SGLT2 inhibitors and GLP1 Receptor Agonists

When and to Whom

SPED SEMIANNUAL CONVENTION,
MARTÍNEZ DE ANDINO'S MEMORIAL LECTURE &
MANUEL PANIAGUA'S POST GRADUATE DIABETES COURSE

DECEMBER 12 & 13, 2020
SPED VIRTUAL EVENTS PLATFORM

Jose M Garcia Mateo, MD, FACE

Diplomate of the American Board of Endocrinology

Diplomate of the American Board of Clinical Lipidology

SPED President

Objectives

- Updated CVOT discussion on GLP1RA and SGLT2i in DM2, ASCVD, CKD and HF.
- Evaluate the difference in these CVOT's for application in clinical practice.
- How CVOT's of these agents are positioned on SOC recommendations from different diabetes amd CV societies.
- Apply this information to commonly seen clinical scenarios for the use of SGLT2i, GLP1 RA or even both of them.

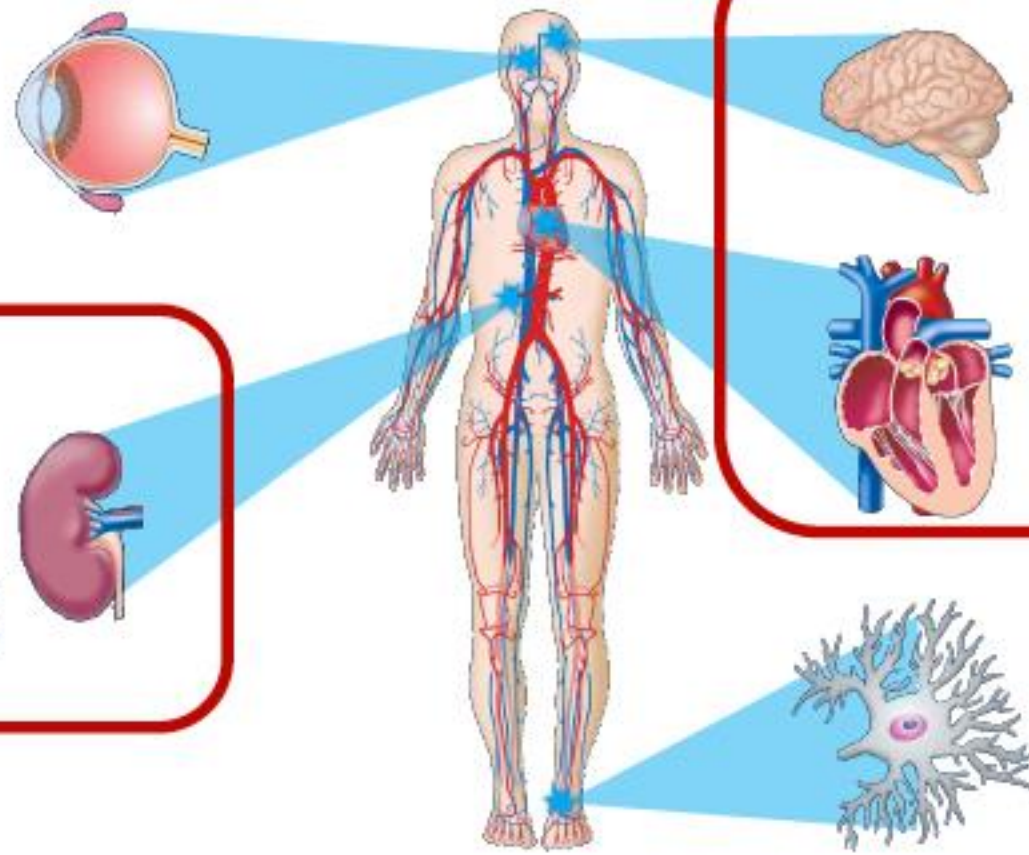
Complications of Diabetes

Diabetic retinopathy

An important cause of blindness in adults[1,2]

Diabetic nephropathy

Leading cause of chronic and end-stage kidney disease (ESKD)[3]



Stroke

Hypertension increasing risk of stroke[4]

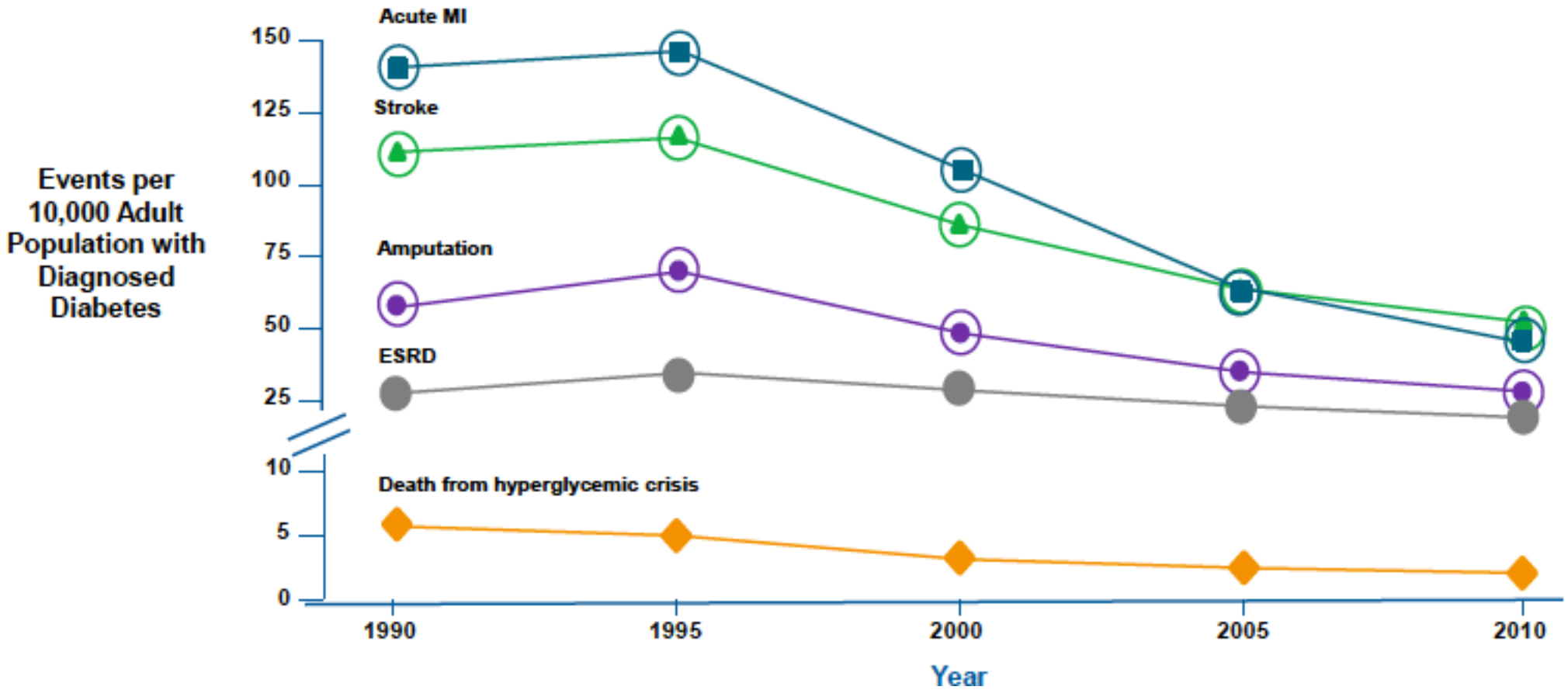
Cardiovascular disease

CVD is major cause of morbidity and mortality[5]

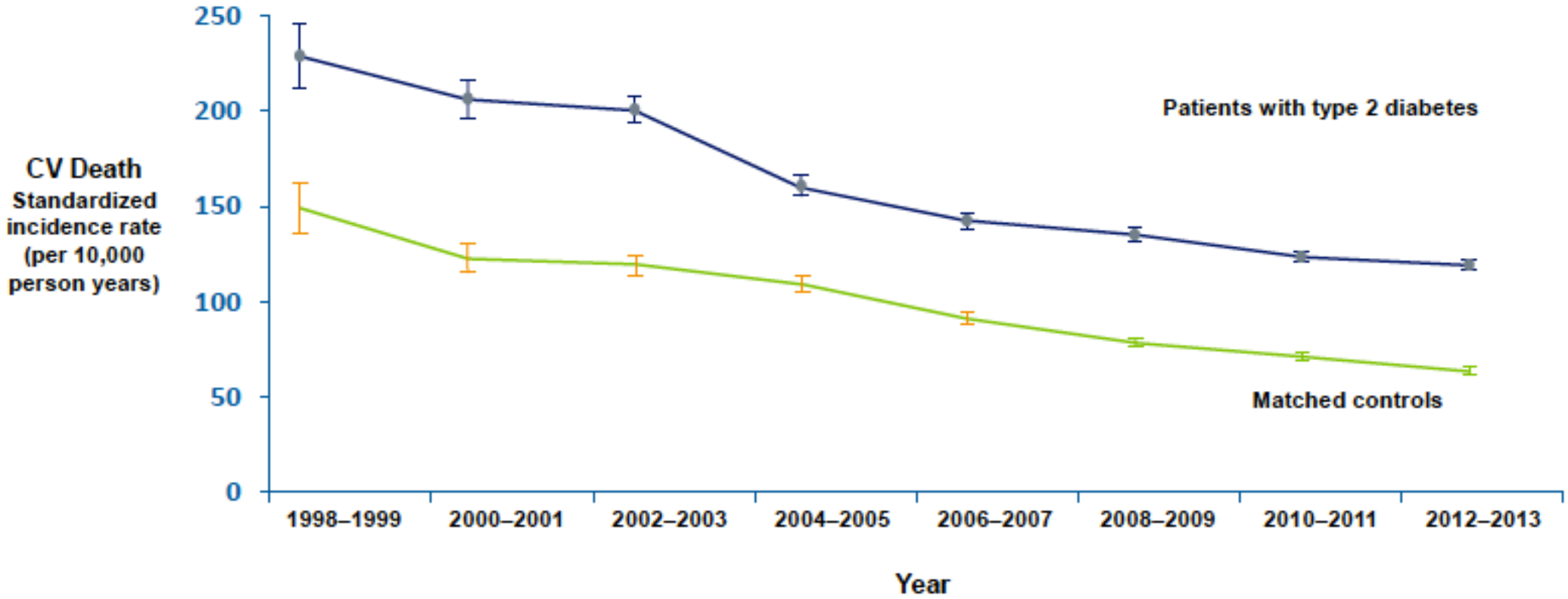
Diabetic neuropathy

Leading cause of non-traumatic lower extremity amputations[6,7]

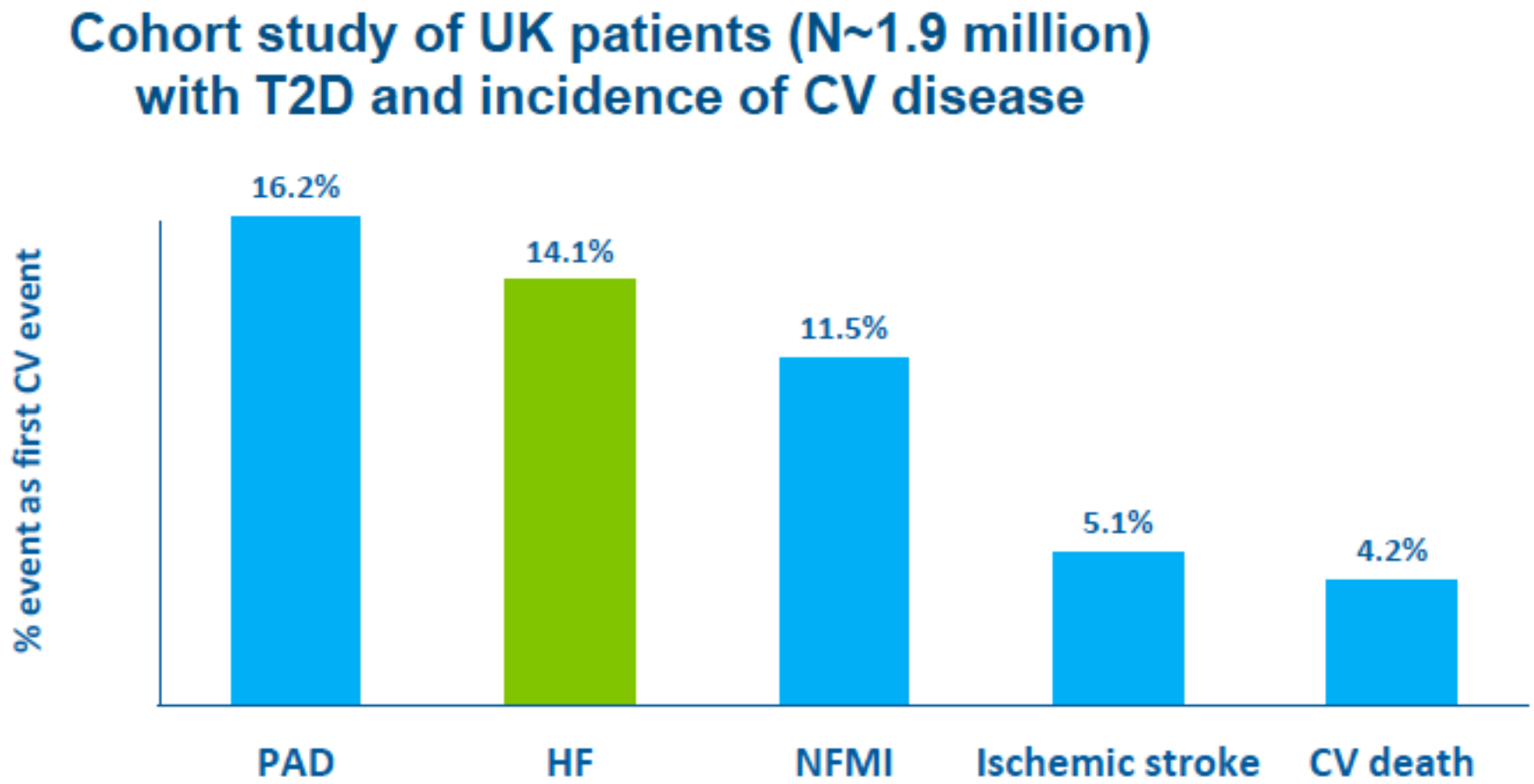
Improvements in Rates of Cardiovascular Disease



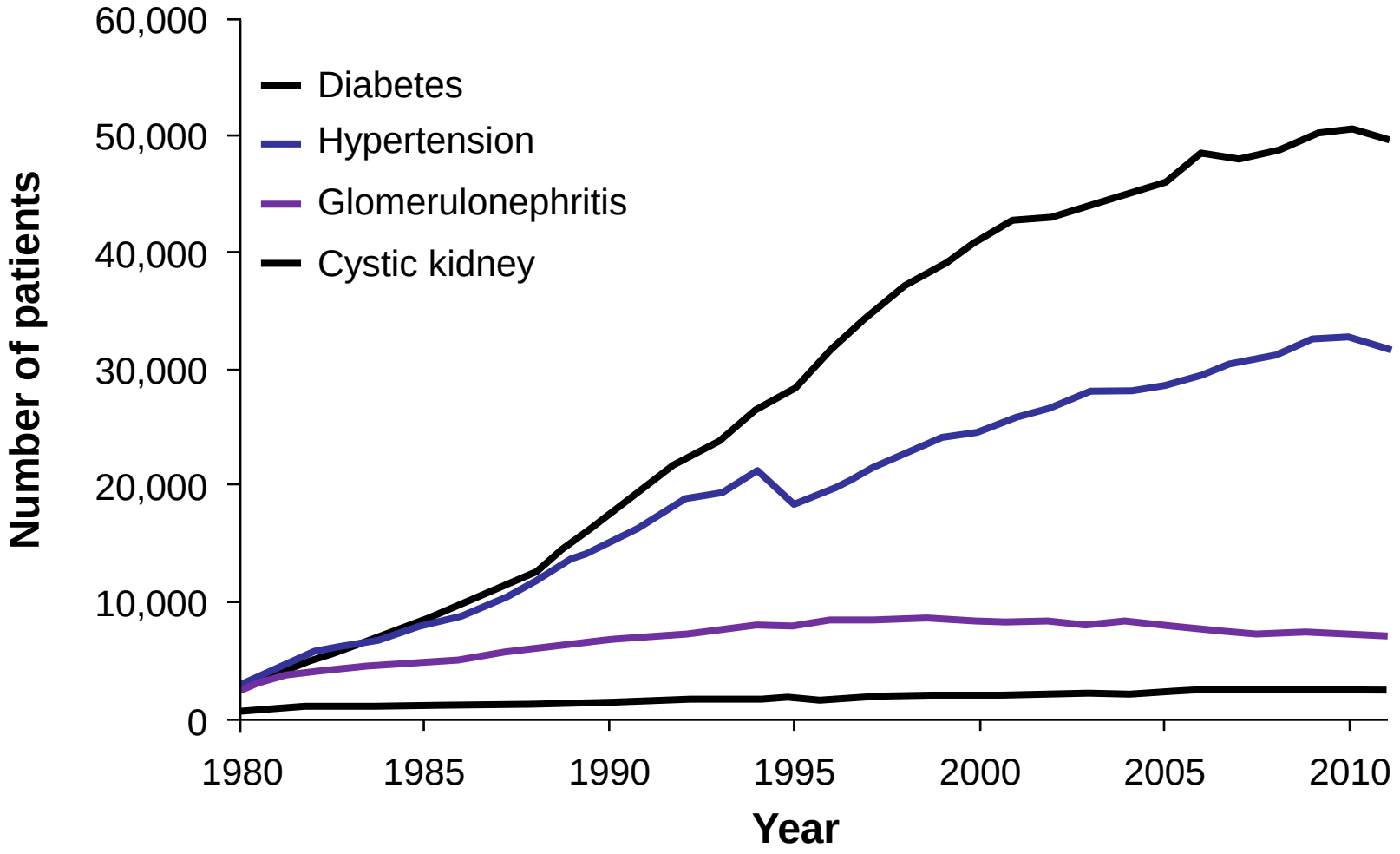
T2DM Still Confers Excess Risk of CVD Death



HF is One of the First Manifestations of T2D-Related CV Disease



Diabetes Is the Leading Cause of Kidney Failure: US Data



Impact of intensive therapy in diabetes in major clinical trials

Study	A1c Baseline → Study End Std / Intensive	Microvascular		CVD		Mortality	
DCCT/EDIC	9 → 9 & 7	↓	↓	↔	↓	↔	↔
UKPDS	9 → 7.9 & 7	↓	↓	↔	↓	↔	↓
ACCORD	8.3 → 7.5 & 6.4	↓		↔		↑ ?	
ADVANCE	7.5 → 7.0 & 6.4	↓		↔		↔	
VADT	9.4 → 8.5 & 6.9	↓		↔	↓*	↔	

Initial Trial Long Term Follow-up

Diabetes Mellitus and Cardiovascular Disease: The Perfect Storm

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

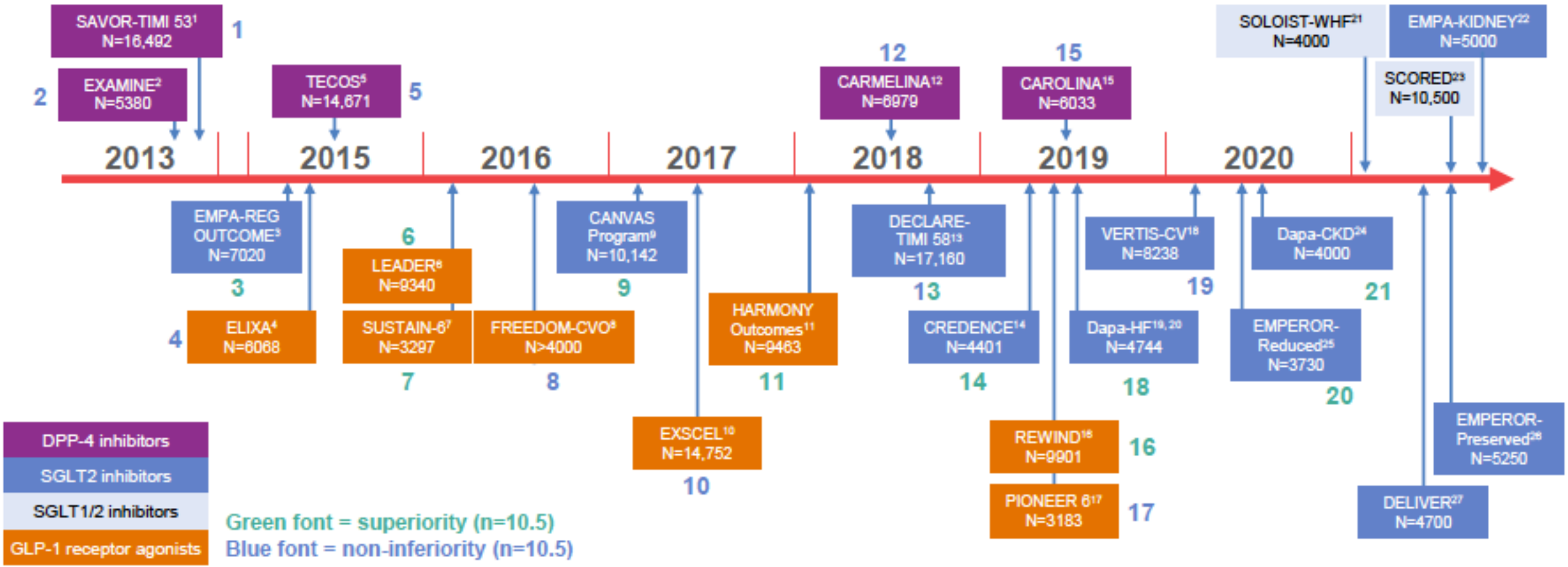
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

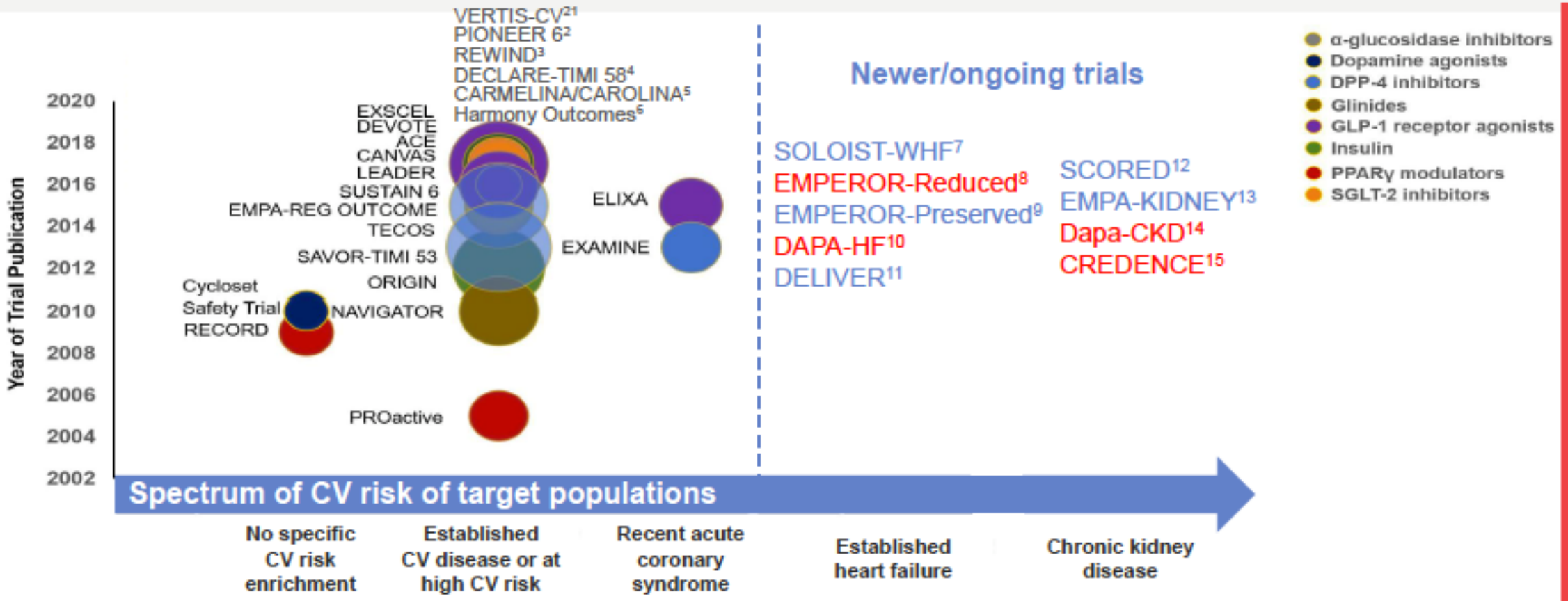
CVOTs in T2D: evidentiary landscape*

26 trials (21 completed), N=197,832



Markers on the timeline represent trial publication dates or estimated completion dates
*Some trials included patients with and without T2D. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1
See notes page for full list of references

