



Data from contemporary CVOTs in diabetes

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Disclosures

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Objectives

- Historical basis of CV and kidney outcomes trials of diabetes medications
- Brief DPP4 trials summary
- Data for SGLT-2i in type 2 diabetes with ASCVD/high ASCVD risk; chronic kidney disease (CKD); heart failure (HF)
- Data for GLP-1RA in type 2 diabetes with ASCVD/high ASCVD risk
- Relevant changes to clinical care guidelines

ASCVD = atherosclerotic cardiovascular disease

Rationale for CVOT

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE

December 17, 2008

Media Inquiries:

Karen Riley, 301-796-4674

Consumer Inquiries:

800 INFO FDA

FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

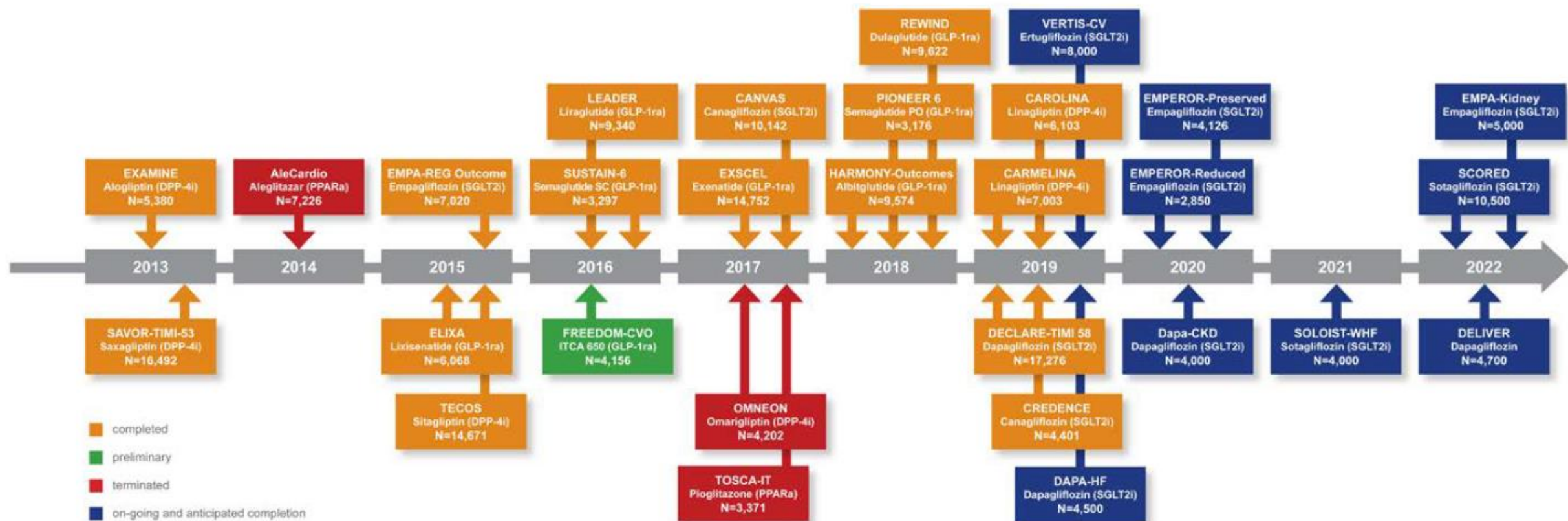
"...sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116994.htm>

COORDINATE-Diabetes



CVOTs



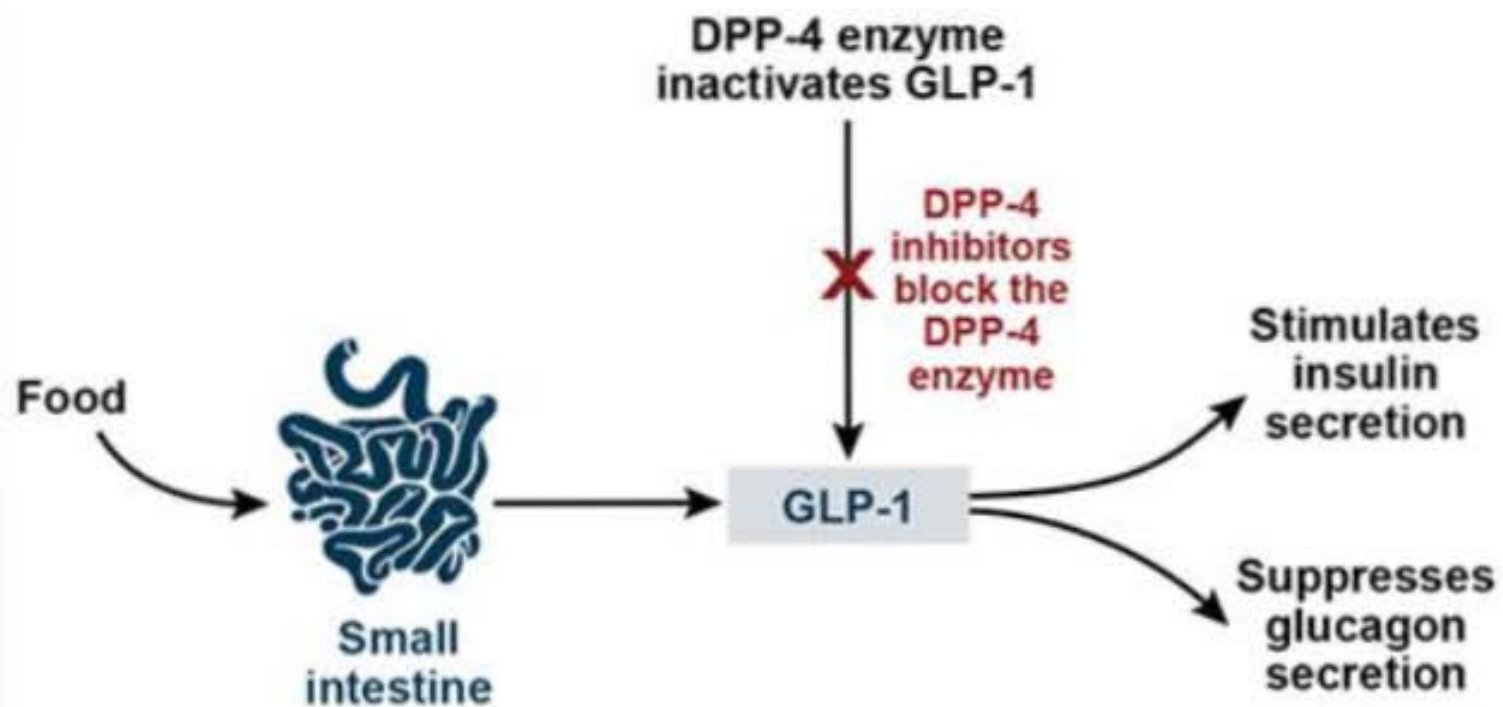
Sharma A et al. Circulation Volume 141, Issue 10, 10 March 2020; Pages 843-862





DPP-4 inhibitors

DPP-4 inhibitors: Glucose-lowering Effects



Meier JJ et al. Nat Rev Endocrinol. 2012



DPP-4 inhibitors

Generic	Trade Name	CV Outcomes Trial	Results Available
saxagliptin	Onglyza	SAVOR-TIMI 53	2013
alogliptin	Nesina	EXAMINE	2013
sitagliptin	Januvia	TECOS	2015
linagliptin	Tradjenta	CARMELINA	2018
		CAROLINA	2019

