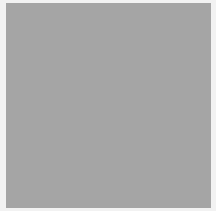
”NG 28-What does it mean for Primary Care”

- Dr Paul Newman & Dr Naresh Kanumilli

Declarations of interest

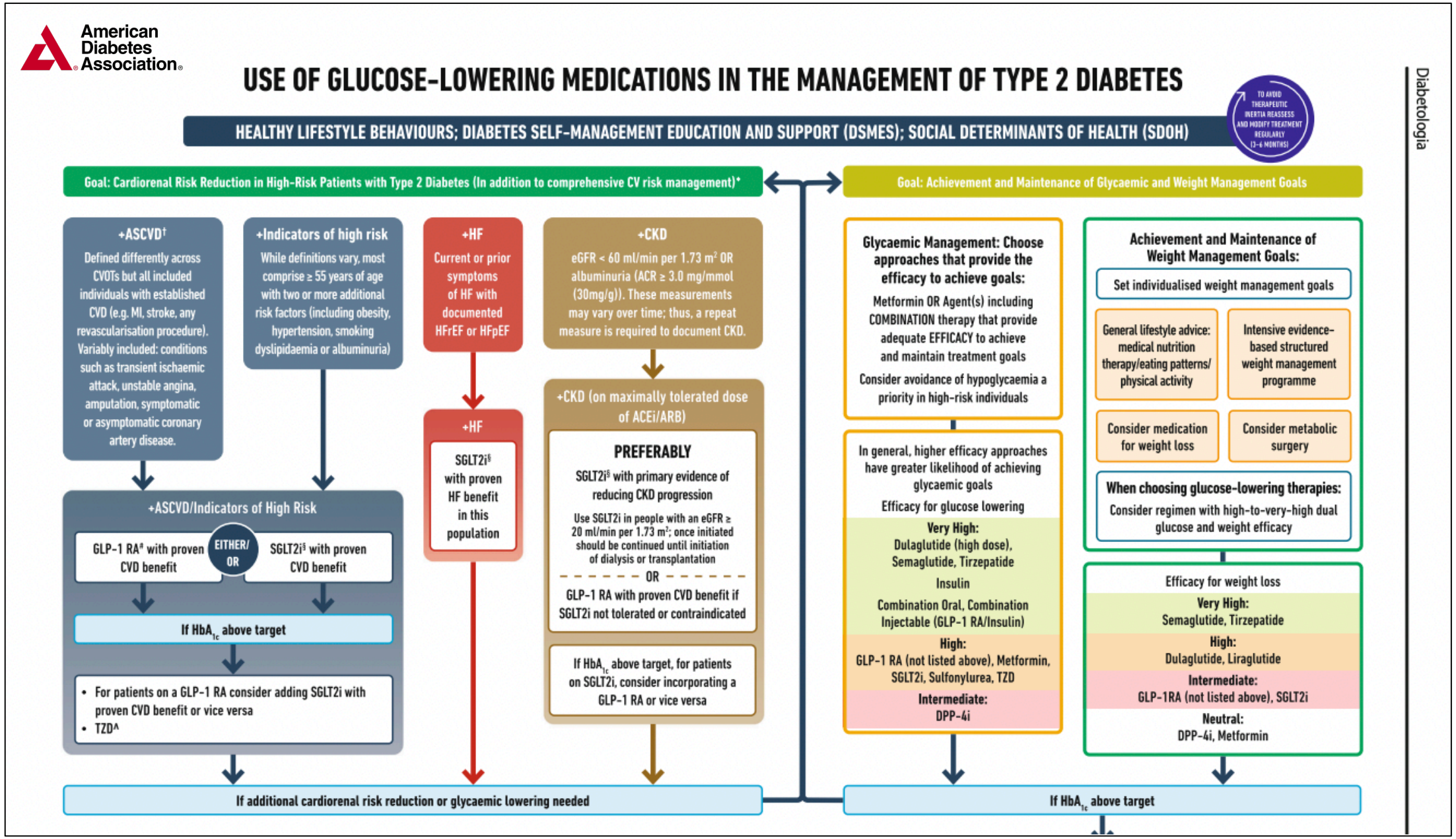
Dr Newman- Has received Honoraira from Novo/AZ