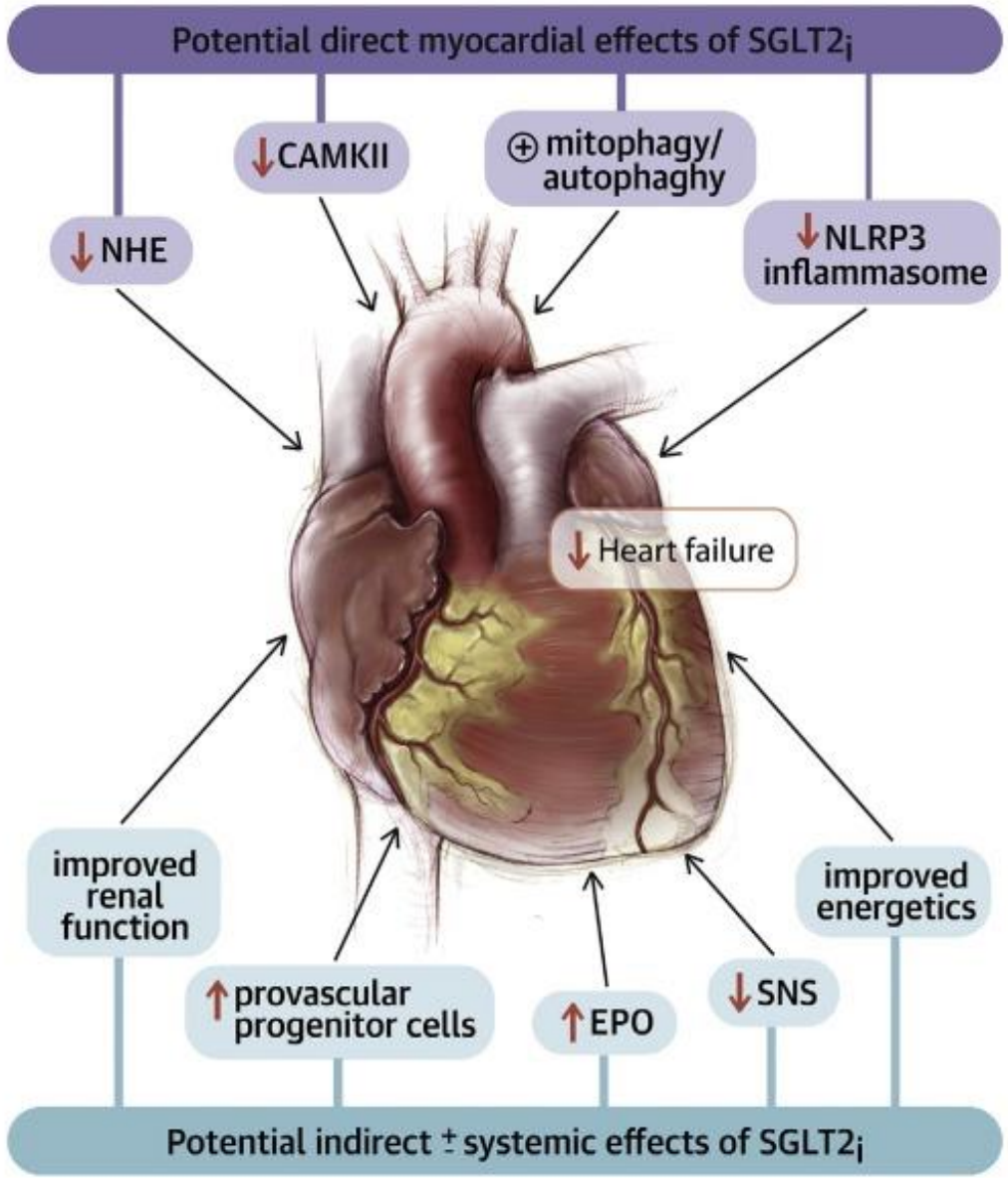
Spectrum of CV risk in target populations of key CVOTs in patients with or without T2D[1]



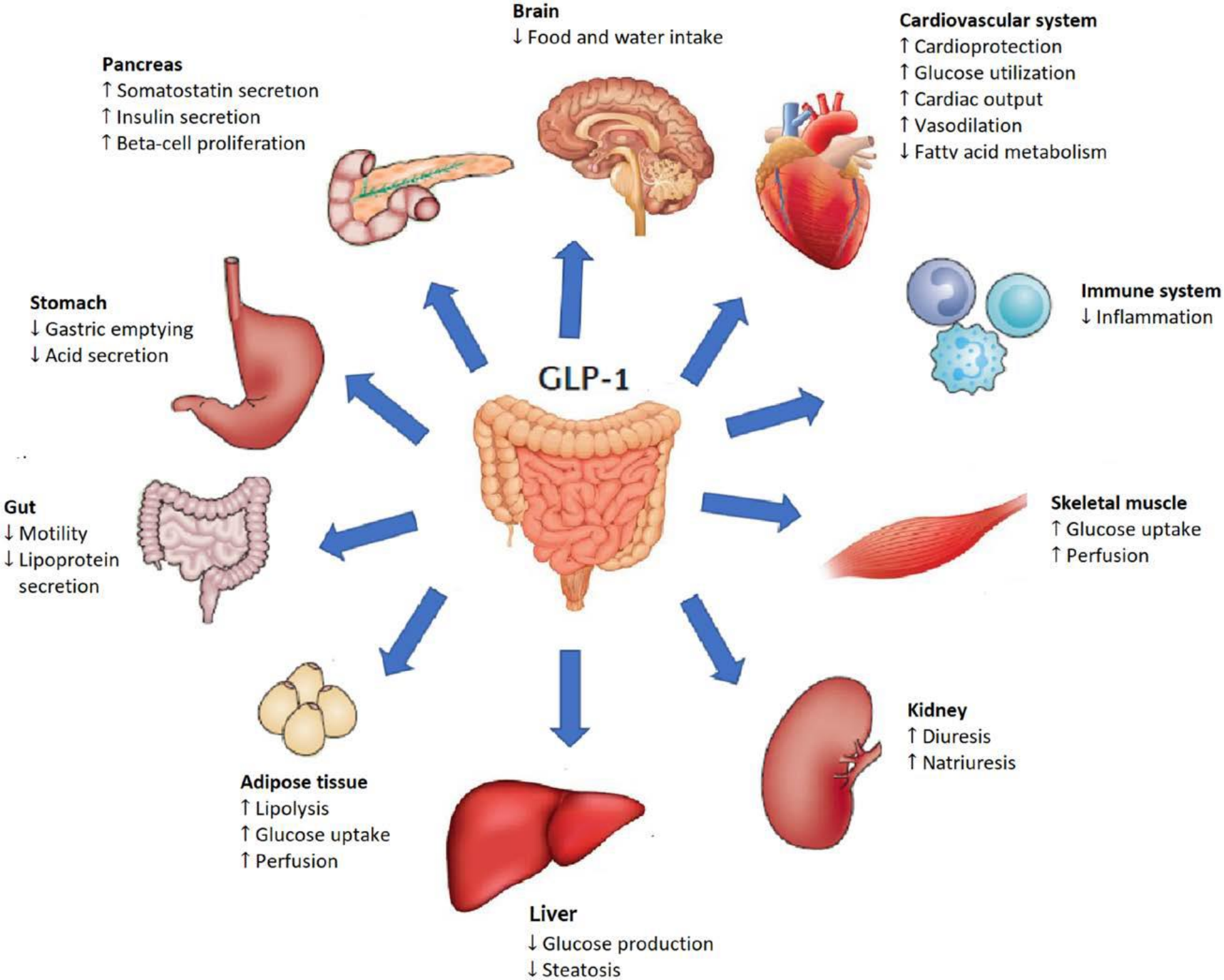
Of the extensive CVOT evidence so far, most data come from patients with established CV disease and high-risk populations

Graph modified by the presenter based on data from Vijayakumar S *et al. Circulation* 2018;137:1060
See notes page for full list of references

CENTRAL ILLUSTRATION: Potential Direct Myocardial and Indirect ± Systemic Effects of SGLT2$_i$



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


Brain
↓ Food and water intake
Pancreas
↑ Somatostatin secretion
↑ Insulin secretion
↑ Beta-cell proliferation
Cardiovascular system
↑ Cardioprotection
↑ Glucose utilization
↑ Cardiac output
↑ Vasodilation
↓ Fatty acid metabolism
Stomach
↓ Gastric emptying
↓ Acid secretion
Immune system
↓ Inflammation
GLP-1
Gut
↓ Motility
↓ Lipoprotein secretion
Skeletal muscle
↑ Glucose uptake
↑ Perfusion
Adipose tissue
↑ Lipolysis
↑ Glucose uptake
↑ Perfusion
Kidney
↑ Diuresis
↑ Natriuresis
Liver
↓ Glucose production
↓ Steatosis

Therapeutic effects on HF and CV outcomes in CVOTs in patients with T2D

HF outcomes	CV outcomes (MACE)		
	+ (Benefit)	+/- (Null)	- (Harm)
+ (Benefit)	• Empagliflozin (EMPA-REG OUTCOME)[1] • Canagliflozin (CANVAS, CREDENCE)[2,3]	• Dapagliflozin (DECLARE, DAPA-HF)[8] • Ertugliflozin (VERTIS-CV)**[21]	
+/- (Null)	• Liraglutide (LEADER)[4] • SC semaglutide (SUSTAIN-6)*[5] • Albiglutide (Harmony Outcomes)†[6] • Dulaglutide (REWIND)[7]	• Insulin glargine (ORIGIN)[9] • Acarbose (ACE)[10] • Lixisenatide (ELIXA)[11] • Exenatide (EXSCEL)[12] • Alogliptin (EXAMINE)[13] • Sitagliptin (TECOS)[14] • Linagliptin (CARMELINA, CAROLINA)[15,16] • Oral semaglutide (PIONEER-6)*[17]	
- (Harm)		• Pioglitazone (PROactive)[18] • Rosiglitazone (RECORD)[19] • Saxagliptin (SAVOR-TIMI 53)[20]	

*Not powered for ruling out HR 1.3 or for superiority; **exploratory analysis for HHF; †HHF or CV death

See notes page for abbreviations and full list of references

CVOT in General
SGLT2i and GLP1RA

Impactful CVOTs of SGLT2 Inhibitors in T2DM
Quantity of Evidence

Trial	Endpoint	Outcome		Substantial evidence	FDA-approved indication
		HR (95% CI)	P value		
EMPA-REG OUTCOME	CVD, MI, Stroke (PEP)	0.86 (0.74, 0.99)	0.038	No	No
	CV death	0.62 (0.49, 0.77)	0.0001	Yes	Yes
CANVAS	CVD, MI, Stroke (PEP)	0.86 (0.75, 0.97)	0.015	No	No
	CVD, MI, Stroke (+ eCVD)	0.82 (0.72, 0.95)	0.007	? Maybe	Yes
	CVD (truncated)	0.96 (0.77, 1.18)	0.95	No	No
	ACM (truncated)	0.90 (0.76, 1.07)	0.24	No	No
DECLARE-TIMI 58	CVD, MI, Stroke (co-PEP)	0.93 (0.84, 1.03)	0.17	No	No
	CV death, HHF (co-PEP)	0.83 (0.73, 0.95)	0.005	? Maybe	No
	CV death	0.98 (0.82, 1.17)	0.851	No	No
	HHF	0.73 (0.61, 0.88)	0.0007	Yes	Yes
VERTIS-CV	#1. CVD, MI, Stroke (PEP)	0.97 (0.85, 1.11)	ns	No	NA
	#2. CV death, HHF (SEP)	0.88 (0.75, 1.03)	0.11	No	
	#3. CV death	0.92 (0.77, 1.11)	0.39	No	
	#4. Renal composite	0.81 (0.63, 1.04)	0.08	No	
	HHF*	0.70 (0.54, 0.90)	0.006*	? Maybe	

CANVAS: MACE in established CVD: 0.82 (0.72, 0.95); p=0.007; in MRF: 0.98 (0.74, 1.30); interaction P=0.18

DECLARE: HHF in established CVD: 0.78 (0.63, 0.97); in MRF: 0.64 (0.46, 0.88); interaction P=0.30

*exploratory; MRF = multiple risk factors, eCVD = established cardiovascular disease

CVOTs with SGLT2 inhibitors

Baseline characteristics

Trial	N	Median F/U, y	Age, y	Female, %	Baseline HbA1c, %	Diabetes duration, y	Established CVD, %	History of HF, %	eGFR <60ml/min/ 1.73^2
EMPA-REG OUTCOME	7,020	3.1	63.1	28.5	8.1	NA	99	10.1	25.9
CANVAS Program	10,142	2.4	63.3	35.8	8.2	13.5	65.6	14.4	20.1
DECLARE-TIMI 58	17,160	4.2	63.9	37.4	8.3	11.8	40.6	10.0	7.4
VERTIS-CV	8,246	3.0	64.4	30.0	8.2	13.0	100	23.7	21.9

High-risk cohort enrolled in VERTIS-CV very similar to EMPA-REG OUTCOME

Empagliflozin versus Ertugliflozin (EMPA-REG OUTCOME, VERTIS-CV)

Variable	EMPA-REG OUTCOME (99% CVD, 10% HF)		VERTIS-CV (100% CVD, 24% HF)	
	Empa	Placebo	Ertu	Placebo
Number	4687	2333	5499	2745
Follow-up (median, y)	3.1	3.1	3.0	3.0
Primary outcome (3-point MACE)	490 37.4/1000PY	282 **43.9**/1000PY	653 39/1000PY	327 **40**/1000PY
	HR 0.86, 0.74-0.99 P=0.04		HR 0.97, 0.85-1.11 P=0.65	
CV death	172 12.4/1000PY	137 **20.2**/1000PY	341 17.6/1000PY*	184 **19.0**/1000PY*
	HR 0.62, 0.49-0.77		HR 0.92, 0.77-1.11	
Nonfatal MI	213 16/1000PY	121 **18.5**/1000PY	310 17.0/1000PY	148 **16.0**/1000PY
	HR 0.87, 0.70-1.09		HR 1.04, 0.86-1.27	
Nonfatal stroke	150 11.2/1000PY	60 **9.1**/1000PY	157 8.0/1000PY	78 **8.0**/1000PY
	HR 1.24, 0.92-1.67		HR 1.00, 0.76-1.32	

Similar placebo event rates confirming comparable risk across the trials

Empagliflozin versus Ertugliflozin (EMPA-REG OUTCOME, VERTIS-CV)

Variable	EMPA-REG OUTCOME (99% CVD, 10% HF)		VERTIS-CV (99.9% CVD, 24% HF)	
	Empa	Placebo	Ertu	Placebo
Number	4687	2333	5499	2745
CV death or HHF (total cohort)	265 19.7/1000PY	198 **30.1**/1000PY	444 23/1000PY	250 **27**/1000PY
	HR 0.66, 0.55-0.79		HR 0.88, 0.75-1.03	
CV death or HHF (with h/o HF)	63.6/1000PY	**85.5**/1000PY	40.1/1000PY	**47.1**/1000PY
	HR 0.72, 0.50-1.04		HR 0.85, 0.66-1.09	
CV death or HHF (without h/o HF)	15.5/1000PY	**24.9**/1000PY	18.8/1000PY	**20.6**/1000PY
	HR 0.63, 0.51-0.78		HR 0.91, 0.75-1.11	
HHF	126 9.4/1000PY	95 **14.5**/1000PY	139 7.3/1000PY	99 **10.5**/1000PY
	HR 0.65, 0.50-0.85		HR 0.70, 0.54-0.90	
Renal composite (Cr x 2, RRT, renal death)	6.3/1000PY	**11.5**/1000PY	175 9.3/1000PY*	108 **11.5**/1000PY*
	HR 0.54, 0.40-0.75		HR 0.81, 0.63-1.04	

Lower incident CV death/HHF rate in VERTIS-CV despite >2-fold higher h/o HF

VERTIS-CV Deep Dive

Why did ertugliflozin not yield favorable CV and renal outcomes?

- Difference in receptor selectivity? Unlikely
- Difference in cardiorenal-metabolic effects? No
- Difference in trial population, design and endpoints? Unlikely
- Secular trends in secondary prevention (BP, lipids)? No
- Imbalance in cardioprotective therapies at baseline or during the trial? Unlikely
- Differences in 'off-target' effects? Unlikely, as HF/renal outcomes going in right direction
- Random variation ("play of chance")? Likely

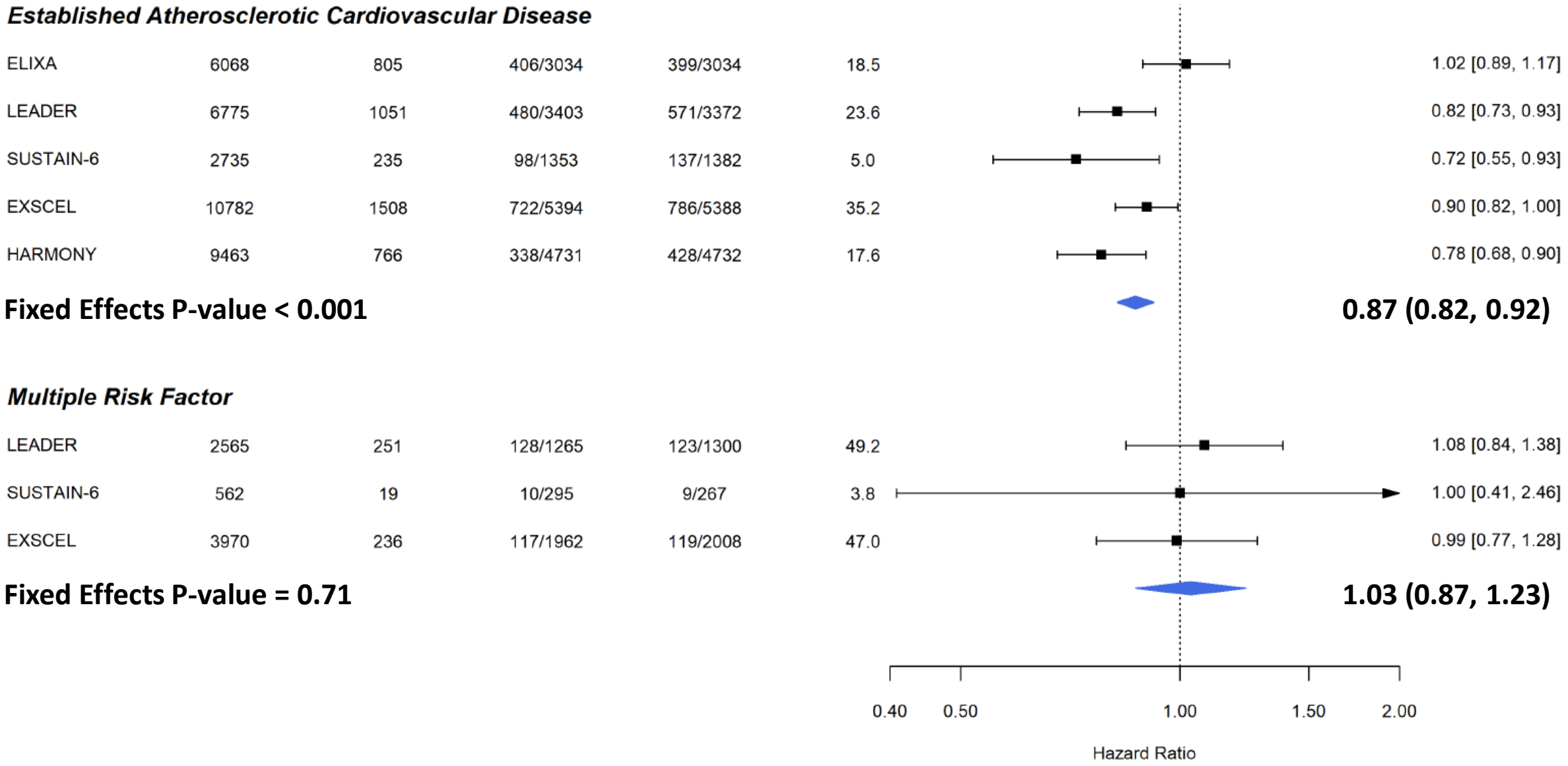
SGLT2 inhibitors in T2DM and ASCVD/MRF: Class or Drug-specific effect?

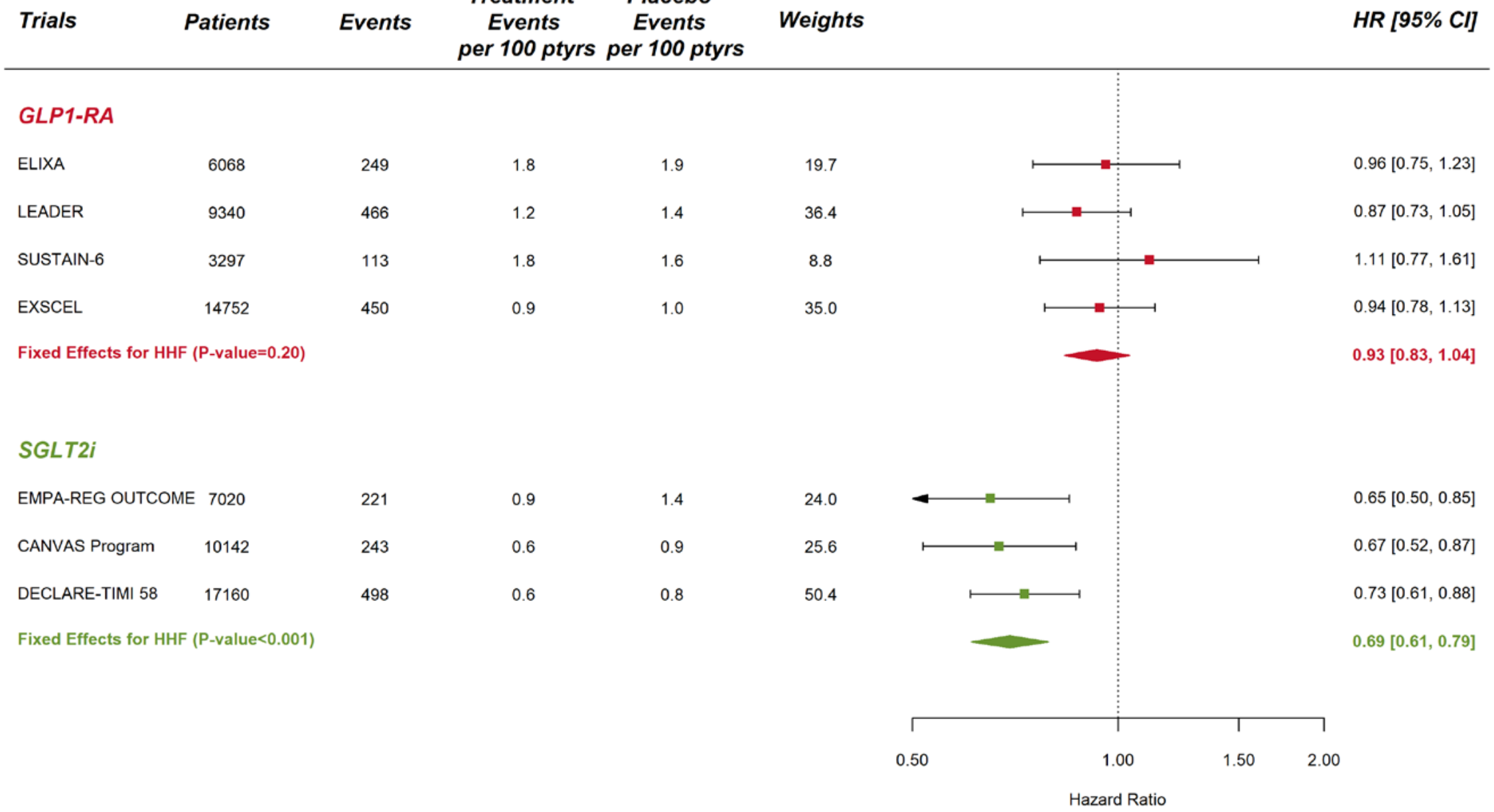
	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
SGLT2 : SGLT1 selectivity	>2500	>250	>1200	>2000
Glycaemic efficacy (glycated haemoglobin, %)	-0.77	-0.88	-0.84	-0.8 to -1.2
Weight change, kg	-2.5	-3.7	-2.9	-3.0
Systolic blood pressure /diastolic blood pressure, mmHg	-5.2/-1.6	-4.7/-1.8	-5.1/-1.8	-4.0/
3P-MACE	↓	↓↓	-	-
HHF	↓↓	↓↓	↓↓↓	↓↓
CV death	↓↓↓	-	-	-
All-cause mortality	↓↓↓	-	-	-
Renal outcomes	↓↓	↓↓	↓↓	↓
Risk of amputation	-	↑↑	-	↑
Bone fractures	-	↑	-	-
Diabetic ketoacidosis	-	-	-	↑
Genitourinary infections	↑↑	↑↑	↑↑	↑↑
Volume depletion	↑	↑↑	↑	↑
Low-density lipoprotein- cholesterol	↑	↑	↑	↑
Hypoglycaemia	-	-	-	-
Acute kidney injury	-	-	↓↓	↓

- Empagliflozin is the only SGLT2i with proven CV and all-cause mortality benefit
- Dapagliflozin is the only SGLT2i with proven benefit in hospitalization for heart failure
- Canagliflozin is the only SGLT2i with proven MACE and CKD risk reduction & increased amputation and fracture risk
- Ertugliflozin has no unique attribute and has the least favorable benefit-risk profile c/w other agents in the class

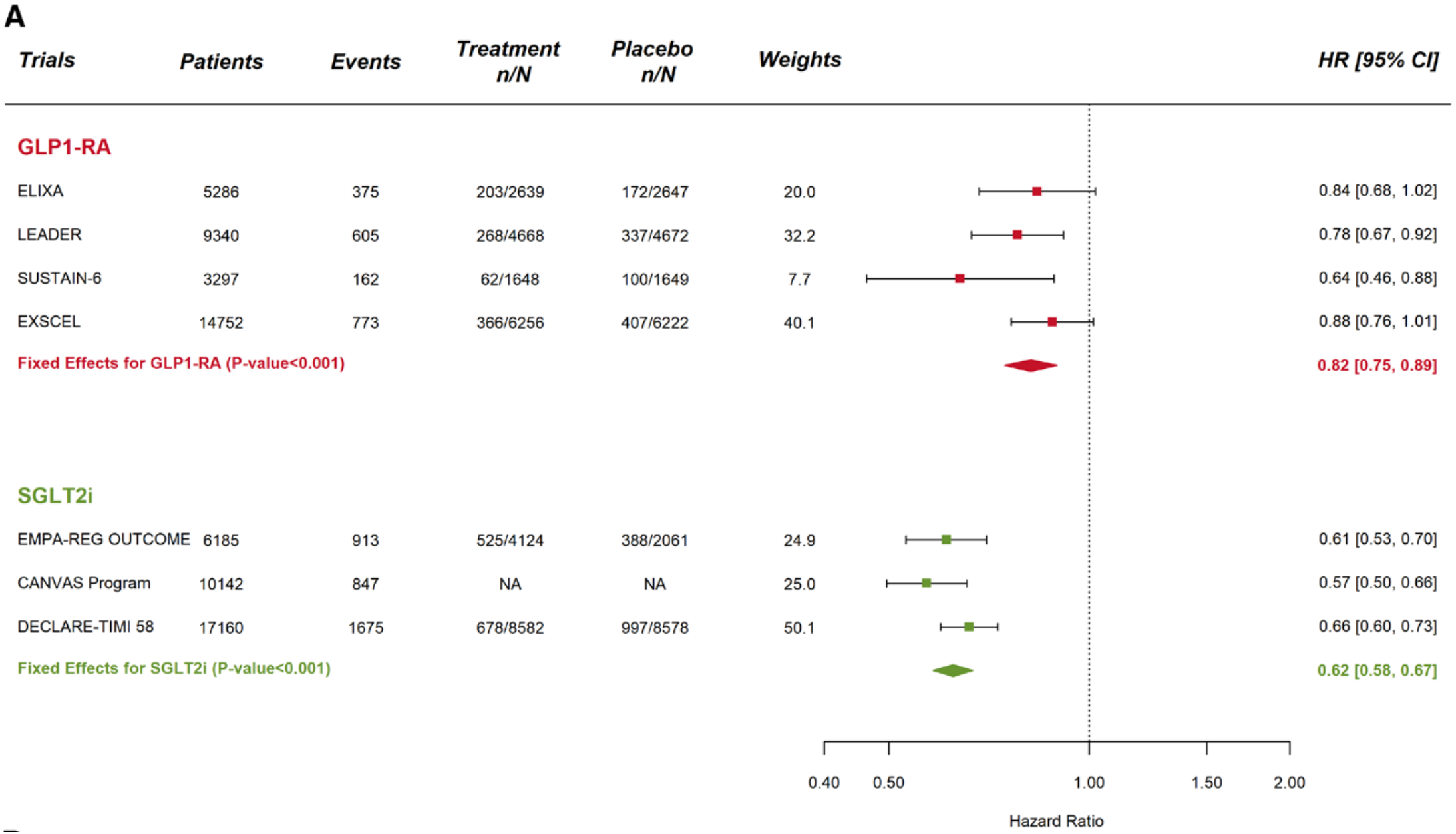
Meta-analysis of MACE (GLP-1 RA CVOTs)

Zelniker et al. Circulation 2019:2022





Meta-analysis of glucagon-like peptide 1 receptor agonist (GLP1-RA) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) trials on hospitalizationfor heart failure (HHF) stratified by drug class.



