SGLT-2s and GLP1s 2.0.

Updates on DM management and beyond

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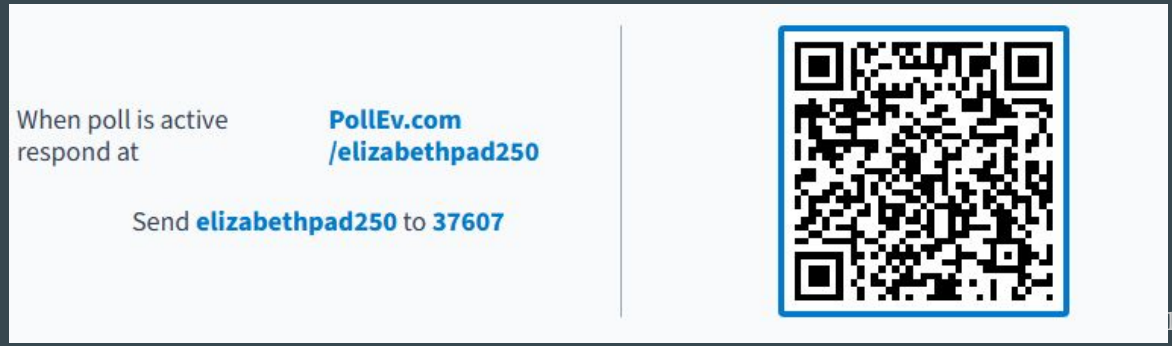
MAFP Winter Conference January 2025.



Objectives

1. Review the most recent guidelines for management of DM2
2. Explore the evidence behind newer non-diabetes indications for SGLT-2s
3. Explore the evidence behind the non-diabetes indications for GLP-1s.

When poll is active respond at **PollEv.com /elizabethpad250**

Send **elizabethpad250** to **37607**

Overview of DM disease burden:

1 in 8 adults has DM. ~95% with DM2.

1 in 3 has preDM (!). Most unaware.

In 2022: 412.9 billion spent on DM (medical and economic costs)

Those living below the poverty level have highest DM and complication rates

--food insecurity, food deserts, lack of safe spaces for exercise complicate

Racial and ethnic disparities: 19% Black, 21% hispanic, 12% White.

AIC GOALS?

The ACP recommended patients with type 2 diabetes be treated to achieve a hemoglobin A1c (HbA1c) level between 7 percent and 8 percent rather than the widely accepted range of 6.5 percent to 7 percent.

Clinical recommendation	Evidence rating	Comments
A1C goals are less than 7% for most nonpregnant patients younger than 65 years; less stringent A1C goals may be appropriate for some patients 65 years and older with multiple comorbidities or a limited life expectancy.[17,22]	C	Disease-oriented evidence; consensus opinion

Differ by organization:
AAFP, ACP, ADA, VA etc

6.5a An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. **A**

6.5b If using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal for many nonpregnant adults is time in range of >70% with time below range <4% and time <54 mg/dL <1% (Fig. 6.1 and Table 6.2). **B**

6.6 On the basis of provider judgment and patient preference, achievement of lower A1C than the goal of 7% may be acceptable and even beneficial if it can be achieved safely t significant hypoglycemia or other adverse effects of treatment. **B**

ss stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients nited life expectancy or where the harms of treatment are greater than the benefits. **B**

Table 2: Determination of HbA1c target ranges[a, b, c, d, e, f]

Major Comorbidity[g] or Physiologic Age	Microvascular Complications		
	Absent or Mild[h]	Moderate[i]	Advanced[j]
Absent[k] >10–15 years of life expectancy	6.0–7.0%[l]	7.0–8.0%	7.5–8.5%[m]
Present[n] 5–10 years of life expectancy	7.0–8.0%[l]	7.5–8.5%	7.5–8.5%[m]
Marked[o] <5 years of life expectancy	8.0–9.0%[m]	8.0–9.0%[m]	8.0–9.0%[m]

HbA1c Laboratory Considerations

NAME THAT MED

Overview of the commonly used meds that are out there

NAME THAT MED

- Cons: B12 deficiency, GI side effects. Avoid for GFR <30. Reduce dose/do not start if GFR <45.
- Potential ASCVD benefit, neutral renal benefits. Neutral/mild weight loss
- Aic reduction 1.5-2%

METFORMIN

- Cons: B12 deficiency, GI side effects. Avoid for GFR <30. Reduce dose/do not start if GFR <45.
- Potential ASCVD benefit, neutral renal benefits. Neutral/mild weight loss
- Aic reduction 1.5-2%

NAME THAT MED

-
    - Cons: Headaches, pancreatitis, ?inc risk bullous pemphigoid. Renal dosing for most.
    - Neutral for ASCVD risk, potential increased HF risk. Neural renal benefit. Neutral weight loss
    - Aic reduction 0.5-1%.

- **DPP-4**

  - Cons: Headaches, pancreatitis, ?inc risk bullous pemphigoid. Renal dosing for most.
  - Neutral for ASCVD risk, potential increased HF risk. Neural renal benefit. Neutral weight loss
  - Aic reduction 0.5-1%.

Sitagliptin, linagliptin, saxagliptin

NAME THAT MED

- Cons: Medullary thyroid cancer hx (FH or self), MEN 2, gastroparesis, pancreatitis, increased risk DM retinopathy complications, injection site reactions
- ASCVD benefit, renal benefit (decreased albuminuria), moderate to high weight loss.
- Aic 1-2%

GLUCAGON LIKE PEPTIDE 1 RECEPTOR AGONISTS (GLP-1s)

  - Cons: Medullary thyroid cancer hx (FH or self), MEN 2, gastroparesis, pancreatitis, increased risk DM retinopathy complications, injection site reactions
  - ASCVD benefit, renal benefit (decreased albuminuria), moderate to high weight loss.
  - Aic 1-2%
- Avoid use with DDP4

- Semaglutide, liraglutide, dulaglutide, exenatide

NAME THAT MED

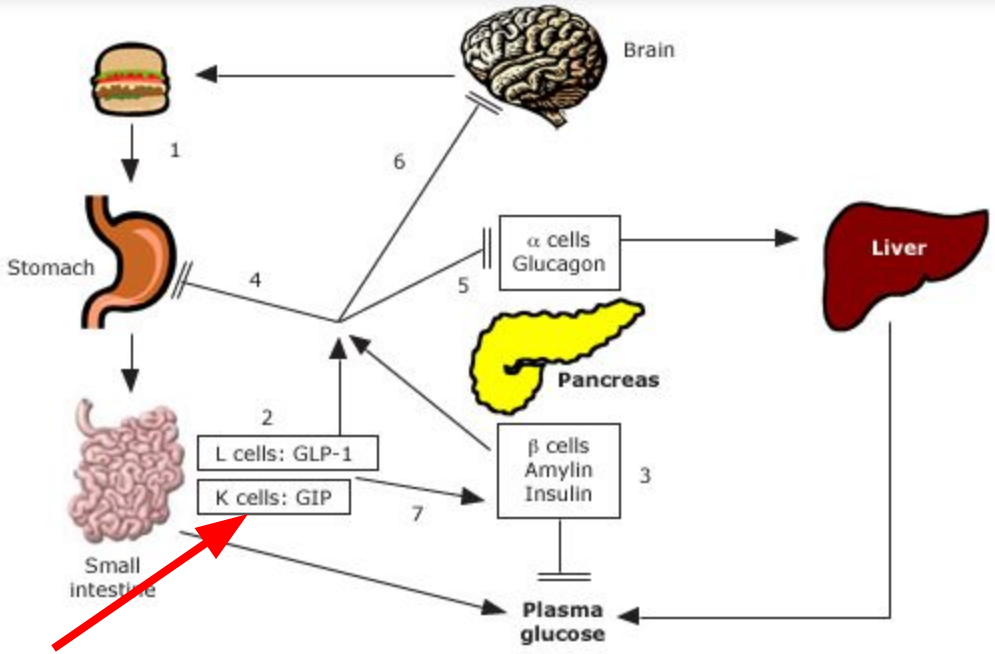
- Cons: increased risk medullary thyroid cancer, avoid w hx of MEN, increased risk of gastroparesis, pancreatitis
- ASCVD, HF and renal benefits neutral based on current evidence. Significant weight loss
- AIC 2-2.5%
- Added glucose-dependent insulotrophic polypeptide

GASTRIC INHIBITOR POLYPEPTIDE/ GLP-1

- Medullary thyroid cancer (FH or self), MEN, gastropareis, pancreatitis,
- ASCVD, HF and renal benefits neutral based on current evidence. Significant weight loss
- AIC 2-2.5%
- Added glucose-dependent insulotrophic polypeptide

- Tirzepetide (Mounjaro or Zepbound)

Multihormonal regulation of glucose



In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

NAME THAT MED

- Cons: GU infections, euglycemic DKA, hypovolemia/hypotension, ?bone fractures, amputations
- ASCVD benefit, renal benefit, mod weight loss
- Aic 0.5-1%

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS (SGLT2)

- Cons: GU infections, euglycemic DKA, hypovolemia/hypotension, ?bone fractures, amputations
- ASCVD benefit, renal benefit, mod weight loss
- Aic 0.5-1%

- Empagliflozin, dapagliflozin, canagliflozin
- Ertugliflozin- moderate evidence for NO benefit in CVD or CKD outcomes. High evidence for benefit for HF.

