

Treatment of patients with diabetes: The role of oral agents

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Agenda

- Oral antidiabetic agents for Adults With Type 2 Diabetes
- Case studies
- Mechanism of action of oral antidiabetic agents



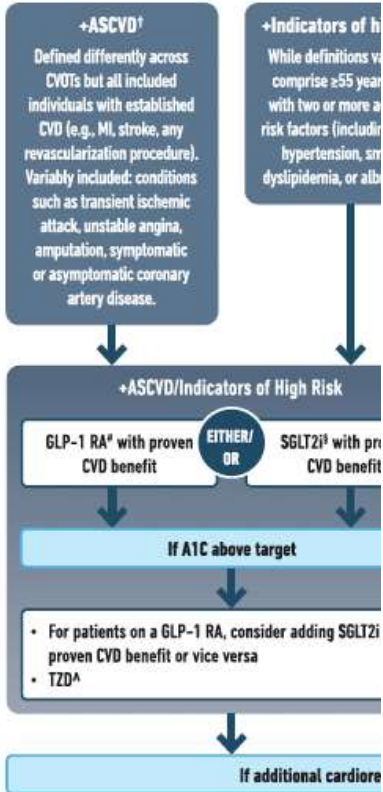
Main Oral Hypoglycemic Agents

-
- Metformin (biguanides)
 - Sulfonylurea
 - Meglitinide
 - Thiazolidinedione
 - DPP-4 inhibitors
 - GLP-1 receptor agonists (semaglutide)
 - SGLT-2 inhibitors

USE OF GLUCOSE-LOWERING MEDICATIONS

HEALTHY LIFESTYLE

Goal: Cardiorenal Risk Reduction in High-Risk Individuals



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, a recommendation is warranted for people with CVD and a weaker recommendation for people with multiple risk factors. These recommendations are based on outcomes seen at higher levels of baseline risk and should be factored into the overall risk-benefit assessment. † For GLP-1 RA, CVOTs demonstrate their efficacy in reducing the risk of MACE. ‡ For SGLT2i, CVOTs demonstrate their efficacy in reducing the risk of MACE. § For GLP-1 RA, CVOTs demonstrate their efficacy in reducing the risk of MACE. ^ For TZD, CVOTs demonstrate their efficacy in reducing the risk of MACE.

Figure 9.3—Use of glucose-lowering medications in people with type 2 diabetes and high-risk conditions. ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide receptor agonist; HbA1c, hemoglobin A1c; MACE, major adverse cardiovascular events; MI, myocardial infarction; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TZD, thiazolidinedione.

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA[#] with proven CVD benefit **EITHER/OR** SGLT2i[§] with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD[^]

2 DIABETES

OF HEALTH (SDOH)



to support self-efficacy in achievement of goals
diagnostic CGM) to identify therapeutic gaps and tailor therapy
H that impact achievement of goals

ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MACE, major adverse cardiovascular events; MI, myocardial infarction; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TZD, thiazolidinedione. Adapted from Davies et al. (84).

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Prioritize avoidance of hypoglycemia in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:

Dulaglutide (high dose),
Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination
Injectable (GLP-1 RA/Insulin)

High:

GLP-1 RA (not listed above), Metformin,
SGLT2i, Sulfonylurea, TZD

Intermediate:

DPP-4i

* In people with HF, CKD, established ICD recommendation is warranted for people are seen at higher levels of baseline renal outcomes trials demonstrate the # For GLP-1 RA, CVOTs demonstrate the

Figure 9.3—Use of glucose-lowering therapies in people with type 2 diabetes: A1C targets and efficacy for glucose lowering and weight management goals.

IN THE MANAGEMENT OF TYPE 2 DIABETES

EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

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Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Prioritize avoidance of hypoglycemia in high-risk individuals

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High:

GLP-1 RA (not listed above), Metformin,
SGLT2i, Sulfonylurea, TZD

Intermediate:

DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice:
medical nutrition
therapy/eating patterns/
physical activity

Intensive evidence-
based structured
weight management
program

Consider medication
for weight loss

Consider metabolic
surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual
glucose and weight efficacy

Efficacy for weight loss

Very High:

Semaglutide, Tirzepatide

High:

Dulaglutide, Liraglutide

Intermediate:

GLP-1 RA (not listed above), SGLT2i

Neutral:

DPP-4i, Metformin

If A1C above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

background use of metformin; † A strong recommendation and thus lower numbers needed to treat iterated and similarly effective; § For SGLT2i, CVOTs with TZD with established/high risk of CVD; ‡ TZD with established/high risk of CVD.

converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; HFREF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TZD, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (84).

First –line therapy

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

1- healthy life style behavior

2- DSME -S

3- Social determinants of health

Factors regarding Drug selection



Efficacy



CV effects
ASCVD/HF

cost

Oral /SC

Hypoglycemia

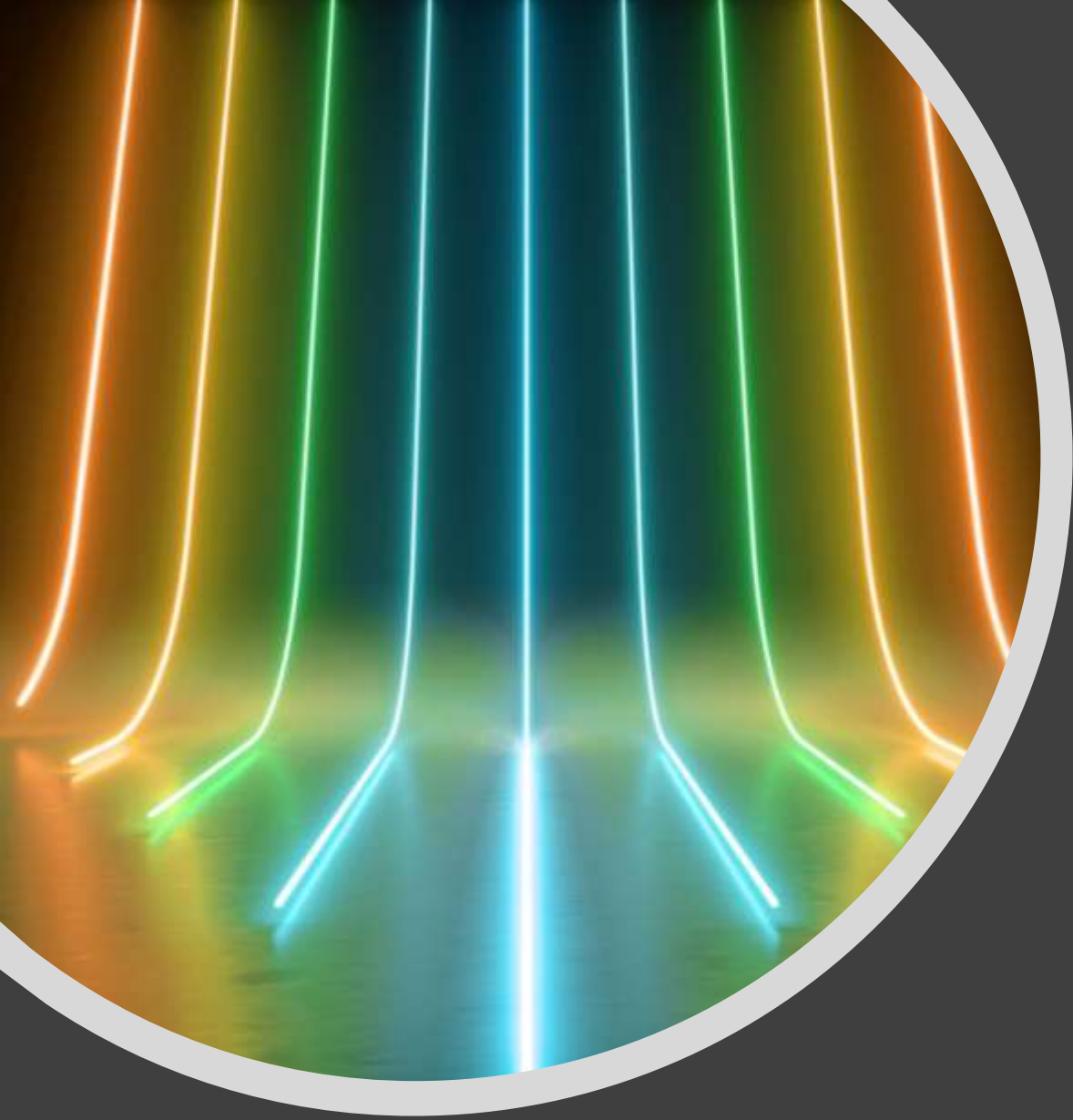


Weight
change



Renal effects

Additional consideration



Pharmacologic Therapy for Adults With T2DM

- 1- Healthy lifestyle behaviors
- 2- Diabetes self-management education and support
- 3- Avoidance of clinical inertia
- 4- Social determinants of health

Should be considered in the glucose-lowering management of type 2 diabetes.



Pharmacologic Therapy for Adults With Type 2 Diabetes

A person-centered shared decision making approach should guide the choice of pharmacologic agents for adults with type 2 diabetes.

Consider the effects on cardiovascular and renal comorbidities; effectiveness; hypoglycemia risk; impact on weight, cost and access; risk for adverse reactions and tolerability; and individual preferences **E**




Pharmacologic Therapy for Adults With Type 2 Diabetes

In adults with type 2 diabetes and established/high risk of ASCVD, HF, and/or CKD , the treatment regimen should include agents that **reduce cardiorenal risk**. A

ADA Recommendations 2024

- 9.10 The glucose-lowering treatment plan should consider approaches that **support weight management** goals for adults with type 2 diabetes. **A**
- 9.11 For adults with type 2 diabetes, use pharmacological strategies that provide **sufficient effectiveness** to achieve and maintain the intended treatment goals. **A**
- 9.12 **Treatment modification** (intensification or deintensification) for adults not meeting individualized treatment goals **should not be delayed**. **A**



Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

- Medication regimen and medication-taking behavior should be **reevaluated at regular intervals (every 3–6 months)** and adjusted as needed to incorporate specific factors that impact choice of treatment .E

ADA
Recommendations
2024

- 9.14 **Early combination therapy** can be considered in adults with type 2 diabetes at treatment initiation to shorten time to attainment of individualized treatment goals. A

ADA Recommendations 2024

- 9.15 In adults with T2DM without cardiovascular and/or kidney disease, pharmacologic agents should address both the individualized glycemic and weight goals. **A**

ADA Recommendations 2024

- 9.16 In adults with type 2 diabetes who have not achieved their individualized glycemic goals, selection of subsequent glucose-lowering agents should take into consideration the:
 - Individualized glycemic and weight goals
 - the presence of other metabolic comorbidities and the risk of hypoglycemia. A

ADA Recommendations 2024

- 9.17 In adults with type 2 diabetes who have not achieved their individualized weight goals, additional weight management interventions (e.g., intensification of lifestyle modifications, structured weight management programs, pharmacologic agents, or metabolic surgery, as appropriate) are recommended. **A**

ADA Recommendations 2024

- 9.25 In adults with T2DM, glucose-lowering agents may be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits (i.e., weight, cardiometabolic, or kidney benefits). **A**

ADA Recommendations 2024


- 9.26 To minimize the risk of hypoglycemia and treatment burden when starting insulin in adults with T2DM, reassess the need for and/or dose of glucose-lowering agents with **higher hypoglycemia risk (sulfonylureas and meglitinides)**. **A**

ADA Recommendations 2024

- 9.28 Routinely assess all people with diabetes for financial obstacles that could impede their diabetes management.
- Clinicians, members of the diabetes care team, and social services professionals should work collaboratively, as appropriate and feasible, to support these individuals by implementing strategies to reduce costs, thereby improving their access to evidence-based care. E

ADA Recommendations 2024

- 9.29 In adults with diabetes and **cost related barriers, consider use of lower cost** medications for glycemic management (i.e., **metformin, sulfonylureas, thiazolidinediones, and human insulin**) within the context of their risks for hypoglycemia, weight gain, cardiovascular and kidney events, and other adverse effects.
E



Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

- **Metformin should be continued upon initiation of insulin therapy** (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits.
A

First Case

A 52 – years- old overweight man diagnosed with T2 DM since 5 months ago.

His BMI =26, he is otherwise healthy, advised for life style modification

His most recent HbA1c is 7.4%

Lipid profile was normal, e GFR= 80ml/min

Normotensive

What is the best next step treatment ?

Best next
step?

24

Metformin plus sitagliptin

Gliclazide MR

Metformin

Empagliflozin

Best next
step?