Meta-analysis of GLP1-RA and SGLT2i trials on hospitalization for a broad kidney end point (stratified by drug class).

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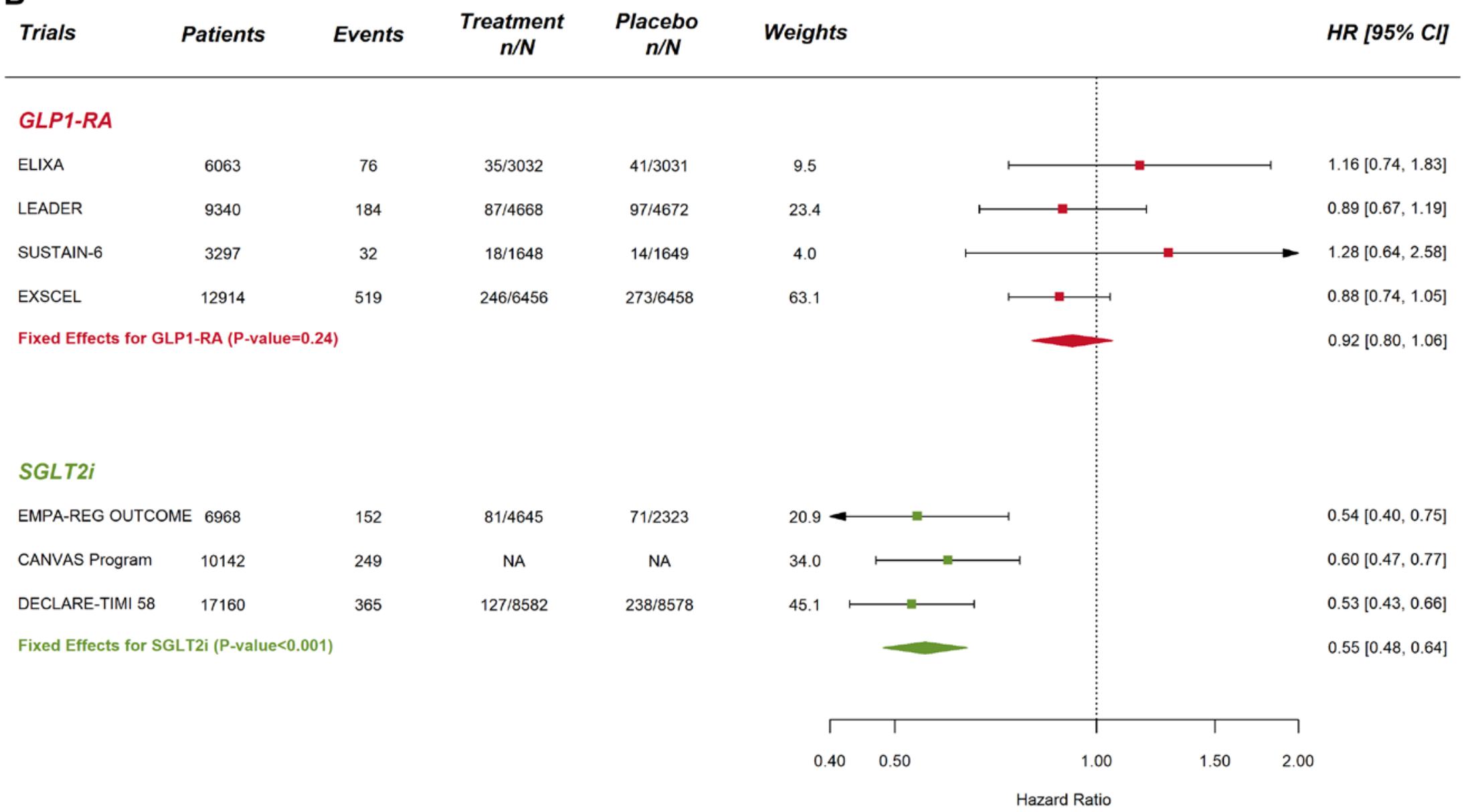


Meta-analysis of GLP1-RA and SGLT2i trials on a kidney outcome excluding macroalbuminuria stratified by drug class

HF trials
SGLT2i predominate

Impactful CVOTs of SGLT2 Inhibitors in HF with reduced EF

Quantity of Evidence

Trial	Endpoint	Outcome		Substantial evidence	FDA-approved indication
		HR (95% CI)	P value		
DAPA-HF, HFrEF (± T2D)	CVD or worsening HF (PEP)	0.74 (0.65, 0.85)	<0.001	Yes	No
	CVD, HHF	0.75 (0.65, 0.85)	<0.001	Yes	Yes
	CVD	0.82 (0.69, 0.98)	0.02*	No	Yes
	HHF	0.70 (0.59, 0.83)	<0.001	Yes	Yes
	Renal composite	0.71 (0.44, 1.16)	0.17	No	No
	ACM	0.83 (0.71, 0.97)	0.02*	No	No
EMPEROR-Reduced, (± T2D)	CVD or HHF (PEP)	0.75 (0.65, 0.86)	<0.001	Yes	NA
	CVD	0.92 (0.75, 1.12)	ns	No	
	HHF (first event)	0.69 (0.59, 0.81)	<0.001	Yes	
	Total HHF (first + recurrent event)	0.70 (0.58, 0.85)	<0.001	Yes	
	Renal composite	0.52 (0.32, 0.77)	0.026*	No	
	ACM	0.92 (0.77, 1.10)	ns	No	

*exploratory due to hierarchical testing strategy

FDA label based on DAPA-HF: *"…to reduce the risk of cardiovascular death **and** hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA Class II-IV)"*

Dapagliflozin vs Empagliflozin in HF with reduced EF (DAPA-HF vs EMPEROR-Reduced)

Characteristic	DAPA-HF		EMPEROR-reduced		
	Dapagliflozin	Placebo	Empagliflozin	Placebo	
Number of participants	2373	2371	1863	1867	
Mean ± SD age, years	66.2 ± 11.0	66.5 ± 10.8	67.2 ± 10.8	66.5 ± 11.2	
Females	564 (23.8%)	545 (23.0%)	437 (23.5%)	456 (24.4%)	
NYHA Class					
II	1606 (67.7%)	1597 (67.4%)	1399 (75.1%)	1401 (75.0%)	
III	747 (31.5%)	751 (31.7%)	455 (24.4%)	455 (24.4%)	
IV	20 (0.8%)	23 (1.0%)	9 (0.5%)	11 (0.6%)	
Mean LVEF (%), mean ± SD	31.2 ± 6.7	30.9 ± 6.9	27.7 ± 6.0	27.2 ± 6.1	
NT-pro BNP, pg/ml, median (Q1-Q3)	1428 (857-2655)	1446 (857-2641)	1887 (1077-3429)	1926 (1153-3525)	
Medical history					
Hospitalization for HF	1124 (47.4%)	1127 (47.5%)	577 (31.0%)*	574 (30.7%)*	*≤ 1yr (27.3% in DAPA-HF)
Diabetes**	1075 (45.3%)	1064 (44.9%)	927 (49.8%)	929 (49.8%)	
Mean ± SD eGFR, ml/min/1.73 m^2 ***	66.0 ± 19.6	65.5 ± 19.3	61.8 ± 21.7	62.2 ± 21.5	
Heart failure medications					
ACE inhibitor	1332 (56.1%)	1329 (56.1%)	867 (46.5%)	836 (44.8%)	
ARB	675 (28.4%)	632 (26.7%)	451 (24.2%)	457 (24.5%)	
MRA	1696 (71.5%)	1674 (70.6%)	1306 (70.1%)	1355 (72.6%)	
ARNI	250 (10.5%)	258 (10.9%)	340 (18.3%)	387 (20.7%)	
Device therapy					
ICD or CRT-D	622 (26.2%)	620 (26.1%)	578 (31.0%)	593 (31.8%)	
CRT-D or CRT-P	190 (8.0%)	164 (6.9%)	220 (11.8%)	222 (11.9%)	

Higher risk cohort enrolled in EMPEROR-Reduced c/w DAPA-HF

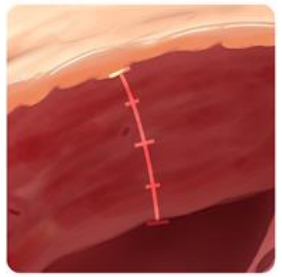
Dapagliflozin vs Empagliflozin in HF with reduced EF (DAPA-HF vs EMPEROR-Reduced)

Variable	DAPA-HF (56% Ischemic CMP)		EMPEROR-Reduced (52% Isch CMP)	
	Dapa	Placebo	Empa	Placebo
Number	2371	2373	1863	1867
Follow-up (median, y)	18.2m	18.2m	16m	16m
CV death/worsening HF (PEP in DAPA-HF)	386 (16.3%) 11.6/100PY	502 (21.2%) **15.6**/1000PY	NA	NA
	HR 0.74, 0.65-0.85, P<0.001		NA	
CV death/HHF (PEP in EMPEROR-Reduced)	382 (16.1%) 11.4/100PY	495 (20.9%) **15.3**/1000PY	361 (19.4%) 15.8/100PY	462 (24.7%) **21.0**/1000PY
	HR 0.75, 0.65-0.85, P<0.001		HR 0.75, 0.65-0.86, P<0.001	
CV death	227 (9.6%) 6.5/100PY	273 (11.5%) **7.9**/100PY	187 (10.0%) 7.6/100PY	202 (10.8%) **8.1**/1000PY
	HR 0.82, 0.69-0.98		HR 0.92, 0.75-1.12	
HHF	231 (9.7%) 6.9/100PY	318 (13.4%) **9.8**/100PY	246 (13.2%) 10.7/100PY	342 (18.3%) **15.5**/1000PY
	HR 0.70, 0.58-0.93		HR 0.69, 0.59-0.81	

Enrichment strategy in EMPEROR-Reduced amplified HHF but not CV death

Dapagliflozin vs Empagliflozin in HF with reduced EF (DAPA-HF vs EMPEROR-Reduced)

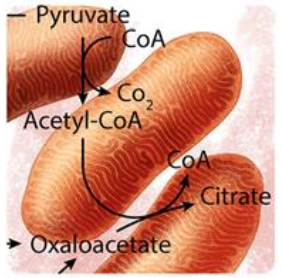
Variable	DAPA-HF (56% Ischemic CMP)		EMPEROR-Reduced (52% Isch CMP)	
	Dapa	Placebo	Empa	Placebo
Number	2371	2373	1863	1867
All-cause mortality	276 (11.6%) 7.9/100PY	329 (13.9%) **9.5**/100PY	249 (13.4%) 10.1/100PY	266 (14.2%) **10.7**/100PY
	HR 0.83, 0.71-0.97		HR 0.92, 0.77-1.10	
Renal composite	28 (1.2%) 0.8/100PY	39 (1.6%) **1.2**/100PY	30 (1.6%) 1.6/100PY	58 (3.1%) **3.1**/100PY
	HR 0.71, 0.44-1.16		HR 0.50, 0.32-0.77	
Change in KCCQ, 8m/52w	6.1 (18.6)	**3.3** (19.2)	5.8 (0.4)	**4.1** (0.4)
	WR 1.18 (1.11-1.26), P<0.001		RD 1.70 (0.5-3.0)	



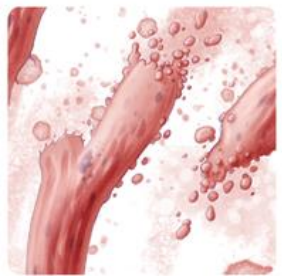
Left ventricle hypertro

↑ Cytokines and inflammation

ECM remodelling



Impaired cardiac metabolism



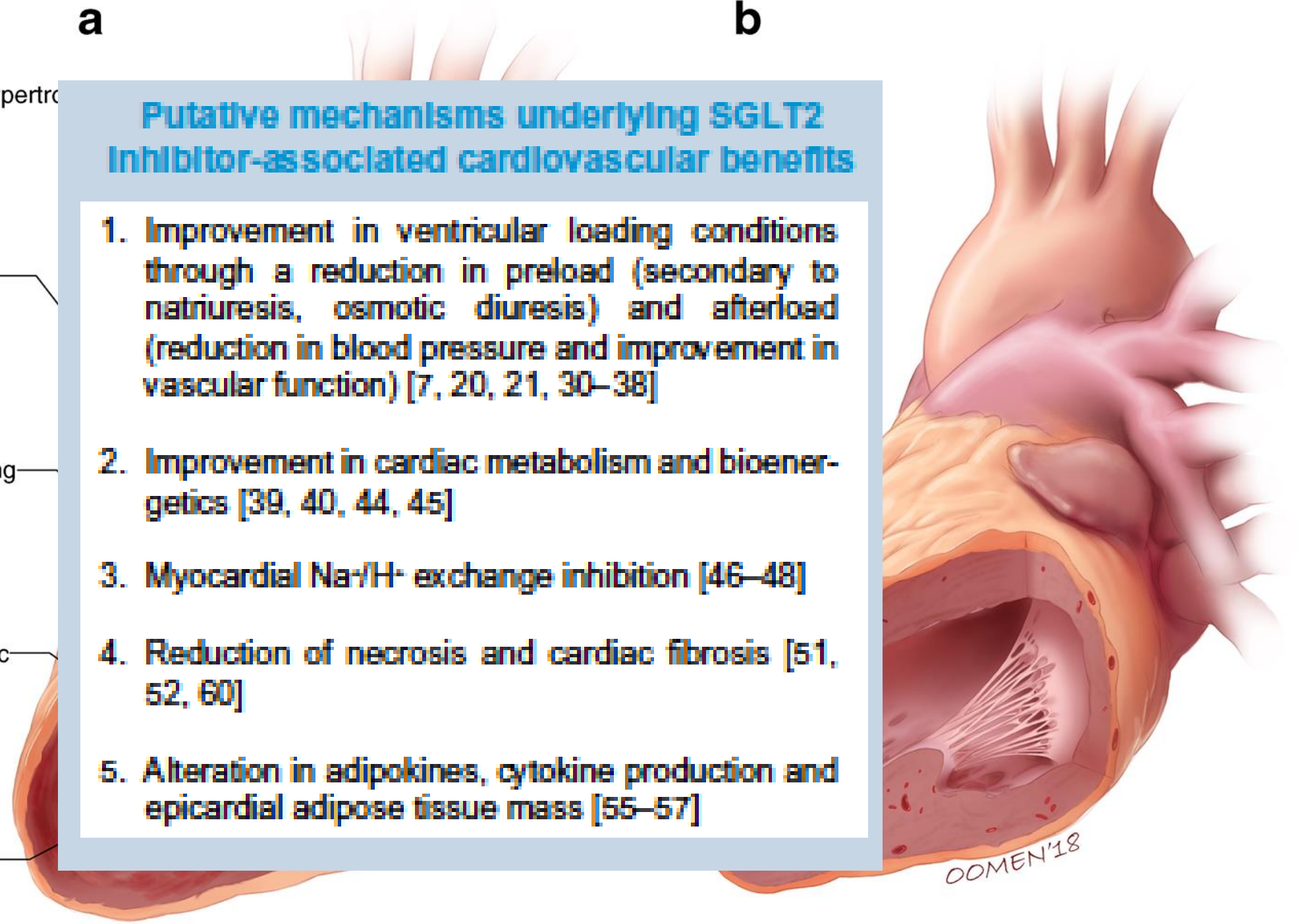
CMC apoptosis

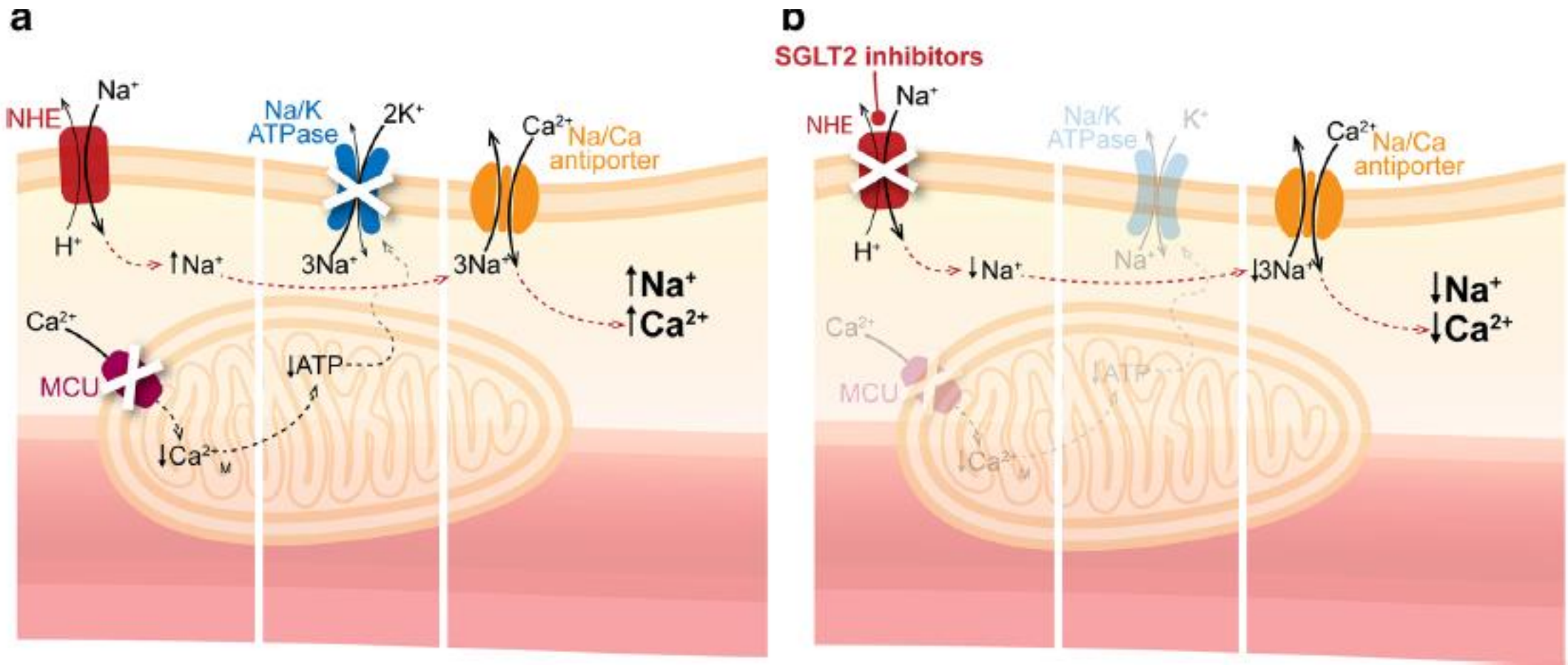
a

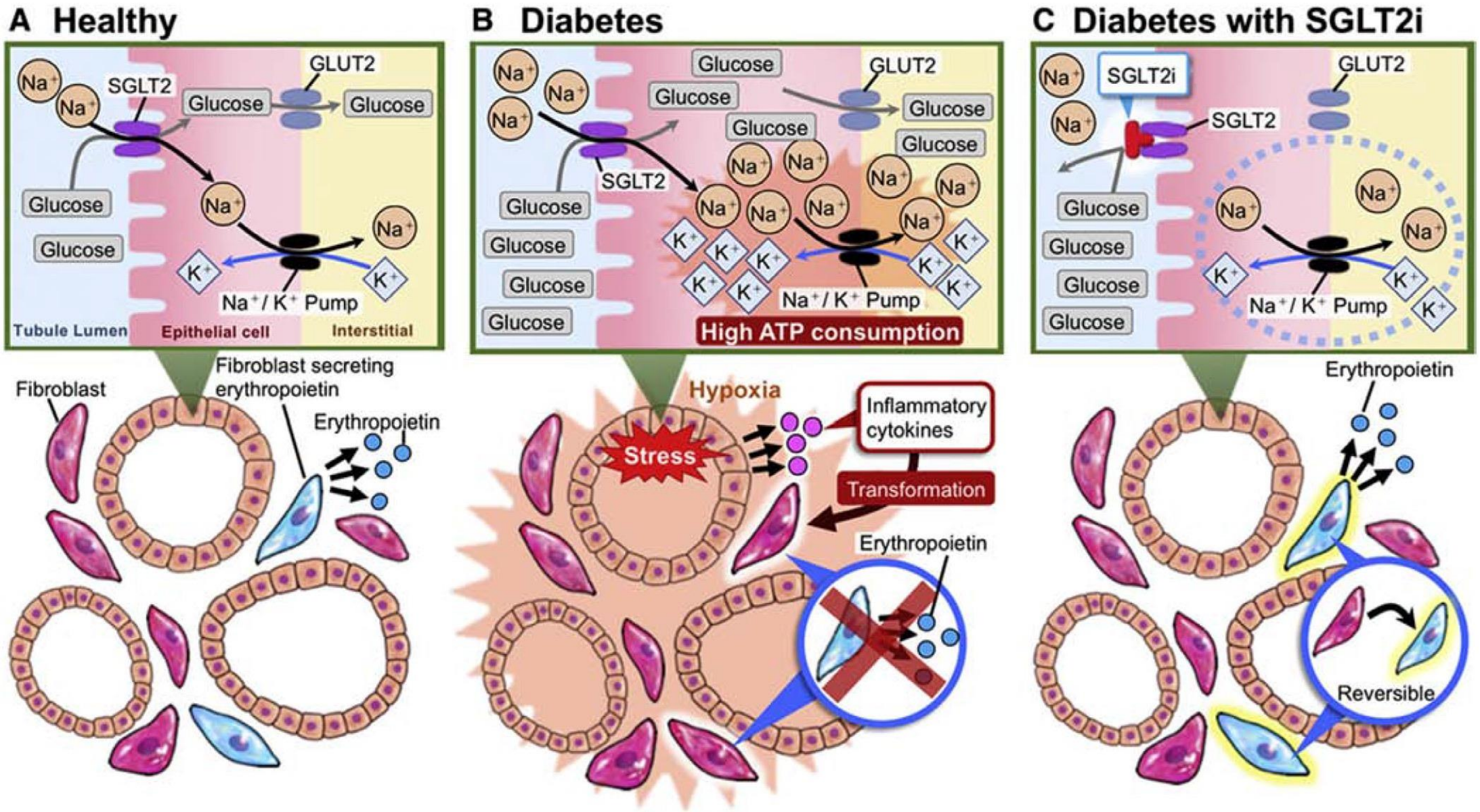
b

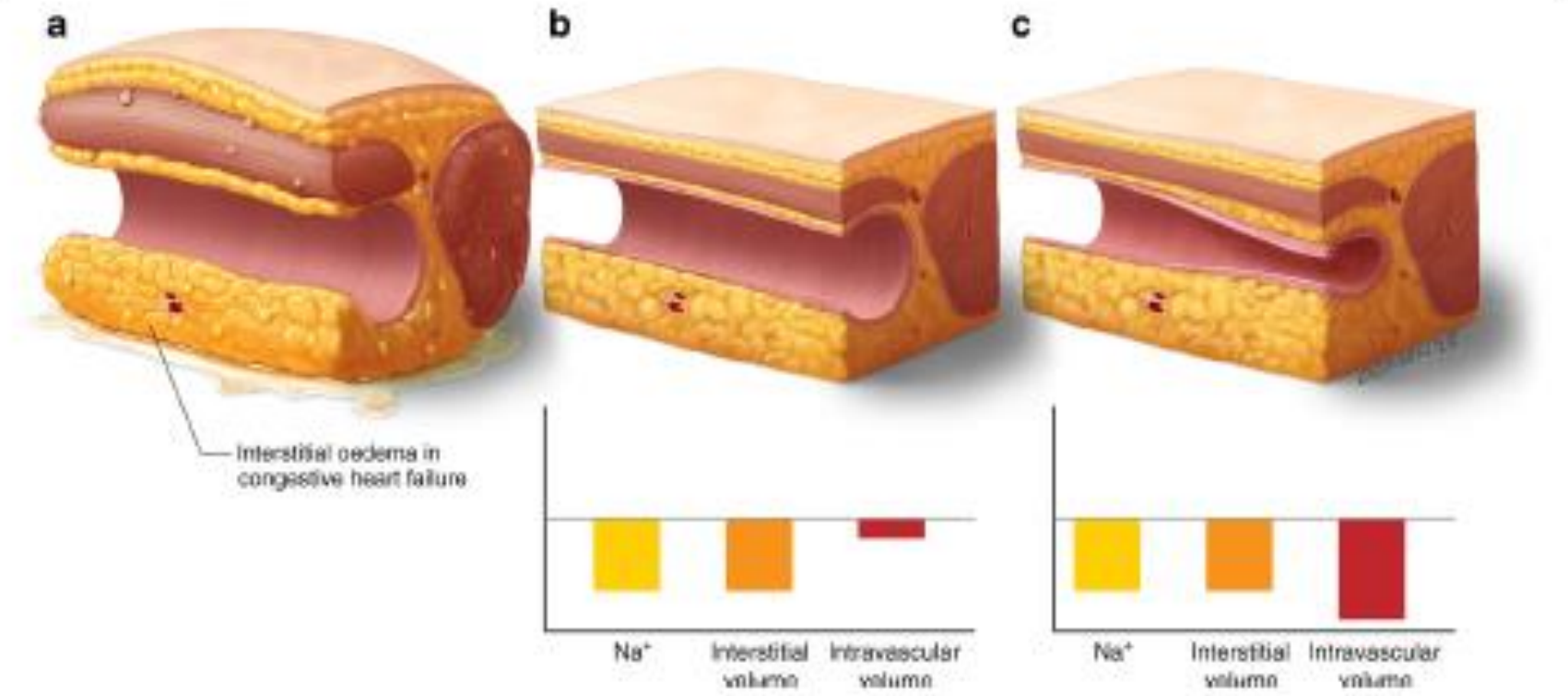
Putative mechanisms underlying SGLT2 inhibitor-associated cardiovascular benefits