Dr Kanumilli- Has received Honoraria from Novo,AZ,BI,Lilly,Sanofi, Napp,Abbott

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



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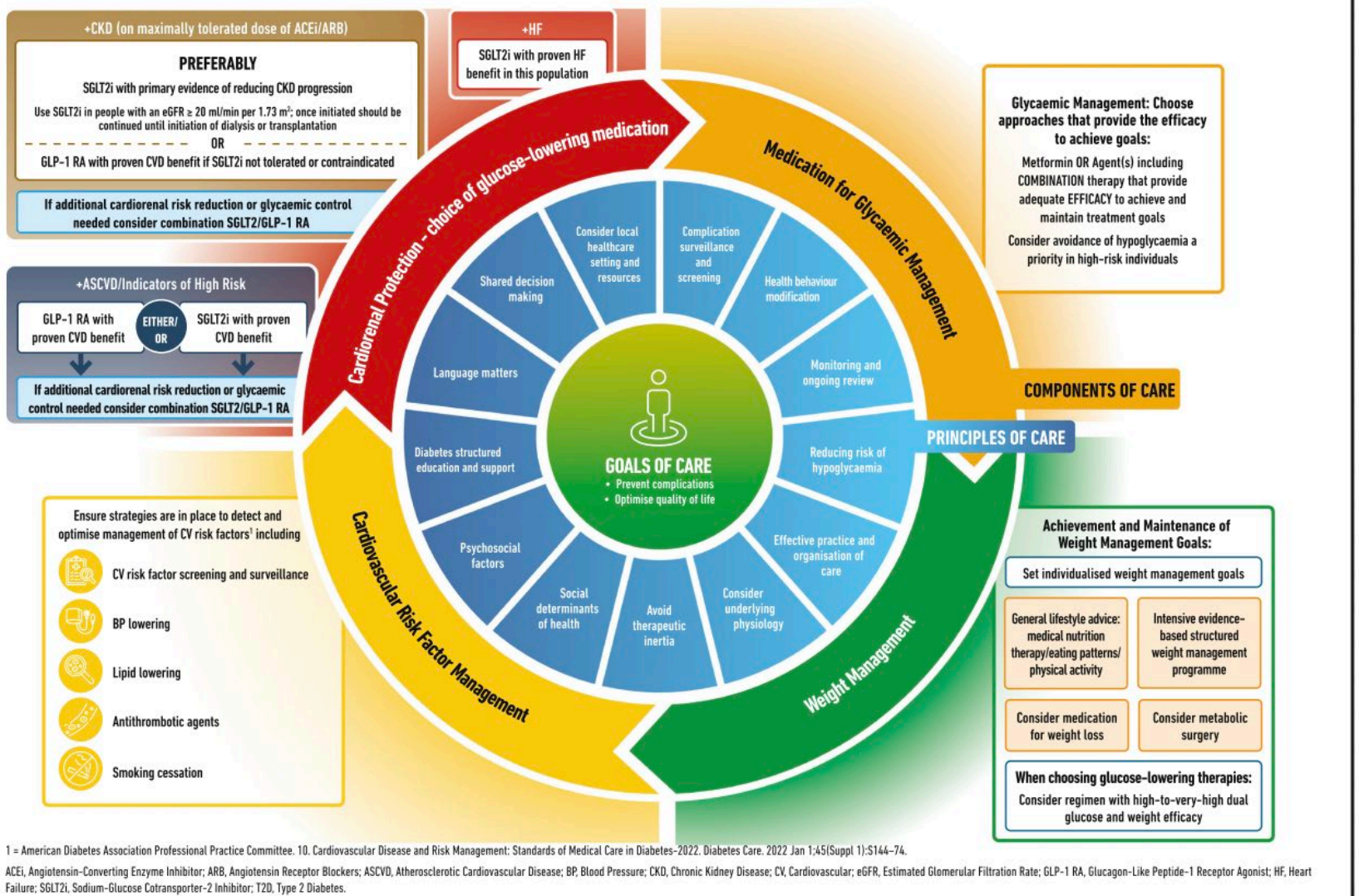


Fig. 4 Holistic person-centred approach to T2DM management

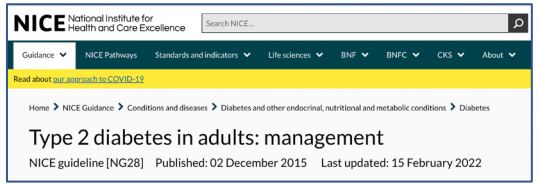
Diabetologia

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

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



How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment — Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider

- DPP-4 inhibitor ('gliptin') or
- Pioglitazone or
- Sulfonylurea

An SGLT2 inhibitor ('flozin') for some people:

- TA 390 Canagliflozin
- TA 390 Dapagliflozin
- TA 390 Empagliflozin
- TA 572 Ertugliflozin

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Not at high CVD risk

Offer
- Metformin
- Or if GI disturbance
- Metformin MR

If metformin contraindicated

Offer
- SGLT2 inhibitor alone

Chronic heart failure or established atherosclerotic CVD

Offer
- Metformin
- or if GI disturbance
- Metformin MR
- and as soon as metfomin tolerability is confirmed, offer
- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated

Consider
- SGLT2 inhibitor alone

High risk of CVD
QRISK2 of 10% or higher

Offer
- Metformin
- or if GI disturbance
- Metformin MR
- and as soon as metfomin tolerability is confirmed, consider
- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

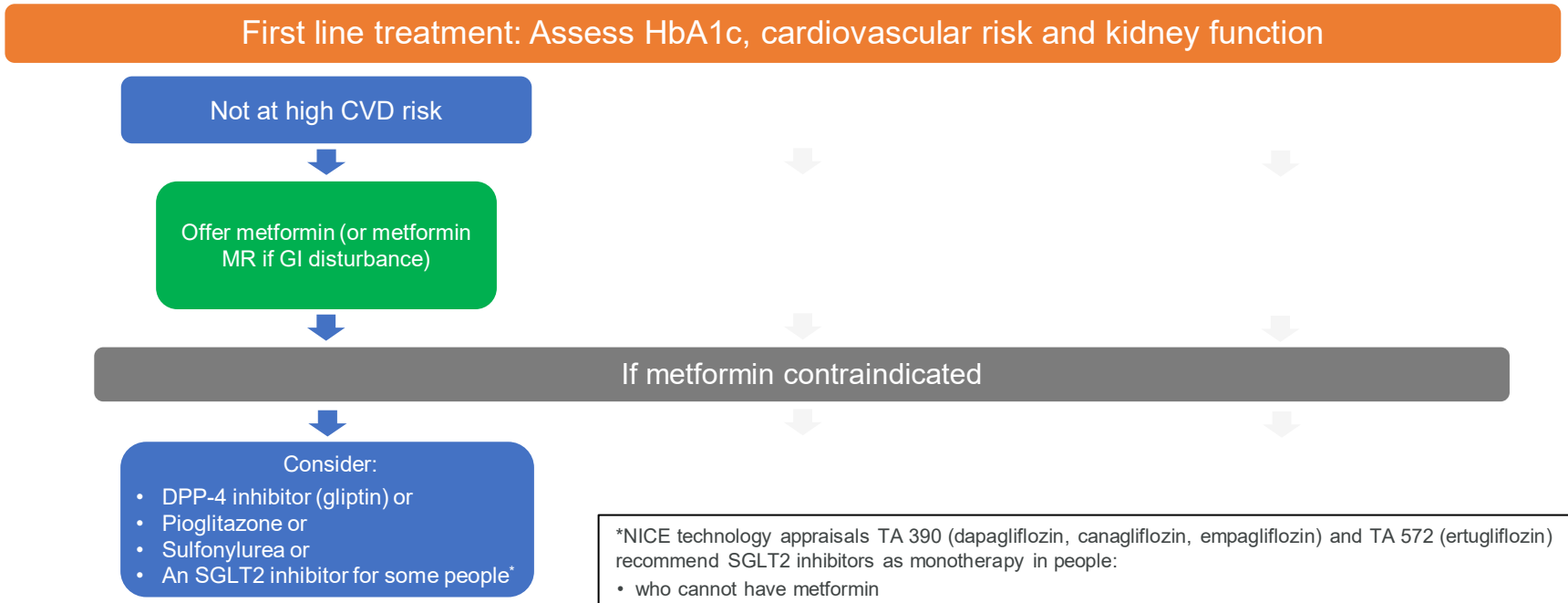
See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

