SGLT-2 Inhibitors and GLP-1 Receptor Agonists: A Cardiovascular Perspective

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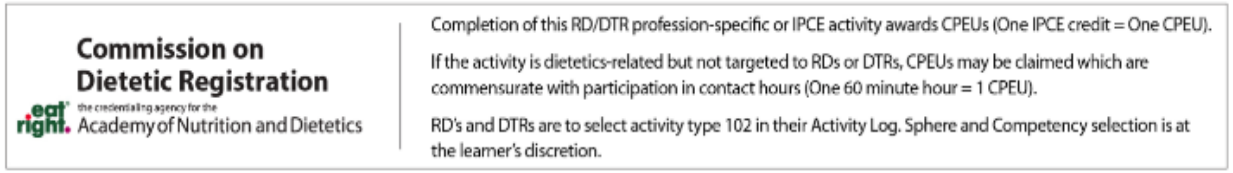

Disclosure

The following speakers and/or planning committee members have identified the following relevant financial relationship(s) with ineligible companies. All other individuals involved with this activity have no relevant financial relationships with ineligible companies to disclose.

- Lauren Oshman, M.D. (Course Co-Director): Stocks in publicly traded companies or stock options, excluding diversified mutual funds – Abbott, AbbVie, Johnson & Johnson, Merck & Co.

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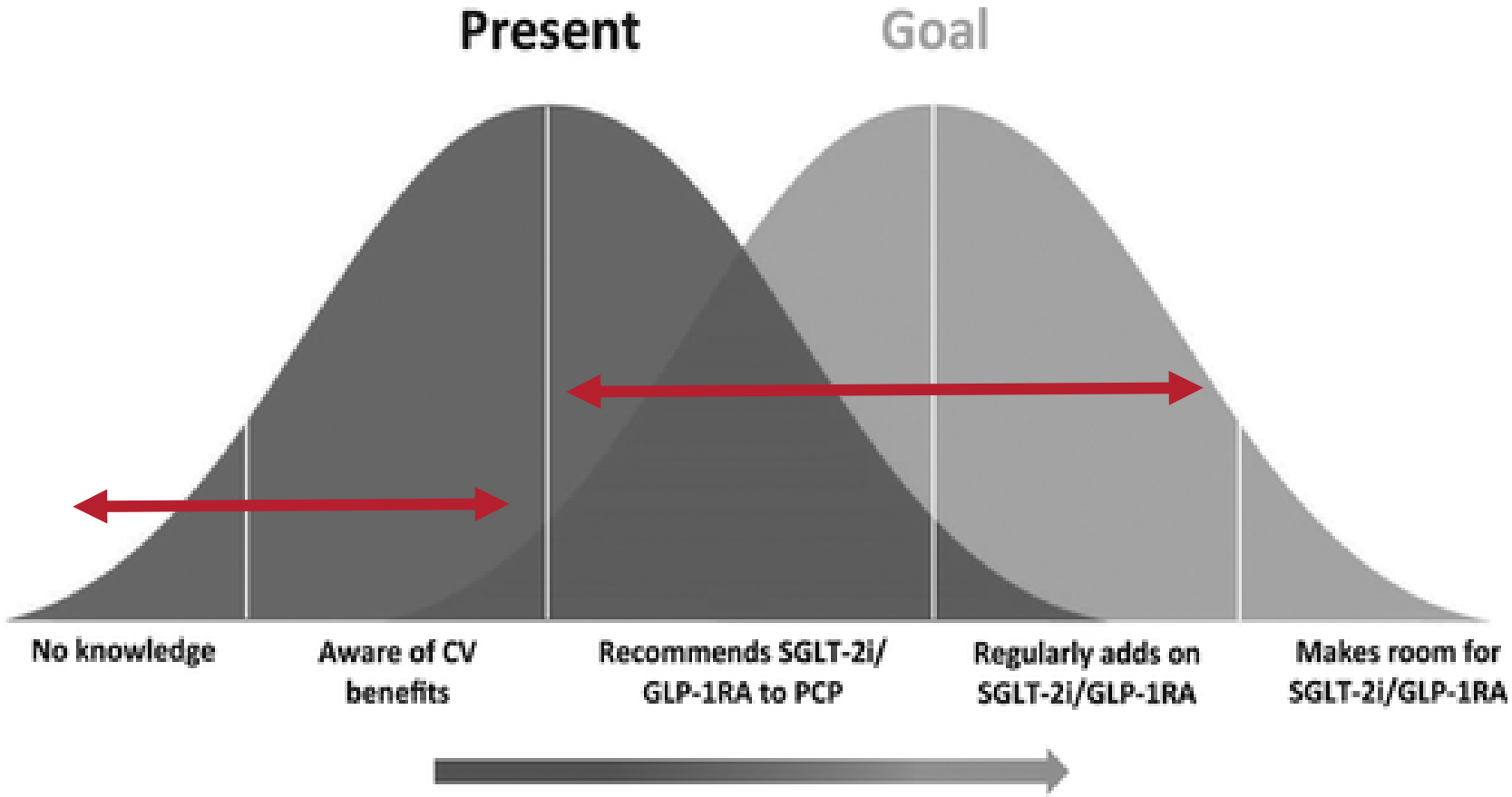
Disclosures

- I receive salary support from the Blue Cross Blue Shield of Michigan Foundation for my role in BMC2.

Agenda

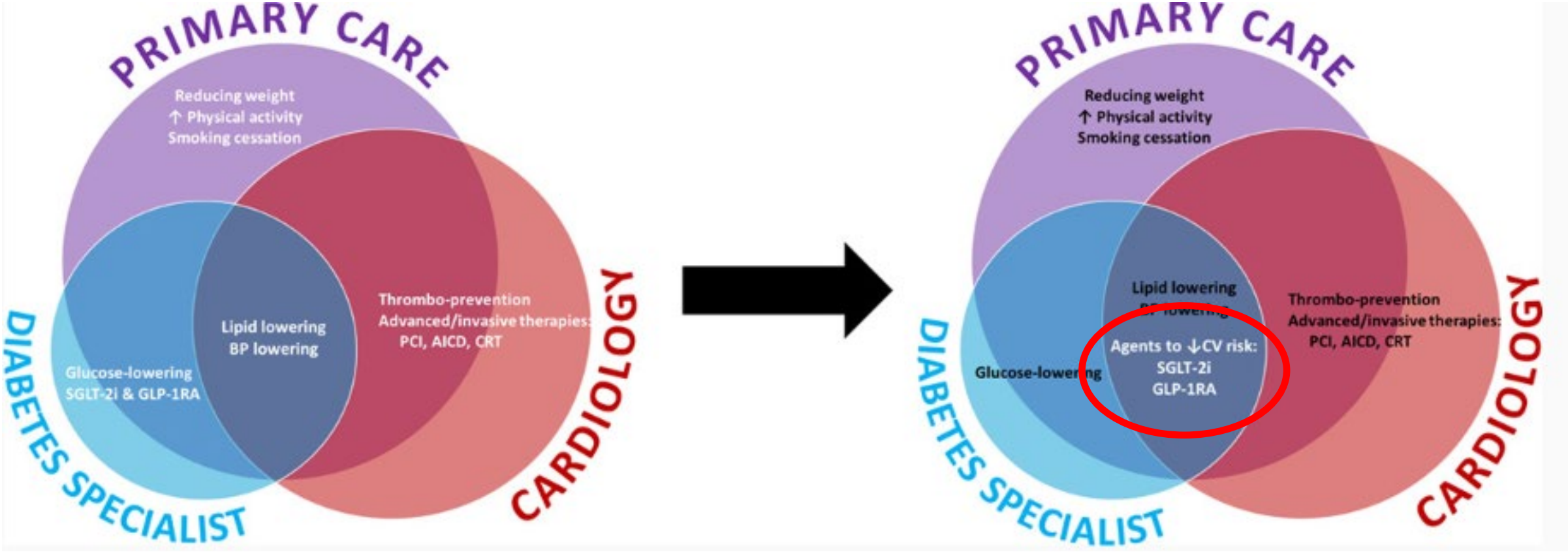
- Evidence supporting the use of SGLT-2i and GLP1-RAs in patients with (or at risk for) CV disease.
- Guidelines supporting the use of SGLT-2i and GLP1-RAs
- Rates of SGLT2i and GLP1-RA use in practice
- Practical tips on prescribing these medications
- Questions

Moving from Evidence to Implementation



Adam J. Nelson. Circulation. Incorporating SGLT2i and GLP-1RA for Cardiovascular and Kidney Disease Risk Reduction: Call for Action to the Cardiology Community, Volume: 144, Issue: 1, Pages: 74-84, DOI: (10.1161/CIRCULATIONAHA.121.053766)

Expanding our armamentarium



Definitions

- **Atherosclerotic CV disease (ASCVD)**: History of ACS/MI, stable/unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or PAD.
- **CV disease**: ASCVD, HF, and CV-related death.
- **Heart Failure**: Symptoms of heart failure (inability to effectively pump blood or elevated filling pressures required to maintain output).
- **High risk for ASCVD**: patients with end organ damage such as LVH, retinopathy, or multiple risk factors (age, HTN, smoking, obesity, dyslipidemia).

Table 4. Classification of HF by LVEF

Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%–49% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

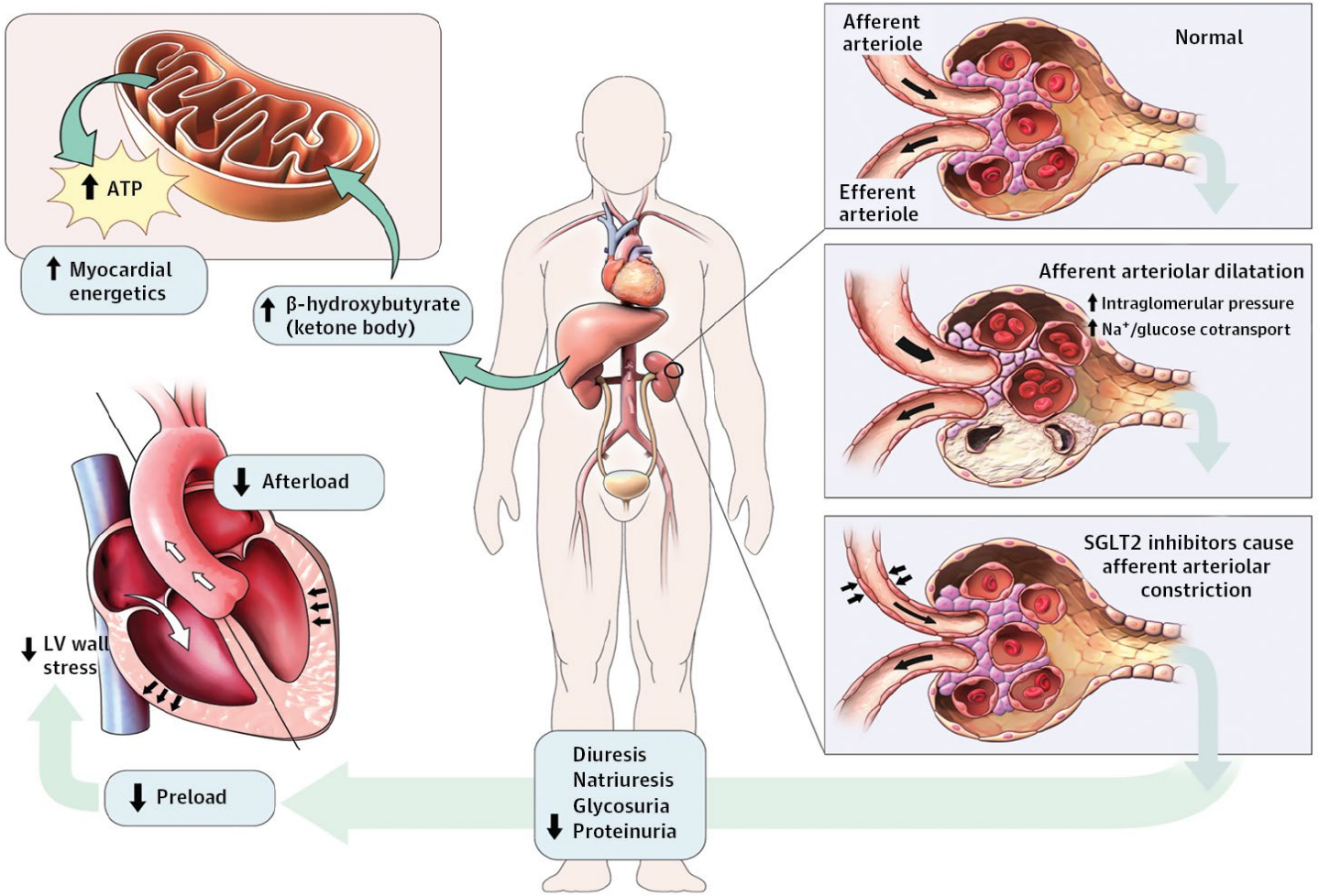
Heidenreich PA., Bozkurt B., Aguilar D., et al. Circulation 2022;145(18):e895–1032.

