A focus on GLP-1 RAs cardiovascular and renal benefits and clinical recommendations

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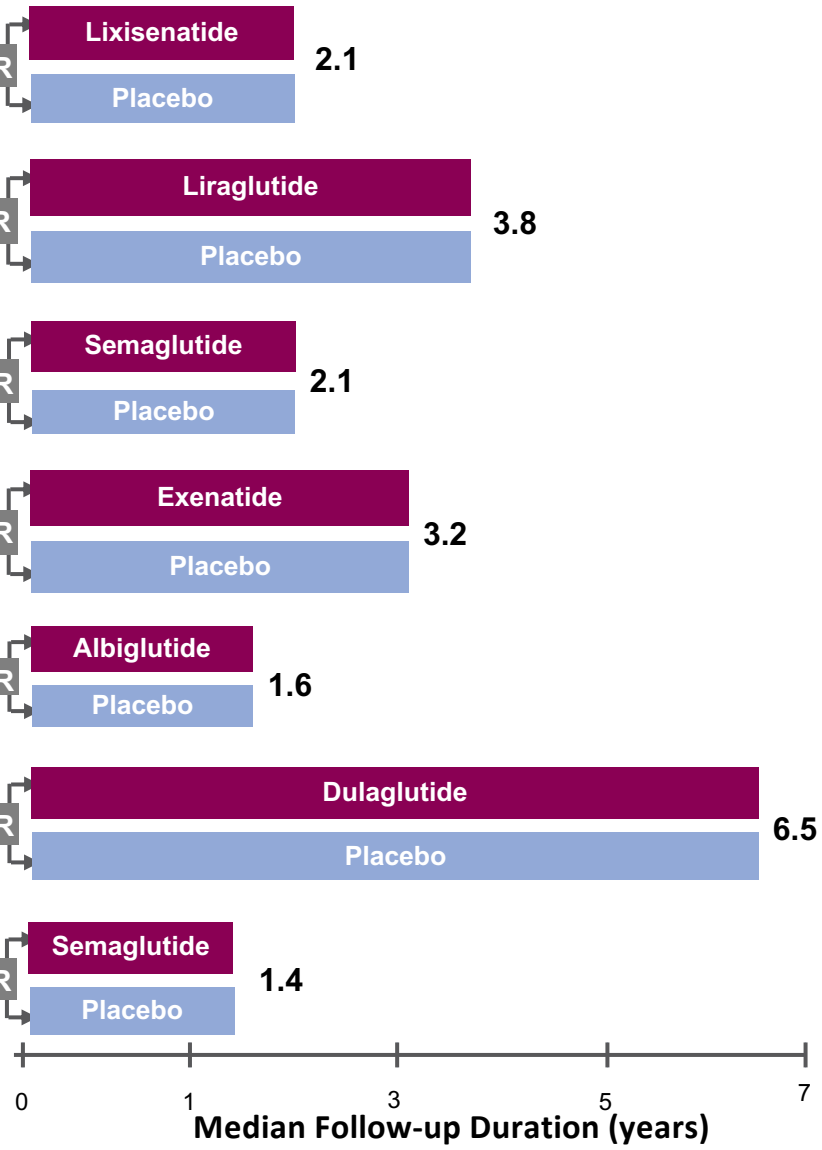
Completed GLP-1 RA CVOTs

	Key inclusion criteria	HbA_{1C} (%)	Median follow-up duration (y)	Drug exposure time (y)	Primary End point
ELIXA (1) N=6068	ACS within 180 days ≥30y	5.5-11.0	Lixisenatide 2.1 / Placebo	1.9 / 2.0	MACE-4 (non-inferiority)
LEADER® (2) Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results N=9340	≥50y with CVD/renal dysfunction/HF, or ≥60y with CV RFs	≥7.0	Liraglutide 3.8 / Placebo	3.5 / 3.5	MACE-3 (non-inferiority for safety/ superiority for efficacy)
SUSTAIN-6 (3) N=3297	≥50y with CVD, or ≥60y with subclinical CVD	≥7.0	Semaglutide 2.1 / Placebo	1.8 / 1.9	MACE-3 (non-inferiority)
EXSCEL (4) N=14752	Established CVD as well as primary prevention (70/30 split), ≥18y	6.5-10.0	Exenatide 3.2 / Placebo	2.4 / 2.3	MACE-3 (non-inferiority for safety/ superiority for efficacy)
HARMONY (5) N=9463	≥40y with established CVD	≥7.0	Albiglutide 1.6 / Placebo	1.4 / 1.3	MACE-3 (non-inferiority for safety/ superiority for efficacy)
REWIND (6,7) N=9901	≥50y with established clinical vascular disease, ≥55y with subclinical vascular disease, or ≥60y with ≥2 CV RFs	≤9.5	Dulaglutide 6.5 / Placebo	5.3 / 5.4	MACE-3 (superiority for efficacy)
PIONEER 6 (8) N=3183	≥50y with CVD, or ≥60y with CV RFs	≥7.0	Semaglutide 1.4 / Placebo	NR / NR	MACE-3 (non-inferiority for safety)



ACS, acute coronary syndrome; CV, cardiovascular; CVD, CV disease; CVOTs, cardiovascular outcomes trials; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HF, heart failure; MACE, major adverse CV events; NR, not reported; R, randomisation; RFs, risk factors; y, years.

