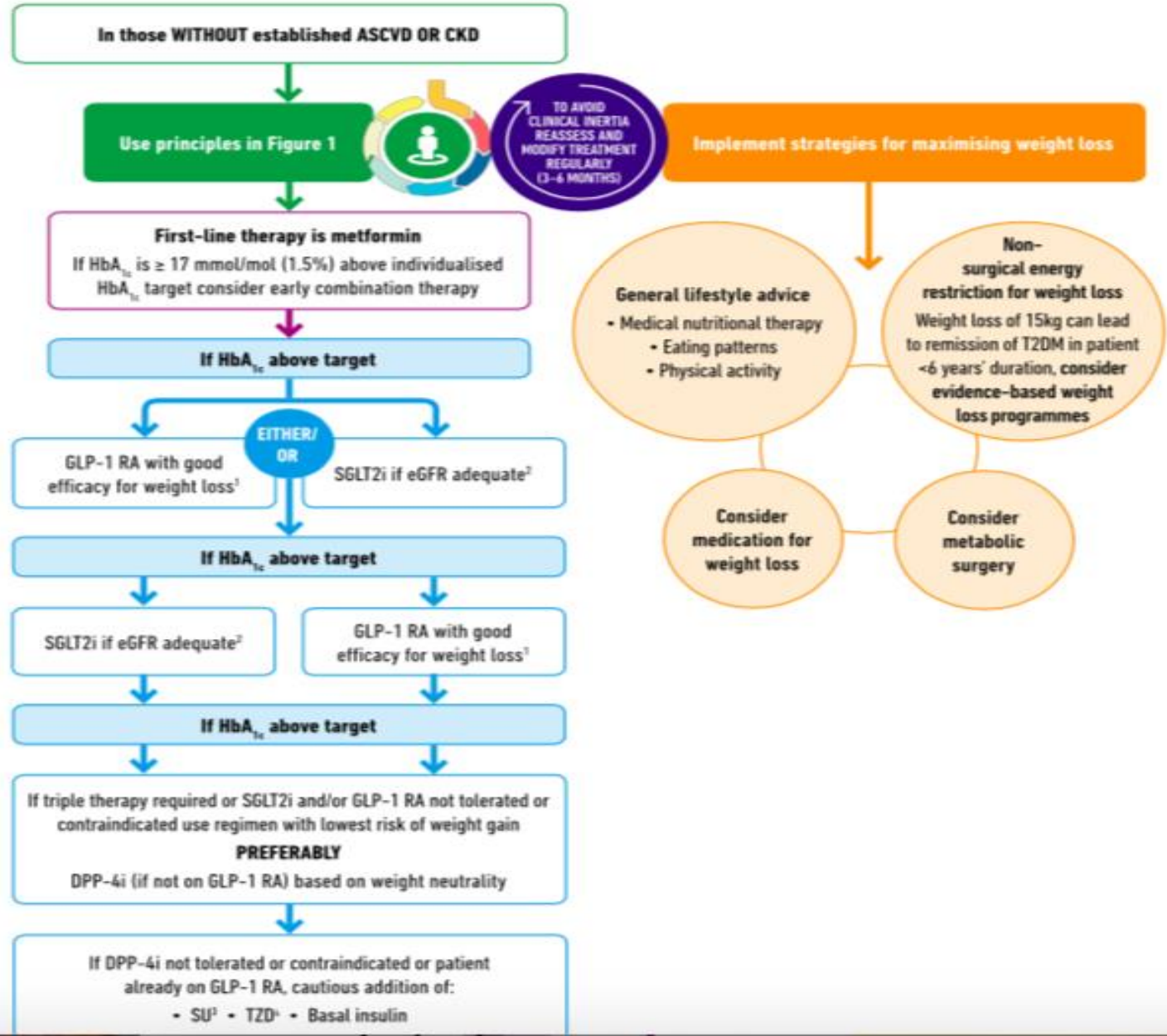
- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower

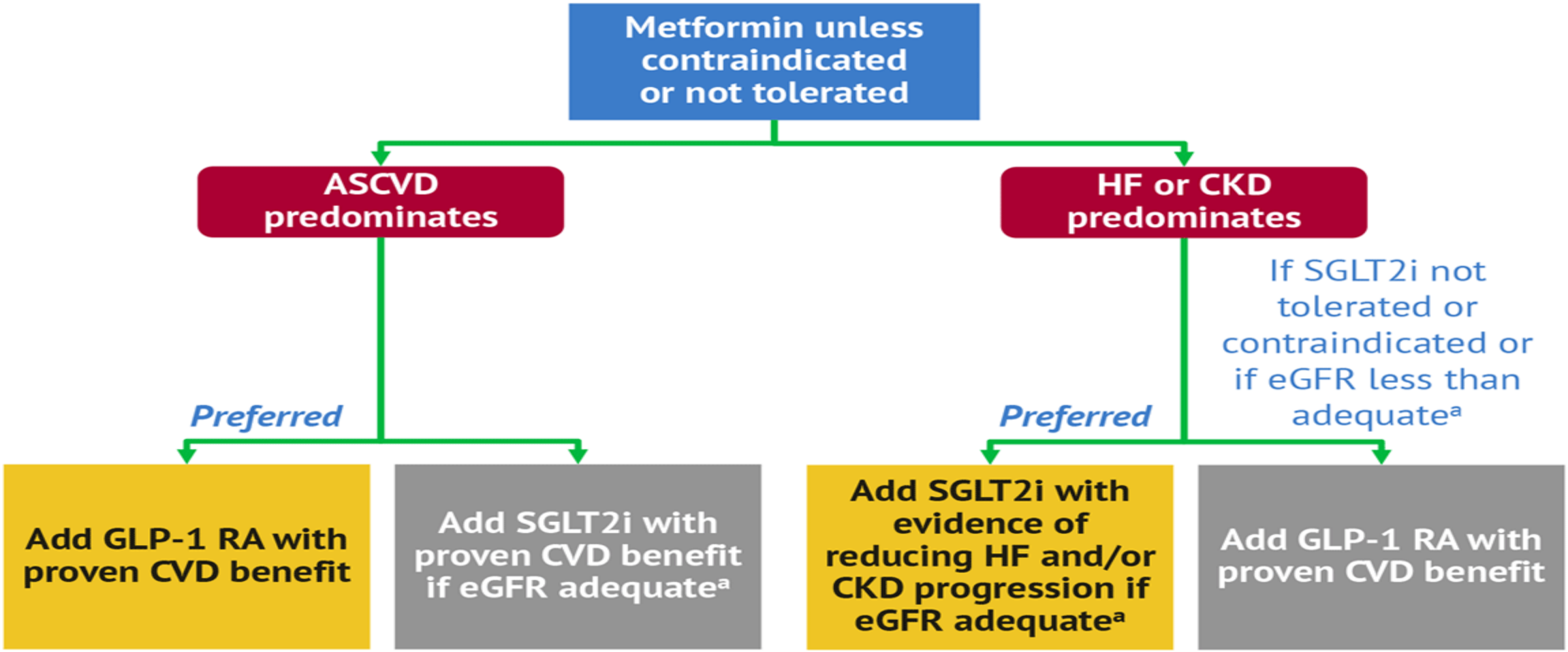
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



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



ADA Guidelines: Glucose-Lowering Medications in Patients at High Risk[4]



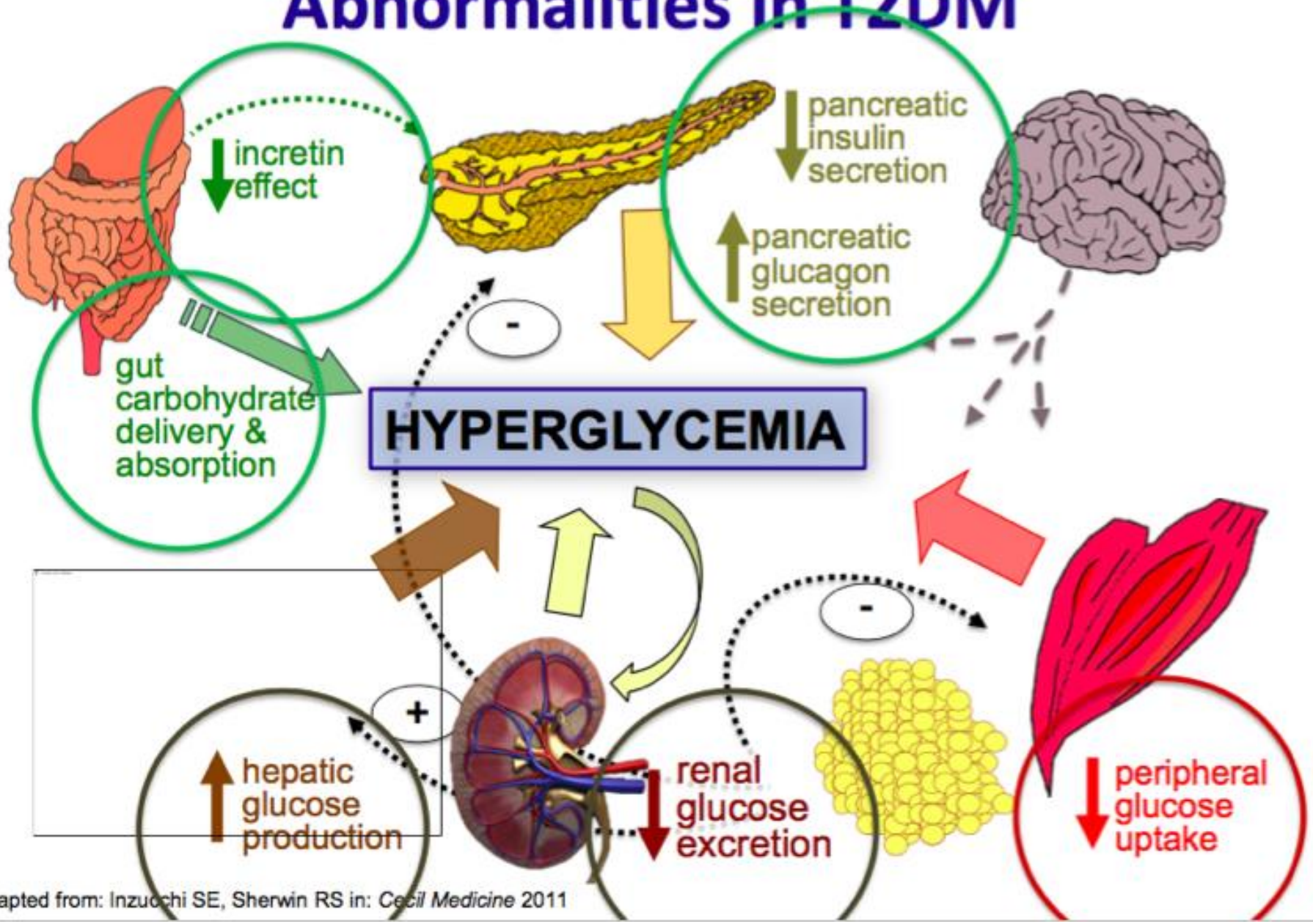
[a] SGLT1i labeling varies by region and individual agent with regard to indicated level of eGFR.

Current approach	New approach
Metformin • First used 1957 • Max dose 2 tabs three time daily • Requires multiple dose titration • High rate of side effects (15-30%)	**Metformin XR** • First used 2004 • 1 tab twice daily • No dose titration • Moderate side effect rate (13%)
Sulphonylurea e.g. Glipizide • First used 1956 • Max dose 2 tabs three time daily • Requires multiple dose titration • Causes hypoglycaemia/ weight gain • Requires BG monitoring • **High secondary failure rate (>4 years)**	**SGLT-2 inhibitor e.g. Empagliflozin** • First used 2013 • 1-tab daily • No dose titration • Causes weight loss • Improves renal & CVD outcomes
Insulin (basal – premixed – basal/bolus) • First used 1922 • One to five injections daily • Requires multiple dose titration • Causes hypoglycaemia/weight gain • Requires BG monitoring	**GLP- agonist e.g. Liraglutide** • First used 2005 • I injection daily • Single dose titration • Causes weight loss • Improves CVD outcomes

Other on-going activities:

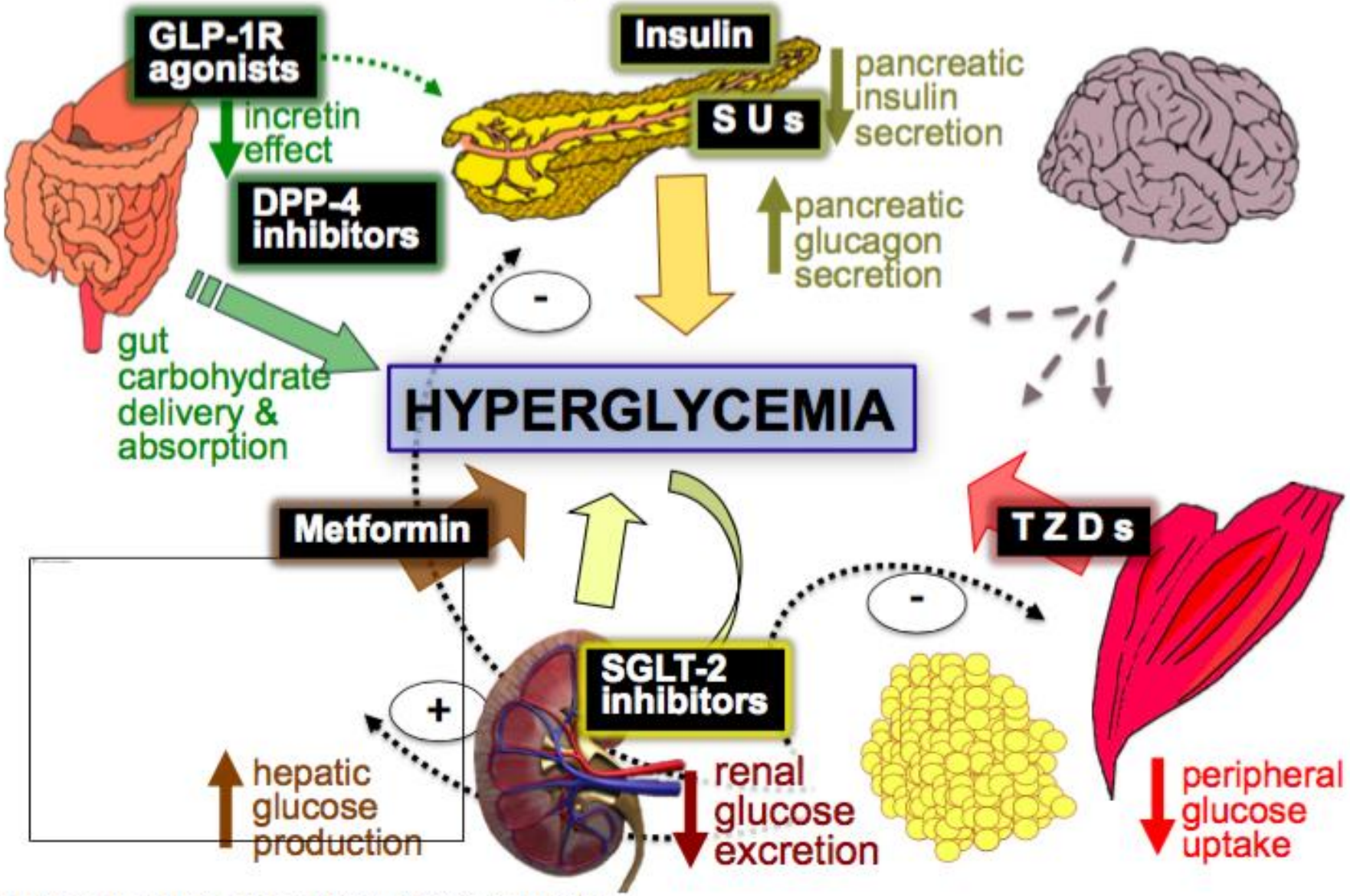
- **NZSSD Diabetes Management Guidelines** – just published
- PWC report ‘The cost of diabetes’ – early intervention (full economic evaluation – to be launched 16.02.2021
- New Pharmac funding – a new **equity based funding** decision (Empagliflozin and Dulaglutide)