25

Metformin plus sitagliptin

Gliclazide MR

Metformin

Empagliflozin

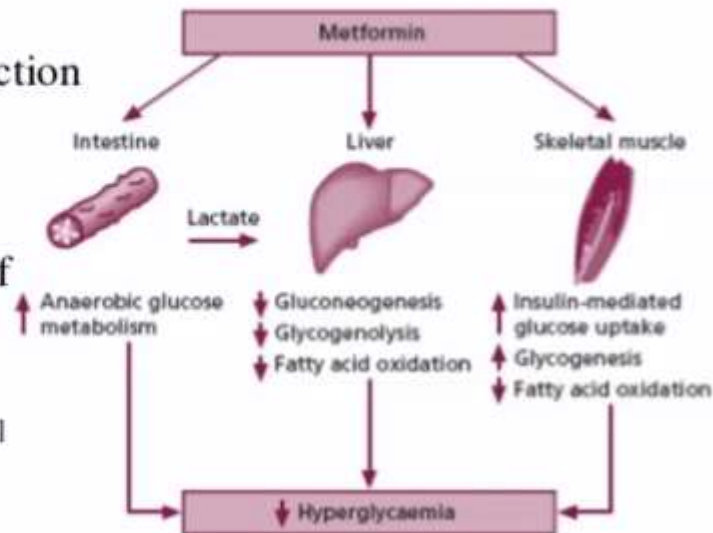
Metformin

	Efficacy ¹	Hypoglycaemia	Weight change ²	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	<ul style="list-style-type: none"> Contraindicated with eGFR <30 ml/min per 1.73 m² 	Oral	Low

Traditionally recommended as first-line glucose-lowering therapy for type 2 diabetes, because of its high efficacy in lowering HbA_{1c}, minimal hypoglycemia risk when used as monotherapy, potential for some modest weight loss, good safety profile, low cost

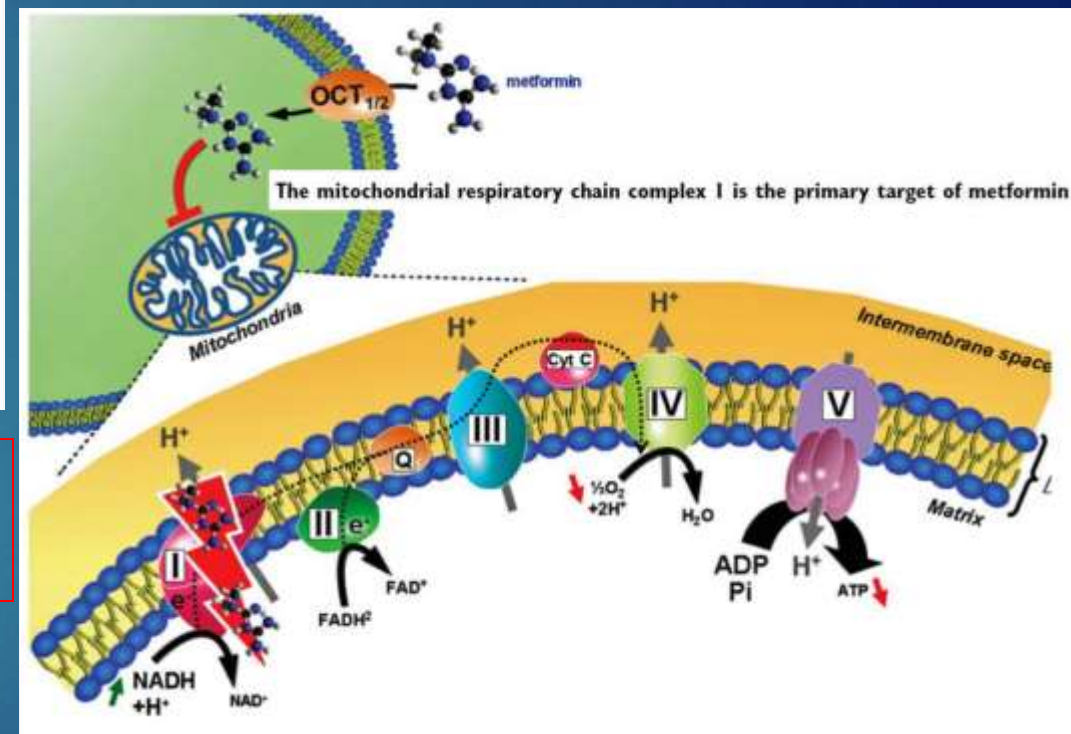
MECHANISM OF ACTION

- Decrease hepatic glucose production through a mild inhibition of the mitochondrial respiratory-chain complex I.[2]
- Decrease intestinal absorption of glucose
- anti-oxidative properties of metformin on endothelial cells[2]



Metformin inhibits this complex

The consequence of *inhibition of the respiratory chain complex I by metformin* is a transient reduction in cellular energy status.



**AMPK
activation**

Metformin

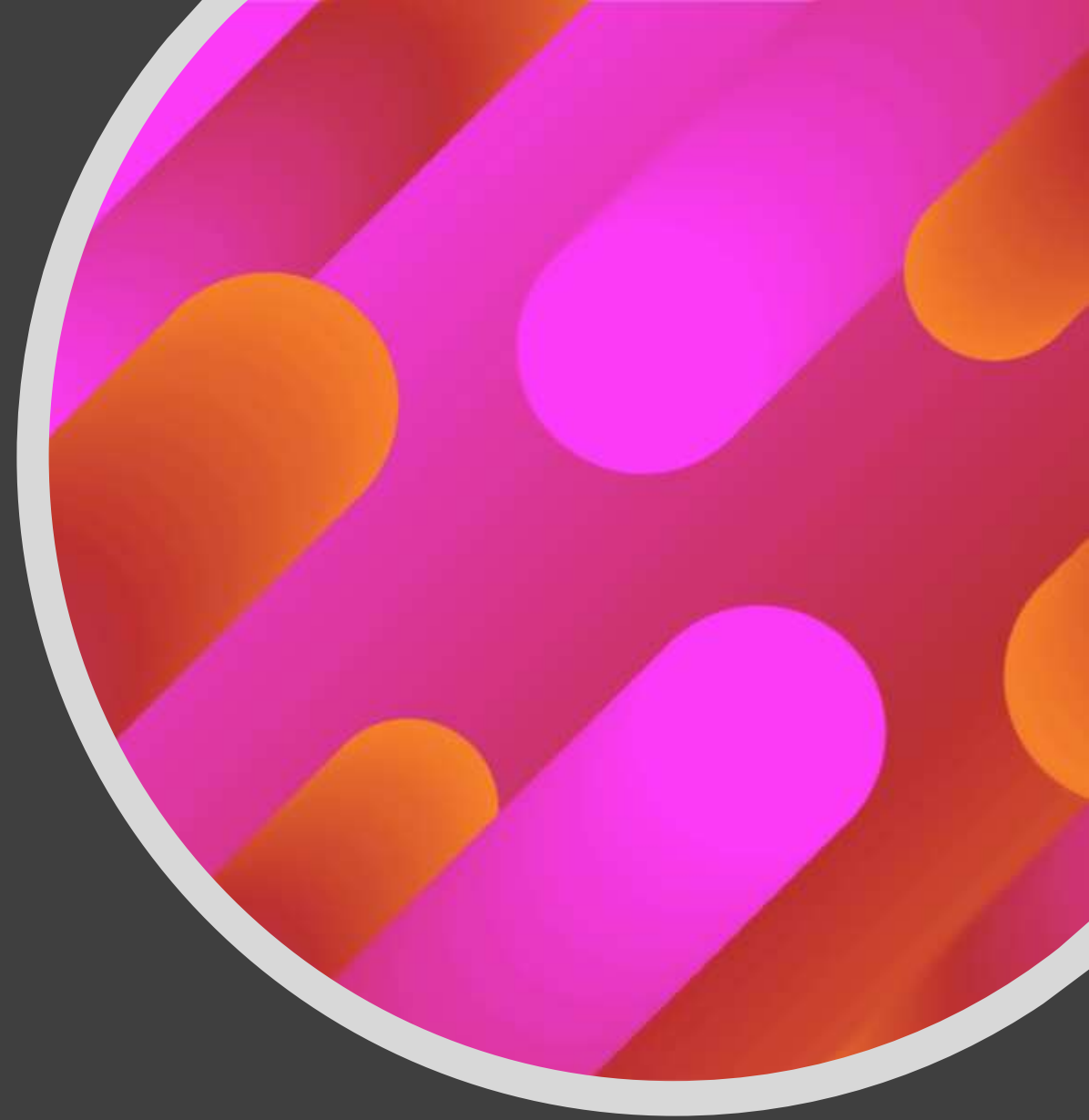
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- In 2016, the FDA revised warning regarding the use of metformin in patients with diabetic kidney disease (DKD)
 - No dose adjustment if eGFR >45 ml/min per 1.73m^2
 - Do not initiate or assess risk/benefit if currently on metformin if eGFR=30-45 ml/min per 1.73m^2
 - Discontinue if eGFR <30 ml/min per 1.73m^2
- Monitor:
 - Estimated GFR
 - Hematologic parameters
 - Vitamin B12 levels every 2-3 years

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

In adults with T2DM and

1. Established or high risk of ASCVD
 2. Heart failure (HF)
 3. And/or chronic kidney disease (CKD)
- treatment plan should include agent(s) that reduce CV and kidney disease risk (SGLT2-i and/or GLP-1 RA) for glycemic management and comprehensive cardiovascular risk reduction, **independent of A1C** and in consideration of person-specific factors. **A**



Second Case study

58 y/o woman

DM since 5 years ago

PMHx:

Comorbidities

HTN

Hyperlipidemia

PE:

BP: 128/78 mmHg

BW: 72 kg

Height: 162 cm

BMI: 27.4 Kg/m²

Lab Test

FBS: 152 mg/dl, HbA1c: 7.8 %

Cr: 1 mg/dl

LFT- AST: 19 - ALT: 26

TSH : Normal

TG: 280 mg/dl
LDL: 105 mg/dl, HDL: 40 mg/dl,
Total Chol: 181

24 hr urine Albumin: 25 mg

Daily Medications

- Sitagliptin/Metformin combination :
50mg/1000 mg BD
- Glibenclamide 5 mg daily
- Atorvastatin: 40 mg daily
- Valsartan/Amlodipine : 160 mg/5 mg once daily

She
experienced
hypoglycemic
attacks



58 y/o ♀

FBS: 152mg/dl
A1c: 7.8 %

Cr: 1
eGFR: 66

TG: 180
LDL: 105
HDL: 40



What is the best next step?

- Reduce Metformin to 500 mg BD and Add Empagliflozin 10 mg.
- Stop Glibenclamide, Add Empagliflozin 10 mg.
- Stop Glibenclamide, reduce Metformin to 500 mg BD, change Sitagliptin to Linagliptin .
- Reduce Glibenclamide dosage, reduce Metformin dosage, and add Empagliflozin 10 mg.

What do you recommend?

Reduce Metformin to 500 mg BD and Add Empagliflozin 10 mg.

Stop Glibenclamide, Add Empagliflozin 10 mg.

Stop Glibenclamide, reduce Metformin to 500 mg BD, change Sitagliptin to Linagliptin

Reduce Glibenclamide dosage, reduce Metformin dosage, and add Empagliflozin 10 mg.

Third case

64 year old
male

DM2 since
2017

Had ACS ,
Secondary
PCI in 2022

TX for
diabetes

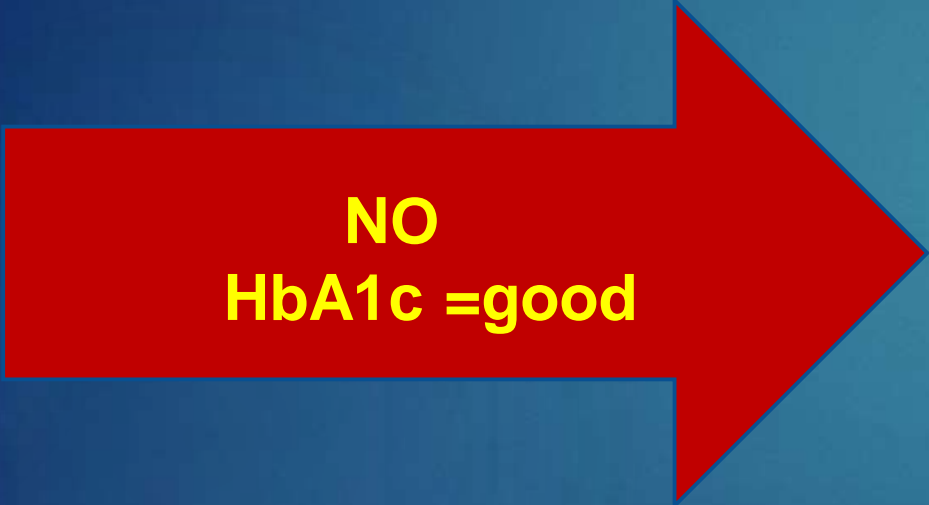
Metformin
1000 BD

HbA1c 6,9%

Do you modify the glucose lowering medication?

35

NO
HbA1c =good



Yes
EBM Treatment



What's your suggestion ?

FIGURE 3: USE OF GLP-1 RA AND SGLT2i

HEALTHY LIFESTYLE BEHAVIOUR

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g. MI, stroke, any revascularisation procedure). Variably included: conditions such as transient ischaemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥ 55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidaemia or albuminuria)



+ASCVD/Indicators of High Risk

GLP-1 RA[#] with proven CVD benefit

EITHER/OR

SGLT2i[§] with proven CVD benefit

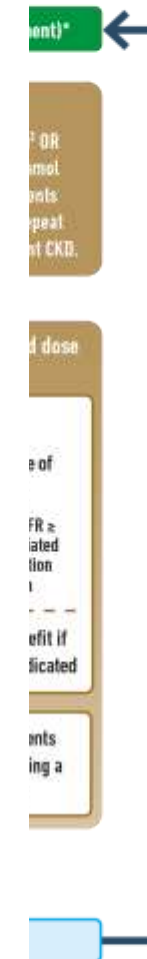
If HbA_{1c} above target

- For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit or vice versa
- TZD[^]



OF TYPE 2 DIABETES

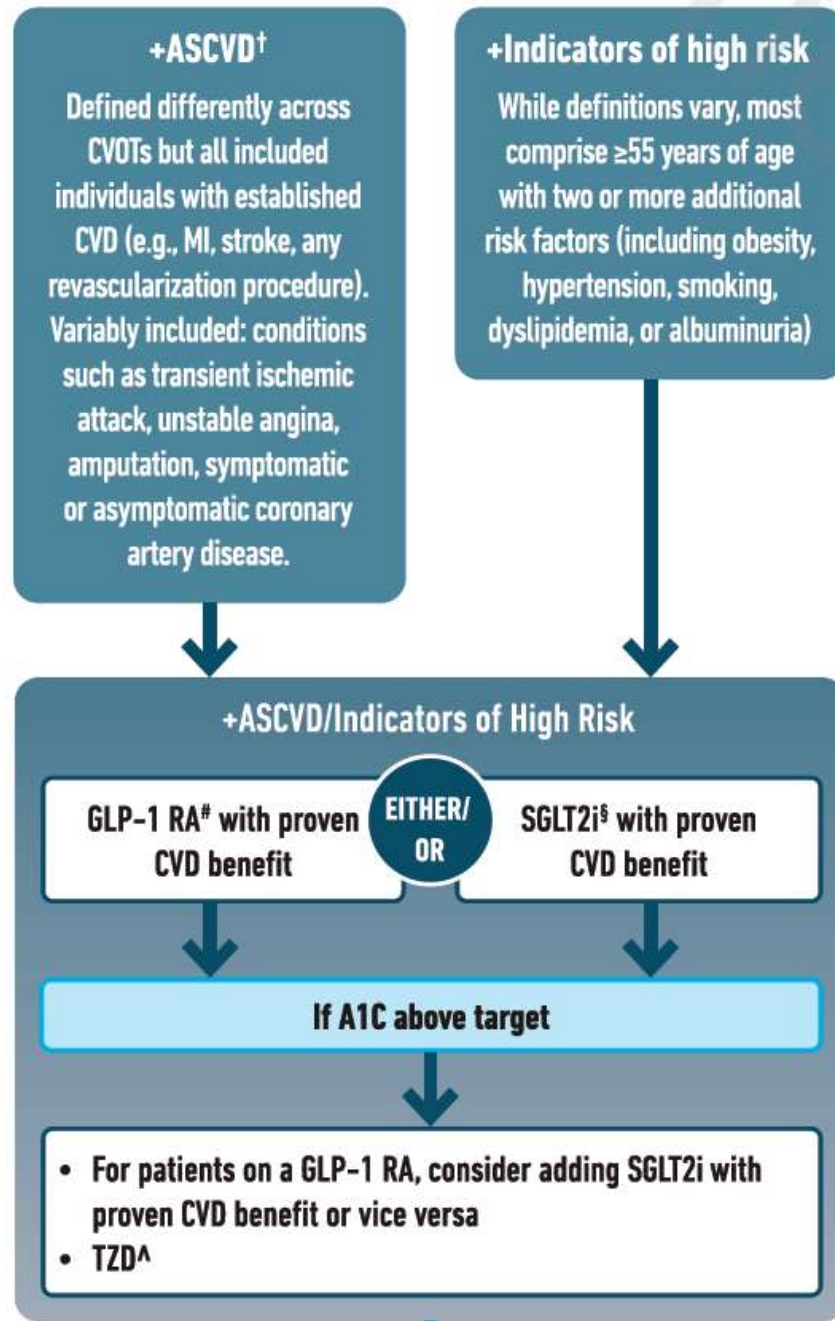
FACTORS OF HEALTH (SDOH)