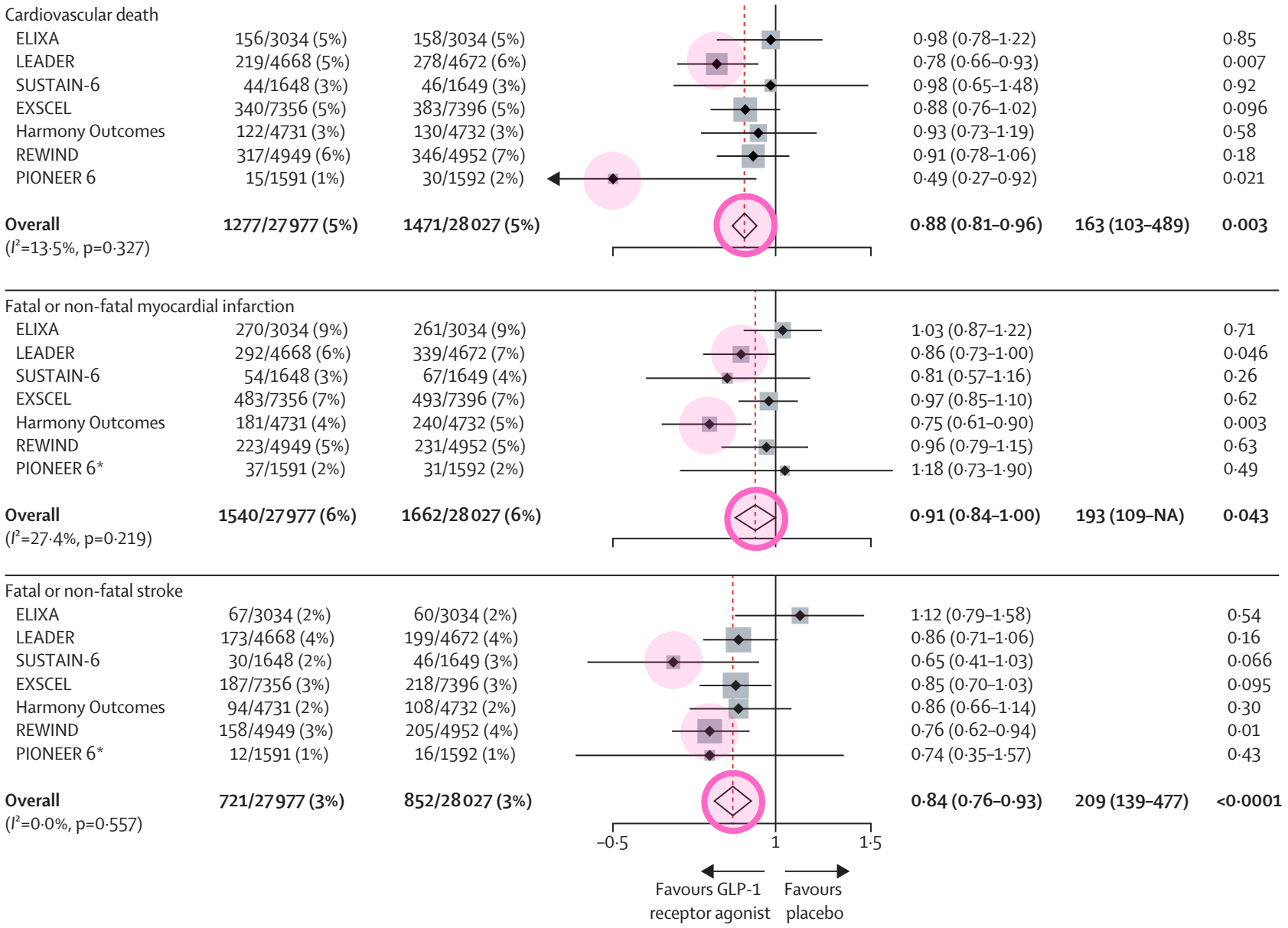
[1]Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257
[2]Marso SP, et al. *N Engl J Med* 2016;375:311–322
[3]Marso SP, et al. *N Engl J Med* 2016;375:1834–1844
[4]Holman RR, et al., *N Engl J Med* 2017;377:1228–1239
[5]Hernandez AF, et al. *Lancet* 2018;392(10157):1519–1529
[6]Gerstein HC, et al. *Diabetes Obes Metab* 2018;20:42–49
[7]https://clinicaltrials.gov/ct2/show/NCT01394952
[8]Husain M, et al *N Eng J Med* 2019

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER 6	
MACE HR	1.02 [95% CI 0.89–1.17])	**0.87 [95% CI 0.78–0.97] p=0.01**	**0.74 [95% CI 0.58–0.95] p=0.02**	0.91 [95% CI 0.83–1.00] p=0.06	**0.78 [95% CI 0.68–0.90] p=0.0006**	**0.88 [95% CI 0.79–0.99] p=0.026**	0.79 [95% CI 0.57-1.11) p=0.17	**Main Outcomes**
All-cause mortality HR	0.94 [95% CI 0.78–1.13]	0.85 [95% CI 0.74–0.97]	1.05 [95% CI 0.74 –1.50]	0.86 [95% CI 0.77–0.97]	0.95 [95% CI 0.79–1.16]	0.90 [95% CI 0.80–1.01]	0.51 [95% CI 0.31-0.84)	

