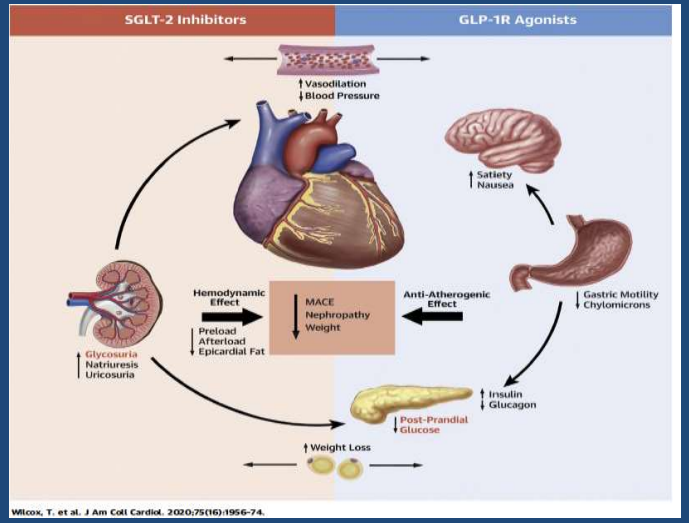
When to add a GLP1-RA, SGLT2i, or both



Thomas Metkus MD PhD
Cardiologist, intensivist, echocardiographer
Director of Cardiac Critical Care, JHM and CICU, JHH
Assistant Professor of Medicine and Surgery
Cardiology and Cardiac Surgery, Departments of Medicine & Surgery
Associate Faculty, Armstrong Institute for Patient Safety and Quality

JOHNS HOPKINS MEDICINE

Learning objectives

- Understand physiology underlying cardiovascular benefit of GLP1-RA and SGLT2i
- Recognize adverse effects of GLP1-RA and SGLT2i
- Prescribe GLP1-RA and SGLT2i for appropriate indications

Case

- 68 yo woman presents to clinic for cardiovascular review
- HFPEF with NYHA class II sx
- Other history includes dyslipidemia, hypertension, diet controlled DM with A1C 6.1%
- Stage II CKD with 1+ proteinuria and GFR 70
- Meds: spironolactone, atorvastatin, amlodipine
- Exam: BMI 37; otherwise normal

Should we add GLP1-RA, SGLT2i, or both?

- DM
- HFPEF
- CKD
- Multiple cardiovascular risk factors

Timeline

1836: Phlorizin isolated from tree bark

1933: Phlorizin shown to completely block renal glucose absorption in humans

1956: First sulfonylurea approved for T2DM

1959: Metformin introduced outside US

1984: Second generation sulfonylureas approved for T2DM

1987: Discovery that GLP1 stimulates insulin

1990: Metformin introduced to United States

1992: GLP1 analog isolated from Gila monster venom glands

1992: SGLT2 cloned

1996: First TZD approved for T2DM

1998: UKPDS 34 Trial published

2005: First CVOT for TZD

2005: First GLP1RA approved for T2DM

2006: First DDP4i approved for T2DM

2007: FDA Black box warning for rosiglitazone, 2009: warning repealed

2008: FDA mandates CVOT for all novel antidiabetic agents

2012: First CVOT for DDP4i

2013: First SGLT2i approved for T2DM

2015: First CVOT for GLP1RA

2015: First CVOT for SGLT2i

2016: FDA issues warnings of risk of heart failure hospitalization for saxagliptin and alogliptin

2019: First SGLTi CVOT showing benefit in expanded primary outcomes (HHF, Renal Events**)

