"Future Therapies Now"

ADA/EASD consensus statement 2022

SGLT2i's and GLP-1 RA's & beyond

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Declarations of interest

Sponsorship EASD NOVO

Speaker Novo and AstraZeneca

ADA/EASD consensus statement 2022 – what is new

- Updated algorithm in the use of glucose lowering Rx and lifestyle and type 2 diabetes management
- Treatment recommendations focus on SGLT2i and GLP-1RA independent of metformin use
- Achieving & maintaining glycaemic control and weight management goals focusing equally on drug efficacy and lifestyle benefits
- SGLT2i & GLP-1RA’s offer organ protection due to their cardio-renal benefits

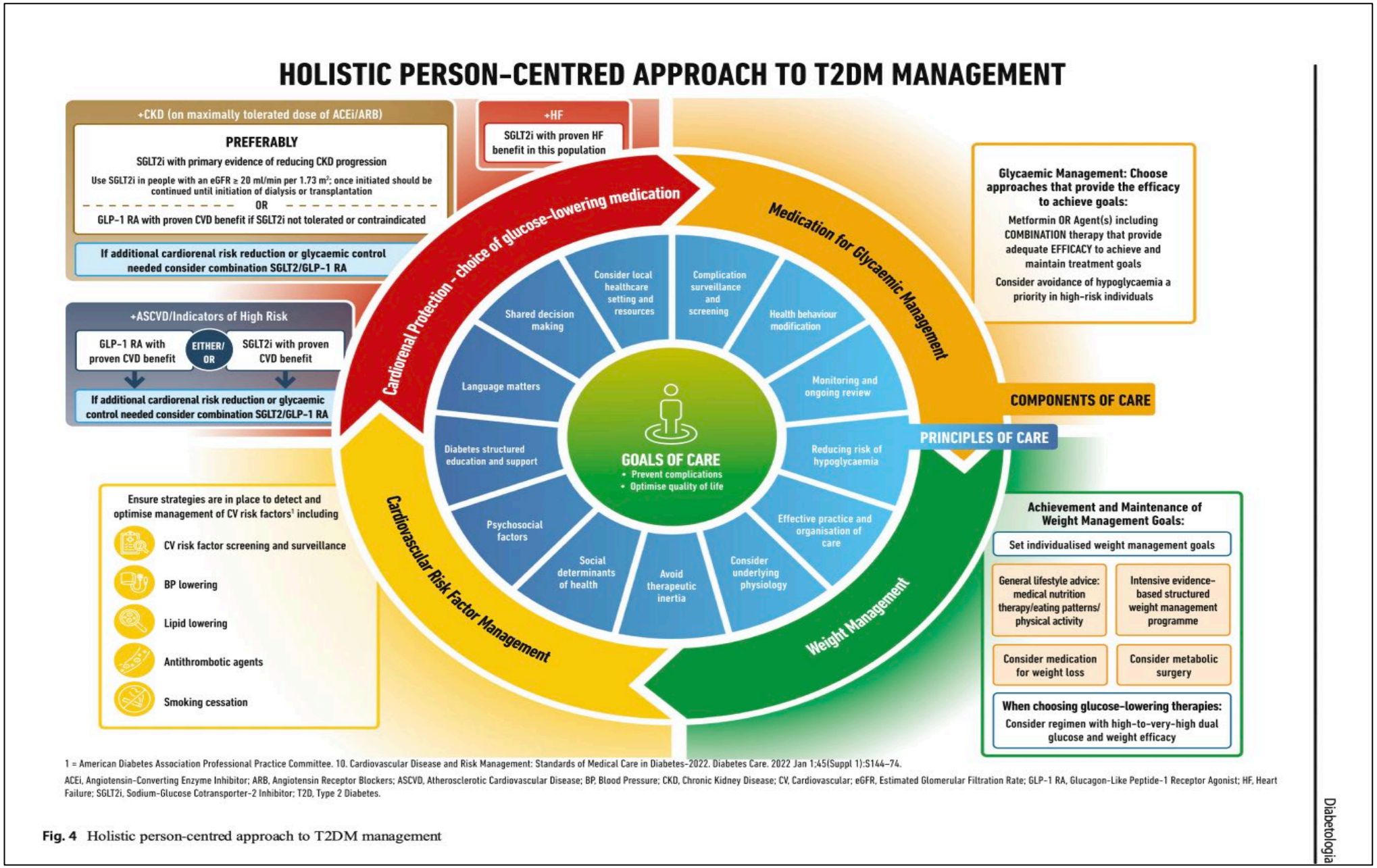
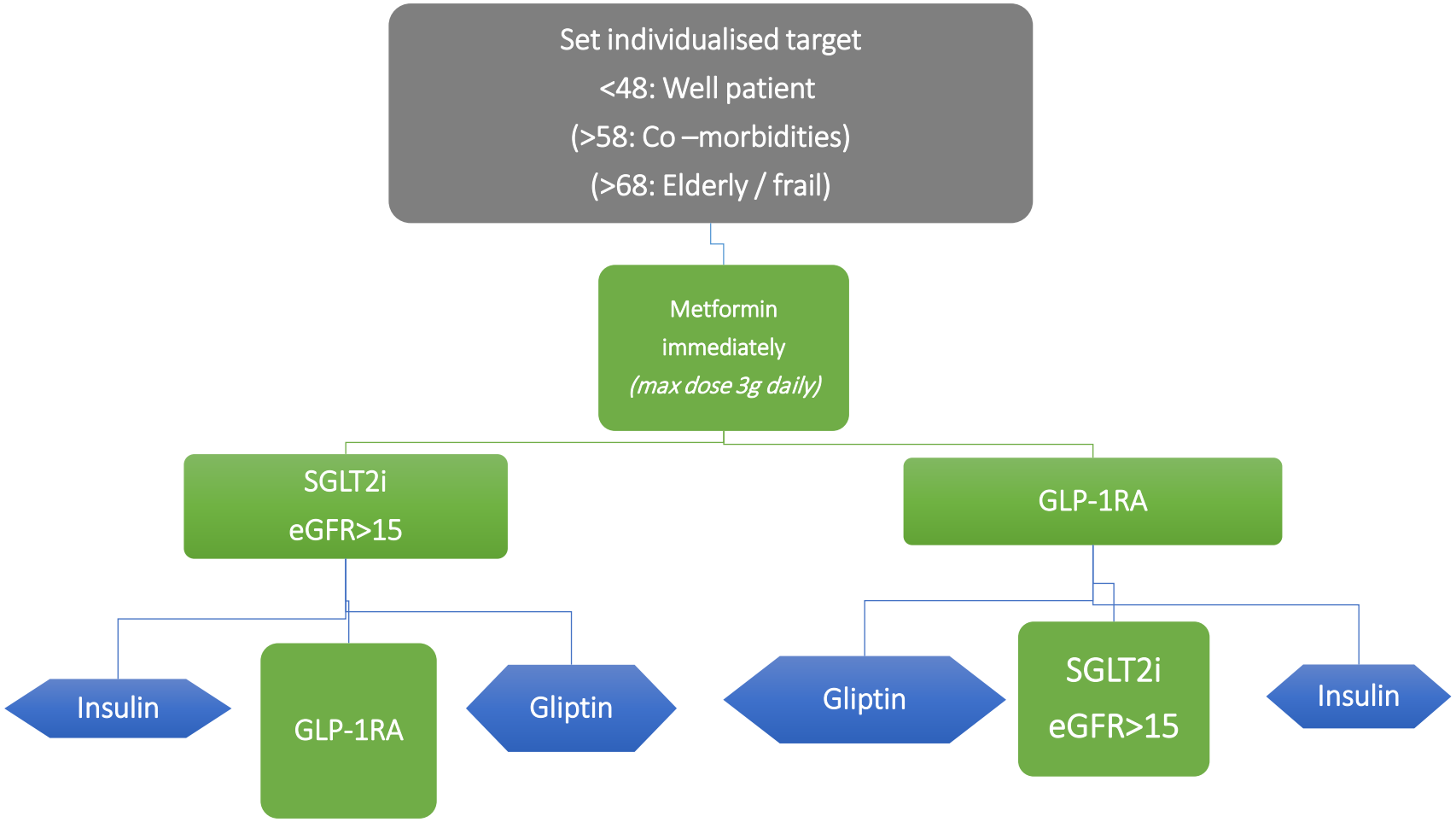


Fig. 4 Holistic person-centred approach to T2DM management

https://diabetologia-journal.org/wp-content/uploads/2022/09/ADAEASDConsensusReport.pdf

Simplified abbreviated algorithm of ADA/EASD consensus statement 2022 for T2DM management



Practical tips for clinicians

- Initial combination therapy with glucose lowering Rx if high HbA1c at diagnosis (>70)[1]
- Initial combination therapy in younger people with T2DM regardless of HbA1c[1]
- If additional glycaemic control is needed incorporate rather than substitute Rx
- Considered de- intensification of Rx in frail older adults & with hypoglycaemic Rx[1]

1. ADA/EASD consensus statement October 2022

Therapeutic Inertia

- Includes failure to intensify management & when people are over treated
- Causes are multifactorial
- Average time to intensification 3 years[1]
- Average delay to starting insulin 7.1years [2]

1.KUNTI ET AL L . DIABETES OBES METAB 2018 20 389-399
2 .KUNTI ET AL. DIABETES CARE 2013 36 3411-3417.