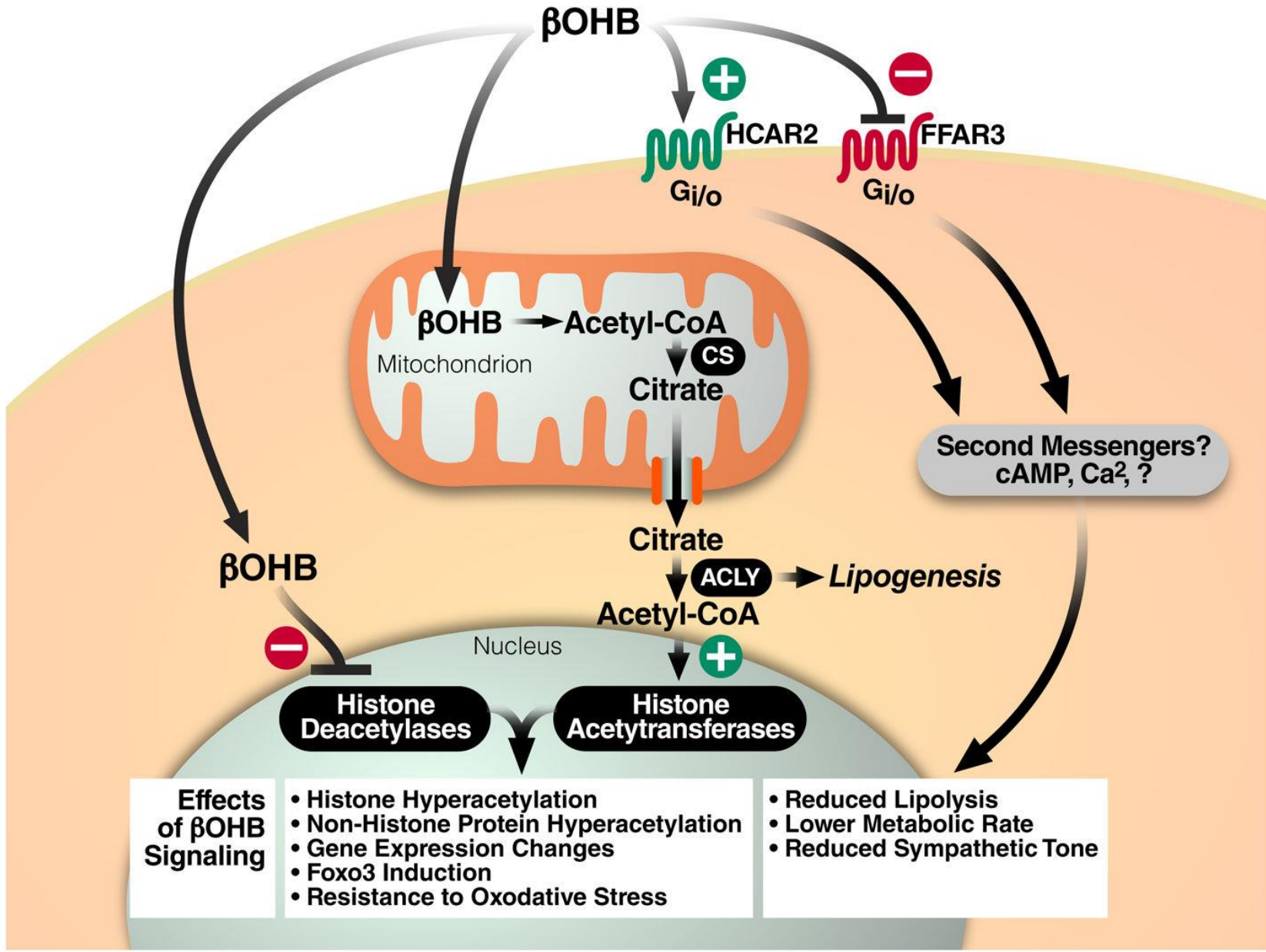
1. Improvement in ventricular loading conditions through a reduction in preload (secondary to natriuresis, osmotic diuresis) and afterload (reduction in blood pressure and improvement in vascular function) [7, 20, 21, 30–38]
2. Improvement in cardiac metabolism and bioenergetics [39, 40, 44, 45]
3. Myocardial Na^+/H^+ exchange inhibition [46–48]
4. Reduction of necrosis and cardiac fibrosis [51, 52, 60]
5. Alteration in adipokines, cytokine production and epicardial adipose tissue mass [55–57]




a
NHE
Na+
H+
↑Na+
Na/K
ATPase
2K+
3Na+
Ca2+
Na/Ca
antiporter
3Na+
↑Na+
↑Ca2+
Ca2+
MCU
↓Ca2+M
↓ATP
b
SGLT2 inhibitors
NHE
Na+
H+
↓Na+
Na/K
ATPase
K+
Na+
Ca2+
Na/Ca
antiporter
↓3Na+
↓Na+
↓Ca2+
Ca2+
MCU
↓Ca2+M
↓ATP


A Healthy
B Diabetes
C Diabetes with SGLT2i
Na+
SGLT2
Glucose
GLUT2
Na+ / K+ Pump
Tubule Lumen
Epithelial cell
Interstitial
High ATP consumption
SGLT2i
Fibroblast
Fibroblast secreting erythropoietin
Erythropoietin
Hypoxia
Stress
Inflammatory cytokines
Transformation
Reversible


a
b
c
Interstitial oedema in congestive heart failure
Na+
Interstitial volume
Intravascular volume
Na+
Interstitial volume
Intravascular volume

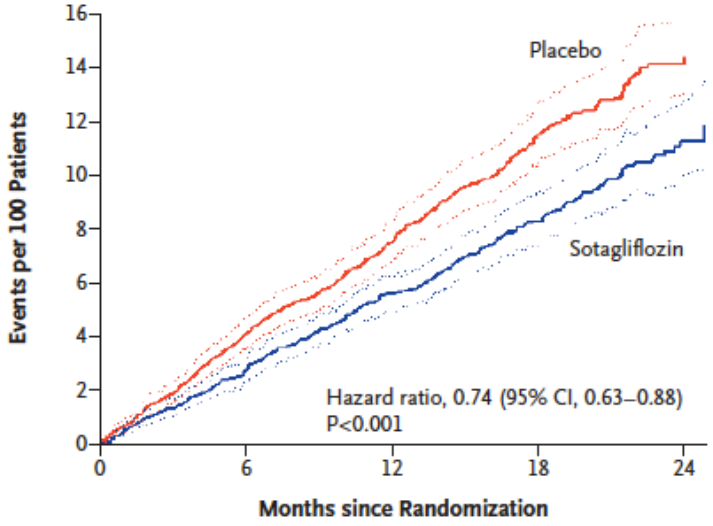

βOHB
HCAR2
Gi/o
FFAR3
Gi/o
βOHB
Acetyl-CoA
CS
Mitochondrion
Citrate
Second Messengers?
cAMP, Ca2, ?
Citrate
βOHB
ACLY
Lipogenesis
Acetyl-CoA
Nucleus
Histone Deacetylases
Histone Acetytransferases
Effects of βOHB Signaling
• Histone Hyperacetylation
• Non-Histone Protein Hyperacetylation
• Gene Expression Changes
• Foxo3 Induction
• Resistance to Oxodative Stress
• Reduced Lipolysis
• Lower Metabolic Rate
• Reduced Sympathetic Tone

New Positive Data on HF outcomes on Sotagliflozin in non macroalbuminuric CKD and recent worsening of HF (rEF and pEF) : SCORED and SOLOIST-WHF. Does SGLT1 inhibition matters??

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

Deepak L. Bhatt, M.D., M.P.H., Michael Szarek, Ph.D., Bertram Pitt, M.D., Christopher P. Cannon, M.D., Lawrence A. Leiter, M.D., Darren K. McGuire, M.D., M.H.Sc., Julia B. Lewis, M.D., Matthew C. Riddle, M.D., Silvio E. Inzucchi, M.D., Mikhail N. Kosiborod, M.D., David Z.I. Cherney, M.D., Ph.D., Jamie P. Dwyer, M.D., Benjamin M. Scirica, M.D., M.P.H., Clifford J. Bailey, Ph.D., Rafael Díaz, M.D., Kausik K. Ray, M.D., Jacob A. Udell, M.D., M.P.H., Renato D. Lopes, M.D., Ph.D., Pablo Lapuerta, M.D., and P. Gabriel Steg, M.D., for the SCORED Investigators*

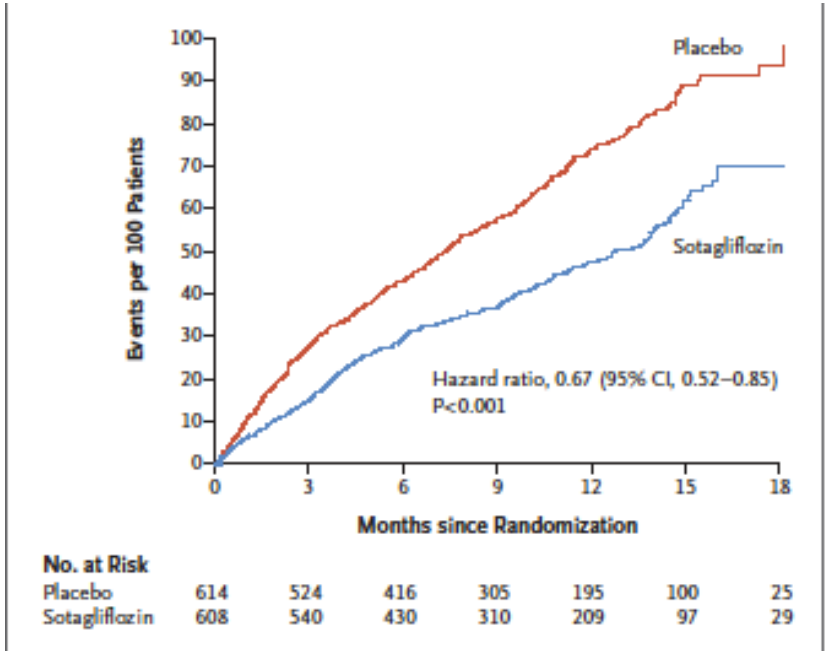


No. at Risk					
Placebo	5292	5160	3914	2061	441
Sotagliflozin	5292	5197	3965	2085	444

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

D.L. Bhatt, M. Szarek, P.G. Steg, C.P. Cannon, L.A. Leiter, D.K. McGuire, J.B. Lewis, M.C. Riddle, A.A. Voors, M. Metra, L.H. Lund, M. Komajda, J.M. Testani, C.S. Wilcox, P. Ponikowski, R.D. Lopes, S. Verma, P. Lapuerta, and B. Pitt, for the SOLOIST-WHF Trial Investigators*



No. at Risk							
Placebo	614	524	416	305	195	100	25
Sotagliflozin	608	540	430	310	209	97	29

CKD trials
SGLT2i predominate

Impactful Cardiorenal Outcome Trials of SGLT2 Inhibitors

Key Quality Attributes

Trial	% with eCVD/HF	Type	Blind	Power (1-β)	MDD (δ)	Missing data	Prematurely stopped
CREDENCE, Diabetic CKD (N=4,401)	50.4%/14.8%	Superiority	DB	90%	HR 0.80	0.9% (0.1%*)	Yes (1st interim analysis: 405 out of 844 events)
DAPA-CKD, CKD (± T2D) (N=4,304)	37.4%/10.8%	Superiority	DB	90%	HR 0.78	0.3% (0.1%*)	Yes (Unplanned interim analysis: 408 out of 681 events)

*Vital status

Key attributes of SGLT2 inhibitor CVOT design support the strength and quality of the data except for premature truncation of both trials

Impactful Cardiorenal Outcome Trials of SGLT2 Inhibitors

Key Baseline Data

Trial	N	Median F/U, y	No. of PEP Events, Planned/ Accrued	Age, y	% CVD	% DM	% HF	UACR, mg/g	eGFR ml/min/ 1.73m^2	PEP IR, placebo*
CREDENCE	4401	2.6	844/585	63	50.4	100	14.8	927	56.2	61.2/1000 PY
DAPA-CKD	4304	2.4	681/509	61.8	37.4	67.5	10.8	950	43.1	75.0/1000 PY

PEP in CREDENCE is ESRD, doubling of serum creatinine (eGFR decline ≥57%), CV or renal death

PEP in DAPA-CKD is ESRD, eGFR decline ≥50%, CV or renal death

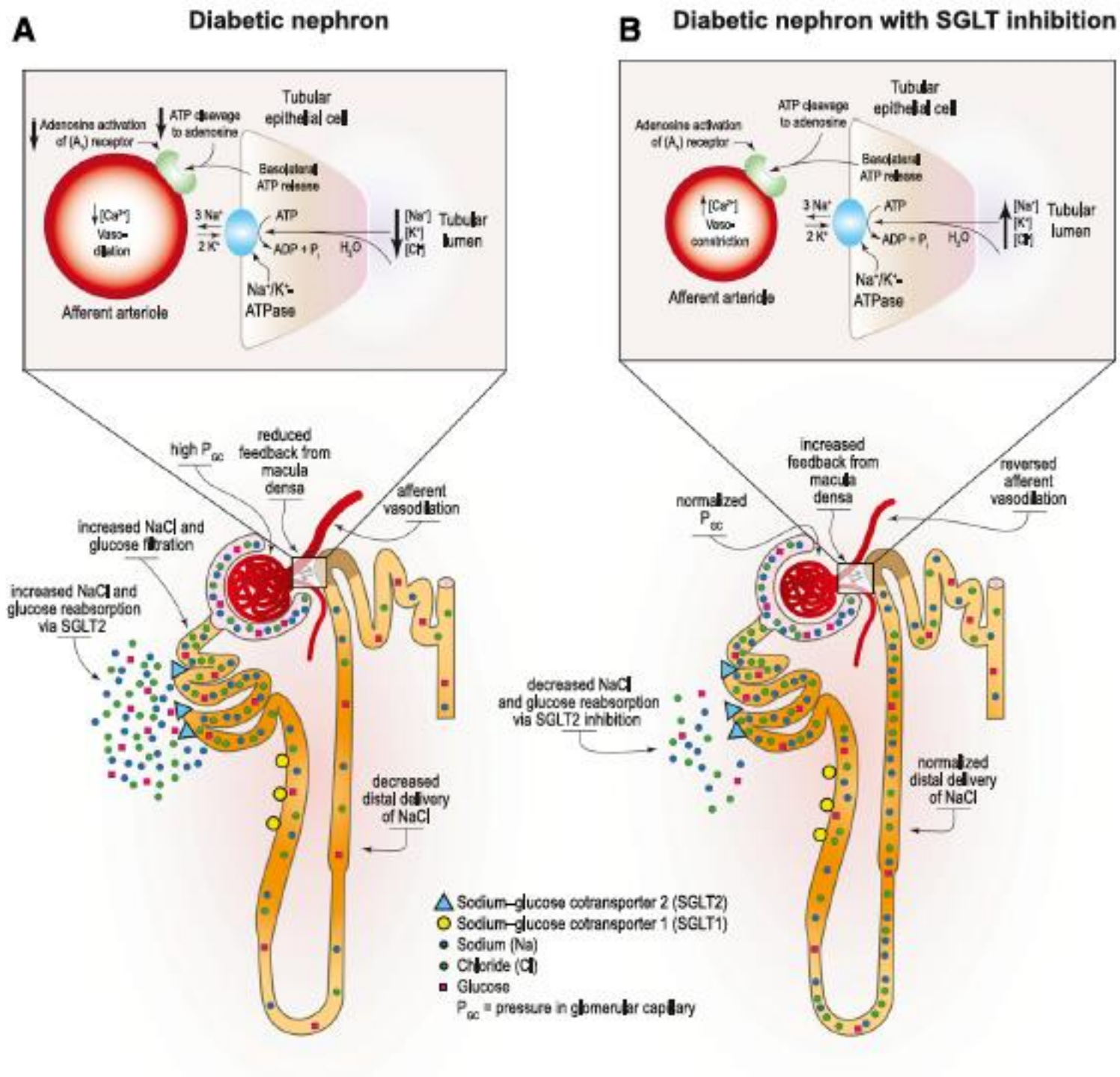
Impactful Cardiorenal Outcome Trials of SGLT2 Inhibitors

Quantity of Evidence

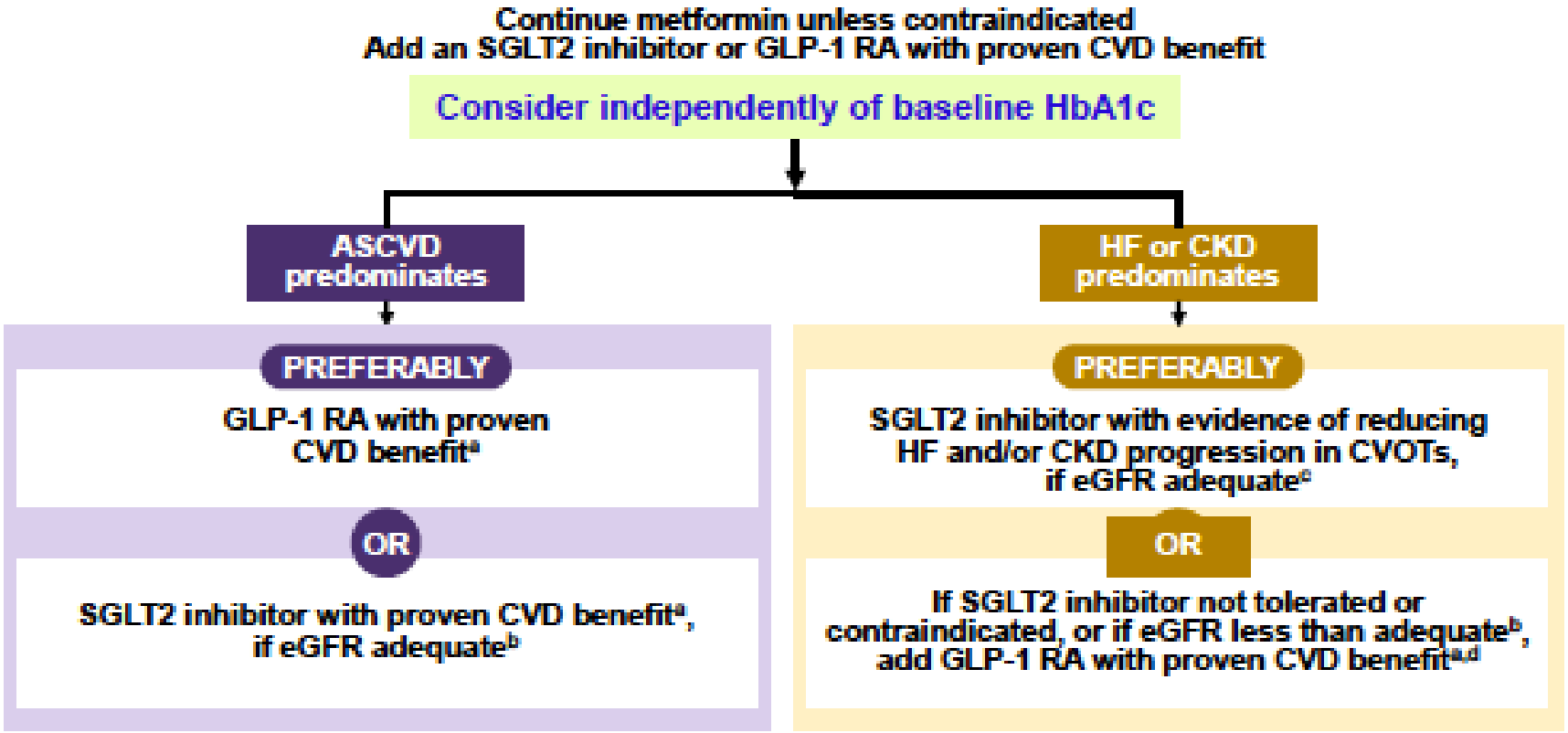
Trial	Endpoint	Outcome		Substantial evidence	FDA-approved indication
		HR (95% CI)	P value		
CREDENCE, Diabetic CKD (N=4,401)	ESRD, Cr x 2, CV or renal death (PEP)	0.70 (0.59, 0.82)	0.00001	Yes	Yes
	CV death, HHF	0.69 (0.57, 0.83)	<0.001	Yes	Yes
	HHF	0.61 (0.47, 0.80)	<0.001	Yes	Yes
	CV death	0.78 (0.61, 1.00)	0.05	No	No
	ACM	0.83 (0.68, 1.02)	ns*	No	No
DAPA-CKD, CKD (± T2D) (N=4,304)	ESRD, eGFR >50%, CV or renal death (PEP)	0.61 (0.51, 0.72)	<0.001	Yes	NA
	CVD, HHF	0.71 (0.55, 0.92)	0.009	Maybe	
	CVD	0.81 (0.58, 1.12)	0.21*	No	
	ACM	0.69 (0.53, 0.88)	0.004*	No	
	Non-CV death	0.55 (0.37, 0.82)	0.002*	No	

*Not applicable due to hierarchical testing strategy

FDA label based on CREDENCE: *"…to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria"*


A
Diabetic nephron
Adenosine activation of (A1) receptor
ATP cleavage to adenosine
Tubular epithelial cell
Basolateral ATP release
↓[Ca2+] Vaso-dilation
3 Na+
2 K+
ATP
ADP + Pi
H2O
[Na+] [K+] [Cl-]
Tubular lumen
Na+/K+-ATPase
Afferent arteriole
high Pgc
reduced feedback from macula densa
afferent vasodilation
increased NaCl and glucose filtration
increased NaCl and glucose reabsorption via SGLT2
decreased distal delivery of NaCl
B
Diabetic nephron with SGLT inhibition
Adenosine activation of (A1) receptor
ATP cleavage to adenosine
Tubular epithelial cell
Basolateral ATP release
↑[Ca2+] Vaso-constriction
3 Na+
2 K+
ATP
ADP + Pi
H2O
[Na+] [K+] [Cl-]
Tubular lumen
Na+/K+-ATPase
Afferent arteriole
increased feedback from macula densa
reversed afferent vasodilation
normalized Pgc
decreased NaCl and glucose reabsorption via SGLT2 inhibition
normalized distal delivery of NaCl
Sodium–glucose cotransporter 2 (SGLT2)
Sodium–glucose cotransporter 1 (SGLT1)
Sodium (Na)
Chloride (Cl)
Glucose
Pgc = pressure in glomerular capillary

