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Diabetes Agents That Prevent CV Events: What Every Clinician Needs to Know

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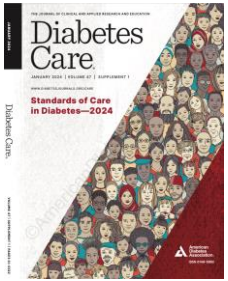
COREWELL HEALTH WILLIAM BEAUMONT UNIVERSITY HOSPITAL
MICHIGAN OSTEOPOROSIS ASSOCIATION SPRING 2024

Disclosure

- I’m married to a drug representative, and she works for Bayer

- I’m a consultant for Novo Nordisk, Boehringer Ingelheim Bayer and Insulet Corporation

Resources


Diabetes Care
JANUARY 2024 | VOLUME 47 | SUPPLEMENT 1
Standards of Care in Diabetes—2024
Diabetes Care


Follow-up of Glycemic Control and Cardiovascular Outcomes in Type 2 Diabetes


Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes


Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes


Kidney Disease and Increased Mortality Risk in Type 2 Diabetes


Diabetic Retinopathy and Other Ocular Findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study


Primary Prevention of Cardiovascular Disease and Type 2 Diabetes in Patients at Metabolic Risk: An Endocrine Society Clinical Practice Guideline


2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes
Summary of Recommendations


It Is Time to Screen for Heart Failure
Why and How?


The NEW ENGLAND JOURNAL of MEDICINE
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes


National Vital Statistics Reports
Deaths: Leading Causes for 2017


The Association Between Different A1C-Based Measures of Glycemia and Risk of Cardiovascular Disease Hospitalization


The Changing Landscape of Diabetes Therapy for Cardiovascular Risk Reduction
JACC State-of-the-Art Review


Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes


Sodium Glucose Cotransporter-2 Inhibition in Heart Failure
Potential Mechanisms, Clinical Applications, and Summary of Clinical Trials

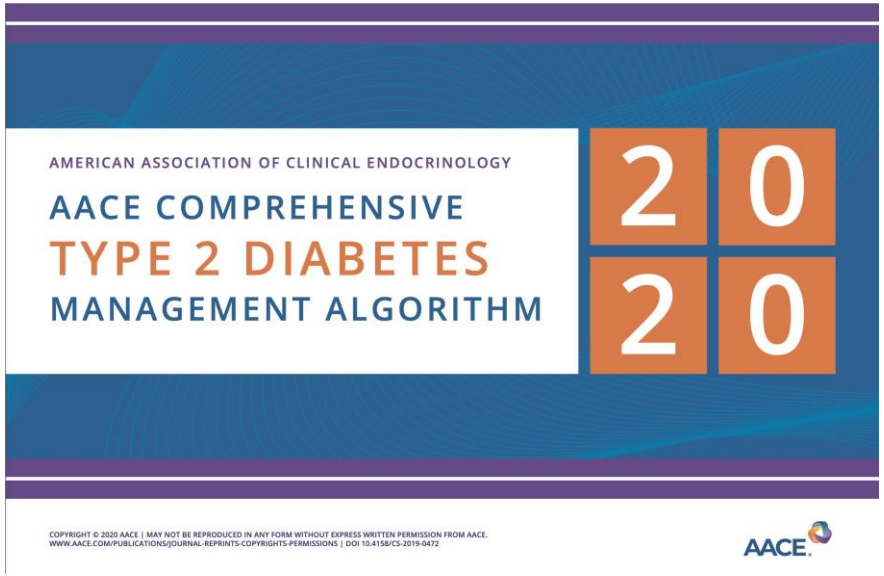

Kidney Disease and Increased Mortality Risk in Type 2 Diabetes


2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines


Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Resources

- https://pro.aace.com/pdfs/diabetes/AACE_2019_Diabetes_Algorithm_03.2021.pdf



Questions

Question Bank › MKSAP Questions › Cardiovascular Medicine › Question 117

Question 117

A 57-year-old woman is seen during a routine follow-up visit for heart failure. She has a 5-year history of ischemic cardiomyopathy with an ejection fraction of 38%. She also has a 15-year history of type 2 diabetes mellitus and diabetic kidney disease. She has had no hospitalizations. Medications are aspirin, atorvastatin, valsartan-sacubitril, metoprolol succinate, and metformin.

Physical examination, including vital signs, is unremarkable.

Laboratory studies show an elevated B-type natriuretic peptide level, a hemoglobin A_{1c} level of 7.0%, a serum creatinine level of 1.5 mg/dL (132.6 µmol/L), and an estimated glomerular filtration rate of 50 mL/min/1.73 m^2.

Which of the following is the most appropriate additional treatment?

A Dapagliflozin

B Glimepiride

C Liraglutide

D Saxagliptin

Objectives

01

Understand cardiometabolic risk and diabetes frequency in the U.S.

02

Be aware of the relationship of diabetes, chronic kidney disease, and the increased risk of cardiovascular death

03

Discuss Heart Failure, microalbuminuria, and the SGLT-2 drug class

04

Learn and use Finerenone, SGLT2's and GLP-1's to decrease Major Adverse Cardiovascular Events (MACE) in patients with type 2 diabetes

2024 ADA Diagnostic Criteria

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Diagnostic Studies for Increased Risk (Pre-Diabetes) or Diabetes		
Diagnostic Test	Increased risk (Pre-diabetes)	Diabetes
Fasting plasma glucose (mg/dL)	100-125	≥126
Plasma glucose 2hr post 75 gram oral glucose tolerance test (mg/dL)	140-199	≥200
Hemoglobin A1c (%)	5.7-6.4	≥ 6.5
Classic symptoms of diabetes or hyperglycemia crisis random plasma glucose (mg/dl)		≥200

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Hemoglobin A1c and Average Blood Sugar Level

A1C level (%)	Estimated average blood glucose (mg/dl)
5	97
6	128
7	154
8	183
9	212
10	240
11	269
12	298
13	326
14	355