Published date: February 2022. This is a summary of the advice in the NICE guideline on type 2 diabetes in adults: management.

https://www.nice.org.uk/guidance/ng28

NICE recommends metformin only as first line treatment for people with T2D not at high risk of cardiovascular disease

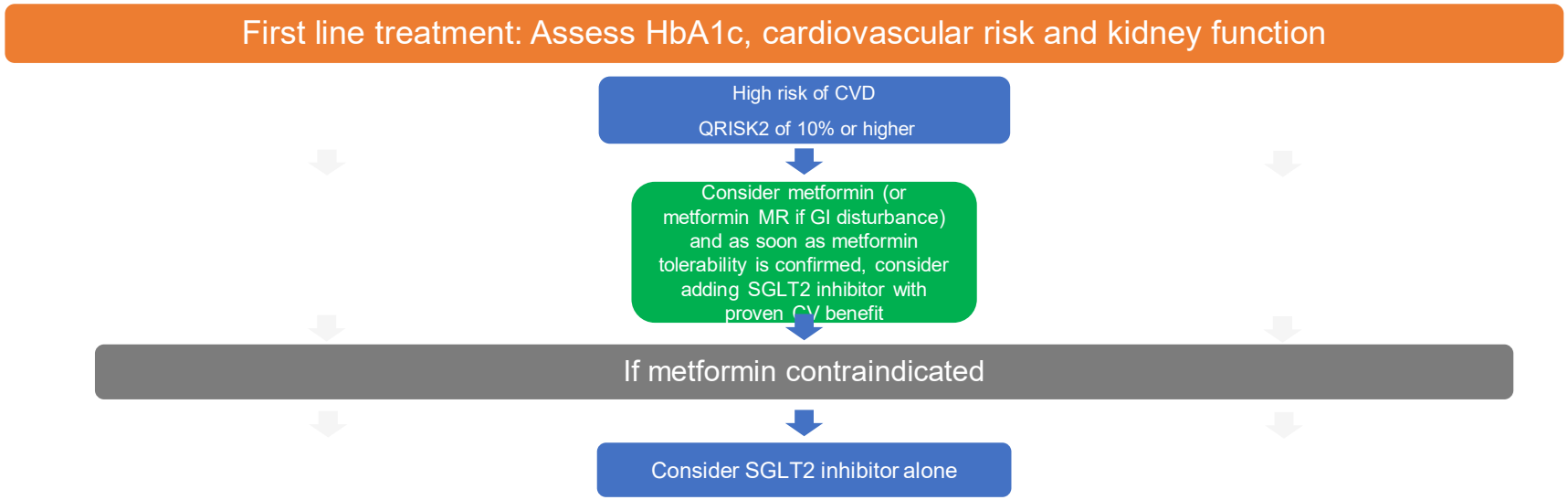


*NICE technology appraisals TA 390 (dapagliflozin, canagliflozin, empagliflozin) and TA 572 (ertugliflozin) recommend SGLT2 inhibitors as monotherapy in people:

- who cannot have metformin
- for whom diet and exercise do not provide adequate glycaemic control
- only if a DPP-4 inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate

CVD, cardiovascular disease.
*Tolerability of Metformin should be assessed before considering/offering an SGLT2i
NICE. NG28. Available at: https://www.nice.org.uk/guidance/ng28/chapter/Recommendations (accessed February 2022).

NICE recommends SGLT2i's as a first-line treatment with metformin for people with T2D at high-risk of CVD



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Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulati
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