Multiple Complex Pathophysiological Abnormalities in T2DM

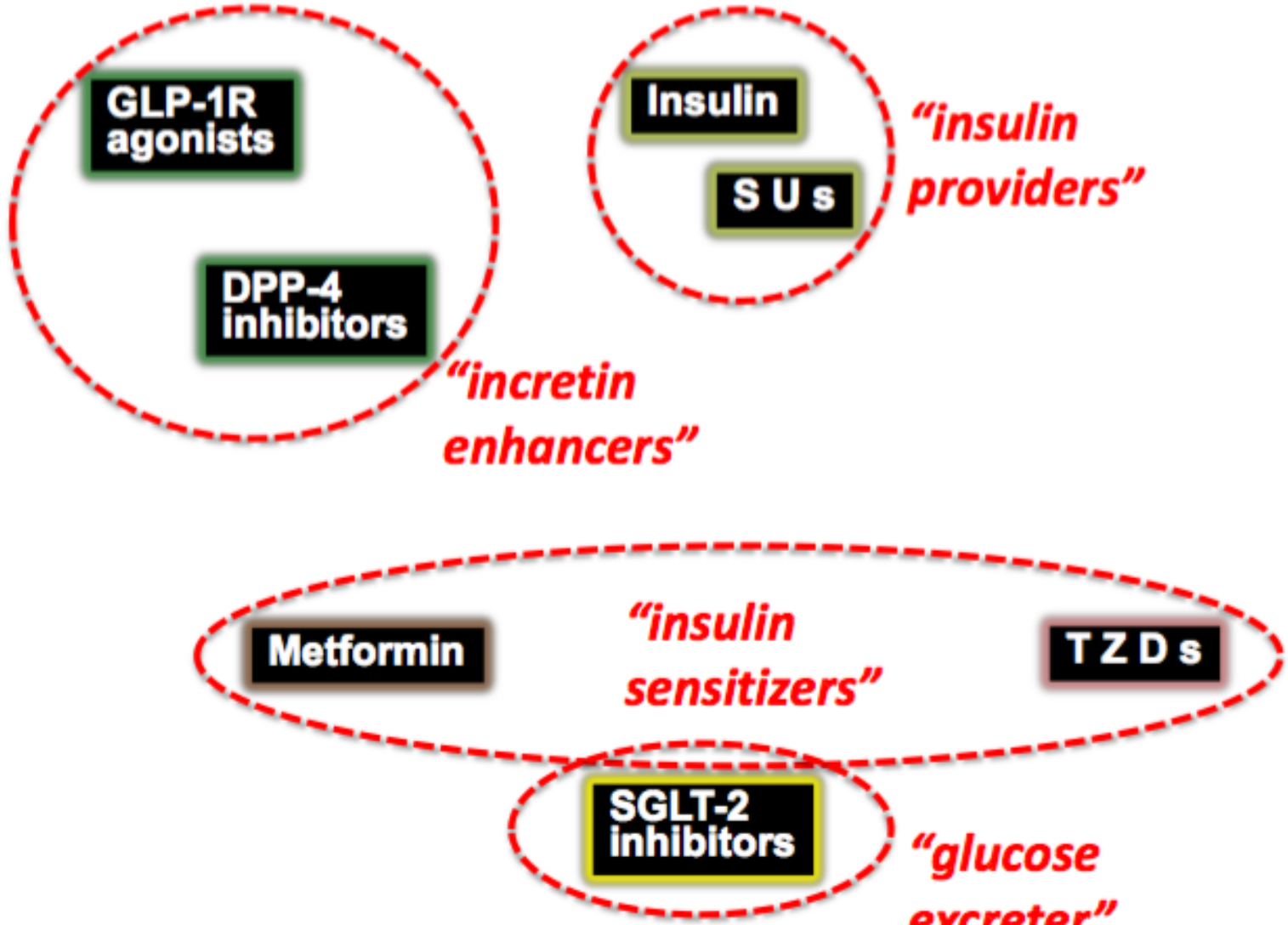


Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

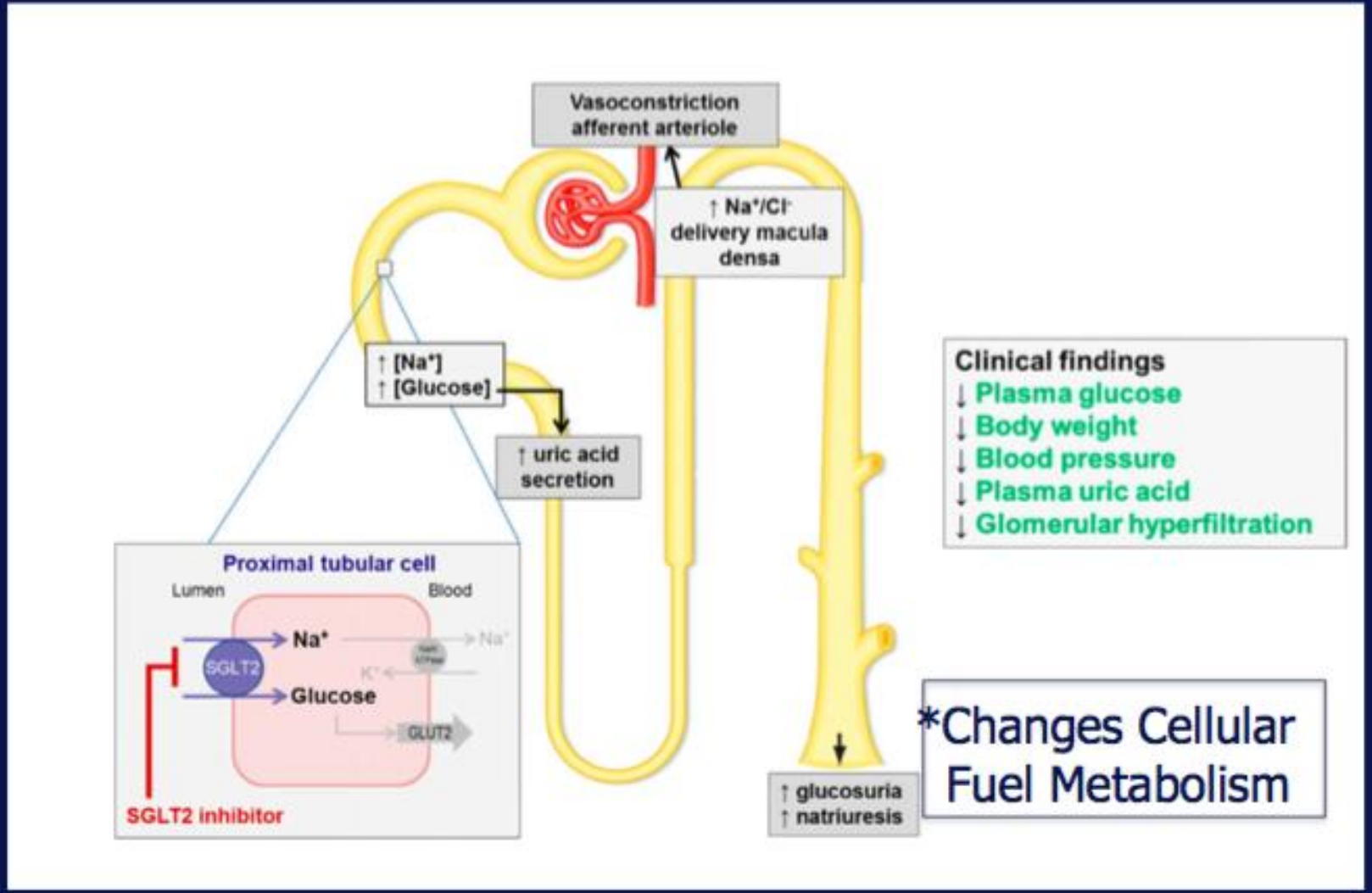
Major Pathophysiologically-Based Therapies for T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011


GLP-1R agonists
DPP-4 inhibitors
"incretin enhancers"
Insulin
S U s
"insulin providers"
Metformin
"insulin sensitizers"
T Z D s
SGLT-2 inhibitors
"glucose excreter"

Effects of SGLT2 Inhibitors

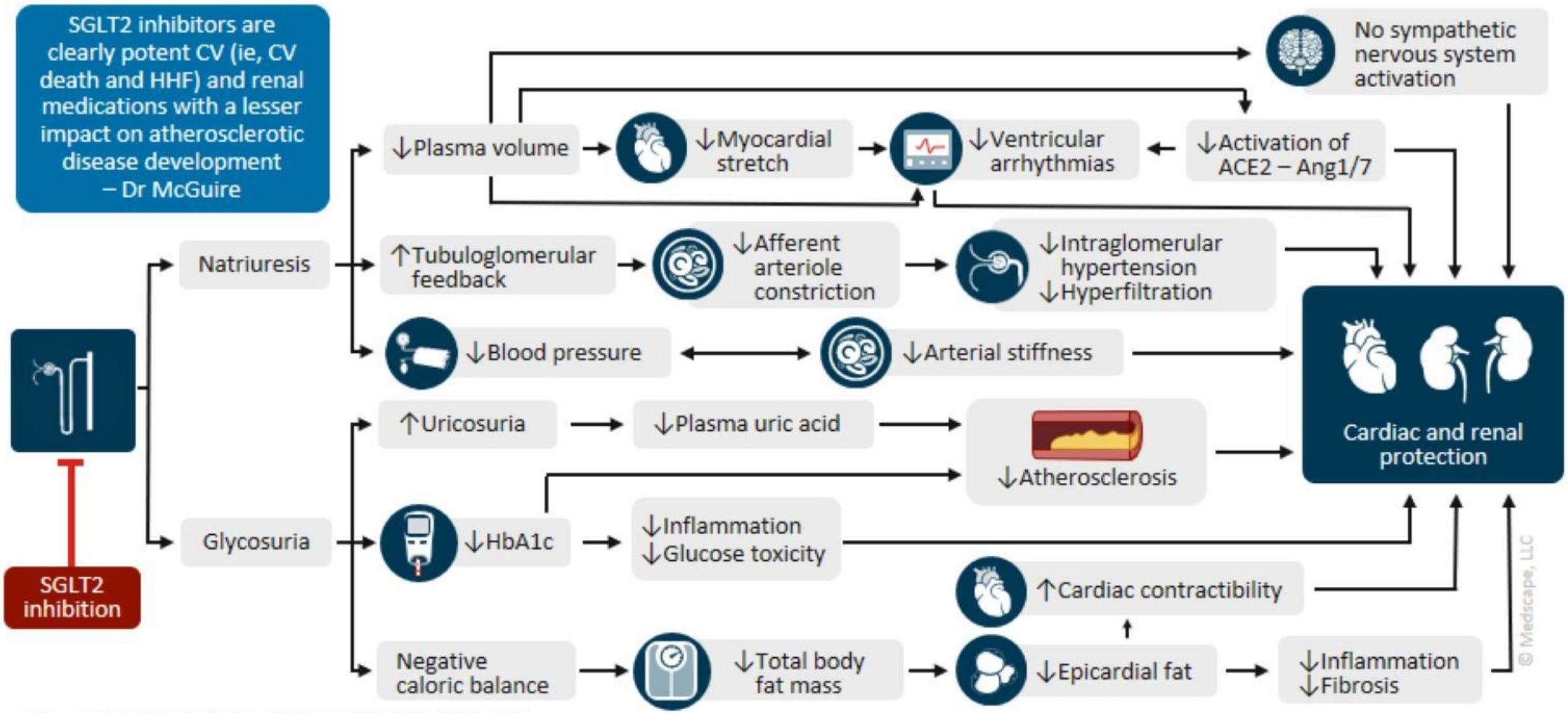


van Bommel et al Clinical J. Amer. Soc. Nephrol. 12:700-710, 2017

*Mudaliar et al Diabetes Care:1115-1122, 2016

Joslin Diabetes Center

Looking Beyond the Kidney and Glucose Modulation…



Heerspink HJ, et al. *Circulation*. 2016;134:752-772.

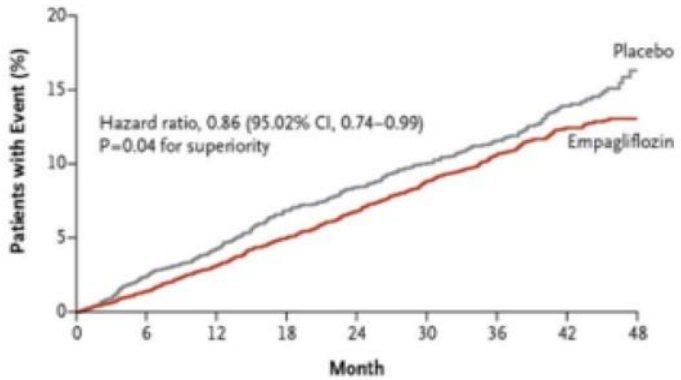
SGLT2 Inhibitor Class

- SGLT2 inhibitors originally approved as glucose-lowering agents
  - Reduce renal glucose absorption
- CV and renal outcomes data have demonstrated this class goes beyond glucose lowering
  - EMPA-REG OUTCOME (empagliflozin)
  - CANVAS Program (canagliflozin)
  - DECLARE-TIMI 58 (dapagliflozin)
  - CREDENCE (canagliflozin)
  - VERTIS-CV (ertugliflozin)

New SGLT2 inhibitor data from the 80th Scientific Sessions of ADA 2020 (conducted virtually)

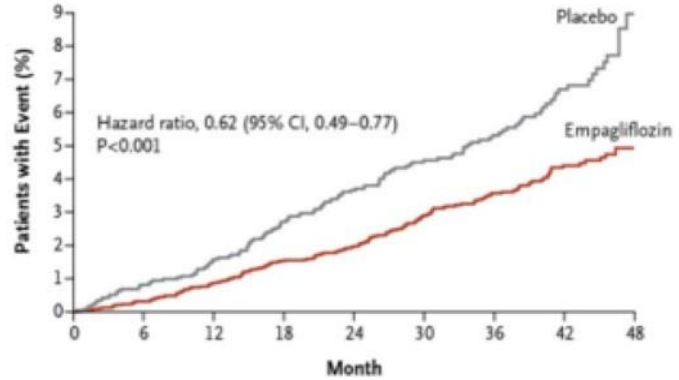
EMPA-REG OUTCOME
CV Outcomes and Death From Any Cause

Primary Outcome



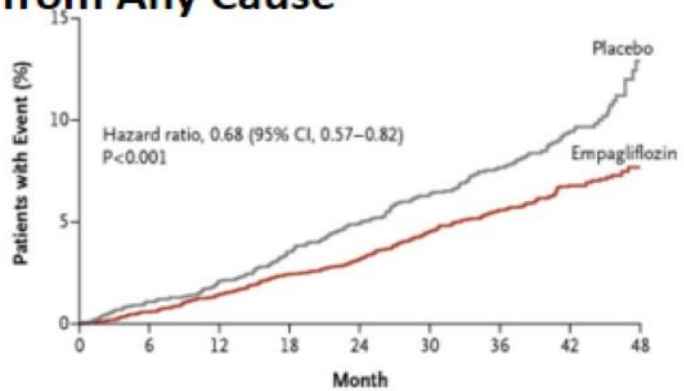
No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Death from CV Causes



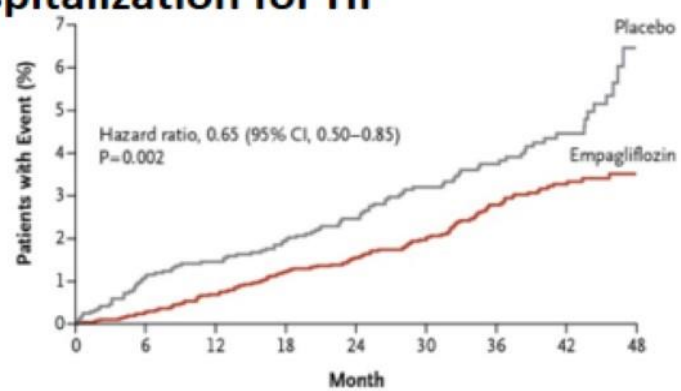
No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Death from Any Cause



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Hospitalization for HF

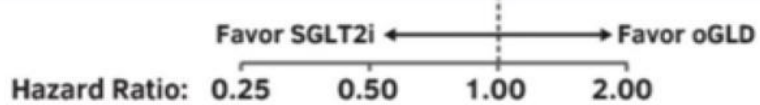


No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

CVD-REAL Study: SGLT2 Inhibitors are Associated With a Significantly Reduced Risk for All-Cause Mortality

- Secondary outcome: risk of all-cause mortality between treatment groups

Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)



P-value for SGLT2i vs oGLD: <0.001

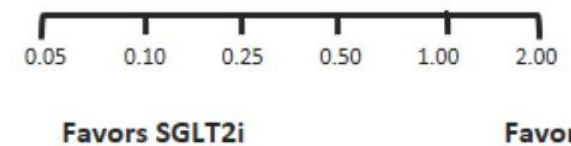
Heterogeneity p-value: 0.09

Kosiborod M, et al. Circulation. 2017. [Epub ahead of print] With permission from Wolters Kluwer Health.