Transition to T2DM

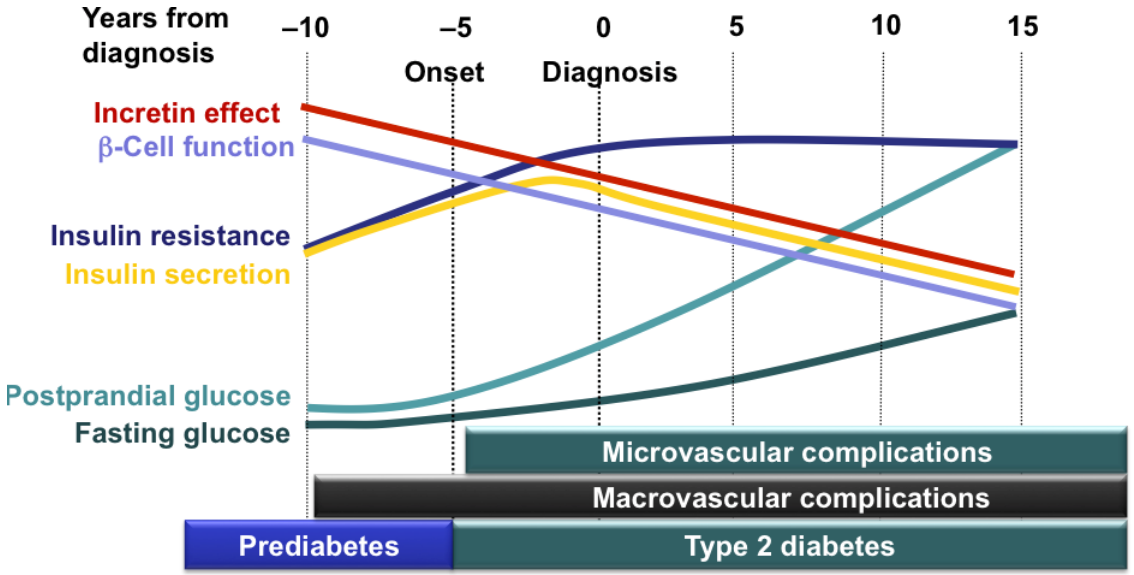

Figure courtesy of CADRE. Adapted from Holman RR. *Diabetes Res Clin Pract*. 1998;40(suppl):S21-S25; Ramlo-Halsted BA, Edelman SV. *Prim Care*. 1999;26:771-789; Nathan DM. *N Engl J Med*. 2002;347:1342-1349; UKPDS Group. *Diabetes*. 1995;44:1249-125 outpatient.**aace.com/sites/all/files/T2DM-S2-Clinical-Presentation.pptx**

Patients With Diabetes

Have 2-3 times increased risk of heart disease

In an outpatient setting in the U.S.

- Are twice as likely to have an encounter with a cardiologist than an endocrinologist
- When having CVD, are 4 times more likely to see a cardiologist than an endocrinologist and are equally likely to have an encounter with a cardiologist as a primary care physician

In Patients With Type 2 Diabetes

- A 1% increase in mean HbA1c was associated with a 22% greater risk of a CV event
- HbA1c reduction alone has not been proven to decrease CV events including mortality
- GLP-1 Receptor Agonists, SGLT-2 inhibitors and Finerenone have been shown to decrease Major Adverse Cardiovascular Events (MACE)

T2DM and Cardiometabolic Disease

- In 2018 approximately 33 million people in the United States(US) had diabetes
- Approximately 100 million people in the US are obese
- Approximately 120 million in the US have hypertension
- This means a significant portion of the US population could be categorized as stage A heart failure - per 2022 guideline

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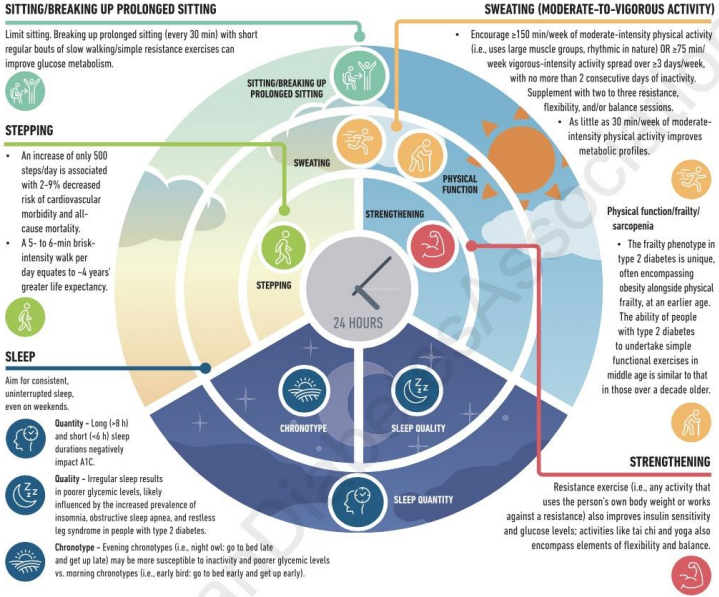
IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIORS FOR TYPE 2 DIABETES



	Glucose/insulin	Blood pressure	A1C	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ **Higher levels/improvement** (physical function, quality of life); ↓ **Lower levels/improvement** (glucose/insulin, blood pressure, A1C, lipids, depression); ? no data available;
↑ Green arrows = **strong evidence**; ↑ Yellow arrows = **medium-strength evidence**; ↑ Red arrows = **limited evidence**.

Figure 5.1—Importance of 24-h physical behaviors for type 2 diabetes. Reprinted from Davies et al. (97).