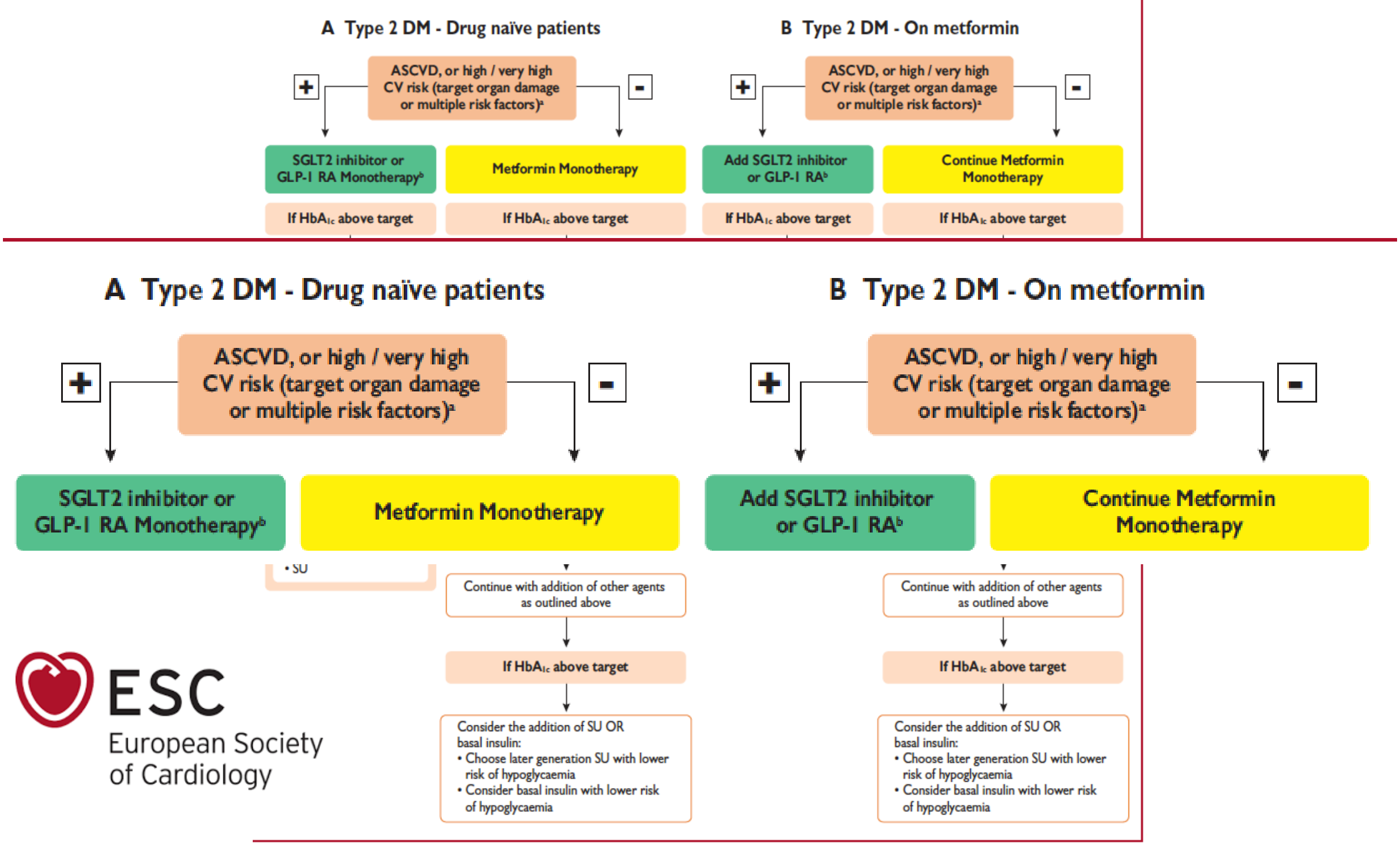
ADA-EASD 2020 consensus report



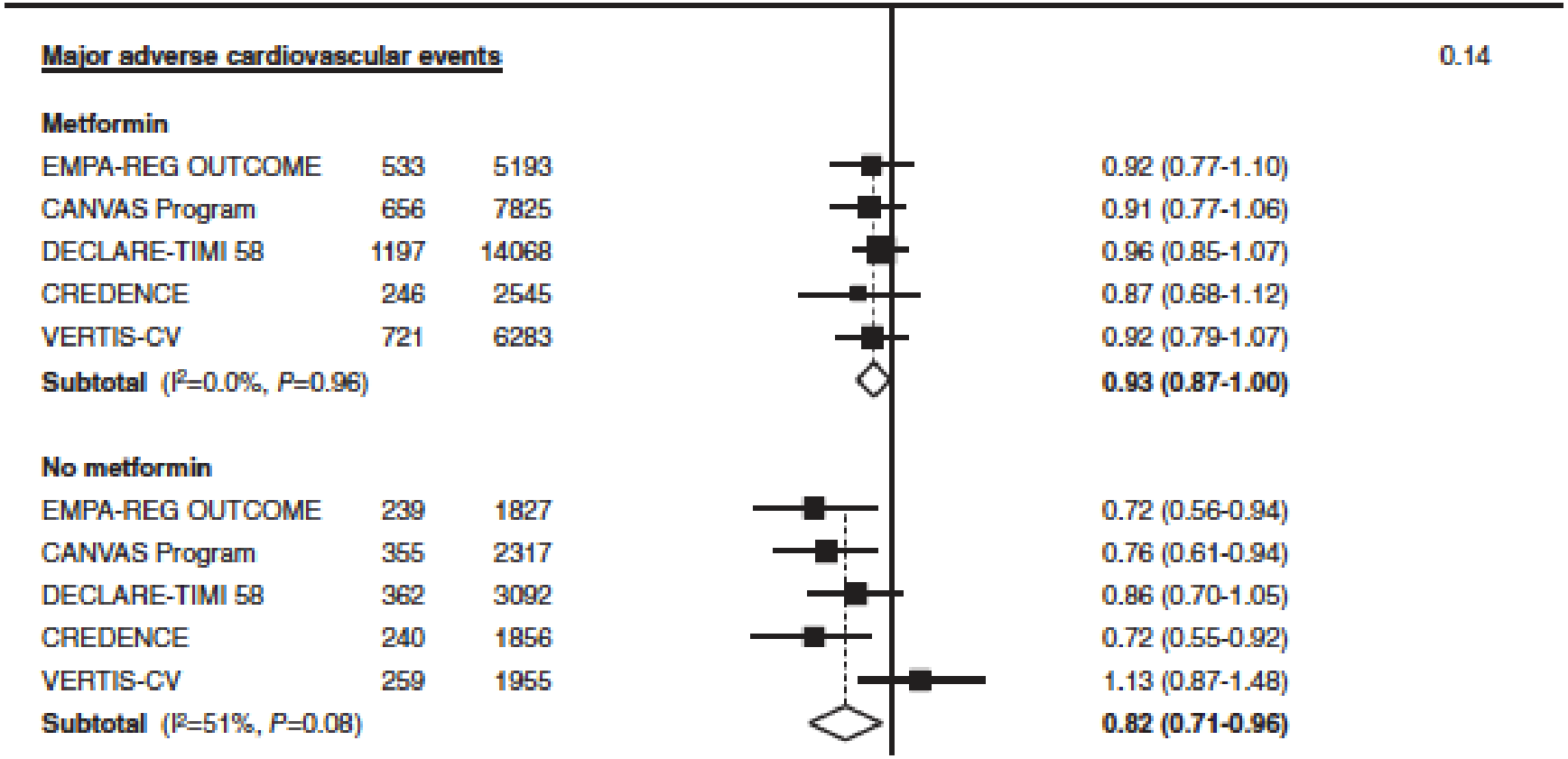
[a]Proven CVD benefit refers to a label indication of reducing CVD events; [b]Be aware that SGLT2 inhibitors vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; [c]Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF; [d]Caution with GLP-1 RA in ESRD

ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; EASD, European Association for the Study of Diabetes; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2, sodium–glucose co-transporter 2

Buse JB, et al. *Diabetologia* 2020;63:221–228

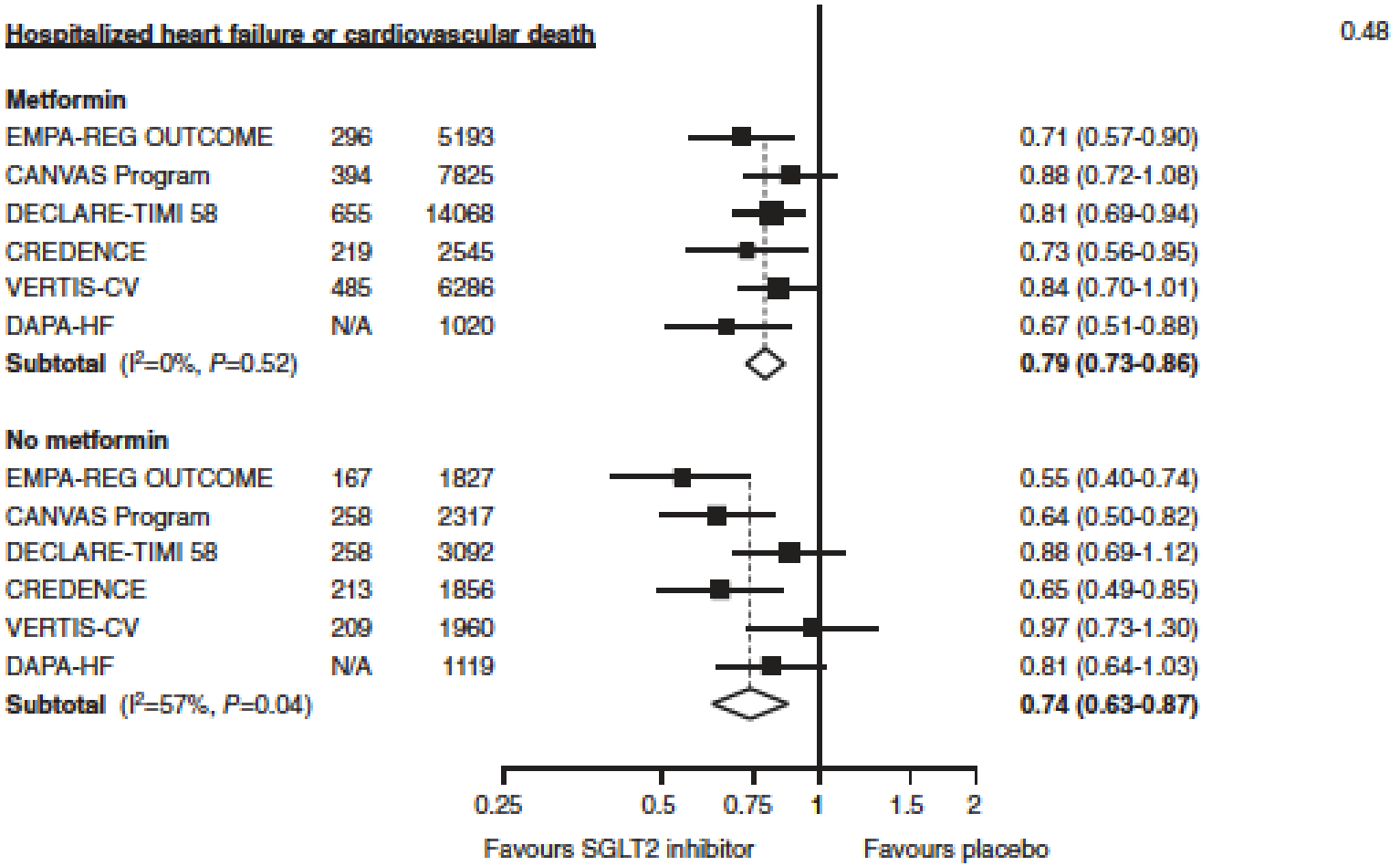

A Type 2 DM - Drug naïve patients
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]
+
-
SGLT2 inhibitor or GLP-1 RA Monotherapy[b]
Metformin Monotherapy
If HbA1c above target
If HbA1c above target
• SU
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU OR basal insulin:
• Choose later generation SU with lower risk of hypoglycaemia
• Consider basal insulin with lower risk of hypoglycaemia
B Type 2 DM - On metformin
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]
+
-
Add SGLT2 inhibitor or GLP-1 RA[b]
Continue Metformin Monotherapy
If HbA1c above target
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU OR basal insulin:
• Choose later generation SU with lower risk of hypoglycaemia
• Consider basal insulin with lower risk of hypoglycaemia
ESC
European Society of Cardiology

Metformin First in DM2 with ASCVD, hHF or CKD ???



Neuen,et al. SGLT2i with and without metformin: A meta-analysis of cardiovascular, kidney andmortality outcomes. Diabetes Obes Metab October 2020;1–9. DOI: 10.1111/dom.14226

Metformin First in DM2 with ASCVD, hHF or CKD ???



Neuen,et al. SGLT2i with and without metformin: A meta-analysis of cardiovascular, kidney andmortality outcomes. Diabetes Obes Metab October 2020;1–9. DOI: 10.1111/dom.14226

EXPERT CONSENSUS DECISION PATHWAY

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

A Report of the American College of Cardiology Solution Set Oversight Committee

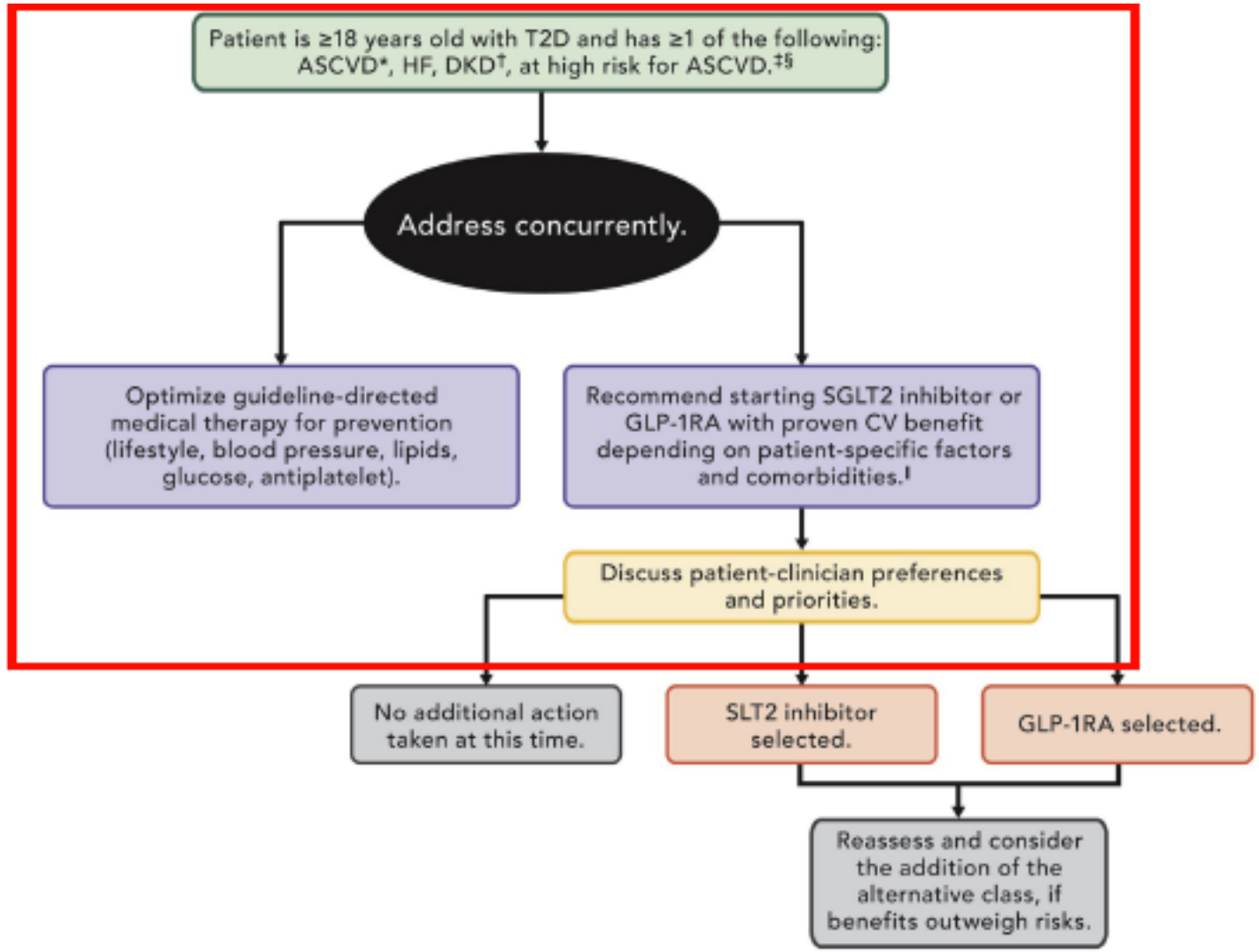
Endorsed by the American Diabetes Association

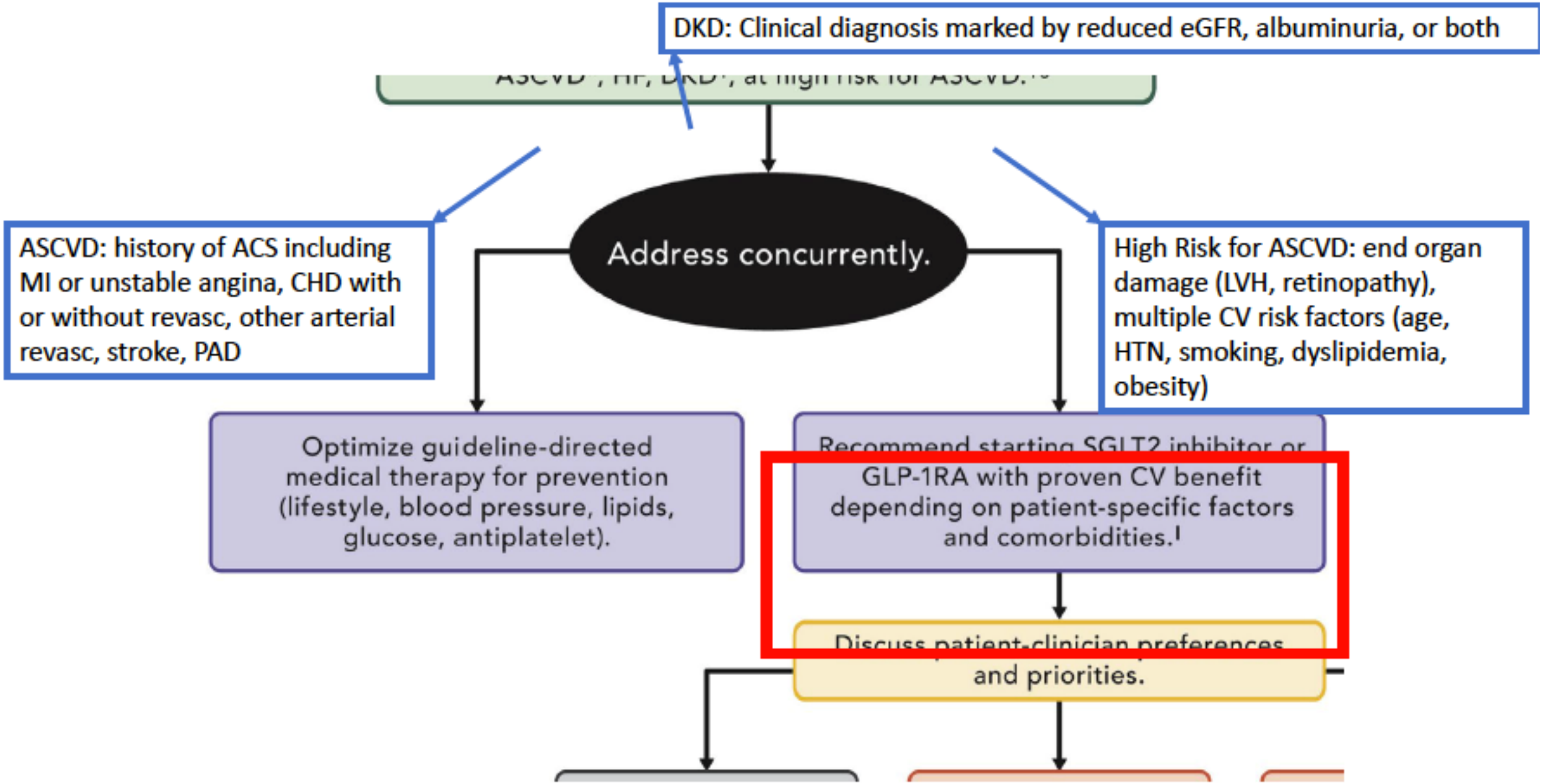
Writing Committee

Sandeep R. Das, MD, MPH, FACC, *Co-Chair*
Brendan M. Everett, MD, MPH, FACC, *Co-Chair*

Kim K. Birtcher, PharmD, MS, CDE, AACC
Jenifer M. Brown, MD
James L. Januzzi, Jr, MD, FACC
Rita R. Kalyani, MD, MHS
Mikhail Kosiborod, MD, FACC
Melissa Magwire, RN, MSN, CDE
Pamela B. Morris, MD, FACC
Joshua J. Neumiller, PharmD, CDCES
Laurence S. Sperling, MD, FACC

Journal of the American College of Cardiology. 2020. pp. 1117–45.


Patient is ≥18 years old with T2D and has ≥1 of the following: ASCVD*, HF, DKD†, at high risk for ASCVD.‡§
Address concurrently.
Optimize guideline-directed medical therapy for prevention (lifestyle, blood pressure, lipids, glucose, antiplatelet).
Recommend starting SGLT2 inhibitor or GLP-1RA with proven CV benefit depending on patient-specific factors and comorbidities.‖
Discuss patient-clinician preferences and priorities.
No additional action taken at this time.
SLT2 inhibitor selected.
GLP-1RA selected.
Reassess and consider the addition of the alternative class, if benefits outweigh risks.


DKD: Clinical diagnosis marked by reduced eGFR, albuminuria, or both
ASCVD: history of ACS including MI or unstable angina, CHD with or without revasc, other arterial revasc, stroke, PAD
Address concurrently.
High Risk for ASCVD: end organ damage (LVH, retinopathy), multiple CV risk factors (age, HTN, smoking, dyslipidemia, obesity)
Optimize guideline-directed medical therapy for prevention (lifestyle, blood pressure, lipids, glucose, antiplatelet).
GLP-1RA with proven CV benefit depending on patient-specific factors and comorbidities.
and priorities.

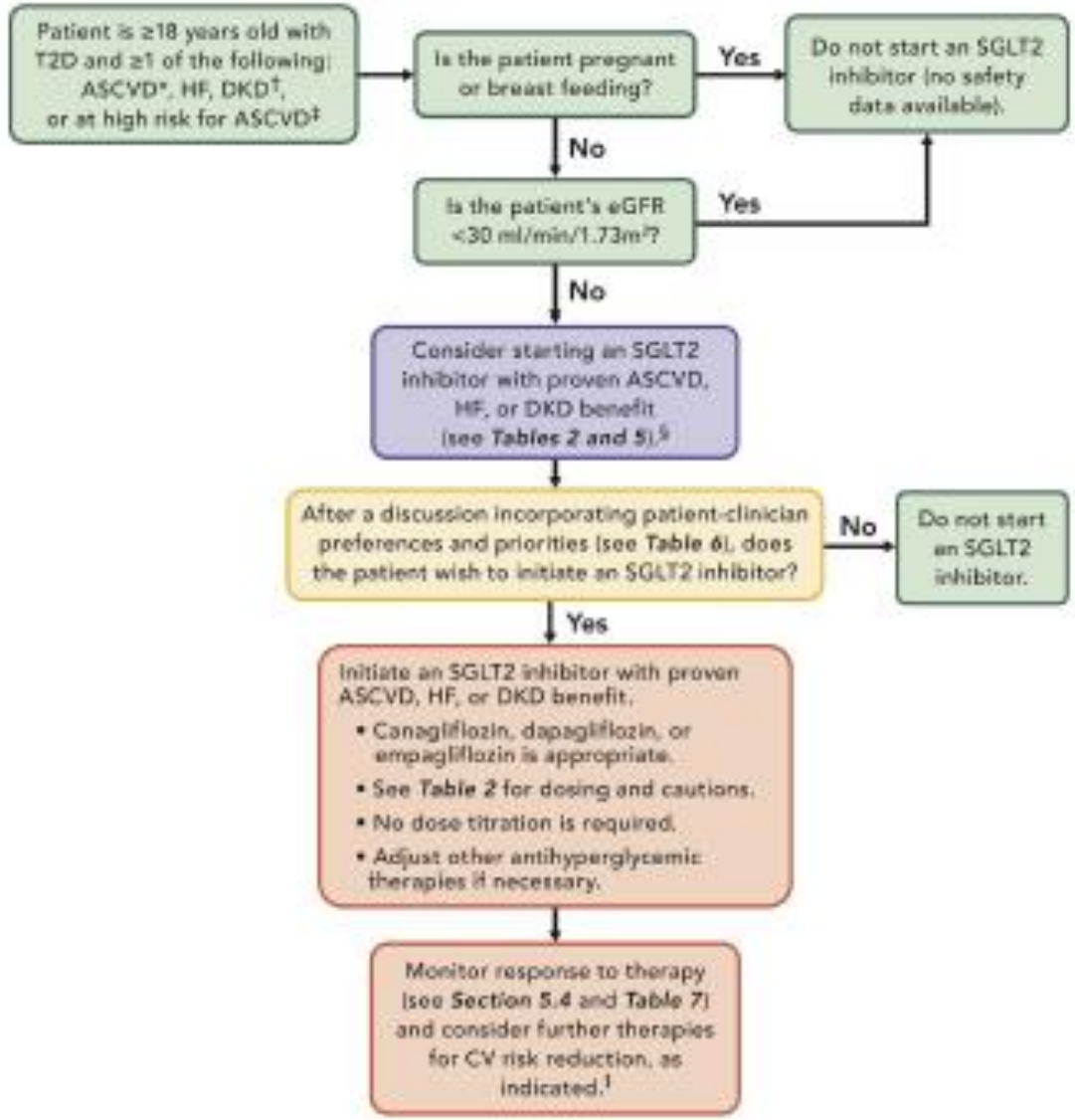
ACC Suggested Approach to Starting an SGLT2i

Indications
- ASCVD
- High risk for ASCVD
- Heart failure
- DKD

eGFR ≥ 30 ml/min/1.73m2

Recommended SGLT2i
- Canagliflozin 100 mg
- Dapagliflozin 10 mg
- Empagliflozin 10 mg
- No need to for dose titration

"Consider further therapies for CV risk reduction as indicated."

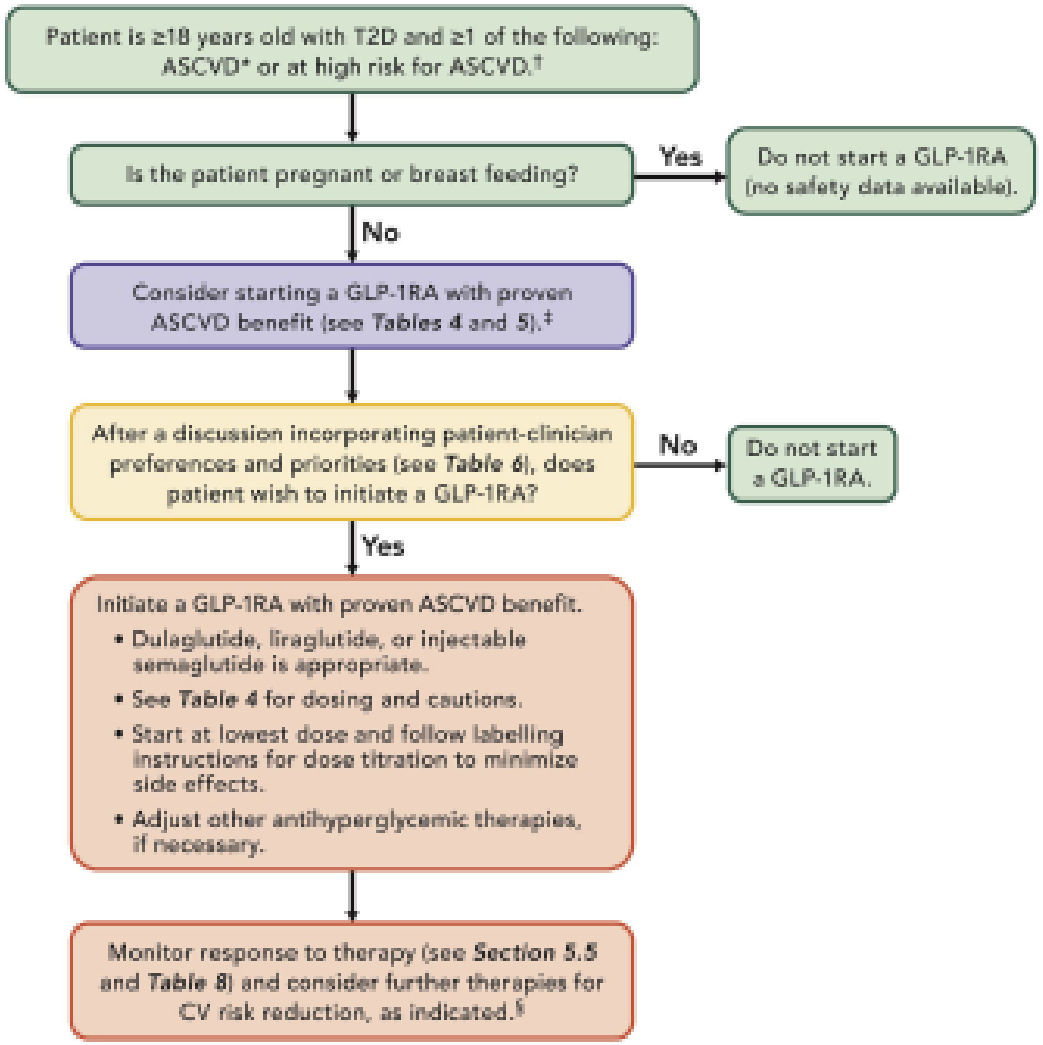


ACC Suggested Approach to Starting a GLP-1RA

Indications
- ASCVD
- High risk for ASCVD

Recommended GLP-1RA
- Dulaglutide
- Liraglutide
- Semaglutide (SC only)
- Start at the lowest dose and follow labelling instructions

"Consider further therapies for CV risk reduction as indicated."