NAME THAT MED

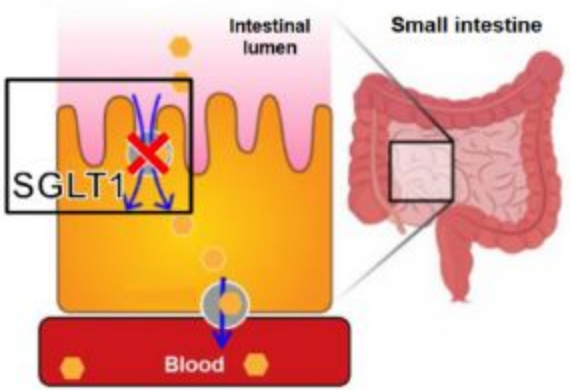
- Cons: GU infections, euglycemic DKA, hypovolemia. Diarrhea, hypoglycemia
- Pros: ASCVD benefit, renal benefit,
- Added effect of glucose reabsorption in the small intestine

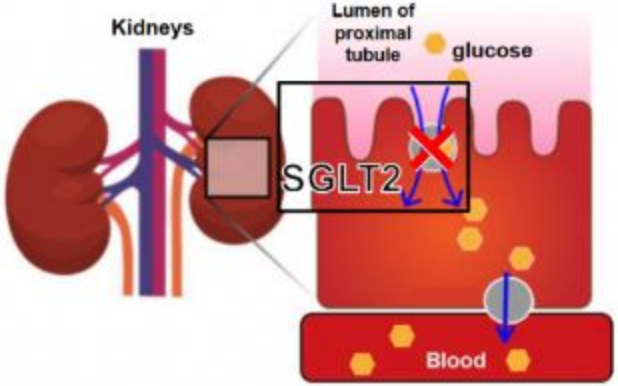
SGLT1/SGLT2 INHIBITORS

- GU infections, euglycemic DKA, hypovolemia. Diarrhea, hypoglycemia
- ASCVD benefit, renal benefit,
- Added affect of glucose reabsorption in the small intestine

- Sotagliflozin

Sotagliflozin: Dual Inhibitor of SGLT1 and SGLT2





- SGLT1 inhibition blunts and delays glucose absorption and reduces postprandial glucose (PPG) excursions[1]
- SGLT2 inhibition reduces glucose reabsorption, lowering blood glucose[2]

1. Dobbins RL et al. 2015; 2. Rieg T et al. 2014

NAME THAT MED

- Cons: Weight gain, increased risk of heart failure, risk of bone fractures
- Pros: Potential ASCVD benefit. Used for NASH
- AIC reduction 1-1.5%

THIAZOLIDINEDIONES (TZDS)

- Potential ASCVD benefit. Used for NASH
- Weight gain, increased risk of heart failure, risk of bone fractures
- AIC reduction 1-1.5%

ROSIGLITAZONE, PIOGLITAZONE

NAME THAT MED

- Cons: Hypoglycemia, weight gain, nausea, photosensitivity. Neutral cardiorenal effects.
- Aic 1-1.5%

Sulfonylureas

- Cons: Hypoglycemia, weight gain, nausea, photosensitivity. Neutral cardiorenal effects. Weight gain.
- Pros: Aic 1-1.5%

Glyburide, glipizide, glimepermide

DM management guidelines/updates

American Diabetes Association- 2024 Standards of Care in Diabetes

Updates include:

Metformin is NOT first line.

Pick your goal: Cardiorenal risk reduction in high risk individuals with DM2

OR Achievement and maintenance of glycemic and weight management goals

EDITORIALS: CONTROVERSIES IN FAMILY MEDICINE

Should Metformin Continue as First-Line Pharmacotherapy for Patients With Type 2 Diabetes? Yes: Metformin Is Still the Best Choice

EDITORIALS: CONTROVERSIES IN FAMILY MEDICINE

Should Metformin Continue as First-Line Pharmacotherapy for Patients With Type 2 Diabetes? No: Other Drugs Have Stronger Evidence of Benefit

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

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

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

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

+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^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR < 60 ml/min per 1.73 m^2 OR albuminuria (ACR ≥ 3.0 mg/mmol (30mg/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 m^2; once initiated should be continued until 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

If additional cardiorenal risk reduction or glycaemic lowering needed

Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals

Glycaemic 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

Consider avoidance of hypoglycaemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycaemic 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

Achievement and Maintenance of Weight Management Goals:

Set individualised weight management goals

- General lifestyle advice: medical nutrition therapy/eating patterns/physical activity
- Intensive evidence-based structured weight management programme
- 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-1RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

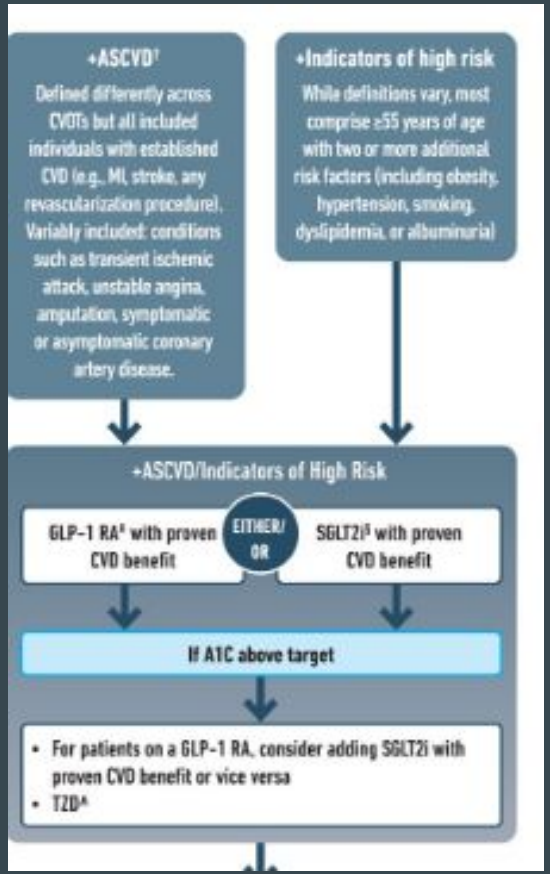
If HbA_{1c} above target

Identify barriers to goals:

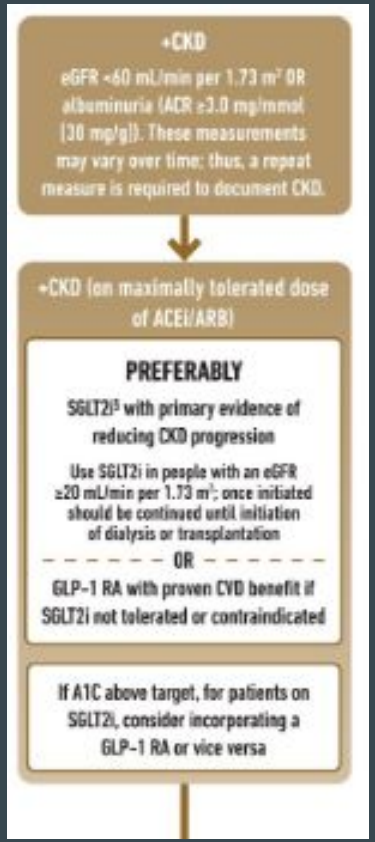
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g. diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact on achievement of goals

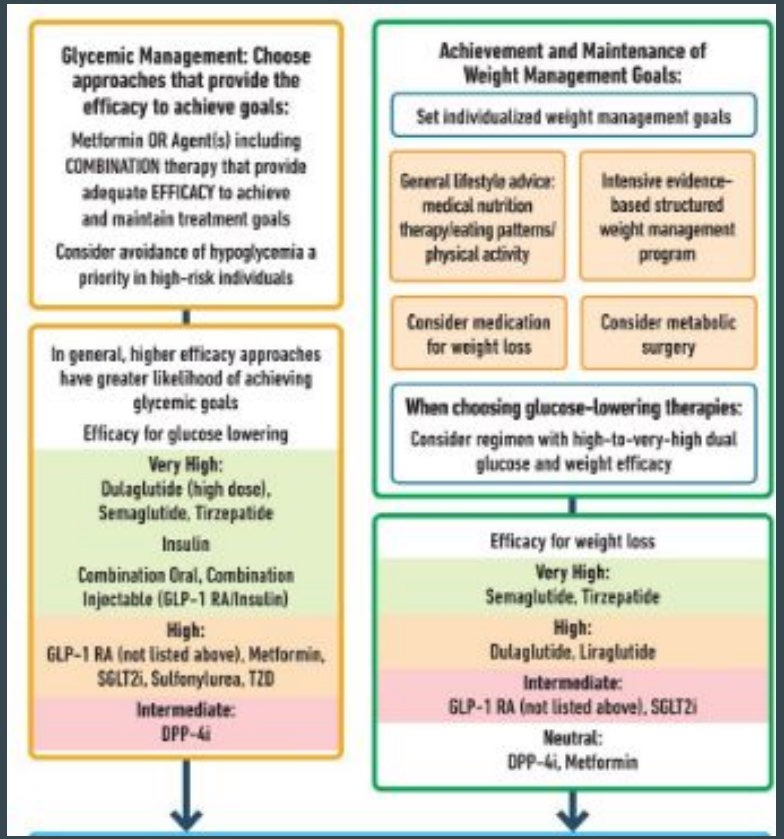
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

ASCVD


+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^

HEART FAILURE


+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[3] 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


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
Consider avoidance of hypoglycemia a priority 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
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

ACP: 2024 Clinical guideline.