CVD-REAL Study: SGLT2 Inhibitors Are Associated With a Significantly Reduced Risk for hHF

- Primary outcome: Risk for hHF in patients with T2D newly initiated on SGLT2 inhibitors vs other glucose-lowering drugs

Database	N	No. of events	HR (95% CI)
USA	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



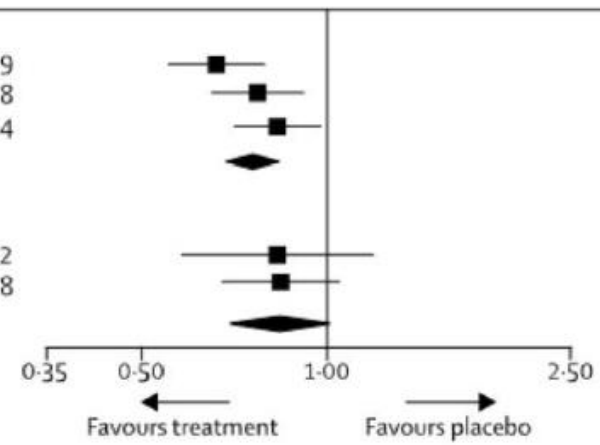
***P* value for SGLT2i vs oGLD: < .001**

Kosiborod M, et al. Circulation. 2017. [Epub ahead of print] With permission from Wolters Kluwer Health.

Meta-Analysis of SGLT2 Inhibitor CVOTs (cont)

CV Death/HHF by Presence of ASCVD

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9	0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8	0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4	0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·76 (0·69–0·84)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2	0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8	0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)							**0·84 (0·69–1·01)**



Zelniker TA, et al. *Lancet.* 2019;393:31-39.

Multi-Organ Response of SGLT2 Inhibitors Demonstrated in Trials

MACE: Efficacy across class is generally modest

CV death: Only EMPA-REG OUTCOME found significant reduction

HHF: Consistent effects across class

Renal: Benefit/trend shown across trials; AEs in line with SGLT2 inhibitor class

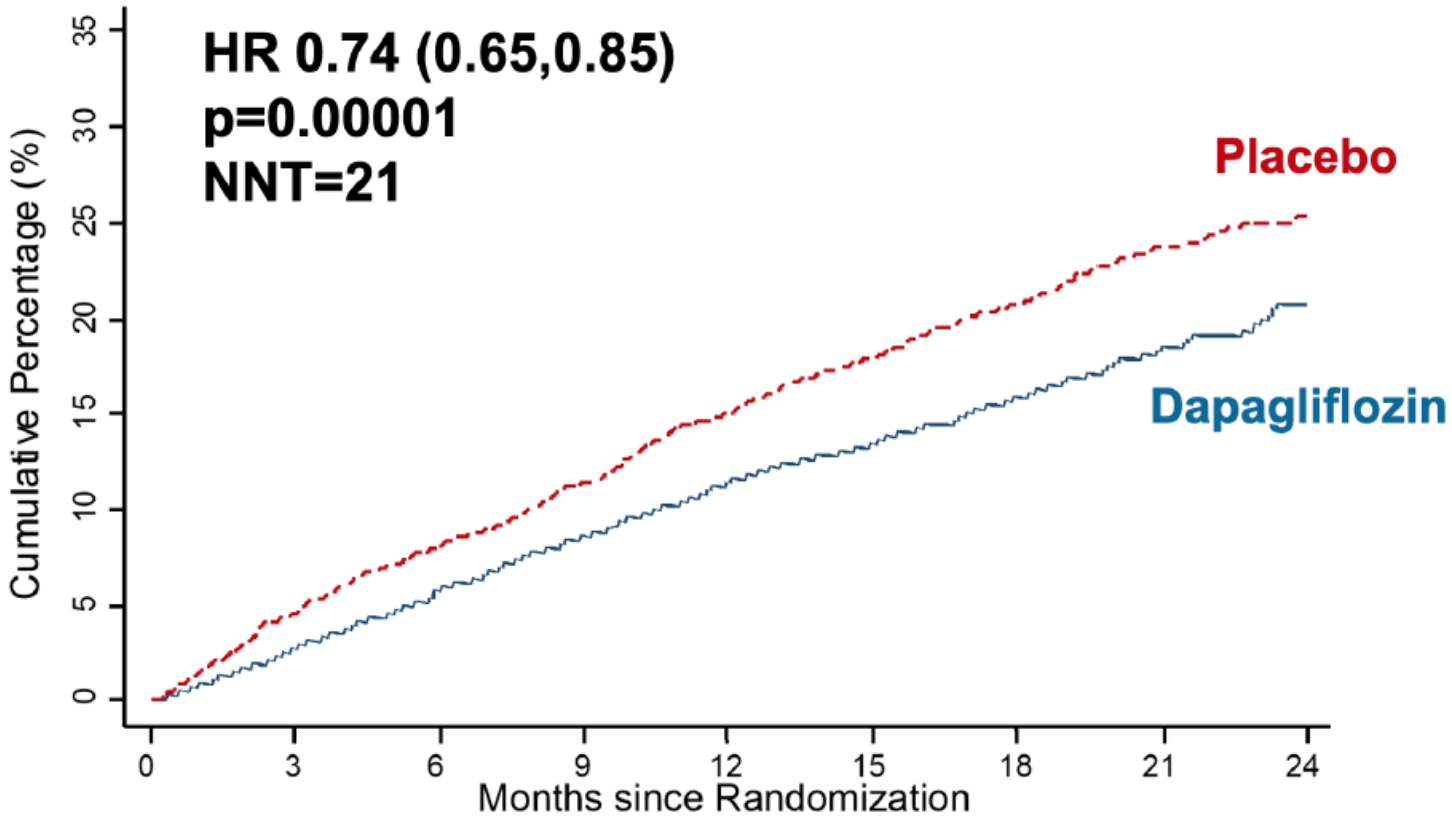
Cannon CP, et al. ADA Virtual 80th Scientific Sessions, June 16, 2020.

DAPA-HF Trial: Overview

Hypothesis	• The SGLT2 inhibitor, dapagliflozin (10 mg QD) would be superior to placebo when added to standard therapy in patients with HFrEF, both with and without T2DM
Key inclusion criteria	• Symptomatic HF; LVEF ≤ 40%; • NT-proBNP ≥ 600 pg/mL; or, ≥ 400 pg/mL if hospitalized for HF within last 12 months; if AF/flutter ≥ 900 pg/mL
Key exclusion criteria	• eGFR <30 mL/min/1.73 m^2 • Symptomatic hypotension or SBP < 95 mmHg • T1DM
Primary endpoint	• Worsening HF event* or CV death

Primary composite outcome

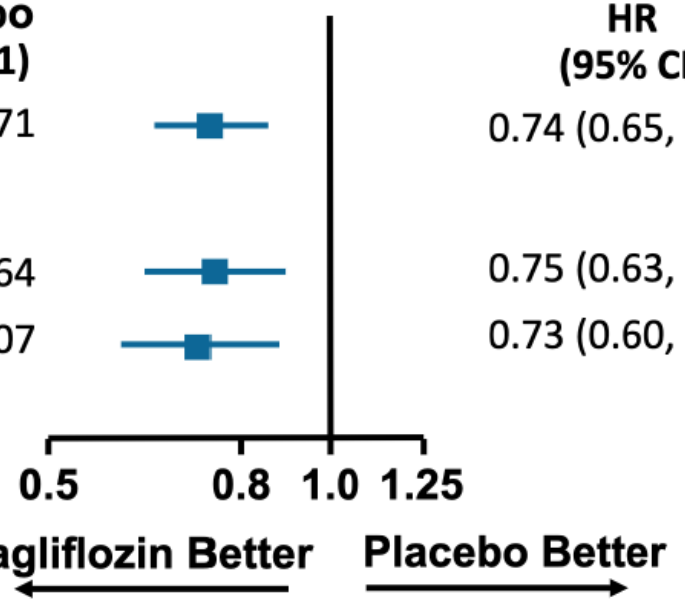
CV Death/HF hospitalization/Urgent HF visit



Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

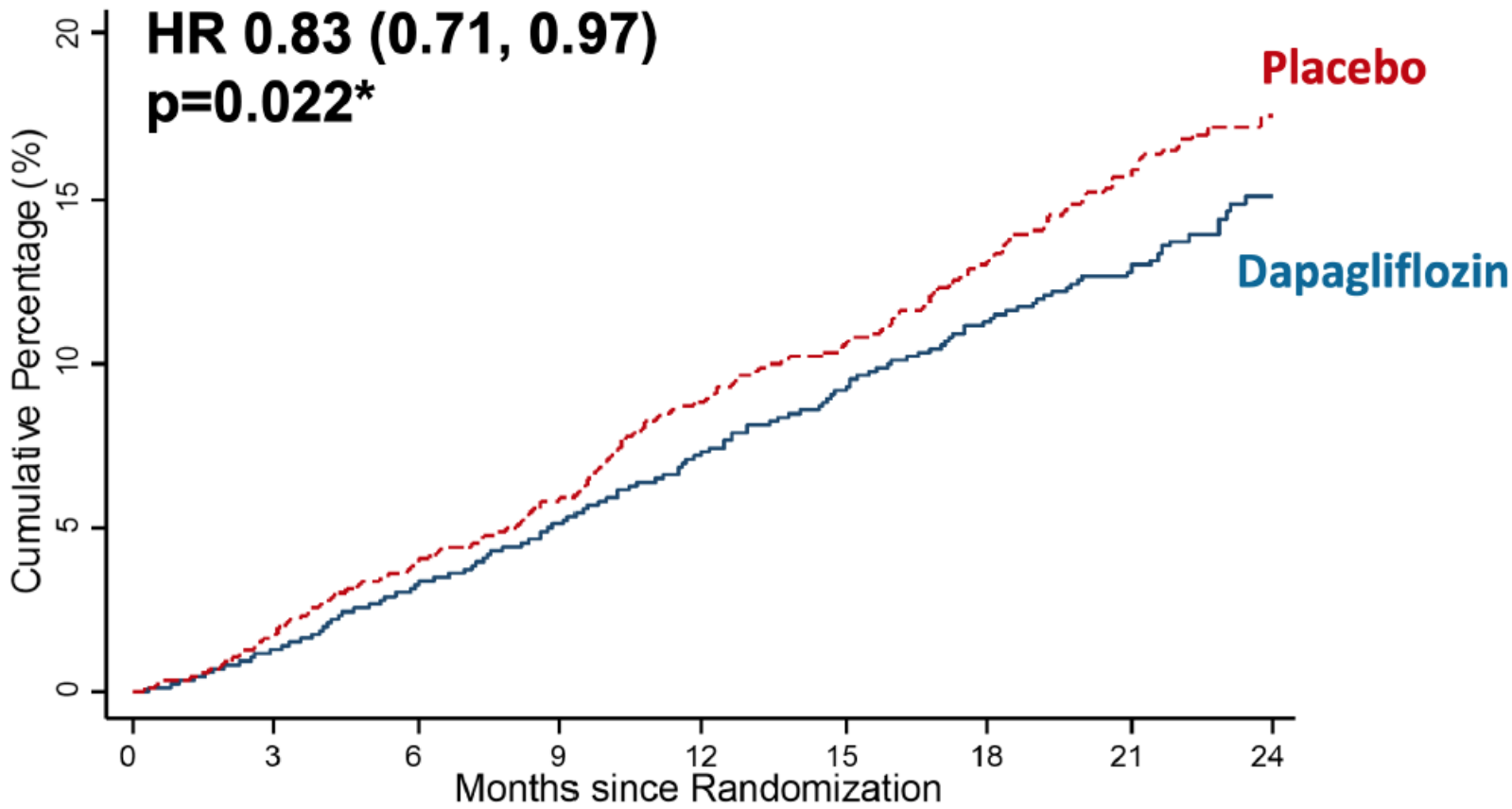
No diabetes/diabetes subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

All-cause death



Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

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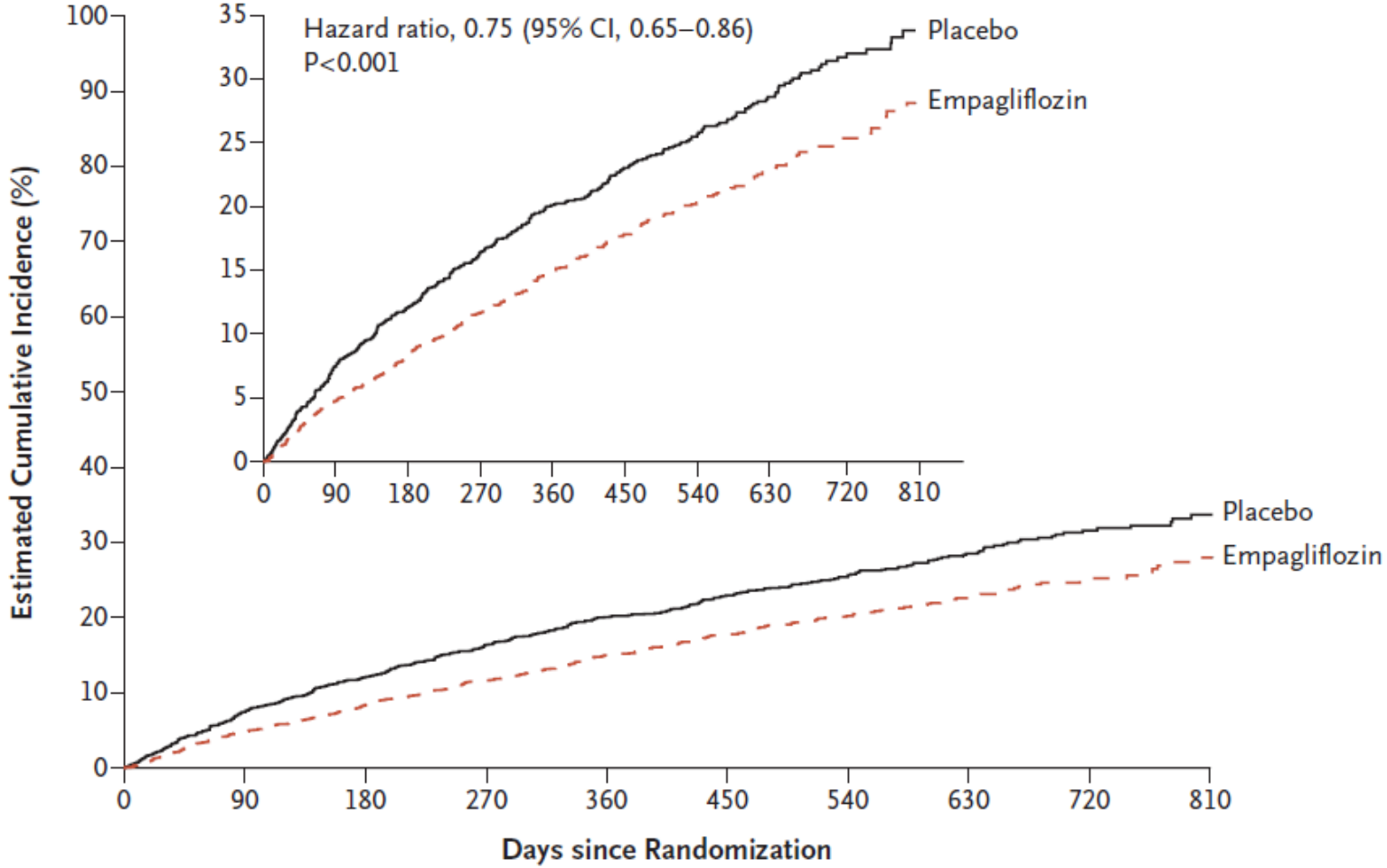
Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