Rationale for new diabetes drugs

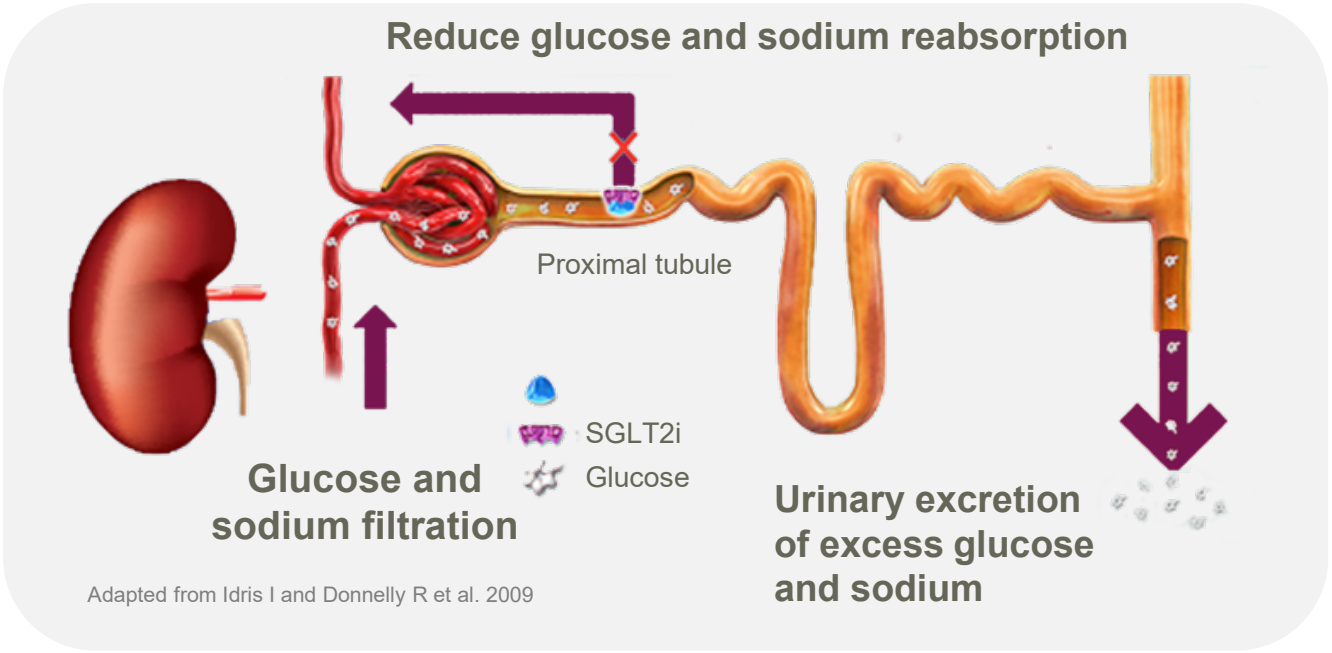
- Both SGLT2i and GLP-1RA injectables improve diabetes control, reduce weight, reduce MACE, improve outcomes in heart failure and CKD[1]
- Finerenone improve CKD outcomes and MACE[2]
- Oral GLP-1RA semaglutide improved diabetes control, reduces weight however MACE outcomes still awaited

1.Giugliano et al Cardiovascular Diabetology 20 189 2021

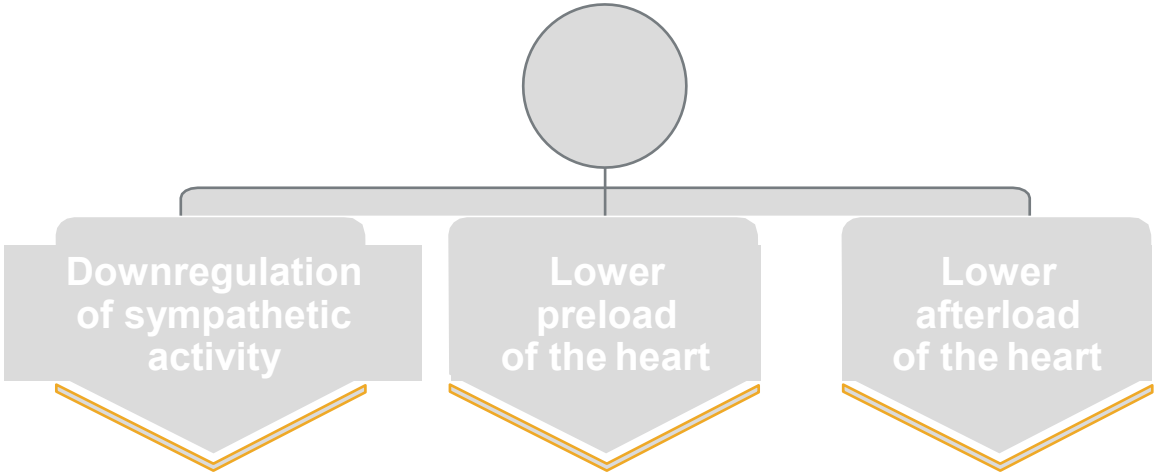
2.Bakris et al NEJM 2020 383 2219-2229 (FIDELIO-DKD)

SGLT2i

Mechanism of action of SGLT2i



SGLT2i *may* influence several physiological functions that can improve heart failure outcomes[2,3]



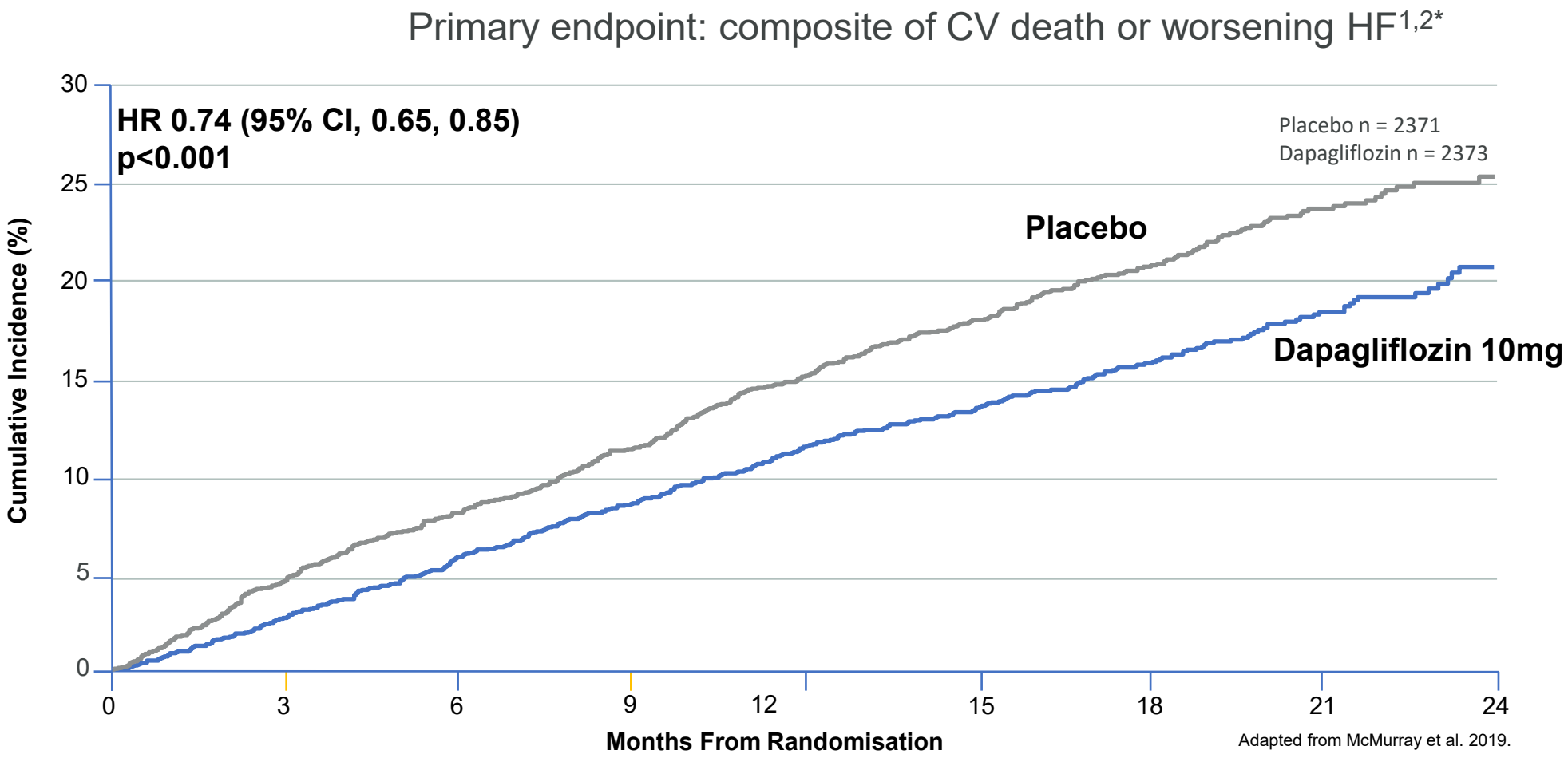
Glycaemic efficacy of SGLT2i's is dependent on renal function[2]