Future: CVOTs for GLP1RA & SGLT2i for primary prevention of CVD and HF*

Key:
Sulfonylureas
Biguanides
TZDs
DDP4i
SGLT2i
GLP1RA

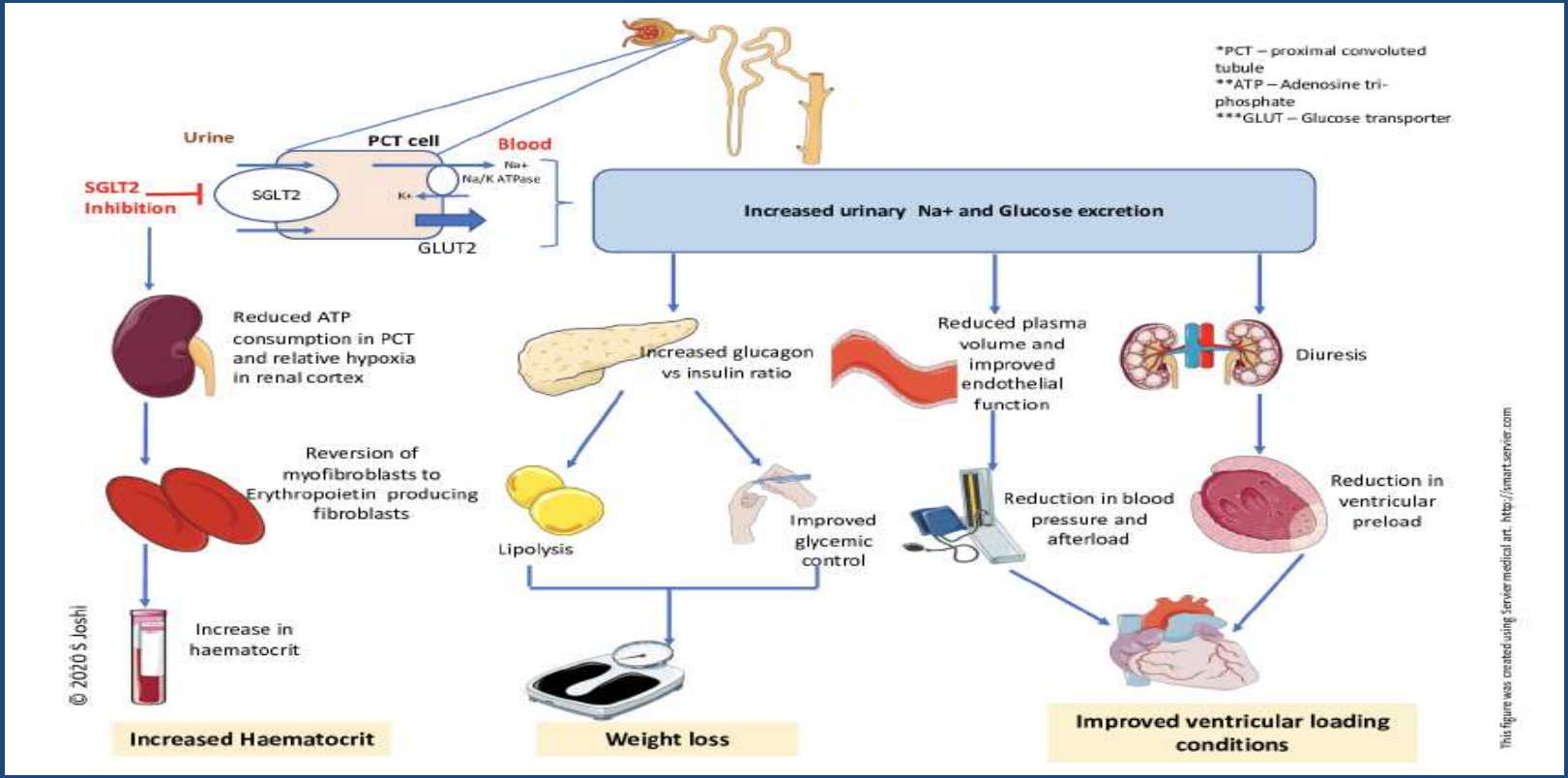
CVOT

* PIONEER, SOUL, DECLARE-TIMI 58
**DAPA-HF, Credence

Adapted from:
- *Drucker DJ, Habener JF, Holst JJ. J Clin Invest 2017; 127: 4217-4227*
- *Mudaliar S et al. Diabetes Care 2015; 38: 2344-2353*

JACC VOL. 75, NO. 16, 2020
APRIL 28, 2020:1956–74

SGLT-2i mechanism



Joshi SS, *et al*. *Heart* 2021;**107**:1032–1038. doi:10.1136/heartjnl-2020-318060

JOHNS HOPKINS MEDICINE

SGLT-2i- “flozins”

- For hyperglycemia, reduce A1C by 0.5-1%
- Reduce weight by 2kg and BP by ~5/2 mmHg

Trials

- EMPA-REG10
  - (empagliflozin vs placebo, n=7020)
- DECLARE-TIMI9
  - (dapagliflozin vs placebo, n=17 160)
- CANVAS15
  - (canagliflozin vs placebo, n=10 142)
- VERTIS11
  - (ertugliflozin vs placebo, n=8246)
- CREDENCE8
  - (canagliflozin v placebo, n=4401)

SGLT-2i- “flozins” AE

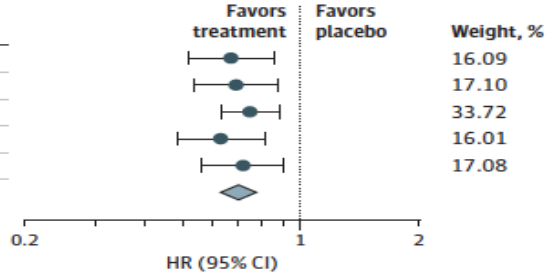
- Polyuria
- Fungal genital infection (10% of women, 5% of men)
- DKA
  - (0.1%, RF include insulin use, illness, and emergency/major surgery)
- GFR? 30 or higher
- Amputation risk with cana?

SGLT-2i HF

Figure 3. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

A Overall HHF

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model ($Q = 1.39$; $df = 4$; $P = .85$; $I^2 = 0.0\%$)					0.68 (0.61-0.76)



JAMA Cardiol. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511

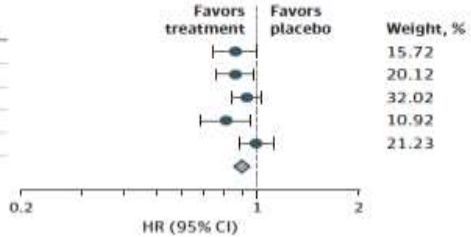
JOHNS HOPKINS MEDICINE

SGLT-2i MACE

Figure 1. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Major Adverse Cardiovascular Events—Composite of Myocardial Infarction, Stroke, or Cardiovascular Death

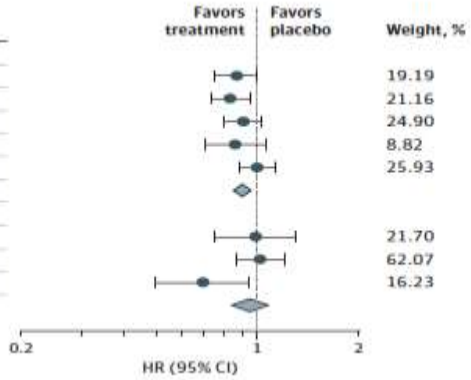
A Overall MACEs

	Treatment		Placebo		Hazard ratio (95% CI)
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model ($Q = 5.22$; $df = 4$; $P = .27$; $I^2 = 23.4\%$)					0.90 (0.85-0.95)



B MACEs by ASCVD status

	Treatment		Placebo		Hazard ratio (95% CI)
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	
Patients with ASCVD					
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model ($Q = 4.53$; $df = 4$; $P = .34$; $I^2 = 11.8\%$)					0.89 (0.84-0.95)
Patients without ASCVD					
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model ($Q = 4.59$; $df = 2$; $P = .10$; $I^2 = 56.5\%$)					0.94 (0.83-1.07)



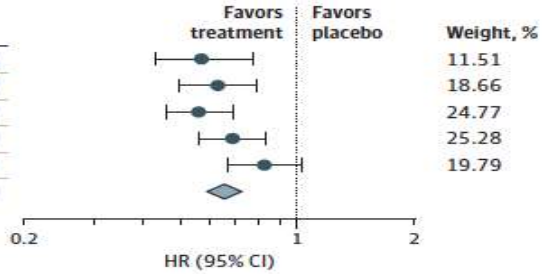
JAMA Cardiol. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511

JOHNS HOPKINS MEDICINE

SGLT-2i renal outcomes

A Overall kidney outcomes

	Treatment		Placebo		Hazard ratio (95% CI)
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; df = 4; P = .09; I^2 = 49.7%)					0.62 (0.56-0.70)