Adding SGLT2i for him

ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Receptor Agonist; HFrEF, Heart Failure with reduced Ejection Fraction; HFrEF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium Glucose Cotransporter 2 Inhibitor; TZD, Thiazolidinedione. [†] In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower number needed to treat. See text for details. [^] Low-dose TZD may be better tolerated and similarly effective; [§] For SGLT2i, CV/renal outcomes trials did not include individuals with T2D with established/high risk of CVD; [#] For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MA

Comprehensive
approach **to CV** risk
reduction



Patients with T2DM with or at high risk for ASCVD, should be treated with a
cardioprotective SGLT2-I and/or GLP-1 RA

Case Scenario - 4

- We want to discuss the management plan for a **55-year-old obese man** with diabetes.
- He had **hypertension and dyslipidemia** for the past 6 years, not adequately controlled

Current treatment include:

- Metformin 1000 mg, Sitagliptin 100mg/day Rosuvastatin 10 mg
- He is **cigarette smoker**
- He reports a **TIA 3 months ago.**

Physical Examination



BP: 148/98 mmHg



BMI: 31.3 kg/m²

The most recent lab data

Current Lab tests are as followings:

FBS: 184 mg/dl

HbA1c: 8.5 %

LDL: 115mg/dl

Cr: 1.44 mg/dl

eGFR: 55 ml/min/1.73 m²

Questions

- How do you manage his diabetes?
- DO we need to change the treatment plan?
- If yes why?
- Which points should be considered?
- Risk actors? (Age, HTN, HLP, Smoker, Obese, CKD)

Questions

- Should we consider renal function in selecting the best strategy to treat hyperglycemia?
- Could you walk us through how you approach to this patient's CKD
- What you do for him?

What would be the best treatment in this patient?

- ☐ 1. Increase Metformin to 2000 mg daily
- ☐ 2. Add Liraglutide 1.8 mg daily
- ☐ 3. Switch to Metformin-DAPA(EMPA) fixed-dose combination: 2000/10 mg daily
- ☐ 4. Add EMPA (DAPA) -Lina fixed combination: 10/5mg daily
- ☐



ADA Recommendations 2024

- 9.19 In adults with type 2 diabetes who have HF (with either reduced or preserved ejection fraction), an SGLT2 inhibitor is recommended, for glycemic management and prevention of HF hospitalizations. **A**

5Th Scenario

- Our patient is a woman, 53 years of age, with a 17-year history of type 2 diabetes, hypertension, and hyperlipidemia and a 35-year history of smoking.
- She had been referred to a diabetes clinic for follow up.
- She presents in the office with shortness of breath, pruritus, and pitting edema of bilateral extremities.
- Her blood pressure is 165/92 mm Hg, heart rate 94 beats per minute (regular rate and rhythm), and respiration 26 breaths per minute.
- She is 157 cm tall and weighs 90 kg (BMI: 35.8 kg/m²).

5Th Scenario

- Based on the serum test results, patient is diagnosed with:
 - a) stage 3 chronic kidney disease
 - b) GFR of 49 mL/min/1.73 m²
 - c) profound microalbuminuria.
- FBS= 185 mg/dl A1c= 8.1% LDL= 95 mg/dl HDL=35mg/ml
- She is considered at high risk for a cardiovascular event due to her long history of diabetes, hypertension, tobacco abuse, and hyperlipidemia, all of which appear to be uncontrolled.

Medications

- Insulin glargine 20 u every night
- Metformin 2000mg
- Sitagliptin 100 mg
- Rosuvastatin 20 mg
- Valsartan/amlodipine 160/10 mg
- HCTZ 25 mg
- ASA 80 mg

Questions

- 1- what is the best choice for treating her hyperglycemia in this patient
- 2- as a practitioner what points do you consider for managing her cardiac problems? (SGLT I –HF studies)
- 3- as practitioner a how do you approach to her kidney problems? (SGLT2-I –CKD studies)