The cardiovascular and mortality benefits of SGLT2i may not be solely dependent on glucose-lowering and are independent of renal function[2,4,5*]

1. Idris I and Donnelly R. Diabetes Obes Metab. 2009;11:79-88.
2. Forxiga 10mg film-coated tablets. Summary of Product Characteristics. September 2022.
3. McMurray JJV, et al. N Engl J Med. 2019;381:1995-2008.
4. Docherty KF, et al. Eur Heart J. 2020;41:2379-2392.
5. Jhund PS et al. Circulation. 2021;143(4):298-309.

*DAPA-HF demonstrated that the benefit of dapagliflozin occurred in patients both with and without diabetes, suggesting that this benefit is independent of any glucose-lowering effect.

In patients with HFrEF, with and without T2DM



26% RRR

4.9% ARR

NNT=21

Risk reduction seen by **28 DAYS**[2]

HR 0.51 (95% CI, 0.28, 0.94) p=0.03

*

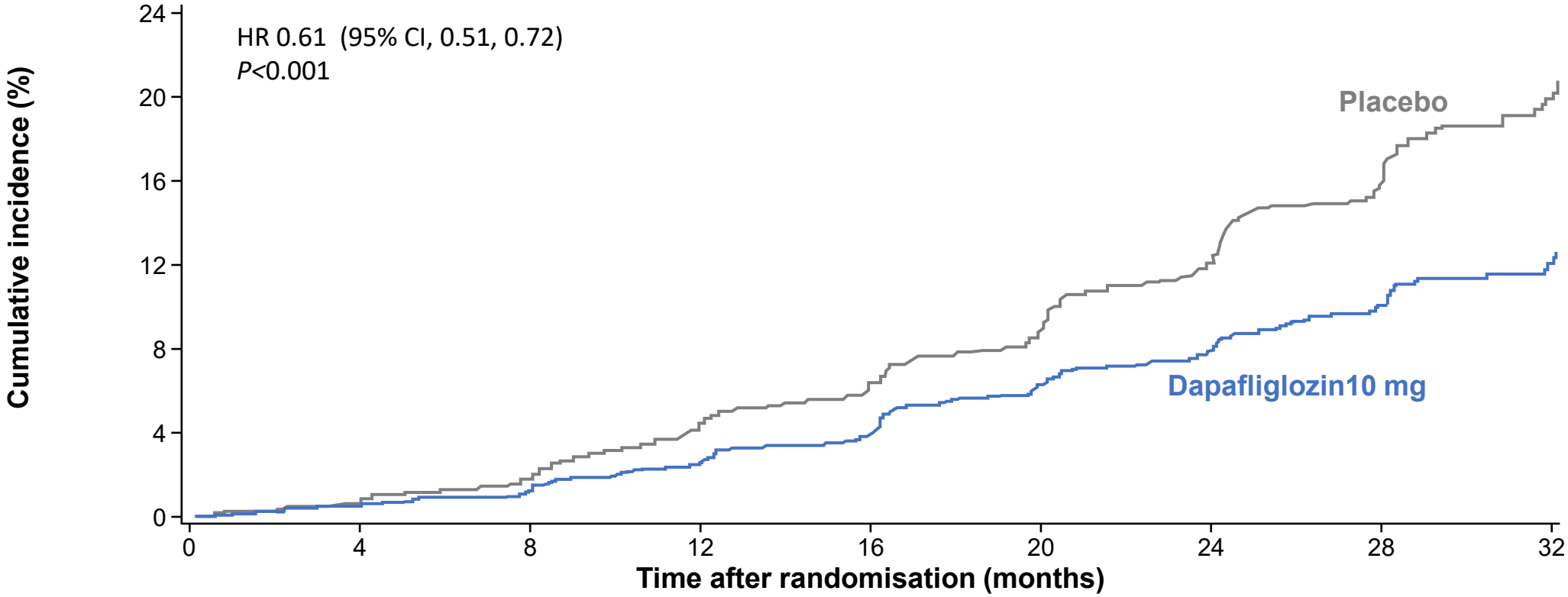
*Worsening HF is defined as hHF or urgent HF visit requiring IV therapy.

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hHF, hospitalisation for heart failure; HR, hazard ratio; IV, intravenous; NNT, number needed to treat; RRR, relative risk reduction; T2D, type 2 diabetes.

References: 1. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008. 2. Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

Dapagliflozin protects your patients with CKD by reducing the risk of declining kidney function (≥50% sustained decline in eGFR), ESKD, and renal or CV death vs placebo[1,2]

DAPA-CKD primary composite endpoint: declining kidney function (≥50% sustained decline in eGFR), ESKD, and renal or CV death vs placebo[1,a]



Median follow-up of 2.4 years

39% RRR

5.3% ARR*

NNT=19

Adapted from Heerspink HJL et al 2020

No. at risk									
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
FORXIGA	2152	2001	1955	1898	1841	1701	1288	831	309

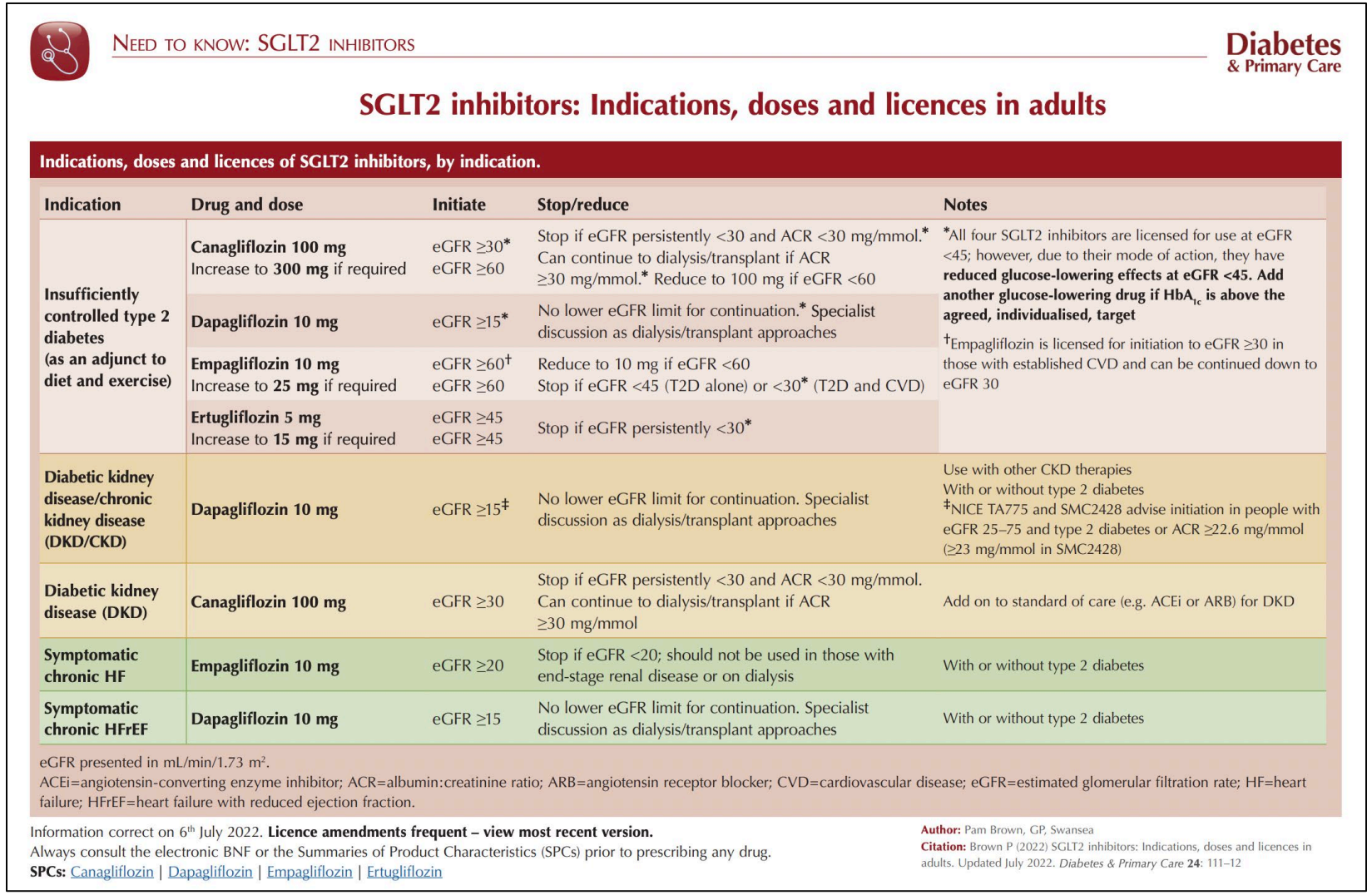
[a]Primary composite endpoint of ≥50% sustained decline in eGFR, reaching ESKD, and CV or renal death. ESKD defined as the need for maintenance dialysis (peritoneal or haemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15 mL/min/1.73 m^2 for at least 28 days. Kidney death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.