Pfeffer, M.A. *et al.* (2015) *N. Engl. J. Med.* 373, 2247–2257; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 311–322; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 1834–1844; Holman, R.R. *et al.* (2017) *N. Engl. J. Med.* 377, 1228–1239; Hernandez, A.F. *et al.* (2018) *Lancet* 392, 1519–1529; Gerstein, H.C. *et al.* (2019) *Lancet* DOI: 10.1016/S0140-6736(19)31149-3; Husain, M. *et al.* (2019) *N. Engl. J. Med.* DOI: 10.1056/NEJMoa1901118.

Caruso I et al., *Trends Endocrinol Metab* 2019

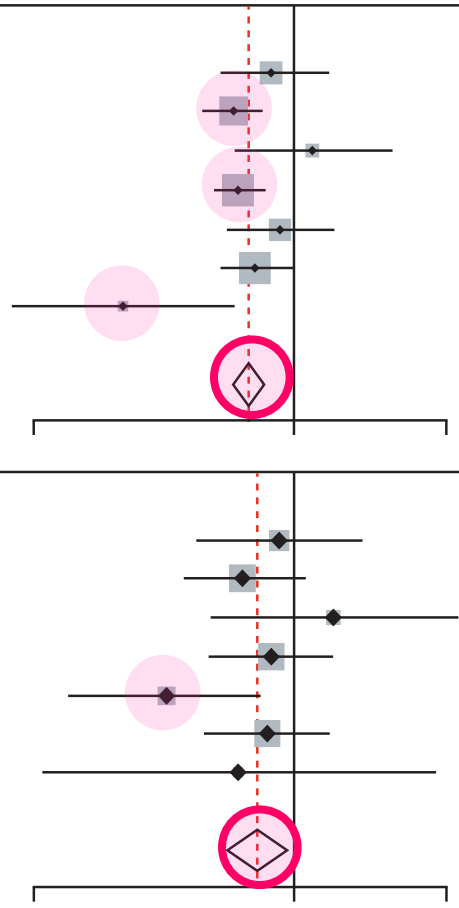
Individual Components of the Primary Endpoint in GLP-1RA CVOTs



Kristensen S, et al, Lancet 2019

All-Cause Mortality and Hospitalization for Heart Failure in GLP-1RA CVOT

	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%)	223/3034 (7%)	0·94 (0·78–1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	295/4732 (4%)	0·95 (0·79–1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80–1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31–0·84)		0·008
Overall (I^2=16·5%, p=0·304)	**1916/27 977 (7%)**	**2246/28 027 (8%)**	**0·88 (0·83–0·95)**	**108 (77 to 260)**	**0·001**
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75–1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73–1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77–1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78–1·13)		0·51
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53–0·94)		<0·0001
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77–1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48–1·44)		0·59
Overall (I^2=0·0%, p=0·595)	**936/27 977 (3%)**	**1016/28 027 (4%)**	**0·91 (0·83–0·99)**	**312 (165 to 2810)**	**0·028**