Diabetes is highly prevalent in patients who experienced HF with both:



```
graph TD; A[Diabetes is highly prevalent in patients who experienced HF with both:] --> B[1- Preserved ejection fraction (HFpEF) "stiff pump" LVEF ≥50%]; B --> C[2- Reduced ejection fraction (HFrEF) "weak pump" (LVEF) ≤40%]; C --> D[Both DM+ HF = 70 to 80% increase in mortality risk, with higher rates of hospitalization];
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1- Preserved ejection fraction (HFpEF) "stiff pump"
LVEF $\geq 50\%$

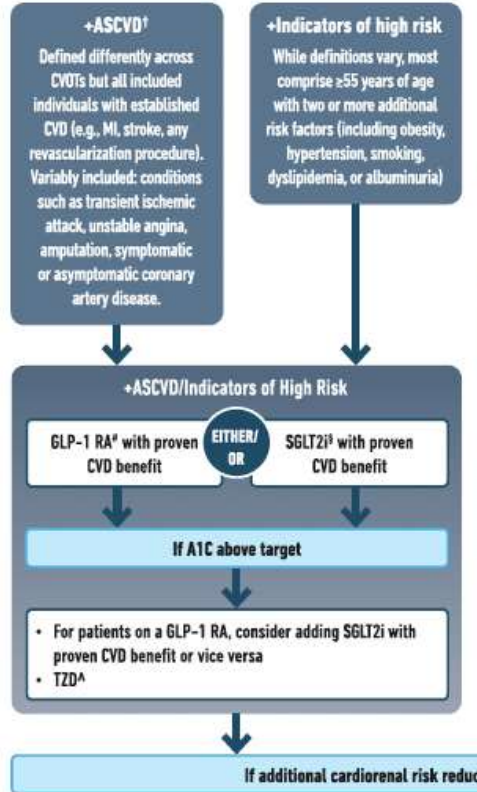
2- Reduced ejection fraction (HFrEF) "weak pump"
(LVEF) $\leq 40\%$

Both DM+ HF = 70 to 80% increase in mortality risk, with higher rates of hospitalization

USE OF GLUCOSE-LOWERING MEDICATIONS

HEALTHY LIFESTYLE BEHAVIORS

Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA is warranted for people with CVD and a weaker recommendation for those with multiple risk factors. † For SGLT2i, CVOTs demonstrate their efficacy in reducing the risk of composite MACE. ‡ For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, and hospitalization for heart failure. § For TZD, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, and hospitalization for heart failure. ¶ For TZD, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, and hospitalization for heart failure.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (84).

+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF
SGLT2i§ with proven HF benefit in this population

MANAGEMENT OF TYPE 2 DIABETES

SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



Comprehensive approach to HF risk reduction with SGLT2-i

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

§ For SGLT2i, CVOTs demonstrate their efficacy in reducing the risk of composite MACE, CV death, and hospitalization for heart failure. § For SGLT2i, CVOTs demonstrate their efficacy in reducing the risk of composite MACE, CV death, and hospitalization for heart failure.

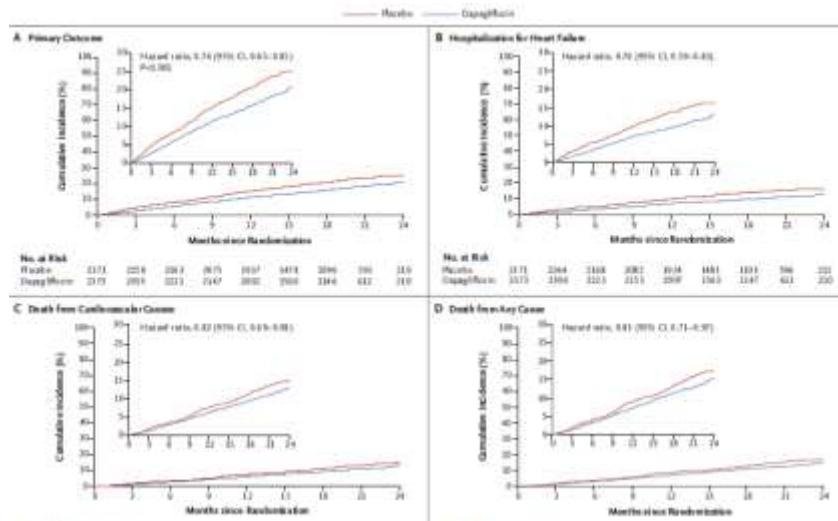
§ For SGLT2i, CVOTs demonstrate their efficacy in reducing the risk of composite MACE, CV death, and hospitalization for heart failure. § For SGLT2i, CVOTs demonstrate their efficacy in reducing the risk of composite MACE, CV death, and hospitalization for heart failure.

These agents should be included in the regimen of care

- 1-irrespective of the need for additional glucose Lowering
- 2-irrespective of metformin use.

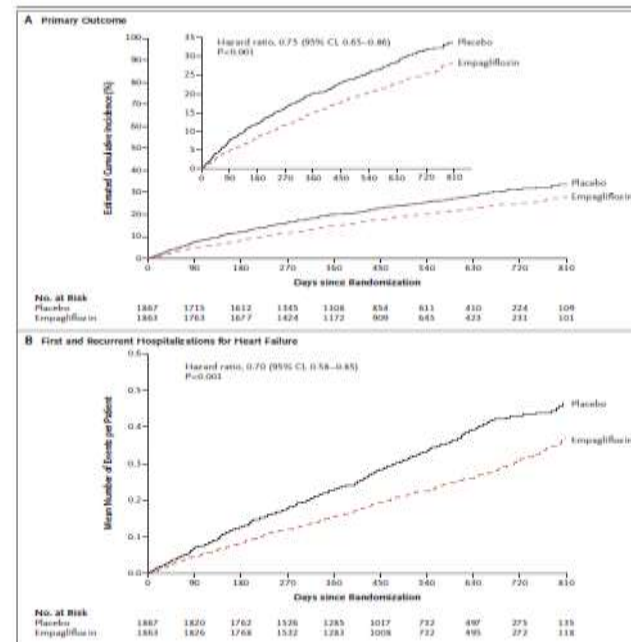
Effect of SGLT2i in people with heart failure

DAPA-HF



N Engl J Med 2019;381:1995-2008

EMPEROR-REDUCED



N Engl J Med 2020;383:1413-1424

EMPEROR-PRESERVED

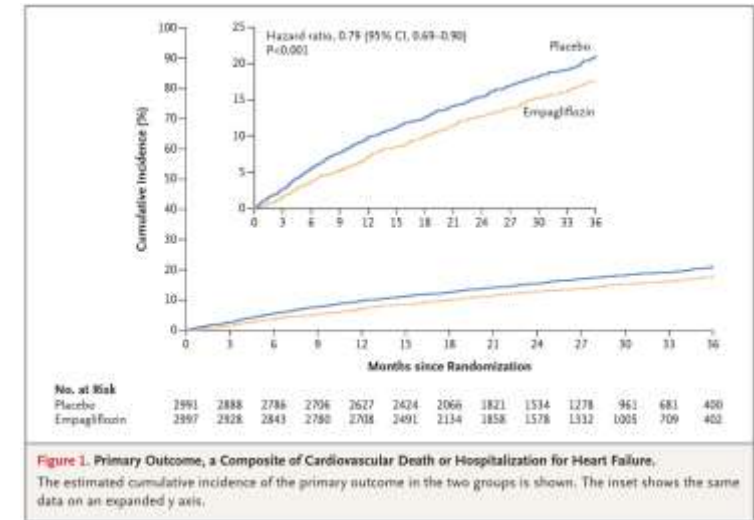
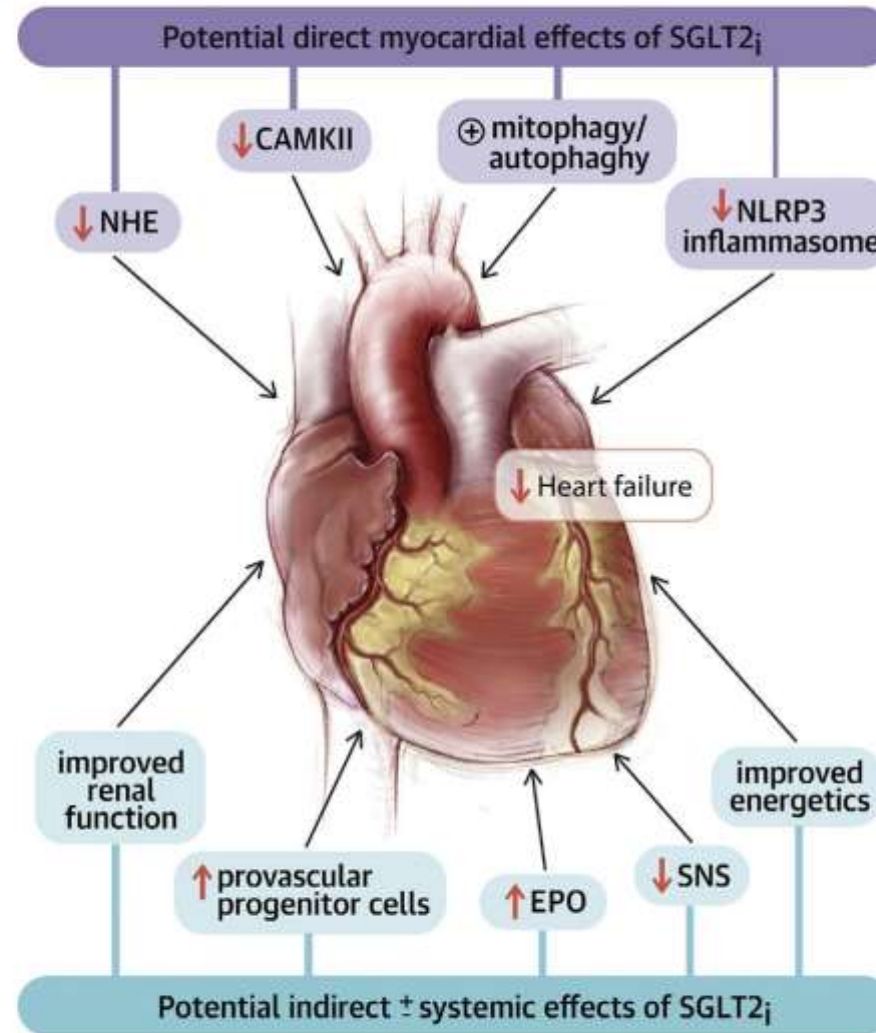


Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

N Engl J Med 2021;385:1451-1461

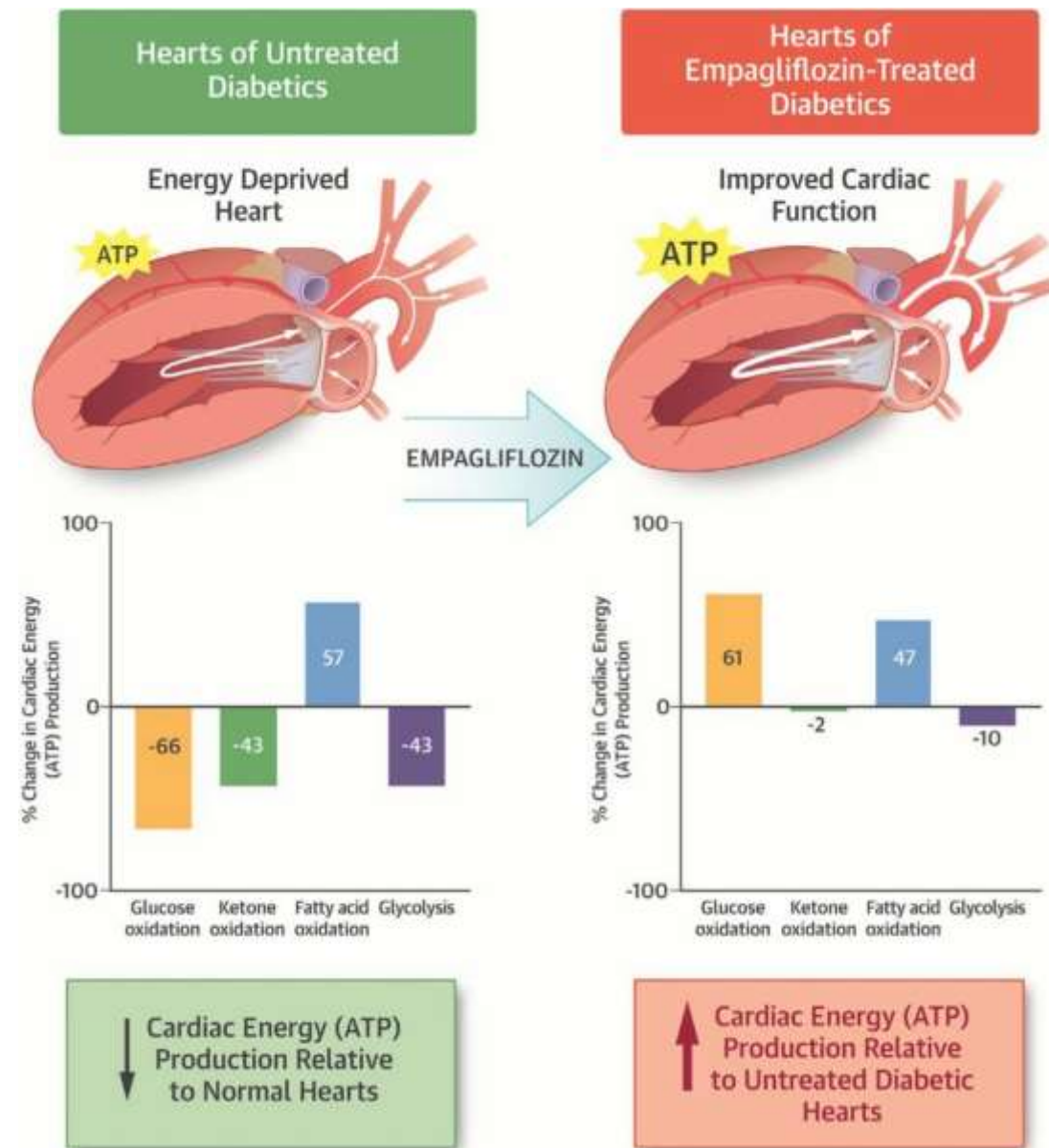
Beneficial effects on heart failure

CENTRAL ILLUSTRATION: Potential Direct Myocardial and Indirect \pm Systemic Effects of SGLT2_i



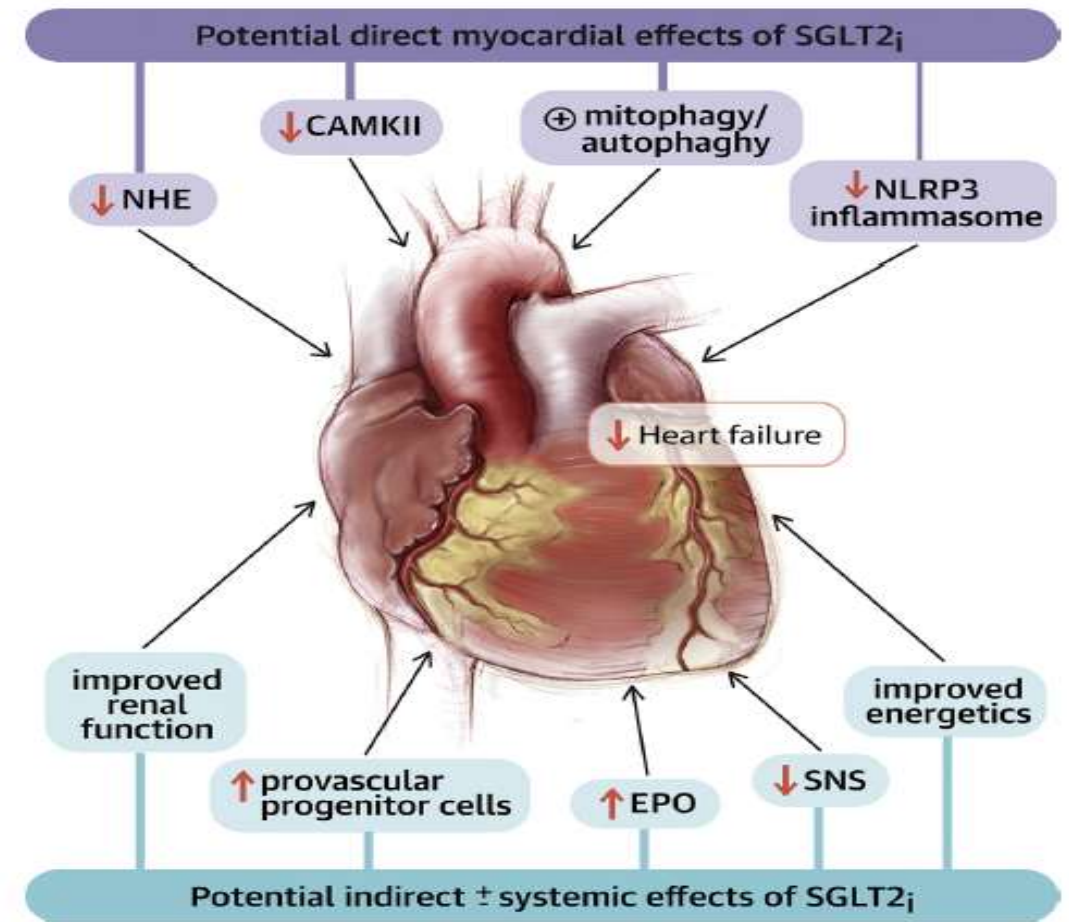
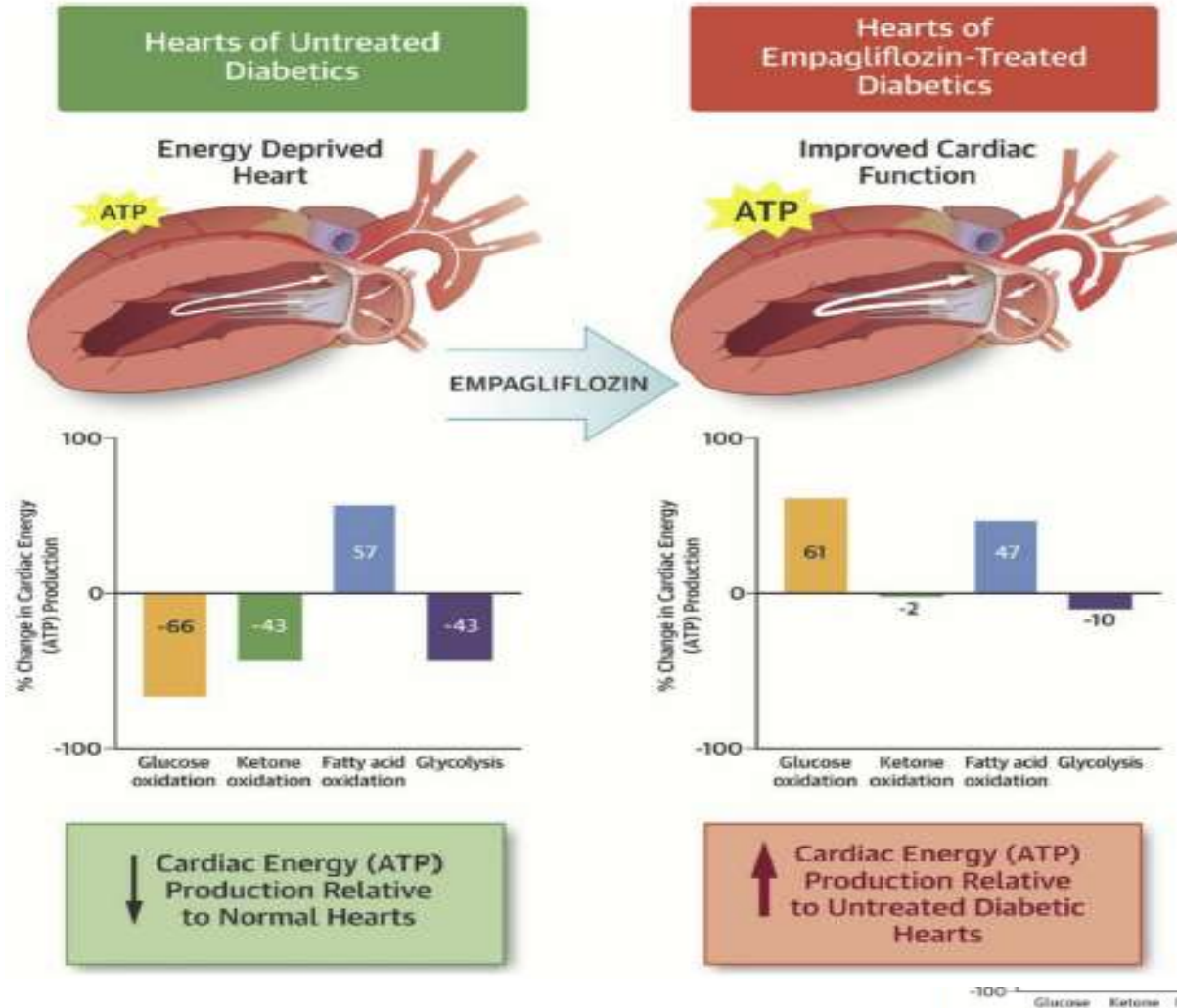
Lopaschuk, G.D. et al. J Am Coll Cardiol Basic Trans Science. 2020;5(6):632-44.

Beneficial effects on heart failure



Gary D. Lopaschuk, and Subodh Verma J Am Coll Cardiol Basic Trans Science 2020;5:632-644

Mechanism of cardiovascular benefit of SGLT2-i



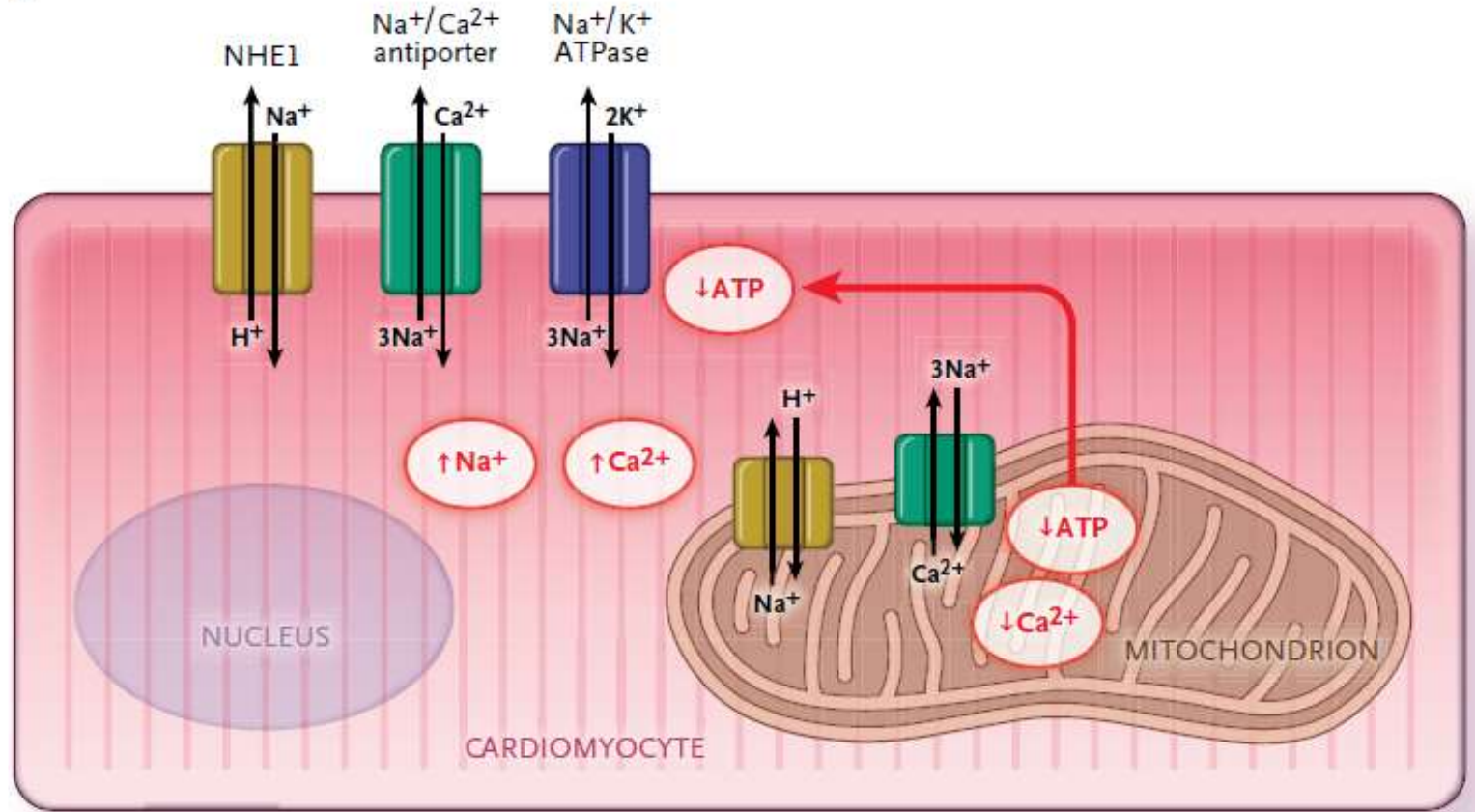
➔ SGLT2 inhibition enhances the cardiac energy pool by increasing cardiac energy production from glucose and fatty acid oxidation, but not ketone oxidation

SGLT2 inhibitors and reduction of interstitial fluid



→ SGLT2 inhibitors may selectively reduce interstitial fluid and this may limit the reflex neurohumoral stimulation that occurs in response to intravascular volume contraction with traditional diuretics

A

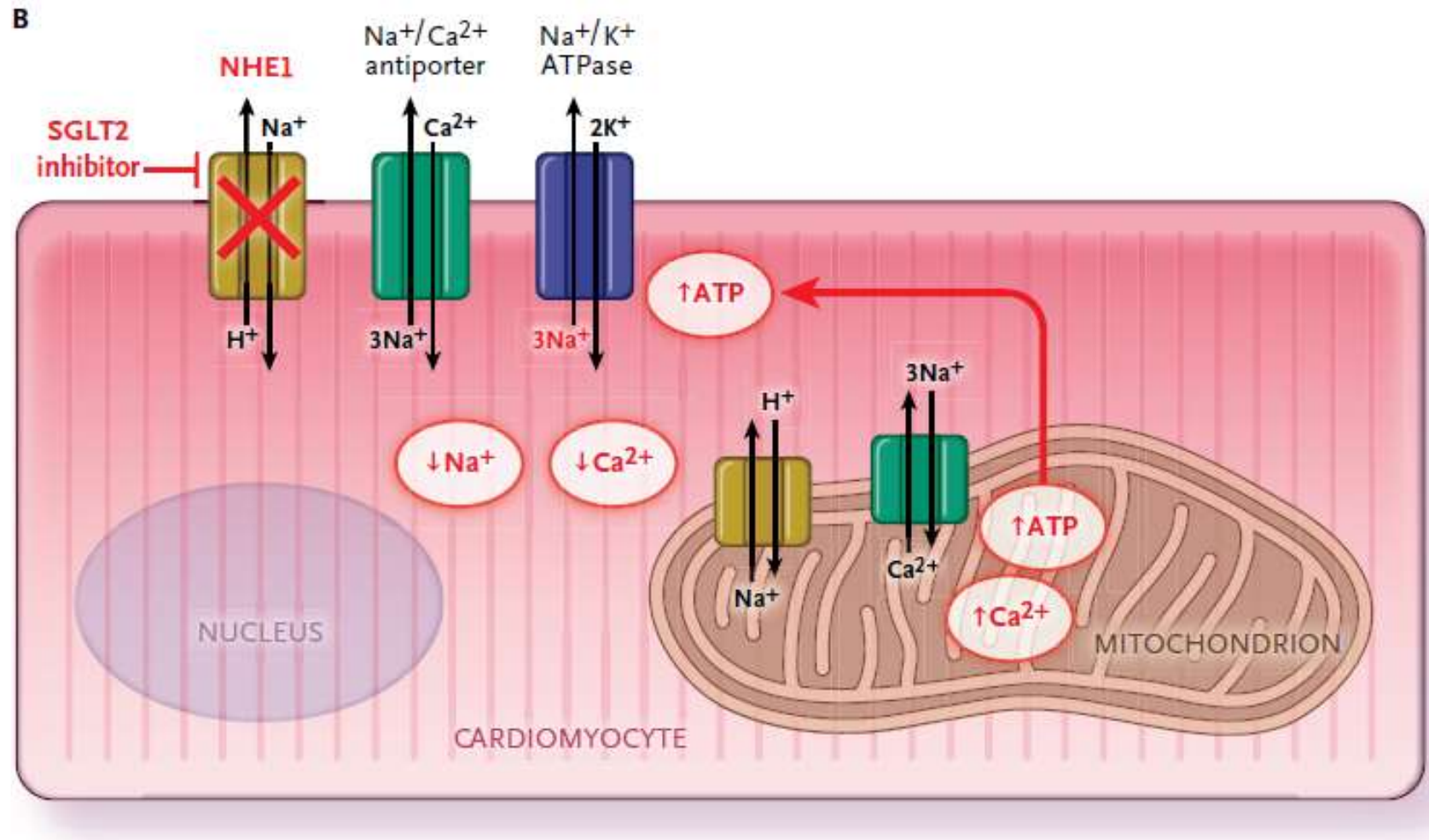


The sodium concentration in cardiomyocytes is increased in many forms of heart failure, and this increase may contribute to altered calcium handling

Reduced mitochondrial Ca²⁺ and mitochondrial ATP generation which in turn may lead to changes in contraction and arrhythmia


SGLT2 inhibition of cardiac NHE1 reduces cytoplasmic Na^+ and Ca^{2+} levels