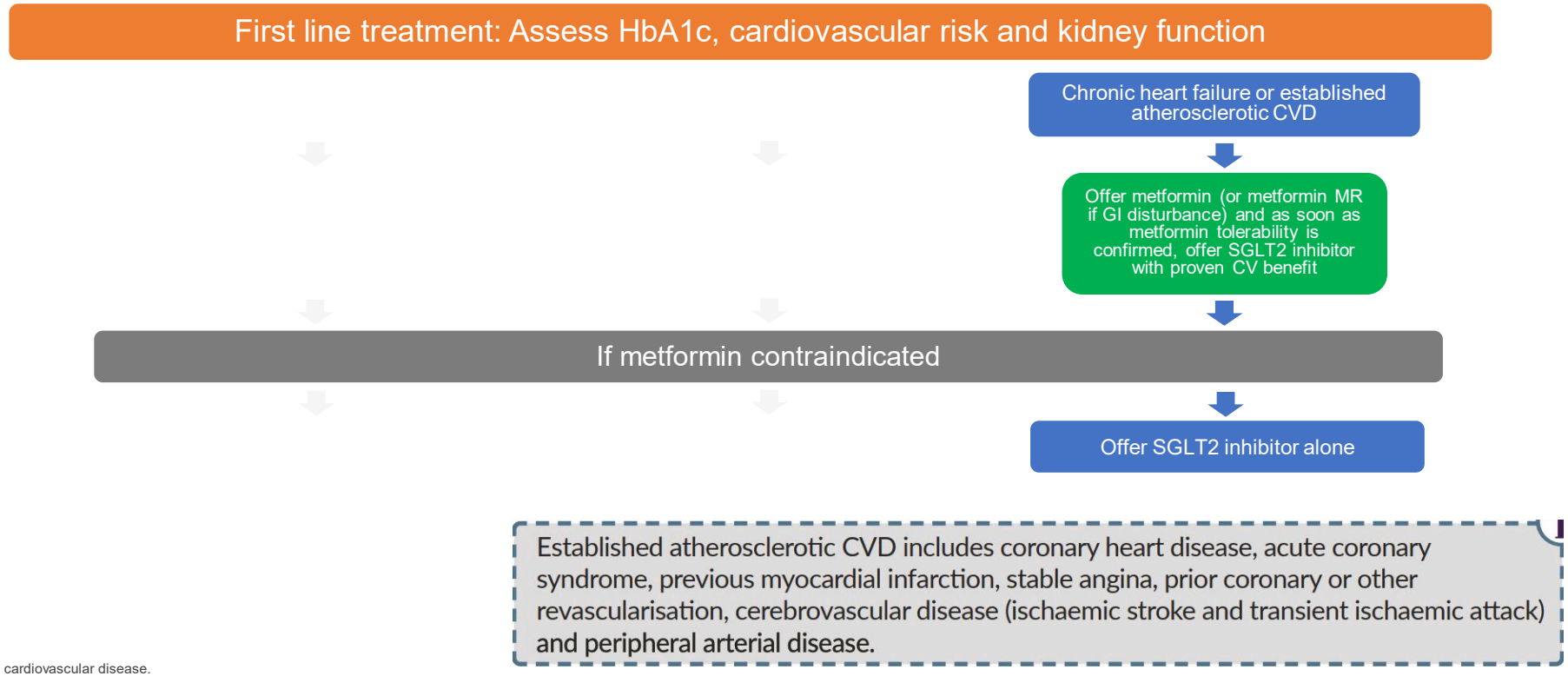
Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

https://www.nice.org.uk/guidance/ng28/resources/visual-summary-full-version-choosing-medicines-for-firstline-and-further-treatment-pdf-10956472093

NICE recommends as a first-line treatment with metformin for people with T2D and chronic heart failure or established atherosclerotic CVD