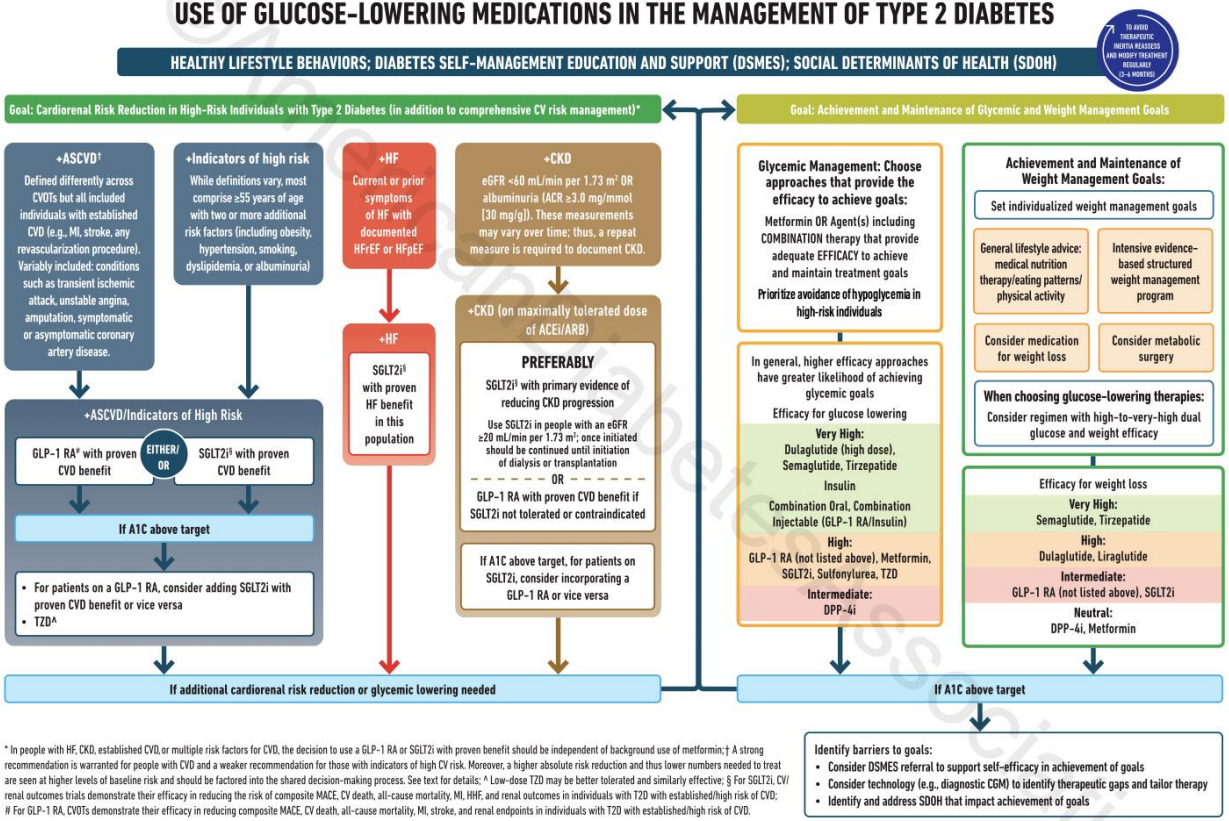


Figure 9.3— Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney 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).

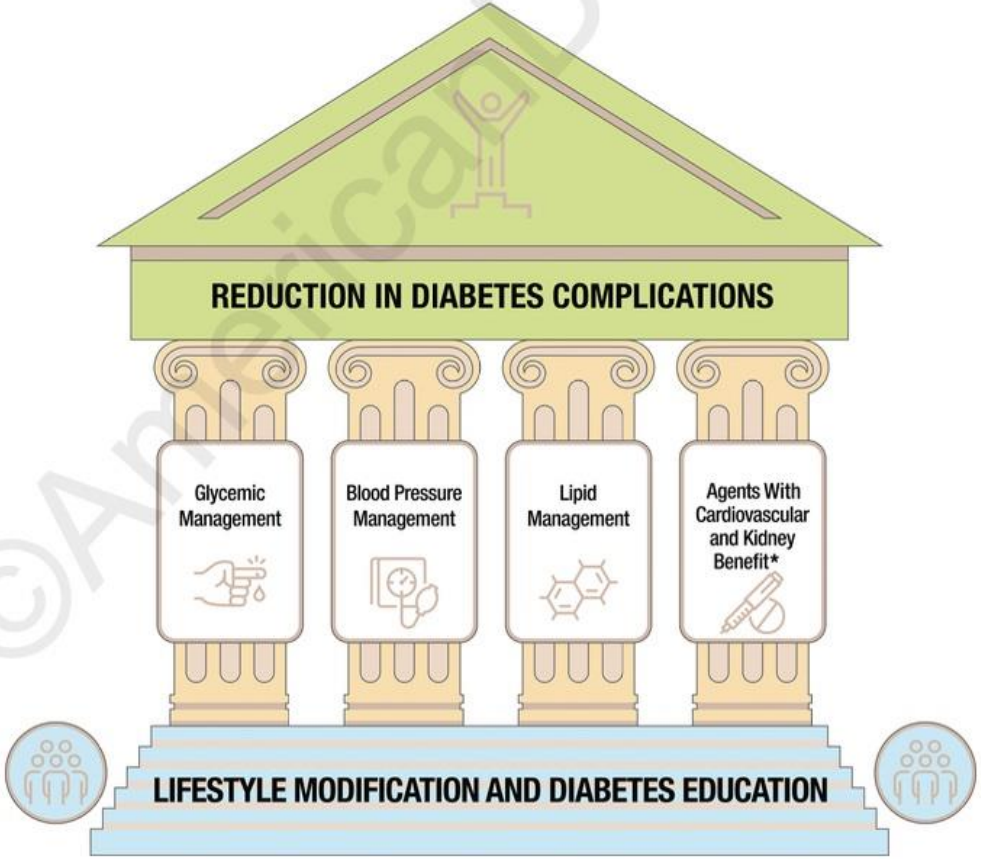
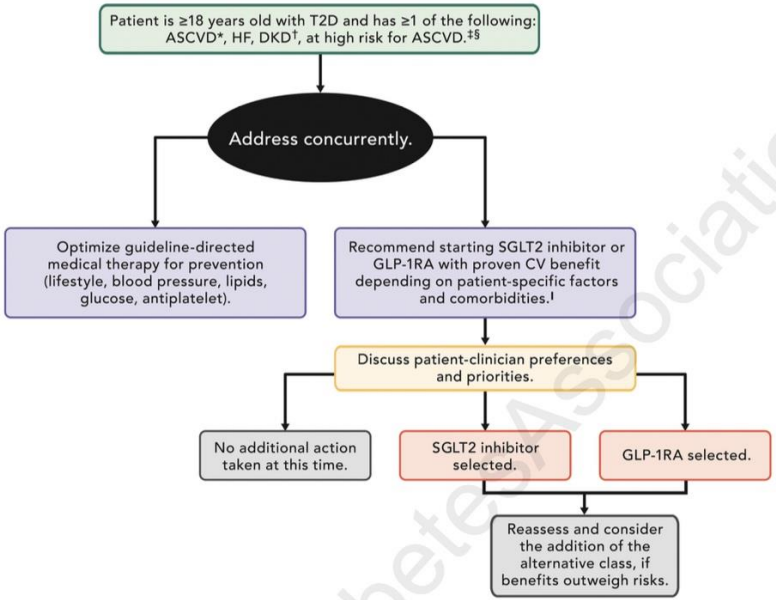


Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.



*ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

†DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

§ Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

ǁ Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes

Figure 10.3—Approach to risk reduction with sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy. Reprinted with permission from Das et al. (309).

T2DM Kidney Disease and Cardiovascular Disease

- **T2DM with CKD (define as GFR<60 or urine albumin creatine ratio >30mg/g) are 3 times more likely to have a cardiovascular death compared to T2DM alone**

- 40% of people with T2DM have stage CKD 3 or worse

- To patients with labs indicating CKD and T2DM, the diagnosis of CKD is only mentioned approximately 12% of time, and rarely are patients aware that they have CKD

Assessing Cardiovascular Risk

Need to know:

- Diabetes
- Chronic Kidney Disease

Kidney Disease

Kidney disease defined by two easy to collect officed based measurements:

- Estimated Glomerular Filtration Rate (eGFR)
- Urine Albumin Creatine Ratio (UACR)

For people with diabetes:

- eGFR – is generally collected in 90% of patients annually
- UACR – is generally missed in 50% of patients annually

Urine Albumin Creatinine Ratio (UACR)

Goes by several names:

- Albumin creatinine ratio
- Urine Microalbumin
- Microalbuminuria
- Protein creatine ratio

This is captured by a spot urine in a office or lab

eGFR and UACR

CKD is classified based on: • 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 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Figure 11.1—Risk of CKD progression, frequency of visits, and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months, [deep red]) according to risks of CKD progression and CKD complications (e.g., cardiovascular disease, anemia, hyperparathyroidism). These are general parameters based only on expert opinion and underlying comorbid conditions, and disease state must be taken into account, as well as the likelihood of impacting a change in management for any individual. CKD, chronic kidney disease; GFR, glomerular filtration rate. Reprinted and adapted from de Boer et al. (1).

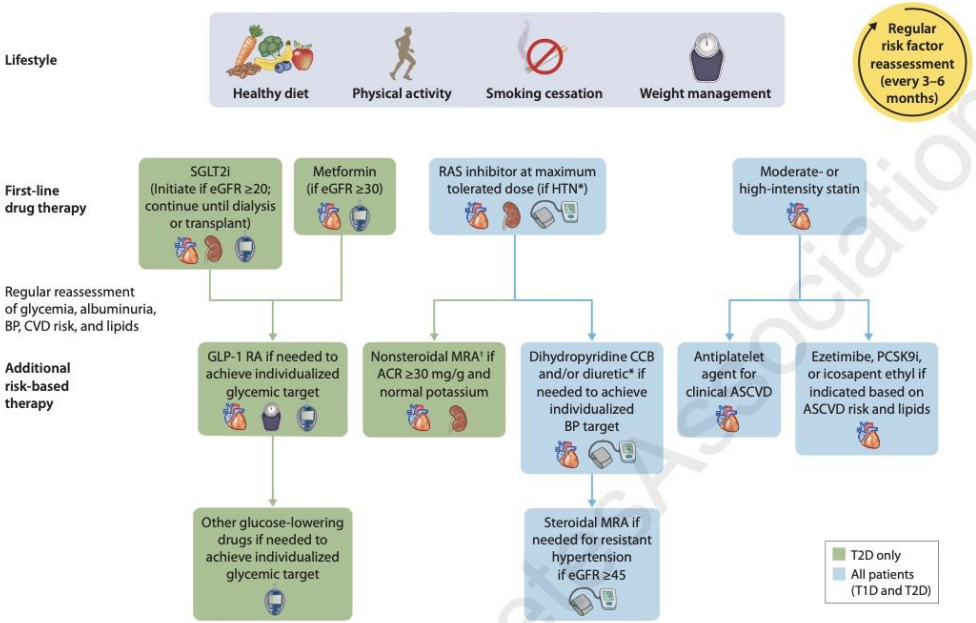


Figure 11.2—Holistic approach for improving outcomes in people with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes. Reprinted from de Boer et al. (1).

"First we insert a balloon to open the clogged artery, then we fill the balloon with helium so you weigh less."

2022 – Heart Failure Guidelines

- Summary statement by American College of Cardiology (ACC), American Heart Association (AHA) and Heart Failure Society of America (HFSA)
- A precedent was made for treating stage A patients prior to the development of structural changes or signs of worsened heart function
- Once patients reach stage C, clinicians use the New York Heart Association (NYHA) Classes I – IV to define functional capacity and specify treatment strategy