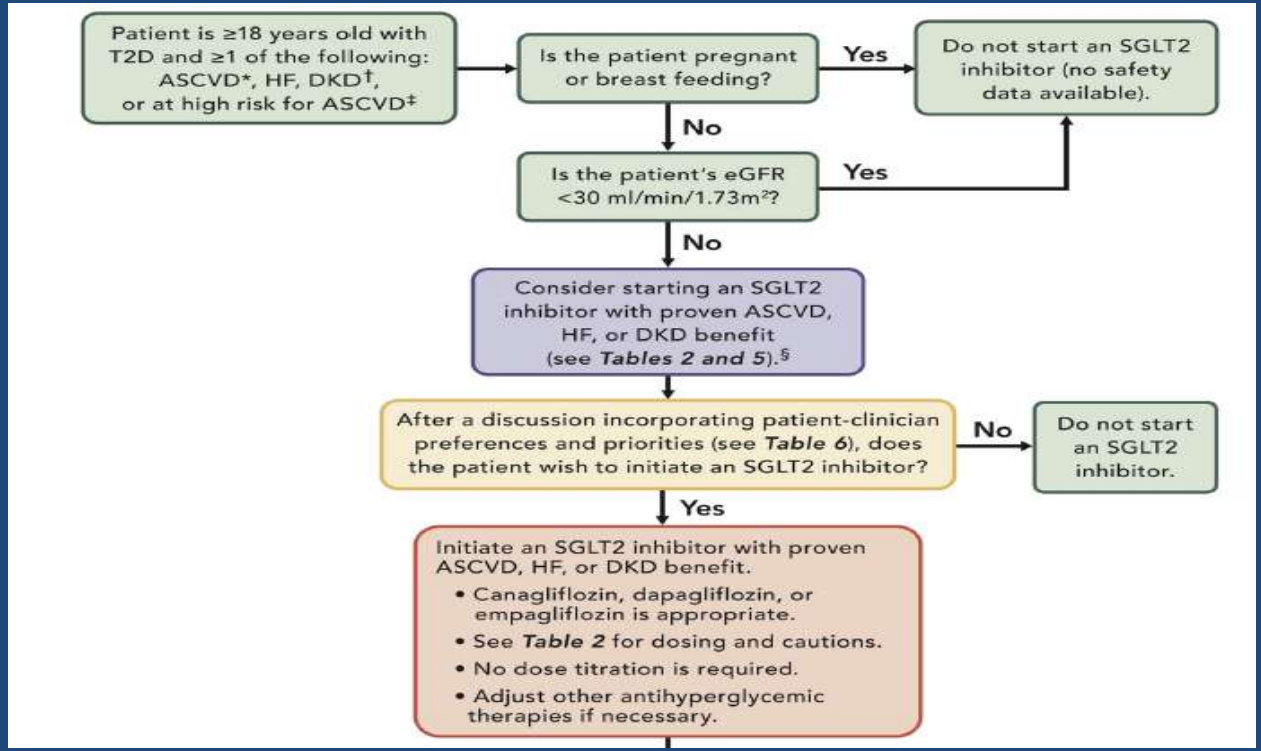


JAMA Cardiol. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511

JOHNS HOPKINS MEDICINE

Summary

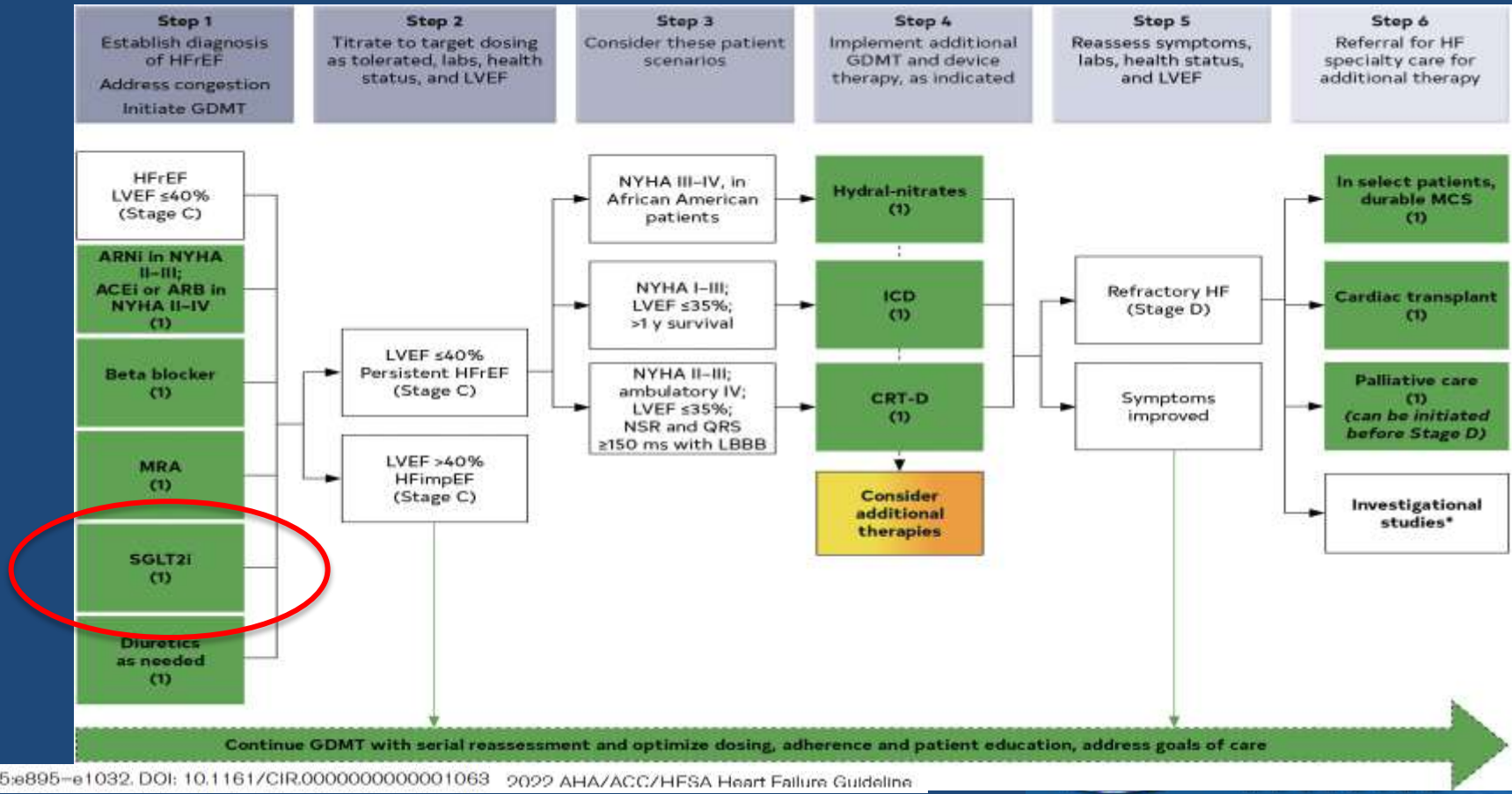
- Any for HF
- Empa, cana, dapa for renal
- Empa, cana for MACE
- Empa for CV death