CVD, cardiovascular disease.
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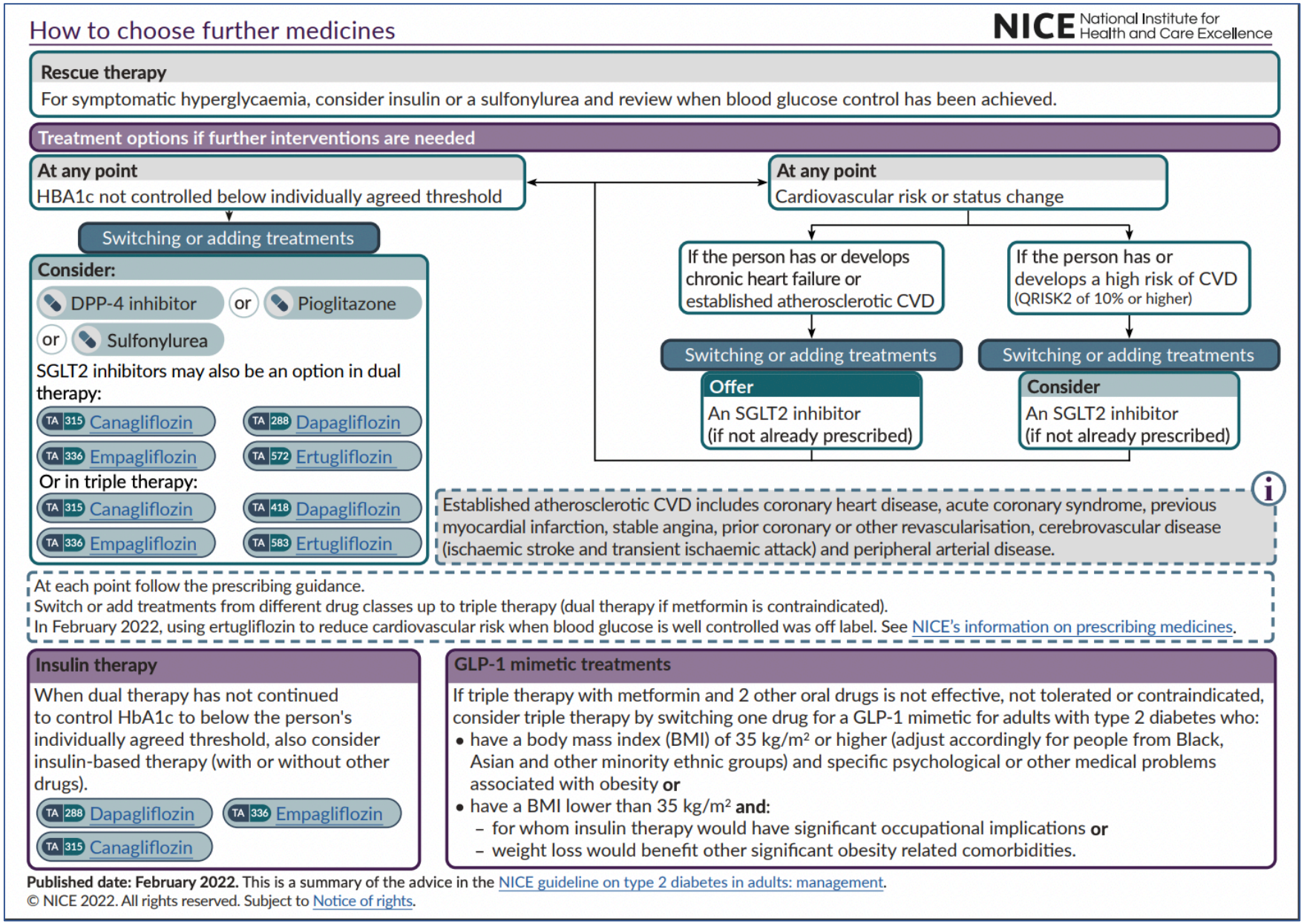
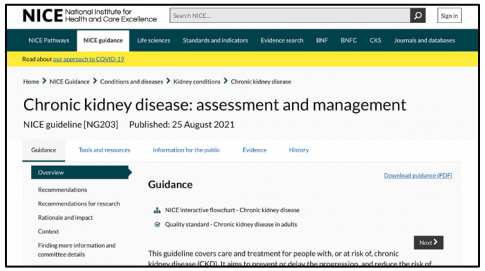
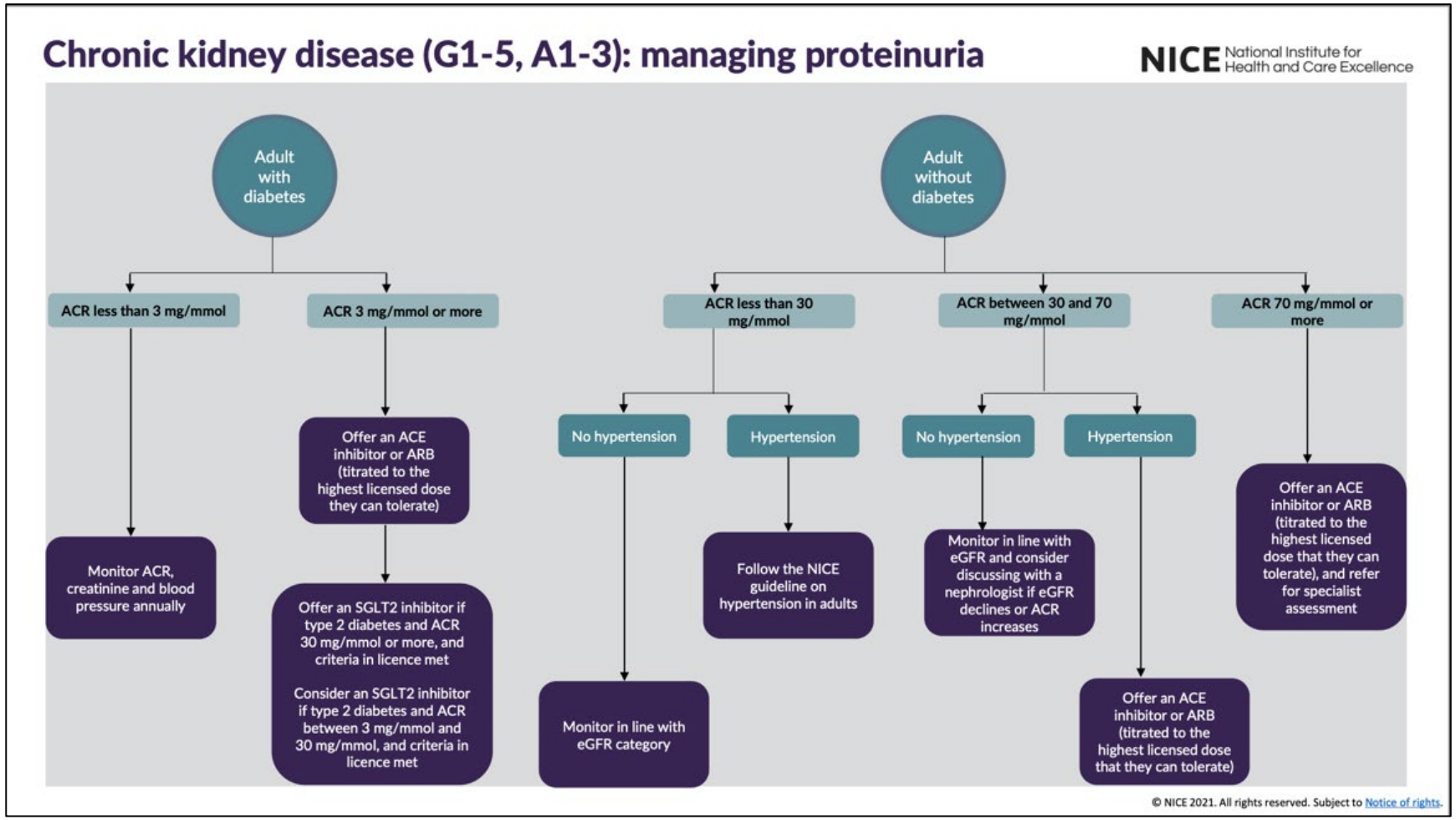