How do we help clinicians and patients choose?

Patient or provider preference	SGLT2i	GLP-1RA
MACE Prevention	+++	+++
HF Prevention	+++	?
Weight Loss	+	+++
Renal Disease	+++	+
Mode of administration	Oral	Subcutaneous (semaglutide PO not yet recommended)
Considerations that may prompt the use of the alternative class	• Severely reduced renal function • History of prior amputation • History of recurrent genital fungal infection • History of DKA • History of fracture • Considering pregnancy or is breast feeding	• Persistent nausea • History of gastroparesis • Active gallbladder disease • History of MEN2 or medullary thyroid CA • History of proliferative retinopathy • Considering pregnancy or is breastfeeding

Das SR, Everett BM, et al. ACC ECDP JACC 2020. pp. 1117–45. doi: 10.1016/j.jacc.2020.05.037

SGLT2i or GLP1-RA?

ASCVD: either class

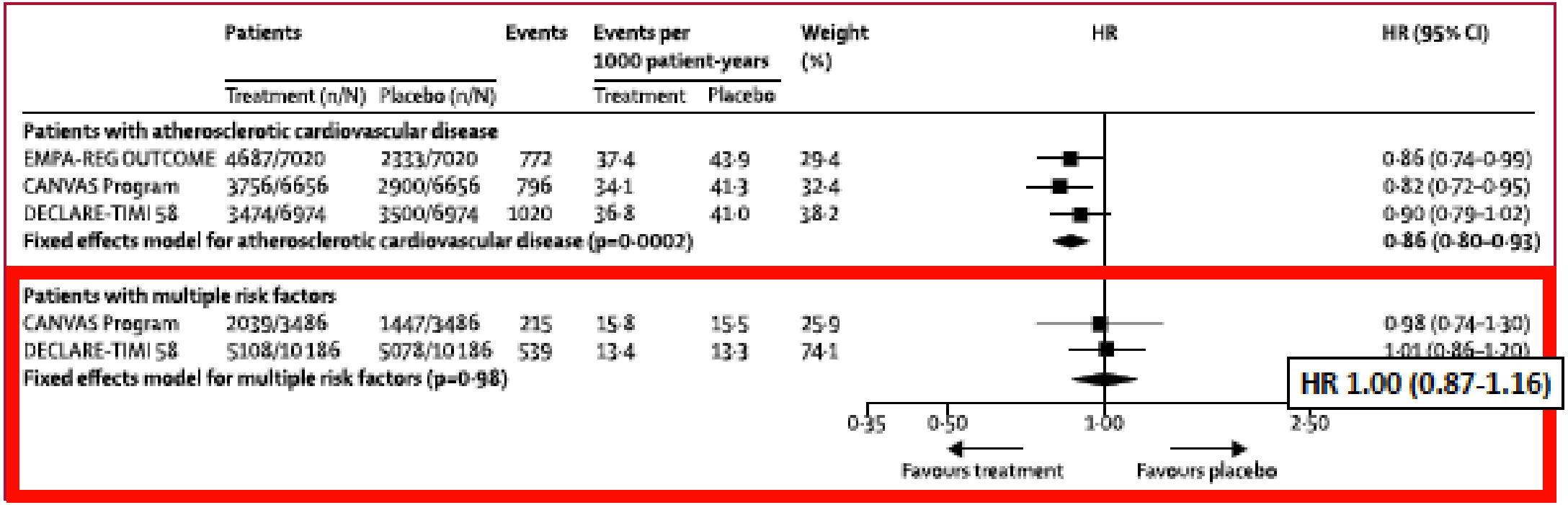
Heart failure: SGLT2i

Diabetic kidney disease: SGLT2i have clear benefit. GLP-1RA benefit more modest/trials ongoing

Areas of Controversy

- **What if your patient has ASCVD risk factors, but not established ASCVD? Is there evidence to support use of SGLT2i or GLP-1RA for cardiovascular event reduction?**

Do SGLT2i prevent MACE in patients without established ASCVD?



VERTIS CV: RCT of ertugliflozin in patients with T2D and established ASCVD: 3-point MACE: HR 0.97, 95% CI 0.85-1.11

Do GLP-1RA prevent MACE in patients without clinical ASCVD?

Trial	Drug	Established Cardiovascular Disease	Proportion with ASCVD at baseline	HR (95% CI)	P-value for interaction
LEADER	Liraglutide	Yes	83%	0.83 (0.74-0.93)	0.04
		No		1.20 (0.86-1.67)	
SUSTAIN-6	Semaglutide SC	Yes	83%	0.72 (0.55-0.93)	0.49
		No		1.00 (0.41-2.46)	
REWIND	Dulaglutide	Yes	31%	0.87 (0.74-1.02)	0.97
		No		0.87 (0.74-1.02)	
Kristensen Meta-analysis	All GLP-1RA trials	Yes	N/A	0.86 (0.79-0.94)	0.22
		No		0.95 (0.83-1.08)	

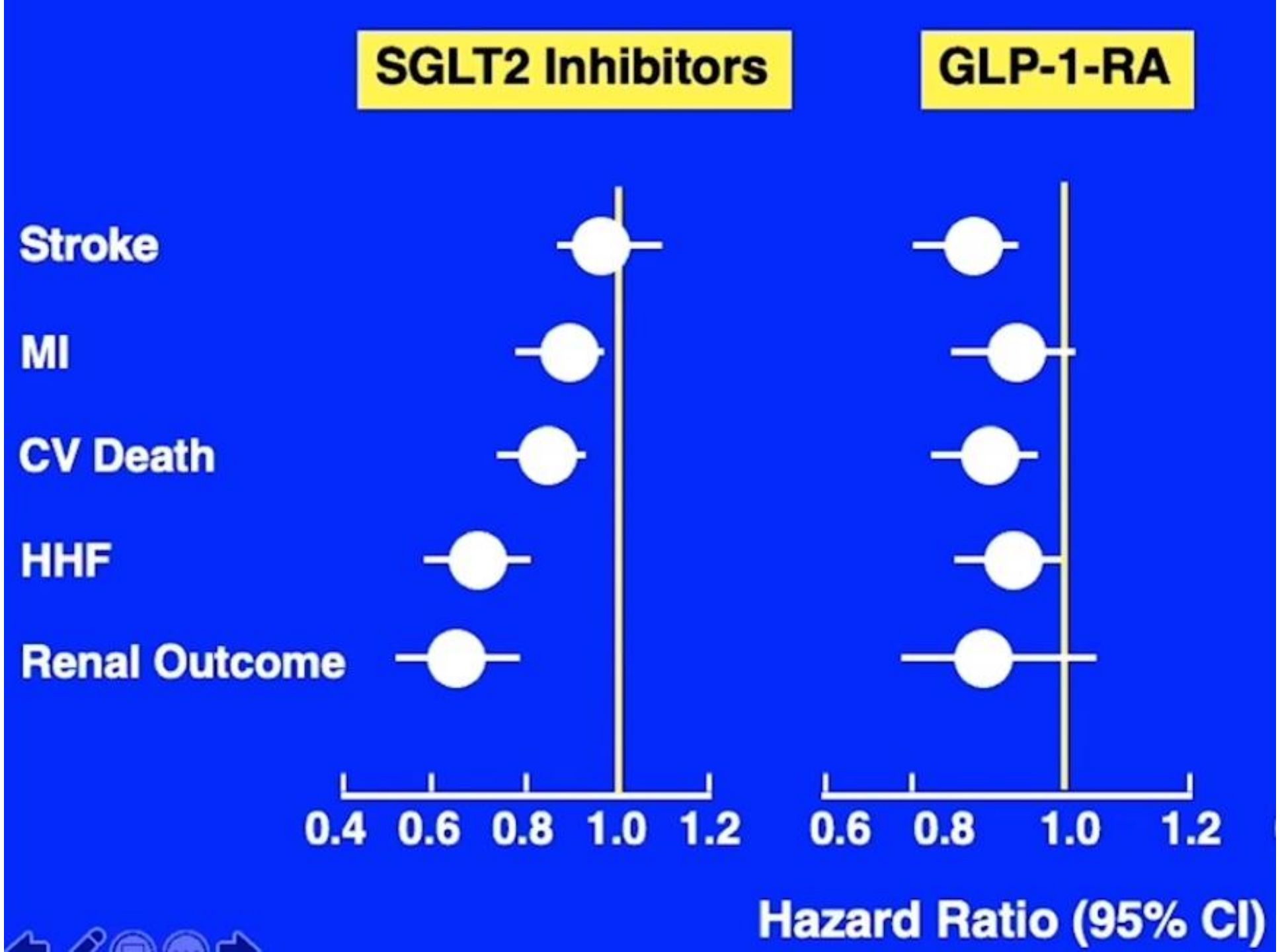
GLP-1 Receptor Agonists and SGLT-2 Inhibitors Use

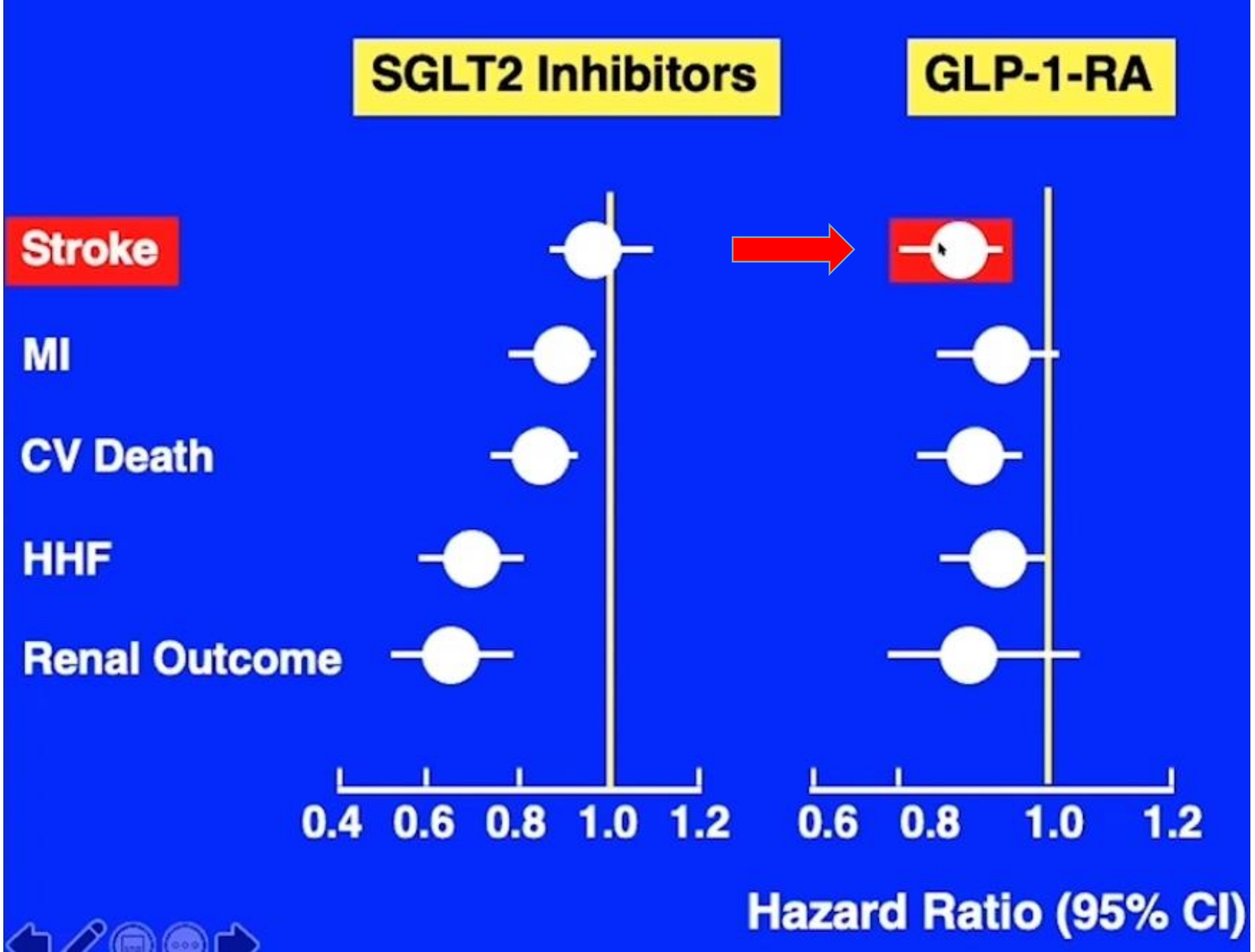
	T2DM - Glycemic Control		MACE Risk Reduction		Prevention of HF		HF Hospitalization in Established HF Patients	
	SGLT2i	GLP-1 RA	SGLT2i	GLP-1 RA	SGLT2i	GLP-1 RA	SGLT2i	GLP-1 RA
T2DM Without Other Risk Factors	Y	Y	Trials needed@	Trials needed@	Trials needed@	Trials needed@	N/A	N/A
T2DM with Risk Factors	Y	Y	Mixed Results$	Mixed Results$	Y	Potential benefit#	N/A	N/A
T2DM with Established ASCVD/High Risk for HF	Y	Y	Y	Y	Y	Potential benefit#	N/A	N/A
T2DM with CKD	Y	Y	Y	Mixed results	Y	Potential benefit#	N/A	N/A
T2DM with Established HFrEF	Y	No (additional trials needed)^	Limited Data*	No (additional trials needed)^	N/A	N/A	Y	No (additional trials needed)
T2DM with Established HFpEF	Y^	Y^	Probably yes /insufficient data$	Probably yes /insufficient data$	N/A	N/A	Trials needed (underway)	Trials needed

Quote from Dr. R. DeFronzo as the “Wizard in Diabetes Care”

INDIVIDUALIZE THERAPY FOR CARDIOVASCULAR PROTECTION

- Statins are better for preventing recurrent MI in patients with prior MI
- Antihypertensive drugs are better for preventing recurrent stroke in patients with prior stroke


SGLT2 Inhibitors
GLP-1-RA
Stroke
MI
CV Death
HHF
Renal Outcome
0.4
0.6
0.8
1.0
1.2
0.6
0.8
1.0
1.2
Hazard Ratio (95% CI)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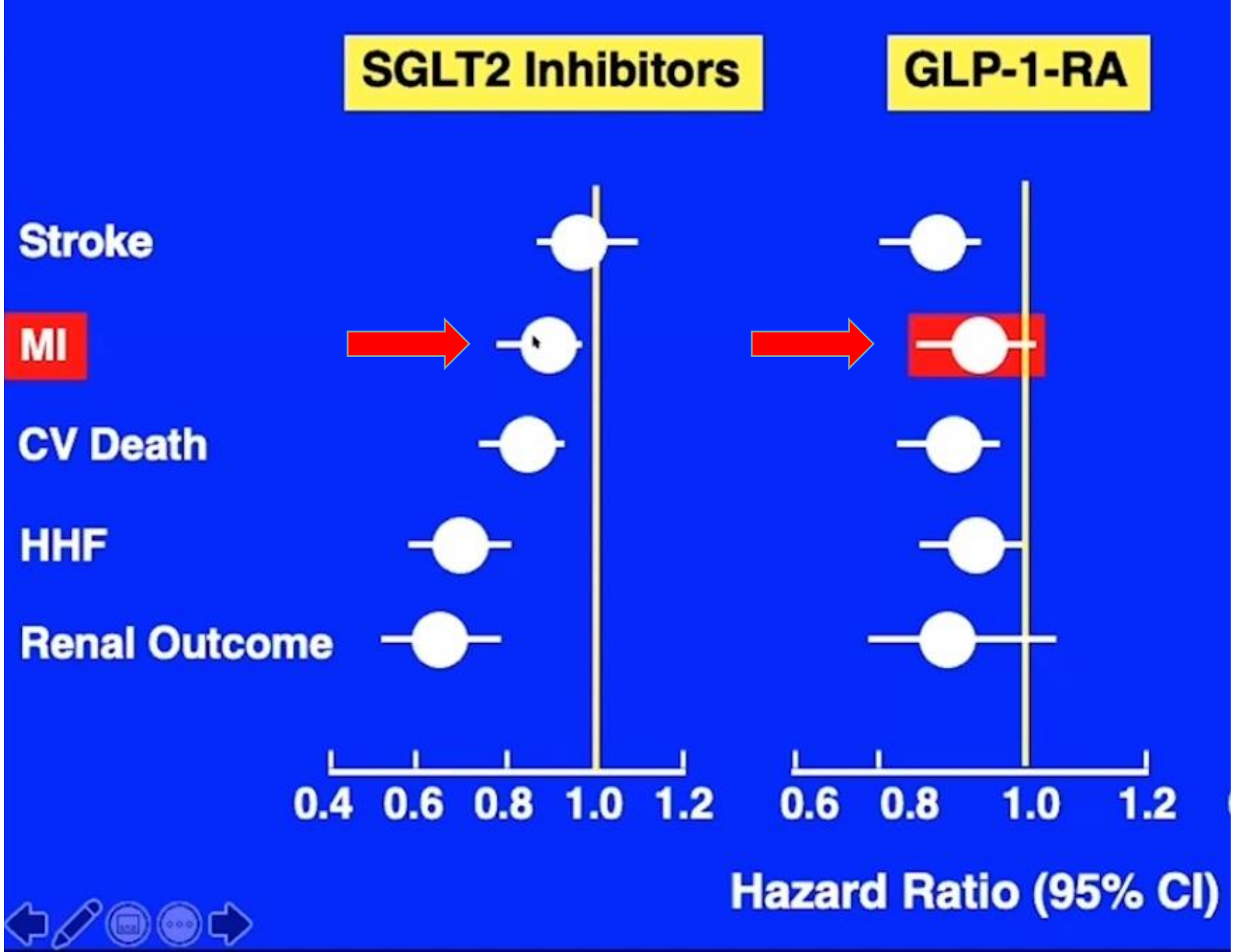
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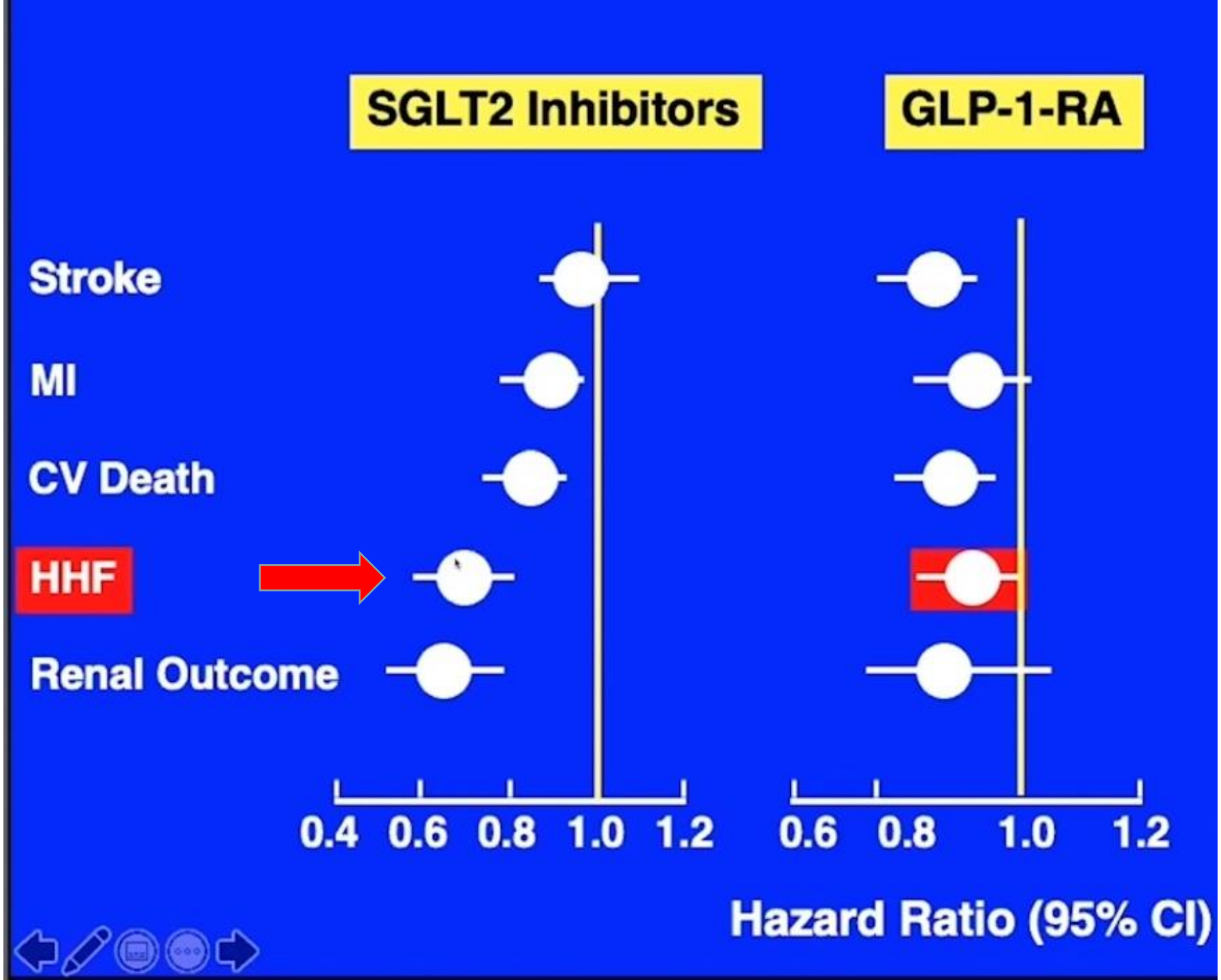
Hazard Ratio (95% CI)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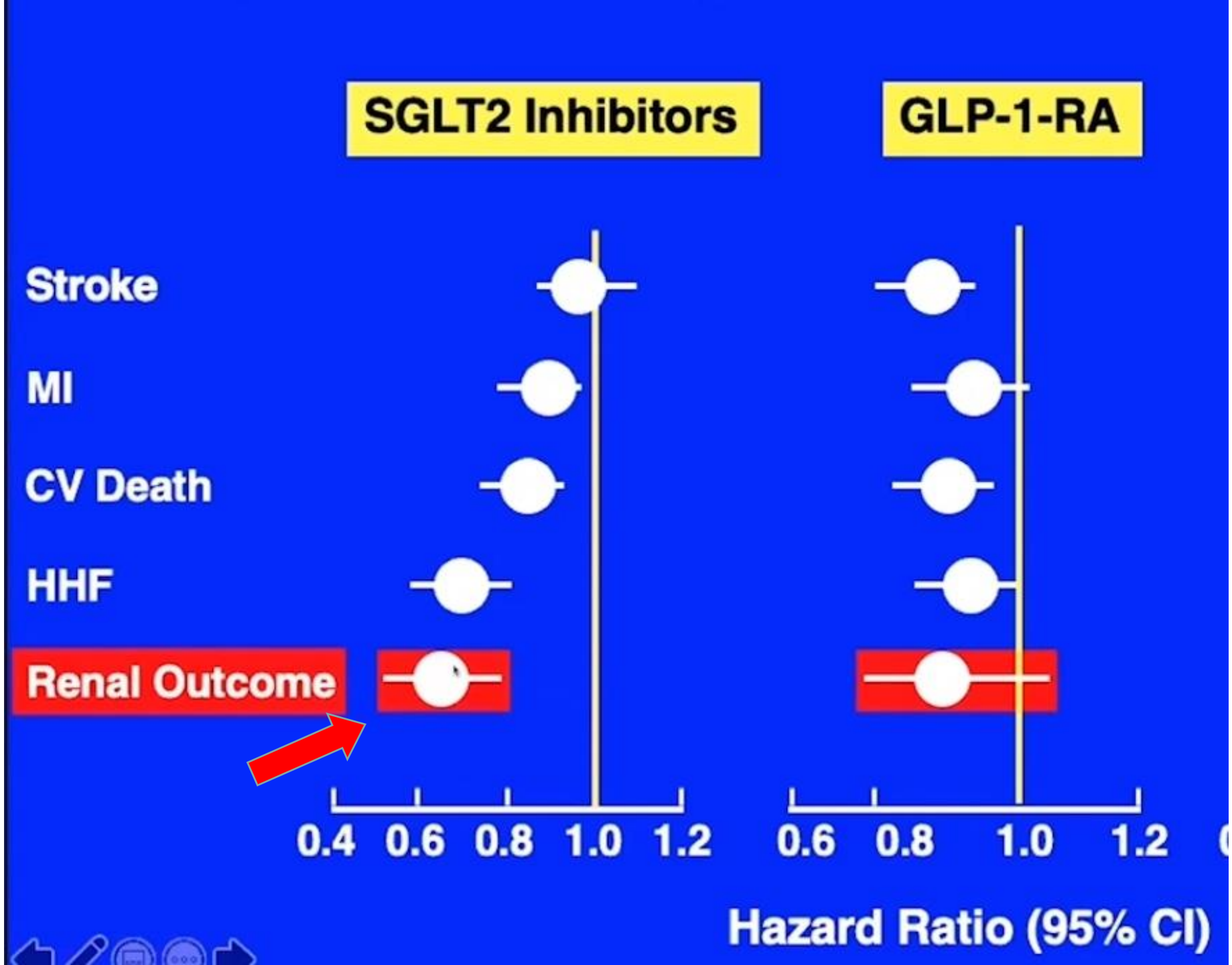

SGLT2 Inhibitors
GLP-1-RA
Stroke
MI
CV Death
HHF
Renal Outcome
0.4
0.6
0.8
1.0
1.2
0.6
0.8
1.0
1.2
Hazard Ratio (95% CI)

Case 1

- 66-year-old DM2 and rEFHF woman with with coronary stent placement 6 months ago.
- No symptoms of ischemia. No hx of MI, stroke or TIA. + leg edema. Hx of PAD with claudication symptoms.
- 2D echo: EF 35%
- On atorvastatin 80 mg, ezetimibe 10 mg, valsartan/sacubitril 97/103 mg BID, carvedilol 25 mg bid, spironolactone 25 mg QD, aspirin 81 mg, ticagrelor 90 mg bid, metformin 500 mg BID, linagliptin 5 mg and pantoprazole.
- Follows a heart-healthy dietary pattern, no smoking.
- PE unremarkable. BP 134/82 mm Hg, BMI 26
- GFR 38 mL/min, K 4.2, CO_2 23, Na 141, Cl 105, FBS 115, A1C 6.5%, UACR 120 mg/g creatinine, NTproBNP 1000 pg/mL. TC 132 mg/dL, TG 210 mg/dL, LDL-C 67 mg/dL, HDL-C 37 mg/dL, nonHDL-C 95 mg/dL. * LDL calculated by Martin Hopkin's equation

Case 1

EF 35%, GFR 38 mL/min, A1C 6.5%, NTproBNP 1000 pg/mL

On SOC therapy for ASCVD and rEFHF

D/C DPP4i and start SGLT2i with proven CV and HF benefits:

Empa ??