Systematic Review of effectiveness and harms of the new DM2 meds (GLP, SGLT, DPP4 and long acting insulin)

Population: Non-pregnant adults with DM2

Prioritized the following outcomes: All-cause mortality, MACE, MI, hospitalization for CHF, progression of CKD, serious adverse effects and severe hypoglycemia

**Weight loss (>10%) was a prioritzed outcome, but data was insufficient.

ACP Recommendation #1

- Add SGLT2 or GLP1 TO metformin and lifestyle modifications in adults with DM2 and inadequate glycemic control. (STRONG Rec. High certainty evidence).

- Use an SGLT2 to reduce the risk for all cause mortality. MACE, progression of CKD and hospitalization for CHF.

- Use a GLP-1 to reduce the risk for all-cause mortality, MACE, and strokes.

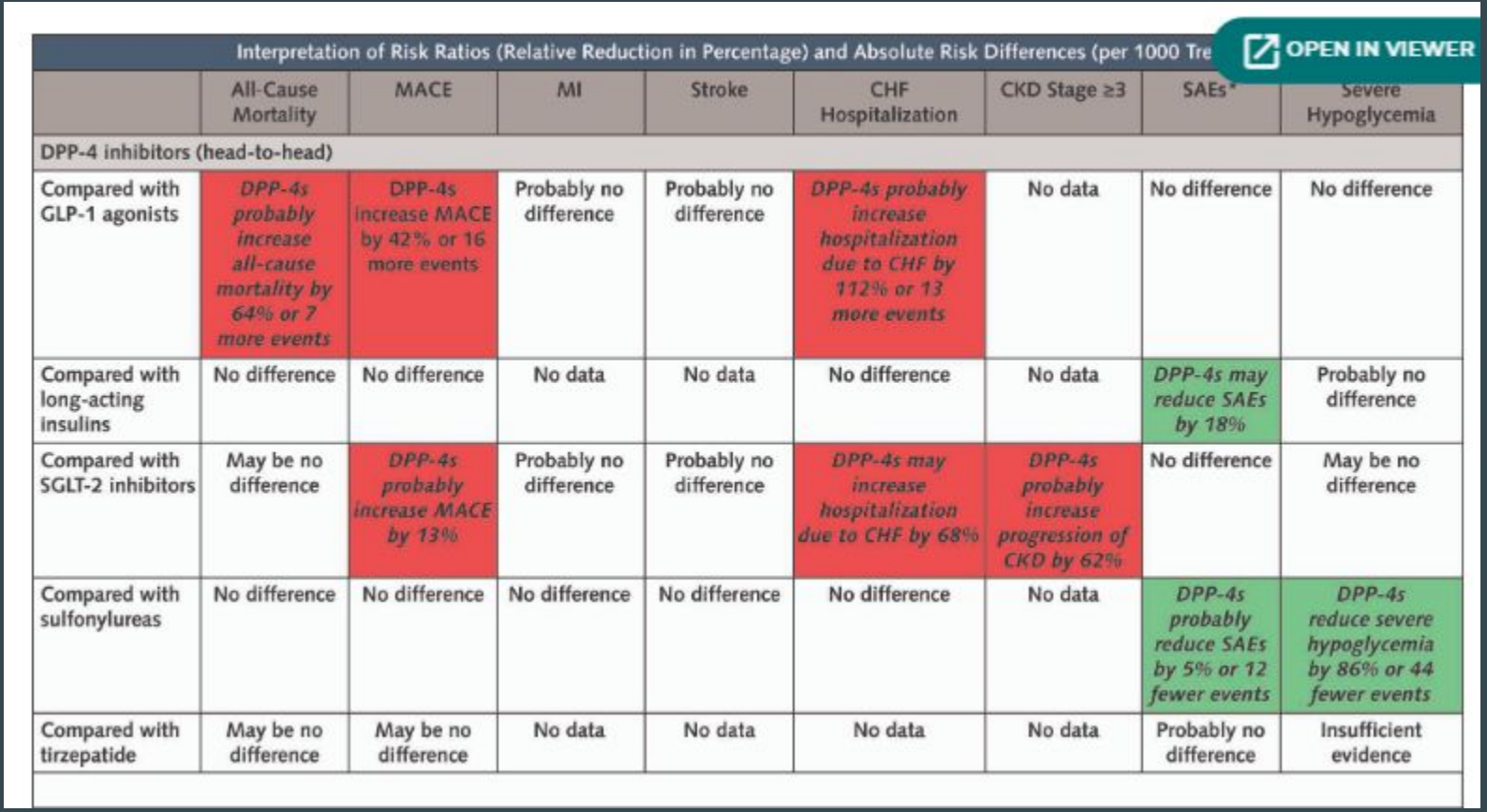
ACP Recommendation #2

- Recommends AGAINST adding a DPP-4 to metformin and lifestyle modifications in adults with DM2 and inadequate glycemic control to reduce morbidity and all-cause mortality (Strong recommendation, high certainty evidence)

Summary of ACP interpretation

Interpretation of Risk Ratios (Relative Reduction in Percentage) and Absolute Risk Differences (per 1000 Treated)								
	All-Cause Mortality	MACE	MI	Stroke	CHF Hospitalization	CKD Stage ≥3	SAEs*	Severe Hypoglycemia
Compared with usual care or placebo								
DPP-4 inhibitors	No difference	No difference	No difference	No difference	No difference	No difference	No difference	No difference
GLP-1 agonists	*Reduce all-cause mortality by 12% or 10 fewer events*	*Reduce MACE by 9% or 11 fewer events*	No difference	*Reduce stroke by 14% or 5 fewer events*	No difference	No data	No difference	Probably no difference
Long-acting insulins	May be no difference	May be no difference	No data	No data	May be no difference	No data	Probably no difference	Insufficient evidence
SGLT-2 inhibitors	*Reduce all-cause mortality by 14% or 9 fewer events*	*Probably reduce MACE by 10% or 12 fewer events*	No difference	No difference	*Reduce hospitalization due to CHF by 36% or 19 fewer events*	*Reduce progression of CKD by 34% or 12 fewer events*	*Reduce SAEs by 7% or 23 fewer events*	*Reduce severe hypoglycemia by 15% or 3 fewer events*
Tirzepatide	May be no difference	Insufficient evidence	No data	No data	No data	No data	No difference	Probably no difference