Kristensen S, et al, Lancet 2019

Trends in Endocrinology & Metabolism

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REVIEWS

Opinion

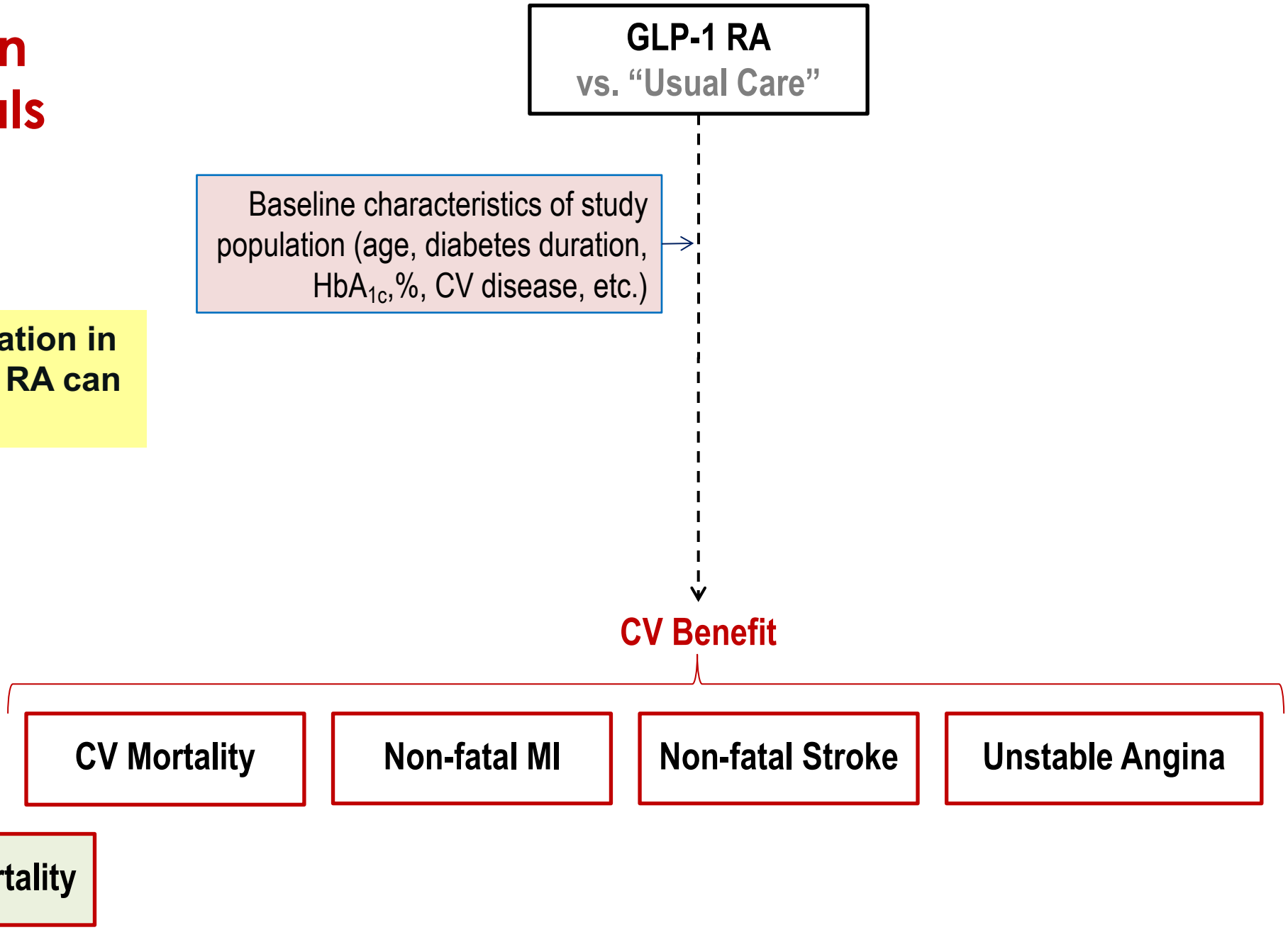
Heterogeneity and Similarities in GLP-1 Receptor Agonist Cardiovascular Outcomes Trials

Irene Caruso,[1] Angelo Cignarelli,[1] and Francesco Giorgino[1,*]

Trends in Endocrinology & Metabolism, September 2019, Vol. 30, No. 9

Potential Factors in CV Outcomes Trials with GLP-1 RAs

Is there a specific T2D population in which CV benefit with GLP-1 RA can be seen?



CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; MI, myocardial infarction; T2D, type 2 diabetes mellitus.

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER 6	
Diabetes duration (years)	9.3	12.8	13.9	12	14.1	10	14.9	Baseline Risk Level
Baseline HbA1c (%)	7.6	8.7	8.7	8.0	8.7	7.3	8.2	
Baseline BMI (kg/m²)	30.1	32.5	32.8	31.7	32.3	32.3	32.3	
History of CVD (%)	100	81.3	83	73.1	100	31.4	84.6	
Hypertension (%)	76.3	90	92.8	90.3	86.4	93.2	95.3	
eGFR <60 (%)	23.2	21.7	28.5	21.7	22.6	22.2	27	
Mortality rate (events/100 patient-yr)	3.1; 3.3	2.1; 2.5	1.8; 1.7	2.0; 2.3	2.4; 2.5	2.1; 2.3	1.1; 2.2	
MACE rate (events/100 patient-yr)	6.4; 6.3	3.4; 3.9	3.2; 4.4	3.7; 4.0	4.6; 5.9	2.4; 2.7	2.9; 3.7	
MACE HR	1.02 [95% CI 0.89–1.17])	**0.87 [95% CI 0.78–0.97] p=0.01**	**0.74 [95% CI 0.58–0.95] p=0.02**	0.91 [95% CI 0.83–1.00] p=0.06	**0.78 [95% CI 0.68–0.90] p=0.0006**	**0.88 [95% CI 0.79–0.99] p=0.026**	0.79 [95% CI 0.57-1.11] p=0.17	Main Outcomes
All-cause mortality HR	0.94 [95% CI 0.78–1.13]	0.85 [95% CI 0.74–0.97]	1.05 [95% CI 0.74 –1.50]	0.86 [95% CI 0.77–0.97]	0.95 [95% CI 0.79–1.16]	0.90 [95% CI 0.80–1.01]	0.51 [95% CI 0.31-0.84)	

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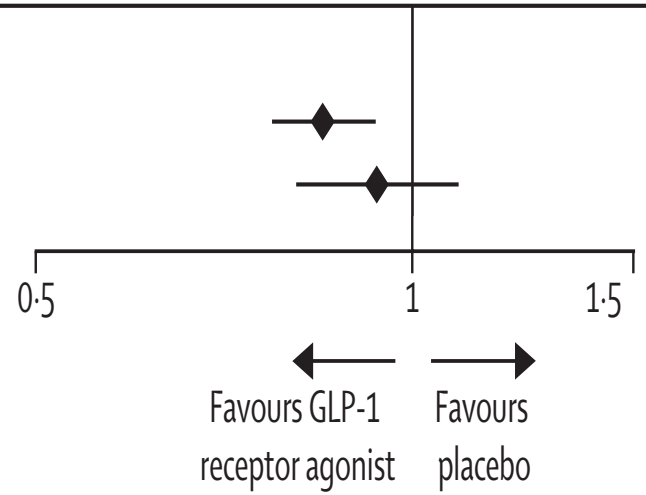
REWIND
Dulaglutide CV Outcomes Trial