Dapa??

Cana??

Case 1

EF 35%, GFR 38 mL/min, A1C 6.5%, NTproBNP 1000 pg/mL

On SOC therapy for ASCVD and rEFHF

D/C DPP4i and start SGLT2i with proven CV and HF benefits:

Empa ?? Good option, FDA approved to decrease CV death. Studied for hHF prevention (EMPEROR-REDUCED).

Dapa?? Good option, FDA approved to decrease hHF and CV death.

Cana?? An option and FDA approved to decrease MACE in DM2 with ASCVD but hx of PAD with claudication based on increased risk of amputations in CANVAS. FDA approved to decrease of hHF, renal endpoints and MACE in patients with UACR > 300 mg/gCreat (not this patient).

Case 2

- 55 y/o male with 11 years history of HTN, dyslipidemia, CKD, ASCVD and CHF stage 3. Non diabetic
- CABG 5 years ago.
- PE: BP 135/80 mmHg, Unremarkable except for bilateral +3 pitting edema, no clinical evidence of PVD.
- FBS 82 mg/dL, GFR 35 ml/hr, LDL 68 mg/dL, HDL 38 mg/dL, TG 160 mg/dL, TC 138 mg/dL, nonHDL 100 mg/dL, ACR 12 mg/g creat, CBC and elytes WNL's
- Last 2D Echo: EF 32%. No evidence of valvular disease.
- Rx: ASA 81mg, rosuvastatin 40 mg daily, sacubitril/valsartan 97/103 mg bid, furosemide 20 mg bid, spironolactone 25 mg daily, carvedilol 25 mg bid.

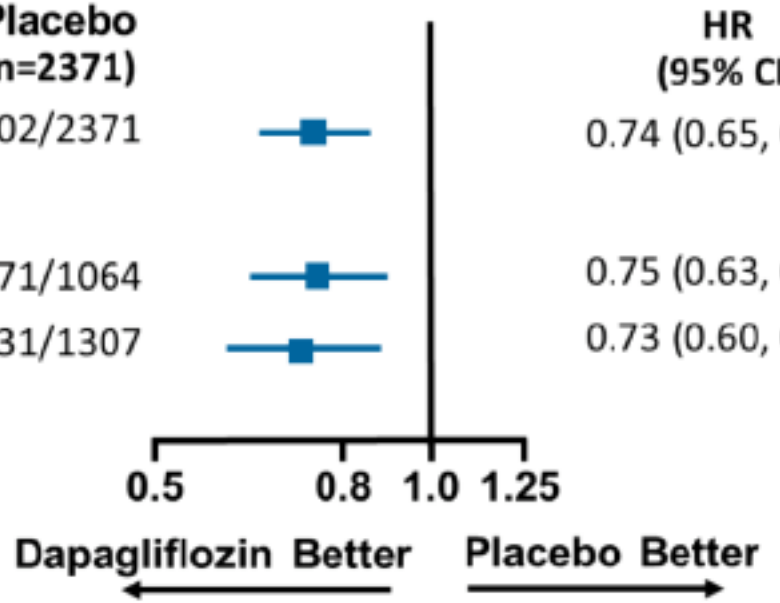
Will you add an SGLT2i even if patient is a non diabetic??

YES (EMPEROR-REDUCED and DAPA-HF)

DAPA-HF: Results in T2DM and Non-DM Patients

Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)

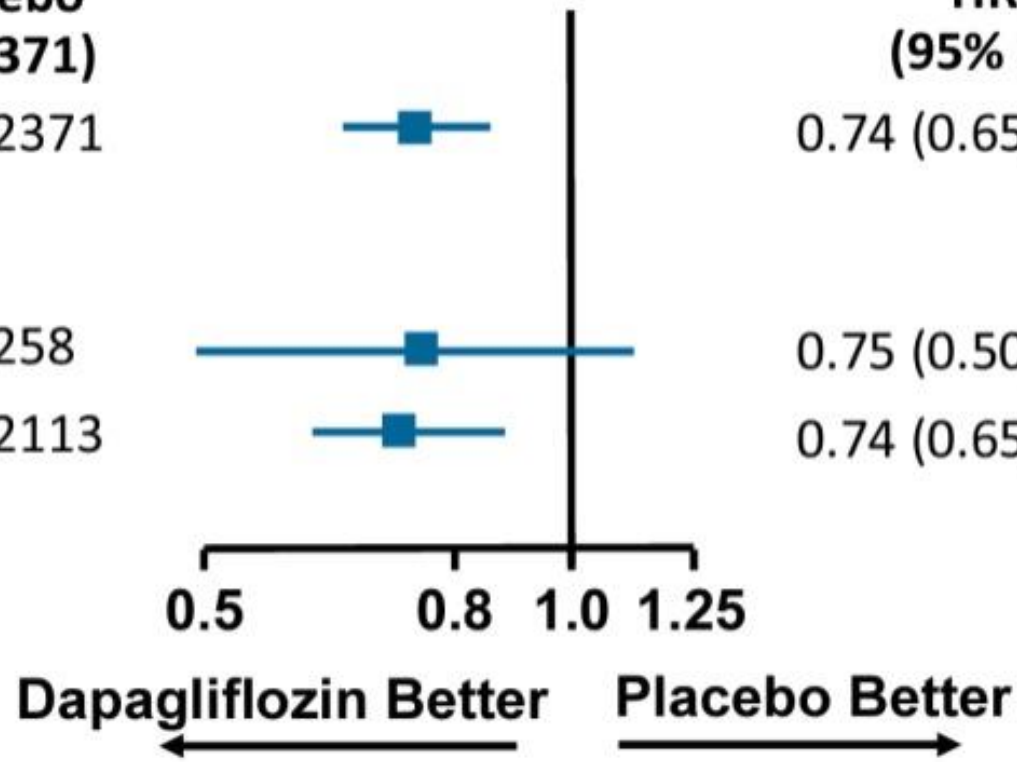


McMurray et al. ESC 2019

AdventHealth

ARNI/no ARNI *post hoc* subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)			
Yes	41/250	56/258	0.75 (0.50, 1.13)
No	345/2123	446/2113	0.74 (0.65, 0.86)



Case 3

- 61 y/o female with DM2 for 18 years, CKD, HTN and dyslipidemia.
- Rx: metformin 1000 mg bid, glimepiride 2 mg and glargine 35 units at bedtime with self adjustment in insulin dose based on SMBG, telmisartan 80 mg QD, amlodipine 5mg QD, atorvastatin 20 mg QD and ASA 81 mg QD.
- A1C 9.2 %, has increased 1.5% in the last 6 months, FBS 112 mg/dL, GFR 32 ml/min, e'lytes WNL's, LDL and nonHDL below thresholds, ACR 105 mg/g creatinine. Due to edema and symptoms suggestive of CHF 2D echo done 6 months ago with normal results and EF 78%.

Which are your recommendations??

Based on high A1C and DM2 w/o eASCVD the best option is dulaglutide based on REWIND

Baseline Characteristics

REWIND
Dulaglutide CV Outcomes Trial

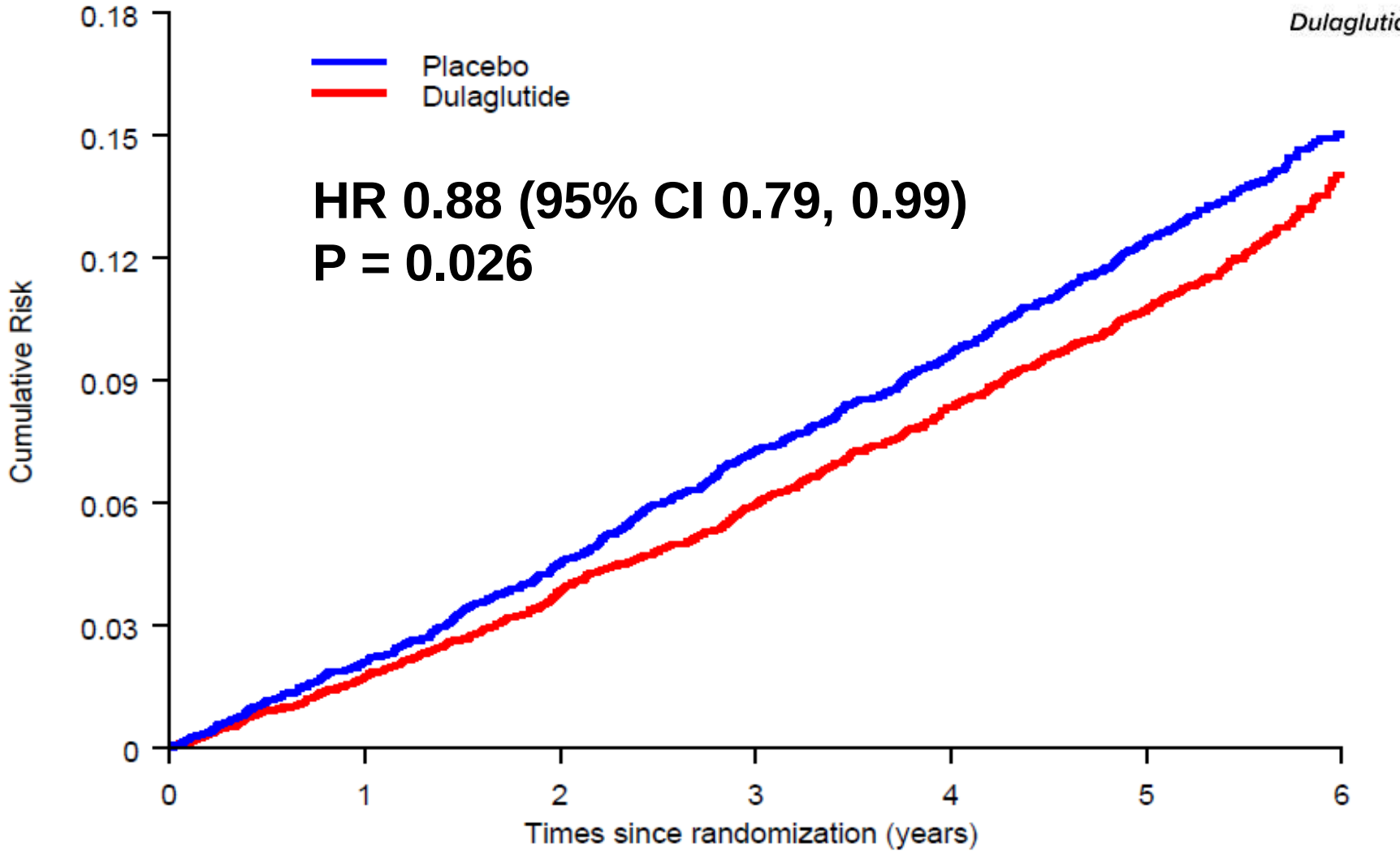
	All Participants N=9901	Dulaglutide N=4949	Placebo N=4952
Age (years)	**66.2**	66.2	66.2
Females (%)	**46.4**	46.6	46.1
White (%)	**75.7**	75.9	75.6
Current Tobacco (%)	**14.2**	14.0	14.4
Prior CV Disease (%)	**31.5**	31.5	31.4
Prior MI or Ischemic Stroke (%)	**20.6**	20.8	20.3
Prior Hypertension (%)	**93.2**	93.0	93.3
Prior Heart Failure (%)	**8.6**	8.5	8.7

History of MI, ischemic stroke, unstable angina with ECG changes, myocardial ischemia on imaging or stress test, or revascularization (coronary, carotid or peripheral)

Dulaglutide's Effect on the CV Composite

Primary Outcome: 1st Occurrence of Nonfatal MI, Nonfatal Stroke, CV Death

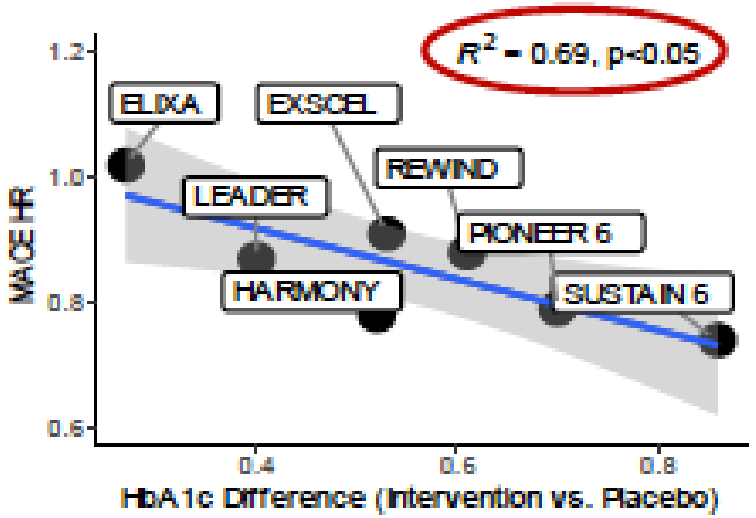
REWIND
Dulaglutide CV Outcomes Trial



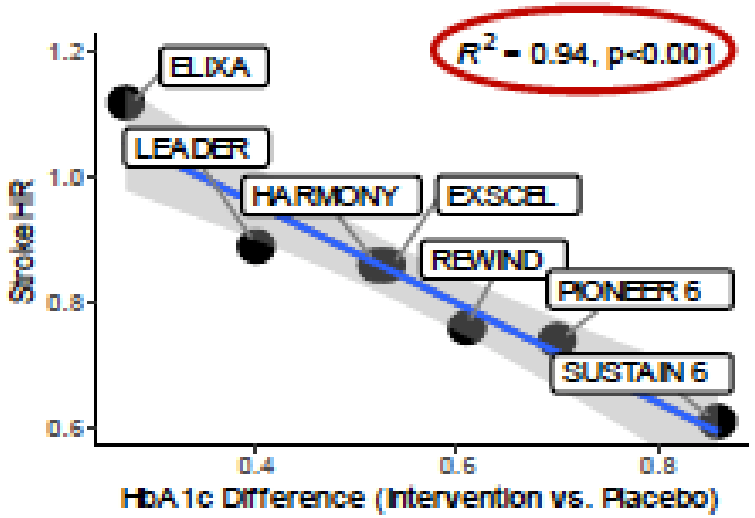
No. at Risk							
Placebo	4952	4791	4625	4437	4275	3575	742
Dulaglutide	4949	4815	4670	4521	4369	3686	741

GLP-1RA & CV Prevention: Role Hyperglycaemia Correction

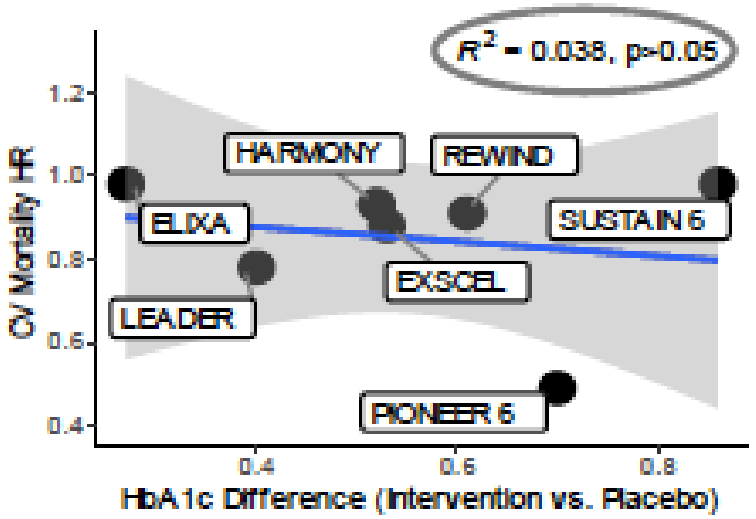
MACE



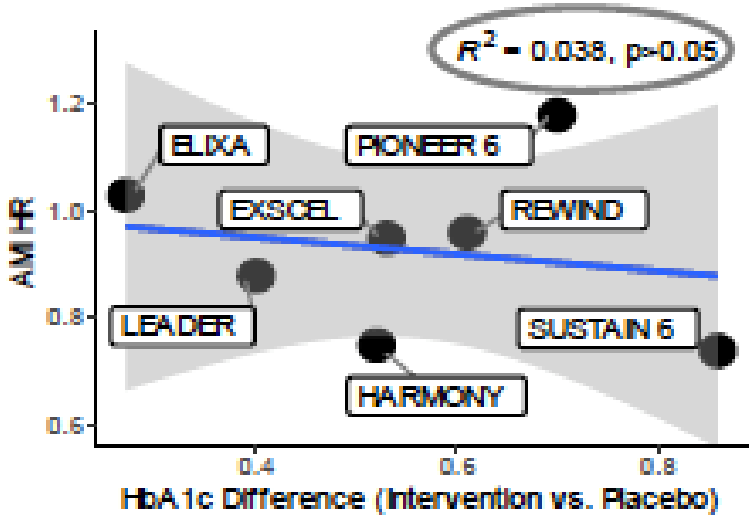
Stroke



CV death



MI



CV, cardiovascular; HbA1c, glycated haemoglobin; HR, hazard ratio; MACE, major adverse CV events; MI, myocardial infarction

Caruso I, et al. *Metabolism* 2020;109:154272

Case 4: *"AN OUTLIER"*

Maria M. 54-year old female with 16-year history of T2D

- 54-year old Latino female
- Seen in clinic for T2D management; No complaints
- PMH: T2D x 16 yrs, obesity, dyslipidemia, HTN, sleep apnea, postmenopausal
- Social History: Seamstress, married with 2 grown children, non-smoker, drinks 1-2 glasses of wine per week

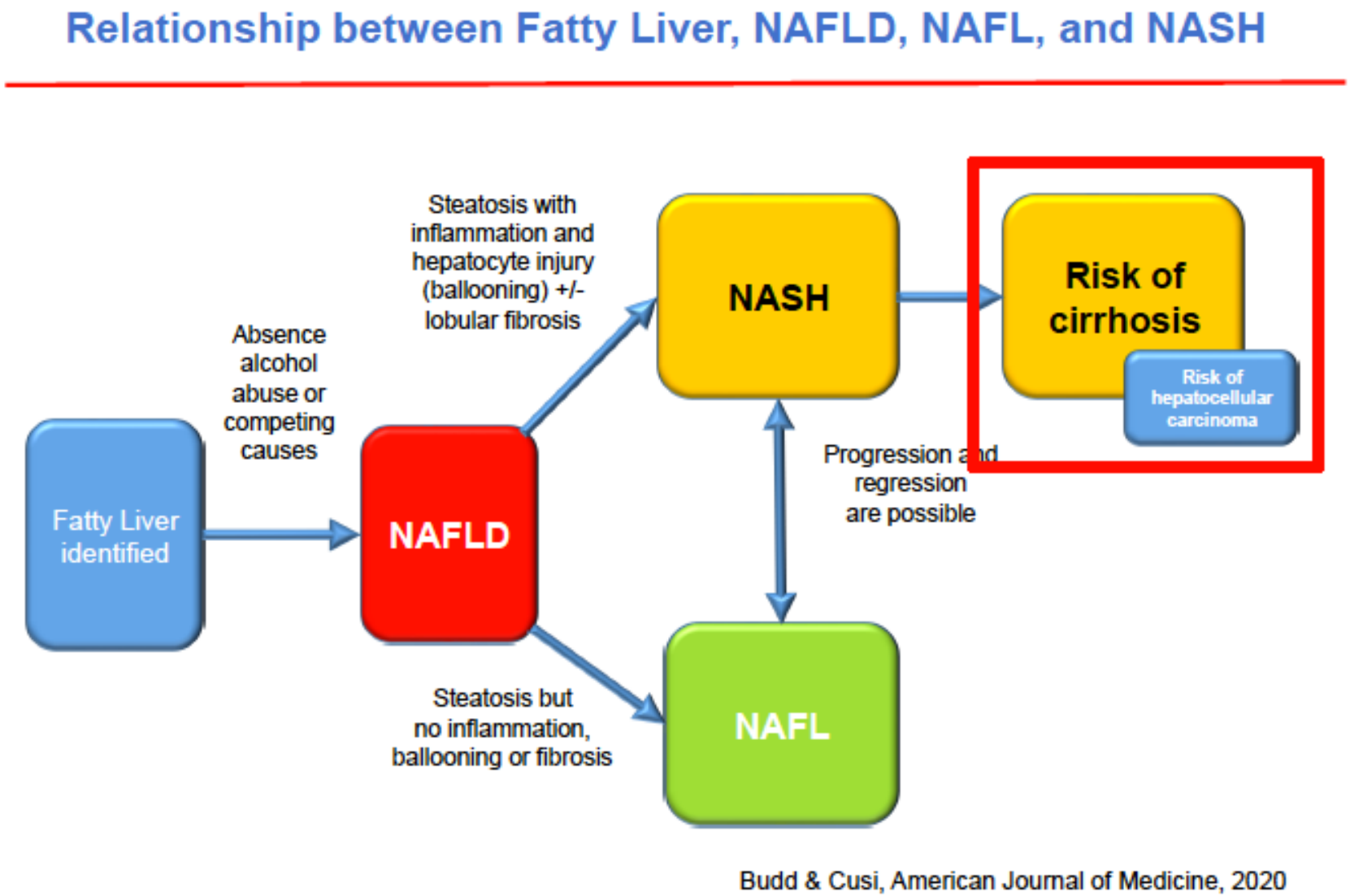
- Meds: metformin 1,000 mg BID, dapagliflozin 10 mg QD, lisinopril 40 mg QD, HCTZ 25 mg QD, atorvastatin 40 mg QD, ASA 81 mg QD
- BP 146/89 mmHg; BMI 34 kg/m^2; Otherwise normal exam
- FPG 210 mg/dL; point-of-care HbA_{1c} 9.4%

Case 4: *"AN OUTLIER"*

Maria: Initial lab work-up

- Normal renal function (eGFR 86 mL/min/1.73 m^2)
- Normal thyroid function
- LDL-C 109 mg/dL; HDL-C 35 mg/dL; triglycerides 260 mg/dL
- ALT 32 U/L (6-41 U/L), AST 45 U/L (9-34 U/L), T. bili 0.88 mg/dL (0.1-1.1 mg/dL)
- Albumin 3.6 g/dL (3.5 – 5.5 g/dL)
- Platelet count 154 x 10^3 µL (140 – 400 x 10^3 µL)

Case 4: *"AN OUTLIER"*



Case 4: *"AN OUTLIER"*

Maria: NAFLD Fibrosis Score and Fib-4 Index

https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score

Parameter
Age, years
AST
ALT
Platelet count, cells x 10^9
BMI
Albumin, g/L
Impaired fasting glucose/DM?

NFS Cutoff Value[1]	Stage
<-1.455	F0–F2
-1.455 to 0.676	Indeterminate
>0.676	F3–F4

Maria's NFS and Fib-2 index:

NFS = 2.8 (>0.675; "Correlated Fibrosis Severity: F3-F4")

Fib-4 index = 2.8 ("indeterminate; further investigation needed")

https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}} = \frac{54 \times 45}{154 \times \sqrt{32}}$$

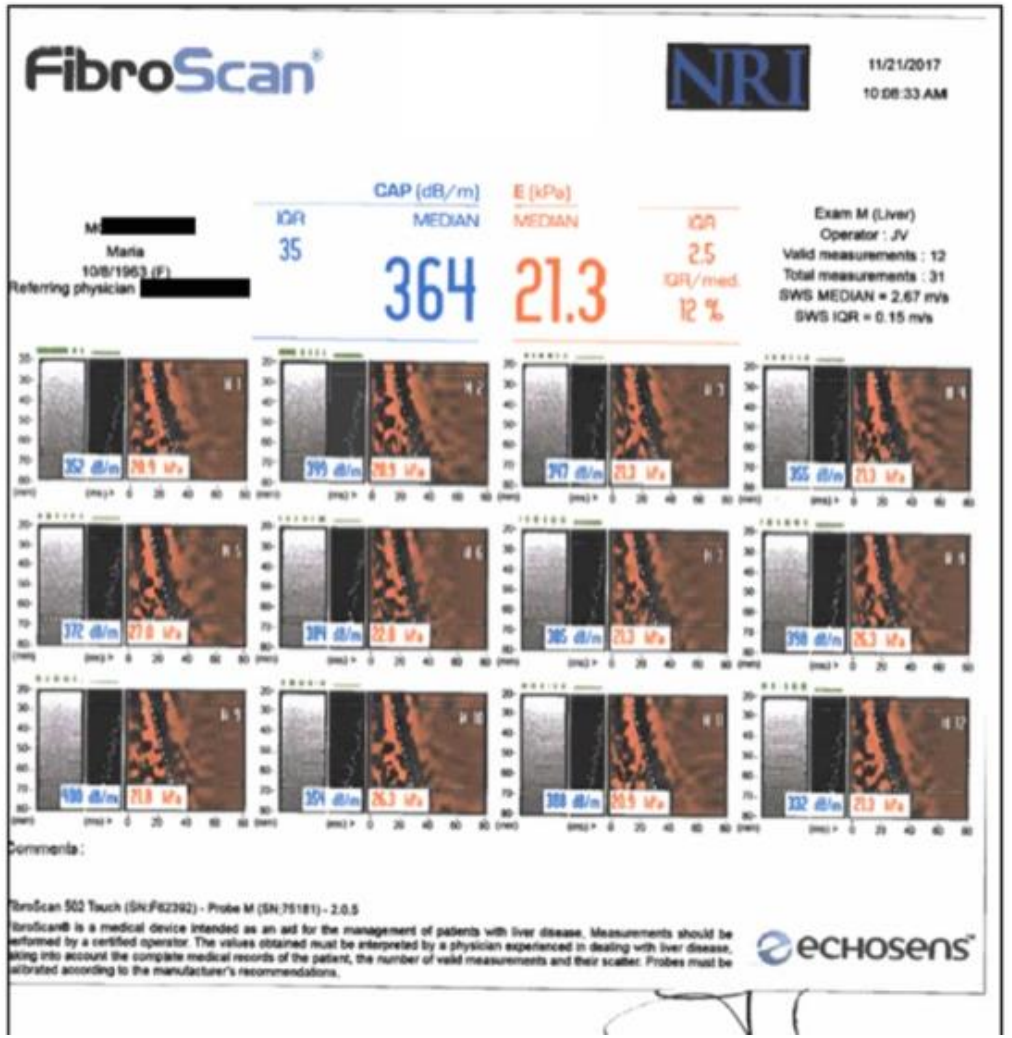
FIB-4 Cutoff Value[2]	Stage
<1.45	F0–F2
1.45 to 3.25	Indeterminate
>3.25	F3–F4

<1.3 "safe"

>2.67 "high risk"

Case 4: *"AN OUTLIER"*

Maria: FibroScan



Case 4: *"AN OUTLIER"*

Polling Question #3

What is the next therapy for Maria for her liver disease now?