DPP-4 inhibitors: primary MACE outcome

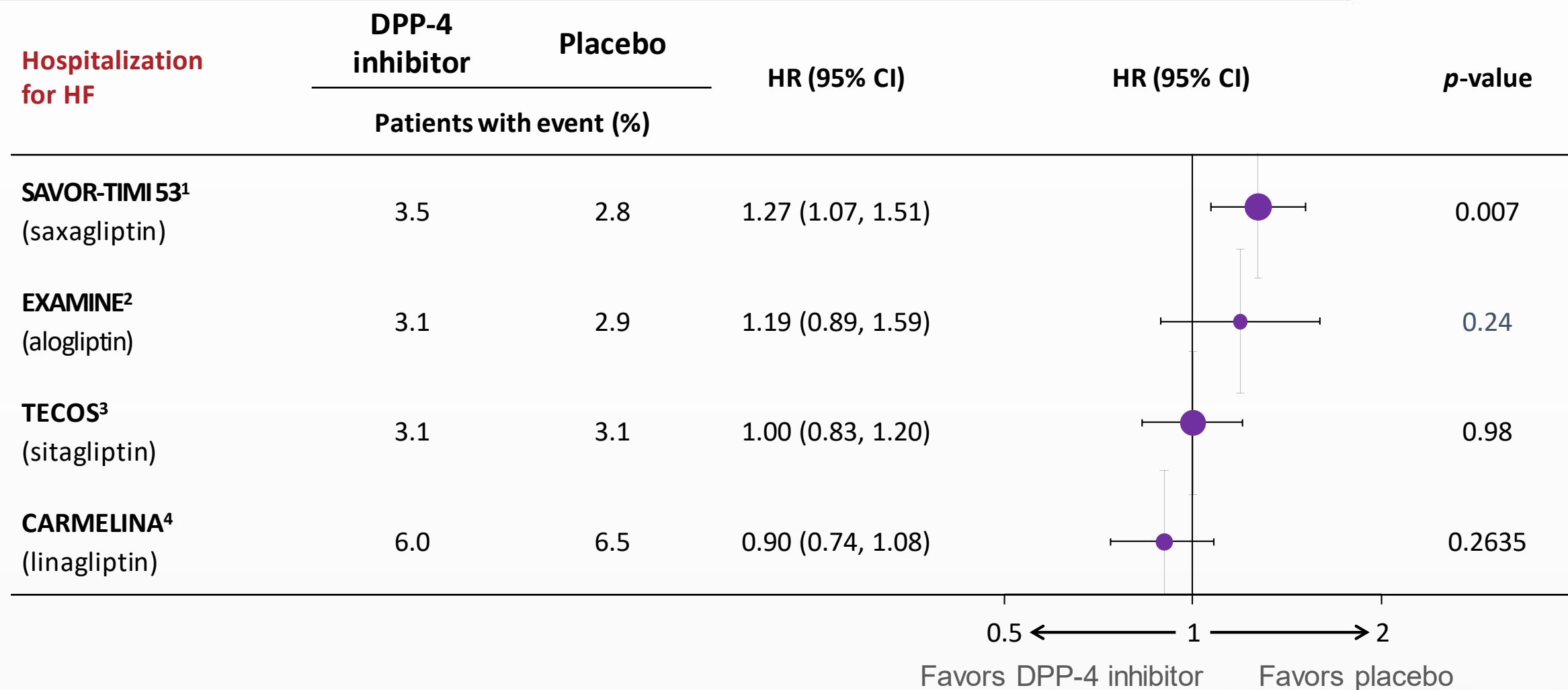
Primary CV outcome	DPP-4 inhibitor	Placebo	HR (95% CI)	HR (95% CI)	p-value
	Patients with event (%)				
SAVOR-TIMI 53¹ (saxagliptin)	7.3	7.2	1.00 (0.89, 1.12)		0.99
EXAMINE² (alogliptin)	11.3	11.8	0.96 (n/a, 1.16)		0.32
TECOS³ (sitagliptin)	11.4	11.6	0.98 (0.89, 1.08)		0.65
CARMELINA⁴ (linagliptin)	12.4	12.1	1.02 (0.89, 1.17)		0.74

MACE = major adverse cardiovascular events

0.5 ← 1 → 2
Favors DPP-4 inhibitor Favors placebo



DPP-4 inhibitors: hospitalization for HF



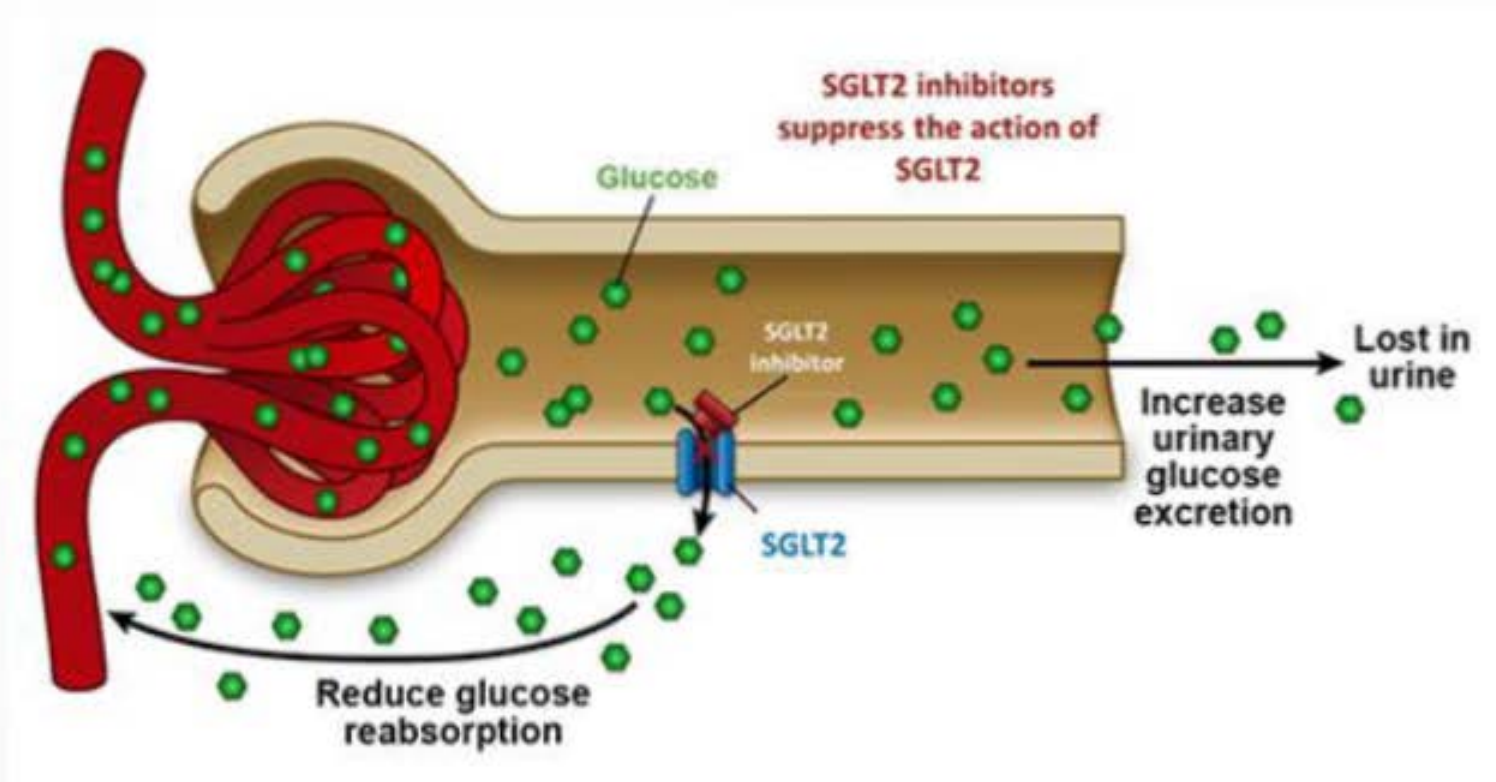
DPP-4 inhibitors

DPP-4 inhibitors do **not** have an indication to reduce risk of MACE



SGLT-2 inhibitors

SGLT-2 inhibitors: Glucose-lowering Effects



Wright EM et al. Physiol Rev 2011

SGLT-2 inhibitors: CVOTs in patients with T2DM and high ASCVD Risk

Generic	Trade Name	Outcomes Trial	Cohort Studied
empagliflozin	Jardiance	EMPA-REG	T2DM with ASCVD
canagliflozin	Invokana	CANVAS	T2DM with ASCVD or high ASCVD risk
dapagliflozin	Farxiga	DECLARE-TIMI	T2DM with ASCVD or high ASCVD risk
ertugliflozin	Steglatro	VERTIS-CV	T2DM with ASCVD

*SGLT1/2 inhibitor, not commercially available in the US

1. Zinman B et al. N Engl J Med 2015; 373:2117-2128
2. Neal B et al. N Engl J Med 2017; 377:644-657
3. Raz I et al. Diabetes Obes Metab. 2018 May;20(5):1102-1110
4. Cannon C et al. Am Heart J 2018;206:11-23