CV Composite in Prespecified Subgroups

Subgroups	Dulaglutide Events/Total (%)	Dulaglutide Rate/100 py	Placebo Events/Total (%)	Placebo Rate/100 py	Hazard Ratio 95% CI	P value for Interaction
Overall	594 /4949 (12.0)	2.4	663 /4952 (13.4)	2.7	0.88 (0.79-0.99)	.
Age						
≥ 66 years	331 /2314 (14.3)	2.9	384 /2350 (16.3)	3.3	0.86 (0.74-1.00)	
< 66 years	263 /2635 (10.0)	1.9	279 /2602 (10.7)	2.1	0.92 (0.78-1.09)	0.571
Sex						
Female	218 /2306 (9.5)	1.8	249 /2283 (10.9)	2.1	0.85 (0.71-1.02)	
Male	376 /2643 (14.2)	2.8	414 /2669 (15.5)	3.1	0.90 (0.79-1.04)	0.598
Duration of Diabetes						
< 5 years	128 /1227 (10.4)	2.0	146 /1192 (12.2)	2.4	0.84 (0.66-1.06)	
5 - 10 years	174 /1446 (12.0)	2.3	196 /1476 (13.3)	2.6	0.89 (0.73-1.09)	
≥ 10 years	292 /2276 (12.8)	2.5	321 /2284 (14.1)	2.8	0.90 (0.77-1.06)	0.877
History of CVD						
Prior CVD	280 /1560 (17.9)	3.7	315 /1554 (20.3)	4.2	0.87 (0.74-1.02)	
No Prior CVD	277 /3093 (8.9)	1.7	317 /3128 (10.1)	2.0	0.87 (0.74-1.02)	0.970
Baseline HbA1c						
≥ 7.2%	328 /2610 (12.6)	2.5	373 /2603 (14.3)	2.9	0.86 (0.74-1.00)	

Meta-analysis of GLP-1RA Trials on the Composite of MI, Stroke, and CV Death by the Presence of ASCVD

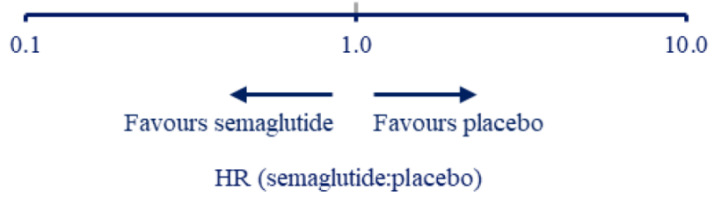
	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	$p_{interaction}$
Established cardiovascular disease				0·22
Yes	2431/21253 (11%)	2755/21202 (13%)	0·86 (0·79–0·94)	
No	480/6428 (7%)	518/6555 (8%)	0·95 (0·83–1·08)	



Kristensen S, et al, Lancet 2019

Semaglutide (SUSTAIN and PIONEER) Reduces Cardiovascular Events in Type 2 Diabetes Across Varying Cardiovascular Risk