DPP4: Direct comparisons

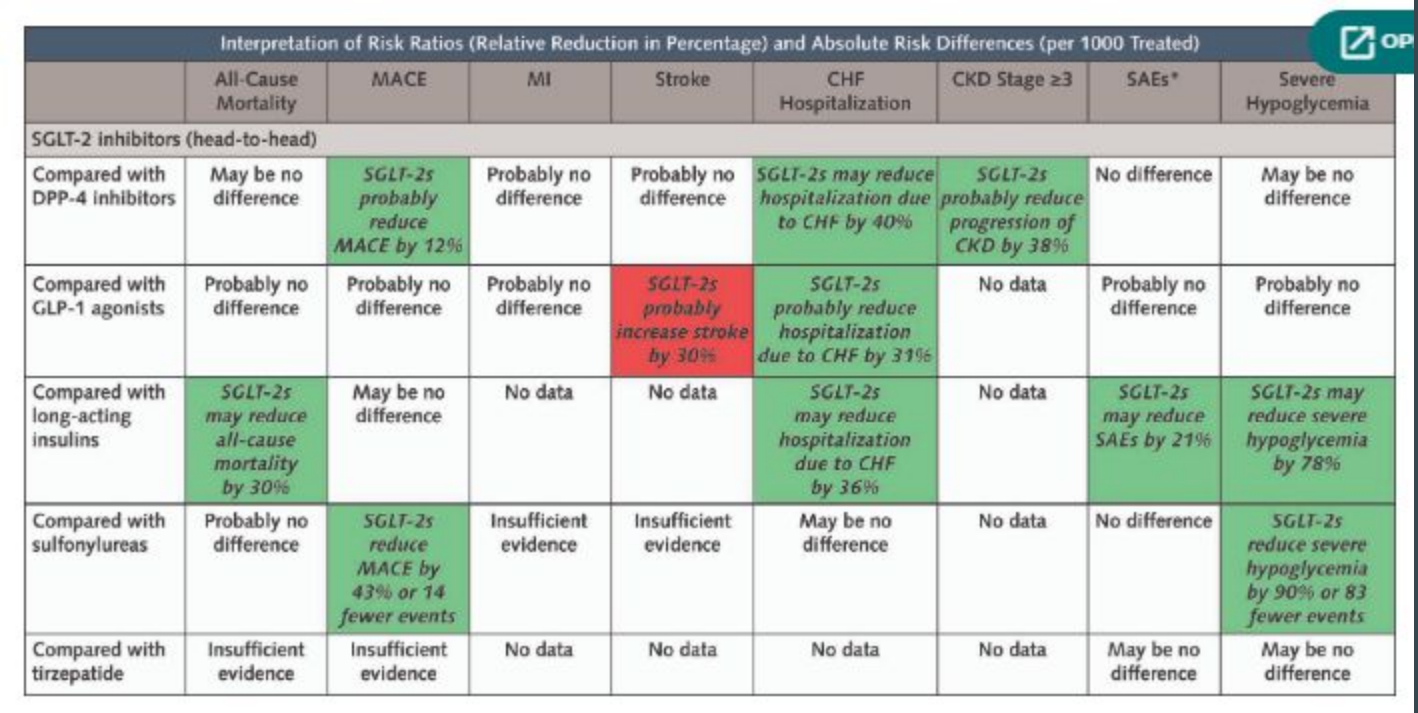


Interpretation of Risk Ratios (Relative Reduction in Percentage) and Absolute Risk Differences (per 1000 Tre								
	All-Cause Mortality	MACE	MI	Stroke	CHF Hospitalization	CKD Stage ≥3	SAEs*	Severe Hypoglycemia
DPP-4 inhibitors (head-to-head)								
Compared with GLP-1 agonists	*DPP-4s probably increase all-cause mortality by 64% or 7 more events*	DPP-4s increase MACE by 42% or 16 more events	Probably no difference	Probably no difference	*DPP-4s probably increase hospitalization due to CHF by 112% or 13 more events*	No data	No difference	No difference
Compared with long-acting insulins	No difference	No difference	No data	No data	No difference	No data	*DPP-4s may reduce SAEs by 18%*	Probably no difference
Compared with SGLT-2 inhibitors	May be no difference	*DPP-4s probably increase MACE by 13%*	Probably no difference	Probably no difference	*DPP-4s may increase hospitalization due to CHF by 68%*	*DPP-4s probably increase progression of CKD by 62%*	No difference	May be no difference
Compared with sulfonylureas	No difference	No difference	No difference	No difference	No difference	No data	*DPP-4s probably reduce SAEs by 5% or 12 fewer events*	*DPP-4s reduce severe hypoglycemia by 86% or 44 fewer events*
Compared with tirzepatide	May be no difference	May be no difference	No data	No data	No data	No data	Probably no difference	Insufficient evidence

GLP-1s: Direct comparisons

GLP-1 agonists (head-to-head)								
Compared with DPP-4 inhibitors	*GLP-1s probably reduce all-cause mortality by 39% or 9 fewer events*	GLP-1s reduce MACE by 30% or 16 fewer events	Probably no difference	Probably no difference	*GLP-1s probably reduce hospitalization due to CHF by 53% or 13 fewer events*	No data	No difference	No difference
Compared with long-acting insulins	*GLP-1s probably reduce all-cause mortality by 38% or 10 fewer events*	GLP-1s reduce MACE by 26% or 13 fewer events	No data	No data	GLP-1s probably reduce hospitalization due to CHF by 46% or 10 fewer events	No data	May be no difference	*GLP-1s probably reduce severe hypoglycemia by 77% or 38 fewer events*
Compared with SGLT-2 inhibitors	Probably no difference	Probably no difference	Probably no difference	*GLP-1s probably reduce stroke by 23%*	*GLP-1s probably increase hospitalization due to CHF by 44%*	No data	Probably no difference	Probably no difference
Compared with sulfonylureas	GLP-1s reduce all-cause mortality by 33% or 8 fewer events	No difference	Insufficient evidence	Insufficient evidence	*GLP-1s probably reduce hospitalization due to CHF by 53% or 13 fewer events*	No data	Probably no difference	*GLP-1s probably reduce severe hypoglycemia by 51% or 7 fewer events*
Compared with tirzepatide	May be no difference	May be no difference	No data	No data	No data	No data	*GLP-1s probably reduce SAEs by 43% or 24*	May be no difference

SGLT2: Direct Comparisons



Interpretation of Risk Ratios (Relative Reduction in Percentage) and Absolute Risk Differences (per 1000 Treated)								
	All-Cause Mortality	MACE	MI	Stroke	CHF Hospitalization	CKD Stage ≥3	SAEs*	Severe Hypoglycemia
SGLT-2 inhibitors (head-to-head)								
Compared with DPP-4 inhibitors	May be no difference	*SGLT-2s probably reduce MACE by 12%*	Probably no difference	Probably no difference	*SGLT-2s may reduce hospitalization due to CHF by 40%*	*SGLT-2s probably reduce progression of CKD by 38%*	No difference	May be no difference
Compared with GLP-1 agonists	Probably no difference	Probably no difference	Probably no difference	*SGLT-2s probably increase stroke by 30%*	*SGLT-2s probably reduce hospitalization due to CHF by 31%*	No data	Probably no difference	Probably no difference
Compared with long-acting insulins	*SGLT-2s may reduce all-cause mortality by 30%*	May be no difference	No data	No data	*SGLT-2s may reduce hospitalization due to CHF by 36%*	No data	*SGLT-2s may reduce SAEs by 21%*	*SGLT-2s may reduce severe hypoglycemia by 78%*
Compared with sulfonylureas	Probably no difference	*SGLT-2s reduce MACE by 43% or 14 fewer events*	Insufficient evidence	Insufficient evidence	May be no difference	No data	No difference	*SGLT-2s reduce severe hypoglycemia by 90% or 83 fewer events*
Compared with tirzepatide	Insufficient evidence	Insufficient evidence	No data	No data	No data	No data	May be no difference	May be no difference

?Metformin

Most studies on the newer agents use them as Add-on therapy

_____

ACP: metformin and lifestyle modifications are the first steps in managing DM2 in most patients.

ACP

--prioritize adding SGLTs inhibitors in patients with DM2 and CHF or CKD

--prioritize adding GLP1 in patients with DM2 and increased risk for CVA, or whom weight loss is a goal.

-AIC goal between 7-8%. De-intensify if patient below 6.5%

- self monitoring of BS might be unnecessary in patients on metformin plus either SGLTS or GLP.

-remove SU or long acting insulins if able when adding GLP1 or SGLT.

--SU and long acting insulin inferior to to SGLT2 and GLP2.

-Clinical evidence for SGLT2 and GLPs as initial treatments is lacking.

#3. Intervention with NO recommendations

Inconclusive evidence to develop recommendations for add-on tirzepatide and add-on long acting insulins to metformin and lifestyle recommendations.

ACP: Insufficient or NO evidence

- Insufficient Evidence:
  - Most studies short term follow up (1-5 years) so longer tem studies needed to understand the benefits/harms long term.
  - Low certainty regarding cost- effectiveness.
- No evidence
  - Effects of GLP-1s on progression of CKD
  - Effects of tirzepitide on MI, stroke, CHF hospitalization and progression of CKD.
  - Evidence lacking for new DM med as first line start.

Case 1:

65 year old. Hx of DM2- well controlled on metformin. Had an MI 5 years ago.

65 year old. Hx of DM2- well controlled on metformin. Had an MI 5 years ago.

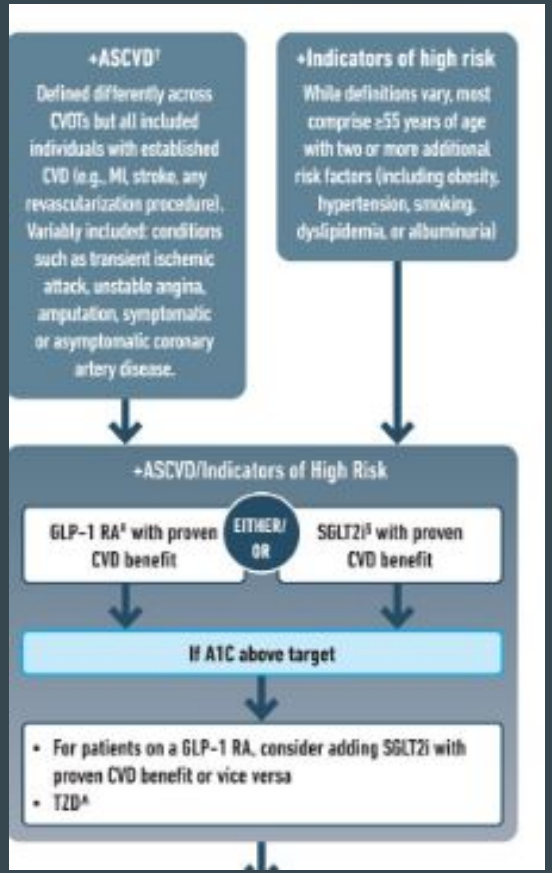
No changes 0%

Add SGLT2 0%

Add GLP1 0%

Stop metformin. Start SGLT2 and GLP1. 0%

Add TZD 0%



High to moderate certainty evidence	Low to very low certainty evidence
Among the most effective	Possibly among the most effective
Among the intermediate effective	Possibly among the intermediate effective
Not convincingly different from standard treatment	Possibly not convincingly different from standard treatment
Among the intermediate harmful	Possibly among the intermediate harmful
Among the most harmful	Possibly among the most harmful

	Standard treatments	SGLT2 inhibitors	GLP-1 receptor agonists
All-cause death 5 years	120 per 1000	**13 fewer** 18 fewer - 6 fewer ⊕⊕⊕⊕	**13 fewer** 19 fewer - 7 fewer ⊕⊕⊕⊕
Cardiovascular death 5 years	79 per 1000	**10 fewer** 15 fewer - 4 fewer ⊕⊕⊕⊕	**10 fewer** 14 fewer - 4 fewer ⊕⊕⊕⊕
Non-fatal myocardial infarction 5 years	108 per 1000	**10 fewer** 18 fewer - 2 fewer ⊕⊕⊕⊕	**9 fewer** 15 fewer - 2 fewer ⊕⊕⊕◯
Non-fatal stroke 5 years	108 per 1000	**1 fewer** 12 fewer - 10 more ⊕⊕⊕◯	**15 fewer** 23 fewer - 6 fewer ⊕⊕⊕⊕

Case 2

72 year old with DM2. Well controlled on metformin and sitagliptin (januvia) She came to clinic with increased edema and SOB recently. You get an echo and it shows an EF of 50%.