Latest guidelines and expert consensus

[2020 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes]

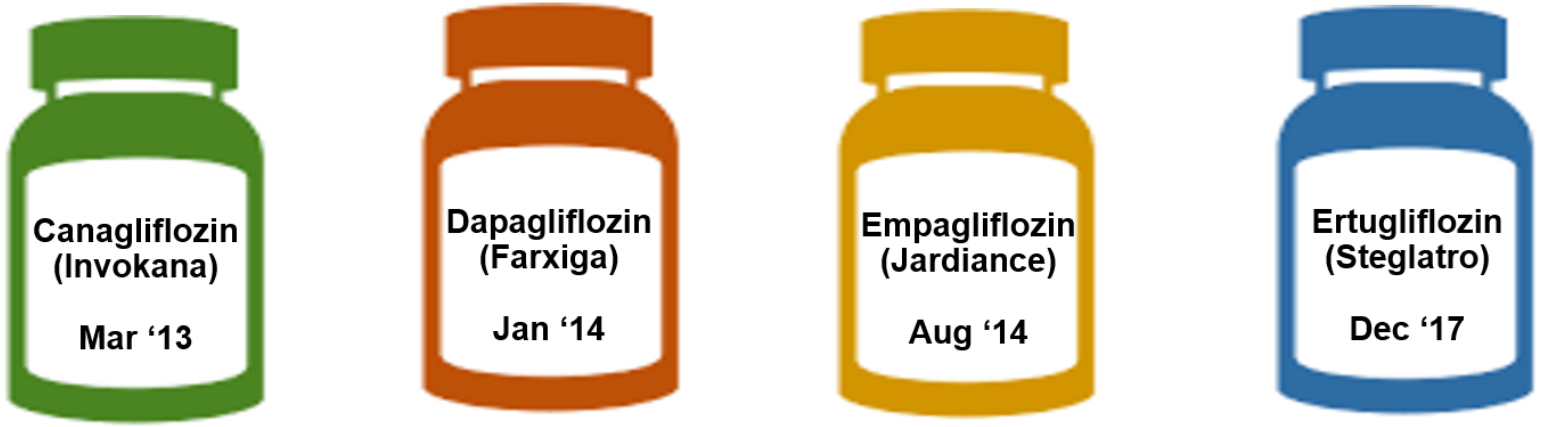
Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

Pleiotropic benefits of SGLT2i



SGLT2i in ASCVD

The "–Flozins": 4 FDA-Approved SGLT2i



Initial Labels for Glycemic Control in T2DM

Additional Labels for CV Risk Reduction in T2DM

↓ MACE ↓ HF Hospitalization ↓ CV Death

Additional Labels for CKD or HF

Albuminuric Diabetic Kidney Disease

- HFrEF with or without T2DM
- CKD with or without T2DM

Slide courtesy of M. Vaduganathan

TABLE 1 Summary of the Published SGLT2 Inhibitor CV and Renal Outcomes Trials

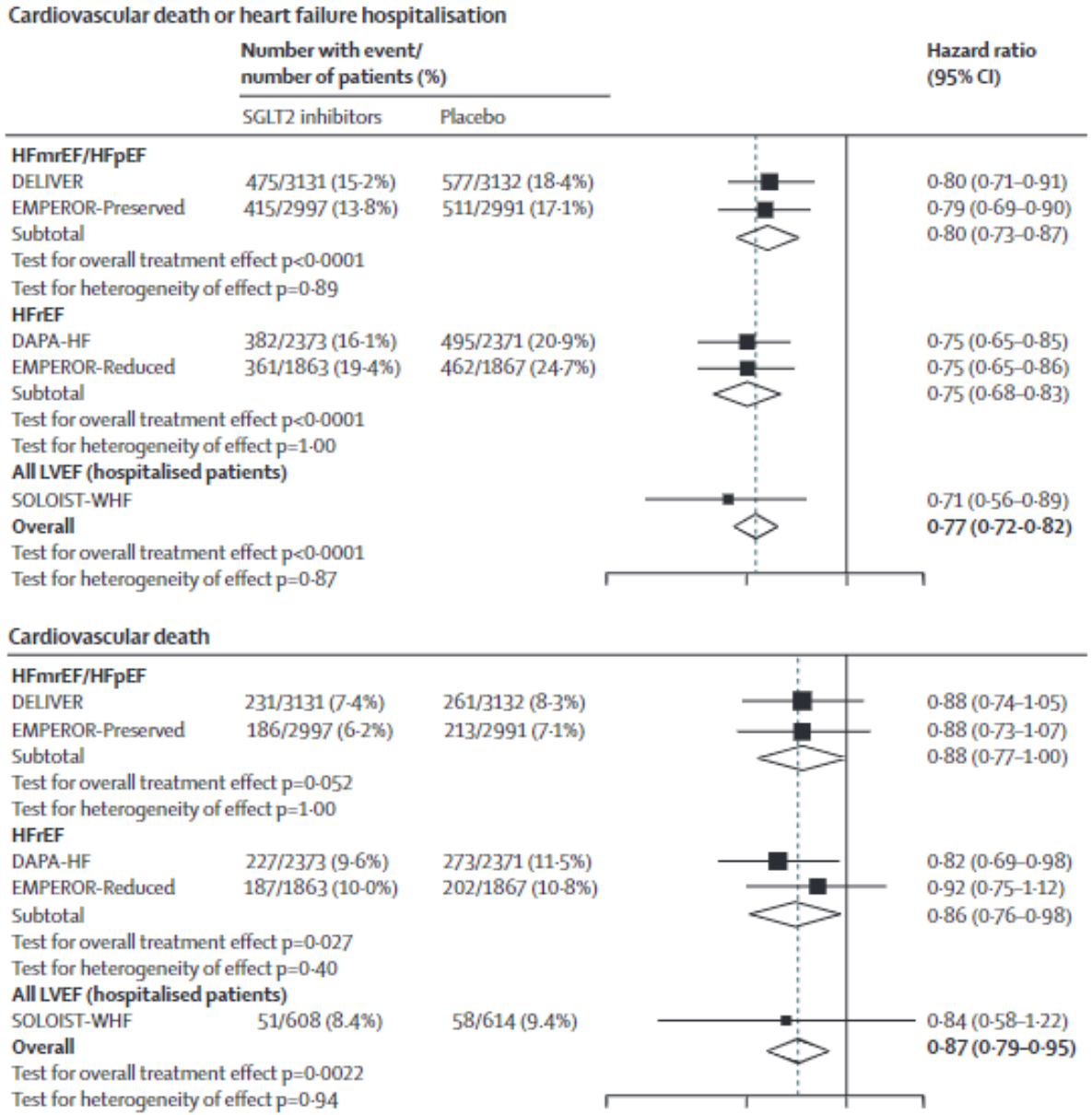
	EMPA-REG OUTCOME (12)	CANVAS/CANVAS-R (16)	DECLARE-TIMI 58 (17)	CREDENCE (19)	DAPA-HF* (47)
Patients enrolled, n	7,020	10,142	17,160	4,401	4,744
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin
Dose	10 or 25 mg PO daily	100 or 300 mg PO daily	10 mg PO daily	100 mg PO daily	10 mg PO daily
Median duration of follow-up (years)	3.1	2.4	4.2	2.6	1.5
Mean baseline HbA1c (%)	8.1	8.2	8.3	8.3	*
Mean duration of diabetes (years)	N/A†	13.5	11.0	15.8	*
Baseline statin use (%)	77	75	75	69	n/a
Baseline prevalence of CV disease/HF (%)	99	72	41	50	Not reported
Baseline prevalence of HF (%)	10	14	10	15	100*
MACE outcome, HR (95% CI)‡	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.93 (0.84–1.03)	0.80 (0.67–0.95)	Not reported
Hospitalization for HF or CV death, HR (95% CI)§	0.66 (0.55–0.79)	0.78 (0.67–0.91)	0.83 (0.73–0.95)	0.69 (0.57–0.83)	0.75 (0.65–0.85)
CV death, HR (95% CI)	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.82 (0.69–0.98)
Fatal or nonfatal MI, HR (95% CI)	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	Not reported	Not reported
Fatal or nonfatal stroke, HR (95% CI)	1.18 (0.89–1.56)	0.87 (0.69–1.09)	1.01 (0.84–1.21)	Not reported	Not reported
All-cause mortality, HR (95% CI)	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.83 (0.71–0.97)
HF hospitalization, HR (95% CI)	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	0.70 (0.59–0.83)
Renal composite endpoint,‖ HR (95% CI)	0.54 (0.40–0.75)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	0.70 (0.59–0.82)	0.71 (0.44–1.16)

SGLT2i and HF trials

	DAPA-HF (n=4744)	DELIVER (n=6263)	EMPEROR-Reduced (n=3730)	EMPEROR-Preserved (n=5988)	SOLOIST-WHF (n=1222)
Investigational drug	Dapagliflozin	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
Enrollment period	2017–18	2018–21	2017–19	2017–20	2018–20
Sites	410 sites in 20 countries	350 sites in 20 countries	520 sites in 20 countries	622 sites in 23 countries	306 sites in 32 countries
Key inclusion criteria	LVEF ≤40%; elevated NT-proBNP; NYHA functional class II–IV	LVEF >40% and evidence of structural heart disease; elevated NT-proBNP; NYHA functional class II–IV; ambulatory or hospitalised patients	LVEF ≤40%; elevated NT-proBNP; NYHA functional class II–IV	LVEF >40%; evidence of structural heart disease or history of heart failure hospitalisation within 12 months; elevated NT-proBNP; NYHA functional class II–IV	Type 2 diabetes; admitted to the hospital, or urgent heart failure visit for worsening heart failure; previous treatment with loop diuretic for >30 days; previous diagnosis of heart failure (>3 months); elevated BNP or NT-proBNP; randomised when haemodynamically stable, before hospital discharge or within 3 days of discharge
	HFrEF	HFrEF	HFrEF	HFmrEF HFpEF	All EFs
Key exclusion criteria	eGFR <30mL/min/1·73m²; SBP <95 mm Hg	eGFR <25 mL/min/1·73 m²; SBP <95 mm Hg	eGFR <20 mL/min/1·73 m²; SBP <100 mm Hg	eGFR <20 mL/min/1·73 m²; SBP <100 mm Hg	eGFR <30 mL/min/1·73 m²
Median follow-up time	18·2 months	28·1 months	16 months	26·2 months	9·0 months
Primary outcome	Time to first cardiovascular death or heart failure hospitalisation or urgent visit	Time to first cardiovascular death or heart failure hospitalisation or urgent visit	Time to first cardiovascular death or heart failure hospitalisation	Time to first cardiovascular death or heart failure hospitalisation	Total number of cardiovascular death and heart failure hospitalisations and urgent visits
Placebo-group event rates					
Heart failure hospitalisation	9·8/100 person-years	6·5/100 person-years	15·5/100 person-years	8·7/100 person-years	..
Cardiovascular death	7·9/100 person-years	3·8/100 person-years	8·1/100 person-years	3·8/100 person-years	12·5/100 person-years
All-cause death	9·5/100 person-years	7·6/100 person-years	10·7/100 person-years	6·7/100 person-years	16·3/100 person-years