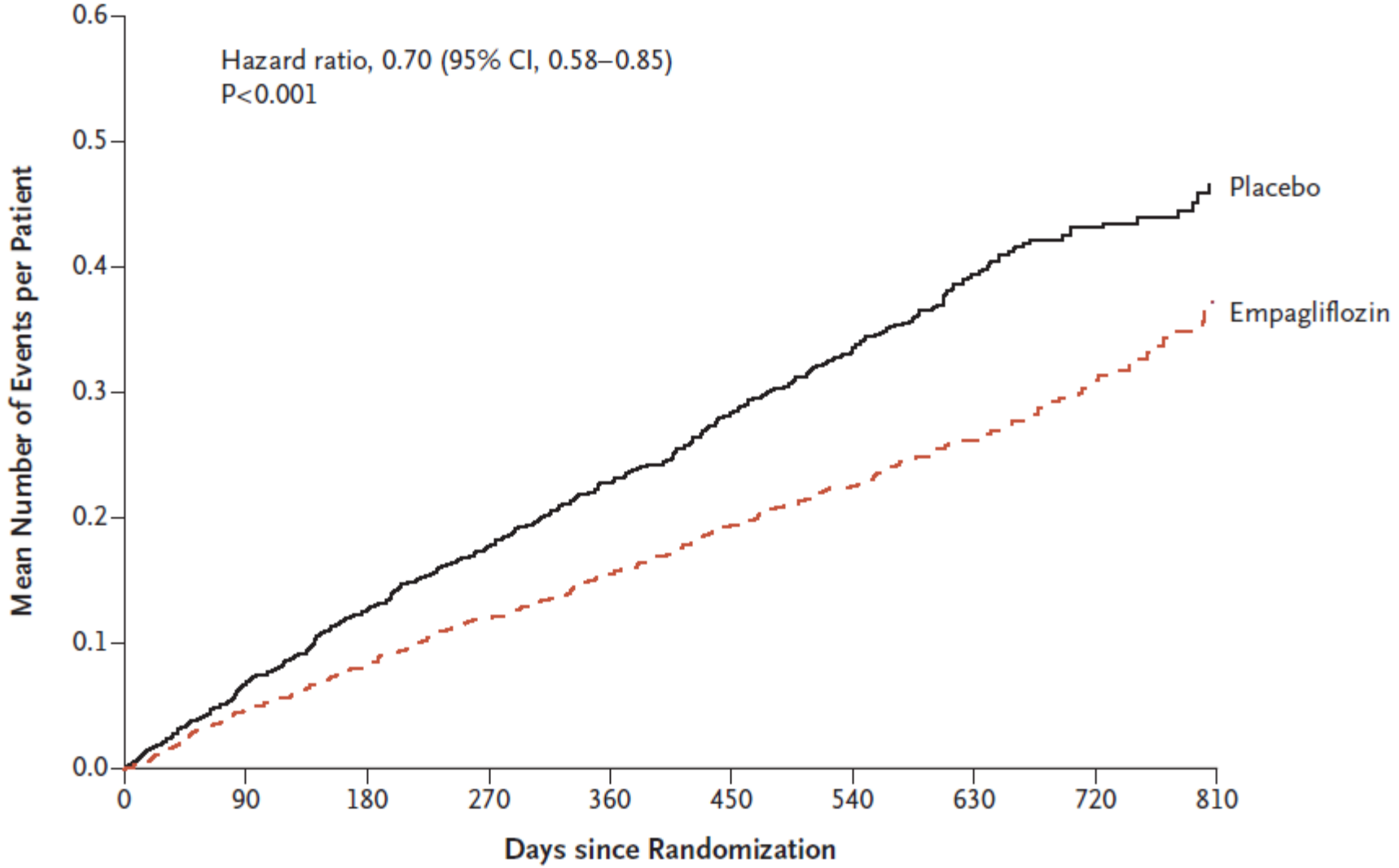
In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

A Primary Outcome



No. at Risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

B First and Recurrent Hospitalizations for Heart Failure



No. at Risk										
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

Absolute benefit of treatment

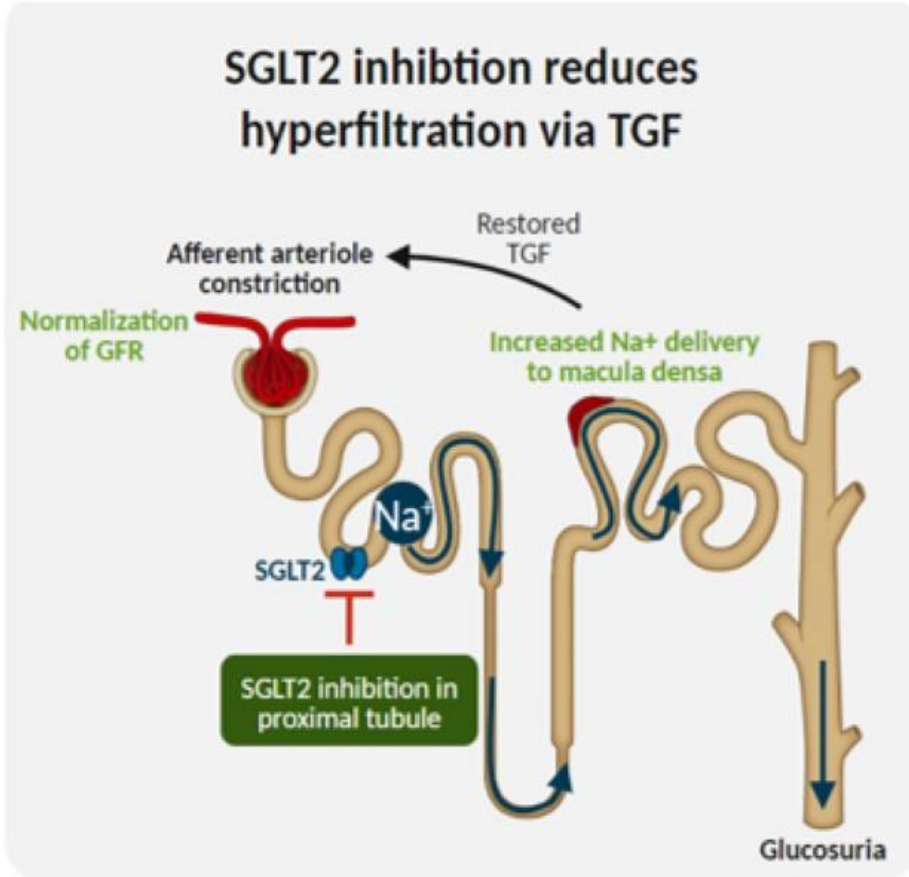
Reduction in events per 1000 person years

Trial	Background therapy	CV death/ HF hospital.	HF hospital.	CV death
PARADIGM-HF (n=8399) enalapril v. sac/val (control v. neprilysin inhib.)	*ACE/ARB 100%* *BB 93%* *MRA 56%*	**26.7**	**15.9**	**15.0**
DAPA-HF (n=4744) placebo v. dapagliflozin	*ACE/ARB* 94%* *BB 96%* *MRA 71%*	**38.7**	**29.2**	**14.0**

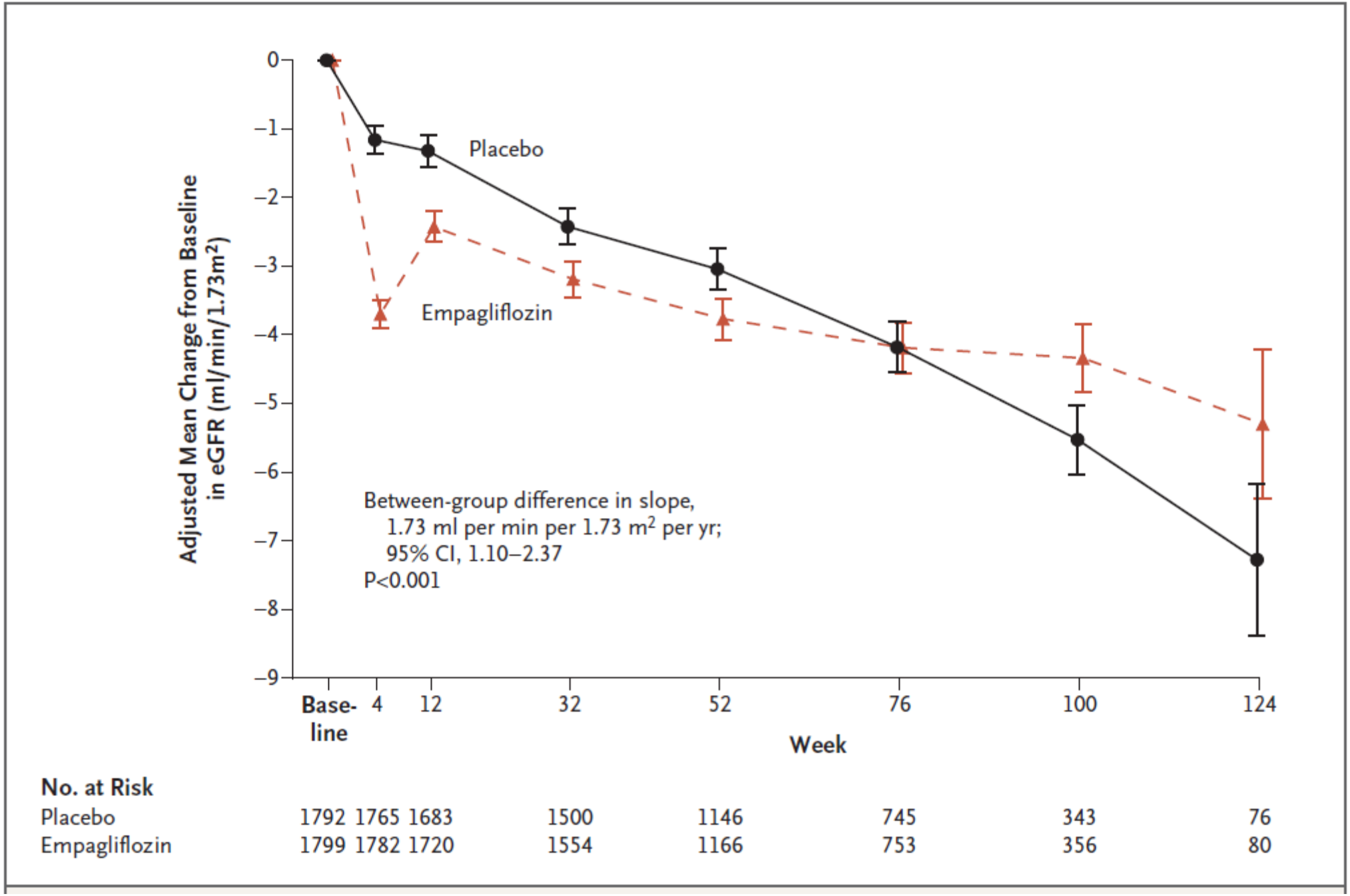
*including sacubitril/valsartan

Renal Benefits

- Decrease in intraglomerular pressure and hyperfiltration



Cherney DZ, et al. *Circulation*. 2014;129:587-597.

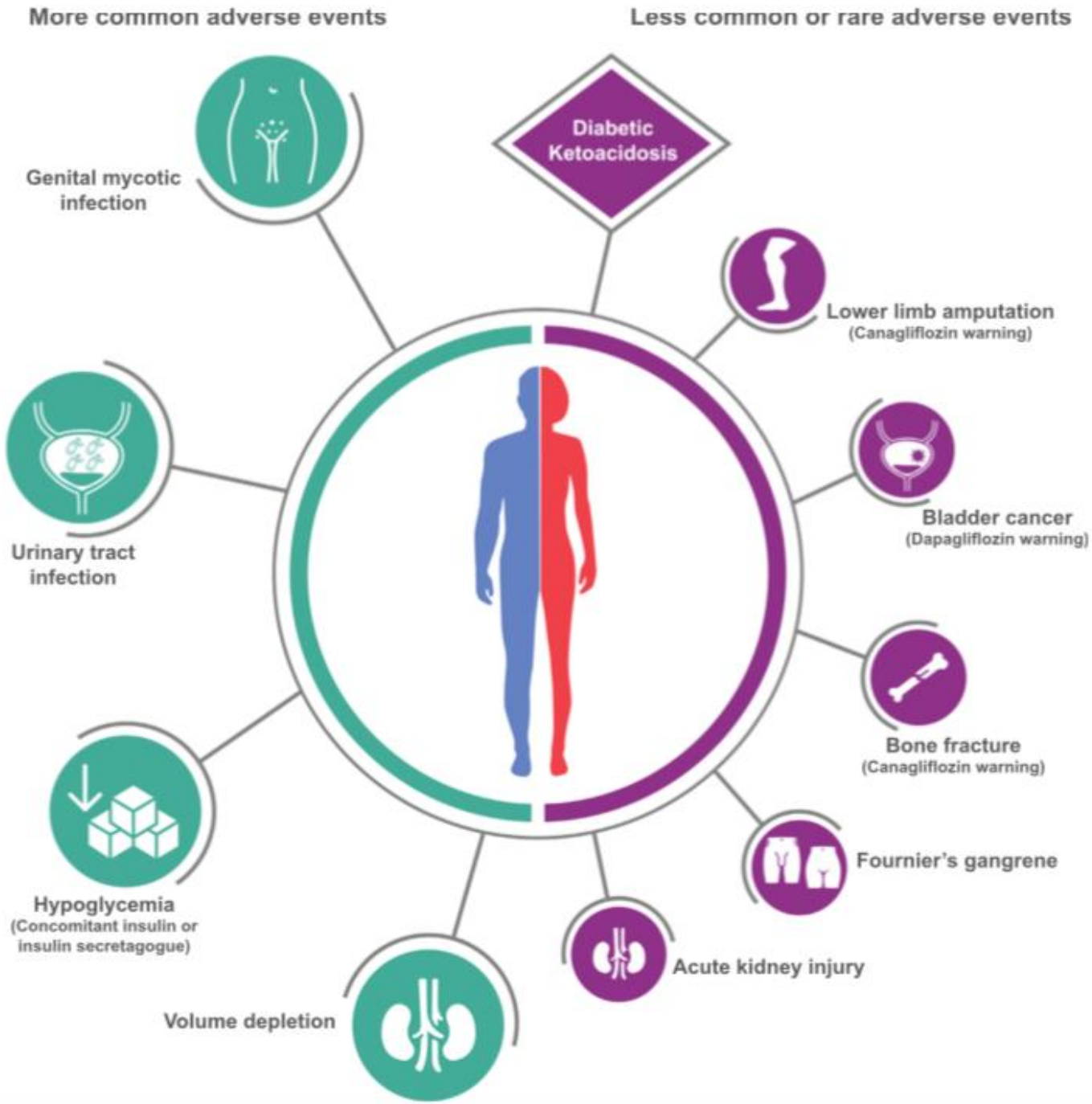


No. at Risk

Placebo	1792	1765	1683	1500	1146	745	343	76
Empagliflozin	1799	1782	1720	1554	1166	753	356	80