72 year old with DM2. Well controlled on metformin and sitagliptin. New dx of HFmrEF with EF 50%.

Add GLP-1 0%

Add SGLT2 0%

Stop DPP-4 and start SGLT2. 0%

stop metformin and add GLP-1 0%

Add SGLT2 and TZD 0%

DM2 with Heart Failure

SGLT-2 inhibitors	*Reduce hospitalization due to CHF by 36% or 19 fewer events*
Tirzepatide	No data

FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin.

Dr Rakesh Sonawane
Senior Medical Advisor at MSD | Medical Affairs | Strategy and Innovation | Digital and AI
Published Apr 6, 2016

Case 3

78 year old with long standing DM2. Aic has trended up and is now 8.0%. Most recent labs have shown GFR decreasing. Over the past 9 months GFR is down at ~45.

Currently on metformin, amlodipine and atorvastatin.

78 year old with DM2/HTN on metformin, amlodipine and atorvastatin. AIc now 8%, GFR now ~45ml/min.

Stop metformin. Start GLP1, start SGLT2

0%

Add SGLT2. stop amlodipine

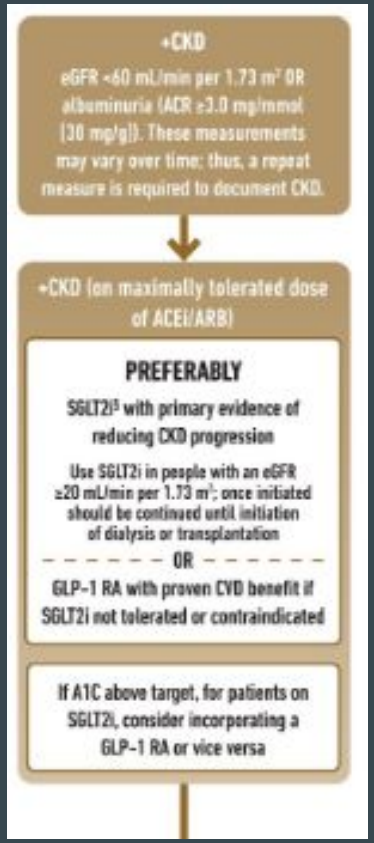
0%

Stop amlodipine, start ACE/ARB, start SGLT2.

0%

Stop metformin, start SGLT2.

0%



SGLT-2 inhibitors	*Reduce progression of CKD by 34% or 12 fewer events*

Metformin Dosing by Glomerular Filtration Rate

GFR (mL/min/ 1.73 m²)	Recommendations
< 60	Discontinue metformin in patients with low muscle mass or serious concurrent illness, or in those who are concurrently receiving renally eliminated or nephrotoxic drugs
45 to 59	Continue metform if none of above conditions exist
30 to 44	Cautiously continue; consider clinical relevance and closely monitor
< 30	Discontinue

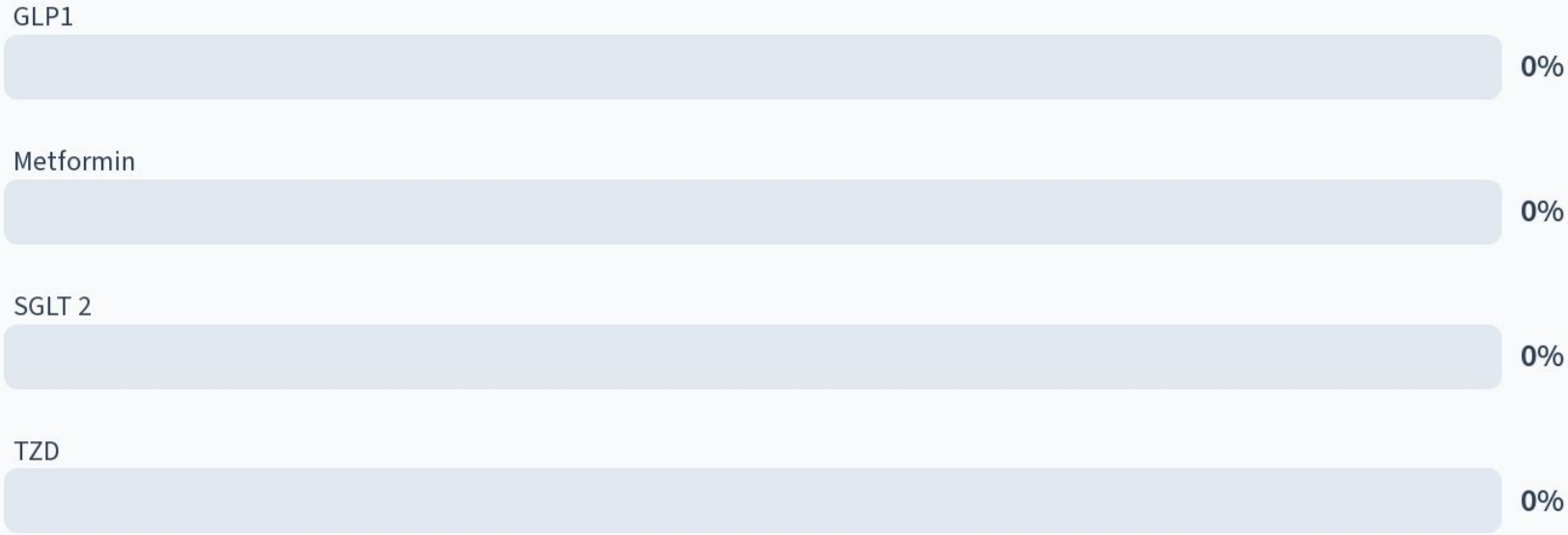
Source: KDIGO, 2012.]

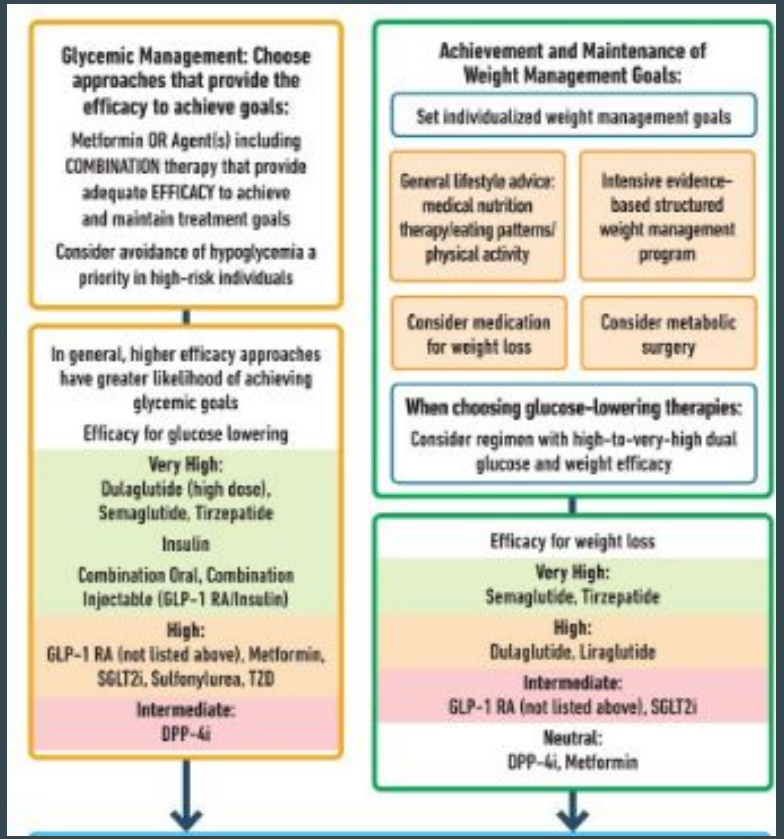
Case 4:

67 year old. New diagnosis of DM2. Aic 7.8%. BMI 38. Normal kidney function.

PMH of HTN on losartan.

67 year old. New diagnosis of DM2. Aic 7.8%. BMI 38.




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
Consider avoidance of hypoglycemia a priority 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
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

Case 5:

36 year old. New dx of DM2. BMI 28. BP wnl. Normal BMP. AIc 11.2%.

36 year old. New dx of DM2. BMI 28. BP wnl. Normal BMP. AIc 11.2%.