JACC VOL 76, NO 9, 2020
SEPTEMBER 1, 2020:1117–45

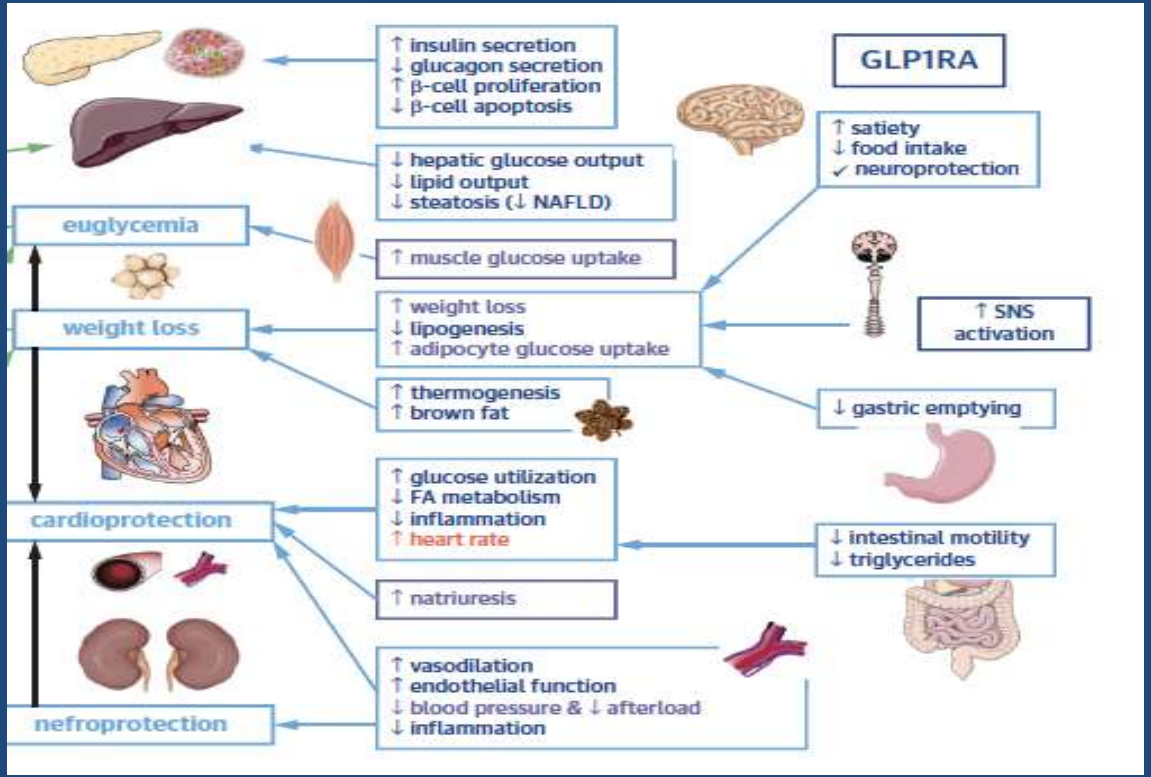
JOHNS HOPKINS MEDICINE

Pillar of GMDT in HF (all EF and all DM status)



Circulation. 2022;145:e895–e1032. DOI: 10.1161/CIR.0000000000001063 2022 AHA/ACC/HFSA Heart Failure Guideline

GLP-1 RA



- Reduce weight
- Reduce A1C
- Increase HR

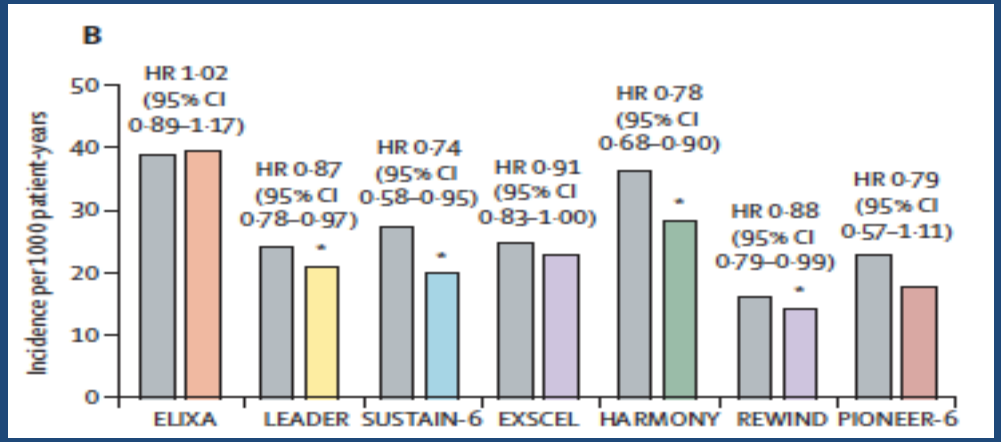
AE

- N/V (up to 10% discontinuation)
- Pancreatitis
- Retinopathy?
- Hypoglycemia?

JACC VOL. 75, NO. 16, 2020
APRIL 28, 2020:1956–74

JOHNS HOPKINS MEDICINE

Cardiovascular event reduction



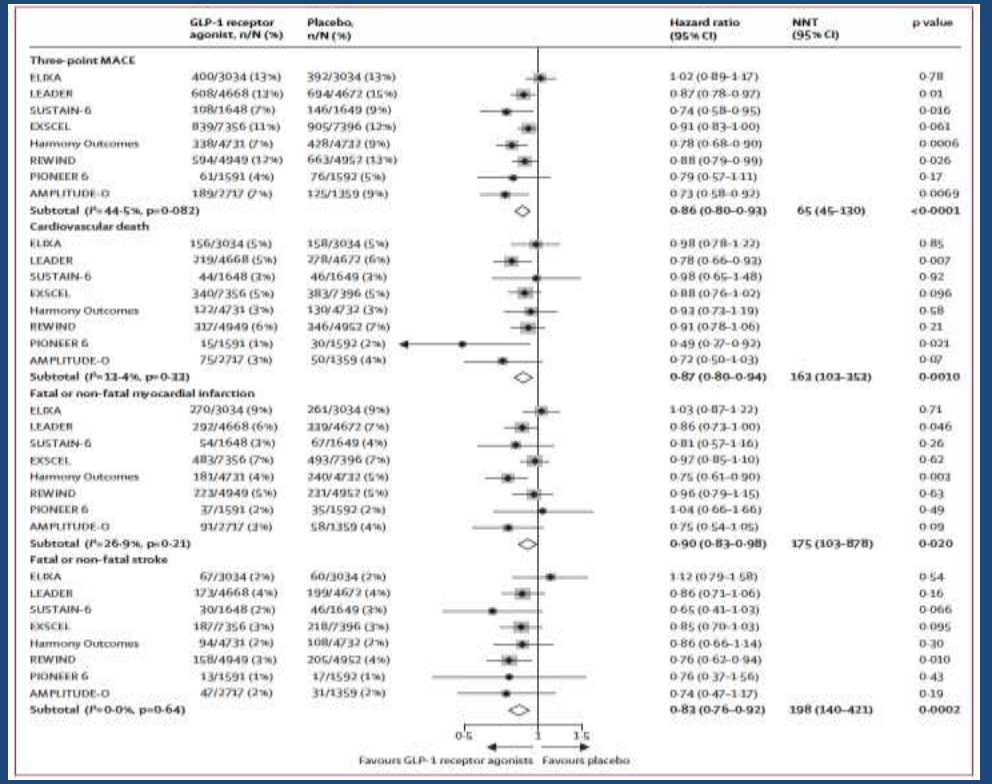
JACC VOL. 75, NO. 16, 2020
APRIL 28, 2020:1956–74