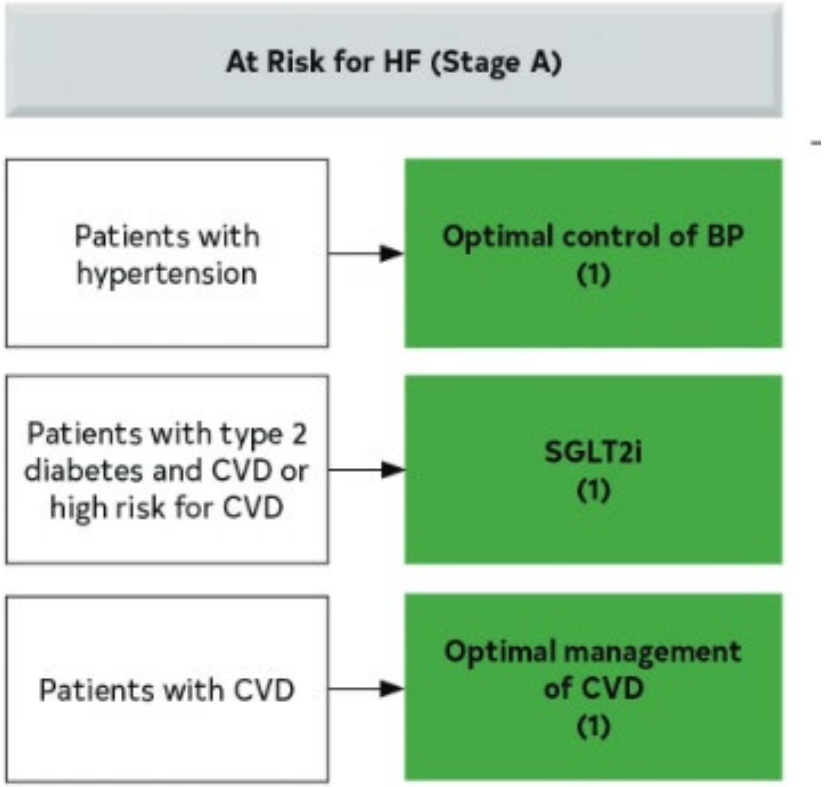
(Table 1 continues on next page)

Vaduganathan M., Docherty KF., Claggett BL., et al. Lancet 2022;400(10354):757–67.



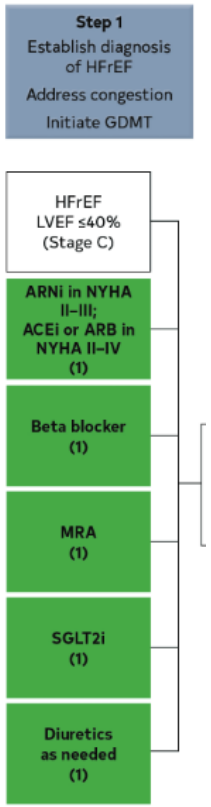
Vaduganathan M., Docherty KF., Claggett BL., et al. Lancet 2022;400(10354):757–67.

SGLT2i for HF: A game-changer

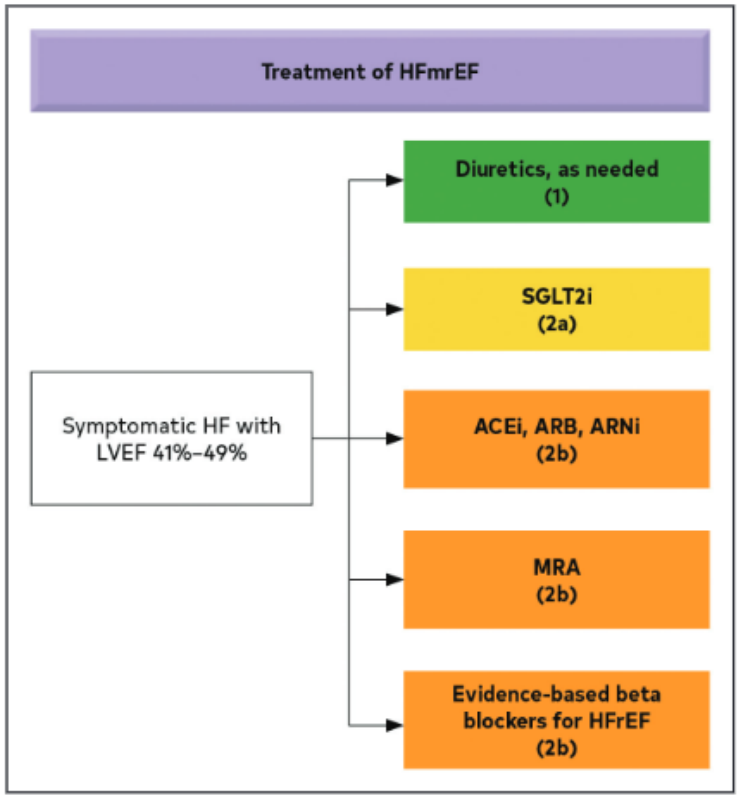


SGLT2i for HF: A game-changer

HFrEF



HFmrEF



HFpEF

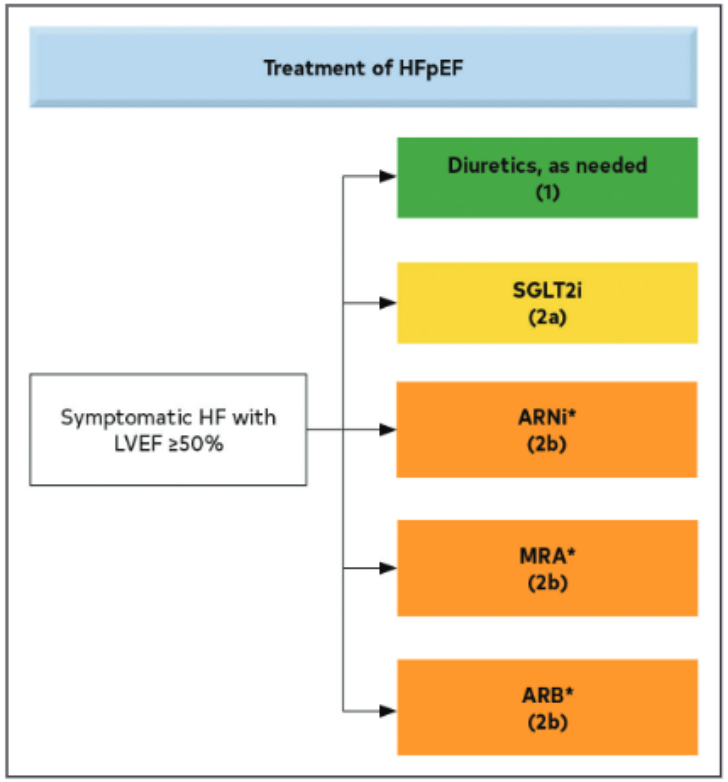


Figure 12. Recommendations for Patients With Preserved LVEF (≥50%).

Heidenreich PA., Bozkurt B., Aguilar D., et al. Circulation 2022;145(18):e895–1032.

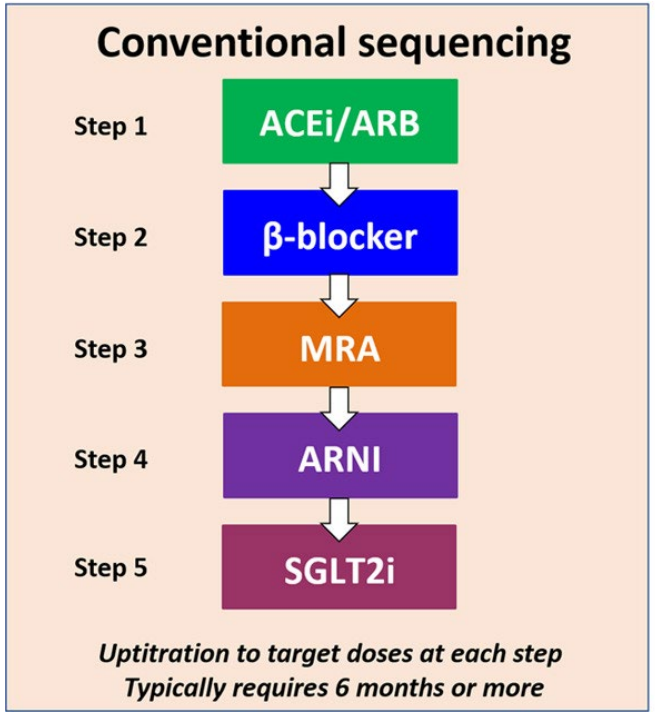
All 4 drugs should be started, but how to do it is less certain…

Step 1 medications may be **started simultaneously** at initial (low) doses recommended for HFrEF.

Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication.