A. Diet and exercise
B. Pioglitazone 30 mg daily
C. Vitamin E 800 IU daily
D. Glargine insulin 20 units SQ daily
E. GLP-1 agonist therapy

Case 4: *"AN OUTLIER"*

Pioglitazone profile: pros and cons in diabetes

Benefits of pioglitazone

- **Liver:**
  - Resolution of NASH in ~ 30 to 40% (placebo-subtracted)
  - Prevention of fibrosis progression
- **Extra-hepatic**
  - Reversal of IR, systemic inflammation, ectopic fat deposition and lipotoxicity
  - Improved lipid panel (lower TG; higher HDL-C)
  - Prevention of type 2 DM and durable metabolic effects in diabetes (ACT NOW, NEJM 2011)
  - Reduction of cardiovascular disease
    - PROACTIVE (Lancet 2006)
    - CHICAGO (JAMA 2007)
    - PERISCOPE (JAMA 2008)
    - IRIS Study (NEJM 2016; Circulation 2017; JAMA 2019)

Khan, Bril, Cusi and Newsome, Hepatology 2019

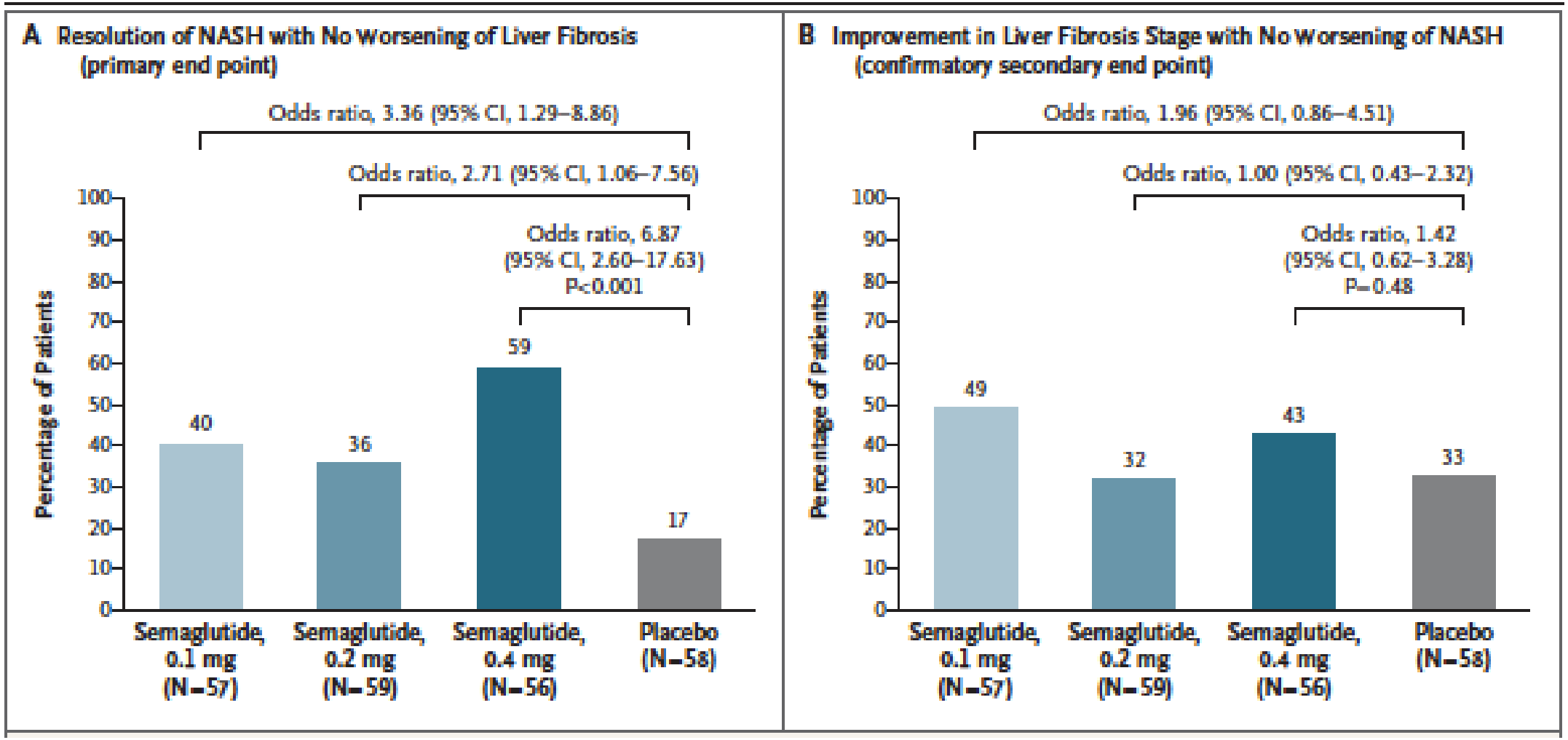
Case 4: *"AN OUTLIER"*

ORIGINAL ARTICLE

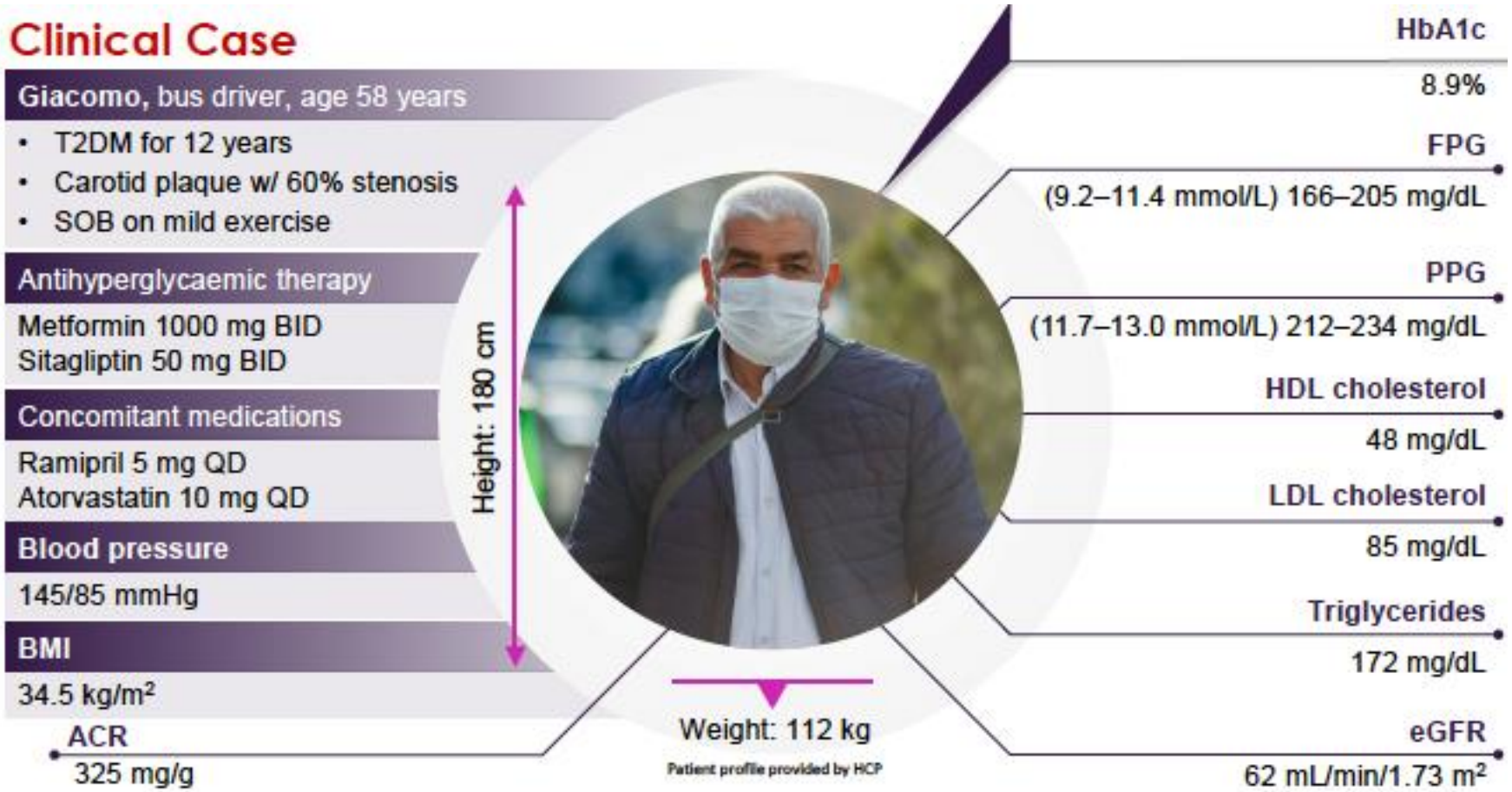
A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

Case 4: *"AN OUTLIER"*



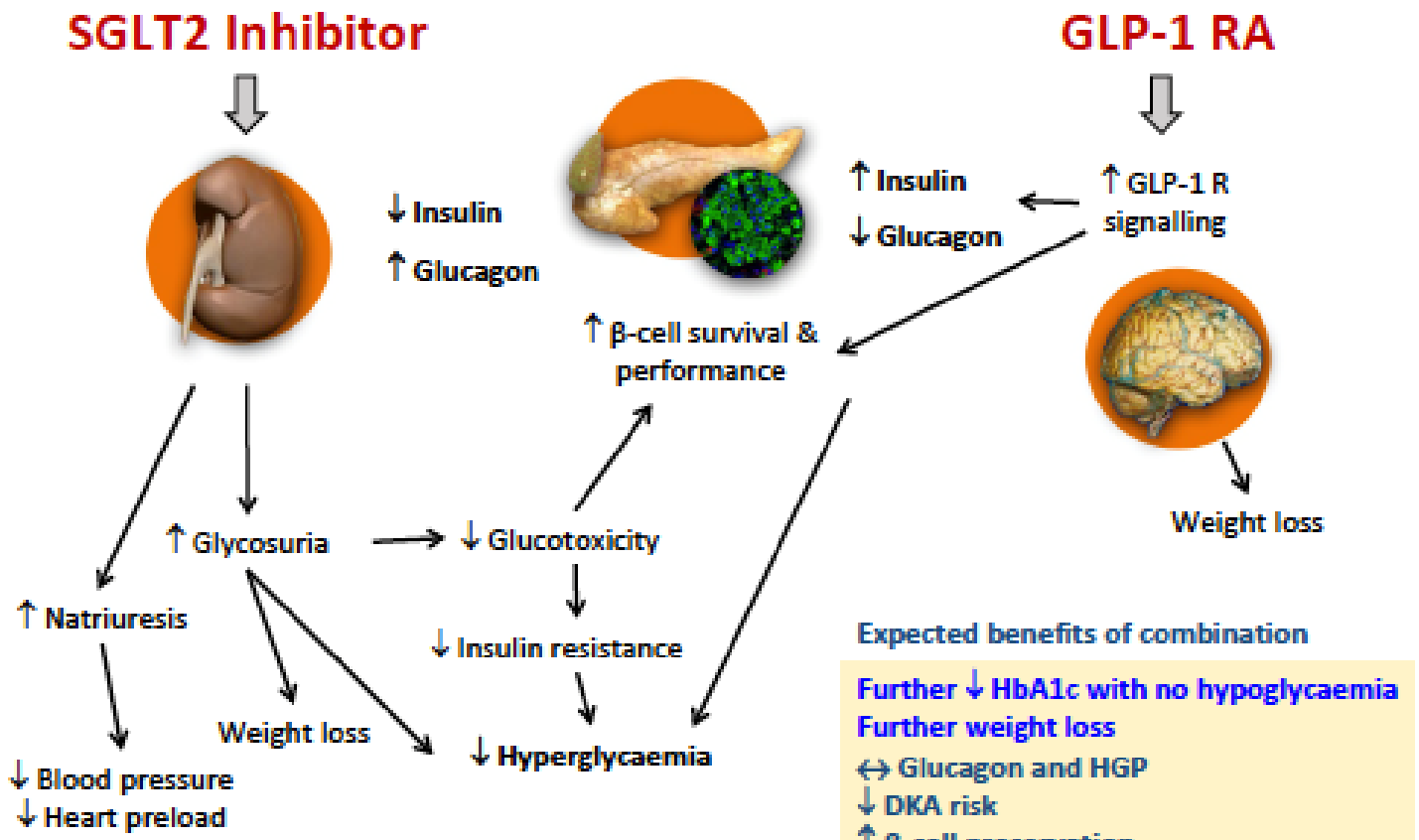
Case 5


Clinical Case
Giacomo, bus driver, age 58 years
• T2DM for 12 years
• Carotid plaque w/ 60% stenosis
• SOB on mild exercise
Antihyperglycaemic therapy
Metformin 1000 mg BID
Sitagliptin 50 mg BID
Concomitant medications
Ramipril 5 mg QD
Atorvastatin 10 mg QD
Blood pressure
145/85 mmHg
BMI
34.5 kg/m²
ACR
325 mg/g
Height: 180 cm
Weight: 112 kg
Patient profile provided by HCP
HbA1c
8.9%
FPG
(9.2–11.4 mmol/L) 166–205 mg/dL
PPG
(11.7–13.0 mmol/L) 212–234 mg/dL
HDL cholesterol
48 mg/dL
LDL cholesterol
85 mg/dL
Triglycerides
172 mg/dL
eGFR
62 mL/min/1.73 m²

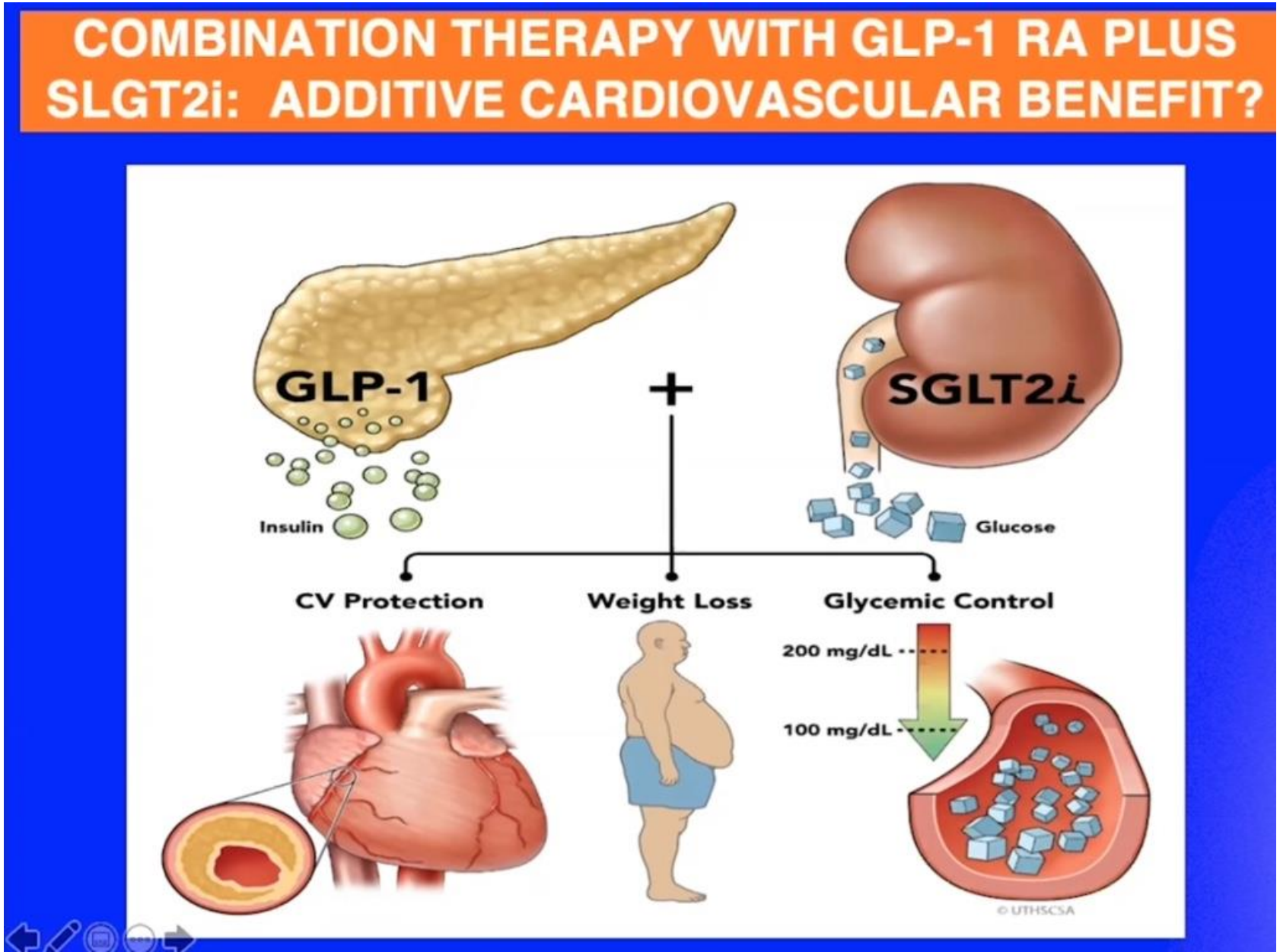
Case 5

- Inadequate glucose control (HbA1c 8.9%, fasting and postprandial hyperglycemia) → correct w/o hypoglycemia
- CV risk → achieve appropriate lipid, blood pressure targets
- Carotid atherosclerosis → manage CVD/risk of stroke
- Shortness of breath (HF?) → prevent HF outcomes
- Obesity → reduce body weight
- Reduced eGFR with macroalbuminuria (G2, A3) → improve eGRF, ACR

Case 5


SGLT2 Inhibitor
GLP-1 RA
↓ Insulin
↑ Glucagon
↑ Insulin
↓ Glucagon
↑ GLP-1 R signalling
↑ β-cell survival & performance
↑ Glycosuria
↓ Glucotoxicity
↑ Natriuresis
↓ Insulin resistance
Weight loss
↓ Hyperglycaemia
↓ Blood pressure
↓ Heart preload
Weight loss
Expected benefits of combination
Further ↓ HbA1c with no hypoglycaemia
Further weight loss
↔ Glucagon and HGP
↓ DKA risk
↑ β-cell preservation
Further ↓ CVD outcomes
Further ↓ nephropathy outcomes

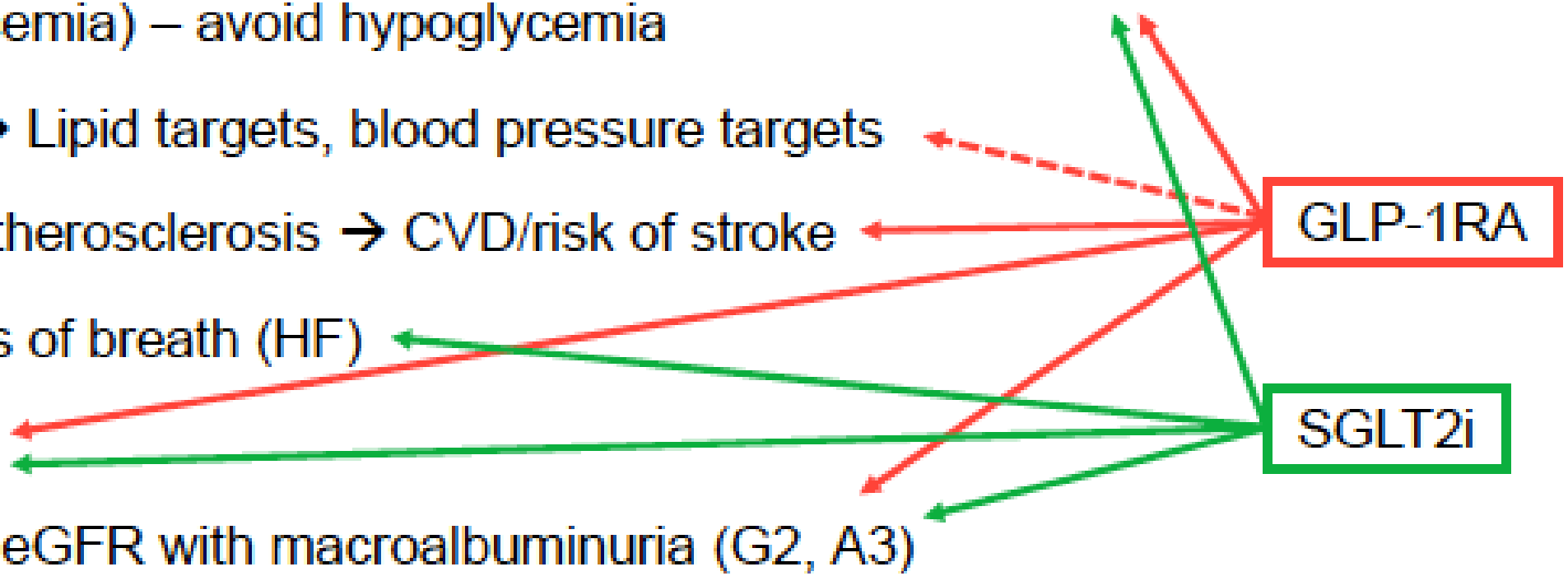
Case 5


COMBINATION THERAPY WITH GLP-1 RA PLUS SLGT2i: ADDITIVE CARDIOVASCULAR BENEFIT?
GLP-1
+
SGLT2i
Insulin
Glucose
CV Protection
Weight Loss
Glycemic Control
200 mg/dL
100 mg/dL
© UTHSCSA

Case 5

Giacomo's Issues

- Inadequate glucose control (HbA1c 8.9%, fasting and postprandial hyperglycemia) – avoid hypoglycemia
- CV risk → Lipid targets, blood pressure targets
- Carotid atherosclerosis → CVD/risk of stroke
- Shortness of breath (HF)
- Obesity
- Reduced eGFR with macroalbuminuria (G2, A3)



Case 5

Clinical Case – 4 months later

Giacomo, bus driver, age 58 years

- Family history of T2DM, HT, obesity
- T2DM for 12 years
- Carotid plaque w/ 60% stenosis

Antihyperglycaemic therapy

Metformin 1000 mg BID
Empagliflozin 5 mg BID
Dulaglutide 1.5 mg OW

Concomitant medications

Ramipril 10 mg QD
Atorvastatin 40 mg QD

Blood pressure

133/82 mmHg

BMI

32.0 kg/m^2

ACR

255 mcg/min

Patient profile provided by HCP

HbA1c

7.8%

FPG

(7.0–8.6 mmol/L) 126–155 mg/dL

PPG

(7.9–9.7 mmol/L) 142–174 mg/dL

HDL cholesterol

51 mg/dL

LDL cholesterol

59 mg/dL

Triglycerides

142 mg/dL

eGFR

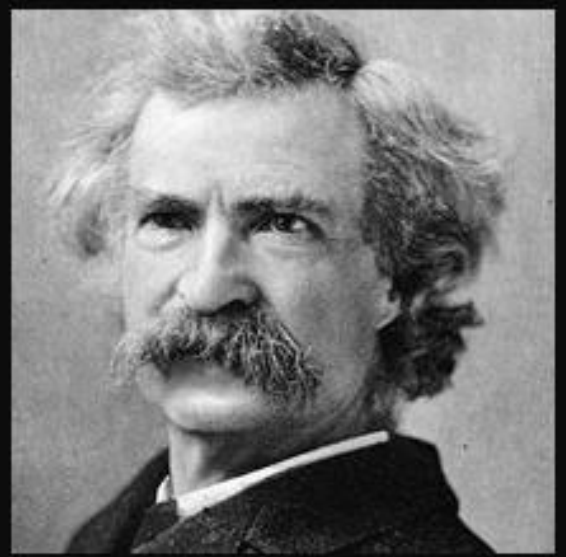
61 mL/min/1.73 m^2

AER, albumin excretion rate; BID, twice daily; BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin;

Conclussions

- CV, renal and HF outcome trials with GLP1RA and SGLT2i has changed T2D management.
- Individualization based on patients baseline characteristics, complications, life expectancy, comorbidities and treatment safety, is the key for the best therapeutic option for each patient.
- Depending of which risk is greater for the patient: stroke, MI, HF or CKD will guide the best option between SGLT2i and GLP1RA's based on published and ongoing trials.
- The HF and renal outcome benefits now extends to the non diabetic population (DAPA-HF, EMPEROR-REDUCED and DAPA-CKD).
- High risk status as NAFLD is a target with these agents, specially promising results with GLP1RA's.
- Future research is needed to evaluate outcomes with the combination of SGLT2i and GLP1RA's, although cost is an issue in clinical practice.

Mark Twain



Good judgment comes from experience. And where does experience come from? Experience comes from bad judgment.

AZ QUOTES