Start metformin

0%

Start metformin and basal insulin

0%

Start Basal/bolus insulin

0%

Start GLP1

0%

Start SGLT2

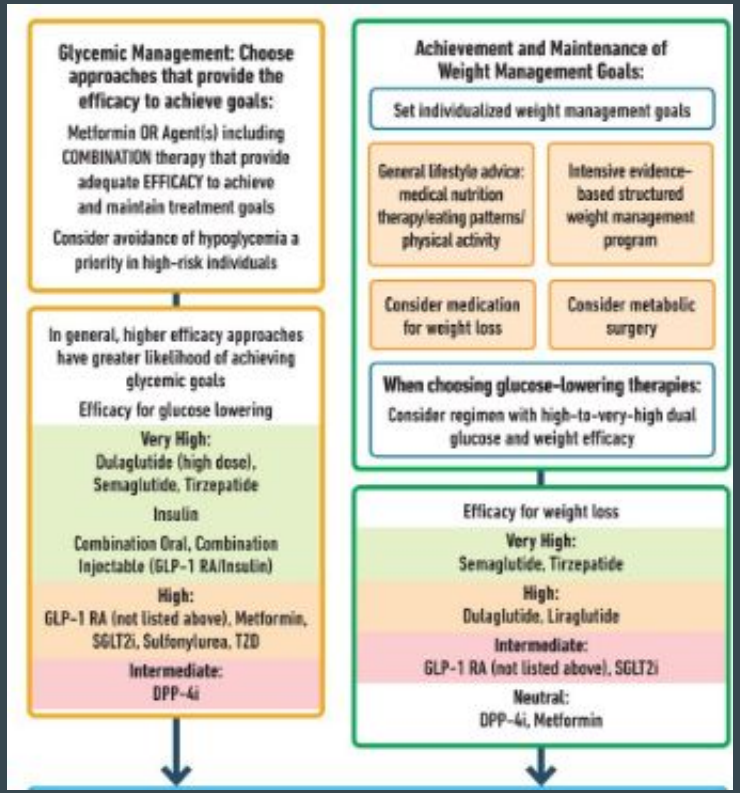
0%

Start metformin and GLP1

0%

Start metformin and sulfonylurea

0%



Recommendation 9.18 was updated to reflect prioritizing glycemic management agents that also reduce cardiovascular and kidney disease risk in adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease. Dec 11, 2023

Interpretation of Risk Ratios (Relative Reduction in Percentage) and Absolute Risk Differences (per 1000 Treated)								
	All-Cause Mortality	MACE	MI	Stroke	CHF Hospitalization	CKD Stage ≥3	SAEs*	Severe Hypoglycemia
Compared with usual care or placebo								
Long-acting insulins	May be no difference	May be no difference	No data	No data	May be no difference	No data	Probably no difference	Insufficient evidence

Case 6:

83 year old. DM2. Aic 6.5%. On DPP4.

83 year old. DM2. Aic 6.5%. On DPP4

No med changes 0%

Add GLP1 0%

Add SGLT2 0%

Stop DPP4. Start metformin. 0%

Stop DPP4 0%

Aic goal <7%

DPP4 with no Cardio-renal benefits and reduces Aic ~0.5%

Can probably just stop meds entirely.

Do not have patients on GLP1 and DPP4 together: No additional benefit

Magic calculator

Explore the evidence

https://matchit.magicevidence.org/230125dist-diabetes1/#!/

What does the AAFP say:

Does not have a specific guideline and has not endorsed any recent guidelines. (2018 NIH “Guiding Principles” and 2016 ACP “Oral Pharmacologic Treatment of DM2)

2024 Article in “American Family Physician”.

WHAT'S NEW ON THIS TOPIC

Type 2 Diabetes Mellitus Noninsulin Pharmacotherapy

In 2016, the U.S. Food and Drug Administration revised the metformin label to reflect its safety in people with an estimated glomerular filtration rate of 30 mL per minute per 1.73 m^2 or greater. When the estimated glomerular filtration rate is between 30 and 45 mL per minute per 1.73 m^2, a maximum daily dosage of 1,000 mg and close monitoring of renal function are recommended.

A large randomized clinical trial showed that empagliflozin (Jardiance), a sodium-glucose cotransporter-2 inhibitor, reduced a composite outcome of myocardial infarction, stroke, and cardiovascular death in people with established arteriosclerotic cardiovascular disease compared with placebo.

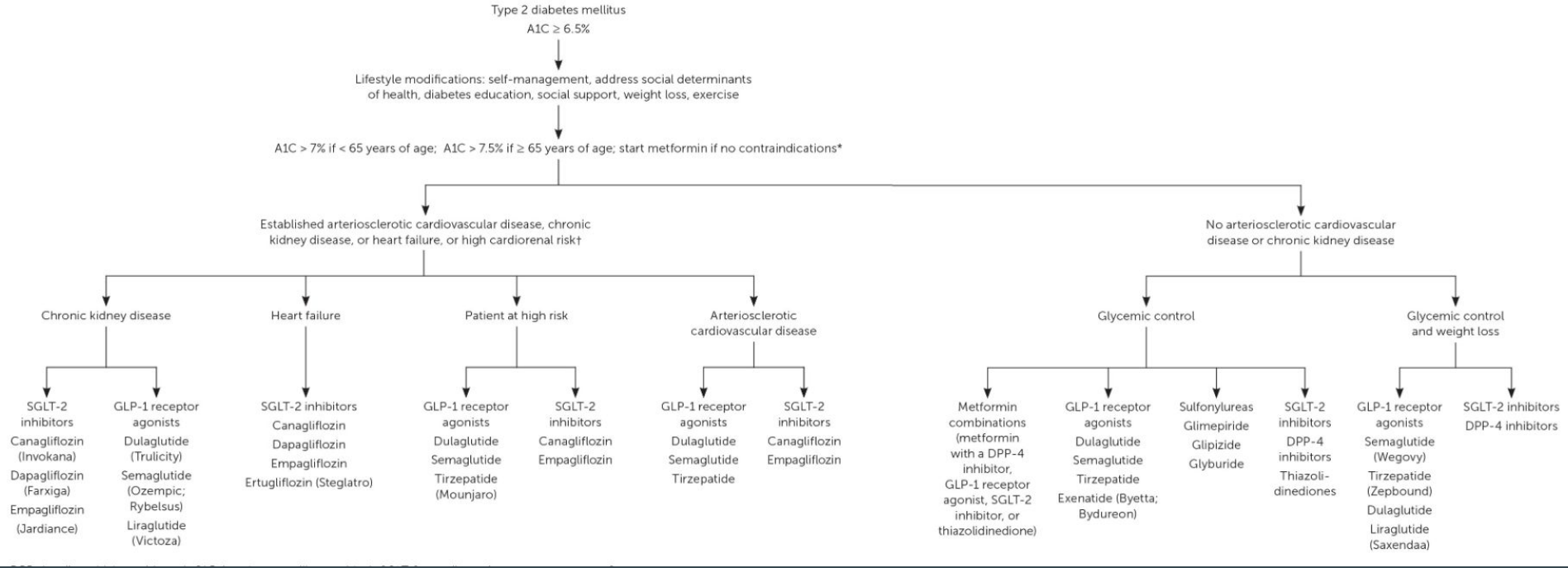
A 2023 systematic review found that glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors reduce cardiovascular-related deaths, nonfatal myocardial infarction, hospital admissions, end-stage renal disease, and all-cause mortality.