Heart failure 4 Stages per ACC/AHA/HFSA 2022

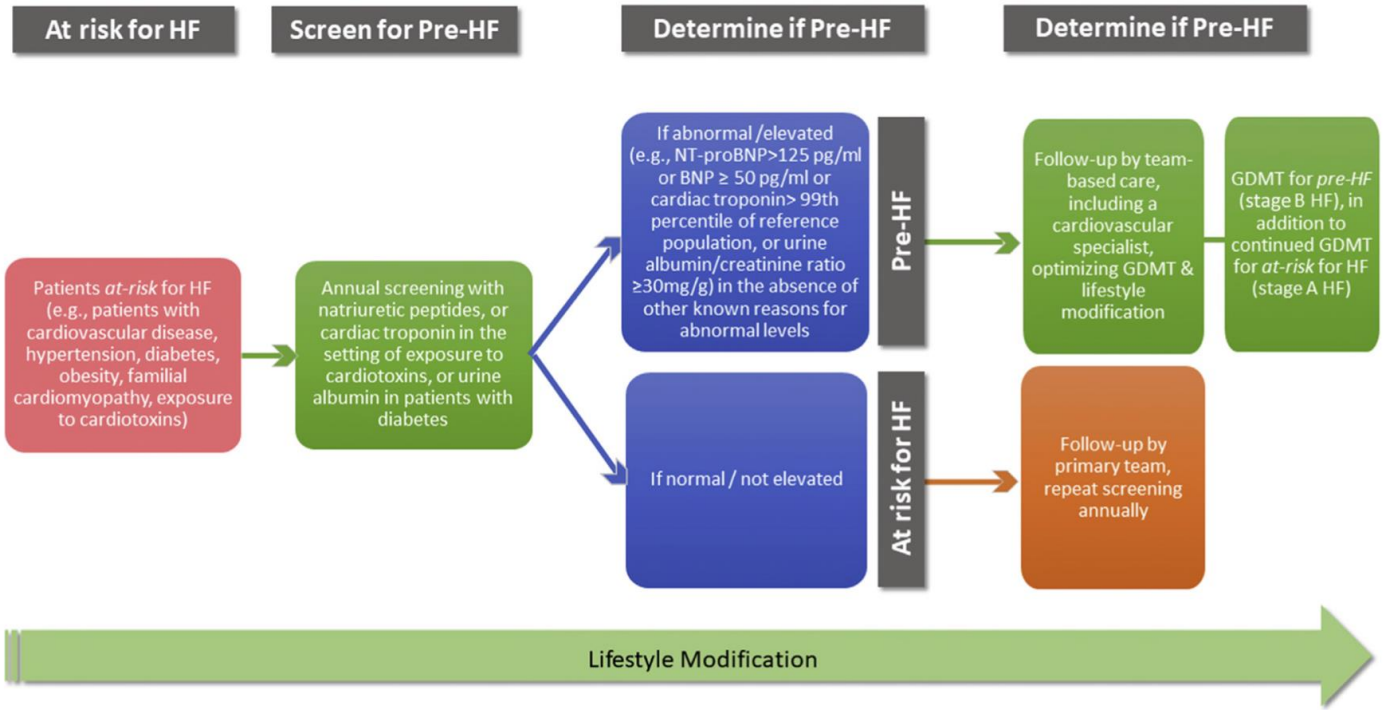
- Stage A: At risk for heart failure but without symptoms. Structural heart disease or blood tests indicate patient has heart muscle injury. Patients include those with high blood pressure, diabetes, metabolic syndrome, obesity, those exposed to medications or treatments that may damage the heart, and those at hereditary risk of heart failure.

- Stage B: Pre-heart failure stage. Patients do not have symptoms nor signs of disease, but are observed with structural heart disease—such as reduced ejection fraction, heart muscle enlargement, heart muscle contraction abnormalities, or valve disease. Ultrasounds may show increased filling pressures. Additionally, stage A risk factors may have progressed, B-type natriuretic peptide may be increased, or cardiac troponin may be consistently elevated.

- Stage C: Symptomatic heart failure. Patients have structural heart disease with current or previous symptoms including shortness of breath, persistent cough, swelling, fatigue and nausea.

- Stage D: Advanced heart failure, with symptoms impacting daily life routines, and difficult-to-control symptoms that result in recurrent hospitalization despite guideline-directed medical treatment.

FIGURE 1 A Contemporary Approach for Screening Patients at Risk for Heart Failure



BNP = B-type natriuretic peptide; GDMT = guideline-directed medical therapy; HF = heart failure; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

Medication To Treat HFrEF Class C

4 classes of medication, including diuretics:

- Angiotensin receptor-neprilysin (ARN) inhibitors
- ACE inhibitors or ARBs
- Mineralocorticoid receptor antagonists (MRA) or beta blockers
- SGLT-2 inhibitors—**For patients with symptomatic chronic HFrEF regardless of type 2 diabetes status**

Guideline Directed Medical Therapy Across Heart Failure Stages

Use this tool to reference guideline directed medical therapy (GDMT) across the four ACC/AHA stages of Heart Failure (HF) as outlined in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. See the guideline for specific patient population criteria.

Drugs that reduce MACE for people with T2DM

- Cardiovascular Outcome Trials (CVOT)

- Major Adverse Cardiovascular Event (MACE): CV-related death, nonfatal myocardial infarction (MI/Heart Attack), or nonfatal stroke

The following are FDA approved to stop MACE in patients with T2DM

- Glucagon Like Peptide-1 receptor agonists
- Sodium-Glucose Cotransporter-2 inhibitors
- Non-Steroidal Selective Mineralocorticoid receptor antagonist

GLP-1 Receptor Agonist with MACE Reduction

- Dulaglutide (Trulicity)
- Liraglutide (Victoza)
- Semaglutide (Ozepmic)

SGLT-2 Inhibitor with MACE reduction

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

Non-steroidal Selective Mineralocorticoid receptor antagonist with MACE reduction

- Finerenone (Kerendia)

So …

Need to consider using:

For stopping Heart failure and hospitalization for heart failure

- **SGLT-2's** and in patients with T2DM and CKD **Finerenone**

For stopping Major Adverse Cardiovascular events in patients with T2DM:

- **GLP-1, SGLT-2, and Finerenone**

Not just my opinion

Because of cardiovascular disease improvements the approach of using of SGLT-2, GLP-1, and finerenone for people with type 2 diabetes is supported by:

- AACE/ACE - American Association of Clinical Endocrinology and American College of Endocrinology
- ADA – American Diabetes Association
- AHA – American Heart Association
- ACC – American College of Cardiology
- ASA – American Stroke Association

Best Approach

Great T2DM therapeutic approaches do the following:

- DECREASE MACE – provide cardiovascular protection
- Improve HbA1c – stop microvascular progression
- Attempt to avoid insulin and sulfonylureas
- Long lasting tolerability
- Glucose lowering efficacy
- Have a weight loss effect
- Improve blood pressure
- Decrease lipid profile
- Decrease side effects (e.g. particularly hypoglycemia)

Realize!

- You have patients with DIABETES and CKD and HF (or just HF risk)!
- You want to help decrease macrovascular events!

- **Please think about GLP-1 class, SGLT-2 class, and Finerenone (As you have in the past with statin/ACE/ARB use)!**

Questions

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Question Bank › MKSAP Questions › Cardiovascular Medicine › Question 117

Question 117

A 57-year-old woman is seen during a routine follow-up visit for heart failure. She has a 5-year history of ischemic cardiomyopathy with an ejection fraction of 38%. She also has a 15-year history of type 2 diabetes mellitus and diabetic kidney disease. She has had no hospitalizations. Medications are aspirin, atorvastatin, valsartan-sacubitril, metoprolol succinate, and metformin.