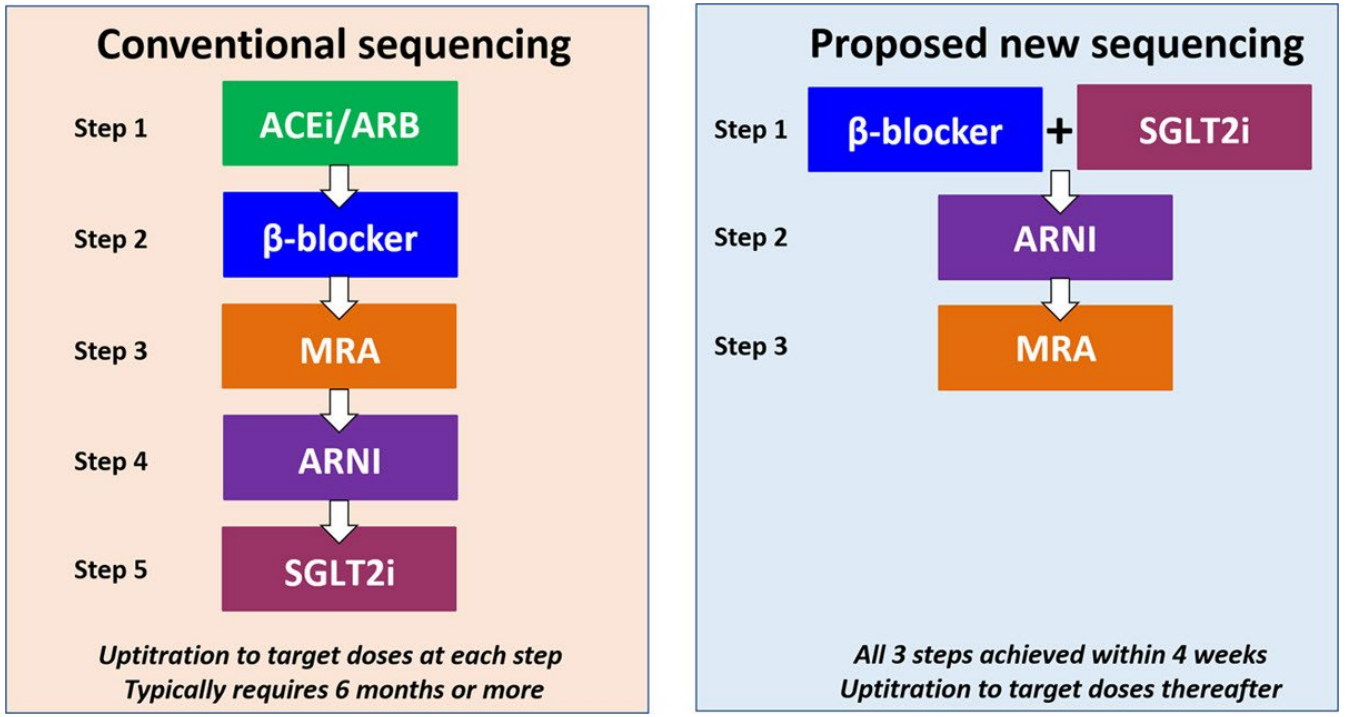
All 4 drugs should be started, but how to do it is less certain…

Option 1: Sequential



All 4 drugs should be started, but how to do it is less certain…

Option 2: Modified sequential process



A summary of SGLTi

TABLE 1 Spectrum of FDA Approved Benefits Afforded by Individual SGLT2 Inhibitor Medications

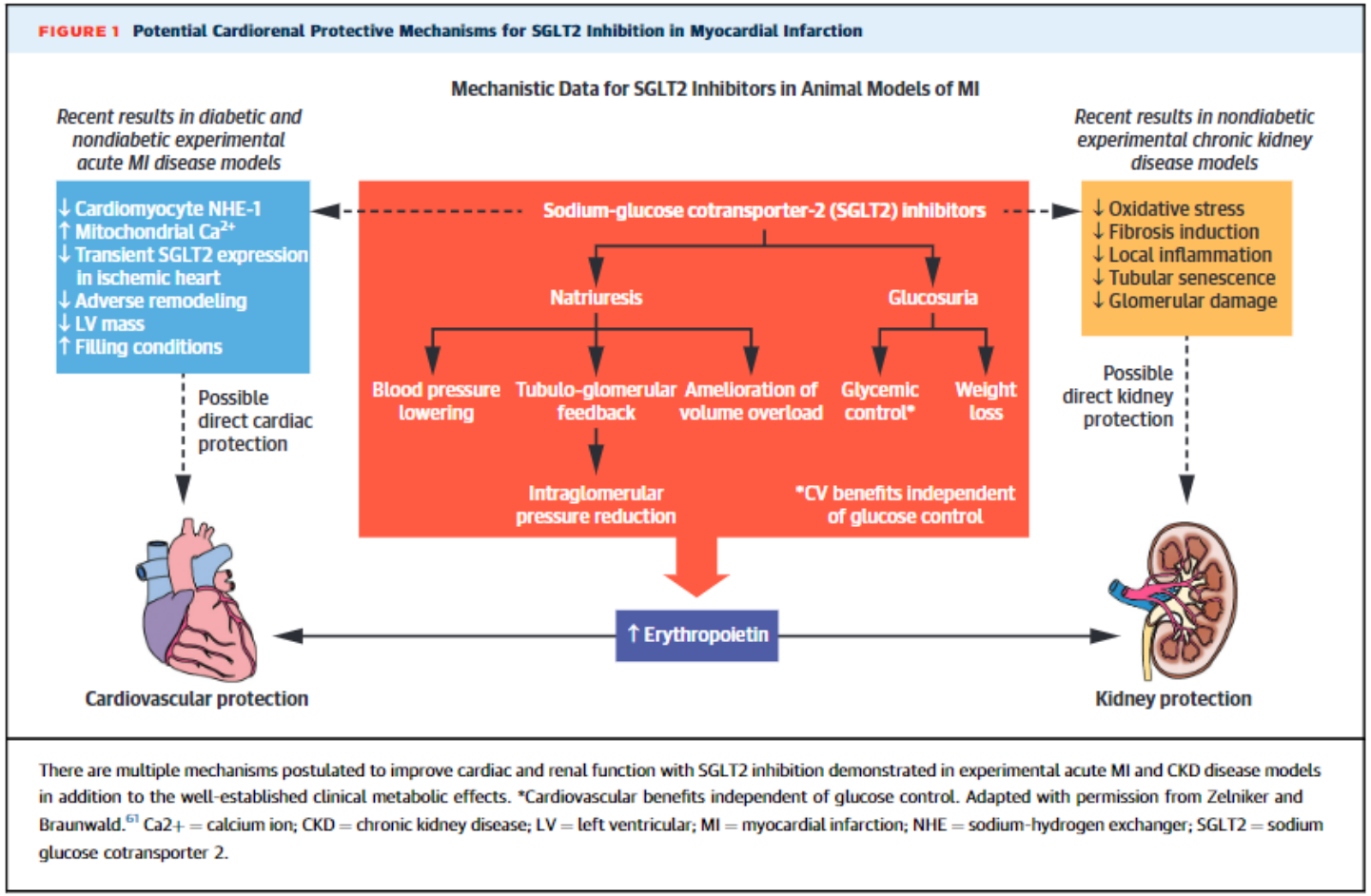
Condition	Drug			
	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Type 2 diabetes	Lowers blood glucose along with diet and exercise	Lowers blood glucose along with diet and exercise	Lowers blood glucose along with diet and exercise	Lowers blood glucose along with diet and exercise
Type 2 diabetes with multiple cardiovascular risk factors[a]			Reduces risk of HF hospitalization	
Type 2 diabetes with known atherosclerotic cardiovascular disease	Reduces risk of death from a cardiovascular cause	Reduces the risk of MACE (MI, stroke, and CV death)	Reduces risk of HF hospitalization	
Type 2 diabetes with diabetic kidney disease (nephropathy)		Reduces the risk of end-stage kidney disease, worsening of kidney function, CV death, and HF hospitalization		
Chronic kidney disease (nephropathy)			Reduces the risk of end-stage kidney disease, worsening of kidney function, CV death, and HF hospitalization	
Chronic heart failure with reduced ejection fraction	Reduces risk of CV death + HF hospitalization		Reduces risk of CV death + HF hospitalization	
Chronic heart failure with preserved ejection fraction	Reduces risk of CV death + HF hospitalization			
Immediately after or within months of an acute MI	Not studied	Not studied	Not studied	Not studied

[a]Cardiovascular risk factors: age ≥55 years in men or ≥60 years in women plus ≥1 of dyslipidemia, hypertension, or current tobacco use.

CV = cardiovascular; HF = heart failure; MACE = major adverse cardiovascular events; MI = myocardial infarction.

Udell Jacob A., Jones W. Schuyler., Petrie Mark C., et al.
J Am Coll Cardiol 2022;79(20):2058–68.

Do you think the benefits of SGLT2i will be extended to other populations (i.e. MI)?



Udell Jacob A., Jones W. Schuyler., Petrie Mark C., et al.
J Am Coll Cardiol 2022;79(20):2058–68.

Do you think the benefits of SGLT2i will be extended to other populations (i.e. MI)?

TABLE 2 Description of Ongoing SGLT2 Inhibitor Trials in Patients With Acute Myocardial Infarction

	EMMY	EMPACT-MI	DAPA-MI
Initiation	2017	2020	2020
Intervention	Empagliflozin 10 mg vs placebo	Empagliflozin 10 mg vs placebo	Dapagliflozin 10 mg vs placebo
Study population	Acute MI	Acute MI	Acute MI
Timing of therapy initiation	Within 3 d	Within 14 d	Within 7-10 d
High-risk features	CK >800 U/L and troponin >10× ULN	New LVEF <45% or signs/symptoms of congestion requiring treatment	New impaired regional or global LV systolic function or Q-wave MI on ECG
Inclusion of patients with T2DM	With and without T2DM	With and without T2DM	No, but patients with hyperglycemia without a prior diagnosis of T2DM are eligible
Primary outcome	Change in NT-proBNP at 6 months	Time to first HF hospitalization or all-cause death	Time to first HF hospitalization or cardiovascular death
Secondary outcomes	Changes in: • Echocardiographic parameters • ketone body levels • HbA1c levels • Body weight	• Total HF hospitalizations or death • Total non-elective CV hospitalizations or death • Total non-elective all-cause hospitalizations or death • Total MI hospitalizations or death • Time to CV death	• Time to first MI, stroke, or CV death • Time to first fatal and nonfatal MI • Time to CV death • Time to all-cause death • Time to new-onset type 2 diabetes
Estimated duration of follow-up	6 mo	~2 y	~3 y
Estimated sample size	476	5,000	6,400
Estimated completion	2022	2023	2023

CK — creatine kinase; CV — cardiovascular; DAPA-MI — Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Heart Failure or Cardiovascular Death in Patients Without Diabetes With Acute Myocardial Infarction; ECG — echocardiogram; EMMY — Impact of EMpagliflozin on Cardiac Function and Biomarkers of Heart Failure in Patients With Acute MYocardial Infarction; EMPACT-MI — Trial to Evaluate the Effect of EMPAgliflozin on Hospitalisation for Heart Failure and Mortality in Patients With aCuTe Myocardial Infarction; HbA1c — hemoglobin A1C; HF — heart failure; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NT-proBNP — N-terminal pro brain natriuretic peptide; T2DM — type 2 diabetes mellitus; SGLT2 — sodium glucose cotransporter 2.

Udell Jacob A., Jones W. Schuyler., Petrie Mark C., et al.
J Am Coll Cardiol 2022;79(20):2058–68.

Practical considerations

TABLE 1 Practical Considerations With Use of SGLT2 inhibitors

Potential Adverse Effect	Practical Considerations
Adverse drug-drug interaction	Pharmacokinetic drug-drug interactions are minimal Canagliflozin is a P-glycoprotein substrate (modest inhibition); co-administration with digoxin may increase plasma levels of digoxin; monitor digoxin levels and for signs and symptoms of toxicity when both are used together
Genital and urinary infections	Mycotic infections more common among females and in uncircumcised males Reinforce importance of adequate hygiene Counsel patients to urgently report genital/perineal tenderness, redness, or swelling No significant increase in risk of urinary tract infections
Hypoglycemia	Uncommon; risk increased with concomitant use of sulfonylureas and insulin
Diabetic ketoacidosis	Avoid pre-emptive substantial reductions in insulin dose Hold dose if acutely ill with limited oral intake, and 3 days before major surgery Use caution with low carbohydrate diets to minimize excessive ketosis Discourage excessive alcohol intake Asymptomatic elevations in beta-hydroxybutyrate are frequent with SGLT2 inhibitors, but only a fraction lead to overt diabetic ketoacidosis Counsel patients regarding potential symptoms of diabetic ketoacidosis (fruity odor on breath, thirst, polyuria, nausea, vomiting, abdominal pain, confusion, and fever)
Renal injury	Baseline and periodic monitoring of renal function is recommended, especially if used in chronic kidney disease Modest decrease in eGFR (3 to 4 ml/min/1.73 m^2) is expected with initiation Currently being investigated in eGFR <30 ml/min/1.73 m^2 Cases of acute kidney injury are rare, except in concert with volume depletion
Volume depletion	Increased risk with concomitant diuretic use; consider diuretic dose adjustment Educate patient about potential for orthostatic hypotension and necessity to monitor daily weights and blood pressure, particularly in the first week of therapy Anticipatory guidance to call healthcare provider if home weight decreases by 3 or more pounds over 24 h, or 5 or more pounds in a week, or in the setting of symptomatic hypotension

Vardeny O., Vaduganathan M. JACC Heart Fail 2019;7(2):169–72.