*The primary composite outcome occurred in 197 patients (9.2%) in the Forxiga group and in 312 patients (14.5%) in the placebo group.

ARR, absolute risk reduction; CI confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction

1. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446; 2. AstraZeneca AB. FORXIGA (dapagliflozin) SmPC. Available at: https://www.medicines.org.uk/emc/product/7607/smpc#gref (Accessed September 2022).
2. Heerspink HJL, et .al. Nephrol Dial Transplant 2020;35:274–282

Helpful resource (Dr Pam Brown)



NEED TO KNOW: SGLT2 INHIBITORS

Diabetes & Primary Care

SGLT2 inhibitors: Indications, doses and licences in adults

Indications, doses and licences of SGLT2 inhibitors, by indication.

Indication	Drug and dose	Initiate	Stop/reduce	Notes
Insufficiently controlled type 2 diabetes (as an adjunct to diet and exercise)	**Canagliflozin 100 mg** Increase to **300 mg** if required	eGFR ≥30* eGFR ≥60	Stop if eGFR persistently <30 and ACR <30 mg/mmol.* Can continue to dialysis/transplant if ACR ≥30 mg/mmol.* Reduce to 100 mg if eGFR <60	*All four SGLT2 inhibitors are licensed for use at eGFR <45; however, due to their mode of action, they have **reduced glucose-lowering effects at eGFR <45. Add another glucose-lowering drug if HbA_{1c} is above the agreed, individualised, target** †Empagliflozin is licensed for initiation to eGFR ≥30 in those with established CVD and can be continued down to eGFR 30
	Dapagliflozin 10 mg	eGFR ≥15*	No lower eGFR limit for continuation.* Specialist discussion as dialysis/transplant approaches	
	Empagliflozin 10 mg Increase to **25 mg** if required	eGFR ≥60† eGFR ≥60	Reduce to 10 mg if eGFR <60 Stop if eGFR <45 (T2D alone) or <30* (T2D and CVD)	
	Ertugliflozin 5 mg Increase to **15 mg** if required	eGFR ≥45 eGFR ≥45	Stop if eGFR persistently <30*	
Diabetic kidney disease/chronic kidney disease (DKD/CKD)	**Dapagliflozin 10 mg**	eGFR ≥15‡	No lower eGFR limit for continuation. Specialist discussion as dialysis/transplant approaches	Use with other CKD therapies With or without type 2 diabetes ‡NICE TA775 and SMC2428 advise initiation in people with eGFR 25–75 and type 2 diabetes or ACR ≥22.6 mg/mmol (≥23 mg/mmol in SMC2428)
Diabetic kidney disease (DKD)	**Canagliflozin 100 mg**	eGFR ≥30	Stop if eGFR persistently <30 and ACR <30 mg/mmol. Can continue to dialysis/transplant if ACR ≥30 mg/mmol	Add on to standard of care (e.g. ACEi or ARB) for DKD
Symptomatic chronic HF	**Empagliflozin 10 mg**	eGFR ≥20	Stop if eGFR <20; should not be used in those with end-stage renal disease or on dialysis	With or without type 2 diabetes
Symptomatic chronic HFrEF	**Dapagliflozin 10 mg**	eGFR ≥15	No lower eGFR limit for continuation. Specialist discussion as dialysis/transplant approaches	With or without type 2 diabetes

eGFR presented in mL/min/1.73 m^2.
ACEi=angiotensin-converting enzyme inhibitor; ACR=albumin:creatinine ratio; ARB=angiotensin receptor blocker; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; HF=heart failure; HFrEF=heart failure with reduced ejection fraction.

Information correct on 6th July 2022. **Licence amendments frequent – view most recent version.**
Always consult the electronic BNF or the Summaries of Product Characteristics (SPCs) prior to prescribing any drug.
SPCs: Canagliflozin | Dapagliflozin | Empagliflozin | Ertugliflozin

Author: Pam Brown, GP, Swansea
Citation: Brown P (2022) SGLT2 inhibitors: Indications, doses and licences in adults. Updated July 2022. *Diabetes & Primary Care* **24**: 111–12

Safety of SGLT2i

- Recent data has increased confidence in the safety of SGLT2i[1]
- SGLT2i increase the risk of mycotic genital infections
- CVOT reported a doubling of DKA rates compared to placebo[2]
- Reduce risks with sick day rules, education of signs and symptoms of DKA & seek prompt medical attention[2]

1.ADA Professional practice committee 2022 diabetes care 45 supplement 1144-174
2.McGuire et al. 2021 JAMA Cardiol 6 (2)148-158

Choosing WHO to treat with an SGLT2i

- First Line if intolerant to Metformin
- Second line to metformin
- Combination with GLP1 RA or insulin
- Establish cardiovascular disease, prior stroke or H.F.
- No history of lower limb amputation or PAD/PVD
- CKD
- Overweight
- Vulnerable to the effects of hypoglycaemia
- Elderly (SOLD study)
- Caution in frail
- Caution in HbA1c >86

Choosing WHO to avoid with an SGLT2i

- Acute illness
- DKA or Hx of
- Eating disorders or ketogenic diets
- Rapid progression to insulin
- Excessive alcohol intake or illicit drug use
- Diabetes due to pancreatic disease
- Genetic diabetes Pregnancy
- Recent major surgery
- History of necrotising fasciitis of the perineum -Fournier's gangrene
- PVD[1]
- Severe hepatic impairment (dapagliflozin 5 mg can be initiated)

1.Barraclough et al 2022 PVD patients derive greater benefits from SGLT2i

DKA T2DM & SGLT2i

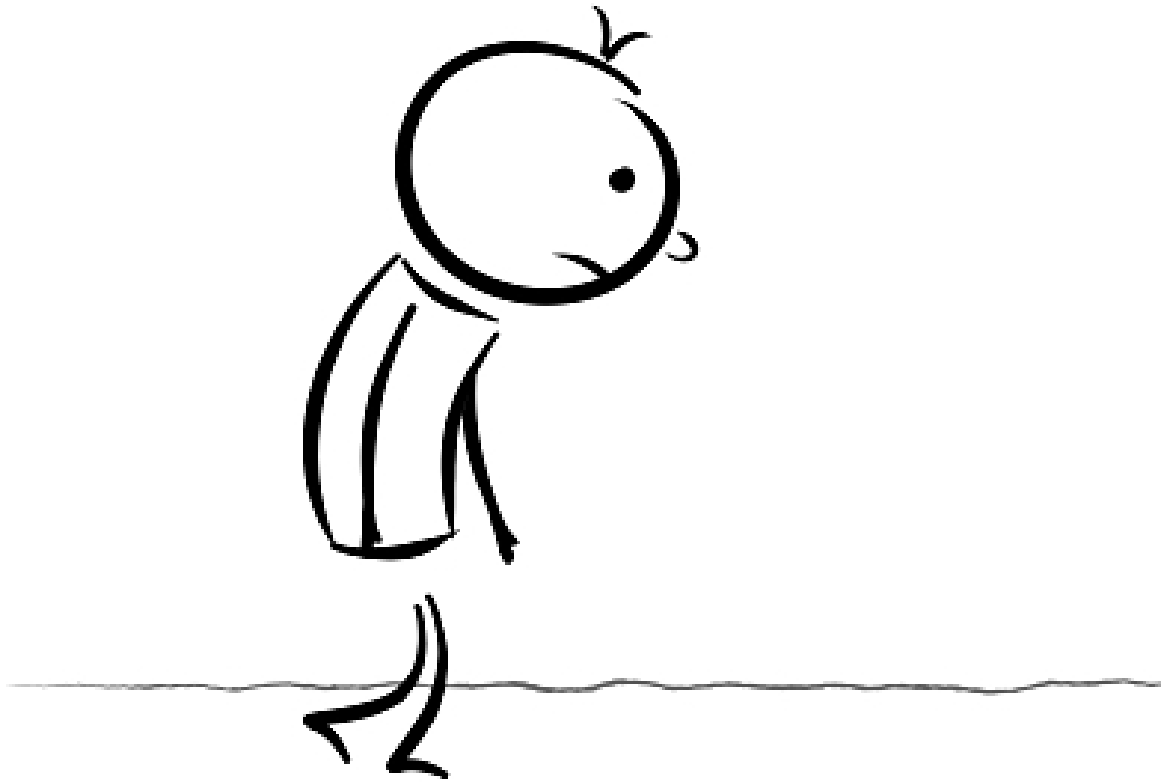
- Diabetes related ketoacidosis is rare but serious complication of T2DM
- All known risk factors for DKA should be considered before starting an SGLT2 inhibitor.
- Some risk factors are not modifiable such as a previous DKA
- Chief modifiable risk factors include:
  - Alcohol (> the recommended UK threshold)
  - Use of illegal drugs
  - Very low carbohydrate ketogenic diet