Physical examination, including vital signs, is unremarkable.

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Which of the following is the most appropriate additional treatment?

A Dapagliflozin

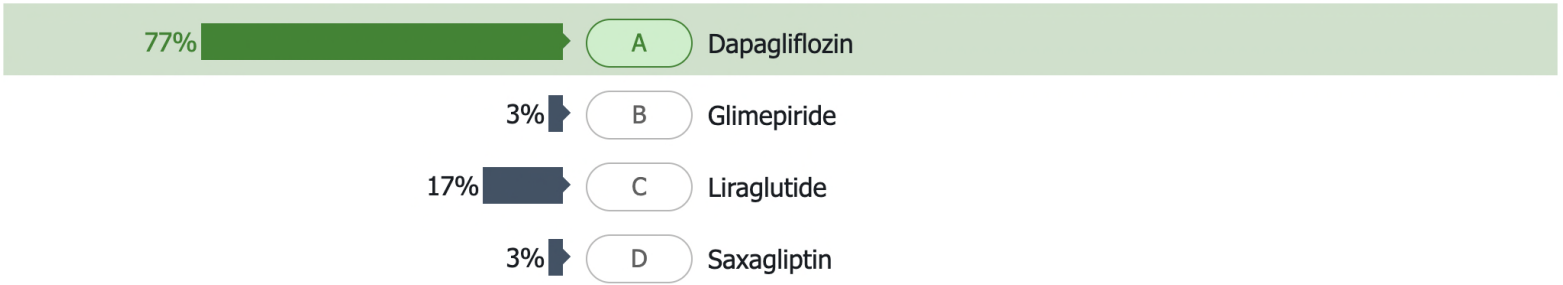
B Glimepiride

C Liraglutide

D Saxagliptin

Answer

Which of the following is the most appropriate additional treatment?



Answer & Critique

Correct Answer: A

You answered A.

Educational Objective: Treat a patient with heart failure and diabetes mellitus with a sodium-glucose cotransporter 2 inhibitor.

Answer

Educational Objective: Treat a patient with heart failure and diabetes mellitus with a sodium-glucose cotransporter 2 inhibitor.

The most appropriate treatment is to add dapagliflozin (**Option A**). This patient has heart failure, type 2 diabetes mellitus, and kidney disease. Evidence shows that the sodium-glucose cotransporter 2 (SGLT2) inhibitors dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin are associated with a reduction in cardiovascular death or hospitalization for heart failure in patients with type 2 diabetes, and dapagliflozin and empagliflozin are effective in patients without diabetes. In addition, for patients with type 2 diabetes, an SGLT2 inhibitor reduces progression of diabetic kidney disease. SGLT2 inhibitors should not be used in patients with type 1 diabetes, increased risk for type 2 diabetic ketoacidosis, or rapidly declining or changing kidney function.

Key Points

- Sodium-glucose cotransporter 2 inhibitors reduce risk for worsening heart failure and cardiovascular death in patients with heart failure with reduced ejection fraction with or without type 2 diabetes mellitus.
- Among patients with type 2 diabetes mellitus who have established atherosclerotic cardiovascular disease or established kidney disease, a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended.

Glimepiride (**Option B**) is a second-generation sulfonylurea. Although the results of many studies have been inconclusive, it seems that the second-generation agents most likely do not have any adverse cardiac effects but also have no cardiac benefit.

Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease (ASCVD) or established kidney disease, the American Diabetes Association and the American College of Cardiology recommend an SGLT2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit. In patients with type 2 diabetes and ASCVD, liraglutide, semaglutide (injectable), and dulaglutide have been shown to decrease cardiovascular death. However, liraglutide (**Option C**) has no effect on heart failure outcomes in patients with established heart failure.

Saxagliptin (**Option D**) is a dipeptidyl peptidase-4 inhibitor, a class of drug that has been shown to have no difference in cardiovascular outcomes compared with placebo. However, depending on the study, there was either a trend toward more heart failure hospitalizations (saxagliptin) or an increased incidence of heart failure (alogliptin). Because of this increased incidence of heart failure hospitalizations, adding saxagliptin as a second-line agent would not be appropriate.

Conclusion

- Remember CKD needs to look at with BOTH eGFR and UACR
- For patients with stage A, B, C, and D Heart failure now use SGLT-2 and if has T2DM and CKD use Finerenone
- Recently, a great discoveries with GLP-1, SGLT-2, and Finerenone have displayed DECREASED MACE in T2DM
- It is important for ALL physicians, but particularly internists, family practice, cardiologists, nephrologists, and endocrinologists be familiar with using GLP-1, SGLT-2, and Finerenone

Thank you!

Questions?

Contact Dr. Michael R. Brennan

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Phone: 586-447-8021
Fax: 586-447-8022

(Call Beaumont Health system and ask to have him Mobile Heartbeat or paged 248-898-5000)_

4.2. Adults With Type 2 Diabetes Mellitus

See Figure 2 for an algorithm for treatment of T2DM for primary prevention of cardiovascular disease.