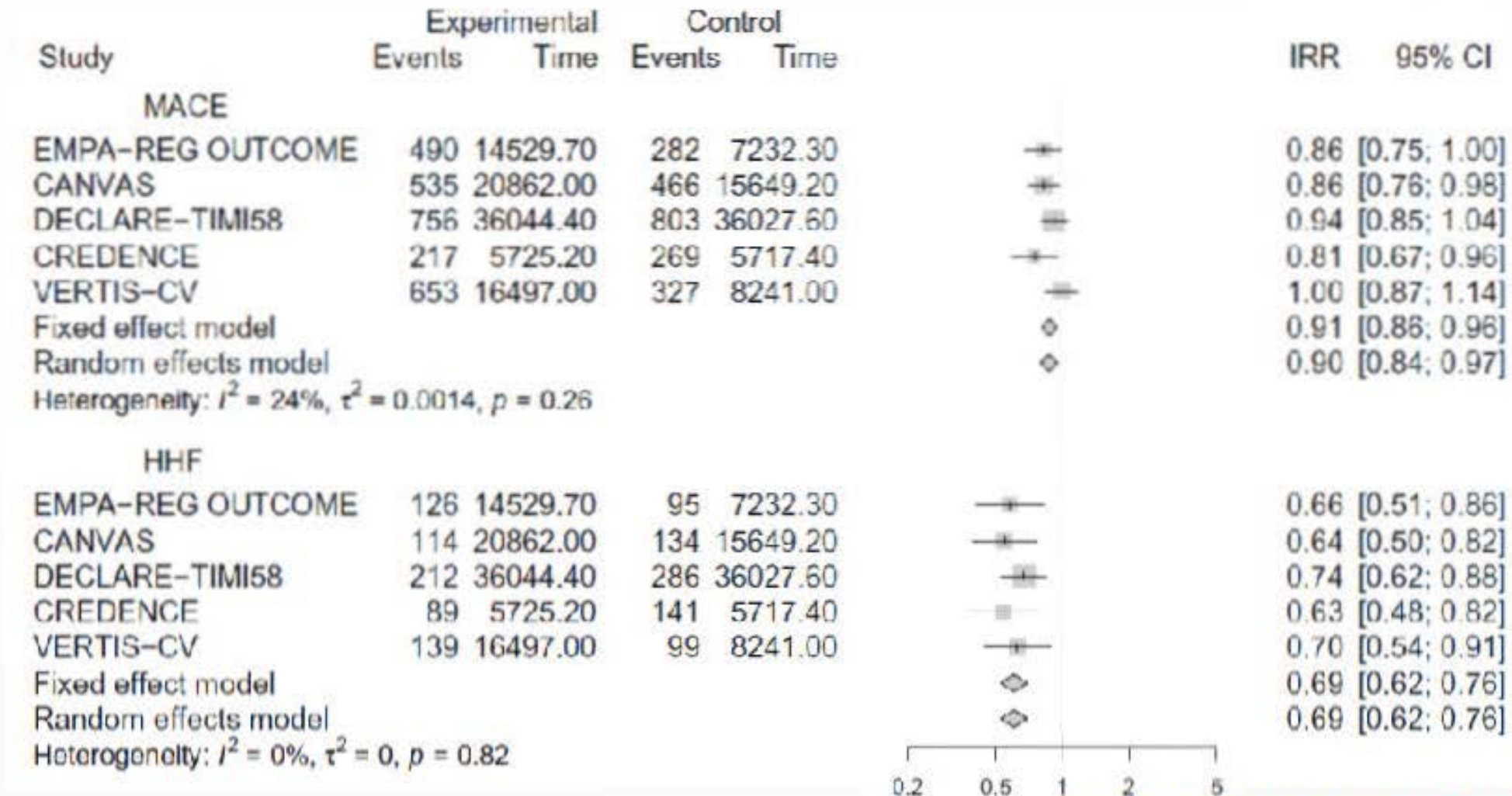
SGLT-2i CVOTs in T2DM with High ASCVD Risk: Baseline Characteristics

	EMPA-REG OUTCOME¹ <i>empagliflozin</i>	CANVAS Program² <i>canagliflozin</i>	DECLARE-TIMI 58³ <i>dapagliflozin</i>	VERTIS-CV⁴ <i>ertugliflozin</i>
Median Follow-Up Time (yrs)	3.1	2.4	4.2	
Trial participants (n)	7020	10142	17160	8238
Mean age (yrs)	63.1	63.3	63.9	64.4
Female sex	28.5	35.8	37.4	30
Established ASCVD	7020 (100%)	6656 (66%)	6974 (41%)	8236 (99.9%)
Established heart failure	706 (10.1%)	1461 (14.4%)	1724 (10.0%)	1900 (23.1%)
eGFR <60 ml/min/1.73 m ²	1819 (25.9%)	2039 (20.1%)	1265 (7.4%)	1807 (21.9%)

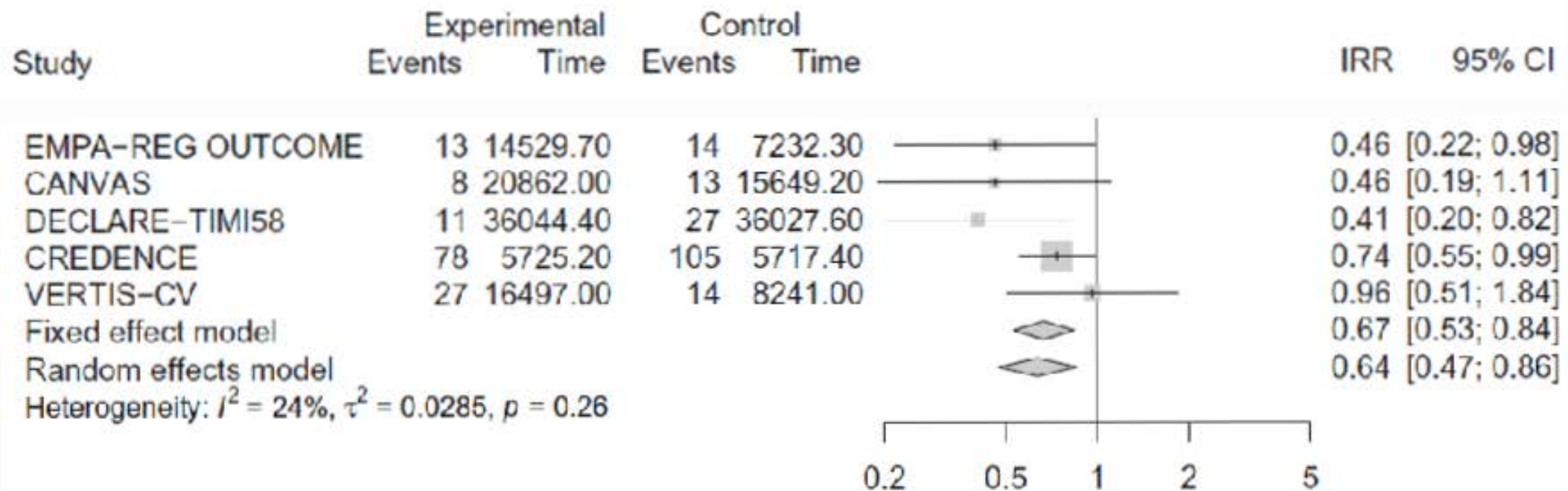
1. Zinman B et al. N Engl J Med 2015; 373:2117-2128 2. Neal B et al. N Engl J Med 2017; 377:644-657 3. Raz I et al. Diabetes Obes Metab. 2018 May;20(5):1102-1110
4. Cannon C et al. Am Heart J 2018;206:11-23



SGLT-2i CVOTs in T2DM with High ASCVD Risk: MACE and HHF meta-analysis



SGLT-2i CVOTs in T2DM with High ASCVD Risk: Clinical End-Stage Kidney Disease meta-analysis