and increases mitochondrial Ca^{2+} levels, resulting in improved mitochondrial respiration (increased ATP production) and viability of cardiomyocytes.



Paradigm of Quadruple Therapy For Heart Failure With Reduced Ejection Fraction





Diabetic kidney
disease



Points to be
considered in
Patients with CKD-
DKD

CKD definition

CKD is defined as:

- Persistent eGFR <60 mL/min/1.73 m²
 - Albuminuria (ACR >30 mg/g)
 - Or other markers of kidney damage, such as hematuria or structure abnormalities.
-
- Importantly, these measurements can vary within individuals over time, and persistence for at least 3 months is therefore required for diagnosis.

CKD identification

- For most people, CKD is not identified as a result of symptoms; **CKD is often diagnosed through routine screening**
- Both the ADA and KDIGO recommend **annual screening of patients with diabetes for CKD.**

CKD identification

- CKD screening should **start at diagnosis of T2D** because evidence of CKD is often already apparent at this time.
- For T1D, screening is recommended commencing **5 years after diagnosis, prior to which CKD is uncommon.**

Calculation of ACR

- Calculation of the ACR in single-voided “spot” urine samples is most convenient to measure albuminuria.
- Early morning urine specimens are ideal, although samples collected any time of day may be used.
- ACR has marked variability; therefore, a confirmatory urine sample within 3–6 months is recommended.

Nephropathy screening in diabetes

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?



Spot urine ACR

and

eGFR

What to do with a positive result?



Repeat and confirm:

- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD



Initiate evidence-based treatments

What defines CKD diagnosis?



Persistent urine ACR ≥ 30 mg/g

and/or



Persistent eGFR < 60 mL/min/1.73 m²

and/or



Other evidence of kidney damage

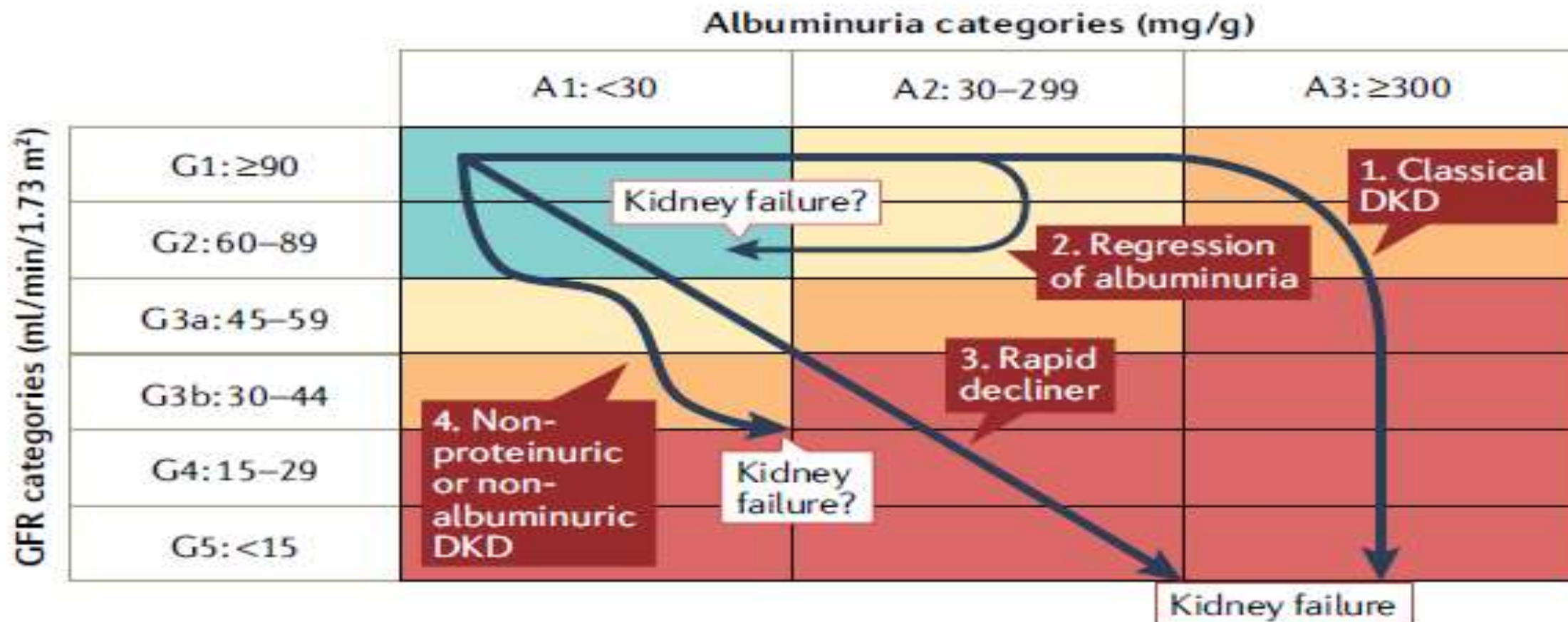
CKD Classification

CKD is classified based on: <ul style="list-style-type: none"> • Cause (C) • GFR (G) • Albuminuria (A) 				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m ²) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Microvascular Complications and Foot Care:

Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S191-S202

Trajectories of kidney function in DKD



ADA Recommendations 2024

- In adults with T2DM who have CKD (with eGFR of 20–60 mL/min per 1.73 m² and/or albuminuria)
- An SGLT2 inhibitor should be used for minimizing progression of CKD, reduction in cardiovascular events, and reduction in hospitalizations for HF
- However, the glycemic benefits of SGLT2 inhibitors are reduced at eGFR <45 mL/min per 1.73 m². **A**

ADA
Recommendations
2024

In adults with T2DM and advanced CKD (eGFR <30 mL/min per 1.73 m²)

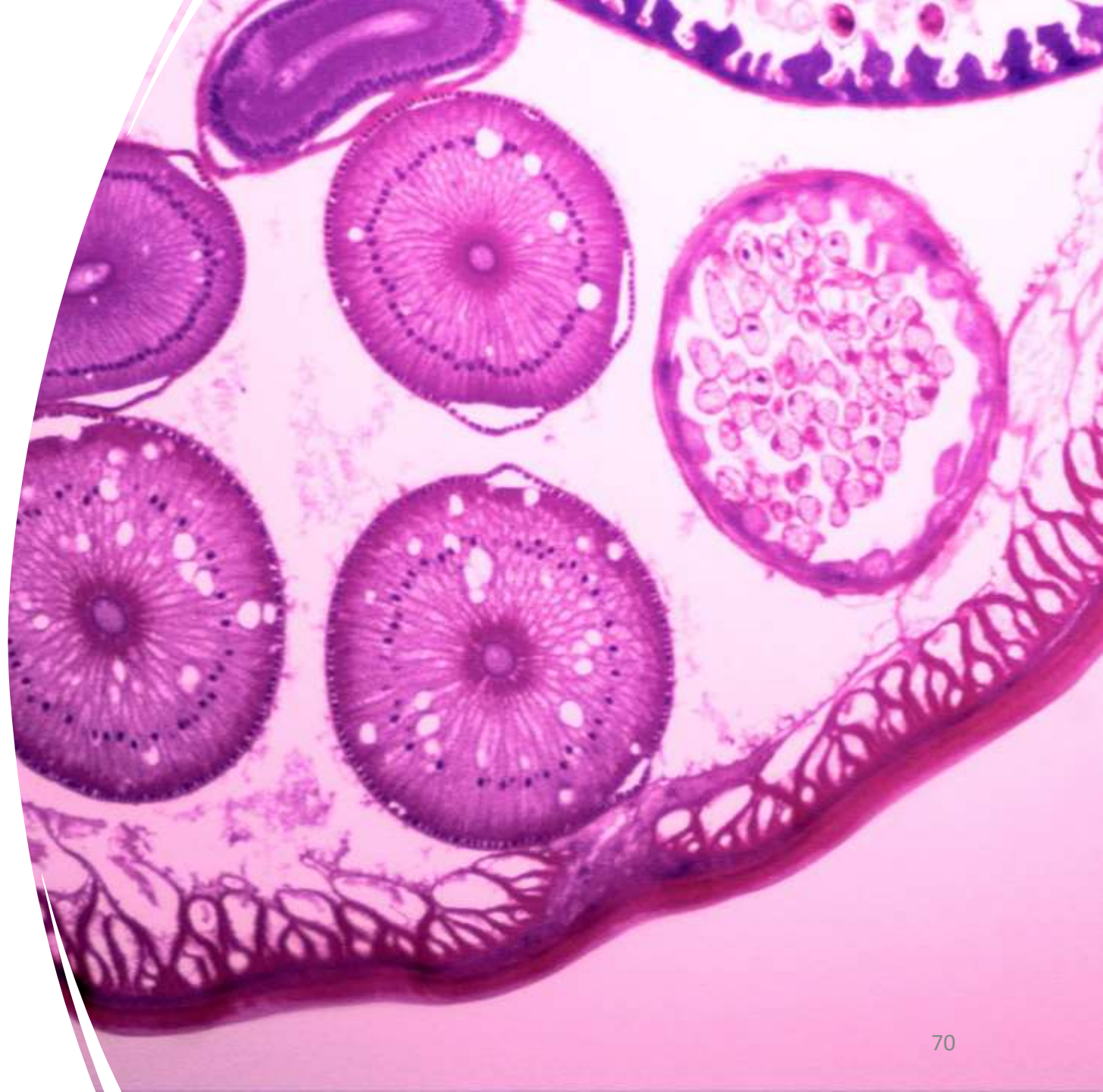
A GLP-1 RA is preferred for glycemic management due to **lower risk of hypoglycemia and for cardiovascular event reduction.** B

Mechanisms of action of SGLT2I

- In patients with **T2DM**, the hyperabsorption of glucose and sodium in the proximal renal tubules by SGLT2 causes afferent arteriolar vasodilatation
- Which causes glomerular hyperfiltration
- Leading to glomerular inflammation, fibrosis
- Ultimately, diabetic kidney disease.

Mechanisms of Action

- The reduction of reabsorption of sodium increases the sodium concentration at the macula densa
- **Tubuloglomerular feedback** activates adenosine receptors, which constrict the afferent glomerular arterioles.
- This constriction reduces glomerular hyperfiltration and thereby reduces further renal damage.





Mechanisms of Action

-
- SGLT2 inhibitors block the renal sodium–hydrogen exchanger 3, which enhances diuresis of sodium and glucose.
 - SGLT2 inhibitors also reduce tubular work and oxygen requirements
 - Reduce the damage associated with hypoxic tubular cell
 - Enhance renal erythropoietin production.

Figure 2. Effects of Sodium–Glucose Cotransporter 2 (SGLT2) Inhibition.

Panel A shows inhibition of SGLT2, with excretion of glucose and sodium ions (Na^+) in the urine. As a result of loss of Na^+ , the extracellular fluid volume contracts, which may result in vasoconstriction of the afferent arterioles. Because glucose reabsorption is coupled to Na^+ absorption, the macula densa senses an increased Na^+ concentration, as shown in Panel B, increasing the