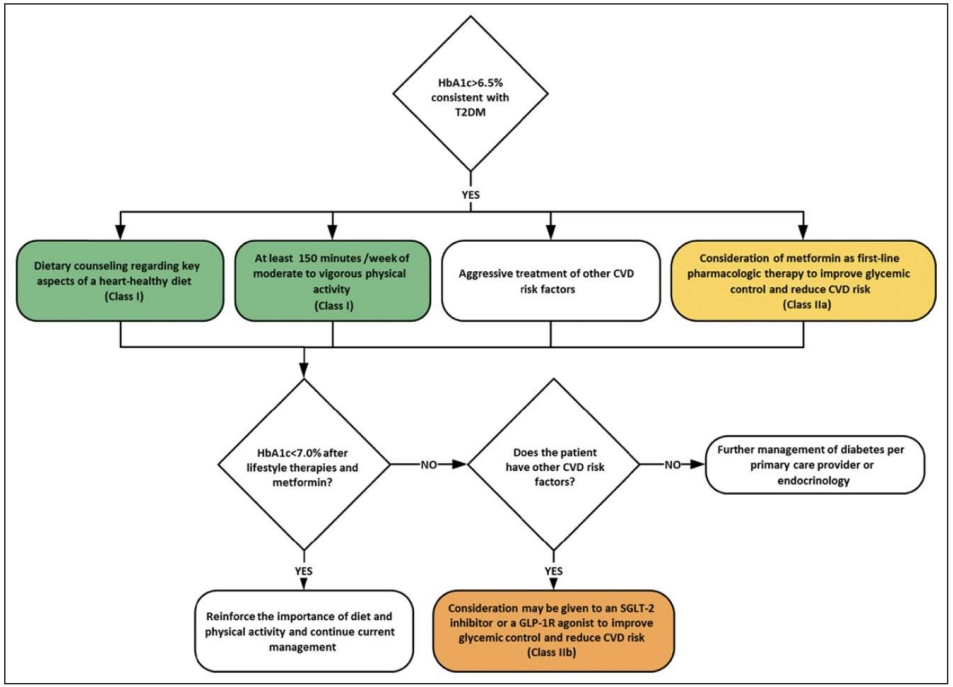

Figure 2. Treatment of T2DM for primary prevention of cardiovascular disease. CVD indicates cardiovascular disease; GLP-1R, glucagon-like peptide-1 receptor; HbA1c, hemoglobin A1c; SGLT-2, sodium-glucose cotransporter 2; and T2DM, type 2 diabetes mellitus.

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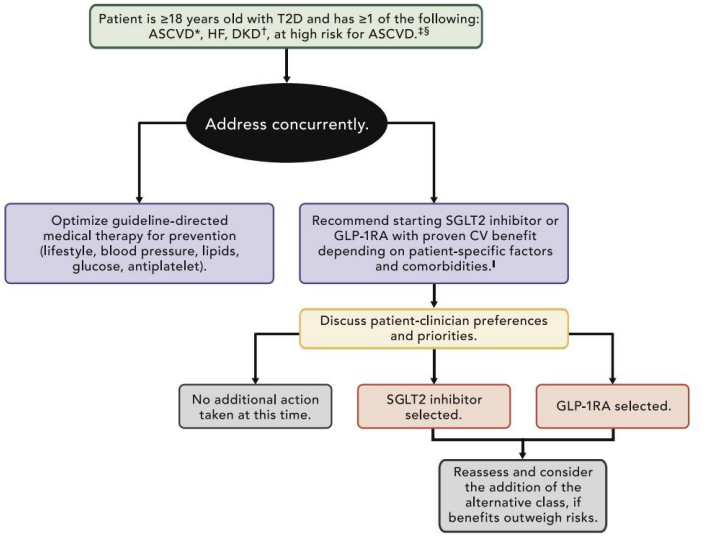
FIGURE 1 Summary Graphic



*ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

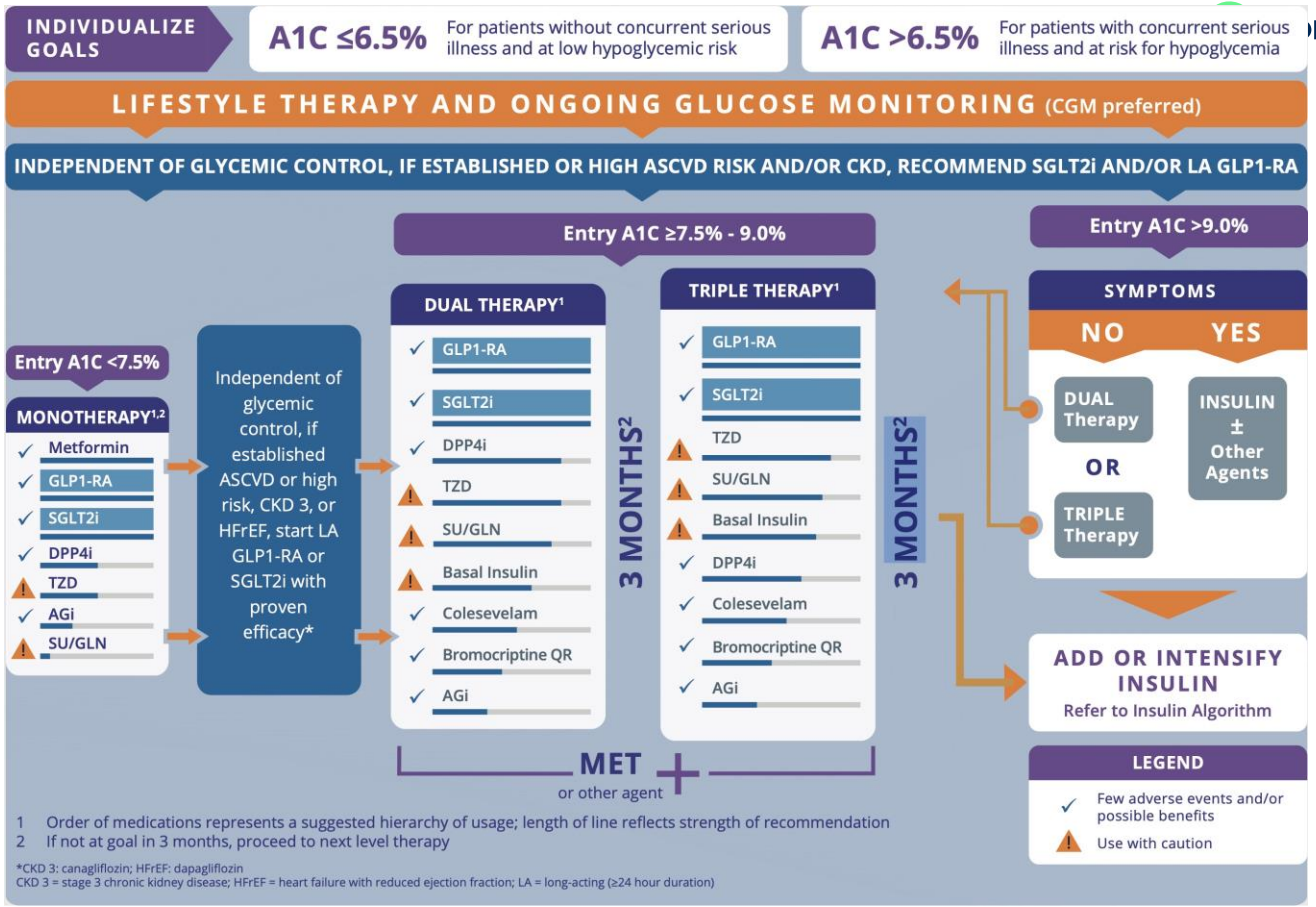
†DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