SGLT2 inhibitors complications & cautions

- **UTI and thrush** (what to do to reduce it happen)
  - Risk of urosepsis and and pyelonephritis
  - Data from the UK paper
  - Hipprex – in NZ
  - Treatment advice (1x Rx than stop)
- **Necrotizing fasciitis of the perineum** (Fournier's gangrene) – rare but serious
  - Better control – less glycosuria
  - Hygiene advice
- **Declining renal function**
  - Monitoring of eGFR
  - Avoid volume depletion (osmotic diuresis) – dehydration, hypotension
  - Especially if other volume loss (diarrhea, vomiting, bowel clearance)
- **Euglycaemic DKA**
  - avoid in DM1
  - Education about symptoms (patient, GP and hospital staff)
  - Often not recognized due to normal blood glucose – delayed/ missed Rx
- **Amputations** (toes) – only with canagliflozin
- **Hypoglycemia** – reduction of other medication


More common adverse events
Less common or rare adverse events
Genital mycotic infection
Diabetic Ketoacidosis
Lower limb amputation
(Canagliflozin warning)
Urinary tract infection
Bladder cancer
(Dapagliflozin warning)
Bone fracture
(Canagliflozin warning)
Hypoglycemia
(Concomitant insulin or insulin secretagogue)
Fournier's gangrene
Acute kidney injury
Volume depletion

TF, 63 female

- 1. Type 2 diabetes, diagnosed 1995, on insulin since 2005
  - - Background diabetic retinopathy /nonproliferative diabetic retinopathy
  - - Mild peripheral neuropathy with dysaesthesia and paraesthesia
  - - Normal renal function with microalbuminuria
- 2. Emotional problems
- 3. Non alcoholic fatty liver disease secondary to metabolic syndrome
  - Liver biopsy 2015: F2 fibrosis; fatty liver disease
  - Fibroscan May 2019 hepatitis stiffness 10.8 kPa consistent with severe fibrosis (F3)

- **Medications**
- 1. Lantus 68 units am
- 2. Apidra 16 units with breakfast, lunch and dinner
- 3. Galvumet 50/1000 mg bd
- 4. Atorvastatin 40 mg nocte
- 5. Paroxetine 20 mg od
- 6. Quinapril 5 mg od
- 7. Aspirin 100 mg od
- 8. Bezafibrate 400 mg

Results (18/06/2020)

- **HbA1c 80 mmol/mol,** ALT 50, other LFT normal, LDL 0.7, eGFR 87, **ACR 6.0**
- **Estimated CV risk**

Recommendations

1. Add additional metformin to increase to previously tolerated dose of 3 g per day
2. Add dapagliflozin 10 mg od (self-funded)
3. Change paroxetine to escitalopram

- She is already on a significant amount of insulin (> 110 units per day), hence I am not keen to increase the insulin further
- She tolerated 3 g of metformin in the past, hence, I added additional metformin to her galvumet.
- They are also happy to self-fund dapagliflozin which should help her with better diabetes control, weight management, will be cardiovascular protective and have a beneficial effect on her microalbuminuria.

	Ref Range	Units	21/02/19 11:33 JAYAVANT, KALACH	30/08/19 11:26 JAYAVANT, KALACH	30/10/19 10:40 BARUA, TAPASH CH	18/06/20 11:19 ASHRAF, SAIRA CH	04/09/20 13:47 SCHMIEDEL, OLE CH
Microalbumin urine	< 30	mg/L	10	**57**	12	15	8
Creatinine urine		mmol/L	1.8	8.6	2.2	2.5	4.2
Alb/Creat ratio	< 3.5	mg/mmol	**5.6**	**6.6**	**5.4**	**6.0**	1.9
Comment							

HbA1c		mmol/mol	**80**	**86**	**73**	**80**	**72**

Reduced Apidra from 16 units TDS to 10 units TDS
Continued Glargine at 60 units od

Glucose 6-10mmol/l
Latest HbA1c awaited

Incretin Therapies: Effects Beyond Glycemic Control

Mudaliar S, Henry RR Eur J Intern Med. **2009** Jul; 20 Suppl 2: p 319-28 (Review)

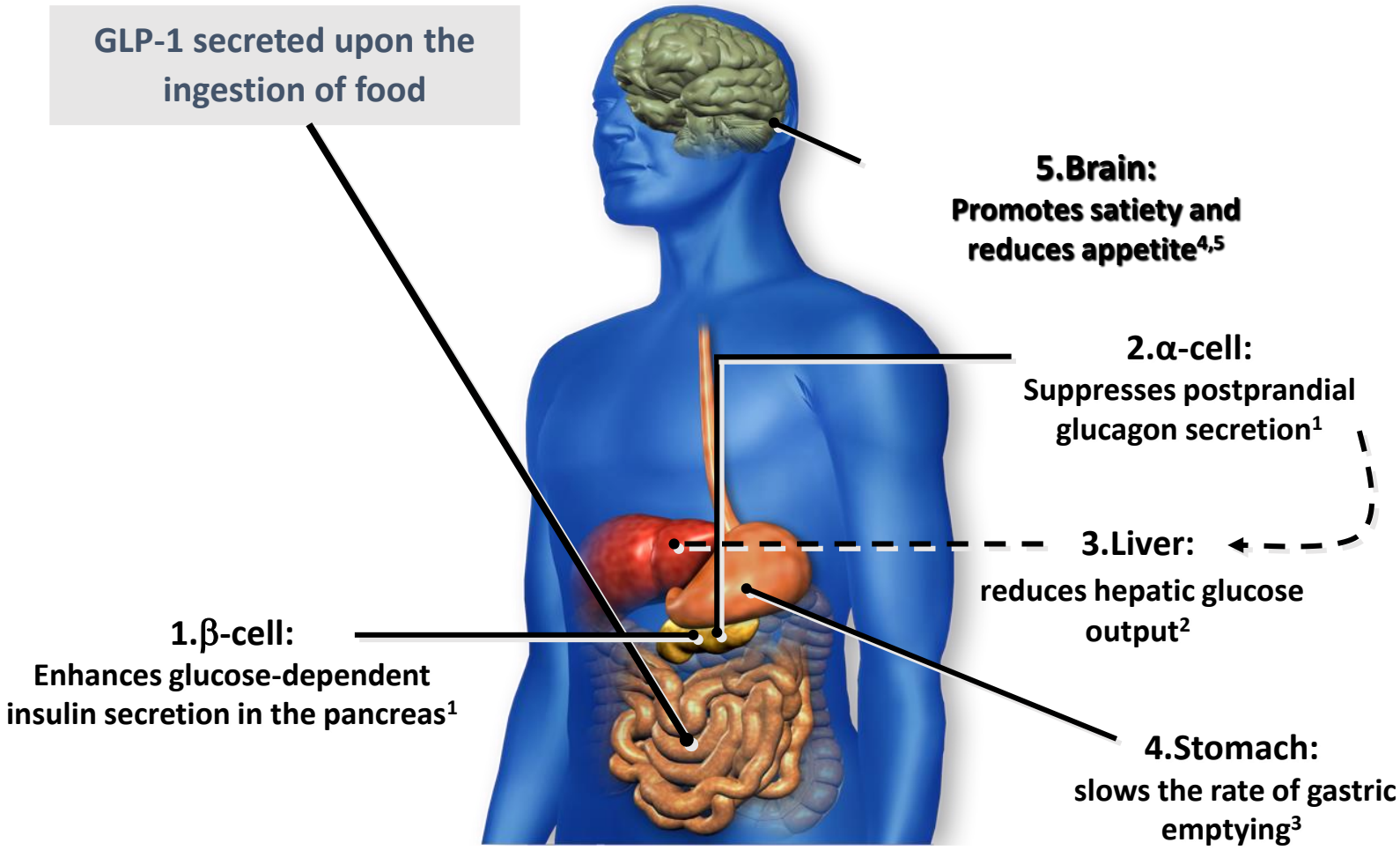
The incretin hormones

1. **glucagon-like peptide-1 (GLP-1)**
2. glucose-dependent insulinotropic polypeptide (GIP)

- peptide hormones produced by the gastrointestinal tract (L cells in the ileum and colon) in response to nutrient entry

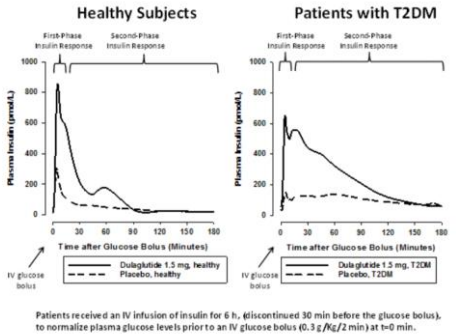
- **play a major role in glucose homeostasis**
  1. stimulate insulin secretion
  2. suppress glucagon secretion
  3. inhibit gastric emptying
  4. reduce appetite and food intake

GLP-1 effects in humans - the natural role of incretins



Adapted from [1]Nauck MA, et al. *Diabetologi*a 1993;36:741–744; [2]Larsson H, et al. *Acta Physiol Scand* 1997;160:413–422; [3]Nauck MA, et al. *Diabetologia* 1996;39:1546–1553; [4]Flint A, et al. *J Clin Invest* 1998;101:515–520; [5]Zander et al. *Lancet* 2002;359:824–830.

The incretin effect
β-cell response to oral vs IV glucose

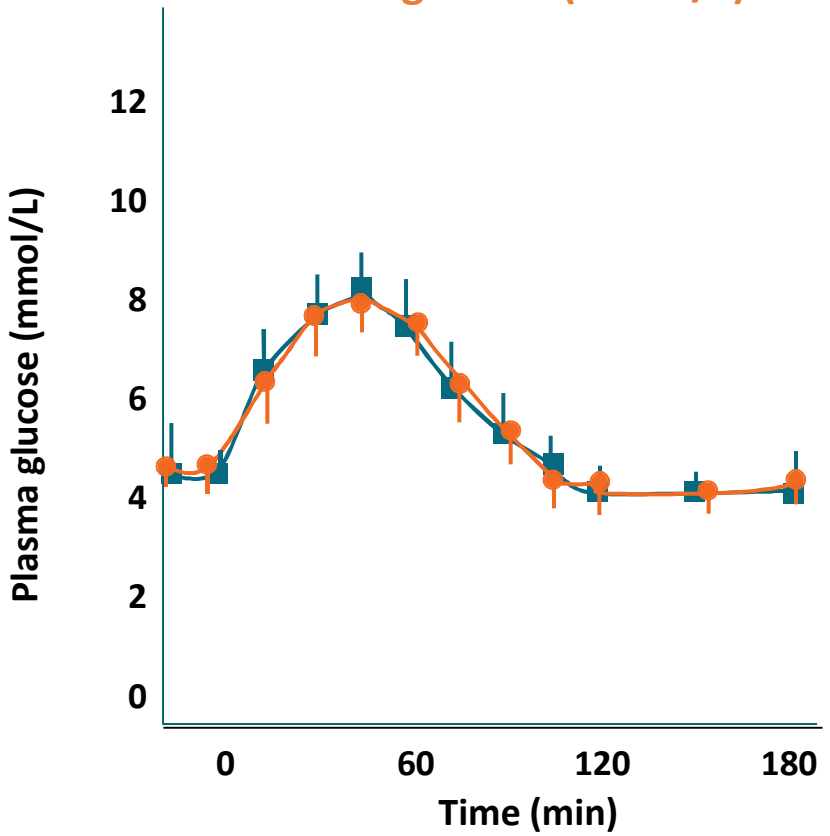


Crossover of healthy subjects (N = 6)

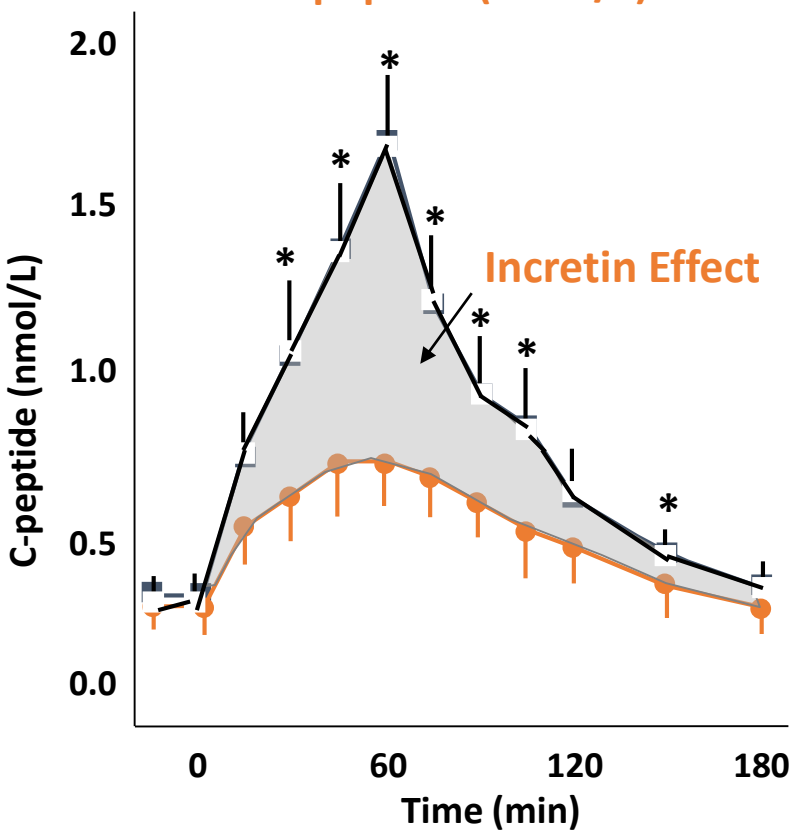
Oral glucose (50 g)

Isoglycaemic intravenous (IV) glucose

Plasma glucose (mmol/L)



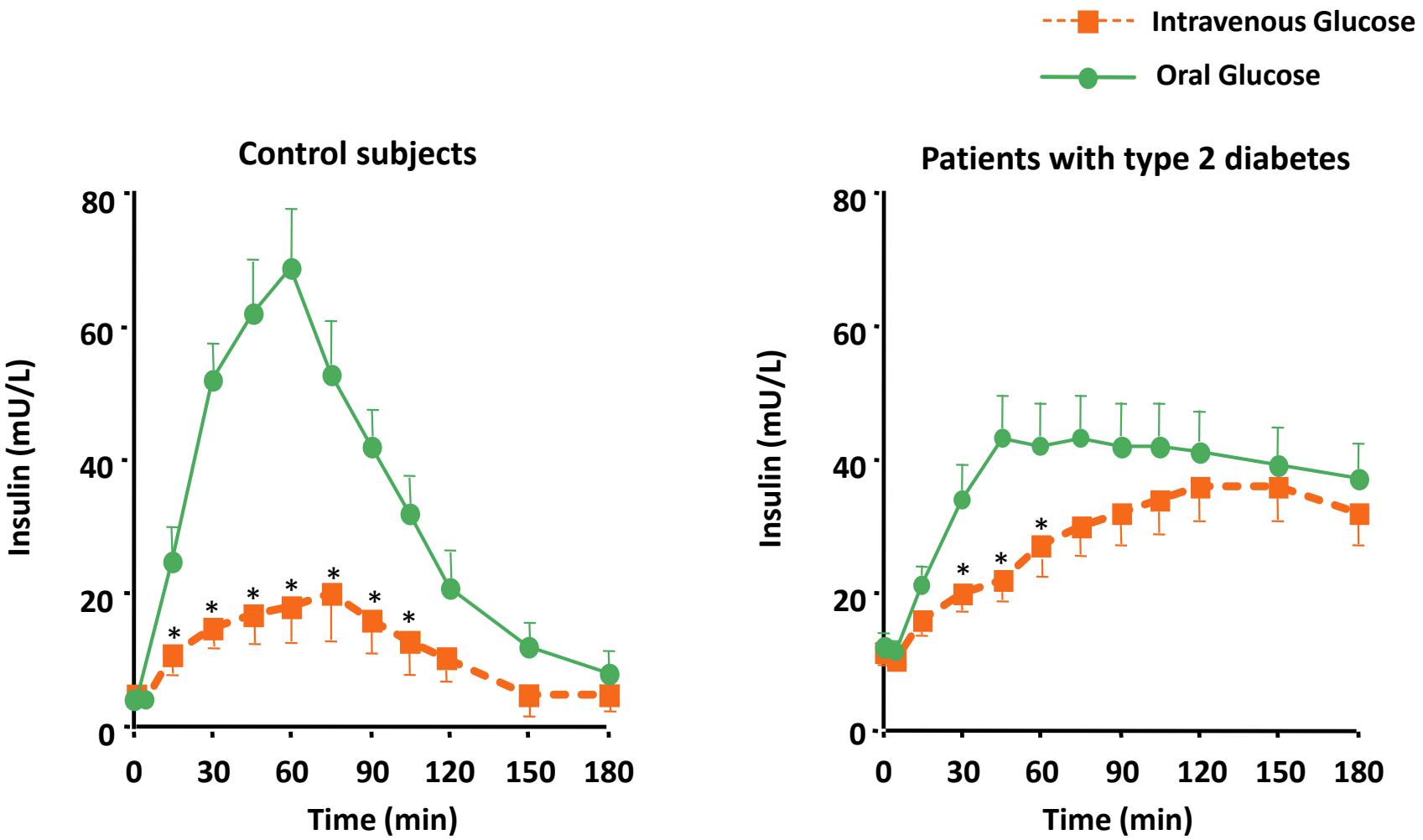
C-peptide (nmol/L)



Mean (SE); *$P \leq 0.05$

Data from Nauck MA, et al. *J Clin Endocrinol Metab* 1986;63:492–498. Plasma glucose values converted to mmol/L from mg/dL using conversion factor of 0.0555; C-peptide values converted to nmol/L from ng/mL using conversion factor 0.333.