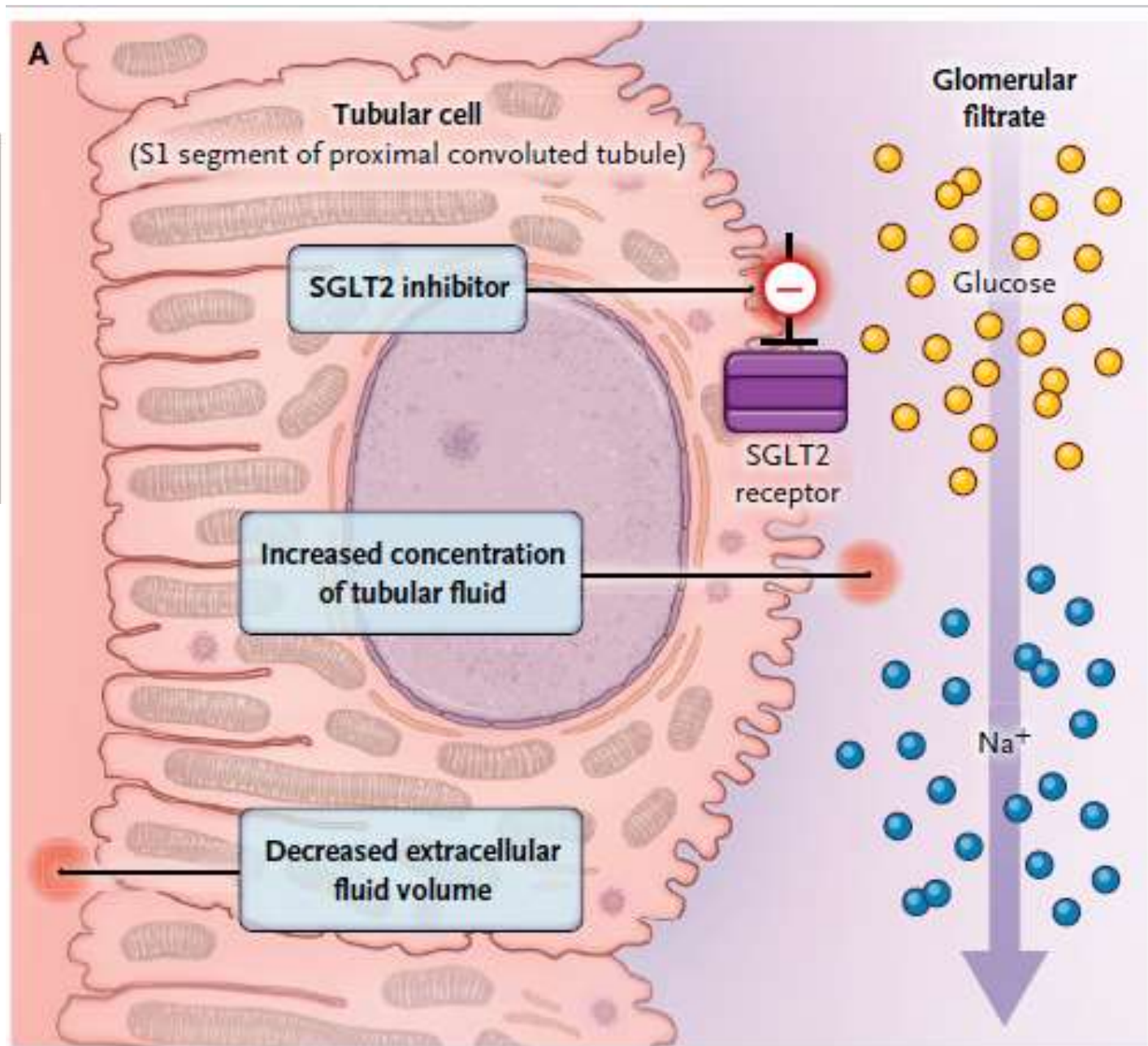
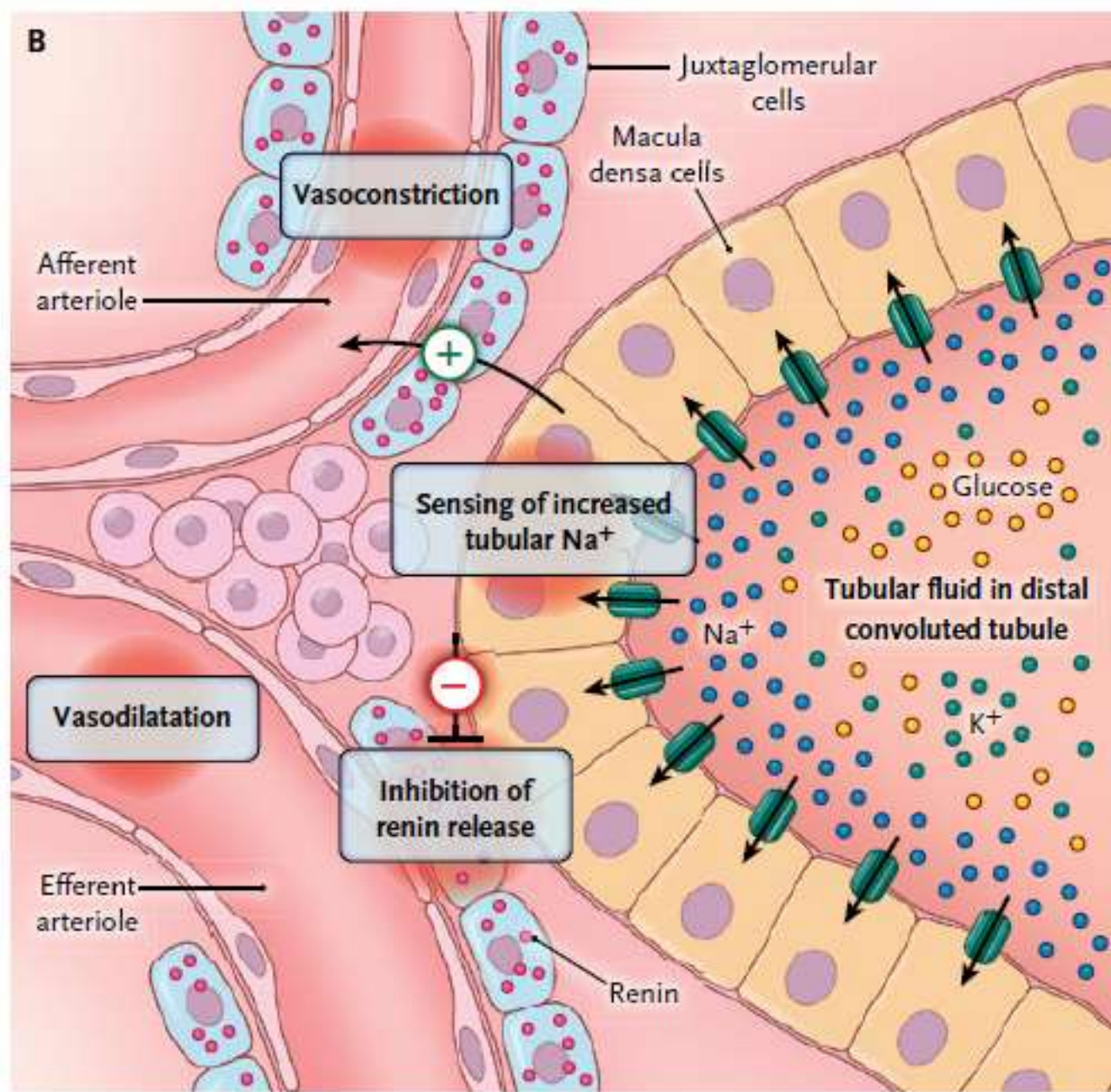
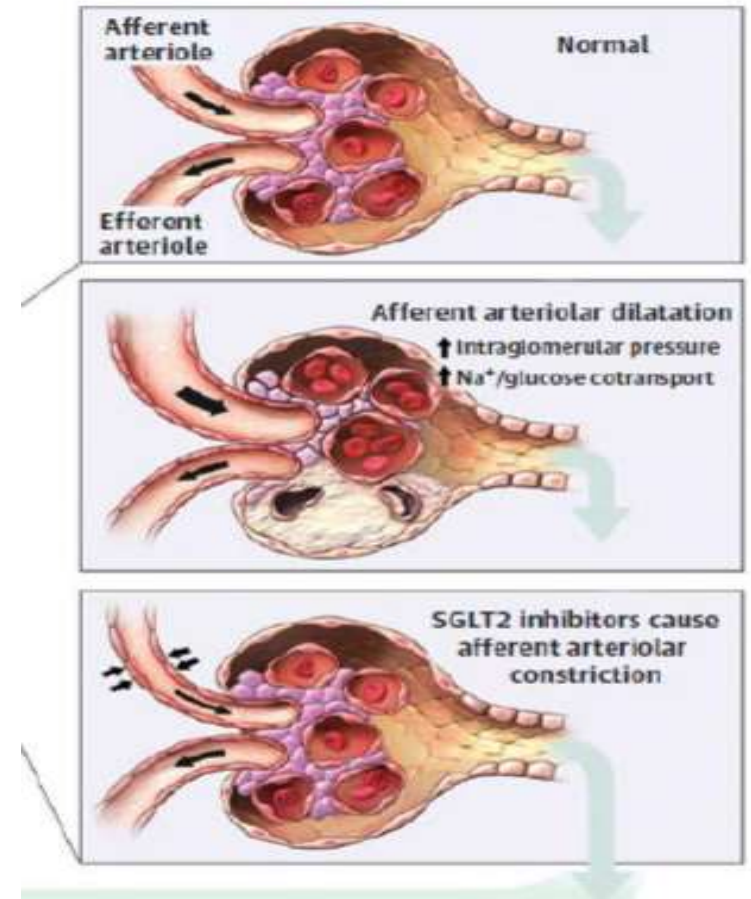
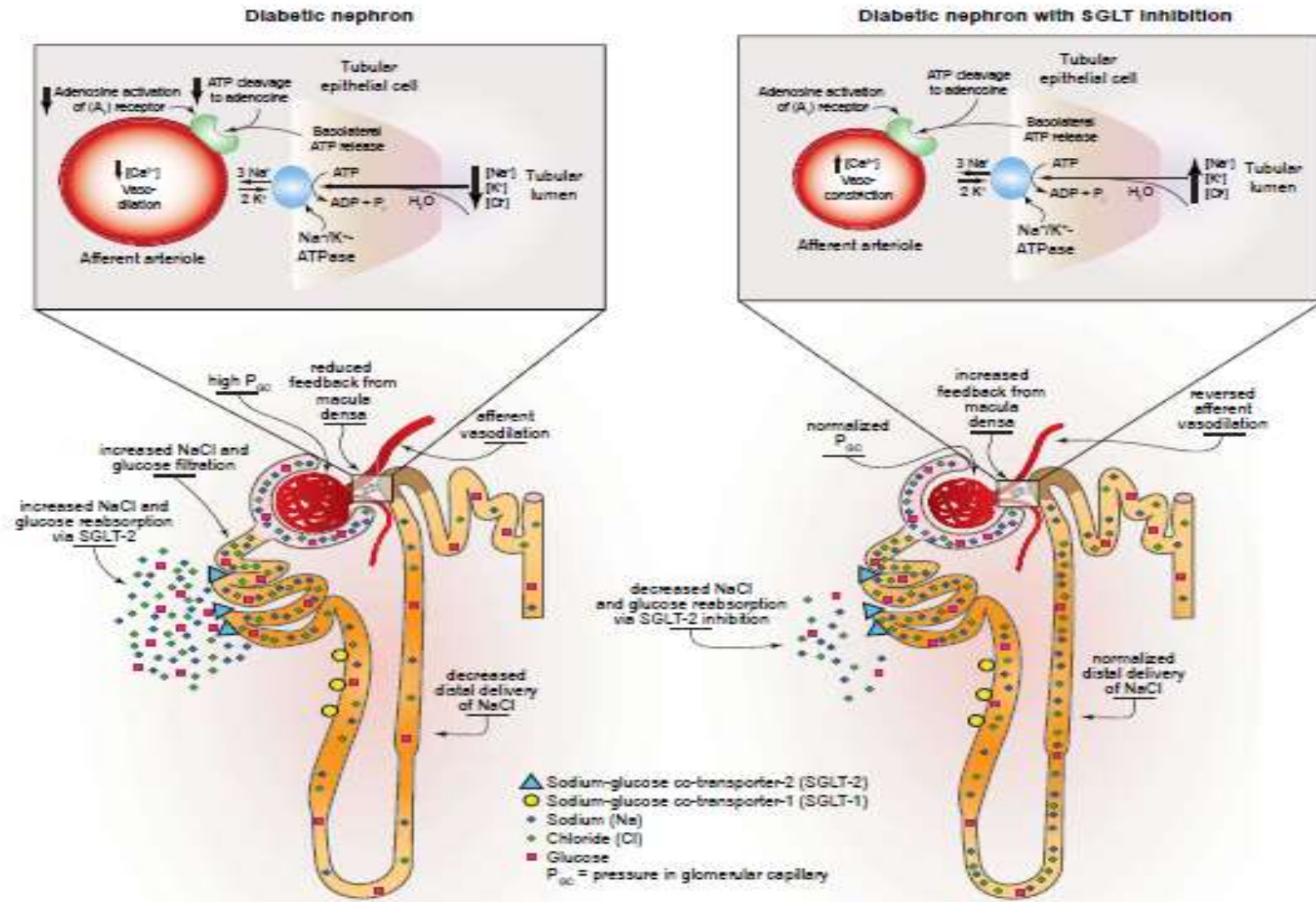


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Panel A shows inhibition of SGLT2, with excretion of glucose and sodium ions (Na^+) in the urine. As a result of loss of Na^+ , the extracellular fluid volume contracts, which may result in vasoconstriction of the afferent arterioles. Because glucose reabsorption is coupled to Na^+ absorption, the macula densa senses an increased Na^+ concentration, as shown in Panel B, increasing the activation of the tubuloglomerular feedback and causing vasoconstriction of the afferent arteriole, which is driven primarily by adenosine-mediated signal cascades. The macula densa inhibits the release of renin from the juxtaglomerular cells, enhancing the dilatation of the efferent arteriole. Vasoconstriction of the afferent arterioles and vasodilatation of the efferent arterioles reduce the glomerular filtration rate. The reduction of intraglomerular hydrostatic pressure represents the renoprotective effect of this drug class. K^+ denotes potassium ion. Modified from Zelniker and Braunwald.⁴⁹



SGLT 2-I and glomerular hemodynamics in diabetes



ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

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Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D.,
Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D.,
Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D.,
for the DAPA-CKD Trial Committees and Investigators*

ABSTRACT

DAPA-CKD trial

4,304 patients with CKD
(UACR 200–5,000 mg/g
and eGFR 25–75
mL/min/1.73 m²), with
or without diabetes

Randomized to
dapagliflozin 10 mg
daily or placebo

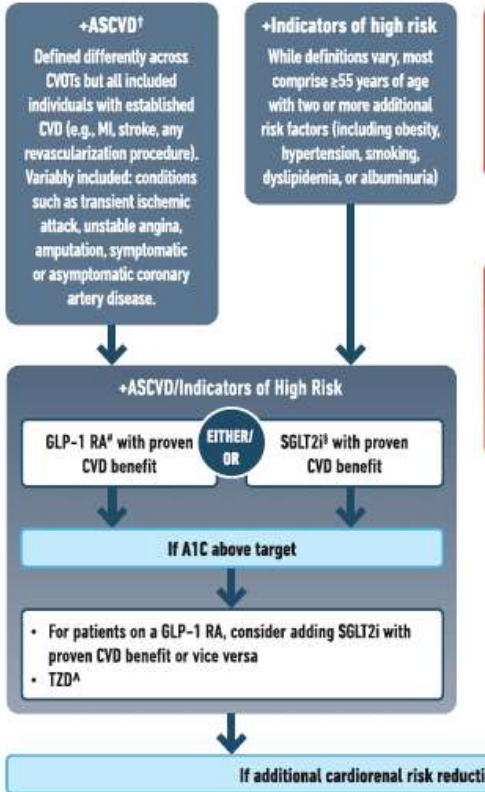
DAPA-CKD trial

- The primary outcome was a composite of sustained decline in eGFR of at least 50%, ESKD , or death from renal or cardiovascular causes.
- The risk of the primary composite outcome was significantly lower with dapagliflozin therapy compared with placebo (HR 0.61 [95% CI 0.51– 0.72])
- Risks for a renal composite outcome of sustained decline in eGFR of at least 50%, ESKD , or death from renal causes (HR 0.56 [95% CI 0.45–0.68])
- Composite of cardiovascular death or hospitalization for heart failure (HR 0.71 [95% CI 0.55–0.92]) ²

USE OF GLUCOSE

HEALTHY LIFESTYLE BEHAVIOR

Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use GLP-1 RA is warranted for people with CVD and a weaker recommendation for those seen at higher levels of baseline risk and should be factored into the shared decision-making process. † For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, and HF hospitalization. ‡ For TZD, the only agent with proven efficacy in reducing composite MACE, CV death, and HF hospitalization is pioglitazone.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes in individuals with cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; TZD, thiazolidinedione; MACE, major adverse cardiovascular events; MI, myocardial infarction; SD, standard deviation.

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i* with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

OF TYPE 2 DIABETES

DETERMINANTS OF HEALTH (SDOH)



Comprehensive approach to kidney risk reduction

Identify barriers to goals:

Consider DSMES referral to support self-efficacy in achievement of goals
Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that impact achievement of goals

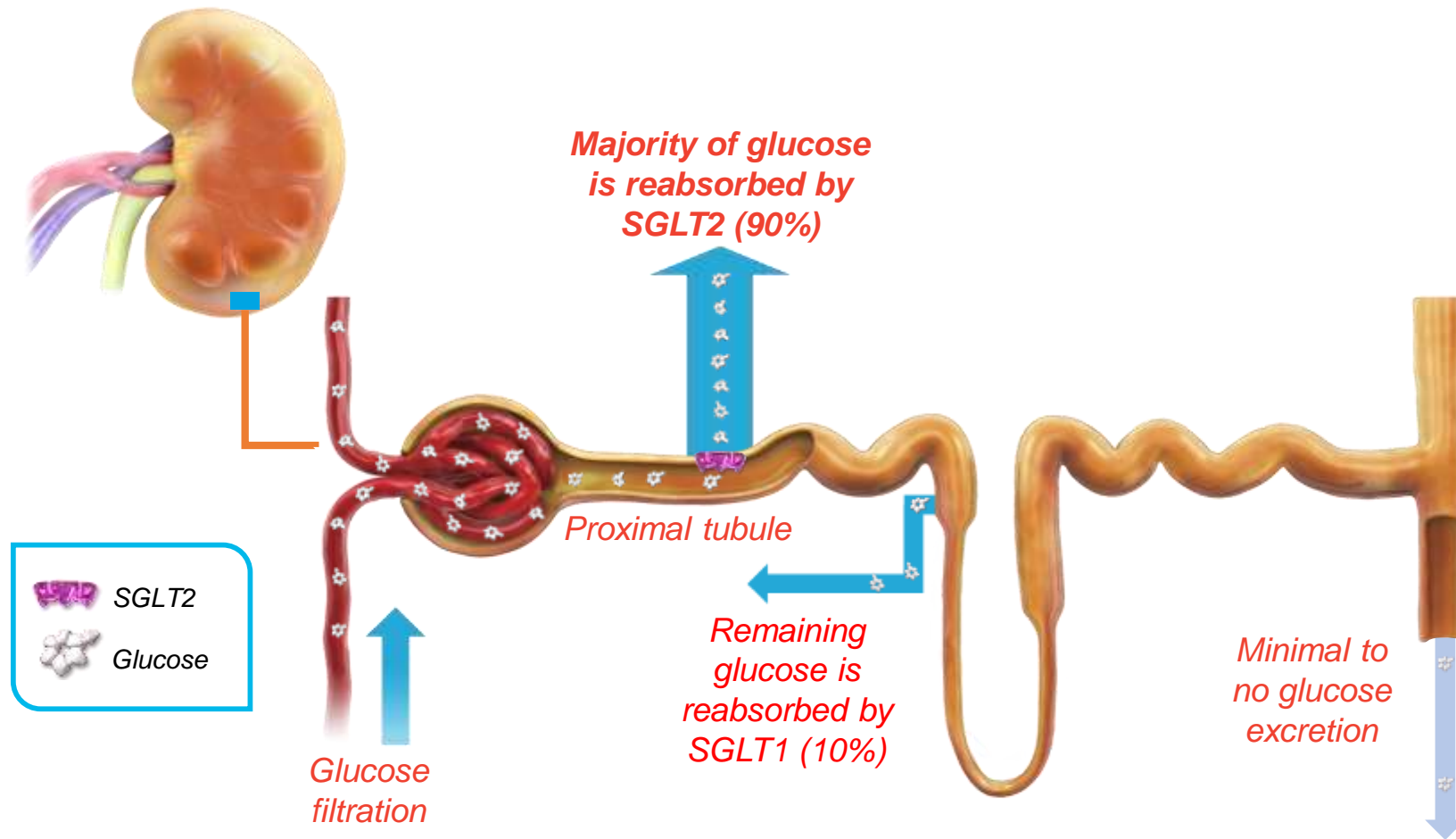
o-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SD, standard deviation; TZD, thiazolidinedione. Adapted from Davies et al. (84).

SGLT2 Inhibitors

	Efficacy ¹	Hypoglycaemia	Weight change ²	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
SGLT2 Inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	<ul style="list-style-type: none"> See labels for renal dose considerations of individual agents Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR 	Oral	High

- *Glucose-lowering mechanism of action:* Reduce renal tubular glucose reabsorption