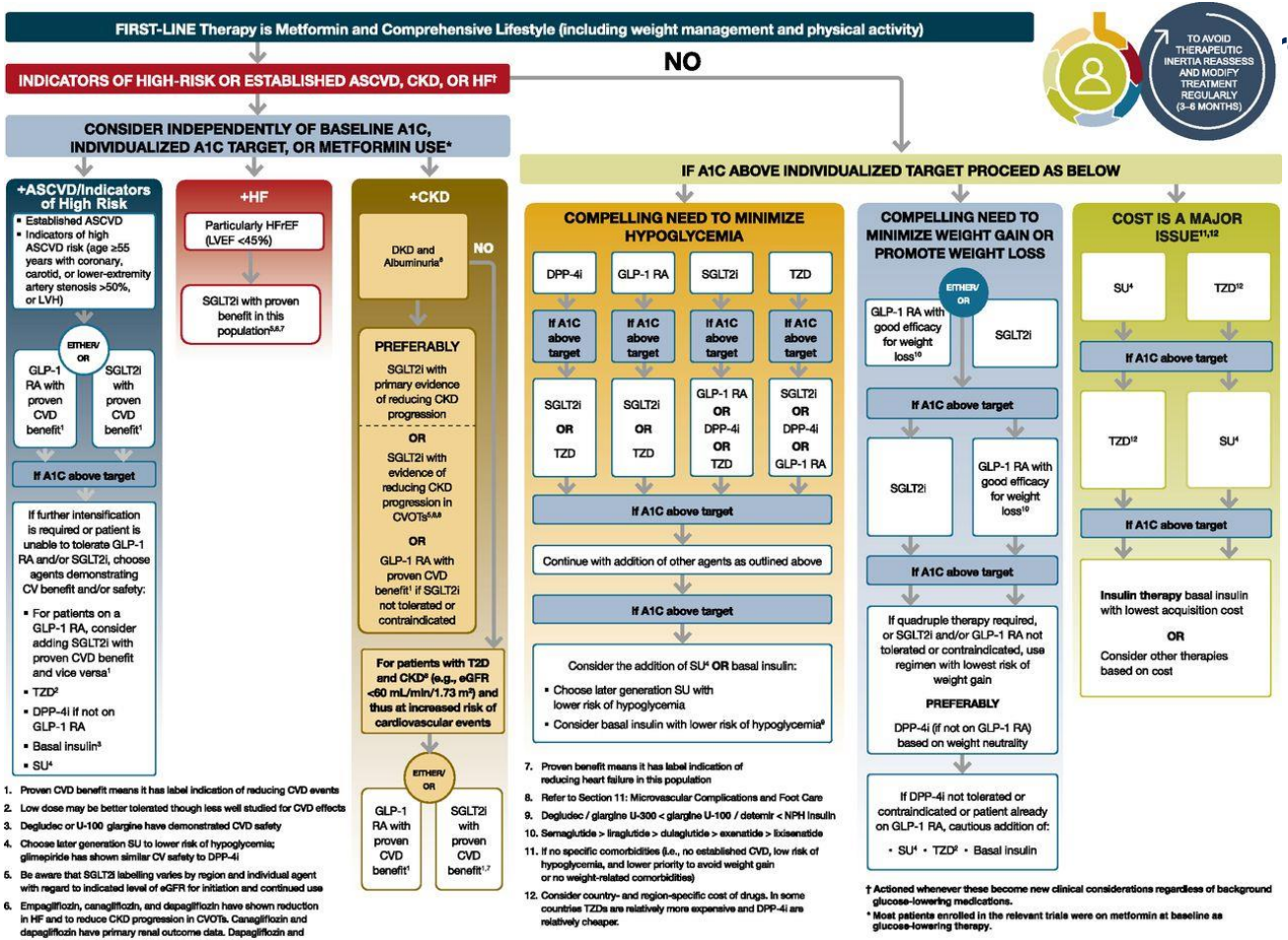
‡ Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

§ Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

‖ Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes


INDIVIDUALIZE GOALS
A1C ≤6.5%
For patients without concurrent serious illness and at low hypoglycemic risk
A1C >6.5%
For patients with concurrent serious illness and at risk for hypoglycemia
LIFESTYLE THERAPY AND ONGOING GLUCOSE MONITORING (CGM preferred)
INDEPENDENT OF GLYCEMIC CONTROL, IF ESTABLISHED OR HIGH ASCVD RISK AND/OR CKD, RECOMMEND SGLT2i AND/OR LA GLP1-RA
Entry A1C <7.5%
MONOTHERAPY1,2
Metformin
GLP1-RA
SGLT2i
DPP4i
TZD
AGi
SU/GLN
Independent of glycemic control, if established ASCVD or high risk, CKD 3, or HFrEF, start LA GLP1-RA or SGLT2i with proven efficacy*
Entry A1C ≥7.5% - 9.0%
DUAL THERAPY1
GLP1-RA
SGLT2i
DPP4i
TZD
SU/GLN
Basal Insulin
Colesevelam
Bromocriptine QR
AGi
3 MONTHS2
TRIPLE THERAPY1
GLP1-RA
SGLT2i
TZD
SU/GLN
Basal Insulin
DPP4i
Colesevelam
Bromocriptine QR
AGi
3 MONTHS2
MET + or other agent
Entry A1C >9.0%
SYMPTOMS
NO
YES
DUAL Therapy
OR
TRIPLE Therapy
INSULIN ± Other Agents
ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm
LEGEND
Few adverse events and/or possible benefits
Use with caution
1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
2 If not at goal in 3 months, proceed to next level therapy
*CKD 3: canagliflozin; HFrEF: dapagliflozin
CKD 3 = stage 3 chronic kidney disease; HFrEF = heart failure with reduced ejection fraction; LA = long-acting (≥24 hour duration)



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.