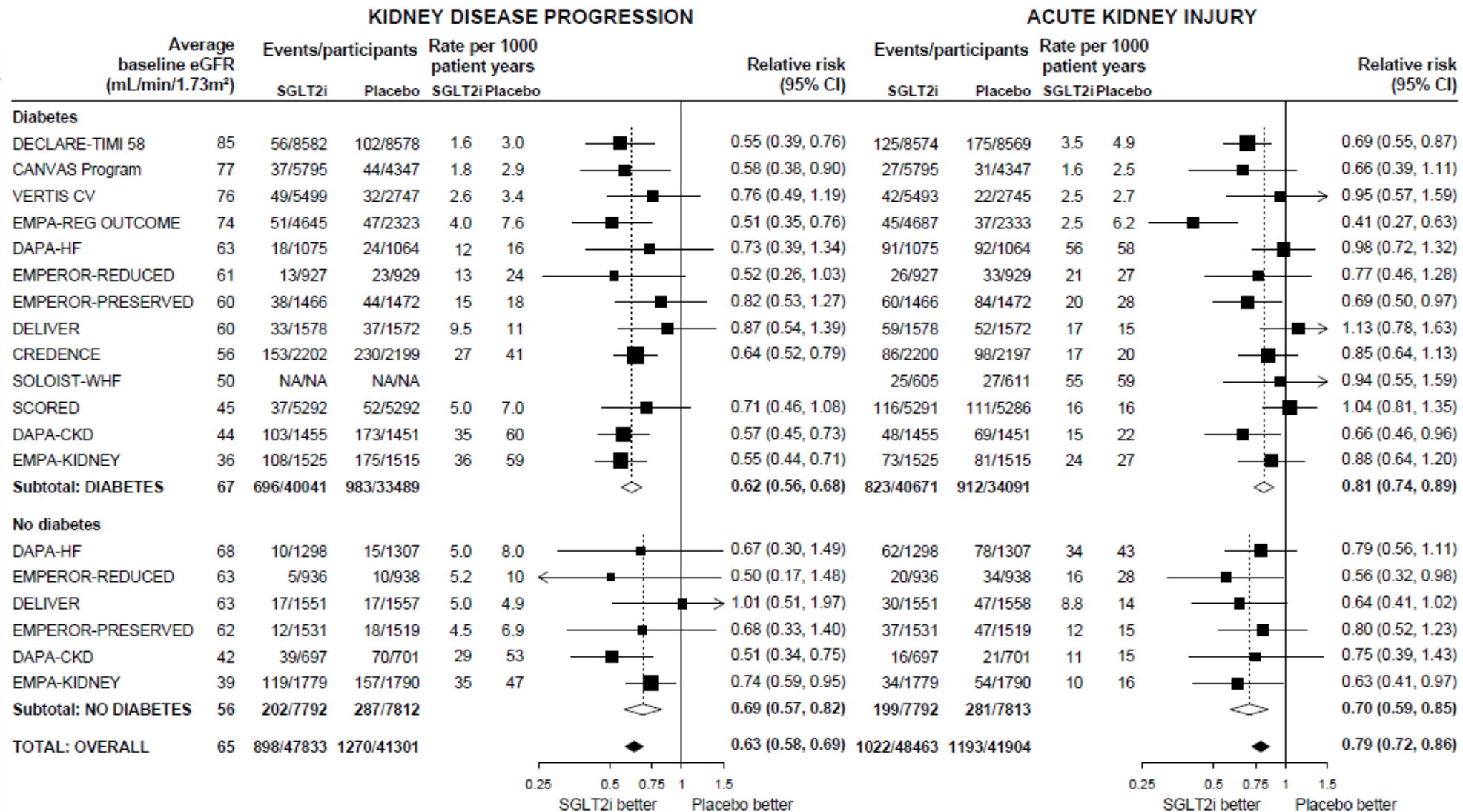


SGLT-2 inhibitors: Outcomes Trials in patients with CKD or HF

Generic	Trade Name	Outcomes Trial	Cohort Studied
empagliflozin	Jardiance	EMPEROR-Reduced	HF with reduced EF
		EMPEROR-Preserved	HF with preserved EF
		EMPA-Kidney	CKD
canagliflozin	Invokana	CREDENCE	T2DM with CKD
dapagliflozin	Farxiga	DAPA-HF	HF with reduced EF
		DELIVER	HF and LVEF > 40%
		DAPA-CKD	CKD
sotagliflozin*	n/a	SOLOIST-WHF	T2DM and recent hospitalization for HF
		SCORED	T2DM with CKD

*SGLT1/2 inhibitor, not commercially available in the US

Effect of SGLT2i on Kidney Disease Outcomes



Trend across trials sorted by eGFR:
 Diabetes p=0.91;
 No diabetes p=0.86;
 Heterogeneity by diabetes status: p=0.30

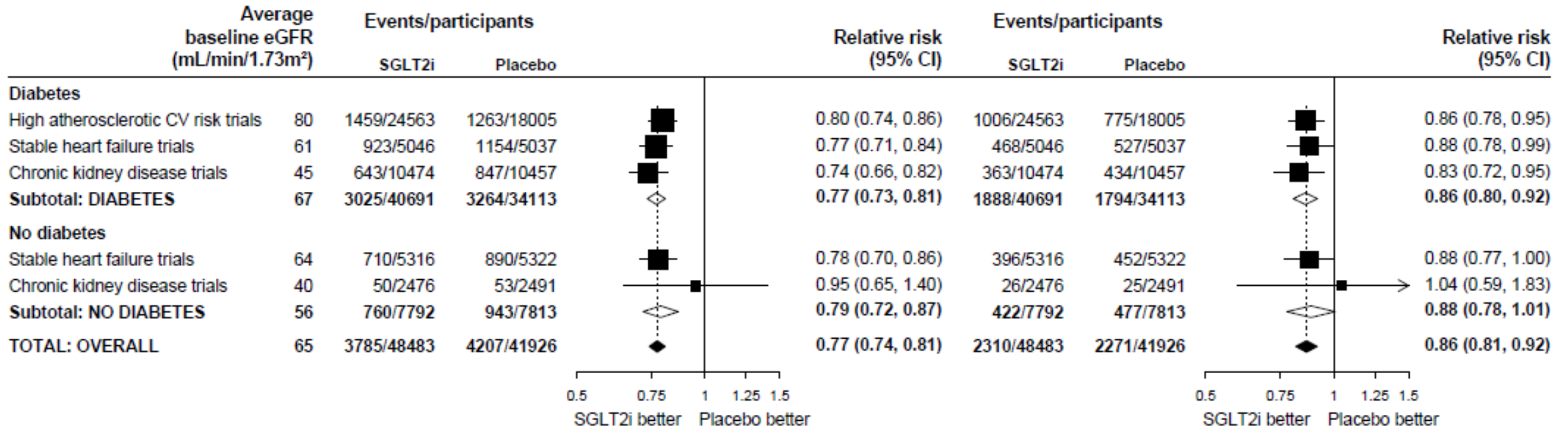
Trend across trials sorted by eGFR:
 Diabetes p=0.04;
 No diabetes p=0.69;
 Heterogeneity by diabetes status: p=0.18