- *Clinical Efficacy Profile:* Intermediate to high glucose-lowering efficacy, lower at lower eGFR; low inherent risk of hypoglycemia; intermediate weight loss
- *Cardiorenal Effects:* Demonstrated protective effects in studied trial populations:
 - Reduction in major adverse cardiovascular events
 - Reduction in overall CV death (with heterogeneity across the class)
 - Reduction in risk of hospitalization for heart failure
 - Reduction in risk of kidney outcomes
- Increased confidence surrounding safety issues of interest

Normal renal glucose handling¹⁻³

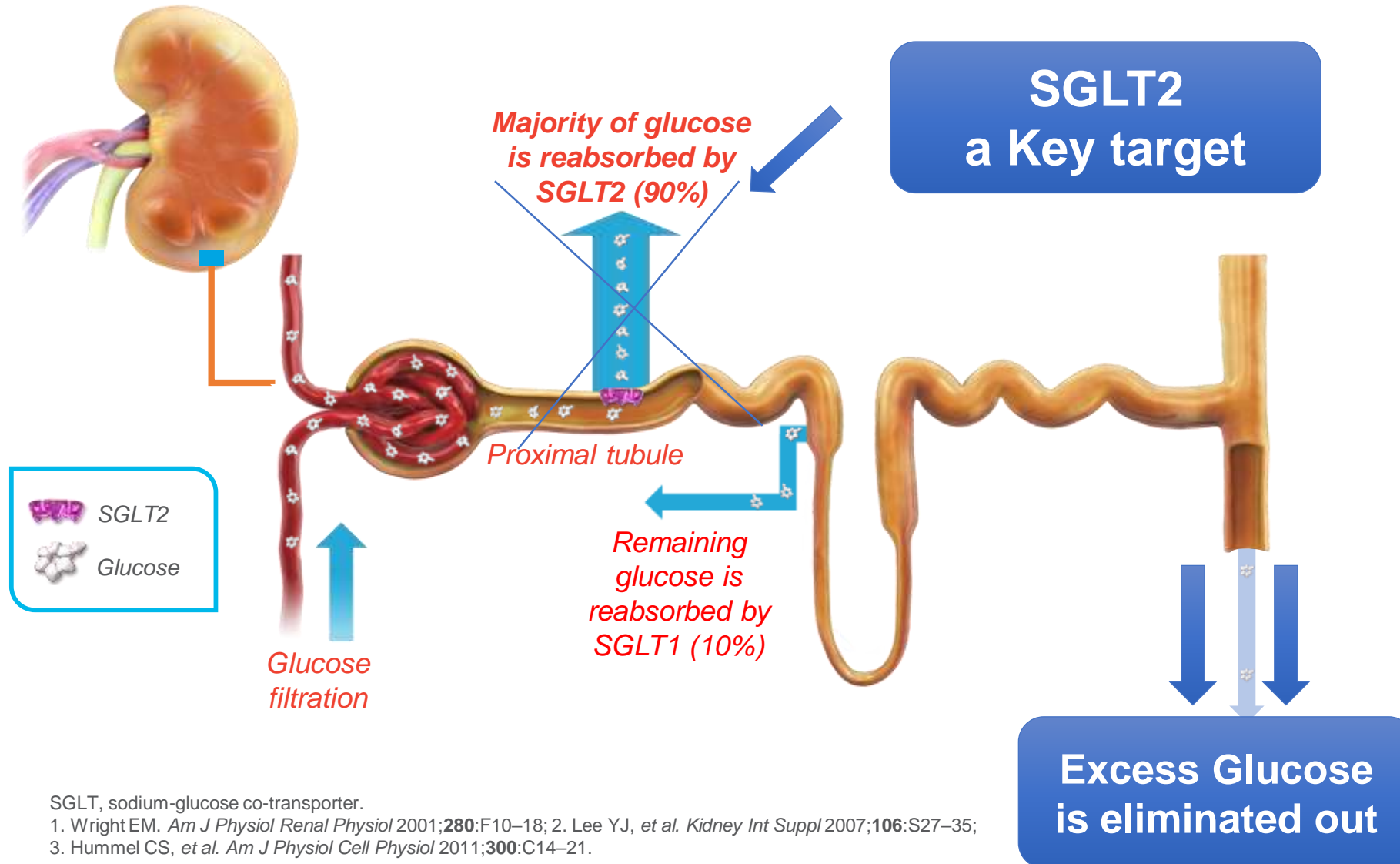


SGLT, sodium-glucose co-transporter.

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, et al. *Kidney Int Suppl* 2007;**106**:S27–35;

3. Hummel CS, et al. *Am J Physiol Cell Physiol* 2011;**300**:C14–21.

Breaking the cycle of sustained Hyperglycemia by inhibiting SGLT2



Mechanism of action of SGLT2 inhibitors

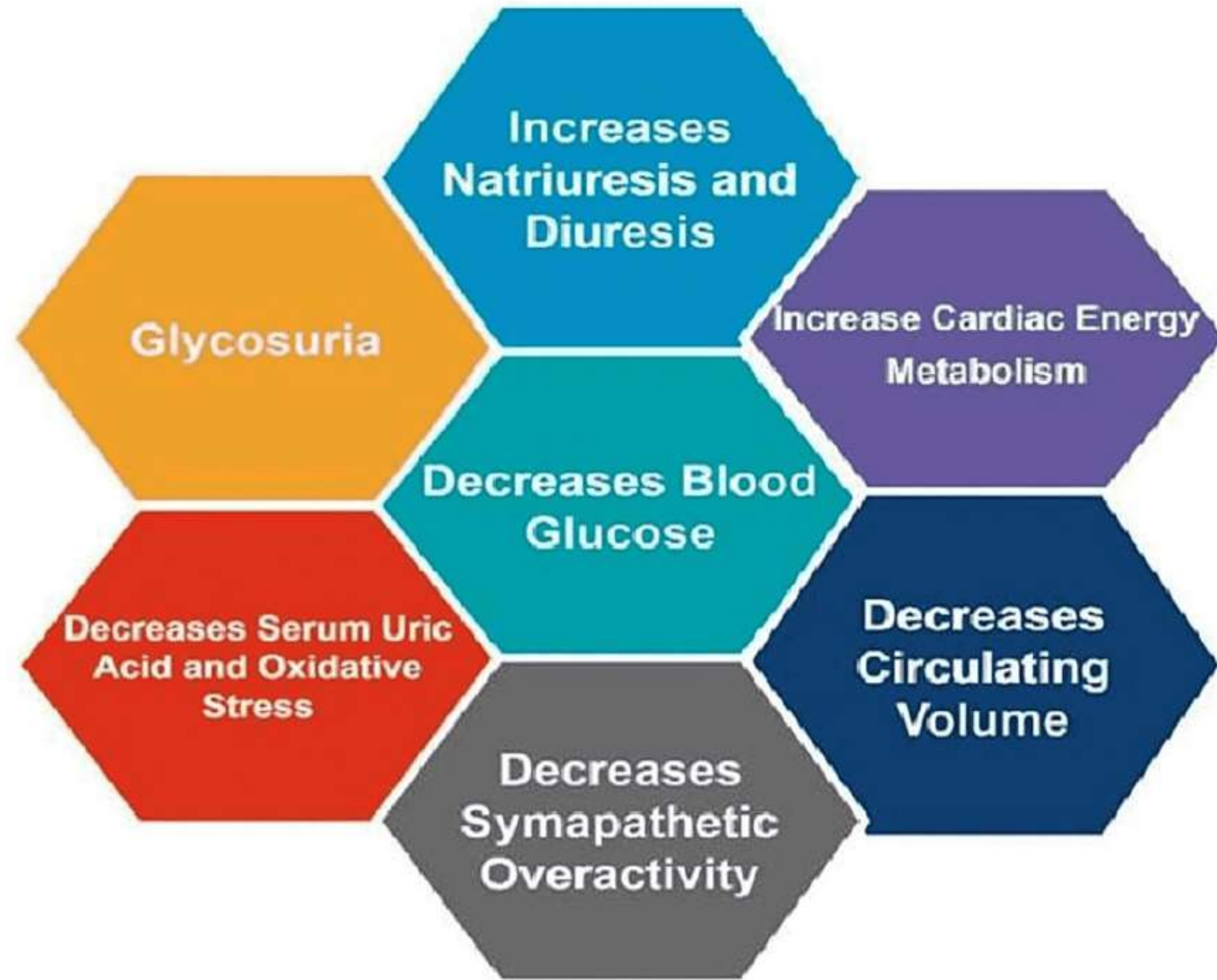


FIGURE 2: Mechanisms of action of SGLT2 inhibitors

Box 2. Situations when SGLT2 inhibitors should not be used.

- Situations where endogenous insulin production is compromised (e.g. type 1 diabetes*, pancreatogenic diabetes, LADA (latent autoimmune disease in adults/slowly evolving immune-mediated diabetes))
- Previous diabetic ketoacidosis
- When renal function lies outside the indication for use (see *Table 2*)
- Severe hepatic impairment[†]
- Acute illness/volume depletion
- Previous Fournier's gangrene (necrotising fasciitis of the perineum)
- Recurrent fungal genital/urinary tract infection
- Existing diabetic foot ulcer
- Pregnancy/breastfeeding
- Excessive alcohol intake
- Eating disorders
- Low-carbohydrate diet (e.g. ketogenic diet)
- Elevated haematocrit
- Caution if previous lower limb amputation
- Caution if history of foot ulceration
- Caution with diuretics (especially in elderly)
- Caution in frail elderly[‡]
- Caution with history of osteoporosis or fracture

*A licence was gained for use of dapagliflozin in type 1 diabetes but this has been recently withdrawn. NICE guidance on sotagliflozin (a dual SGLT1/SGLT2 inhibitor) in type 1 diabetes has been issued but this agent is not currently available on the NHS.

[†]Dapagliflozin may be initiated at a dose of 5 mg once daily.

[‡]Empagliflozin not recommended in those aged >85 years.

Box 4. Advice for patients on avoiding diabetic ketoacidosis when taking SGLT2 inhibitors.

- Maintain good fluid intake
- Avoid a very-low-carbohydrate or ketogenic diet
- Temporarily stop SGLT2 inhibitor in situation of acute illness, vomiting and diarrhoea, inability to eat and drink, or 48 hours prior to planned major surgery (to reduce risk of DKA and acute kidney injury)
- Awareness of DKA symptoms: nausea, vomiting, abdominal pain, shortness of breath, thirst, increased urination, malaise, fruity smell on breath
- If DKA suspected, stop SGLT2 inhibitor, seek medical advice (even if blood glucose levels not unduly raised)

	Stage 3b (eGFR 30–44 mL/min/1.73 m ²)	Stage 4 (eGFR 15–29 mL/min/1.73 m ²)	Stage 5 (eGFR <15 mL/min/1.73 m ²)
Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
SGLT2 inhibitors*			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily†	Initiation not recommended with eGFR <25 mL/min/1.73 m ² ; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily†	Initiation not recommended with eGFR <20 mL/min/1.73 m ² ; may continue if tolerated for kidney and CV benefit until dialysis	
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m ²		

	Stage 3b (eGFR 30–44 mL/min/1.73 m ²)	Stage 4 (eGFR 15–29 mL/min/1.73 m ²)	Stage 5 (eGFR <15 mL/min/1.73 m ²)
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Use not recommended	
Miglitol	No dose adjustment required	Use not recommended	

Choosing glucose-lowering medication in people with chronic kidney disease

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i[§] with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR \geq 20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

----- OR -----

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If HbA_{1c} above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

Conclusions and recommendations