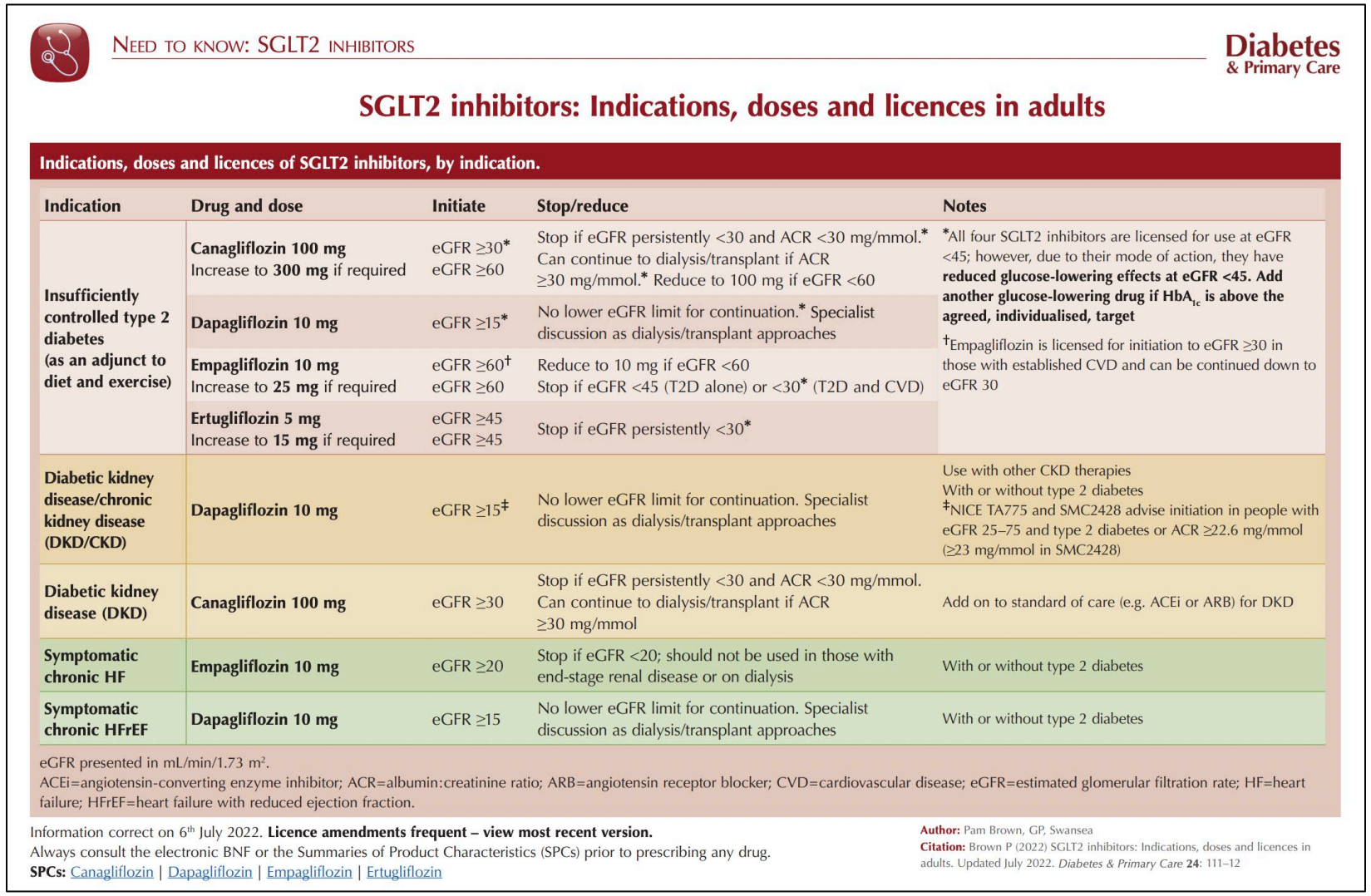
https://www.nice.org.uk/guidance/ng28





https://www.nice.org.uk/guidance/ng203

Helpful Resources



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

There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m2, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m2. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m2

https://diabetesonthenet.com/diabetes-primary-care/sglt2i-indications-doses-licences/

Helpful Resources

Indications, doses and starting/stopping recommendations of SGLT2 inhibitors, by drug name.

Drug	Indication	Drug and dose	Initiate	Stop/reduce	Notes
Canagliflozin	**Insufficiently controlled type 2 diabetes**	**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	*Licensed for initiation to eGFR ≥30 but reduced glucose lowering below eGFR 45; add another glucose-lowering drug if needed
	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
Dapagliflozin	**Insufficiently controlled type 2 diabetes**	**Dapagliflozin 10 mg**	eGFR ≥15†	No lower eGFR limit for continuation.† Specialist discussion as dialysis/transplant approaches	†Licensed for initiation to eGFR ≥15 but reduced glucose lowering below eGFR 45; add another glucose-lowering drug if needed
	Diabetic/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 DKD/CKD therapies With or without type 2 diabetes ‡NICE TA775 and SMC2428 advise initiation in people with eGFR 25–75 and T2DM or ACR ≥22.6 mg/mmol
	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
Empagliflozin	**Insufficiently controlled type 2 diabetes**	**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+CVD)¶	¶Licensed for initiation to eGFR ≥30 in those with established CVD and can be continued to eGFR 30, but reduced glucose lowering below eGFR 45; add another glucose-lowering drug if needed
	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
Ertugliflozin	**Insufficiently controlled type 2 diabetes**	**Ertugliflozin 5 mg** Increase to **15 mg** if required	eGFR ≥45 eGFR ≥45	Stop if eGFR persistently <30**	**Licensed for continuation to GFR ≥30 but reduced glucose lowering below eGFR 45; add another glucose-lowering drug if needed

eGFR presented in mL/min/1.73 m².
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

There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m2, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m2. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m2

https://diabetesonthenet.com/diabetes-primary-care/sglt2i-indications-doses-licences/

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.