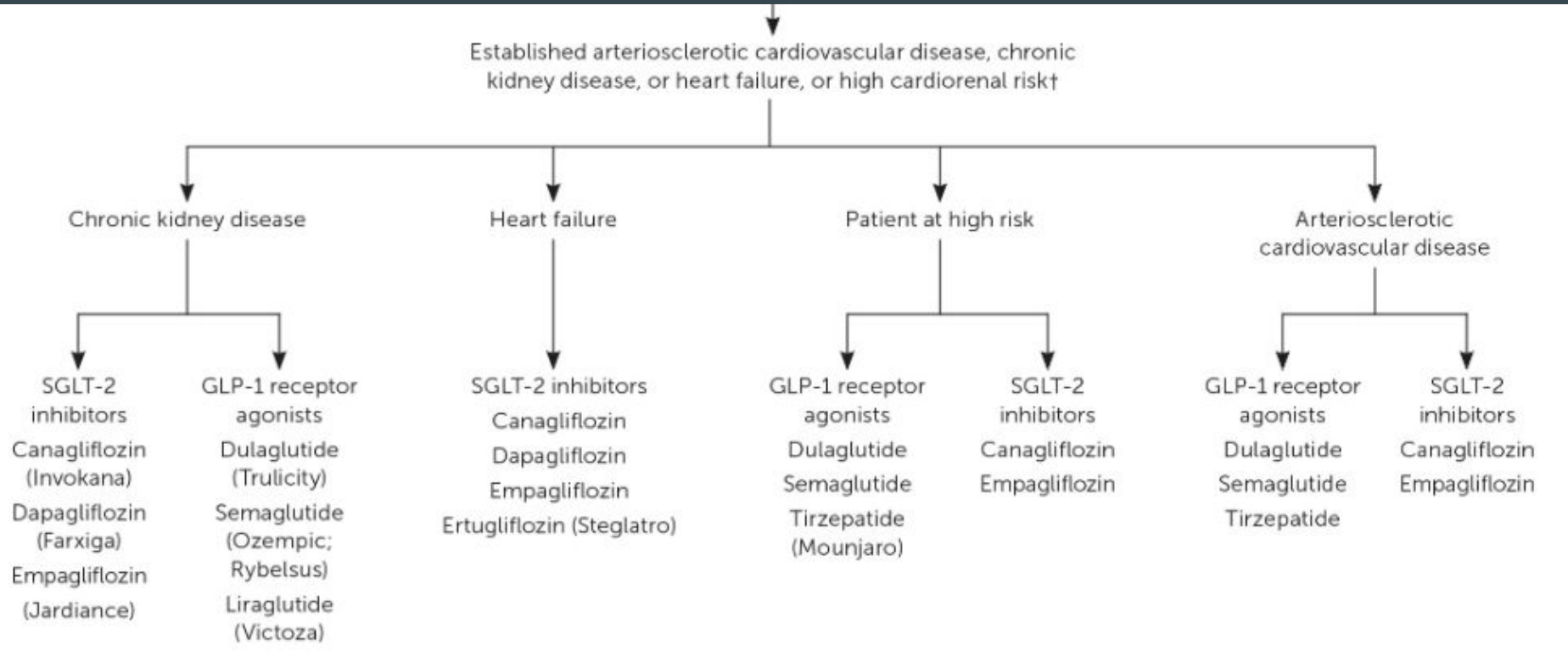
SORT: KEY RECOMMENDATIONS FOR PRACTICE

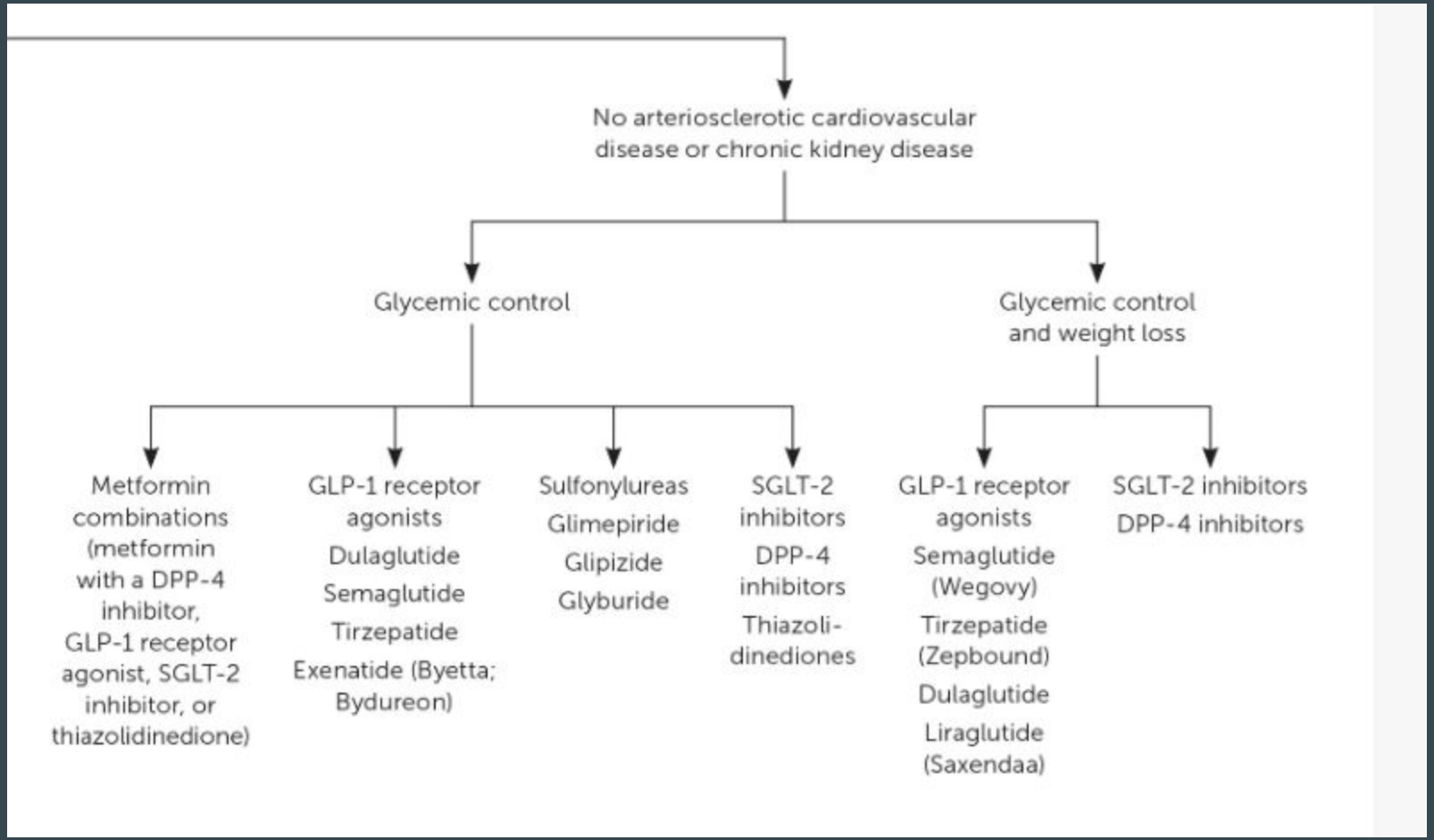
Clinical recommendation	Evidence rating	Comments
A1C goals are less than 7% for most nonpregnant patients younger than 65 years; less stringent A1C goals may be appropriate for some patients 65 years and older with multiple comorbidities or a limited life expectancy.[17,22]	C	Disease-oriented evidence; consensus opinion
Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals.[17–19,21,22]	C	Disease-oriented evidence; consensus opinion
Metformin should be used as first-line therapy for the management of type 2 diabetes mellitus due to its effectiveness and low cost.[23,33]	A	Strong recommendation, moderate-quality evidence
Initiate a sodium-glucose cotransporter-2 inhibitor or glucagon-like peptide-1 receptor agonist for patients with arteriosclerotic cardiovascular disease or kidney disease.[26,43,45,54]	A	Consistent evidence in randomized clinical trials and meta-analyses

FIGURE 1.

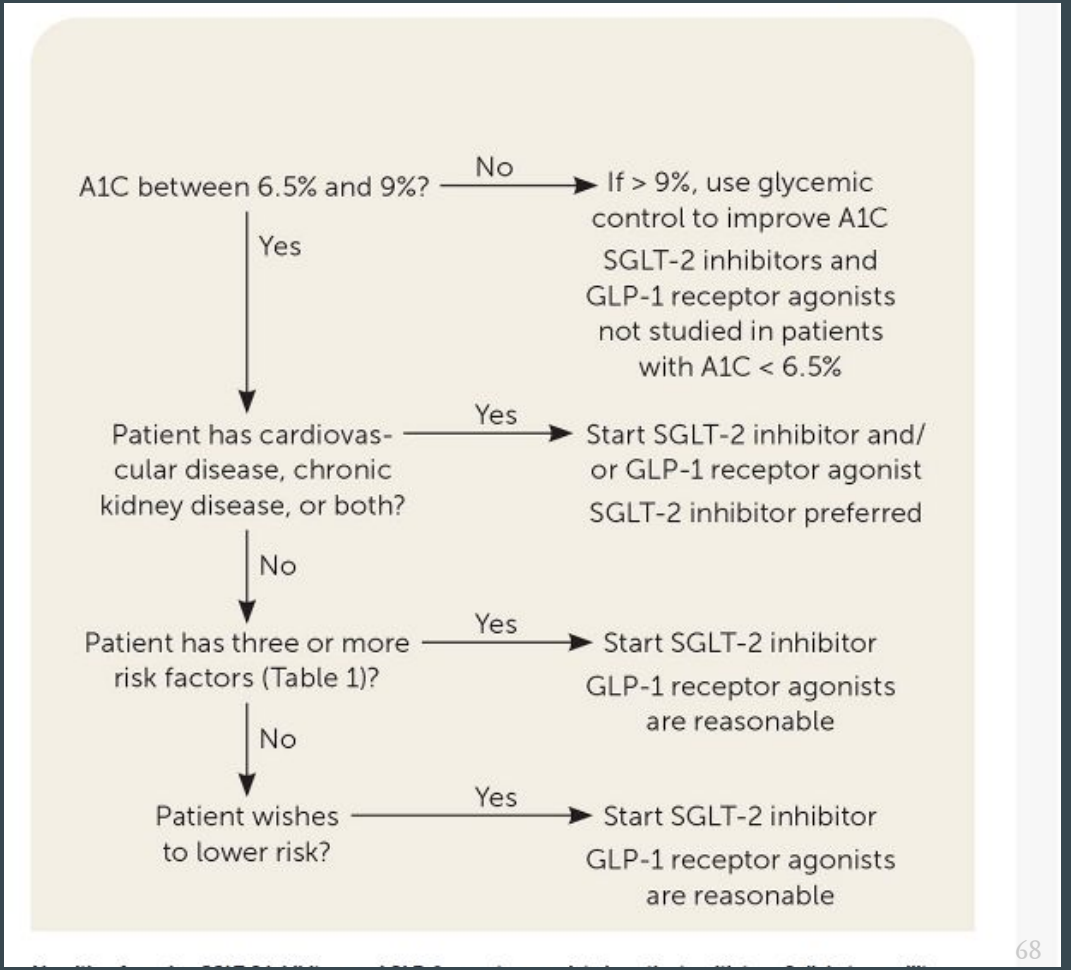
Print




Established arteriosclerotic cardiovascular disease, chronic kidney disease, or heart failure, or high cardiorenal risk†
Chronic kidney disease
Heart failure
Patient at high risk
Arteriosclerotic cardiovascular disease
SGLT-2 inhibitors
Canagliflozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)
GLP-1 receptor agonists
Dulaglutide (Trulicity)
Semaglutide (Ozempic; Rybelsus)
Liraglutide (Victoza)
SGLT-2 inhibitors
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin (Steglatro)
GLP-1 receptor agonists
Dulaglutide
Semaglutide
Tirzepatide (Mounjaro)
SGLT-2 inhibitors
Canagliflozin
Empagliflozin
GLP-1 receptor agonists
Dulaglutide
Semaglutide
Tirzepatide
SGLT-2 inhibitors
Canagliflozin
Empagliflozin