- In people with CKD, **SGLT-2 inhibitors and GLP-1RA** reduce risk of MACE independent of eGFR.
- In people with CKD, **SGLT2i** also reduce risks of HF and kidney outcomes (including end-stage kidney disease).
- In people with **CKD and eGFR ≥ 20 ml/min per 1.73 m²**, an **SGLT2i** with proven benefit should be initiated to reduce risks of MACE, HF and kidney outcomes.
- If such treatment is not tolerated or is contraindicated, a GLP-1RA with proven CV outcomes benefit could be considered

Sulfonylureas

	Efficacy ¹	Hypoglycaemia	Weight change ²	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Neutral	<ul style="list-style-type: none"> Glyburide: generally not recommended in chronic kidney disease Glipizide and glimepiride: initiate conservatively to avoid hypoglycaemia 	Oral	Low

- High glucose-lowering efficacy, inexpensive and accessible
- A heterogeneous group - sulfonylureas with lower risk of hypoglycemia to be selected when considered for therapy
- No difference in the incidence of MACE in patients at high CV risk treated with glimepiride or linagliptin

Sulfonylureas

- Mechanism of action (MOA): stimulating insulin secretion from beta cells in the pancreas. It may also increase insulin sensitivity and lower hepatic glucose production.
 - Higher risk of hypoglycemia
- Glipizide is the preferred agent as clearance and half-life are not affected by a reduction in eGFR.
 - Less hypoglycemia risk in CKD compared to other agents
- Glyburide is avoided in patients with CKD because of active metabolites (one as active as parent, one 75% active)
- Glimepiride is also not preferred due to active metabolites (33% active compared to parent drug)

Thiazolidinediones

	Efficacy ¹	Hypoglycaemia	Weight change ²	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	<ul style="list-style-type: none"> No dose adjustment required Generally not recommended in renal impairment due to potential for fluid retention 	Oral	Low

- High glucose-lowering efficacy, durability of glycemic effect
- Beneficial effects in NASH seen with pioglitazone
- Side effects (e.g., weight gain, fluid retention) can be mitigated by optimizing dosing strategies (e.g., using lower doses) and combining therapy with other medications (SGLT2 inhibitors, GLP-1 RA) that promote weight loss and sodium excretion

Thiazolidinedione

- Peroxisome proliferator-activated receptor- γ agonist:
 - \uparrow insulin-dependent glucose disposal & \downarrow insulin resistance in the periphery and in the liver
- Onset slower during which time there is a low hypoglycemia risk
- Metabolized by the liver
- Fluid retention and acute heart failure are major limiting side effects
 - Avoid in advanced heart failure or advanced CKD patients
- Concern in CKD patients with mineral and bone disease due to increased risk of fracture & bone loss.
- Monitor liver function test, fluid retention and congestive heart failure, and bone health

DPP-4 Inhibitors

	Efficacy ¹	Hypoglycaemia	Weight change ²	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	<ul style="list-style-type: none"> Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment No dose adjustment required for linagliptin 	Oral	High

- Intermediate glucose-lowering efficacy, neutral effect on weight, generally well tolerated, minimal risk of hypoglycemia
- Early combination treatment with metformin and a DPP-4i (vildagliptin) increased glycemic durability compared to stepwise approach to therapy
- Cardiovascular safety demonstrated

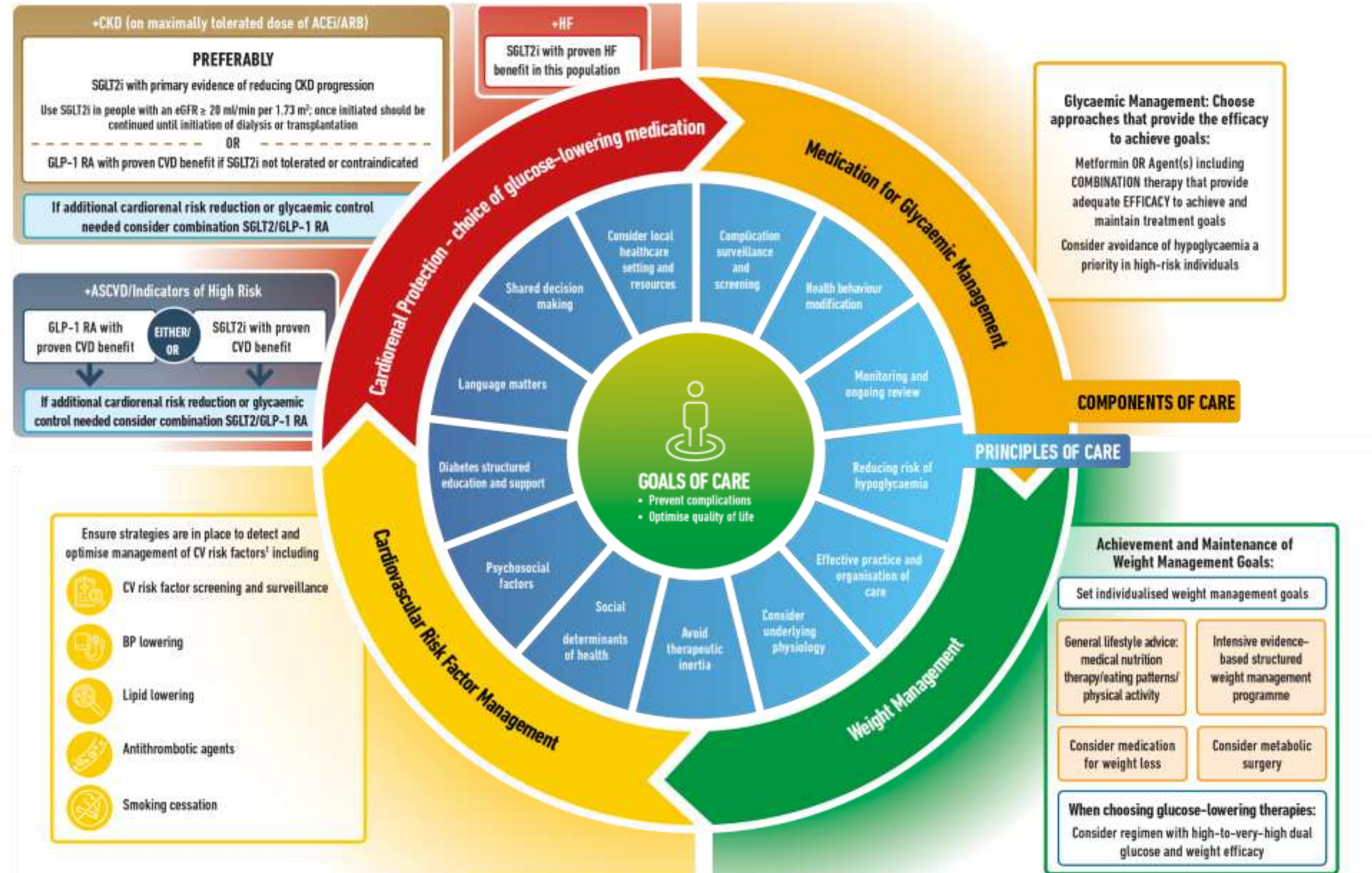
Dipeptidyl Peptidase-4 Inhibitor

- MOA: protects glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide (GLP-1) from inactivation.
 - ↑ insulin release & ↓ glucagon levels in the circulation
- Can be used in patients with CKD but lower doses are required for sitagliptin, saxagliptin and alogliptin.
 - **Linagliptin: no dose adjustment needed**
- A reduction in albuminuria has been seen with all DPP-4 inhibitors
- Generally well-tolerated but may cause headache, pancreatitis, arthralgia and upper respiratory infection



Neumiller JJ et al. J Am Soc Nephrol 2017;28

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT



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.