Manchester Cardio-Metabolic Pathway

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Community Type 2 Diabetes
Management, Education and Support

The Manchester
Cardio-Renal Pathway

Salford Royal NHS
NHS Foundation Trust

Font Colour

NHS
Greater Manchester and Eastern Cheshire
Strategic Clinical Networks

NHS
Manchester University
CODES
COmmunity Diabetes Education & Support

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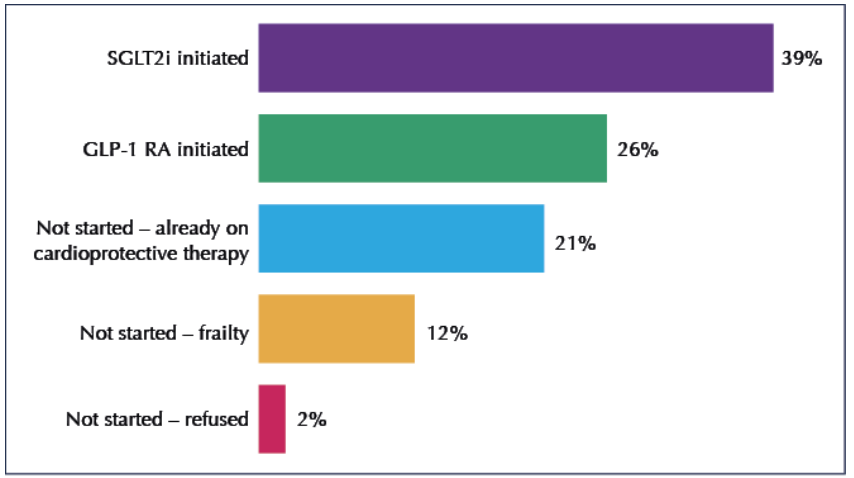
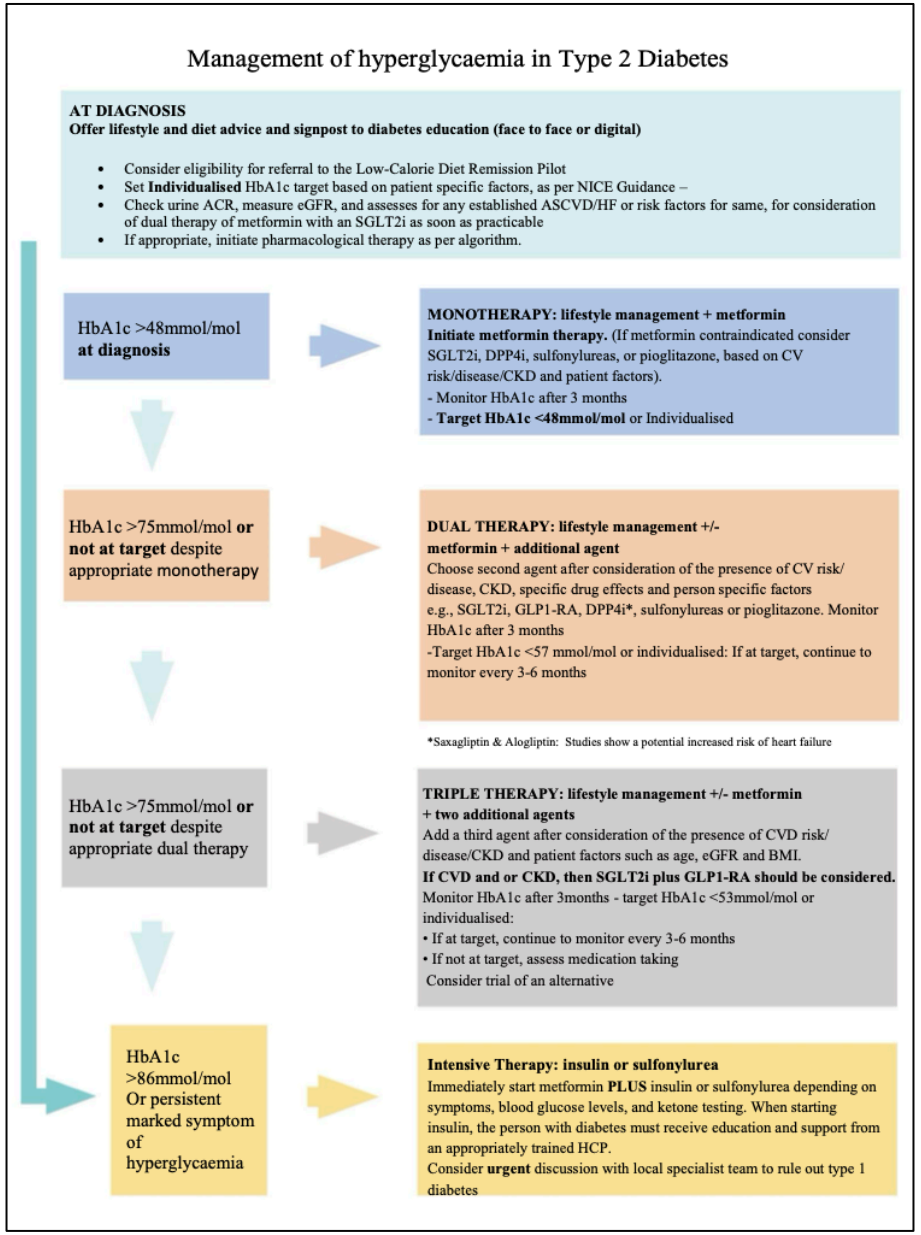


Figure 4. Treatment changes among patients in the Manchester Cardio-Metabolic Pathway. GLP-1 RA=glucagon-like peptide-1 receptor agonist; SGLT2i=sodium–glucose cotransporter 2 inhibitor.

https://diabetesonthenet.com/Journal-diabetes-nursing/late-party-two-year-outcomes-manchester-codes-community-diabetes-education-and-support-pilot/ [Accessed September 2021]

Manchester Cardio-Metabolic Pathway



Management of hyperglycaemia in Type 2 Diabetes

AT DIAGNOSIS
Offer lifestyle and diet advice and signpost to diabetes education (face to face or digital)

- Consider eligibility for referral to the Low-Calorie Diet Remission Pilot
- Set **Individualised** HbA1c target based on patient specific factors, as per NICE Guidance –
- Check urine ACR, measure eGFR, and assesses for any established ASCVD/HF or risk factors for same, for consideration of dual therapy of metformin with an SGLT2i as soon as practicable
- If appropriate, initiate pharmacological therapy as per algorithm.