Glucagon-like peptide 1 receptor agonists (GLP-1RAs)

GLP-1 receptor agonists

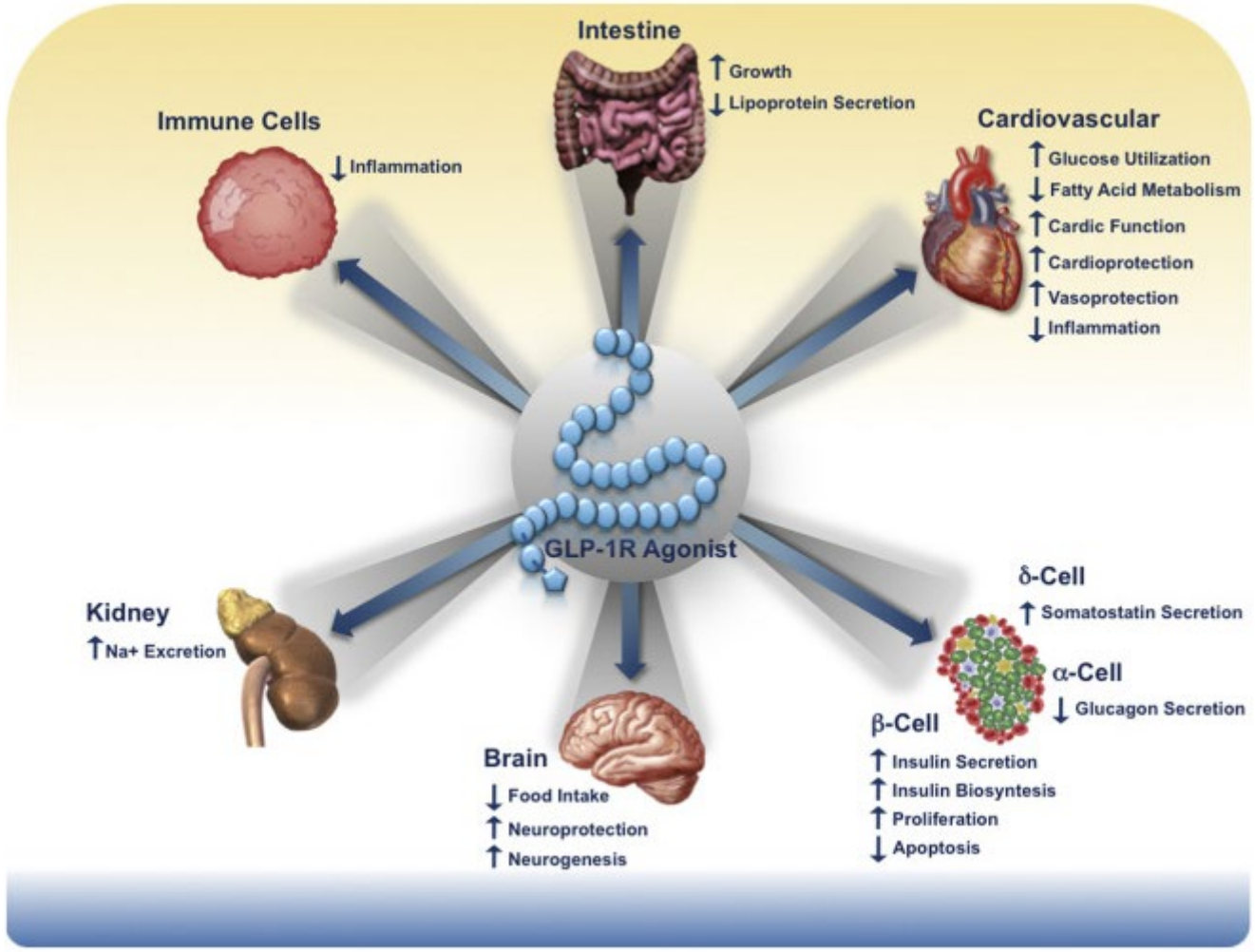
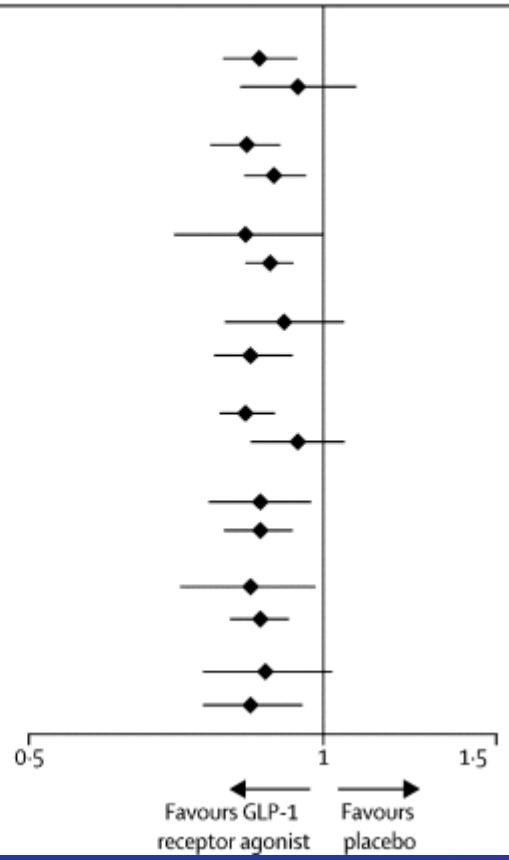


TABLE 3 Summary of the GLP-1RA CV Outcomes Trials

	ELIXA (77)	LEADER (14)	SUSTAIN-6* (15)	EXSCEL (78)	REWIND (16)	PIONEER-6 (79)
Patients enrolled	6,068	9,340	3,297	14,752	9,901	3183
Drug	Lixisenatide	Liraglutide	Semaglutide SQ	Exenatide QW	Dulaglutide	Semaglutide oral
Dose	10 mcg or 20 mcg per day	1.8 mg or max tolerated dose per day	0.5 mg or 1 mg per week	2 mg per week	1.5 mg per week	14 mg or max tolerated dose per day
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4	1.3
Baseline HbA1c	7.7	8.7	8.7	8.0	7.2	8.2
Mean duration of diabetes (years)	9.3	12.8	13.9	12.0	9.5	14.9
Baseline statin use (%)	93	72	73	74	66	85
Baseline prevalence of ASCVD†/HF (%)	100	81	72	73	31	85
Baseline prevalence of HF (%)	22	18	24	16	9	NR
Primary outcome, HR (95% CI)‡	4-point MACE 1.02 (0.89-1.17)	3-point MACE 0.87 (0.78-0.97)	3-point MACE 0.74 (0.58-0.95)	3-point MACE 0.91 (0.83-1.00)	3-point MACE 0.88 (0.79-0.99)	3-point MACE 0.79 (0.57-1.11)
CV death, HR (95% CI)	0.98 (0.78-1.22)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.88 (0.76-1.02)	0.91 (0.78-1.06)	0.49 (0.27-0.92)
Fatal or nonfatal MI, HR (95% CI)§	1.03 (0.87-1.22)	0.86 (0.73-1.00)	0.74 (0.51-1.08)	0.97 (0.85-1.10)	0.96 (0.79-1.15)	1.18 (0.73-1.90)
Fatal or nonfatal stroke, HR (95% CI)§	1.12 (0.79-1.58)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.85 (0.70-1.03)	0.76 (0.62-0.94)	0.74 (0.35-1.57)
All-cause mortality, HR (95% CI)	0.94 (0.78-1.13)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	0.86 (0.77-0.97)	0.90 (0.80-1.01)	0.51 (0.31-0.84)
HF hospitalization, HR (95% CI)‖	0.96 (0.75-1.23)	0.87 (0.73-1.05)	0.86 (0.48-1.55)	0.94 (0.78-1.13)	0.93 (0.77-1.12)‖	1.11 (0.77-1.61)
Renal composite outcome¶	0.84 (0.68-1.02)	0.78 (0.67-0.92)	0.64 (0.46-0.88)	0.88 (0.76-1.01)	0.85 (0.77-0.93)	0.64 (0.46-0.88)

GLP-1RA Meta-Analysis across 8 Large-Scale Trials of 60K+ Participants with Type 2 Diabetes

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	$p_{interaction}$
Established cardiovascular disease				0·24
Yes	2431/21253 (11%)	2755/21202 (13%)	0·86 (0·80–0·93)	
No	480/6428 (7%)	518/6555 (8%)	0·94 (0·83–1·07)	
Baseline HbA_{1c}*				0·22
High	1645/14507 (11%)	1865/14298 (13%)	0·85 (0·78–0·91)	
Low	1300/13407 (10%)	1442/13661 (11%)	0·91 (0·84–0·98)	
Median duration of follow-up				0·53
<3 years	907/11004 (8%)	1042/11007 (9%)	0·84 (0·71–1·00)	
≥3 years	2041/16973 (12%)	2262/17020 (13%)	0·89 (0·84–0·94)	
Drug dosing				0·34
Daily	1069/9293 (12%)	1162/9298 (12%)	0·92 (0·80–1·05)	
Weekly	1879/18684 (10%)	2142/18729 (11%)	0·85 (0·78–0·93)	
Human GLP-1 homology				0·06
Yes	1709/17587 (10%)	2007/17597 (11%)	0·84 (0·79–0·90)	
No	1239/10390 (12%)	1297/10430 (12%)	0·95 (0·85–1·06)	
BMI, kg/m²				1·00
<30†	1254/11752 (11%)	1403/11904 (12%)	0·87 (0·78–0·98)	
≥30†	1679/16116 (10%)	1892/16011 (12%)	0·87 (0·81–0·92)	
Age, Years				0·79
<65‡	1249/14195 (9%)	1346/13948 (10%)	0·85 (0·72–0·99)	
≥65‡	1705/13782 (12%)	1965/14079 (14%)	0·87 (0·81–0·93)	
Baseline eGFR, mL/min per m²				0·72
<60	771/5341 (14%)	865/5432 (16%)	0·88 (0·76–1·03)	
≥60	1576/17653 (9%)	1773/17598 (10%)	0·85 (0·76–0·96)	



↓ 14% in MACE
↓ 12% in Mortality
↓ 11% in HF Hospitalization
↓ 21% in Kidney Outcome

no increase in risk of severe hypoglycaemia, retinopathy, or pancreatic adverse effects

Slide Courtesy of M. Vaduganathan

Contraindications	■ History of serious hypersensitivity reaction to drug ■ Pregnancy or breast feeding ■ Severe renal impairment or end-stage renal failure (exenatide, lixisenatide) ■ Personal or family history of medullary thyroid cancer ■ Personal or family history of MEN2
Cautions	■ Hypoglycemia risk increased with insulin, sulfonylureas, or glinides. ■ May delay gastric emptying; not recommended in patients with clinically meaningful gastroparesis. This effect is usually transient with longer-acting GLP-1Ras. ■ Care should be taken in patients with prior gastric surgery, including bariatric surgery. ■ Diabetic retinopathy complications were reported with semaglutide (injectable), although it is unclear if this is a direct effect of the drug or due to other factors such as rapid improvement in blood glucose control.
Adverse effects to monitor	■ Nausea, vomiting, diarrhea, headache, weakness, or dizziness ■ Hypoglycemia when given with insulin, sulfonylureas, or glinides. ■ Weight loss ■ Injection site reactions

CV = cardiovascular; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; MACE = major adverse cardiovascular events; MEN2 = multiple endocrine neoplasia, type 2; MI = myocardial infarction; PO = "per os," by mouth; QW = once weekly; SC = subcutaneous; T2D = type 2 diabetes.