INTERCURRENT ILLNESS, MEDICINES, AKI AND SICK DAY RULES

SAD MAN

- **S**GLT2i
- **A**CEi
- **D**iuretics

- **M**etformin
- **A**RB
- **N**SAIDs



Finerenone

- Non-steroidal selective mineralocorticoid receptor antagonist
- FIDELIO--DKD STUDY (NEJM Dec 2020)
- Finerenone improve outcomes in CKD with type 2 diabetes
- Resulted in a lower risk of CKD progression (H.R. 0.82) and MACE events (H.R. 0.89) than placebo
- FIGARO DKD Demonstrated that the finerenone reduces new onset H.F. and improves other H.F. outcomes in patients with CKD and type 2 diabetes [1]

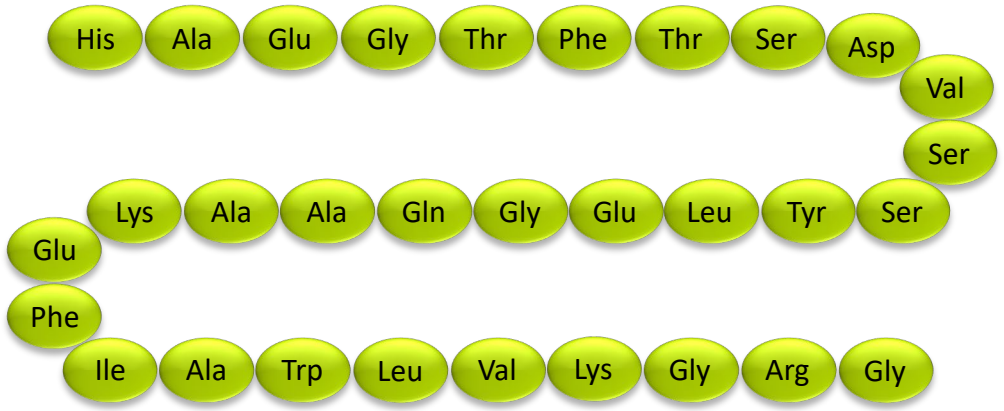
1.Filippatos G, Anker SD, Agarwal R, et al., on behalf of the FIGARO-DKD Investigators. Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial. *Circulation* 2022;145:437-47.

GLP-1 RA

What is GLP-1?

- GLP-1 is a peptide comprised of 31 amino acids
- Member of incretin family

Human endogenous GLP-1



Enzymatic degradation by DPP-4

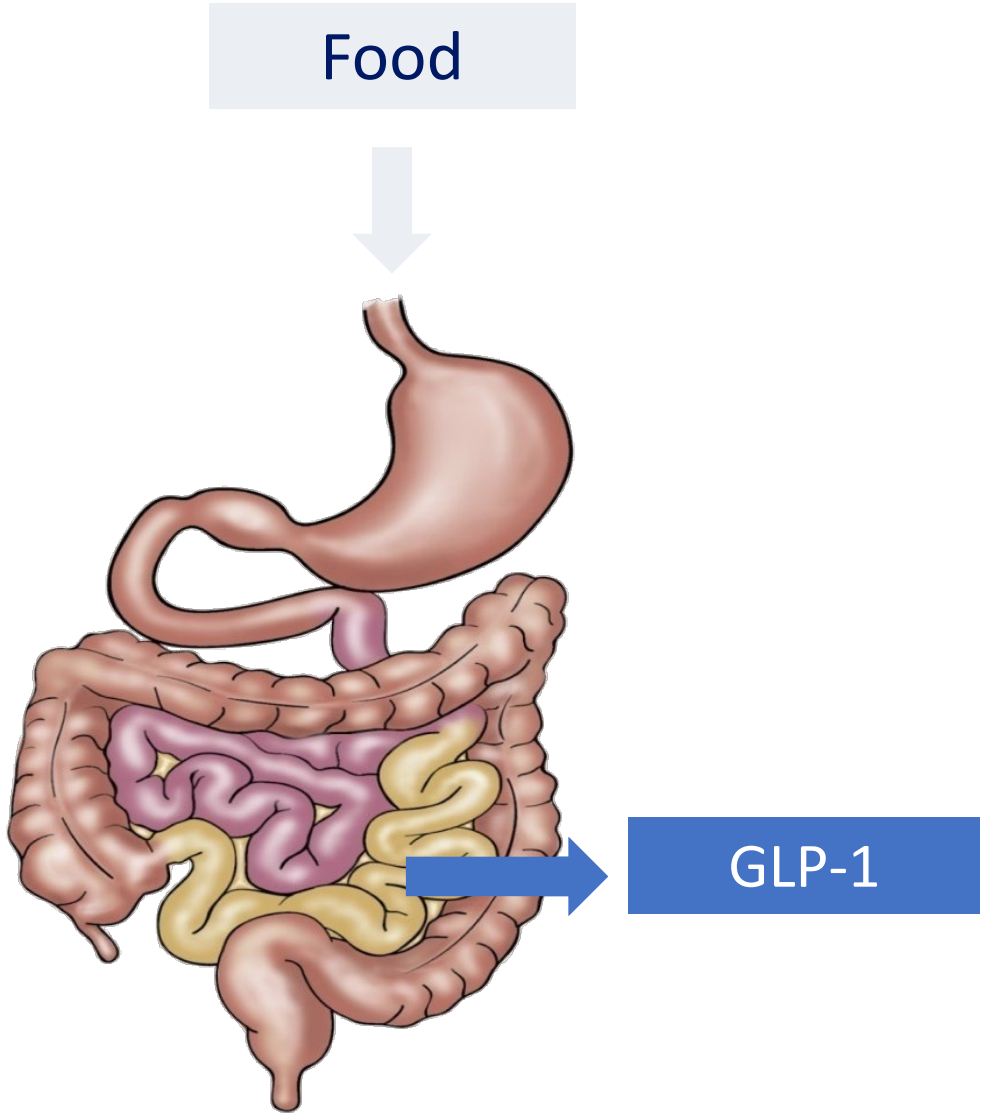
$t_{½}$=1.5–2 min

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; $t_{½}$, half-life

Merchenthaler *et al. J Comp Neurol* 1999;403:261–80; Baggio, Drucker. *Gastroenterology* 2007;132:2131–57; Ducker, Nauck. *Lancet* 2006;368:1696–705

Glucagon-like peptide-1

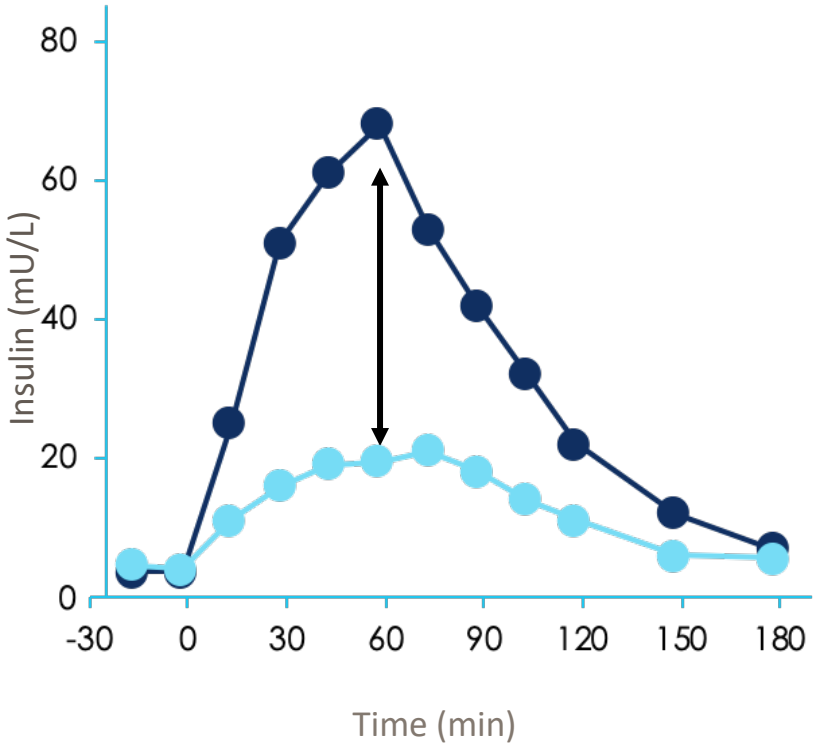
- GLP-1 is released from intestinal L-cells in response to eating[1]
- GLP-1 secretion is impaired in people with T2DM[2]