Effect of SGLT2i on HF and Mortality Outcomes

CARDIOVASCULAR DEATH or HOSPITALISATION FOR HEART FAILURE

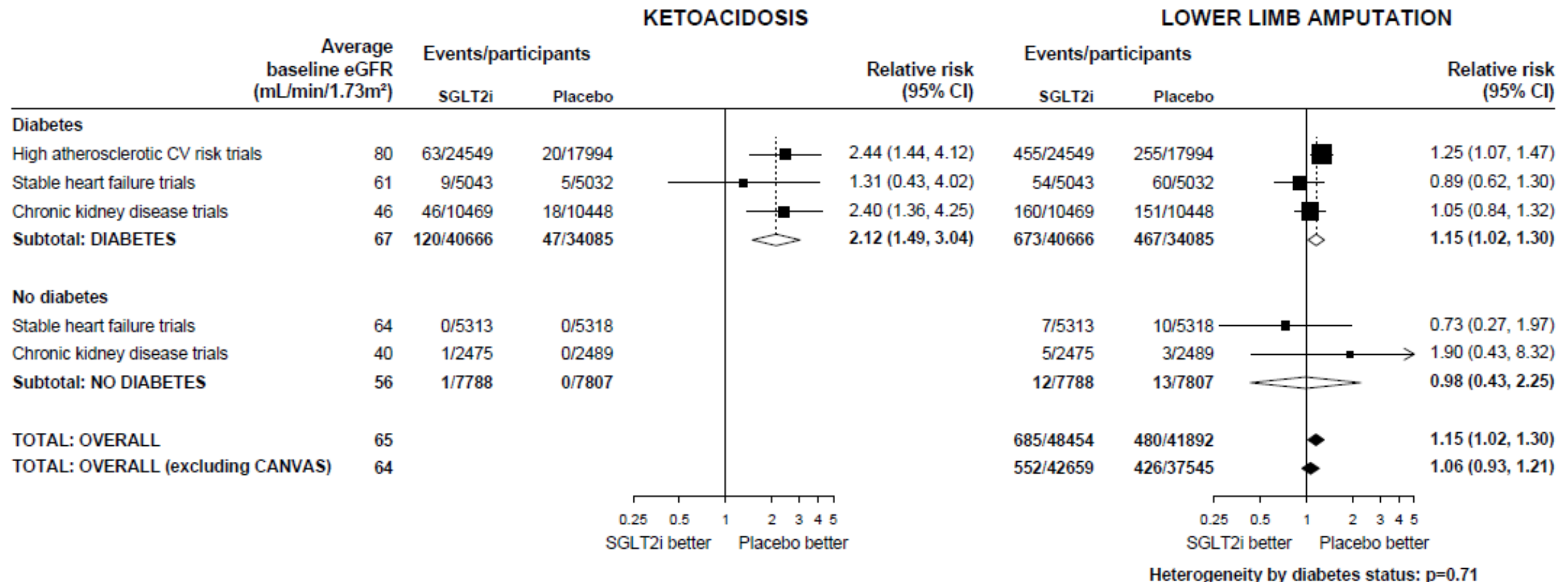
CARDIOVASCULAR DEATH



Heterogeneity by diabetes status: p=0.67

Heterogeneity by diabetes status: p=0.68

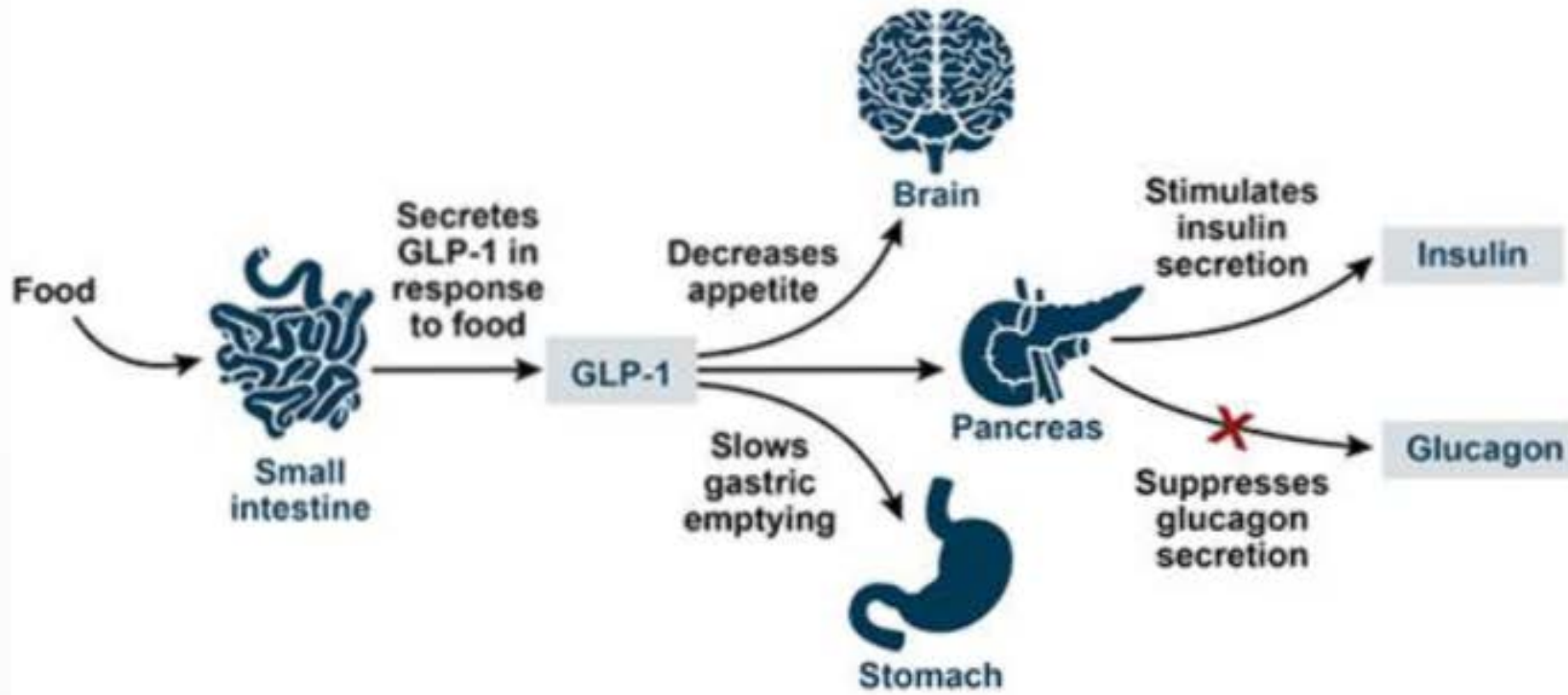
Safety: Effect of SGLT2i on DKA and Amputations





GLP-1 receptor agonists

GLP-1 receptor agonists



Meier JJ et al. Nat Rev Endocrinol. 2012



GLP-1RA CV Outcomes Trials

Generic	Trade Name	CV Outcomes Trial	Results Available
lixisenatide	Adlyxin	ELIXA	2015
liraglutide	Victoza	LEADER	2016
semaglutide	Ozempic	SUSTAIN-6	2016
exenatide	Bydureon	EXSCEL	2017
albiglutide*	Tanzeum	HARMONY	2018
dulaglutide	Trulicity	REWIND	2019

*albiglutide is no longer manufactured

Sharma A et al. Circulation Volume 141, Issue 10, 10 March 2020; Pages 843-862

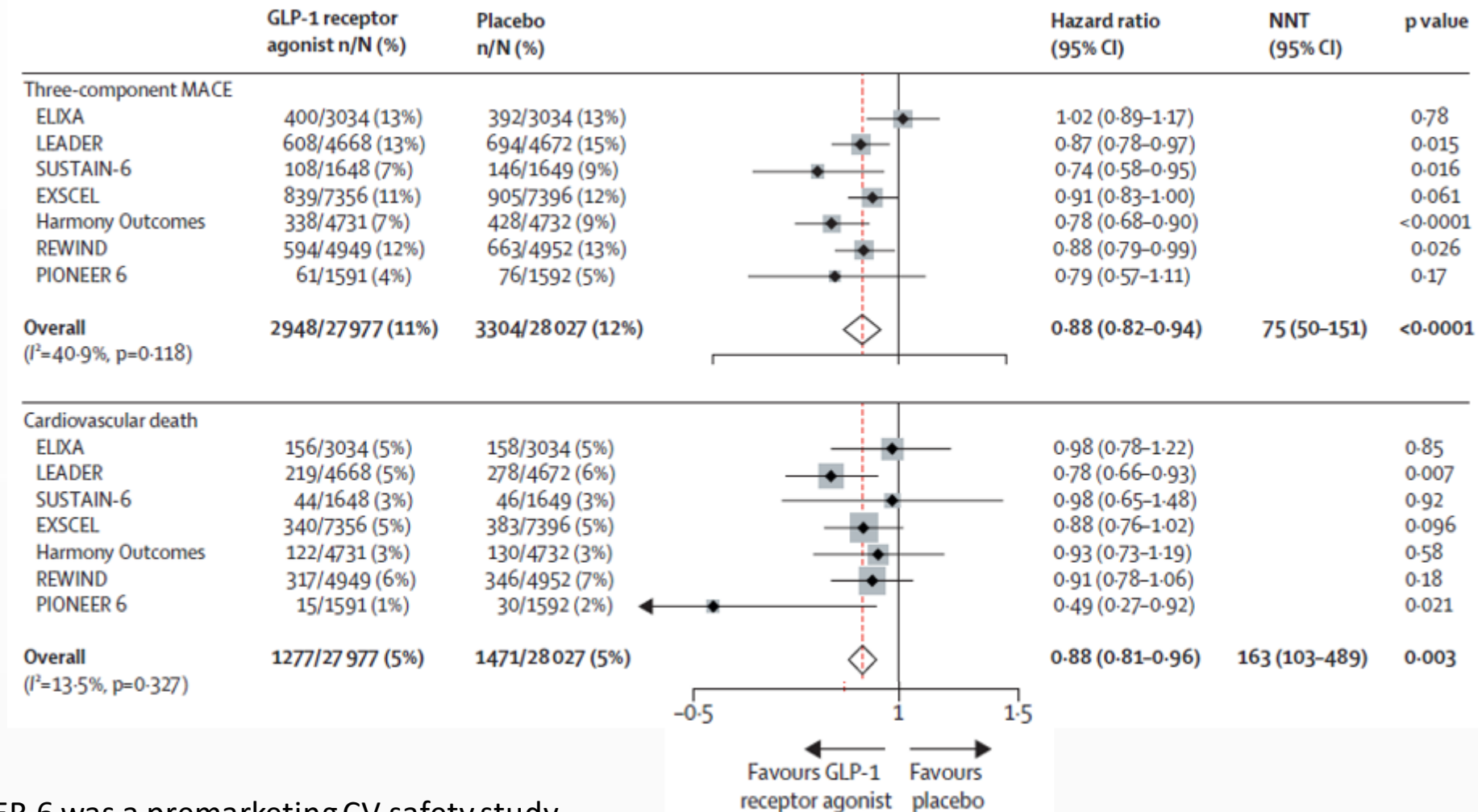
GLP-1RA CVOTs: key baseline characteristics