No arteriosclerotic cardiovascular disease or chronic kidney disease
Glycemic control
Glycemic control and weight loss
Metformin combinations (metformin with a DPP-4 inhibitor, GLP-1 receptor agonist, SGLT-2 inhibitor, or thiazolidinedione)
GLP-1 receptor agonists
Dulaglutide
Semaglutide
Tirzepatide
Exenatide (Byetta; Bydureon)
Sulfonylureas
Glimepiride
Glipizide
Glyburide
SGLT-2 inhibitors
DPP-4 inhibitors
Thiazoli-dinediones
GLP-1 receptor agonists
Semaglutide (Wegovy)
Tirzepatide (Zepbound)
Dulaglutide
Liraglutide (Saxendaa)
SGLT-2 inhibitors
DPP-4 inhibitors

BMJ Rapid Evidence Review:



So what to do:

My opinion:

Younger/longer life expectancy: Aic <7%, everyone else 7-8%. (most ~7.5%)

NEW DX:
-For now start with metformin for most UNLESS compelling indication for another agent:
--HF or CKD: SGLT2

-Weight loss as a goal: GLP1 or SGLT

-KNOWN ASCVD: SGLT2.

If already on metformin and has indication for another agent: look to add on. If well controlled, conversation with patient regarding stopping metformin.

One more guideline!

VA has a 2023 Guideline. Short easy to read and evidence based.

Ultimately similar recommendations of adding SGLT2 and GLP1s.

CASE 7:

Betty is a 33 year old female with DM2 (last AIc 7.4%) on metformin 1000mg BID, semaglutide SQ 1g per week and empagliflozin 10mg once per day.

Also on losartan 50mg once per day for HTN.

She comes in to clinic for a pregnancy test- it comes back positive. This is unexpected but she desires to continue the pregnancy

What meds need adjusting ASAP?

33 year old DM2. New pregnancy. On metformin, semaglutide and empagliflozin for DM. Losartan for HTN. What meds need adjusting?

Stop all current meds. Start NPH and labetalol.

0%

Stop semaglutide, empagliflozin and losartan. Start NPH and nifedipine ER.

0%

Stop semaglutide and losartan. Continue metformin, empagliflozin and add sulfonylurea. Remain off BP meds.

0%

Stop empagliflozin. Continue other meds. Add CGM for closer monitoring.

0%

DM and Pregnancy

- GLP-1s, SGLTS and DPP4
  - Limited evidence.
  - Potential risks of congenital malformations
  - Ideally these are STOPPED pre-pregnancy. (for GLP1- recs are 2 months prior).
- SU (glyburide)
  - Previously used during pregnancy
  - Recent studies suggest transplacntal transfer and possible increased risk of adverse outcomes vs insulin.
- Metformin
  - Ok to continue.
- Insulin
  - Remains first line.
- ACE/ARB
  - Should be discontinued ASAP.

RAPID REVIEW

Case 8: Heart Failure

67 year old. Comes in with progressive edema, SOB and sp02 89%

BP 122/88, weight up 24lbs, HR 89

PMH HTN, tobacco use/COPD

Meds: losartan 50mg daily; spiriva, albuterol prn

Decelines ER referral. You start furosemide 40mg daily, get labs and are able to get him an echo 2 days later.

BMP, CBC unremarkable, BNP 1200, TSH wnl

Echo: EF 35%, dilated R and L atria, dilated LV. Enlarged IVC.

New Dx of HFrEF.

EF <40%.

(He also declines a referral to cardiology at this time).

What meds are indicated?

67 year old. New dx of HFrEF. EF 40%.

MRA. SGLT2. BB. ACE/ARB/ARNI

0%

MRA. BB. Lasix. Amlodipine

0%

Amlodipine. HCTZ. ARNI. SGLT2

0%

SGLT2. Lasix. ACE/ARB. BB

0%

Guideline Direced Medical Therapy for HFrEF:

ACE or ARB or ARNI

BB

MRA

SGLT2

Indirect Evidence for this regimen.

HFpEF?

What is first line therapy for HFpEF with NYHA II and III sx?

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea) are present at rest. If any physical activity is undertaken, discomfort increases.

SGLT2 are first line for HFpEF

ACC 2023 Expert Consensus on Management of HFpEF

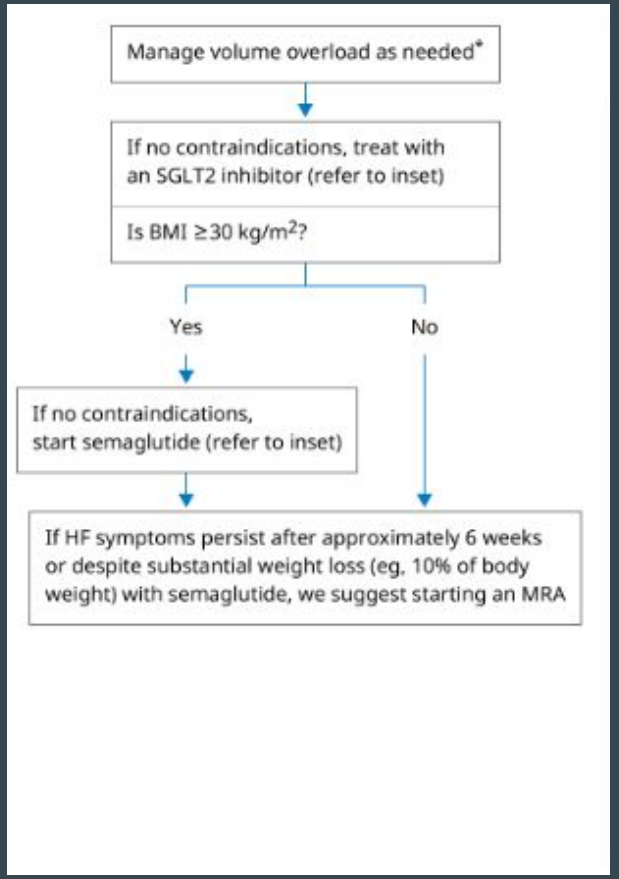
- SGLT2 for HFpEF.
- MRA may be beneficial IF LVEF <55-60% or elev BNP.
- ARNIs beneficial in HFpEF w EF<60% and women.
- BB only if another indication (Hx of MI or AF)

- BNP lower in obesity. So suspicion may have to be higher.
- Primary management of HFpEF is managing comorbidities: HTN, obesity, DM, AF, OSA

HFpEF

Newer management recommendations.

Includes SGLT2 and GLP1.



CKD

54 year old with CKD 3b (GFR ~35 and >300 albuminuria.
What kidney protective meds are recommended?

54 year old with CKD 3b. What meds are recommended for kidney protection?

Finerone. SGLT2 0%

SGLT2. BB 0%

Lasix. ACE/ARB 0%

ACE/ARB. SGLT2 0%

For Severe Range Albuminuria: ACE/ARB AND SGLTS

KDIGO 2024 Guideline:

ACE/ARB

-ACE/ARB for CKD and severely increased albuminuria

-ACE/ARB for CKD and moderately increased albuminuria (less supportive data) +/- diabetes

Continue ACE/ARB in patients with CKD even when GFR <30.

SGLTS

-DM2 with CKD (GFR >20) treat with a SGLT2

--ok to continue if GFR drops below 20 unless not tolerated.

-CKD and significant proteinuria or HF

-CKD (GFR 20-45) and less significant proteinuria (less evidence of benefit)

GLP1s approved for weight loss

-Trzepitide (GLP1/GIP)with the most weight loss benefit.

--might consider semaglutide or liraglutide at highest doses if CV protection valued.

-Insurance often not covering.

Tirzepetide (GLP1/GIP) Approved for OSA

-more than likely a result of weight loss, and not a separate independent effect.

-Suspect will not be covered by insurance

Others

GLP1 for alcohol.
Not enough data, but human studies thus far disappointing.

And then there is this:

2025 Meta-Analysis

SGLT-2 Inhibitors Reduce Cardiovascular Mortality, but Benefit Is Modest, Even in Patients With Established Heart Disease

TAKE HOME

Probably reasonable to continue mefformin first line, unless compelling reasons for alternative meds.

- Known ASCVD: GLP1 or SGLT
- HF: SGLTS
- CKD: SGLTs. (after ACE/ARB)

Avoid DPP4s and SU. Avoid insulin if able.

Consider re-adding TZDs to your med armamentarium.

For HF , reduced or preserved: SGLT2.

For CKD with significant albuminuria- add SGLTS (with ACE/ARB)

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