TABLE 5 **Opportunities to Initiate an SGLT2 inhibitor or a GLP-1RA With Demonstrated CV or Renal Benefit in Patients With T2D***

- In a patient with T2D and ASCVD (SGLT2 inhibitor or GLP-1RA)
- At the time of diagnosis of clinical ASCVD (SGLT2 inhibitor or GLP-1RA), DKD, and/or HF (SGLT2 inhibitor)† in a patient with T2D on a drug regimen that does not include an SGLT2 inhibitor or GLP-1RA with CV benefit
- At the time of diagnosis of T2D in a patient with clinical ASCVD (SGLT2 inhibitor or GLP-1RA), DKD, and/or HF (SGLT2 inhibitor)††
- At hospital discharge (with close outpatient follow-up) after admission for an ASCVD (SGLT2 inhibitor or GLP-1RA) or HF (SGLT2 inhibitor) event§
- In a patient with T2D and diabetic kidney disease (SGLT2 inhibitor, alternatively GLP-1RA for eGFR <30 ml/min/1.73 m^2)‡
- In patients determined to be at high risk of ASCVD‖ (SGLT2 inhibitor or GLP-1RA) or HF (SGLT2 inhibitor)††

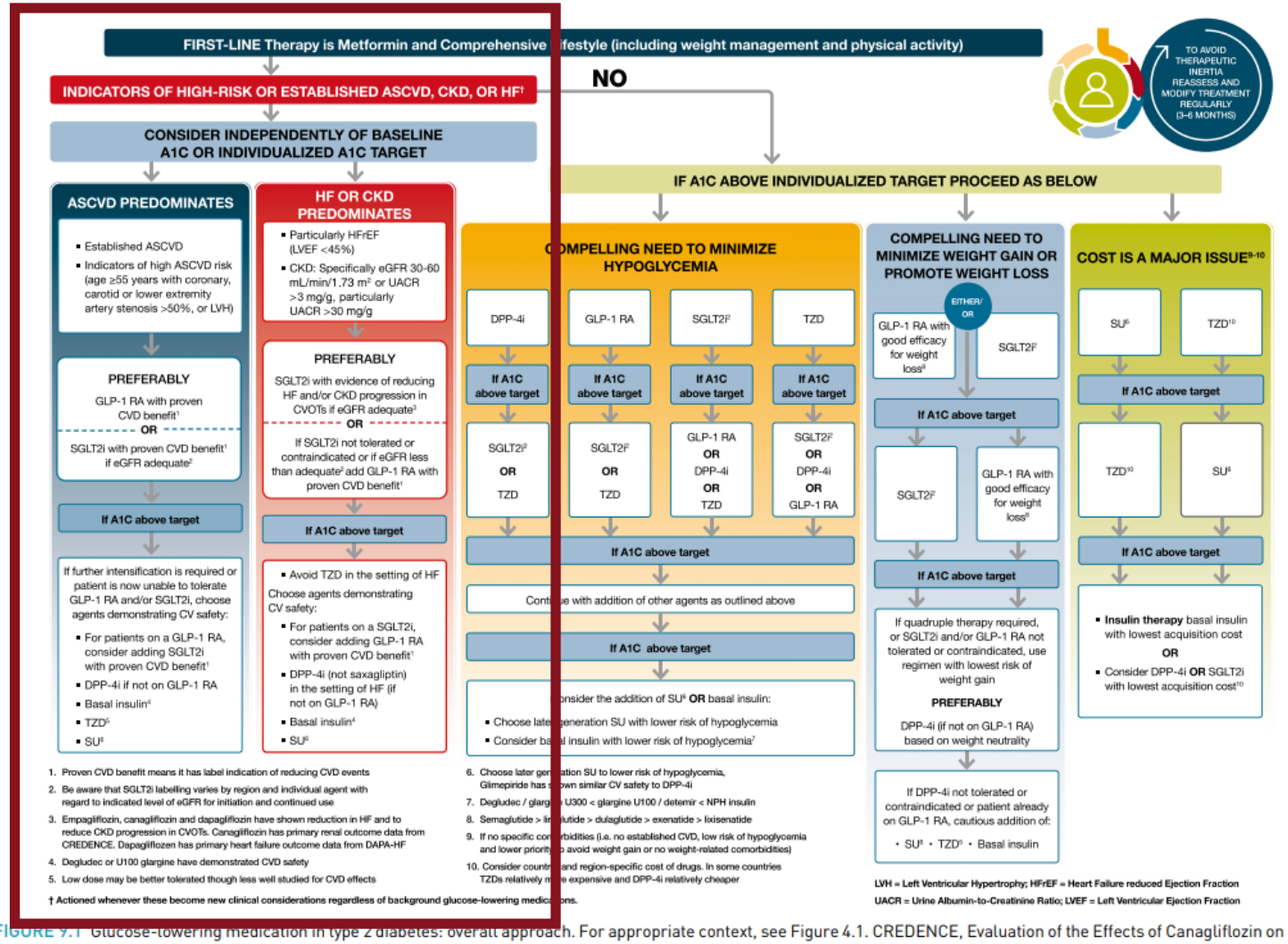
TABLE 6 Patient and Clinician Preferences and Priorities for Considering SGLT2 Inhibitors With Demonstrated CV Benefit Versus GLP-1RAs With Demonstrated CV Benefit

Preference or Priority	Consider Using an SGLT2 Inhibitor First When Patient and Clinician Priorities Include:	Consider Using a GLP-1RA First When Patient and Clinician Priorities Include:
MACE prevention	+++	+++
HF prevention	+++	
Weight loss	+	+++
Renal disease progression prevention	+++	+
Mode of administration	Oral	Subcutaneous
Considerations that may prompt use of an alternative class	■ Severely reduced kidney function*,† ■ History of prior amputation, severe peripheral arterial disease, or active diabetic foot ulcers (caution with canagliflozin) ■ History of recurrent genital candidiasis ■ History of diabetic ketoacidosis ■ History of fracture (caution with canagliflozin) ■ The patient is considering pregnancy ■ The patient is breast feeding	■ Persistent nausea, despite appropriate dietary education and low doses ■ History of gastroparesis ■ Active gallbladder disease ■ History of MEN2 or medullary thyroid cancer ■ History of proliferative retinopathy (caution with semaglutide or dulaglutide) ■ The patient is considering pregnancy ■ The patient is breast feeding

*eGFR <45 ml/min/1.73 m^2 is currently a caution due to a decrease in glycemic efficacy (not due to safety), but ongoing studies are testing whether SGLT2 inhibitors offer renal benefits in these patients. The FDA label for canagliflozin allows use of canagliflozin to an eGFR of 30 ml/min/1.73m^2 specifically for patients with DKD.
†Use clinical judgement when initiating an SGLT2 inhibitor in a patient who will be starting or up-titrating an ACE inhibitor or ARB if the patient's renal function is impaired

ACE = angiotensin-converting enzyme; ARB = angiotensin reception blocker; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MACE = major adverse cardiovascular event; MEN2 = multiple endocrine neoplasia type 2; SGLT2 = sodium-glucose cotransporter-2.

These medications have been incorporated into the newest Diabetes Guidelines

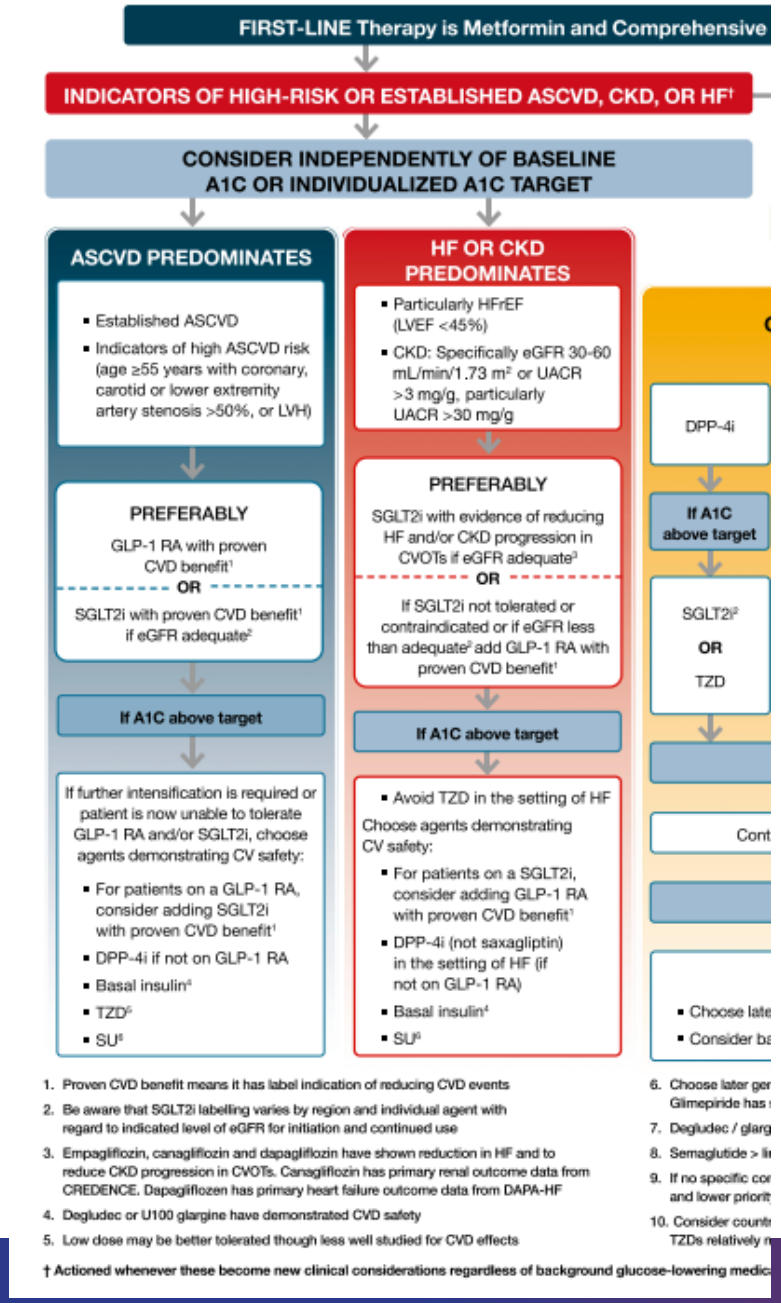


American Diabetes Association. Standards of Medical Care in Diabetes-2020 Abridged for Primary Care Providers. Clin Diabetes 2020;38(1):10–38.

FIGURE 9.1 Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see Figure 4.1. CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy. CVOTs, CV outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, GLP-1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41:2669–2701 and Buse JB, Wexler DJ, Tsapas A, et al. Diabetes Care 19 December 2019 [Epub ahead of print]. DOI: 10.2337/dci19-0066.