	ELIXA¹ n=6,068	LEADER² n=9,340	SUSTAIN-6³ n=3,297	EXSCEL⁴ n=14,752	HARMONY⁵ n = 9463	REWIND⁶ n = 9901
	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Abiglutide	Dulaglutide
Mean age, years	60.3	63.1	64.6	62.0	64.1	66.2
Female sex, %	30.7	35.7	39.3	38	30.6	46.3
Mean duration of diabetes, years	9.3	12.7	13.9	12	14.1	10.0
Mean baseline HbA _{1c} , %	7.7	8.7	8.7	8.0	8.8	7.3
Primary prevention, %	0	~19	~17	27	0	68.6
Heart failure, %	12.4	17.1	23.6	16.2	20.3	8.6

1. Bentley-Lewis R et al. Am Heart J 2015;169:631-638.e7 2. Marso S et al. Am Heart J 2013;166:823-830.e5 3. Marso S et al. N Engl J Med 2016;375:1834-44. 4. Mentz R et al. Am Heart J 2017;187:1-9 5. Green J et al. Am Heart J . 2018 Sep;203:30-38 6. Gerstein H et al. Diabetes Obes Metab. 2018;20:42–49.

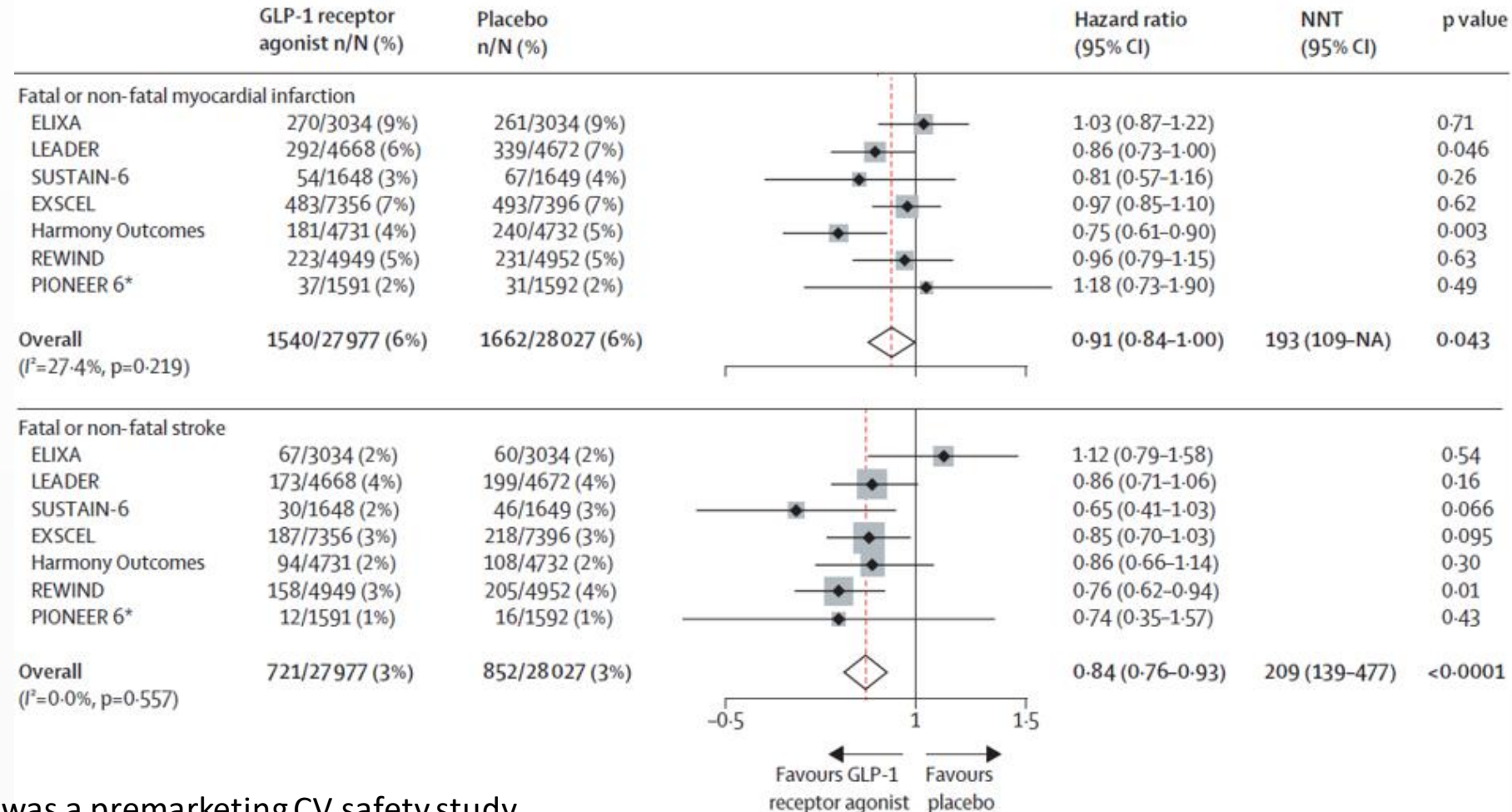


GLP-1RA CVOTs: MACE and CV death meta analysis



PIONEER 6 was a premarketing CV safety study

GLP-1RA CVOTs: MI and Stroke meta analysis

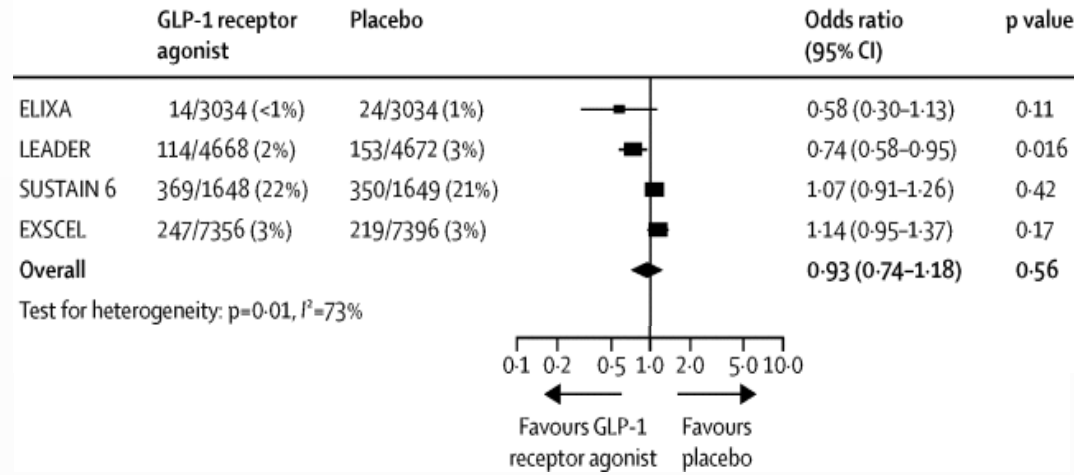


PIONEER 6 was a premarketing CV safety study

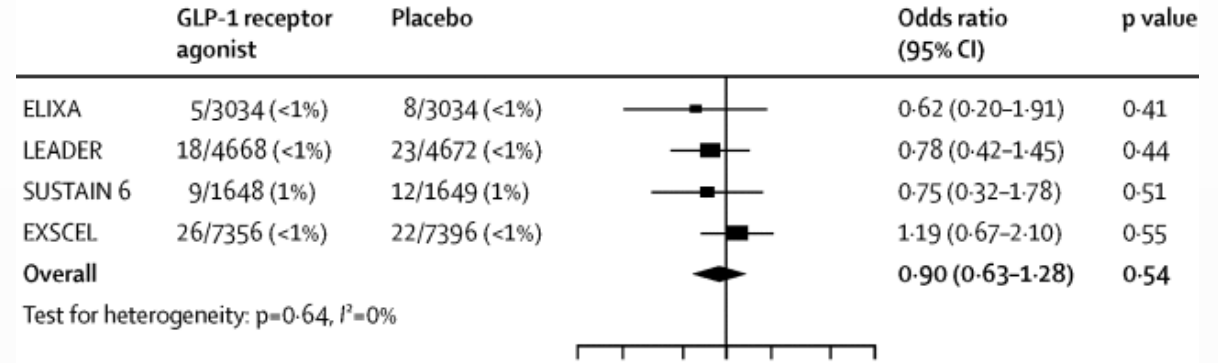


GLP-1RA CVOTs: safety

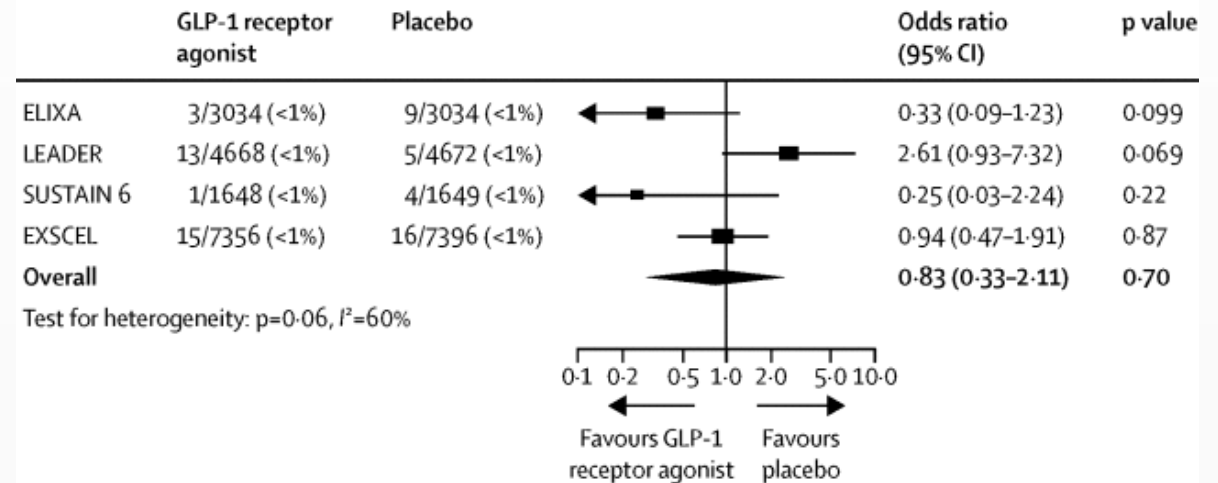
A Severe hypoglycaemia



B Pancreatitis



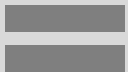