TABLE 3 GLP1RA Cardiovascular Outcome Trials

	ELIXA Lixisenatide (n = 6,068)	LEADER Liraglutide (n = 9,340)	SUSTAIN-6 Semaglutide (n = 3,297)	EXSCEL Exenatide Every Week (n = 14,752)	HARMONY Albiglutide Every Week (n = 9,463)	REWIND Dulaglutide Every Week (n = 9,901)	PIONEER-6 Semaglutide Oral (n = 3,182)
Median follow-up, yrs	2.1	3.8	2.1	3.2	1.6	5.4	1.3
Mean age, yrs	60	64	54	62	64	66	66
Female, %	30	36	39	38	31	46	32
Mean BMI, kg/m²	30.2	NR	NR	NR	32.3	32.3	32.3
HbA1c, %	7.7	8.7	8.7	8.1	8.8	7.3	8.2
Baseline metformin, %*	76	73	76	74	81	**57**	**51**
Baseline eGFR†	76	75	75	76	79	75	74
eGFR† <60, %	23	23	28.5	18	23	22	27
Prior CVD, %	100	81	83	73	100	32	85
Prior HF, %	22	18	24	16	20	9	NR
3P-MACE	1.02 (0.89-1.17)	**0.87 (0.78-0.97)**	**0.74 (0.58-0.95)**	0.91 (0.83-1.00)	**0.78 (0.68-0.90)**	**0.88 (0.79-0.99)**	0.79 (0.57-1.11)
CV death	0.98 (0.78-1.22)	**0.78 (0.66-0.93)**	0.98 (0.65-1.48)	0.88 (0.76-1.02)	0.93 (0.73-1.19)	0.91 (0.78-1.06)	0.49 (0.27-0.92)
Nonfatal MI	1.03 (0.87-1.22)	0.86 (0.73-1.00)‡	0.74 (0.51-1.08)§	0.97 (0.85-1.10)	**0.75 (0.61-0.90)**‡	0.96 (0.79-1.16)‡	1.18 (0.73-1.90)§
Nonfatal stroke	1.12 (0.79-1.58)	0.86 (0.71-1.06)‡	**0.61 (0.38-0.99)**§	0.85 (0.70-1.03)	0.86 (0.66-1.14)‡	0.76 (0.61-0.95)‡	0.74 (0.35-1.57)§
All-cause mortality	0.94 (0.78-1.13)	**0.85 (0.74-0.97)**	1.05 (0.74-1.50)	0.86 (0.77-0.97)	0.95 (0.79-1.16)	0.90 (0.80-1.01)	0.51 (0.31-0.84)
HHF	0.96 (0.75-1.23)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)	NR	0.93 (0.77-1.12)	0.86 (0.48-1.55)
Renal events‖	0.81 (0.66-0.99)	**0.78 (0.67-0.92)**	**0.64 (0.46-0.88)**	0.85 (0.73-0.98)	NR	**0.85 (0.77-0.93)**	NR
Weight loss¶	0.7 (0.9-0.5)	2.3 (2.5-2.0)	2.9 (2.3-3.5)/3.6 (3.8-4.9)*	1.3 (1.1-1.4)	0.83 (0.6-1.1) at 16 months	1.5 (1.3-1.7)	2.9/4.3#