The incretin effect is reduced in patients with type 2 diabetes



*$P \leq .05$ compared with respective value after oral load.
Nauck MA, et al. *Diabetologia* 1986;29:46–52.

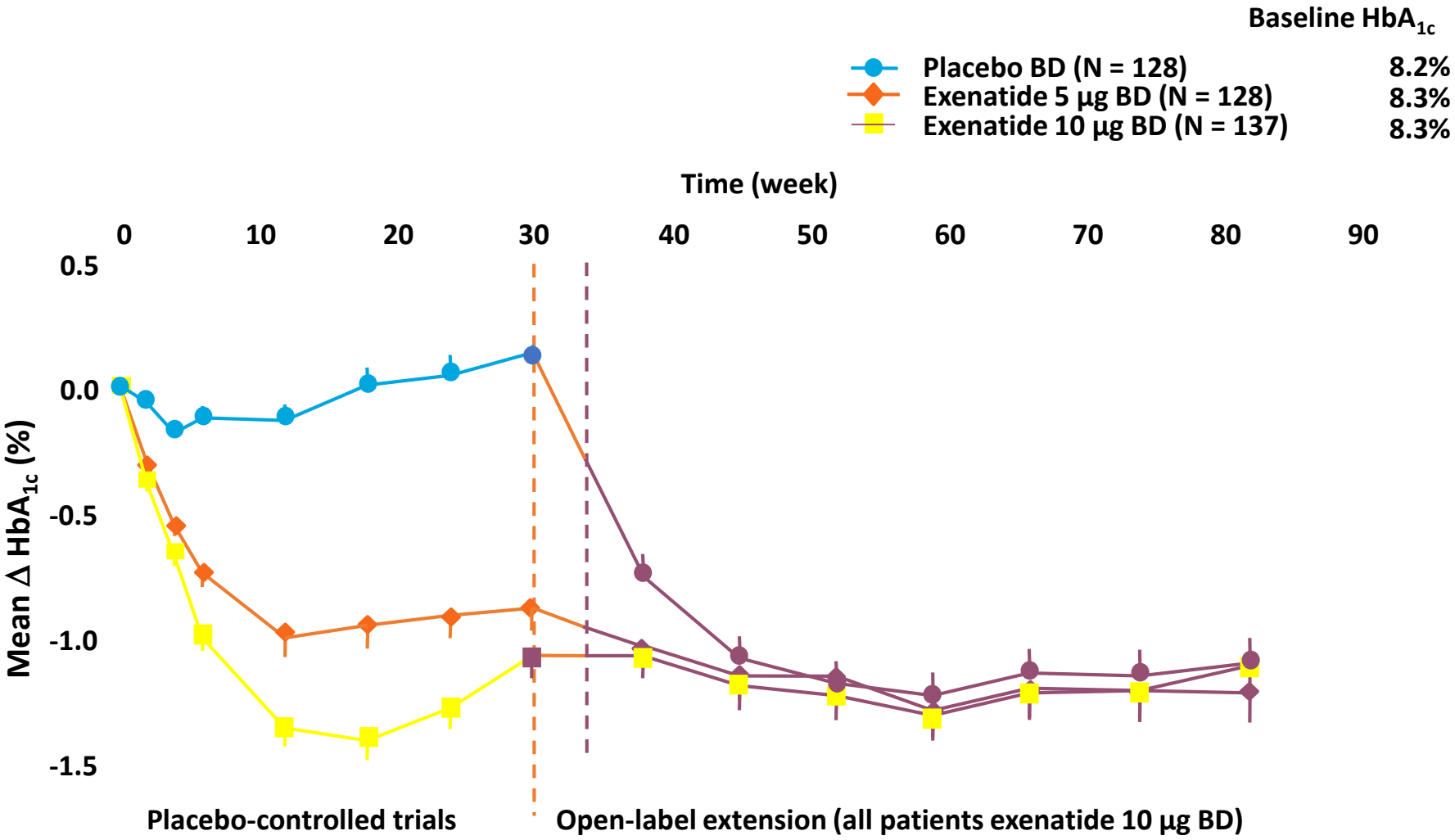
Different GLP1 agonists

Available in NZ (none funded)

- Exenatide bd
- Exenatide LAR (1x week)
- Liraglutide 3mg (for weight management)
- **Dulaglutide s/c**

- **International**
- Exenatide bd
- Exenatide LAR (1x week)
- Liraglutide 1.8 mg
- Liraglutide 3mg (for weight management)
- Semaglutide s/c and oral
- Lixisenatide s/c
- Dulaglutide s/c

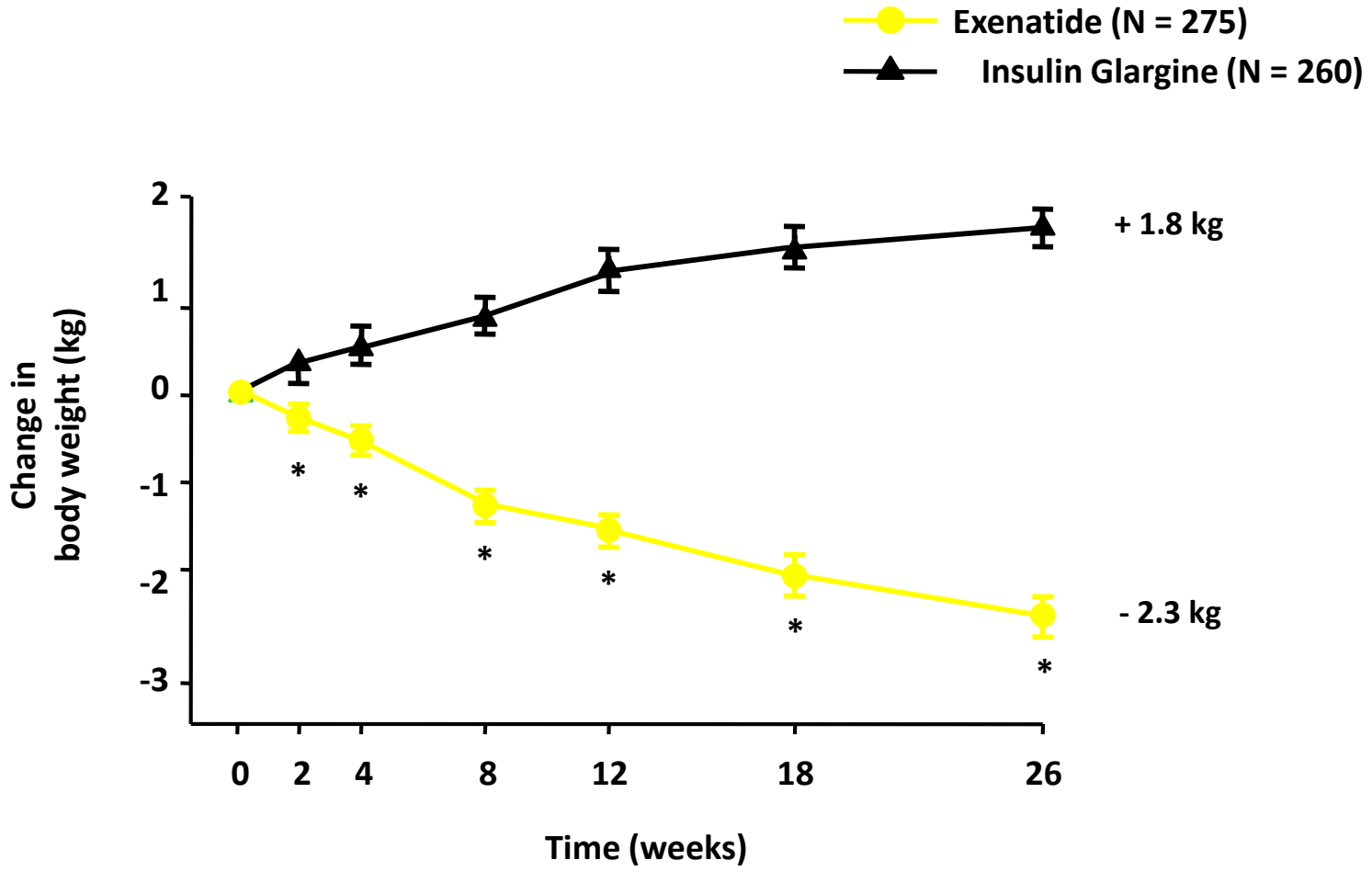
Open-label extension study – combined 82-week completers data. Exenatide sustained HbA_{1c} reductions



82-wk completers; Mean (SE)

Adapted from Blonde L, et al. Poster presented at the American **Diabetes Association Meeting 2005 (Abstract 477P)**

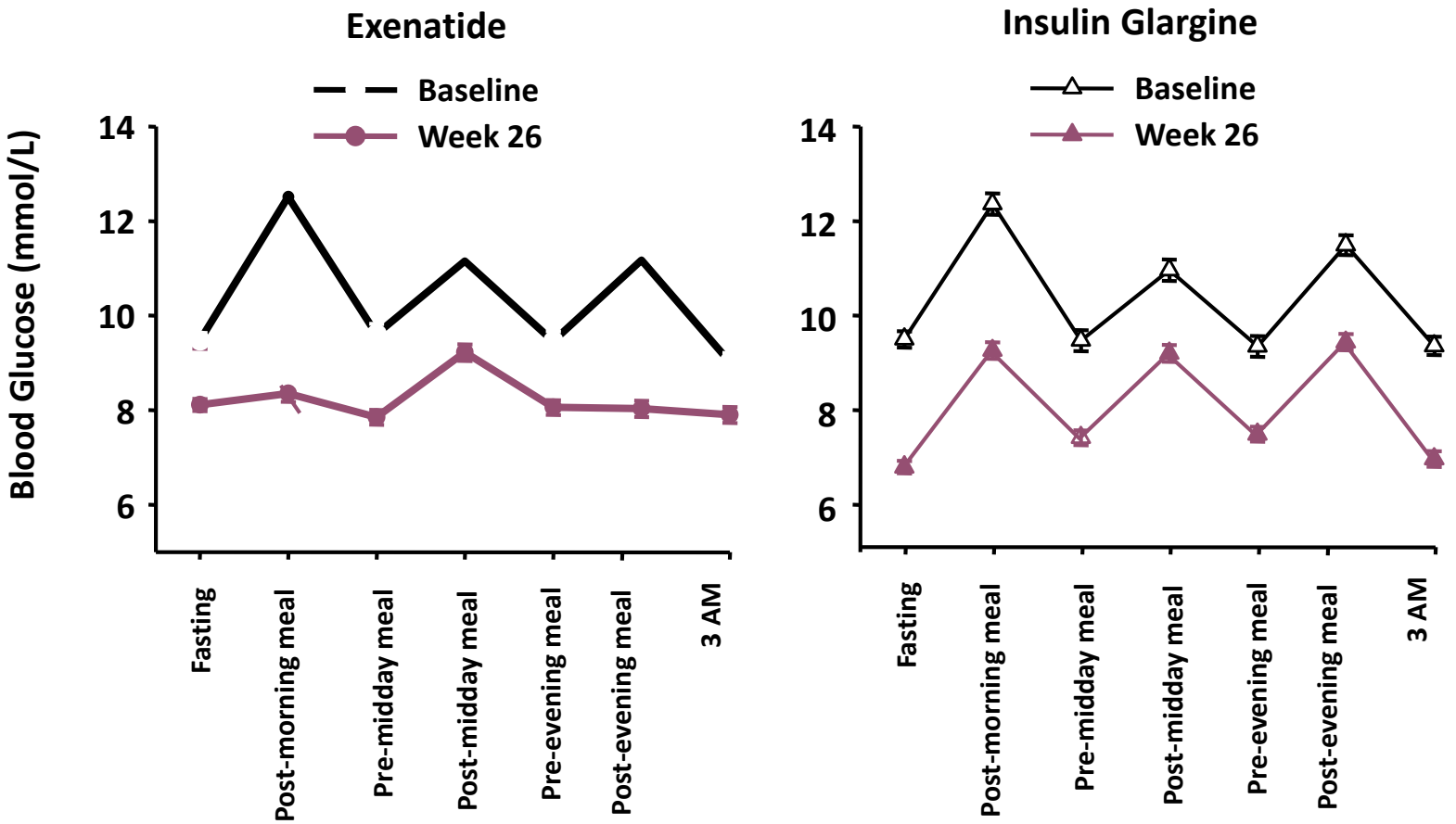
Change in body weight over time, ITT population



ITT population: exenatide (N = 275) insulin glargine (N = 260), Mean ± SD shown; * $P < 0.0001$, exenatide versus insulin glargine at same time point

Heine R, et al. *Ann Intern Med* 2005;143:559–569.

Exenatide Reduced Postprandial Glucose Excursions



Heine RJ, et al

GLP1 agonists – common side effects

	Placebo (N = 483)	Exenatide 5 µg and 10 µg BD (N = 963)
Nausea	**18%**	**44%**
Vomiting	**4%**	**13%**
Diarrhoea	**6%**	**13%**
Feeling jittery	**4%**	**9%**
Dizziness	**6%**	**9%**
Headache	**6%**	**9%**
Dyspepsia	**3%**	**6%**

Overall incidence ≥5% and incidence of Exenatide > placebo
BYETTA® (exenatide) US Prescribing Information, February 2007, data on file.