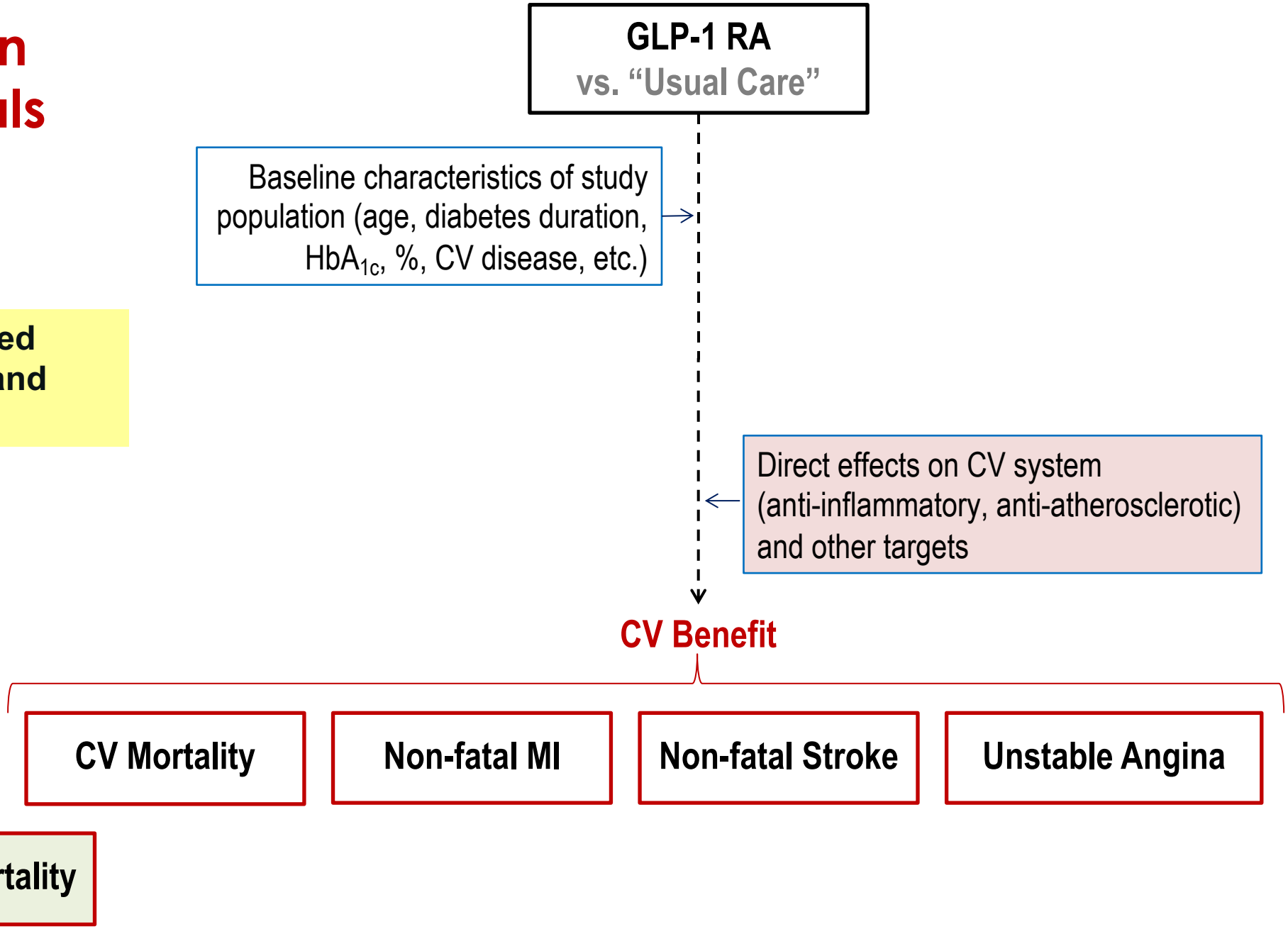
			Time to first event	No. of events/analyzed subjects [incidence rate per 100 subject-years]				
				Semaglutide	Placebo	HR	(95% CI)	Interaction *P*-value
SUSTAIN 6 + PIONEER 6	Total population			169/3,239 [3.1]	222/3,241 [4.2]	0.76	(0.62, 0.92)	
	Evidence of CVD	Established CVD and/or CKD		155/2,703 [3.5]	205/2,727 [4.6]	0.75	(0.61, 0.93)	0.944
		CV risk factors only		14/536 [1.5]	17/514 [2.0]	0.77	(0.38, 1.57)	
	By prior MI or stroke	Yes		107/1,366 [4.8]	132/1,429 [5.8]	0.83	(0.64, 1.07)	0.292
		No		62/1,859 [2.0]	90/1,800 [3.0]	0.67	(0.48, 0.92)	
	Prior HF (NYHA Class II or III)	Yes		51/473 [6.4]	49/488 [6.0]	1.06	(0.72, 1.57)	0.046
		No		116/2,747 [2.5]	172/2,739 [3.8]	0.67	(0.53, 0.84)	



Husain M et al., DOM 2020

Potential Factors in CV Outcomes Trials with GLP-1 RAs

Do exendin-4 and GLP-1 based agonists differ in signalling and bioeffects?



CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; MI, myocardial infarction; T2D, type 2 diabetes mellitus.

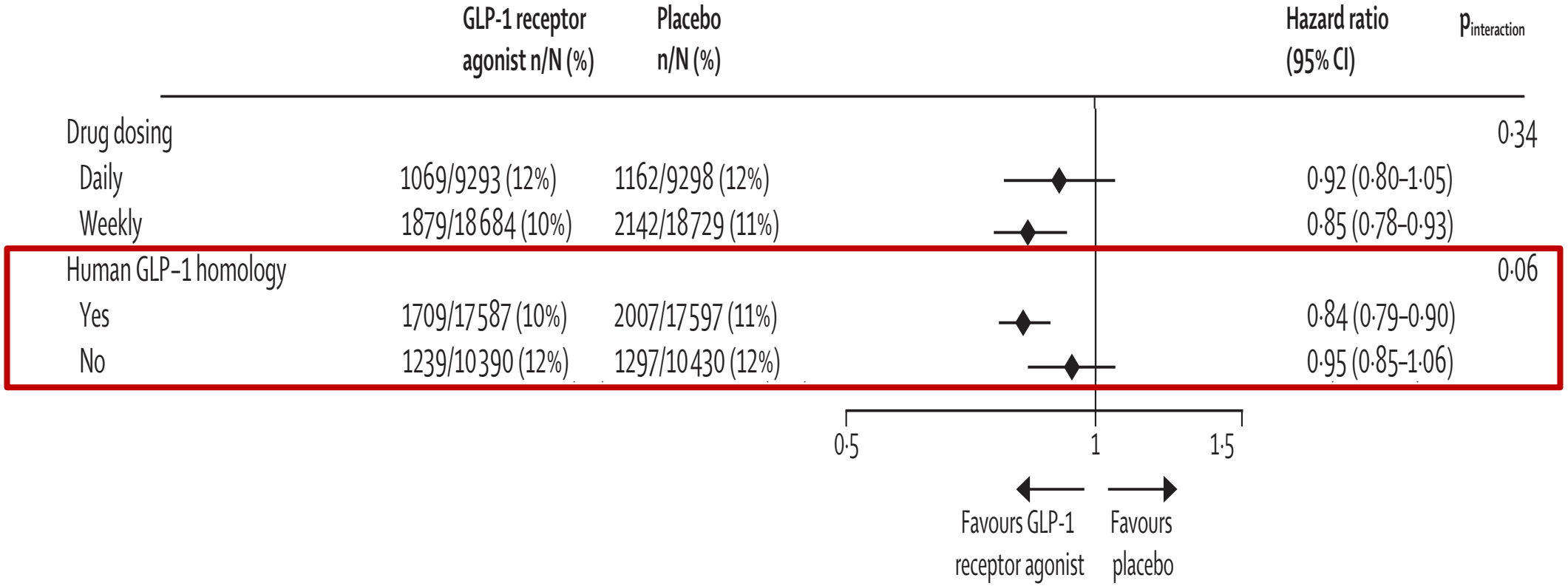
	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY
MACE HR	1.02 (0.89–1.17)	**0.87 (0.78–0.97)**	**0.74 (0.58–0.95)**	0.91 (0.83–1.00)	**0.78 (0.68–0.90)**
GLP-1 RA	Lixisenatide	Liraglutide	Semaglutide	Exenatide LAR	Albiglutide
GLP-1 RA Backbone	Exendin-4	Human GLP-1	Human GLP-1	Exendin-4	Human GLP-1