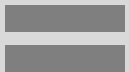
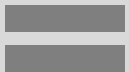
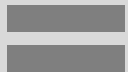



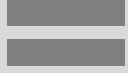






C Pancreatic cancer











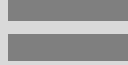


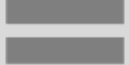




CVOT summary

MACE Outcomes in Trials of T2DM with High ASCVD Risk

	SAVOR TIMI-53	EXAMINE	TECOS	CARMELINA		
DPP-4 inhibitor	 NEUTRAL	 NEUTRAL	 NEUTRAL	 NEUTRAL		
	LEADER	ELIXA	SUSTAIN-6	EXSCEL	HARMONY	REWIND
GLP-1 RA	 BENEFICIAL	 NEUTRAL	 BENEFICIAL	 NEUTRAL	 BENEFICIAL	 BENEFICIAL
	EMPA-REG	CANVAS	DECLARE	VERTIS		
SLGT2-Inhibitor	 BENEFICIAL	 BENEFICIAL	 NEUTRAL	 NEUTRAL		



HF Outcomes in Trials of T2DM with High ASCVD Risk

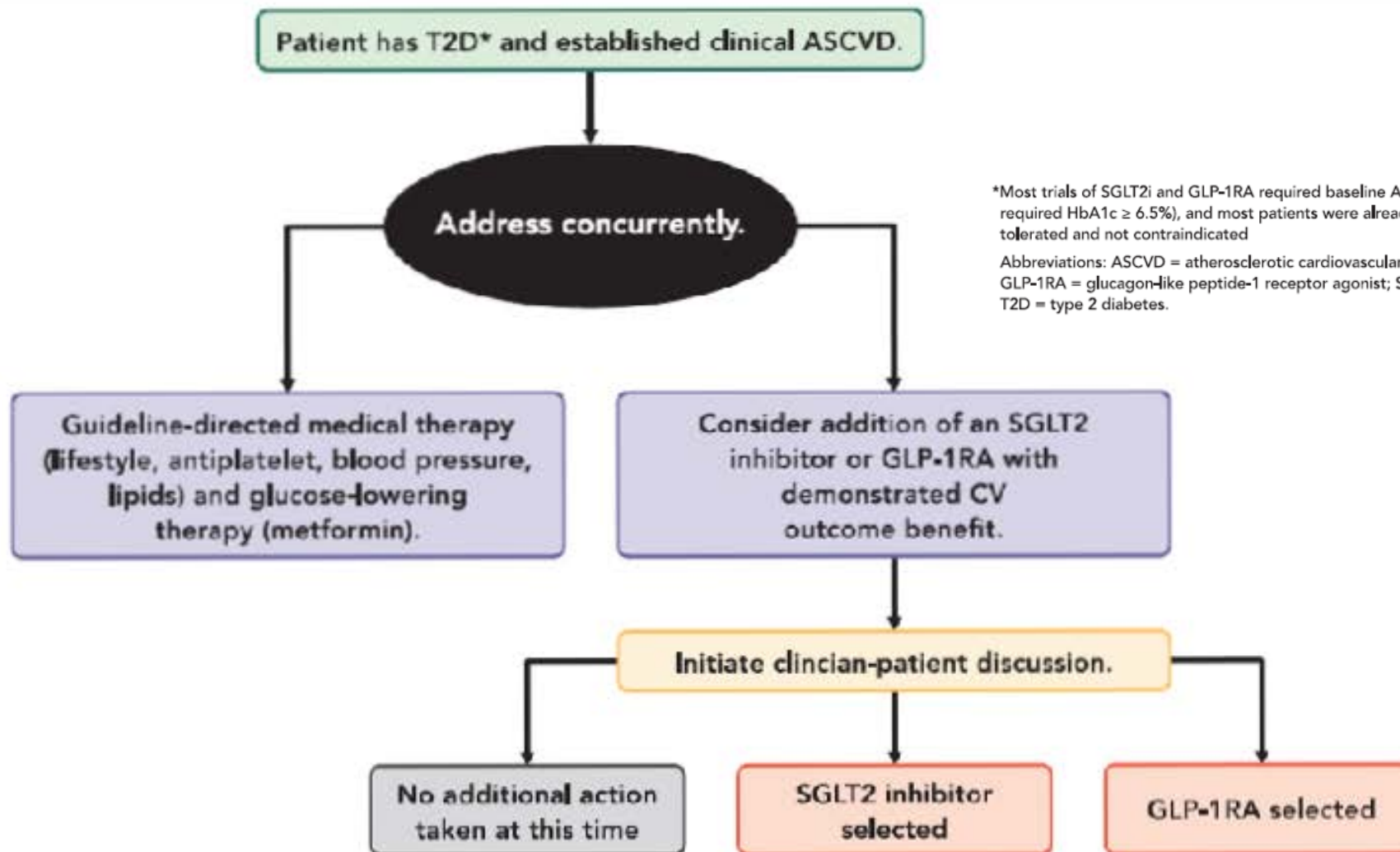
	SAVOR TIMI-53	EXAMINE	TECOS	CARMELINA		
DPP-4 inhibitor	 INCREASED RISK	 NEUTRAL	 NEUTRAL	 NEUTRAL		
	LEADER	ELIXA	SUSTAIN-6	EXSCEL	HARMONY	REWIND
GLP-1 agonist	 NEUTRAL	 NEUTRAL	 NEUTRAL	 NEUTRAL	 BENEFICIAL	 NEUTRAL
	EMPA-REG	CANVAS	DECLARE	VERTIS		
SLGT2-Inhibitor	 BENEFICIAL	 BENEFICIAL	 BENEFICIAL	 BENEFICIAL		



Comparative meta-analysis

	SGLT-2	GLP-1RA
MACE	0.87 [0.82, 0.92]	0.86 [0.80, 0.93]
HHF	0.69 [0.61, 0.79]	0.93 [0.83, 1.04]
Renal	0.55 [0.48, 0.64]	0.92 [0.80, 1.06]