HbA1c >48mmol/mol **at diagnosis**

MONOTHERAPY: lifestyle management + metformin
Initiate metformin therapy. (If metformin contraindicated consider SGLT2i, DPP4i, sulfonylureas, or pioglitazone, based on CV risk/disease/CKD and patient factors).
- Monitor HbA1c after 3 months
- **Target HbA1c <48mmol/mol** or Individualised

HbA1c >75mmol/mol **or not at target** despite appropriate monotherapy

DUAL THERAPY: lifestyle management +/- metformin + additional agent
Choose second agent after consideration of the presence of CV risk/ disease, CKD, specific drug effects and person specific factors e.g., SGLT2i, GLP1-RA, DPP4i*, sulfonylureas or pioglitazone. Monitor HbA1c after 3 months
-Target HbA1c <57 mmol/mol or individualised: If at target, continue to monitor every 3-6 months

*Saxagliptin & Alogliptin: Studies show a potential increased risk of heart failure

HbA1c >75mmol/mol **or not at target** despite appropriate dual therapy

TRIPLE THERAPY: lifestyle management +/- metformin + two additional agents
Add a third agent after consideration of the presence of CVD risk/ disease/CKD and patient factors such as age, eGFR and BMI.
If CVD and or CKD, then SGLT2i plus GLP1-RA should be considered.
Monitor HbA1c after 3months - target HbA1c <53mmol/mol or individualised:
• If at target, continue to monitor every 3-6 months
• If not at target, assess medication taking
Consider trial of an alternative

HbA1c >86mmol/mol Or persistent marked symptom of hyperglycaemia

Intensive Therapy: insulin or sulfonylurea
Immediately start metformin **PLUS** insulin or sulfonylurea depending on symptoms, blood glucose levels, and ketone testing. When starting insulin, the person with diabetes must receive education and support from an appropriately trained HCP.
Consider **urgent** discussion with local specialist team to rule out type 1 diabetes

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

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

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

DKA T2DM & SGLT2i

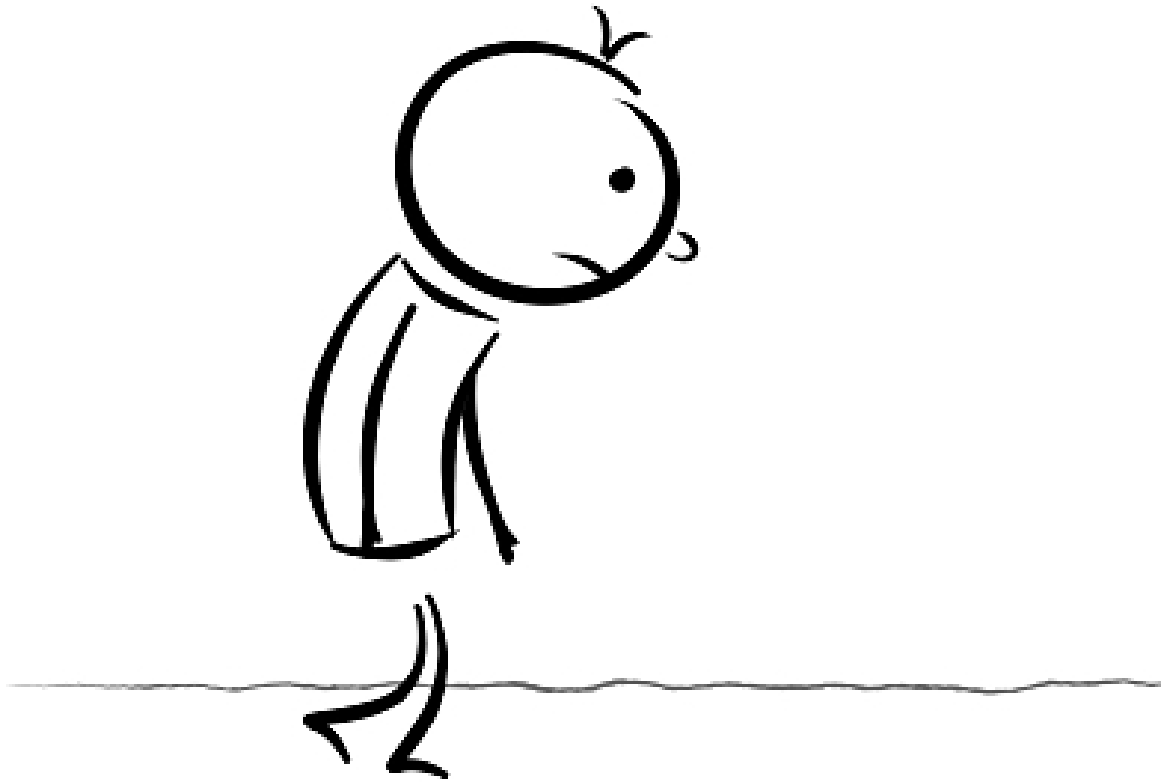
- Diabetes related ketoacidosis is rare but serious complication of T2DM
- All known risk factors for DKA should be considered before starting an SGLT2 inhibitor.
- Some risk factors are not modifiable such as a previous DKA
- Chief modifiable risk factors include:
  - Alcohol (> the recommended UK threshold)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



GLP-1 RA

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)

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

CLINICAL GUIDANCE, DEVICES, EDITOR'S PICK, INSULINS, WORKFORCE ISSUES

PCDS statement: Managing the temporary shortage of NovoRapid FlexPen devices

Hannah Beba

9 Nov 2022 Early View

Advice on switching to alternative devices or insulins during the temporary shortage.

https://diabetesonthenet.com/diabetes-primary-care/pcds-statement-flexpen-shortage/


Questions?