When to Use the GLP-1 RA Class[2,8]

CVD risk

(Heart attack, stroke, ischemic event)

or

HbA1c lowering

(HbA1c >8%)

or

Weight loss

Tailoring GLP-1 RA Therapy Based on Your Patient's Needs[8,9,11-13]

Exenatide QW	**Lowest rate of discontinuation due to GI AEs**
Liraglutide	**Most titratable**
Semaglutide SC	**Highest efficacy for weight loss**
Semaglutide PO	**Oral tablet with specific instructions**
Dulaglutide	**Easiest injection device to use**

Cardiovascular Outcomes Trials: GLP-1 RAs[6,7]

- All GLP-1 RAs show efficacy in HbA1c lowering and weight loss
- Reduction in MACE for liraglutide, dulaglutide, semaglutide SC
- CV mortality benefit for liraglutide and semaglutide PO
- Renal benefit for liraglutide, dulaglutide, semaglutide SC

The NEW ENGLAND JOURNAL of MEDICINE

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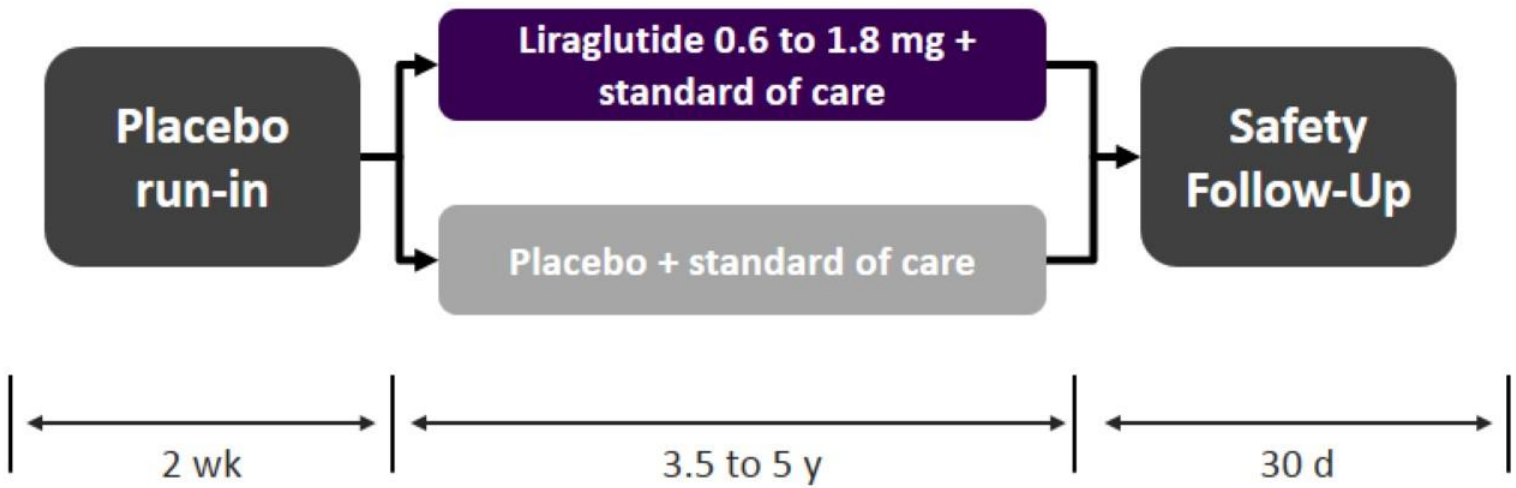
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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



Key inclusion criteria

- T2D, $HbA_{1c} \geq 7.0\%$
- Antidiabetic drug-naïve; OADs and/or basal/premix insulin
- Age ≥ 50 y and established CVD or chronic renal failure **OR**
- Age ≥ 60 y and risk factors for CVD

Key exclusion criteria

- T1D
- Use of GLP-1 RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familiar or personal history of MEN-2 or MTC

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

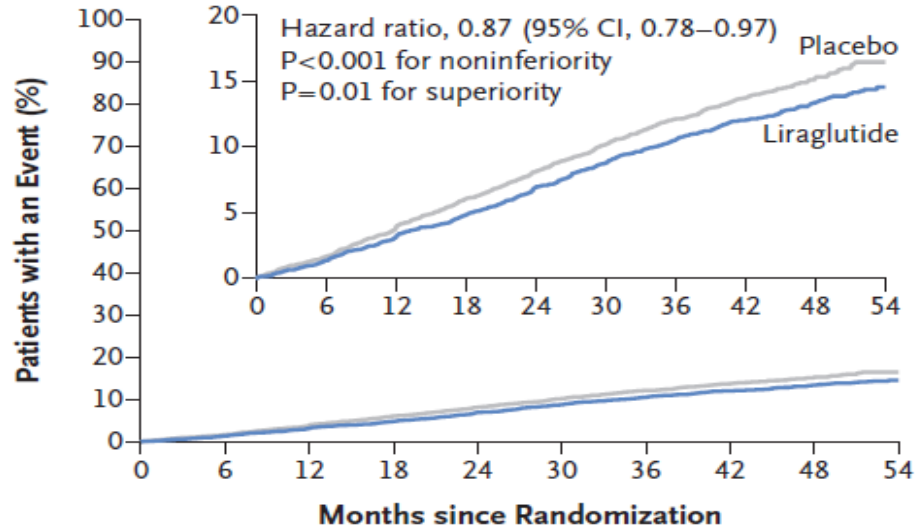
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

- **9340 patient type 2 diabetes and high cardiovascular risk** to receive liraglutide or placebo.
- The primary composite outcome - first occurrence of **death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.**

RESULTS

- The median follow-up was **3.8 years.**
- The **primary outcome** occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, **0.87;** 95% CI, **0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority)**
- Fewer patients **died from cardiovascular causes** in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, **0.78;** 95% CI, **0.66 to 0.93; P=0.007)**
- The rate of **death from any cause** was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, **0.85; 95% CI, 0.74 to 0.97; P=0.02)**
- The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events.

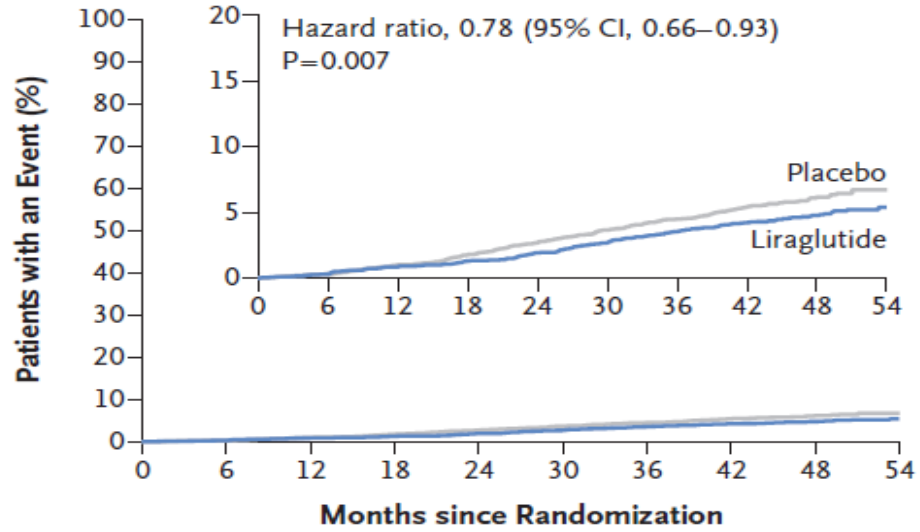
A Primary Outcome



No. at Risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

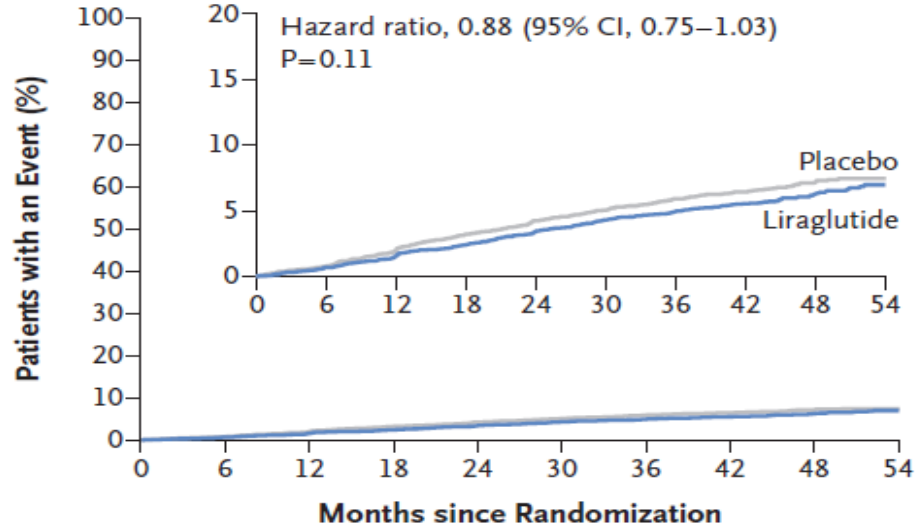
B Death from Cardiovascular Causes



No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

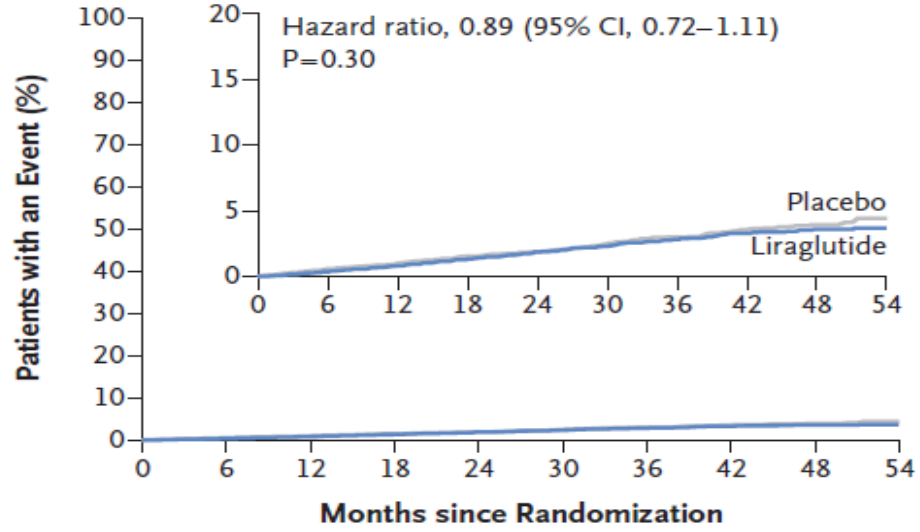
C Nonfatal Myocardial Infarction



No. at Risk

Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

D Nonfatal Stroke



No. at Risk

Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

Saxenda (Liraglutide 3mg s/c od)

- **SCALE trial programme**
  - Phase 3 SCALE
  - Scale obesity and pre-diabetes
  - SCALE OSA trial
  - SCALE Diabetes
  - SCALE Insulin

Licenced with MedSafe in 2020 for **treatment of obesity** (not DM)

- Liraglutide is a glucagon like peptide-1 (GLP-1) receptor agonist, marketed as **Saxenda® and Victoza®**
- Victoza® is a 1.8 mg daily subcutaneous injection of liraglutide that was approved by the FDA in 2010 for management of type 2 diabetes

first major phase III trial to study (Lancet 2009)

- compared four different doses of liraglutide (1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg once daily) with placebo and open-label **orlistat** (120 mg tds)
- The primary endpoint was change in body weight among the intention-to-treat (ITT) population at the end of 20 weeks
- The estimated mean weight loss in the ITT population was significantly greater with all doses of liraglutide as compared with placebo (**4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg** for liraglutide **1.2 mg, 1.8 mg, 2.8 mg, and 3.0 mg**, respectively vs. **2.8 kg for placebo**; $p < 0.01$ for all doses)

- Psychiatric disorders were slightly more frequent and mean pulse rate was slightly increased with liraglutide treatment as compared to placebo and orlistat.

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

*Hertzel C Gerstein, Helen M Colhoun, Gilles R Dagenais, Rafael Diaz, Mark Lakshmanan, Prem Pais, Jeffrey Probstfield, Jeffrey S Riesmeyer, Matthew C Riddle, Lars Rydén, Denis Xavier, Charles Messan Atisso, Leanne Dyal, Stephanie Hall, Purnima Rao-Melacini, Gloria Wong, Alvaro Avezum, Jan Basile, Namsik Chung, Ignacio Conget, William C Cushman, Edward Franek, Nicolae Hancu, Markolf Hanefeld, Shaun Holt, Petr Jansky, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Ernesto German Cardona Munoz, Valdis Pirags, Nana Pogosova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev, for the REWIND Investigators**

Lancet 2019; 394: 121–30

Published Online
June 10, 2019
http://dx.doi.org/10.1016/S0140-6736(19)31149-3

Methods This multicentre, randomised, double-blind, placebo-controlled trial was done at 371 sites in 24 countries. Men and women aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo.

Dulaglutide and cardiovascular outcomes in type 2 diabetes **(REWIND):** a double-blind, randomised placebo-controlled trial

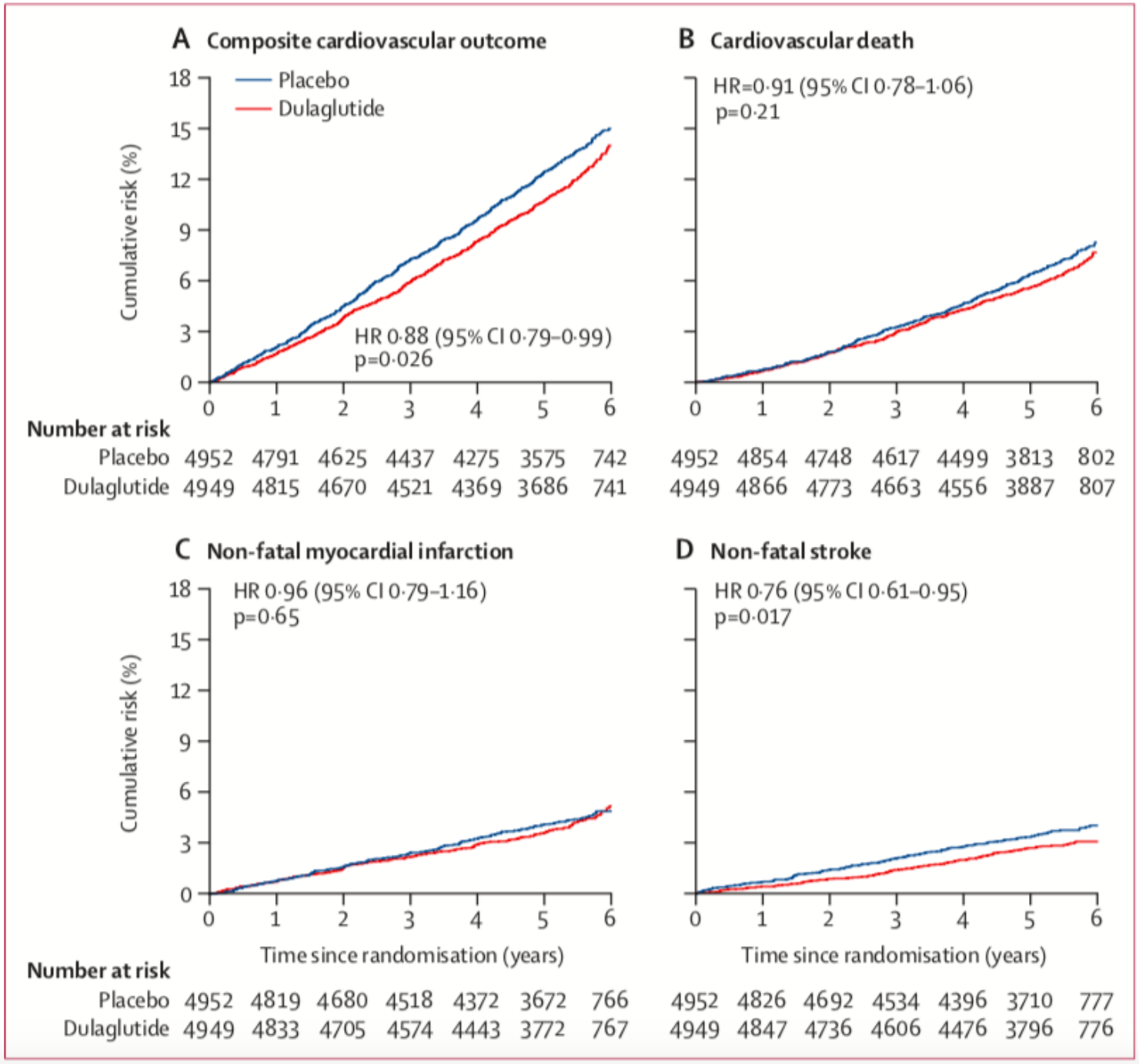
- primary outcome was the first occurrence of the **composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes** (including unknown causes), which was assessed in the intention-to-treat population.