2018 ACC Expert Consensus Decision Pathway



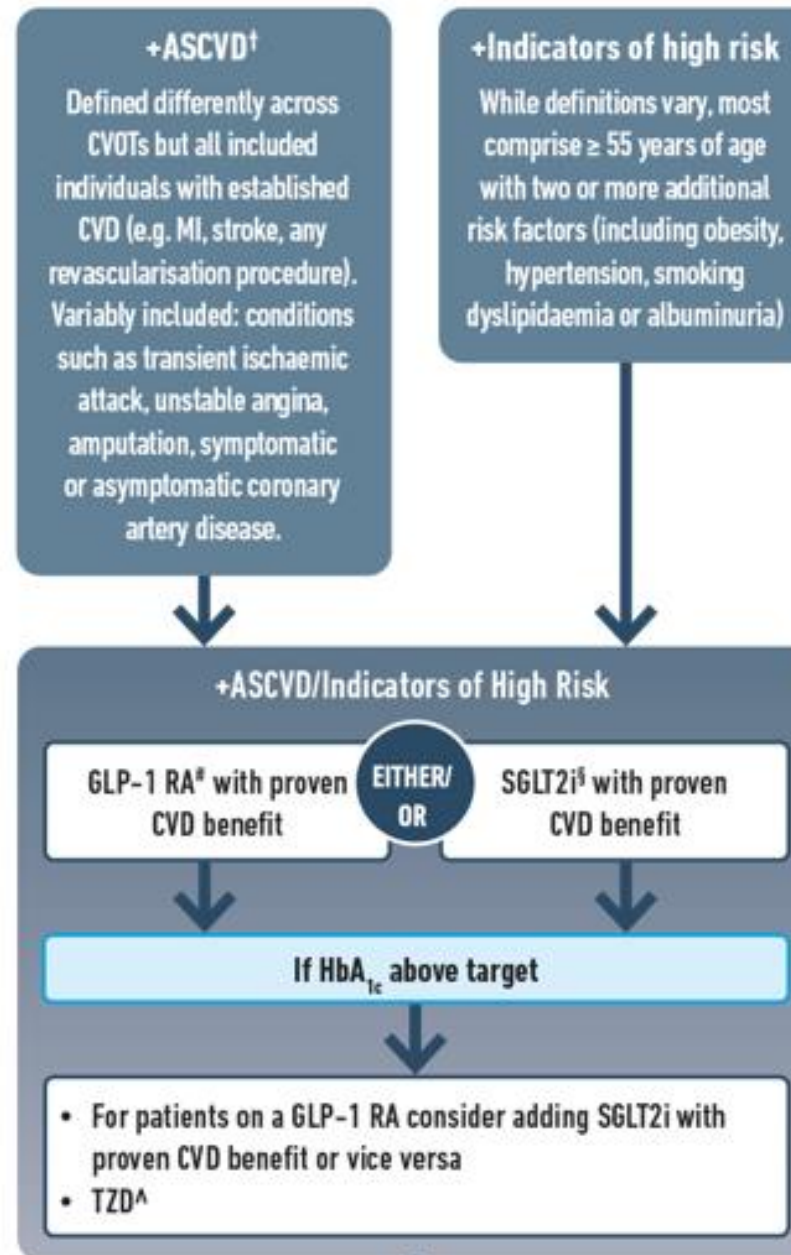
*Most trials of SGLT2i and GLP-1RA required baseline A1C $\geq 7\%$ (Example: EXSCEL Trial required HbA1c $\geq 6.5\%$), and most patients were already on metformin as first-line therapy if tolerated and not contraindicated

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes.



ADA Guidelines

Treatment of T2DM with high ASCVD risk



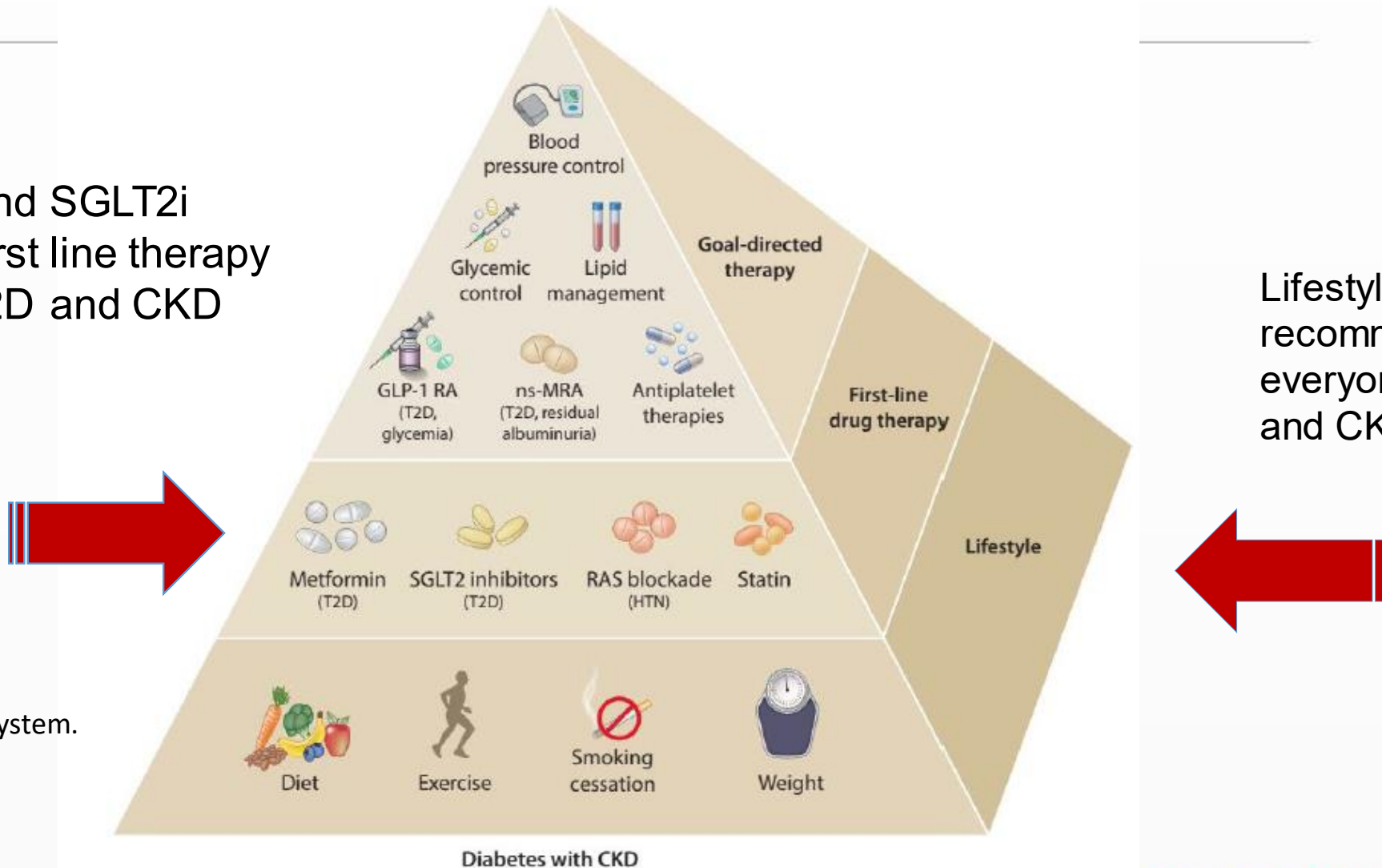
1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022. 2. *Diabetes Care* December 2022, Vol.46, S1-S4. doi:<https://doi.org/10.2337/dc23-Sint>



KDIGO Guideline: Care of T2DM with CKD

RAS blockade and SGLT2i recommended first line therapy in people with T2D and CKD

Lifestyle therapy recommended for everyone with T2D and CKD



RAS, renin-angiotensin system.



SGLT2i IN HF

2022 ACC/AHA/HFSA Heart Failure Guideline

Stage of HF	Recommendation	COR
Stage A, at risk for HF	To prevent HF hospitalization in patients with T2D who have CVD or are at high risk for CVD	1
Stage C, symptomatic HF		
HFrEF	To reduce HF hospitalization and CV mortality in patients with symptomatic chronic HFrEF, regardless of the presence of T2D	1
HFpEF	To reduce HF hospitalizations and CV mortality in patients with HFpEF	2a
HFmrEF	To reduce HF hospitalizations and CV mortality in patients with HFmrEF	2a

COR, class of recommendation; CVD, cardiovascular disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes



Summary

- Every patient with DM + ASCVD should be considered for a CVOT DM drug
- Numerous SGLT-2i and GLP-1RA have proven efficacy
 - DPP-4i have not shown CV benefit
- Select agents with demonstrated outcomes benefit to treat high risk patients. These currently include:
 - SGLT2i: empagliflozin, canagliflozin, dapagliflozin
 - GLP-1RA: liraglutide, injected semaglutide, dulaglutide