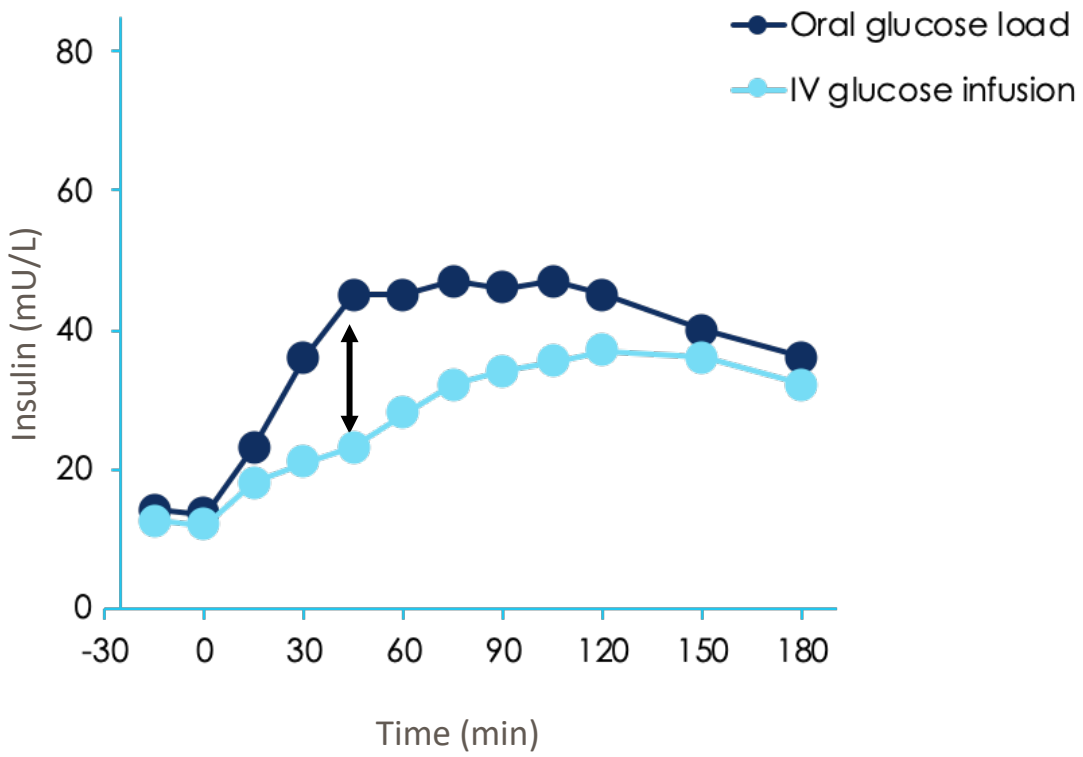
1. Drucker DJ et al. Lancet. 2006;368:1696–1705;
2. Toft-Nielsen MB et al. J Clin Endrocrinol Metab. 2001;86:3717–3723.

The Incretin Effect Is Reduced in People With T2DM

In healthy people, insulin secretion is enhanced after oral vs. IV glucose

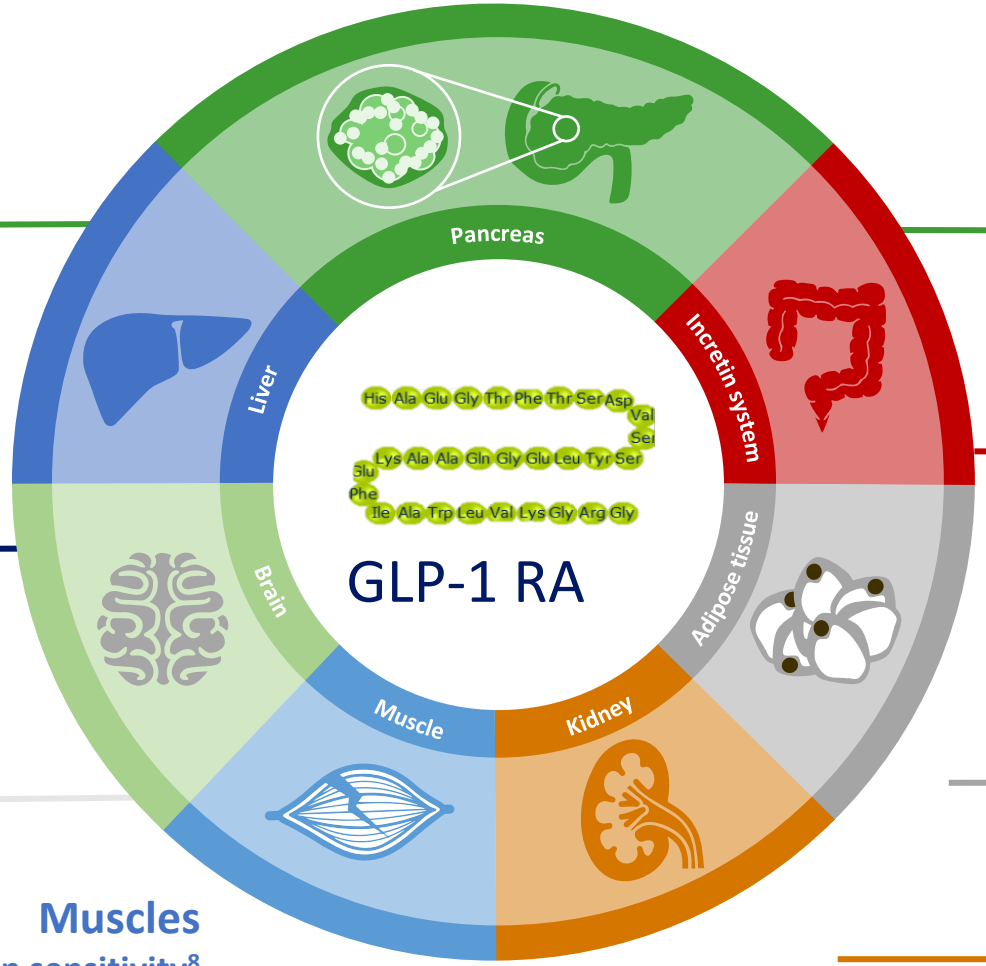


The incretin effect is diminished inT2DM



Nauck MA et al. *Diabetes Obes Metab*. 2018;20:5-21.

Pharmacological effects of GLP-1RA's



Pancreas (beta cell)
↑ beta-cell function[1]
↑ Insulin biosynthesis[1]

Pancreas (alpha cell)
↓ Glucagon secretion[1]

Liver
↓ Hepatic glucose production[6]
↑ Hepatic insulin sensitivity[6]
↓ *De novo* lipogenesis[6]
↓ Steatosis[7]

GI tract
↓ Gastric emptying[5]

Brain
↓ Body weight[2]
↓ Food intake[1]
↑ Satiety[3,4]

Adipose tissue
↓ Lipotoxicity[6]

Muscles
↑ Insulin sensitivity[8]

Kidneys
↑ Natriuresis[1]

Portions of the content presented in this slide may originate from non-human studies, ie, animal and in vitro studies. GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

1. Campbell JE and Drucker DJ. Cell Metab. 2013;17:819–37; 2. Baggio LL and Drucker DJ. J Clin Invest 2014;124:4223–6; 3. Flint A et al. J Clin Invest 1998;101:515–20; 4. Blundell J et al. Diabetes Obes Metab. 2017;19:1242–51; 5. Tong J, D'Alessio D. Diabetes. 2014;63:407–9; 6. Armstrong MJ et al. J Hepatol 2016;64:399–408; 7. Armstrong MJ et al. Lancet. 2016;387:679–90; 8. MacDonald PE et al. Diabetes 2002;51(Suppl. 3):S434–42.

GLP-1RA

- CV safety /no reduction in MACE : lixisenatide & exenatide
- CV benefit/ reduction in MACE : liraglutide semaglutide and dulaglutide
- Injectables :Average reduction in MACE 14% semaglutide 26% (SUSTAIN6)
- Oral semaglutide: cardiovascular risk profile not inferior to placebo (PIONEER 6)

How to use GLP-1 RA safely and effectively https://Diabetesonthenet (Nicky Milne)

NICE NG28 (2015)	SIGN 154 (2017)	ADA/EASD consensus (2019)
If triple therapy with metformin and two other oral drugs is ineffective, not tolerated or contraindicated, HCPs should consider combination therapy with metformin, sulfonylurea and GLP-1 RA as below.	People with BMI ≥30 kg/m² (or ethnicity-adjusted equivalent) combined with oral glucose-lowering drugs, basal insulin or both as third- or fourth-line treatment, when adequate glycaemic control not achieved.	Second-line use for people with established atherosclerotic CVD or indicators of high risk (age >55 years with coronary, carotid or lower extremity artery stenosis >50% or left ventricular hypertrophy). Use GLP-1 RA with proven CVD benefit: subcutaneous semaglutide>liraglutide> dulaglutide.
BMI ≥35 kg/m² (adjust for ethnicity) and specific psychological or other medical problems associated with obesity.	As an alternative to insulin in people for whom combinations of oral glucose-lowering drugs did not produce adequate glycaemic control.	For people where heart failure or CKD predominates, use a GLP-1 RA with proven CVD benefit if an SGLT2 inhibitor is not tolerated or is contraindicated, or if eGFR is less than adequate for SGLT2i initiation. Use as third agent in those within this cohort who fail to meet HbA_{1c} target despite metformin and SGLT2i. Also consider second-line use after metformin where there is compelling need to minimise weight gain or promote weight loss, or a compelling need to minimise hypoglycaemia.
BMI <35 kg/m² when insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.	Consider a GLP-1 RA with proven cardiovascular benefit for people with type 2 diabetes and established cardiovascular disease (CVD) (currently liraglutide and subcutaneous semaglutide).	GLP-1 RAs preferred to insulin if greater glucose-lowering effect of an injectable medication needed; insulin recommended if extreme, symptomatic hyperglycaemia.
Only continue GLP-1 RAs if the person has had a beneficial metabolic response: reduction of ≥11 mmol/mol (1.0%) in HbA_{1c} **and** a weight loss of ≥3% of initial body weight in 6 months.	Continue GLP-1 RA at each stage if **either** individualised HbA_{1c} target achieved **or** HbA_{1c} falls >5.5 mmol/mol (0.5%) in 3–6 months. Discontinue GLP-1 RA if ineffective.	People unable to maintain glycaemic targets on basal insulin + oral medications can have treatment intensified with GLP-1 RAs, SGLT2 inhibitors or prandial insulin.

What is the role of the incretin hormone GLP-1?

- Increases insulin secretion and insulin sensitivity.
- Increases beta-cell mass and maintains beta-cell function.
- Increases glucose disposal.
- Delays gastric emptying.
- Reduces appetite by increasing satiety.

What are GLP-1 RAs?

- Chemical modification of GLP-1 produces drugs that bind to the GLP-1 receptor, producing the same effects as the native protein.
- Current therapies all have a similar mechanism of action.
- Effects in type 2 diabetes include reductions in HbA_{1c} and weight. Some therapies have additionally demonstrated cardiovascular benefits (dulaglutide, liraglutide and semaglutide).
- GLP-1 RA therapies are injectable, apart from oral semaglutide, and they have different profiles, which affect dosing frequency.

Citation: Milne N (2020) How to use GLP-1 receptor agonist therapy safely and effectively. *Diabetes & Primary Care* **22**: 135–6

Assessing suitability

People to consider	Prescribe with caution	Unsuitable people
● People with type 2 diabetes and high BMI, adjusted for ethnicity	● People in whom weight loss would cause concern (e.g. frailty)	● Type 1 diabetes
● People with type 2 diabetes and significant risk of cardiovascular disease (CVD)	● People with a history of gallstones	● Children (although liraglutide is licensed for use in adolescents and children aged ≥10 years with type 2 diabetes
● People with type 2 diabetes and established CVD	● Women of child-bearing age (ensure adequate contraception)	● Pregnant women
● People with type 2 diabetes and CKD or heart failure, unsuitable for SGLT2 inhibitors	● People with irritable bowel syndrome or gastro-oesophageal reflux disease (GORD)	● History of, or risk factors for, pancreatitis*
	● People with renal or hepatic impairment	● History of medullary thyroid cancer or multiple endocrine neoplasia type 2
	● Active proliferative or pre-proliferative retinopathy†	

*For example: idiopathic acute pancreatitis, gallstones, alcohol abuse, trauma and hypertriglyceridaemia.

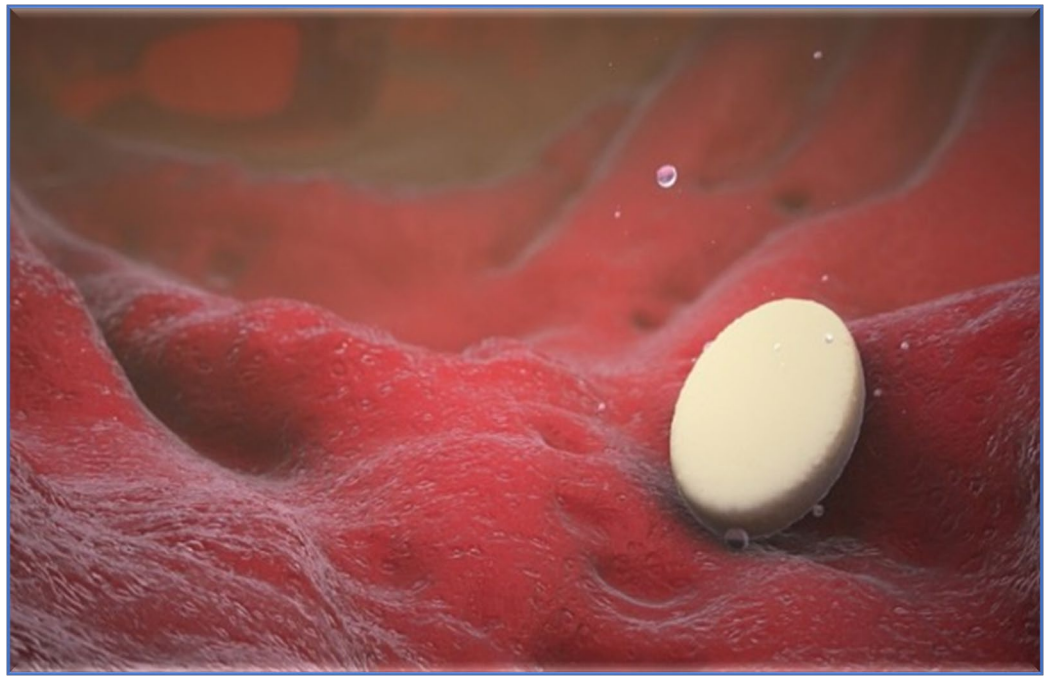
†Non-significant increase in retinopathy with liraglutide versus placebo in LEADER (0.6 vs 0.5 events per 100 patient-years respectively; hazard ratio, 1.15); retinopathy complications occurred in 3.0% of the semaglutide group and 1.8% in the placebo group (hazard ratio, 1.76) in SUSTAIN-6.

SmPC for semaglutide advises caution in people with background retinopathy who are taking insulin therapy.

Take with 30ml-100ml water. No liquids, food or tablets for 30 mins

Semaglutide tablets are absorbed in the stomach

Absorption of semaglutide requires co-formulation with 300mg SNAC



SNAC causes a local increase of pH leading to higher solubility and protection from proteolytic degradation

NAC, sodium N-(8-(2-hydroxybenzoyl) amino) caprylate.

GLP-1RA Caution / Side Effects

- Common side effects :Nausea, vomiting & diarrhoea diminish over time.
- Burping , constipation , cholelithiasis ,appetite reduced &weight loss.
- DKA reported with combination with insulin after rapid reduction in insulin
- Caution in retinopathy with insulin as increase risk of progression.
- Hypoglycaemia in patients treated with insulin.
- Interaction with levothyroxine – take in evening.
- No dose adjustment needs in elderly, CKD or hepatic impairment
- For surgery stop Xultropy and Suliqua
- Commencing liver reduction, stop GLP1

Tirzepatide

- Poly-functional peptide modeled on the native GIP peptide sequence[1]
- Acts as a dual agonist and binds to both GIP (glucose dependent insulinotropic polypeptide) and GLP-1 receptors[1]
- Once weekly injection
- Safe in renal and hepatic failure