	REWIND	PIONEER 6
MACE HR	**0.88 (0.79–0.99)**	0.79 (0.57-1.11)
GLP-1 RA	Dulaglutide	Semaglutide
GLP-1 RA Backbone	Human GLP-1	Human GLP-1

GLP-1 RA, glucagon-like receptor agonist; MACE, major adverse cardiovascular event; HR, hazard ratio.

Adapted from: Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247–2257; Marso SP, et al. *N Engl J Med*. 2016;375:311–22; Marso SP, et al. *N Engl J Med*. 2016 375:1834–1844; Holman RR, et al. *N Engl J Med*. 2017;377:1228–1239; Hernandez AF, et al. *Lancet*. 2018;392(10157):1519–1529

Do exendin-4 vs GLP-1 based agonists differ in signaling and bioeffects?



Kristensen S, et al, *Lancet* 2019

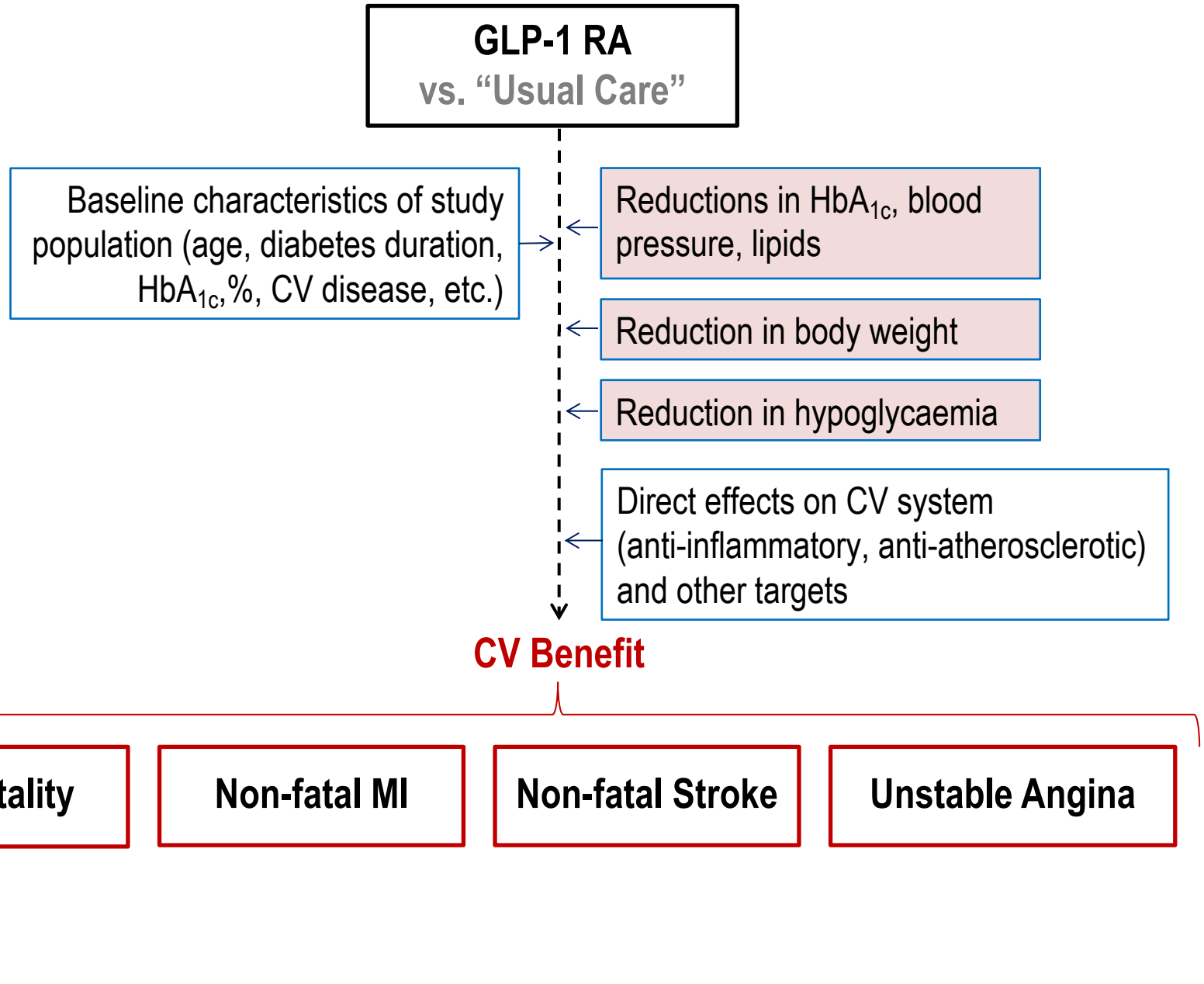
Effects of GLP-1 or GLP-1 Receptor Agonists in Human Studies, with Potential Impact on Cardiovascular Function