GLP-1 RA with Proven CVD Benefit

- **Dulaglutide**
- **Liraglutide**
- **Injectable Semaglutide**

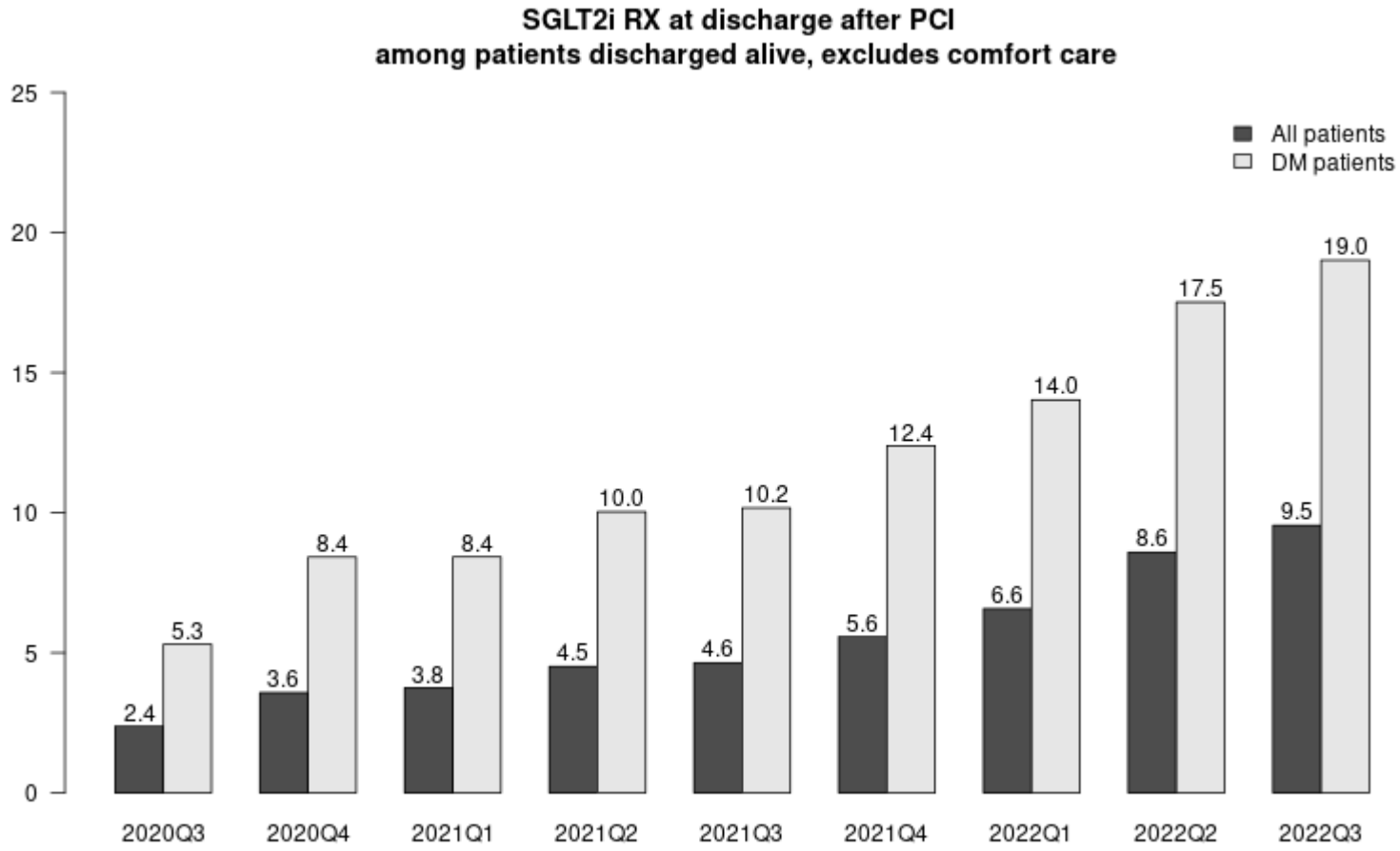


SGLT2i with Proven CVD Benefit

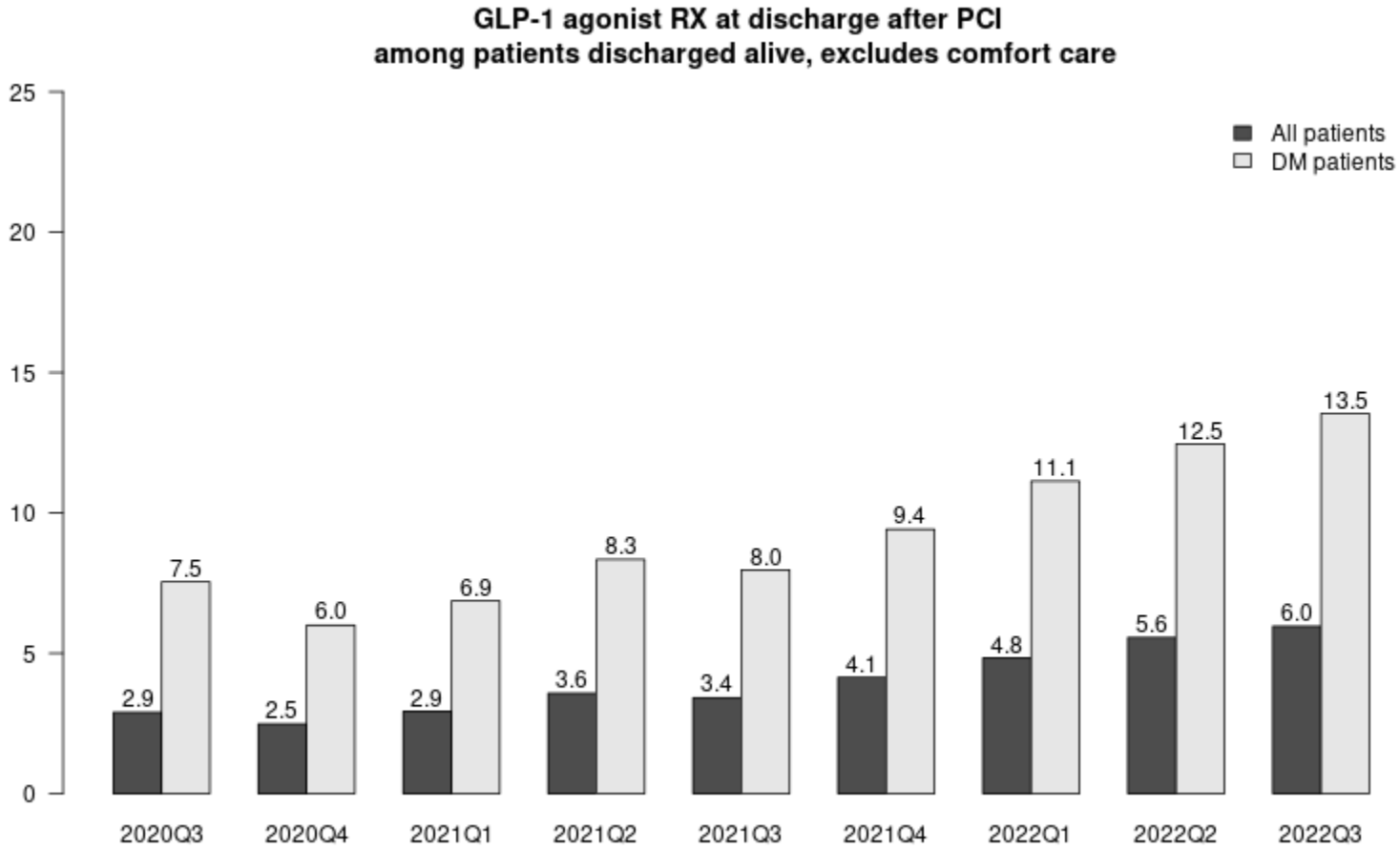
- **Canagliflozin**
- **Dapagliflozin**
- **Empagliflozin**

American Diabetes Association. Standards of Medical Care in Diabetes-2020 Abridged for Primary Care Providers. Clin Diabetes 2020;38(1):10–38.

How are we currently doing? SGLT2i after PCI



How are we currently doing? GLP-1 RA after PCI



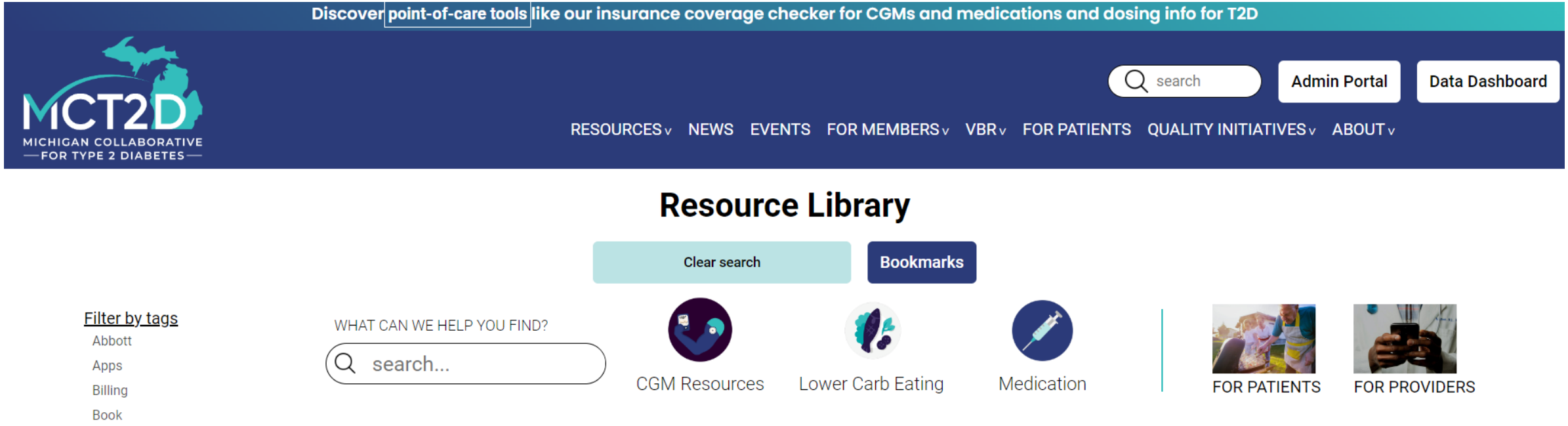
Practical considerations: Coordination of Care between PCPs + Specialists

Poll and Discussion

1. How would you prefer a patient's cardiologist to handle SGLT2is/GLP-1Ras among patients with type 2 diabetes mellitus?
    1. I would prefer the cardiologist to prescribe the medication first
    2. I would prefer the cardiologist to make recommendations about prescribing

2. If the cardiologist does prescribe the SGLT2i/GLP-1 RA, would you prefer the cardiologist to continue to prescribe the medication or transition follow-up to primary care?
    1. Continue prescribing
    2. Transition follow up to primary care

Practical considerations: Education and Copays



https://www.mct2d.org/resource-library

The Benefits of Newer Diabetes Medications

GLP-1 RA

MCT2D MICHIGAN COLLABORATIVE FOR TYPE 2 DIABETES

Have you been prescribed one of these medications?

Dulaglutide (Trulicity)	Semaglutide (Rybelsus)
Liraglutide (Victoza)	Exenatide (Byetta)
Semaglutide (Ozempic)	Exenatide XR (Bydureon BCise)

Did you know that these medications can do more that help lower your blood sugar? Other benefits include:

- All GLP-1 RA's can help reduce your weight.
- Many GLP-1 RA's lower risk of heart attack and stroke. Rybelsus does not reduce these risks.