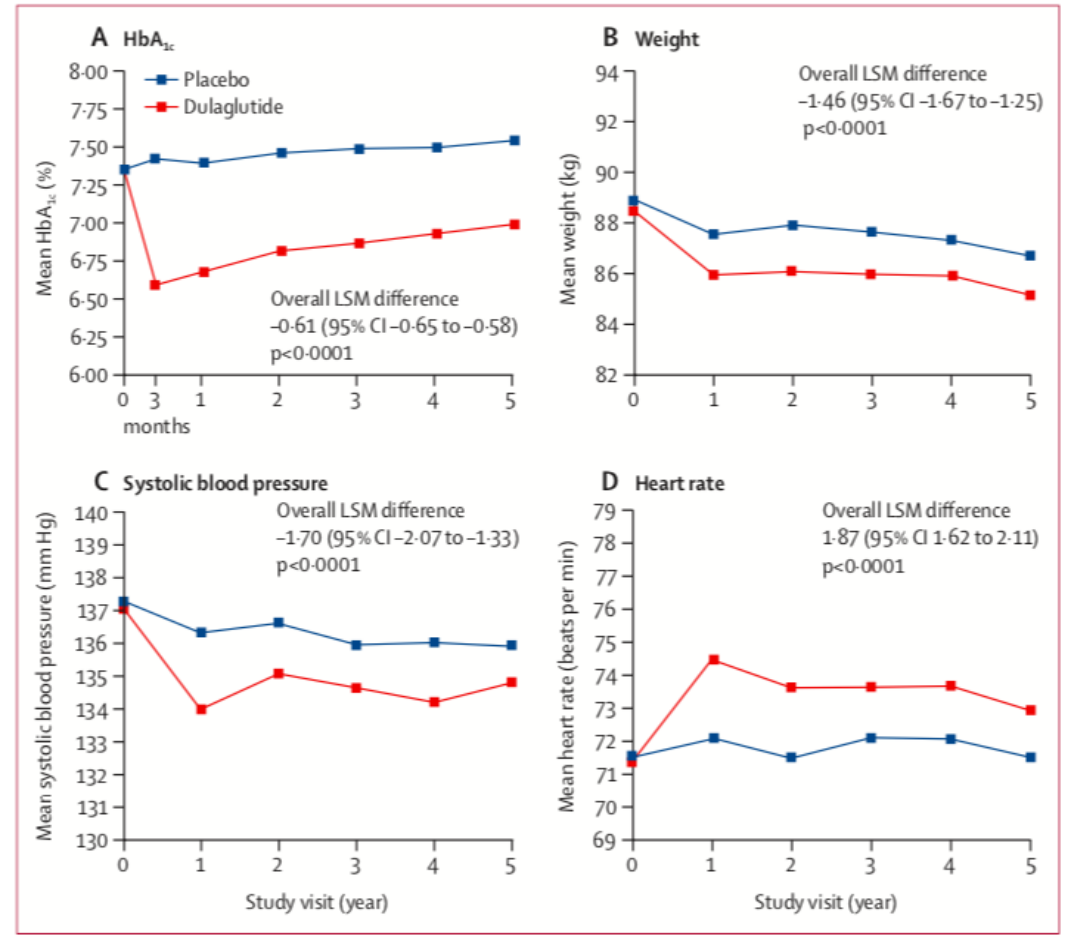
- 9901 participants (mean age 66·2 years [SD 6·5], median HbA_{1c} 7·2% [IQR 6·6–8·1]

- During a **median follow-up of 5·4 years** (IQR 5·1–5·9), the primary composite outcome occurred in **594** (12·0%) participants in the dulaglutide group and in **663** (13·4%) participants in the placebo group (hazard ratio [HR] **0·88, 95% CI 0·79–0·99; p=0·026)**

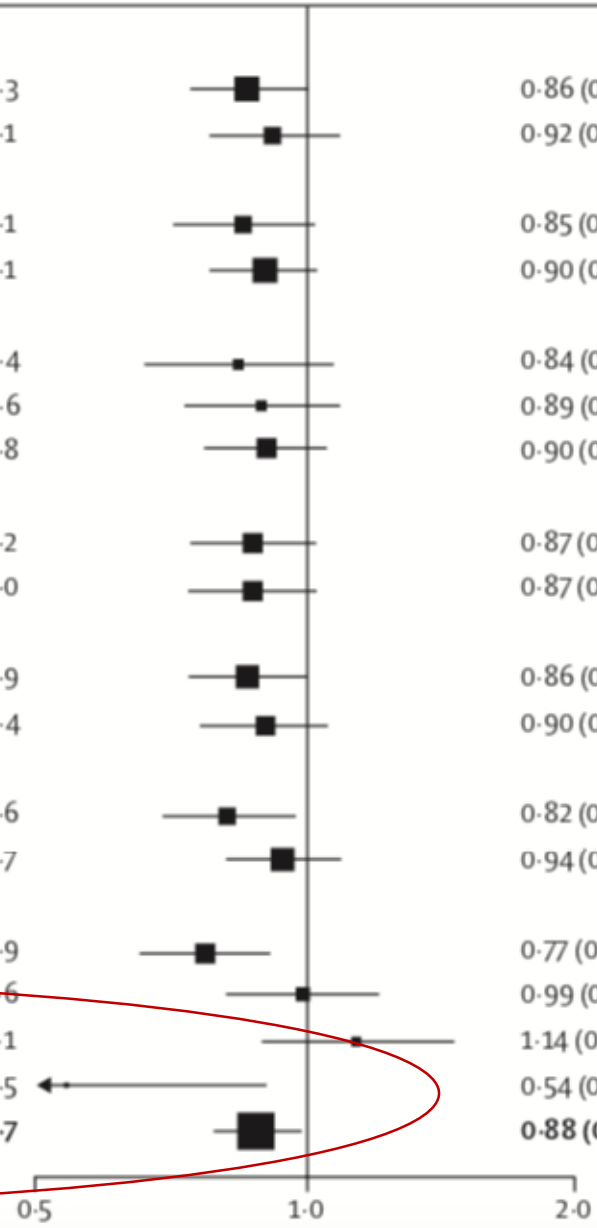
- **All-cause mortality did not differ between groups** (HR 95% CI 0·80–1·01; p=0·067)

- 2347 (47·4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34·1%) participants assigned to placebo (p<0·0001)


A Composite cardiovascular outcome
Placebo
Dulaglutide
Cumulative risk (%)
HR 0·88 (95% CI 0·79–0·99)
p=0·026
B Cardiovascular death
HR=0·91 (95% CI 0·78–1·06)
p=0·21
Number at risk
Placebo 4952 4791 4625 4437 4275 3575 742
Dulaglutide 4949 4815 4670 4521 4369 3686 741
4952 4854 4748 4617 4499 3813 802
4949 4866 4773 4663 4556 3887 807
C Non-fatal myocardial infarction
HR 0·96 (95% CI 0·79–1·16)
p=0·65
D Non-fatal stroke
HR 0·76 (95% CI 0·61–0·95)
p=0·017
Time since randomisation (years)
Number at risk
Placebo 4952 4819 4680 4518 4372 3672 766
Dulaglutide 4949 4833 4705 4574 4443 3772 767
4952 4826 4692 4534 4396 3710 777
4949 4847 4736 4606 4476 3796 776


A HbA1c
Placebo
Dulaglutide
Mean HbA1c (%)
Overall LSM difference
−0·61 (95% CI −0·65 to −0·58)
p<0·0001
months
B Weight
Overall LSM difference
−1·46 (95% CI −1·67 to −1·25)
p<0·0001
Mean weight (kg)
C Systolic blood pressure
Overall LSM difference
−1·70 (95% CI −2·07 to −1·33)
p<0·0001
Mean systolic blood pressure (mm Hg)
Study visit (year)
D Heart rate
Overall LSM difference
1·87 (95% CI 1·62 to 2·11)
p<0·0001
Mean heart rate (beats per min)
Study visit (year)

	Dulaglutide		Placebo		Hazard ratio (95% CI)	$p_{interaction}$
	Events/patients (%)	Incidence (per 100 person-years)	Events/patients (%)	Incidence (per 100 person-years)		
Age (years)						0·57
≥66	331/2314 (14·3%)	2·9	384/2350 (16·3%)	3·3	0·86 (0·74–1·00)	
<66	263/2635 (10·0%)	1·9	279/2602 (10·7%)	2·1	0·92 (0·78–1·09)	
Sex						0·60
Female	218/2306 (9·5%)	1·8	249/2283 (10·9%)	2·1	0·85 (0·71–1·02)	
Male	376/2643 (14·2%)	2·8	414/2669 (15·5%)	3·1	0·90 (0·79–1·04)	
Duration of diabetes (years)						0·88
<5	128/1227 (10·4%)	2·0	146/1192 (12·2%)	2·4	0·84 (0·66–1·06)	
5–10	174/1446 (12·0%)	2·3	196/1476 (13·3%)	2·6	0·89 (0·73–1·09)	
≥10	292/2276 (12·8%)	2·5	321/2284 (14·1%)	2·8	0·90 (0·77–1·06)	
History of cardiovascular disease*						0·97
Yes	280/1560 (17·9%)	3·7	315/1554 (20·3%)	4·2	0·87 (0·74–1·02)	
No	277/3093 (8·9%)	1·7	317/3128 (10·1%)	2·0	0·87 (0·74–1·02)	
Baseline HbA_{1c}*						0·75
≥7·2%	328/2610 (12·6%)	2·5	373/2603 (14·3%)	2·9	0·86 (0·74–1·00)	
<7·2%	263/2329 (11·3%)	2·2	289/2334 (12·4%)	2·4	0·90 (0·76–1·06)	
BMI (kg/m^2)						0·21
≥32	254/2281 (11·1%)	2·1	308/2302 (13·4%)	2·6	0·82 (0·69–0·96)	
<32	340/2667 (12·7%)	2·5	355/2650 (13·4%)	2·7	0·94 (0·81–1·09)	
Region						0·0080
Europe	248/2174 (11·4%)	2·2	315/2165 (14·5%)	2·9	0·77 (0·65–0·90)	
Latin America	191/1511 (12·6%)	2·6	190/1510 (12·6%)	2·6	0·99 (0·81–1·21)	
USA and Canada	132/1032 (12·8%)	2·4	117/1039 (11·3%)	2·1	1·14 (0·89–1·47)	
Asia Pacific	23/232 (9·9%)	1·9	41/238 (17·2%)	3·5	0·54 (0·32–0·89)	
Overall	**594/4949 (12·0%)**	**2·4**	**663/4952 (13·4%)**	**2·7**	**0·88 (0·79–0·99)**	**NA**



AUSTRALIAN PRODUCT INFORMATION – TRULICITY (DULAGLUTIDE RCH) AUTOINJECTOR

HOW TO USE IT?

1. As monotherapy OR in combination with other glucose-lowering medicinal products including insulin
2. To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have:
   - established cardiovascular disease or
   - multiple cardiovascular risk factors

- INCLUSIONS
  - No dose adjustment is required for mild, moderate and severe renal impairment (eGFR> 15ml/min)
  - No dose adjustment is required based on age (not for <18 years)
  - No dose adjustment is required based on hepatic impairment.
- CONTRAINDICATIONS
  - Significant gastrointestinal disease (do not use in patients with gastroparesis)
  - Not for patents at risk of pancreatitis (previous pancreatitis, alcohol, high TG)
  - Not in pregnancy and lactation
  - Type 1 diabetes and DKA

Adverse Reaction	Dulaglutide 1.5 mg N=834	Placebo N=568
Nausea	21.1%	5.3%
Vomiting[a]	12.7%	2.3%
Diarrhoea[b]	12.6%	6.7%
Abdominal Pain[c]	9.4%	4.9%
Decreased Appetite	8.6%	1.6%
Dyspepsia	5.8%	2.3%
Fatigue[d]	5.6%	2.6%

Hypoglycaemia risk

- Increased when used with insulin or SU

Tachycardia /AF

- HR 2-4bpm increased
- AF (low risk 1.9%)

Table 3. Summary of Efficacy Results from Dulaglutide Phase 3 studies (Intention to Treat)

	Study	N	HbA1c (%)		Change FBG (mmol/L)	%Patients at target <7.0%	Change body weight (kg)
			Change	Endpoint			
Monotherapy Study H9X-MC-GBDC							
Primary Time Point 26 weeks	Dulaglutide 1.5 mg	269	-0.78††	6.81††	-1.61	61.5#	-2.29
	Metformin	268	-0.56	7.03	-1.34	53.6	-2.22
Final Time Point 52 weeks	Dulaglutide 1.5 mg	269	-0.70††	6.89††	-1.56#	60.0#	-1.93
	Metformin	268	-0.51	7.08	-1.15	48.3	-2.20
Add on to metformin Study H9X-MC-GBCF							
Primary Time Point 52 weeks	Dulaglutide 1.5 mg	304	-1.10††	7.02††	-2.38##	57.6##	-3.03##
	Sitagliptin	315	-0.39	7.73	-0.90	33.0	-1.53
Final Time Point 104 weeks	Dulaglutide 1.5 mg	304	-0.99††	7.13††	-1.99##	54.3##	-2.88##
	Sitagliptin	315	-0.32	7.80	-0.47	31.1	-1.75
Add on to metformin & TZD Study H9X-MC-GBDA							
Primary Time Point 26 weeks	Dulaglutide 1.5 mg	279	-1.51‡‡,††	6.55‡‡,††	-2.36**,##	78.2**,##	-1.30**
	Placebo	141	-0.46	7.44	-0.26	42.9	1.24
	Exenatide BID	276	-0.99**	7.05**	-1.35**	52.3*	-1.07**
Final Time Point 52 weeks	Dulaglutide 1.5 mg	279	-1.36††	6.66††	-2.04##	70.8##	-1.10
	Exenatide BID	276	-0.80	7.23	-1.03	49.2	-0.80

	Add on to insulin lispro ± metformin Study H9X-MC-GBDD						
Primary Time Point 26 weeks	Dulaglutide 1.5 mg	295	-1.64††	6.83††	-0.27##	67.6#	-0.87##
	Insulin glargine	296	-1.41	7.05	-1.58	56.8	2.33
Final Time Point 52 weeks	Dulaglutide 1.5 mg	295	-1.48††	6.99††	0.08##	58.5#	-0.35##
	Insulin glargine	296	-1.23	7.23	-1.01	49.3	2.89

The ideal patient

- Has established CV disease or CV risk factors (REWIND)
- Has established renal disease (slows progression and reduces MAU)
- Is established on MF (minimal difference compared to MF alone)
- Ideally is also already on other oral DM medications (SU, Pio, SGLT2)
- Greatest benefit if already on prandial insulin (see data sheet)
- Has higher BMI (>30kg/m2)
- Lives in Oceania (i.e. NZ) - REWIND

- REMEMBER TO STOP VILDAGLIPTIN !!

How to Initiate GLP-1 RAs

Starting a GLP-1 RA[8,9]

- Dose up slowly and titrate down in cases of more severe nausea or vomiting
- Consider reducing doses of other drugs associated with GI adverse events
- Antiemetics can be of benefit (anecdotal)

Other AEs include injection-site reactions, headache, and nasopharyngitis[10]

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/ OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target			
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia[7]

COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/ OR

- GLP-1 RA with good efficacy for weight loss[8]
- SGLT2i[2]

If HbA_{1c} above target

SGLT2i[2]	GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} above target

If triple 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[6]
- TZD[5]
- Basal insulin

COST IS A MAJOR ISSUE[9–10]

SU[6]	TZD[10]
If HbA_{1c} above target	
TZD[10]	SU[6]

If HbA_{1c} above target

- **Insulin therapy** basal insulin with lowest acquisition cost

OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower