ADA/EASD consensus statement 2022

DR. PAUL M. NEWMAN

- Sponsorship EASD NOVO (2022) Menarini (2023)

- Speaker fee NOVO AstraZeneca Bayer
- Declarations of interest

- Updated algorithm in the use of glucose lowering medications and lifestyle and type 2 diabetes management.
- Treatment recommendations focus on SGLT2i and GLP-1 receptor agonists independent of metformin use.
- Section on achieving & maintaining glycaemic control and weight management goals focusing on drug efficacy and lifestyle benefits. Giving equal status to both.
- Use of the term **'organ-protection'** when using these drugs for cardiorenal benefits.
- ADA/EASD consensus statement 2022 – what is new

KEY POINTS TO EMPHASISE

Informed by evidence generated in the past 3 years

Greater focus on social determinants of health and systems and equality of care

Emphasis on holistic person-centred care

Greater focus on weight goals as an essential component of comprehensive care

Consolidation of evidence from CVOTs

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

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

GOALS OF DIABETES CARE

Prevent complications

Optimise quality of life

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IMPORTANCE OF GLYCAEMIC CONTROL

Averting symptomatic hyperglycaemia

Substantial and enduring reduction in microvascular complications

- 50-76% reduction DCCT with HbA1c 7% vs 9%
- 25% reduction UKPDS with HbA1c 7% vs 7.9%
- Greatest benefit with reduction from higher levels of HbA1c

Uncertainty regarding macrovascular benefit of BG control in T2D

Benefits emerge slowly while harms of glucose control medications can be more immediate

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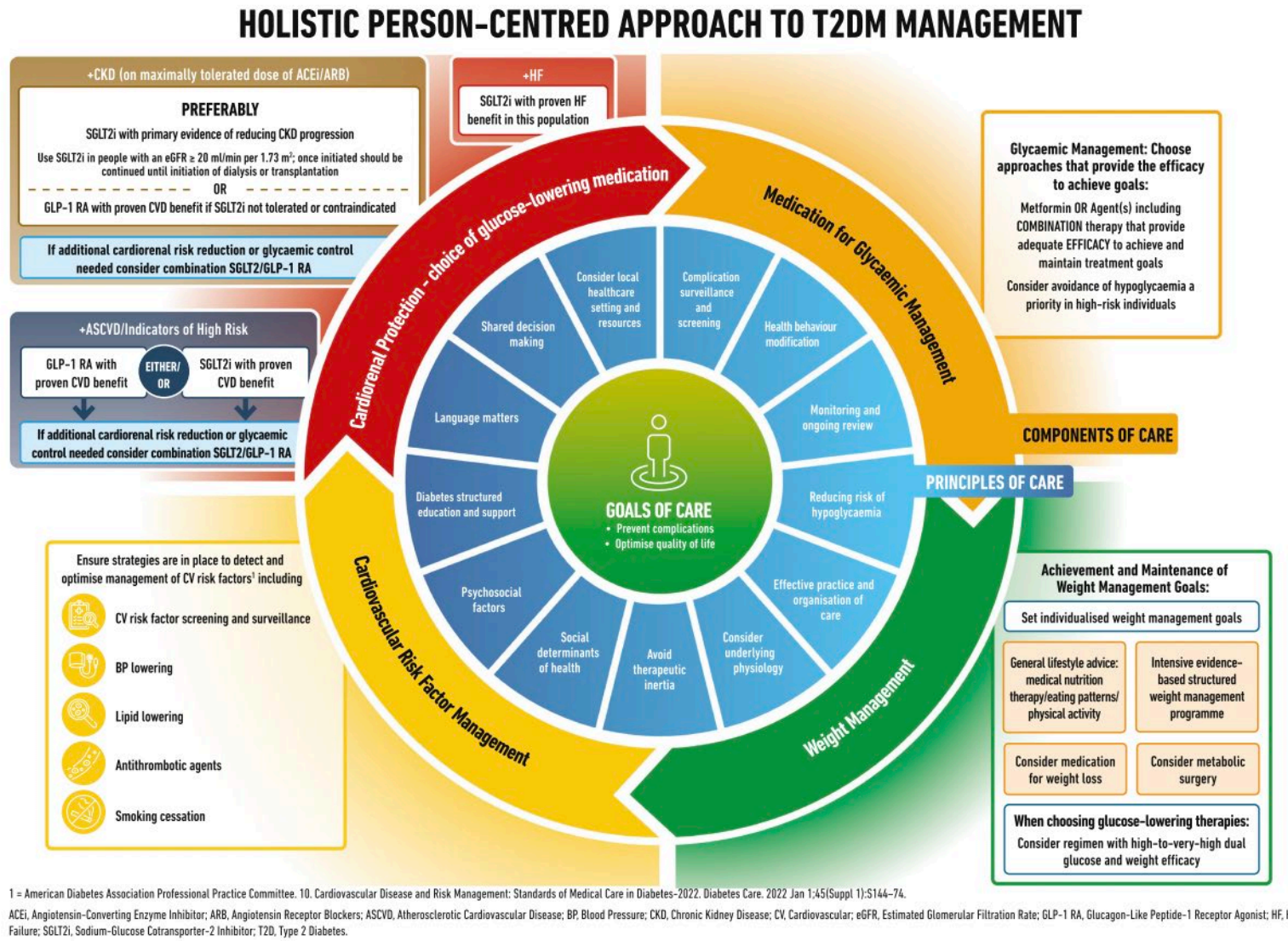

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

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

Fig. 4 Holistic person-centred approach to T2DM management

Diabetologia

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

SHARED DECISION-MAKING IN TYPE 2 DIABETES

Shared decision-making can improve

- decision quality
- knowledge about risks, safety, and benefits
- incorporation of individual preferences and values when formulating a management plan

Ethical imperative for support of person's autonomy

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WEIGHT REDUCTION AS A TARGETED INTERVENTION

- Weight reduction has mostly been seen as a strategy to improve glycaemic management and reduce the risk for weight-related complications.
- It was recently suggested that weight loss of 5-15% should be a primary target in management for many people living with type 2 diabetes.
- A higher magnitude of weight loss confers better outcomes, and a 5-10% loss confers metabolic improvement, and a loss of 10-15% or more of body weight can have a disease-modifying effect, and lead to remission of diabetes.
- Weight loss may exert benefits that extend beyond glycaemic management to improve risk factors for cardiometabolic disease and quality of life.

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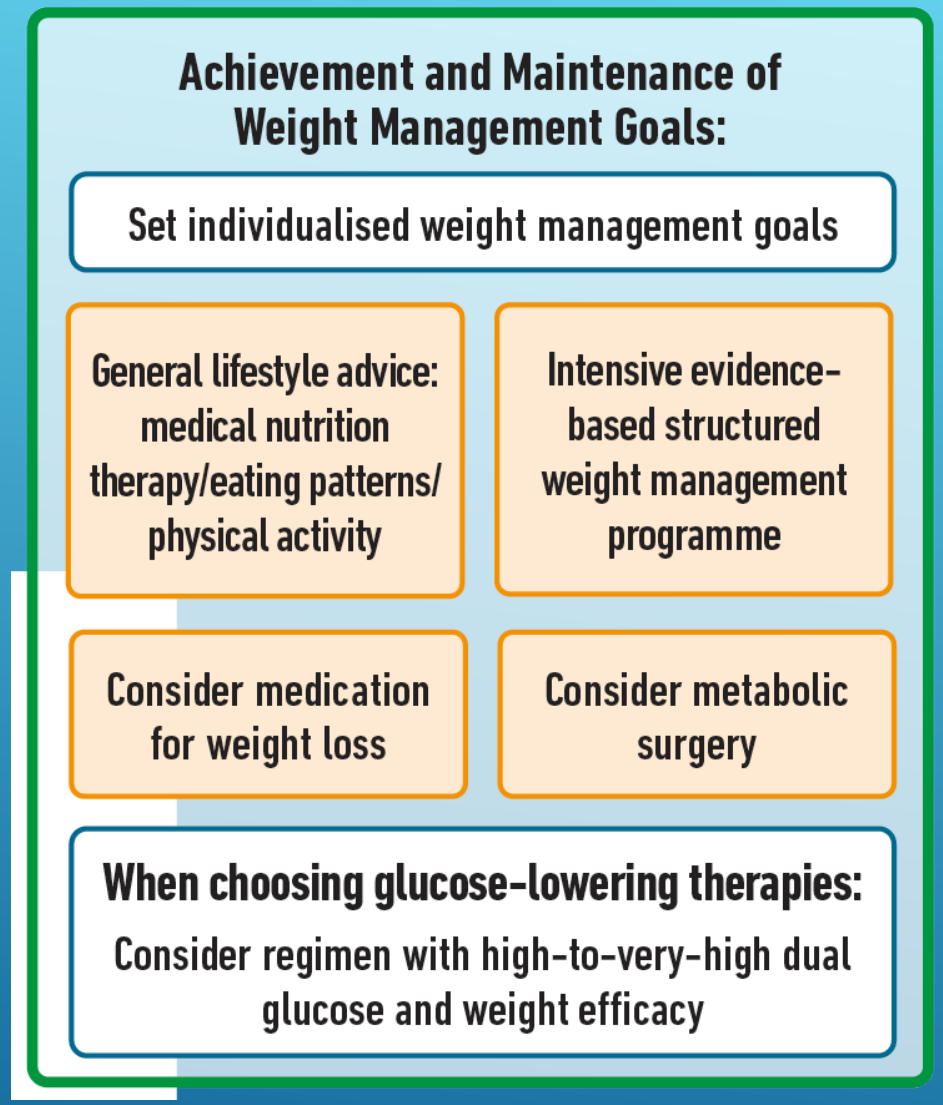

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FIGURE 2: IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIOURS FOR TYPE 2 DIABETES

SITTING/BREAKING UP PROLONGED SITTING

Limit sitting. Breaking up prolonged sitting (every 30 min) with short regular bouts of slow walking/simple resistance exercises can improve glucose metabolism.

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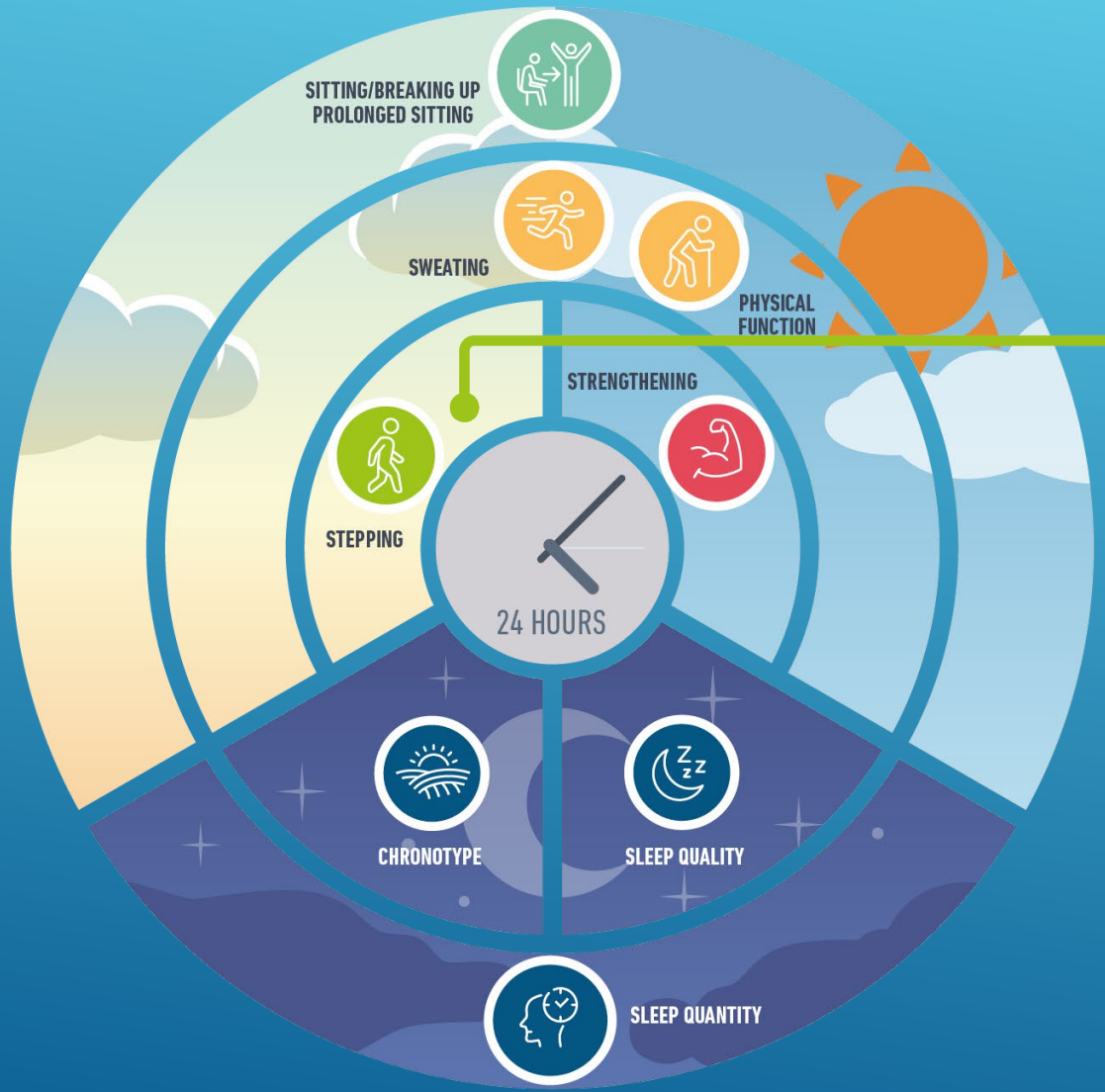

STEPPING

- An increase of only 500 steps/day is associated with 2-9% decreased risk of cardiovascular morbidity and all-cause mortality.
- A 5 to 6 min brisk intensity walk per day equates to ~4 years' greater life expectancy.

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FIGURE 2: IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIOURS FOR TYPE 2 DIABETES

SLEEP

Aim for consistent, uninterrupted sleep, even on weekends.

Quantity – Long (>8h) and short (<6h) sleep durations negatively impact HbA1c.

Quality – Irregular sleep results in poorer glycaemic levels, likely influenced by the increased prevalence of insomnia, obstructive sleep apnoea and restless leg syndrome in people with type 2 diabetes.

Chronotype – Evening chronotypes (i.e. night owl: go to bed late and get up late) may be more susceptible to inactivity and poorer glycaemic levels vs morning chronotypes (i.e. early bird: go to bed early and get up early).

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LANGUAGE MATTERS

- Communication between people living with type 2 diabetes and health care team members is at the core of integrated care
- Clinicians must recognise how language matters
- Language in diabetes care should be neutral, free of stigma, and based on facts; be strengths-based (focus on what is working), respectful, and inclusive; encourage collaboration; and be person-centred
- People living with diabetes should not be referred to as "diabetics," or described as "noncompliant," or blamed for their health condition.

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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]

1KUNTI ET AL L . DIABETES OBES METAB 2018 20 389-399

2 KUNTI ET AL. DIABETES CARE 2013 36 3411-3417.

COMBINATION THERAPY

Increasing evidence and rationale:

(1) Increased durability of glycaemic effect, potential to address therapeutic inertia

(2) Simultaneous targeting of multiple pathophysiologic processes characterised by T2DM
Potential impact on medication burden, adherence, and treatment persistence

(3) Complementary clinical benefits (glycaemia, weight, cardiovascular risk profile)

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- initial **combination** therapy with glucose lowering agents and high HbA1c at diagnosis i.e. greater than 70.[1]

- In younger people with type 2 diabetes regardless of HbA1c.[1]

- If additional glycaemic control is needed ,incorporate rather than substitute glucose lowering therapies.

- Considered de- intensification of therapy in frail older adults and in the setting of hypoglycaemia causing medications.[1]

PRACTICAL TIPS FOR CLINICIANS

ADA/EASD consensus statement October 2022

RATIONALE FOR NEW DIABETES DRUGS

Both SGLT2 inhibitors and GLP-1 receptor agonists 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-1 receptor agonist semaglutide improved diabetes control, reduces weight however MACE outcomes still awaited.

1Giugliano etal Cardiovascular Diabetology 20 189 2021

2 Bakris etal NEJM 2020 383 2219-2229 (FIDELIO-DKD)

CHOOSING GLUCOSE-LOWERING MEDICATION IN PEOPLE WITH HEART FAILURE

In people with heart failure SGLT2i should be used because they improve heart failure and kidney outcomes.

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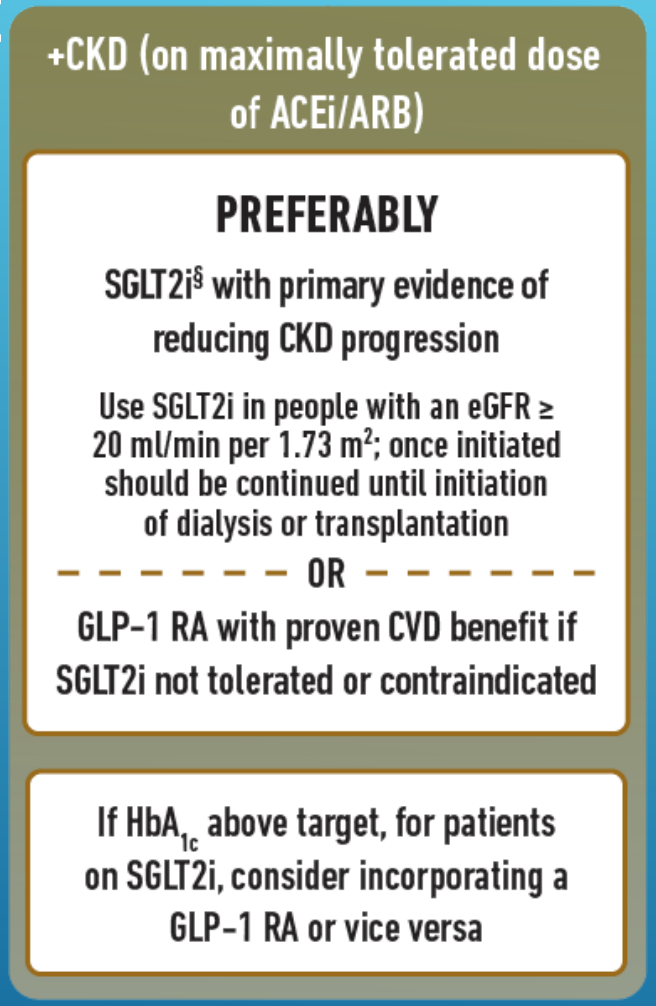
CHOOSING GLUCOSE-LOWERING MEDICATION IN PEOPLE WITH CHRONIC KIDNEY DISEASE



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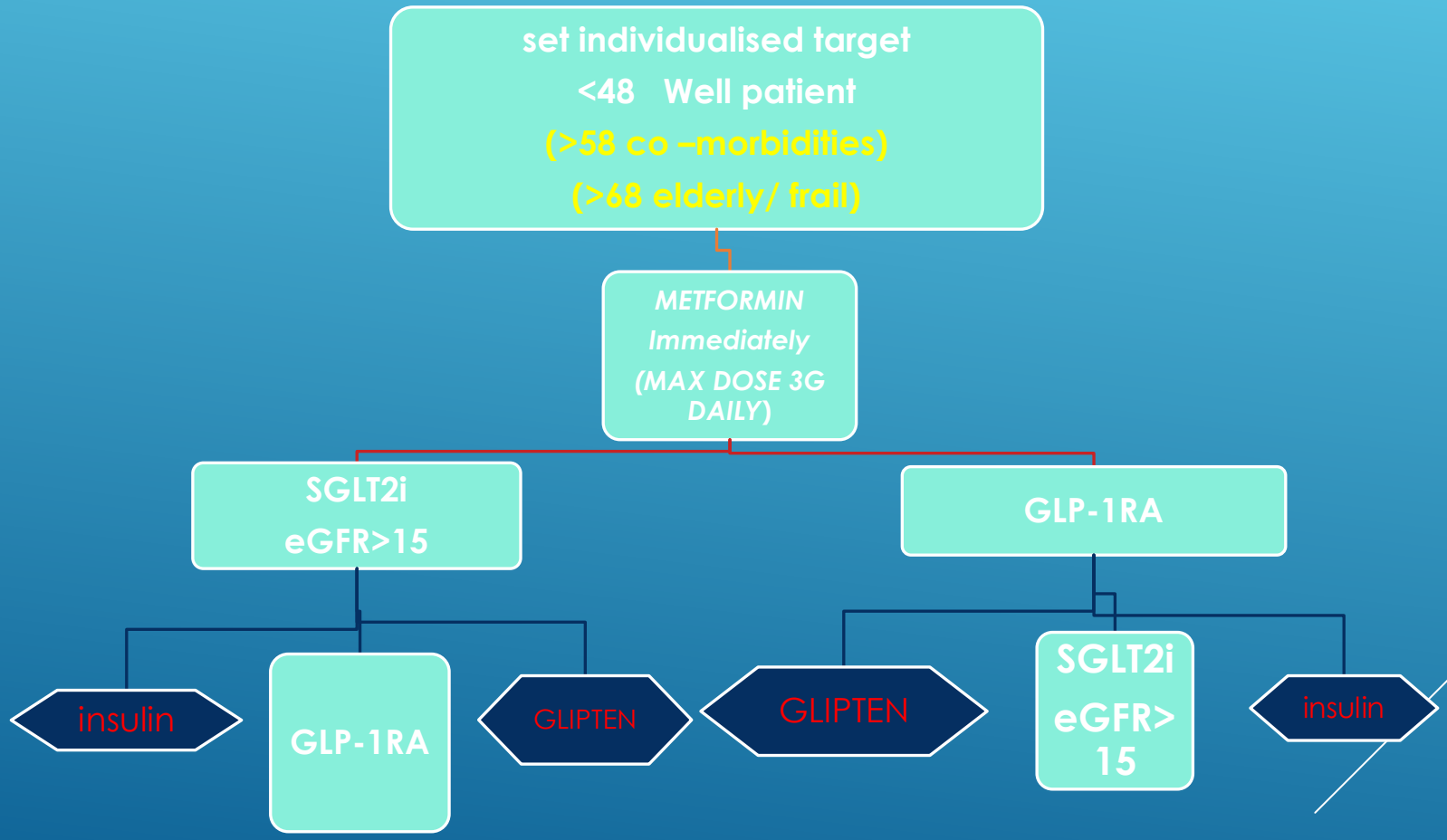
CAREME PATHWAY
ADA/EASD OCTOBER2022

INTENSIFICATION AT 3/12 INTERVALS



SAFETY OF SGLT2I

- Recent data has increased confidence in the safety of SGLT2i[1]
- Their use is associated with increased risk of mycotic genital infections which are reported to be typically mild and treatable
- Cardiovascular outcome trials of reported DKA rates of 0.1-0.6 compared to less than 0.1 to 0.3% with placebo with very low rates in heart failure.[2]
- Risks can be mitigated with education of signs and symptoms of DKA and advised to seek prompt medical attention as well as discontinuation of medication in clinical situations that predisposed in DKA ie SICK DAY RULES[2].

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

Intercurrent illness, medicines, AKI and sick day

SAD MAN

SGLT2i
ACEi
Diuretics

Metformin
ARB
NSAIDs

FINERENONE

- Nonsteroidal selective mineralocorticoid receptor antagonist

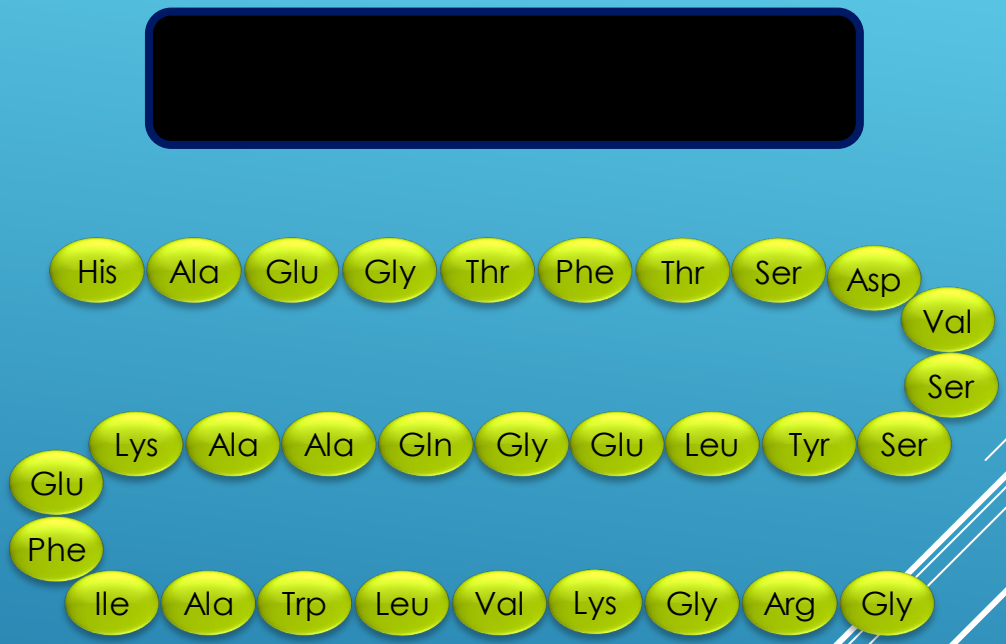
- FIDELIO--DKD STUDY (NEJM Dec 32020)
- Finerenone improve outcomes in CKD with type 2 diabetes
- Resulted in a lower risks of CKD progression (H.R. 0.82 and MACE events (H.R.0.89)than placebo
- FIGARO DKD Demonstrated that the finerenone reduces new onset H.F.and improves other H.F. outcomes in patients with CKD and type 2 diabetes. [1]

- (13 Nov 2021 circulation 2022 145:437-447)

GLP-1 RA

WHAT IS GLP-1

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



Enzymatic degradation by DPP-4

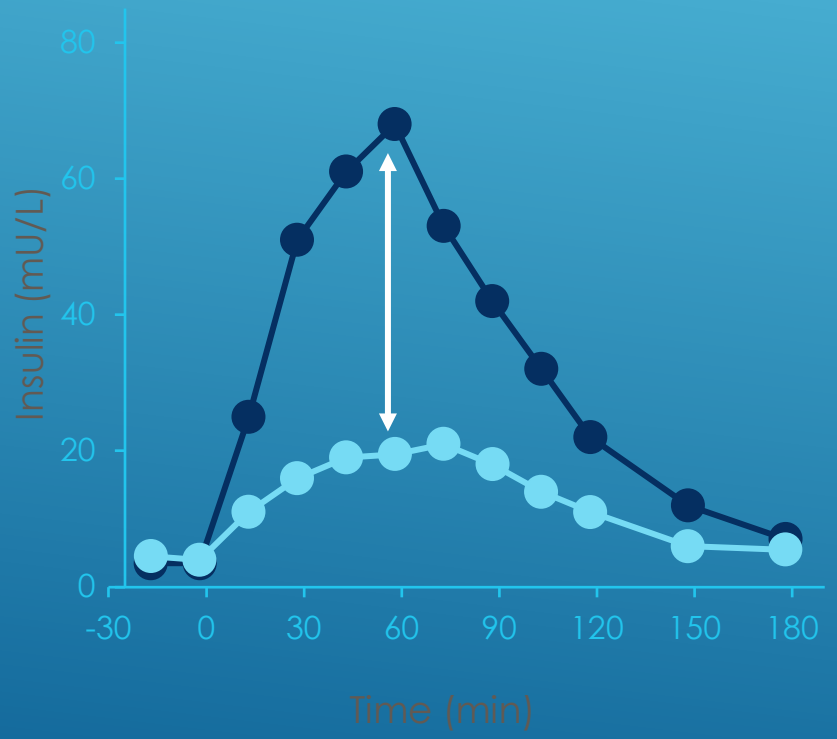
$t_{½}$=1.5–2 min

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

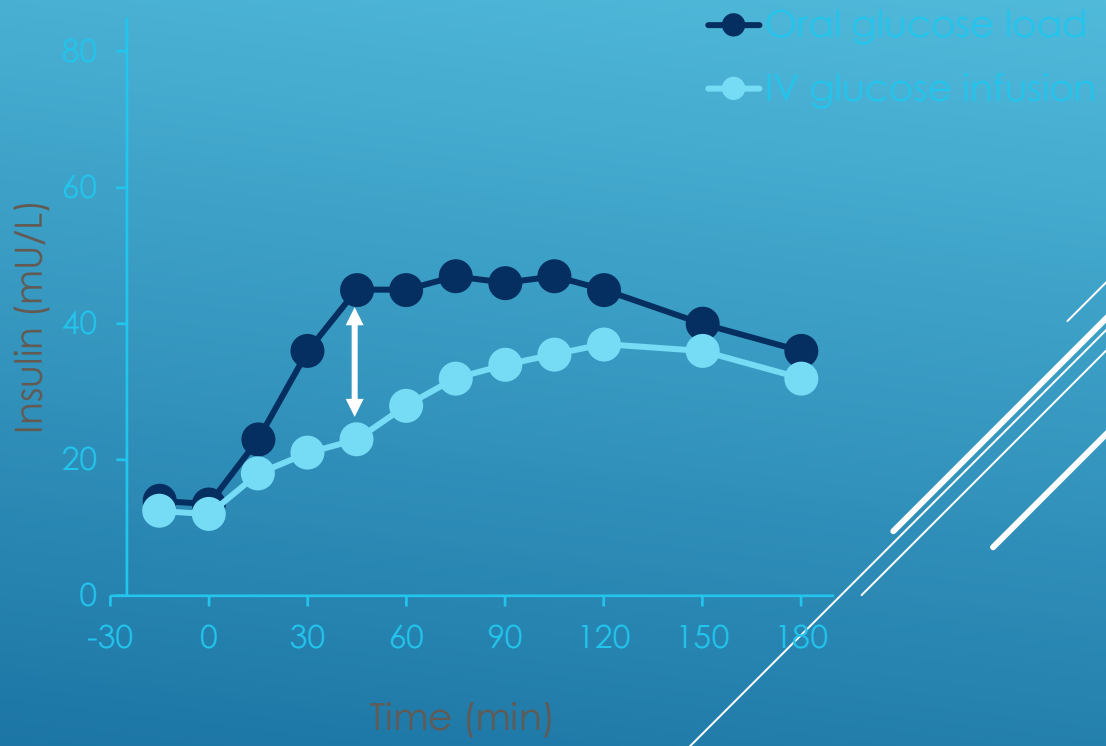
Merchenthaler *et al. J Comp Neurol* 1999;403:261–80; Baggio, Drucker. *Gastroenterology* 2007;132:2131–57; Ducker, Nauck. *Lancet* 2006;368:1696–705

THE INCRETIN EFFECT IS REDUCED IN PEOPLE WITH T2D

In healthy people, insulin secretion is enhanced after oral vs. isoglycemic IV administration of glucose (incretin effect).