Side effects are usually mild and may improve or go away in time. These include:

Mild stomach or intestinal side effects are the most common and improve or go away in a few weeks.

- Nausea or vomiting
- Worsening acid reflux
- Diarrhea or constipation
- Stomach discomfort/cramping
- Skin reaction at site of injection

When should I call my health care team?

If you experience:

- Blurred vision
- Severe stomach pain
- Upper stomach pain, that moves to your back, with or without fever
- Low blood sugars (less than 70)

How is the medication taken?

Most are injected (weekly or daily) under the skin on your stomach – for some you do NOT even see the needle!

See our How-To Video Series to learn GLP-1 RA injection:
michmed.org/JQzJw

Rybelsus is an oral medication that must be taken with 4 oz of water 30 minutes before eating the first meal of the day. It must be taken prior to other medications, including thyroid medication.

How can I lessen or avoid side effects?

- Listen to your body for signs of being full (this might surprise you!)
- Eat smaller meals
- Avoid eating within 1-2 hours of going to bed
- Avoid fatty, greasy, or spicy foods
- Drink plenty of water daily
- Monitor your blood sugar if on insulin or glipizide, glyburide, or glimepiride
- Your health care team may adjust these medications if your blood sugar is too low

Affording these medications:

For patients with:

- Commercial insurance: GLP1-RAs are generally covered, but insurance may not cover all medications. Check with your insurance to see which are covered and tell your health care team. ***MCT2D Coverage guide: michmed.org/jmKmn*** You may have a copay. Use the link below to find a copay savings card that may lower your out-of-pocket cost.
  If you have a high deductible plan, you will have to pay the full cost of the medication until your deductible is met.
- Medicare Part D: You may have a copay. Copay savings cards cannot be used with Medicare insurance. Talk to your doctor about Patient Assistance Programs. Patients with an annual income of less than $50,000 may be able to get the medication for free.
- Michigan Medicaid: A least one of these medications will be covered by your insurance. These medications do not have a generic version. Check with your insurance to see which medications is preferred. This will have the lowest out—of-pocket cost to you.

Medication Copay Savings Card Programs Reference Guide
michmed.org/dJJk5

Patient Assistance Program (PAP) Guide
michmed.org/kQQrY

The Benefits of Newer Diabetes Medications

SGLT2is

MCT2D
MICHIGAN COLLABORATIVE FOR TYPE 2 DIABETES

Have you been prescribed one of these medications?

Dapagliflozin (Farxiga)
Canagliflozin (Invokana)
Empagliflozin (Jardiance)
Ertugliflozin (Steglatro)

Side effects are usually mild and may improve or go away in time. These include:

- Increased urination
- Yeast infection
- Urinary tract infection
- Dehydration
- Low blood pressure

How is the medication taken?

These are oral medications that should be taken once a day. Because they make you urinate more, you should take them in the morning.

When should I call my health care team?

- Unexplained fatigue, loss of appetite, or shortness of breath
- Intense pain of genitals or rectum with a fever and/or feeling unwell
- Unexplained falls
- Being unable to eat
- Unexplained, frequent low blood sugars (less than 70)
- If you are started on a new blood pressure medication
- If you are scheduled for surgery and need to stop your medications
- If you decide to start following a low carb diet (less than 100 grams of total carbohydrate daily)

Did you know that these medications can do more that help lower your blood sugar? Other benefits include:

- Protect kidney function and prevent the need for dialysis.
- Lower risk of having or dying from a heart attack, stroke, or heart failure
- Lower blood pressure
- Mild weight loss

How can I lessen or avoid side effects?

- Drink 6 to 8 glasses of water daily
- Avoid drinking water too close to bedtime
- Practice good genital hygiene (ensure you wipe yourself dry after urinating) and shower daily (in hot summer months, consider showering multiple times per day)
- Use cotton underwear
- Monitor your blood pressure at home
- Monitor your blood sugar at home if on insulin, glipizide, glyburide, or glimepiride
- Notify your doctor if another doctor/specialist starts you on a blood pressure medication

What should I expect after starting an SGLT2i?

After starting this medicine, you may see a small decrease in your kidney function (slight increase in your creatinine/decrease in your eGFR.) **This is an expected short-term effect of the medicine, and kidney function will be better overall in the long-term**

You can also expect to see a decrease in protein leakage in your urine (decrease in uACR).

Affording these medications:

For patients with:

- Commercial insurance: GLP1-RAs are generally covered, but insurance may not cover all medications. Check with your insurance to see which are covered and tell your health care team. ***MCT2D Coverage guide: michmed.org/jmKmn*** You may have a copay. Use the link below to find a copay savings card that may lower your out-of-pocket cost.
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Medication Copay Savings Card Programs Reference Guide
michmed.org/dJJk5

Patient Assistance Program (PAP) Guide
michmed.org/kQQrY

Medication Copay Savings Card Programs Reference Guide

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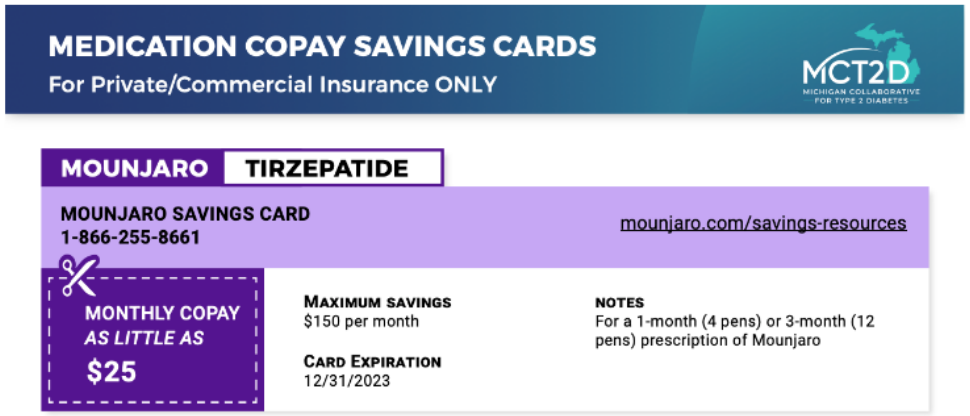

SGLT2 and GLP1 copay savings program information compiled in one handy reference guide. Last updated March 10, 2023.

Drug makers sometimes offer discount cards, sometimes called copay savings coupons, that provide a discount on your copy for select drugs. If you are a

Patient Assistance Program (PAP) Guide for Patients with Medicare Part D and Uninsured

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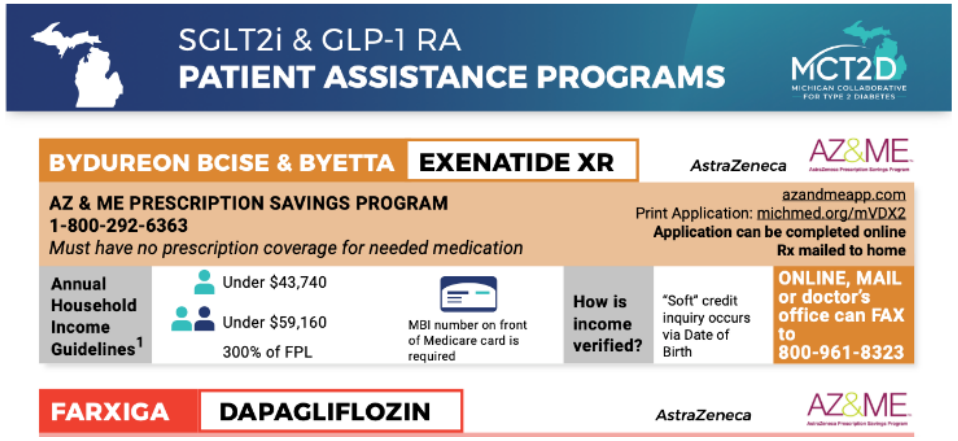


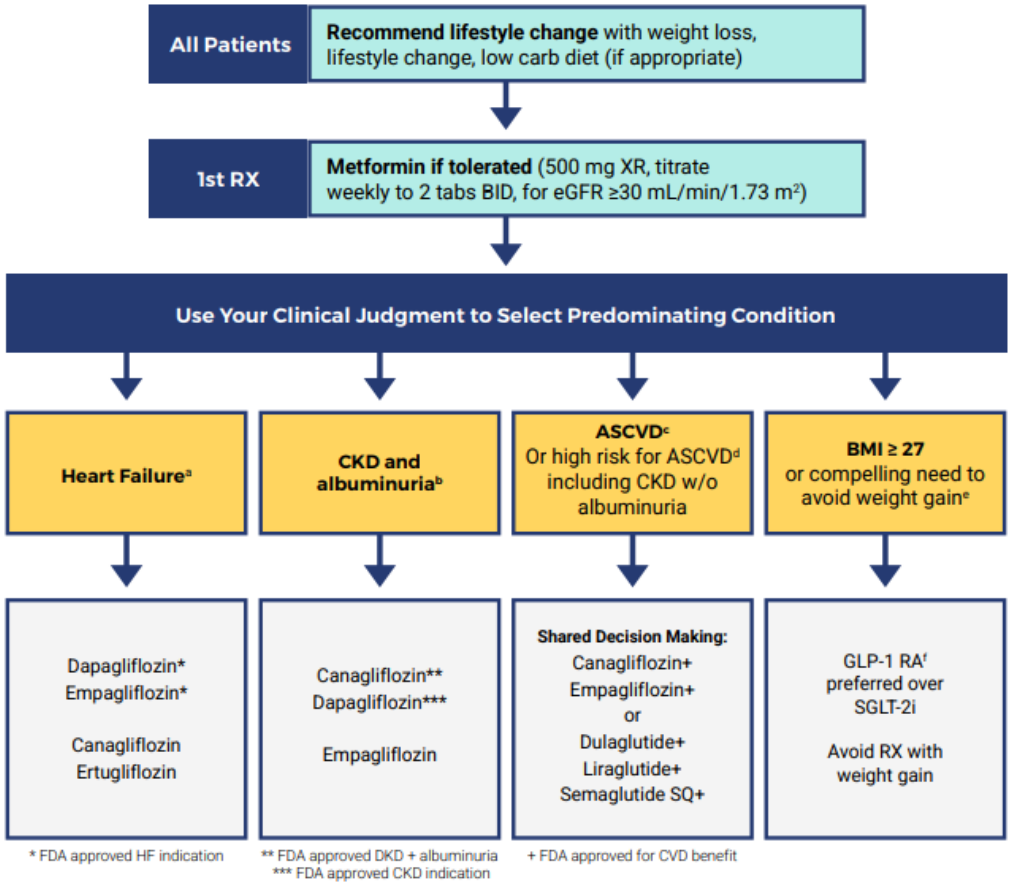
Your patient may qualify for free medications as part of each drug manufacturer's patient assistance program (PAP). Use this guide for patients who have Medicare Part D or who are uninsured to find the right PAP and overview of the program's qualifications and application process.

Clinician Decision Aid
SGLT2 Inhibitor / GLP-1 RA for T2D

Why this aid?

SGLT2 inhibitors and GLP-1 receptor agonists are two newer classes of medications for diabetes that reduce hyperglycemia, reduce endogenous insulin production, and improve cardiovascular and renal outcomes, weight loss, and mortality in Type 2 Diabetes.

This aid is meant to be used alongside your own clinical judgment and prescribing information to guide individualization of diabetes treatment.



Thank you!

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