1. Coskun T, et al. *Mol Metab*. 2018;18:3-14.
2. Urva S, et al. *Diabetes*. 2020;69(suppl 1):Abstract 971-P.

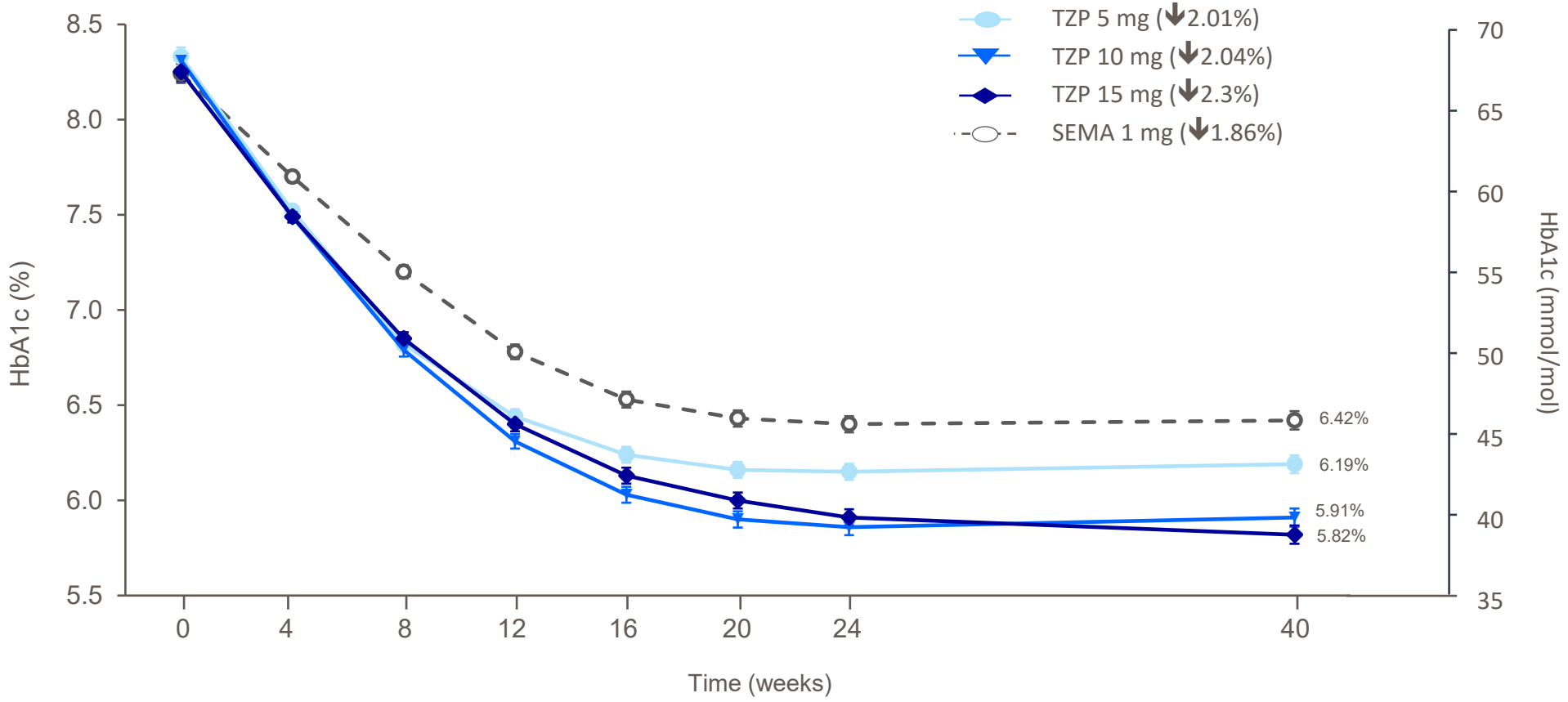
Tirzepatide

In the SURPASS clinical trial program, treatment with tirzepatide 5 mg, 10 mg, and 15 mg in people with T2D resulted in:

- Greater reduction in HbA1c compared to placebo, semaglutide 1 mg, and basal insulin
- Reduction in body weight

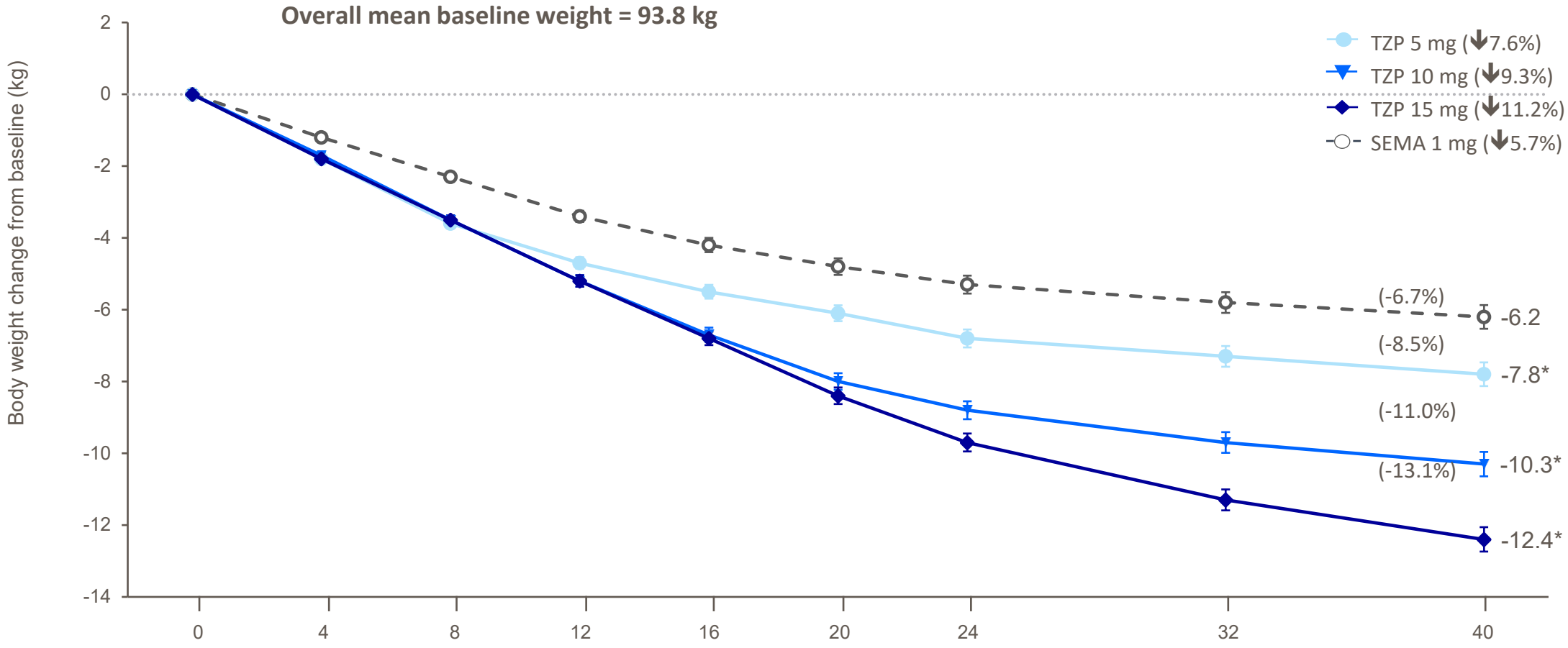
The most common AEs with tirzepatide treatment were gastrointestinal in nature, mostly mild or moderate in severity and occurred early (during dose-escalation)

Surpass2 trial - HbA1c over 40 weeks



Data are LSM (SE); mITT population (efficacy analysis set). ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the dose of TZP 5 mg, 10 mg, and 15 mg and SEMA 1 mg were achieved. Data labels are % HbA1c.
ANOVA = analysis of variance; HbA1c = glycated hemoglobin; LSM = least squares mean; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Eng J Med*. 2021;3856 ():503-515.

SURPASS-2 trial - Body Weight Change Over Time



Data are LSM (SE); mITT population (efficacy analysis set). ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate weeks dose of TZP 5 mg, 10 mg, 15 mg, and SEMA 1 mg were achieved.
Data labels are weight in kg (% change from baseline).
*P<001 vs. SEMA.
ANOVA = analysis of variance; LSM = least squares mean; mITT = modified intent to treat; MMRM = mixed model repeated measures; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Eng J Med.* 2021;385(6):503-515.

SGLT2i summary

- SGL2i can initiate down to eGFR > 45 for glycaemic control
- In eGFR <45 use other diabetes Rx for glycaemic control
- In heart failure can initiate down to eGFR >15 for both Preserved and Reduced (DAPA)
- Sick day rules if unwell or infection STOP temporarily
- Uncommon but serious side effects include DKA, Fournier's gangrene and lower limp amputation
- All SGLT2i were associated with reduced risk of MACE ,hospitalisation for heart failure, cardiovascular death and kidney outcomes, but not for ischaemic stroke.
- (Finerenone reduces progression of CKD and MACE)

GLP-1RA Summary

- Increase insulin production & reduce glucagon production
- Decreases food intake , increase satiety &causes weight loss
- CV benefit/ reduce MACE : liraglutide, semaglutide & dulaglutide (injectable)
- Oral semaglatide now available
- Avoid in pancreatitis
- Tirzepatide both GLP-1RA and GIP agonist
- Tirzepatide leads to greater fall in A1c & weight compared to GLP-1RA alone

Questions?