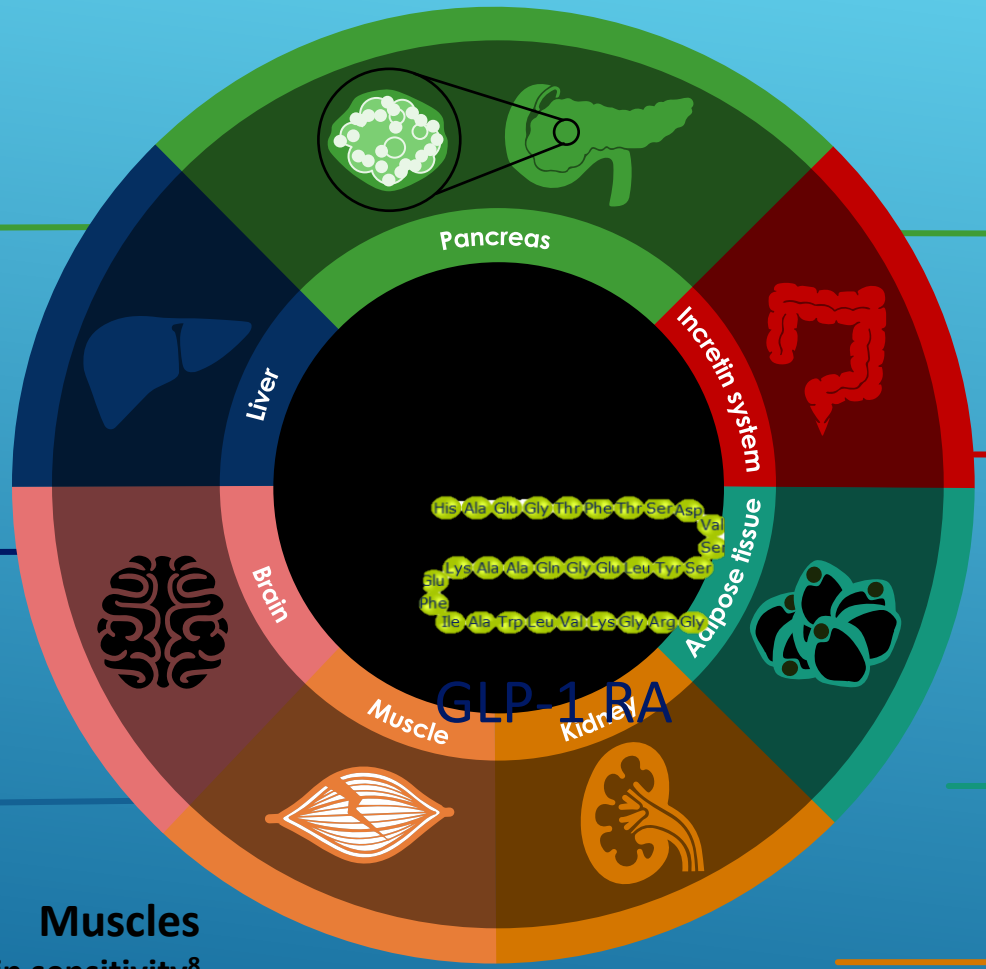
The incretin effect is diminished in people with T2D.



IV = intravenous; T2D = type 2 diabetes.

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

PHARMACOLOGICAL EFFECTS OF GLP-1 RA'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)

- <5% of patients in the UK are treated with GLP-1 RAs[1]

- Earlier Type 2 diabetes management with significant improvement to HbA1c & weight reduction, [2–9]

- 1. Farmer et al. Clinical Therapeutics. 2021; 43(2): 320-335;2. Aroda VR et al. Diabetes Care 2019;42:1724–32; 3. Rodbard HW et al. Diabetes Care 2019;42:2272–2281; 4. Rosenstock J et al. JAMA 2019;321:1466–80; 5. Pratley R et al. Lancet 2019;394:39–50; 6. Mosenzon O et al. Lancet Diabetes Endocrinol 2019;7:515–27; 7. Pieber TR et al. Lancet Diabetes Endocrinol 2019;7:528–39; 8. Zinman B et al. Diabetes Care 2019;42:2262–2271; 9. Davies M et al. JAMA 2017.318;1460–1470; 10. Spain CV et al. Clin Ther 2016;38)7):1653–64.

WHY AN ORAL GLP-1 RA?

- 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](gl
- Once weekly injection
- Safe in renal and hepatic failure

TIRZEPATIDE

Note: This 3-dimensional rendering of tirzepatide is not an exact reproduction of the molecule and should be used for representative purposes only.
GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.

PLACE OF INSULIN IN TYPE 2 DIABETES

The use of a GLP-1 RA should be considered prior to initiation of insulin.

When initiating insulin, start with a basal insulin and intensify the dose in a timely fashion, titrating to achieve the individualised fasting glycaemia target set for every person.

When insulin is initiated, continue organ-protective glucose-lowering medications and metformin.

Refer for DSMES when initiating insulin or advancing to basal-bolus therapy.

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PLACE OF TECHNOLOGY

Technology can be useful in people with type 2 diabetes but needs to be part of an holistic plan of care and supported by DSMES.

Consider CGM in people with type 2 diabetes on insulin.

Adapt the clinic/system to optimise effective use of technology among people with type 2 diabetes, particularly to support behaviour change through self-monitoring.

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SUMMARY ADA/EASD CONSENSUS STATEMENT 2022

- Gives equal status to lifestyle, Rx , weight management and organ protection
- Organ protection Rx SGLT2i & GLP1 RA
- Emphasis on holistic person-centred care
- Greater focus on weight goals as an essential component of comprehensive care
- All SGLT2i's were associated with reduced risk of MACE.
- SICK DAY RULES- educate
- GLP1 RA CV benefit/ reduced MACE :liraglutide semaglutide &dulaglutide