Lancet 2021; 398: 262–76

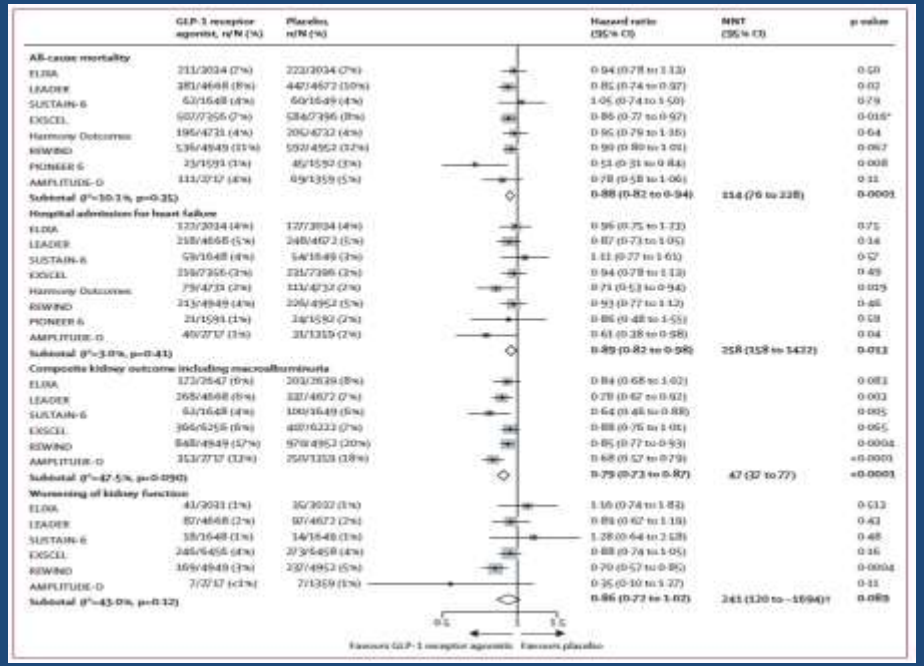
Meta analysis: MACE, renal outcomes, HF



	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I²=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·21
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
AMPLITUDE-O	75/2717 (3%)	50/1359 (4%)	0·72 (0·50–1·03)		0·07
Subtotal (I²=33·4%, p=0·13)			**0·87 (0·80–0·94)**	**162 (103–353)**	**0·0010**
Fatal or non-fatal myocardial infarction					
ELIXA	270/3034 (9%)	261/3034 (9%)	1·03 (0·87–1·22)		0·71
LEADER	292/4668 (6%)	339/4672 (7%)	0·86 (0·73–1·00)		0·046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0·81 (0·57–1·16)		0·26
EXSCEL	483/7356 (7%)	493/7396 (7%)	0·97 (0·85–1·10)		0·62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0·75 (0·61–0·90)		0·003
REWIND	223/4949 (5%)	231/4952 (5%)	0·96 (0·79–1·15)		0·63
PIONEER 6	37/1591 (2%)	35/1592 (2%)	1·04 (0·66–1·66)		0·49
AMPLITUDE-O	91/2717 (3%)	58/1359 (4%)	0·75 (0·54–1·05)		0·09
Subtotal (I²=26·9%, p=0·21)			**0·90 (0·83–0·98)**	**175 (103–878)**	**0·020**
Fatal or non-fatal stroke					
ELIXA	67/3034 (2%)	60/3034 (2%)	1·12 (0·79–1·58)		0·54
LEADER	173/4668 (4%)	199/4672 (4%)	0·86 (0·71–1·06)		0·16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0·65 (0·41–1·03)		0·066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0·85 (0·70–1·03)		0·095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0·86 (0·66–1·14)		0·30
REWIND	158/4949 (3%)	205/4952 (4%)	0·76 (0·62–0·94)		0·010
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0·76 (0·37–1·56)		0·43
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	0·74 (0·47–1·17)		0·19
Subtotal (I²=0·0%, p=0·64)			**0·83 (0·76–0·92)**	**198 (140–421)**	**0·0002**

0·5 1 1·5

Favours GLP-1 receptor agonists Favours placebo



	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	222/3034 (7%)	0·94 (0·78 to 1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74 to 0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74 to 1·50)		0·79
EXSCEL	607/7356 (7%)	684/7396 (8%)	0·86 (0·77 to 0·97)		0·016*
Harmony Outcomes	195/4731 (4%)	206/4732 (4%)	0·95 (0·79 to 1·15)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80 to 1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31 to 0·84)		0·008
AMPLITUDE-O	111/2717 (4%)	69/1359 (5%)	0·78 (0·58 to 1·06)		0·11
Subtotal (I²=30·1%, p=0·25)			**0·88 (0·82 to 0·94)**	**114 (76 to 228)**	**0·0001**
Hospital admission for heart failure					
ELIXA	123/3034 (4%)	127/3034 (4%)	0·96 (0·75 to 1·23)		0·71
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73 to 1·05)		0·14
SUSTAIN-6	58/1648 (4%)	54/1649 (3%)	1·11 (0·77 to 1·61)		0·57
EXSCEL	159/7356 (2%)	221/7396 (3%)	0·94 (0·78 to 1·13)		0·49
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53 to 0·94)		0·019
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77 to 1·12)		0·46
PIONEER 6	21/1591 (1%)	34/1592 (2%)	0·86 (0·48 to 1·55)		0·59
AMPLITUDE-O	46/2717 (2%)	31/1359 (2%)	0·61 (0·38 to 0·98)		0·04
Subtotal (I²=3·0%, p=0·41)			**0·89 (0·82 to 0·98)**	**258 (158 to 1432)**	**0·013**
Composite kidney outcome including macroalbuminuria					
ELIXA	173/2647 (6%)	203/2639 (8%)	0·84 (0·68 to 1·02)		0·083
LEADER	265/4668 (6%)	337/4672 (7%)	0·78 (0·67 to 0·92)		0·002
SUSTAIN-6	61/1648 (4%)	108/1649 (6%)	0·54 (0·40 to 0·88)		0·005
EXSCEL	366/6255 (6%)	407/6222 (7%)	0·88 (0·76 to 1·01)		0·065
REWIND	848/4949 (17%)	978/4952 (20%)	0·85 (0·77 to 0·93)		0·0004
AMPLITUDE-O	353/2717 (13%)	259/1359 (19%)	0·68 (0·57 to 0·79)		<0·0001
Subtotal (I²=47·5%, p=0·090)			**0·79 (0·73 to 0·87)**	**47 (32 to 77)**	**<0·0001**
Worsening of kidney function					
ELIXA	41/2031 (1%)	35/2032 (1%)	1·16 (0·74 to 1·83)		0·513
LEADER	87/4668 (2%)	97/4672 (2%)	0·89 (0·67 to 1·18)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64 to 2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74 to 1·05)		0·16
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57 to 0·86)		0·0004
AMPLITUDE-O	7/2717 (<1%)	7/1359 (1%)	0·35 (0·10 to 1·27)		0·11
Subtotal (I²=43·0%, p=0·12)			**0·86 (0·73 to 1·02)**	**241 (120 to −1694)†**	**0·083**

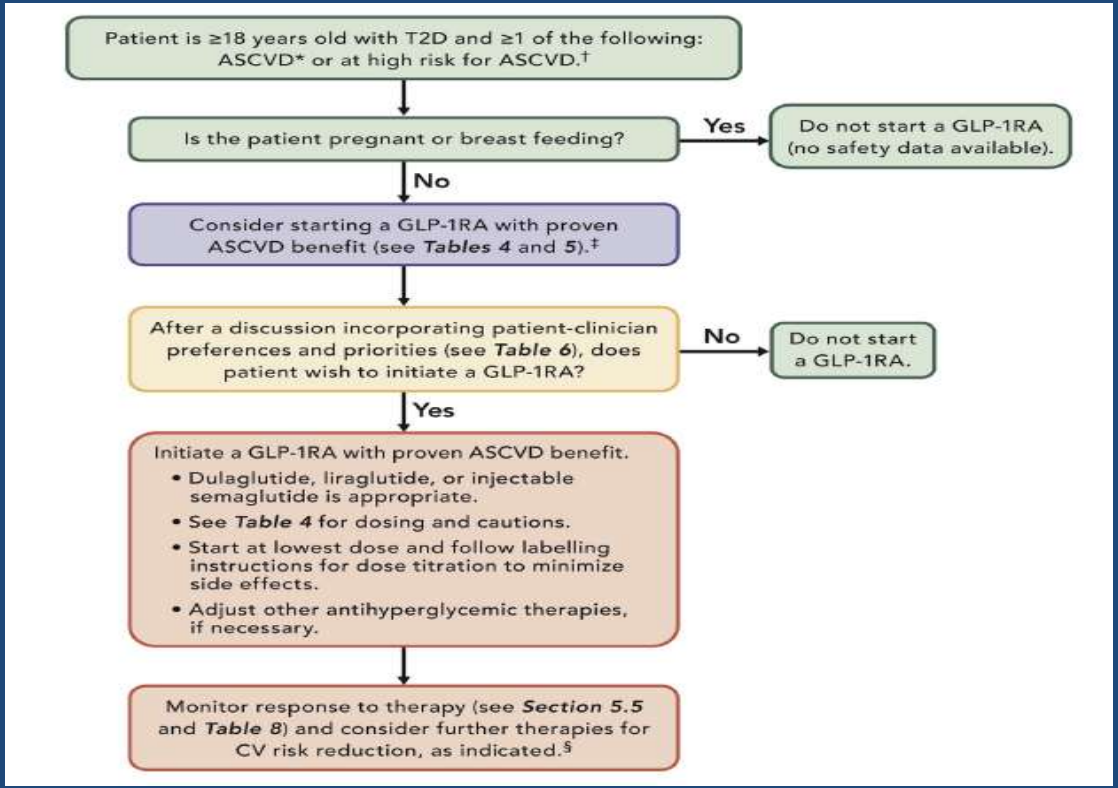
0·5 1 1·5

Favours GLP-1 receptor agonists Favours placebo

Lancet Diabetes Endocrinol 2021
9: 653–62

JOHNS HOPKINS MEDICINE

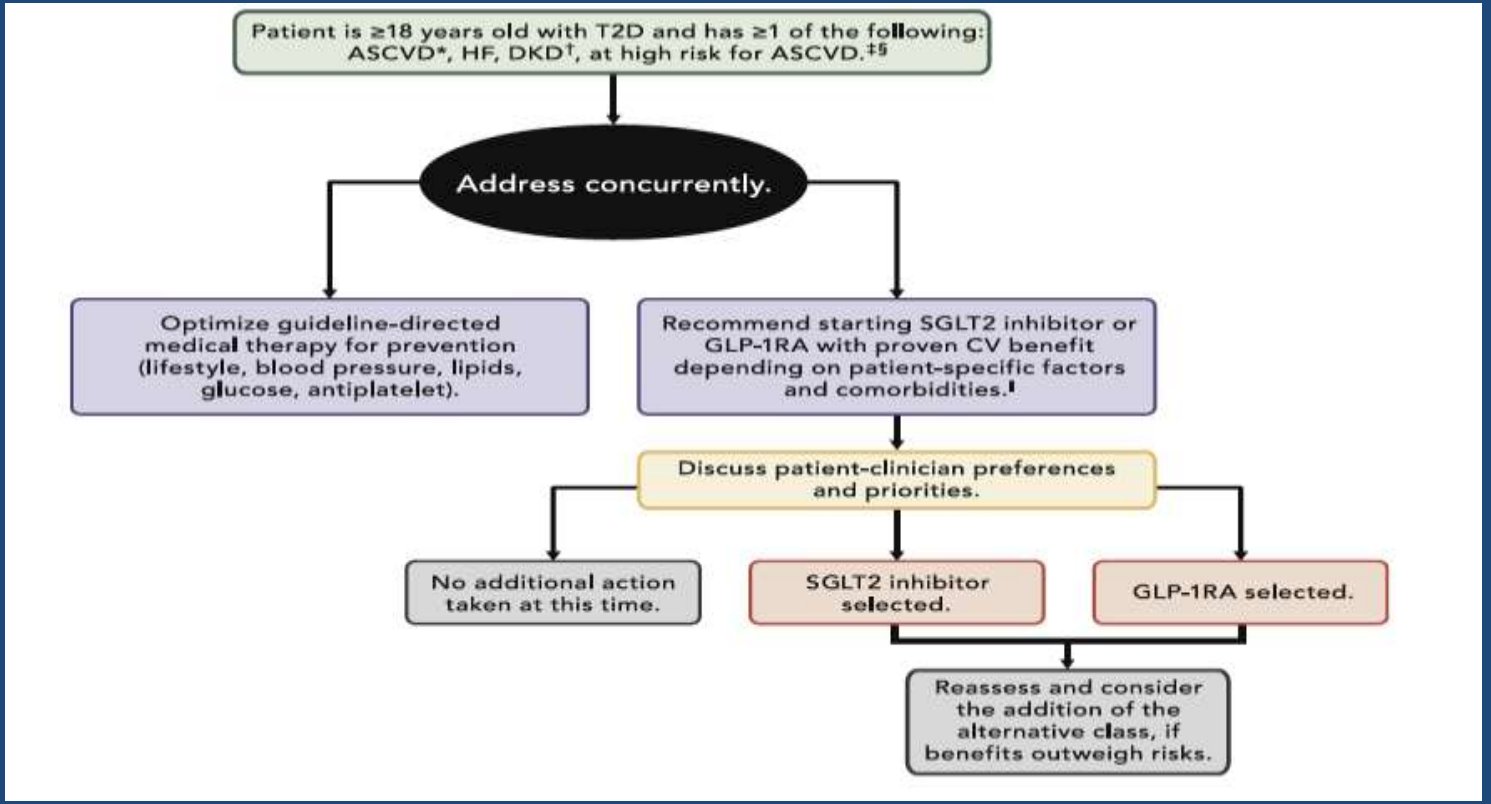
Summary



JACC VOL 76, NO 9, 2020
SEPTEMBER 1, 2020:1117–45

JOHNS HOPKINS MEDICINE

Put it all together



JACC VOL 76, NO 9, 2020
SEPTEMBER 1, 2020:1117–45

JOHNS HOPKINS MEDICINE

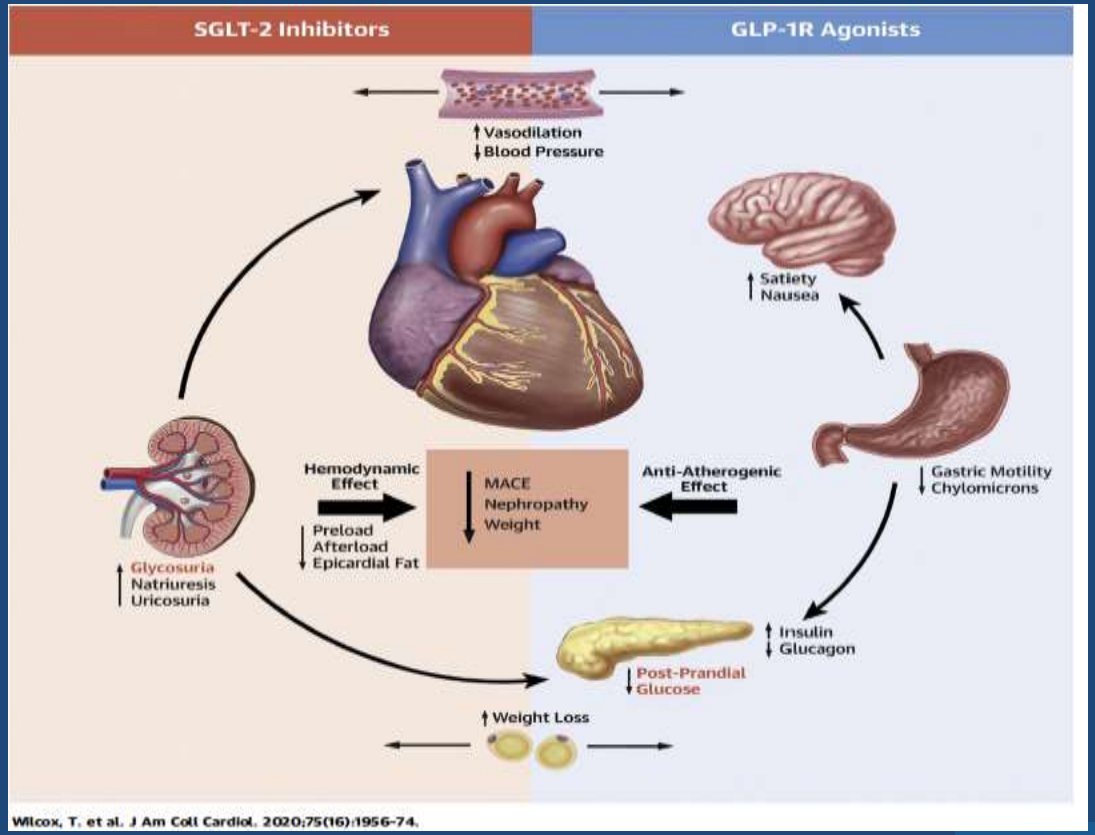
Put it all together

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

JACC VOL 76, NO 9, 2020
SEPTEMBER 1, 2020:1117–45

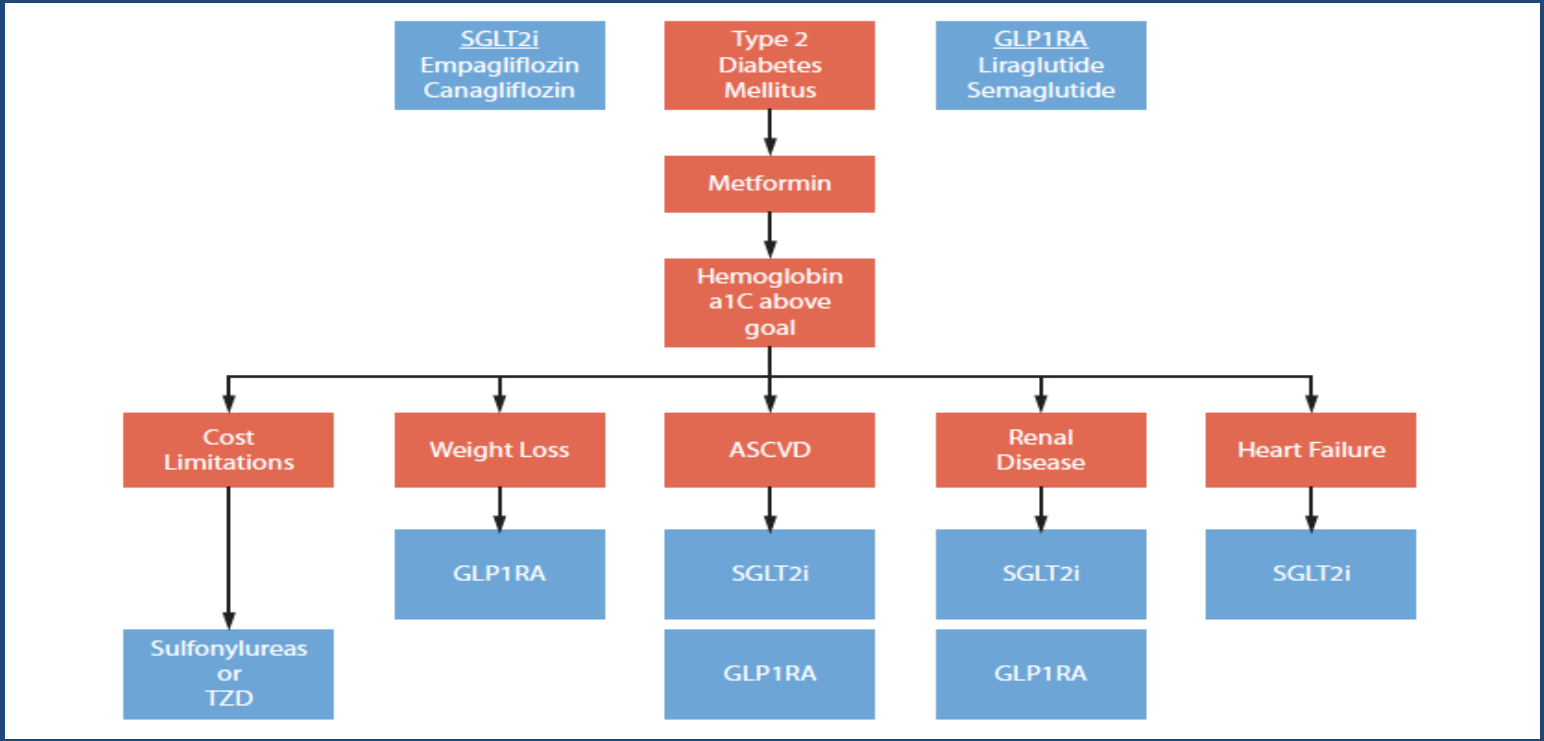
Put it all together



Wilcox, T. et al. J Am Coll Cardiol. 2020;75(16):1956-74.

JOHNS HOPKINS MEDICINE

Put it all together



JACC VOL. 75, NO. 16, 2020
APRIL 28, 2020:1956–74

JOHNS HOPKINS
MEDICINE

Case conclusion
Should we add GLP1-RA, SGLT2i, or both?

- DM
- HFPEF
- CKD
- Multiple cardiovascular risk factors

- Start with SGLT2i; we added combination therapy with addition of GLP1

Learning objectives

- Understand physiology underlying cardiovascular benefit of GLP1-RA and SGLT2i
- Recognize adverse effects of GLP1-RA and SGLT2i
- Prescribe GLP1-RA and SGLT2i for appropriate indications

Thanks!

tmetkus1@jhmi.edu

JOHNS HOPKINS
MEDICINE