Effect	GLP-1 [7-36 amide or 7-37]	Liraglutide	Exenatide
Cardioprotection against ischemia	↑ LVEF; ↑ regional wall motility	preserved LVEF after PCI/NSTEMI	↑ salvage index after STEMI; ↓ infarct size

ACh, acetylcholine; CAD, coronary artery disease; CPC, cardiac progenitor cell; CV, cardiovascular; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HUVEC, human umbilical vein endothelial cell; IL, interleukin; LVEF, left ventricular ejection fraction; NO, nitric oxide; ns, not significant; NSTEMI, non ST-elevated myocardial infarction; PCI, percutaneous coronary intervention; T2D, type 2 diabetes mellitus; TNF, tumour necrosis factor.
Adapted from Nauck MA, et al. *Circulation.* 2017;136:849–870

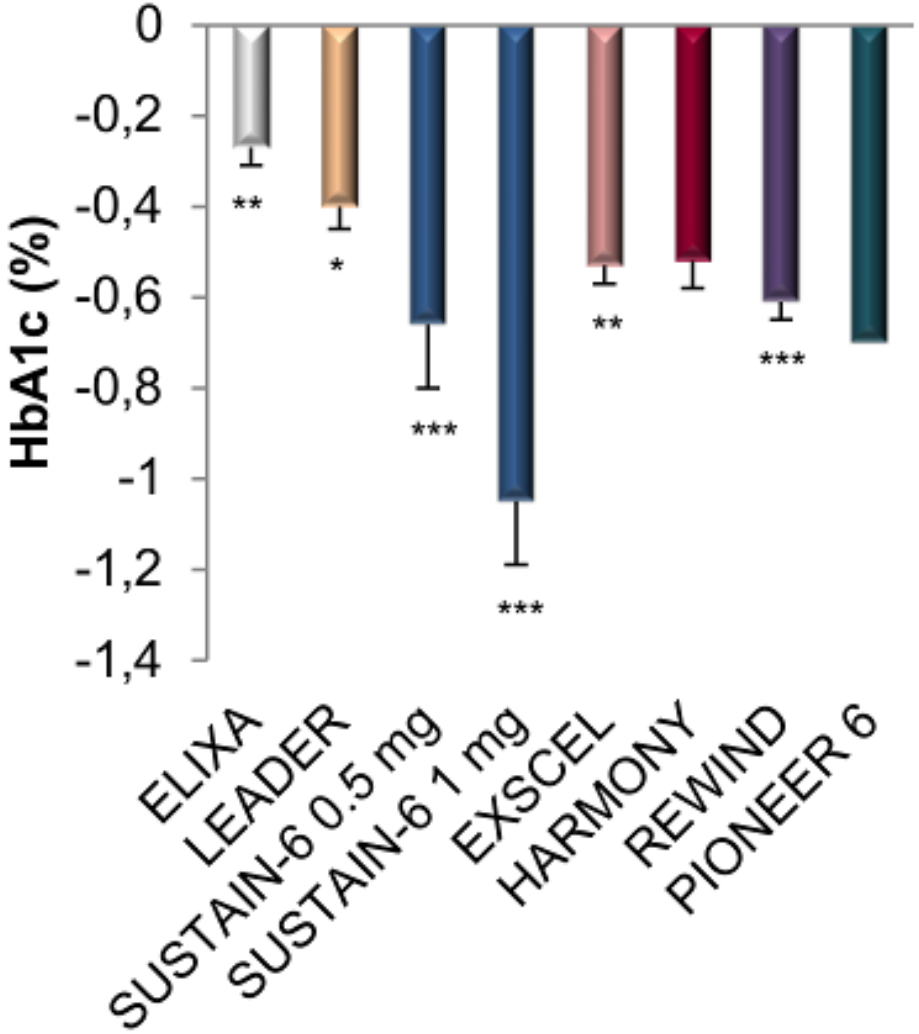
Potential Factors in CV Outcomes Trials with GLP-1 RAs

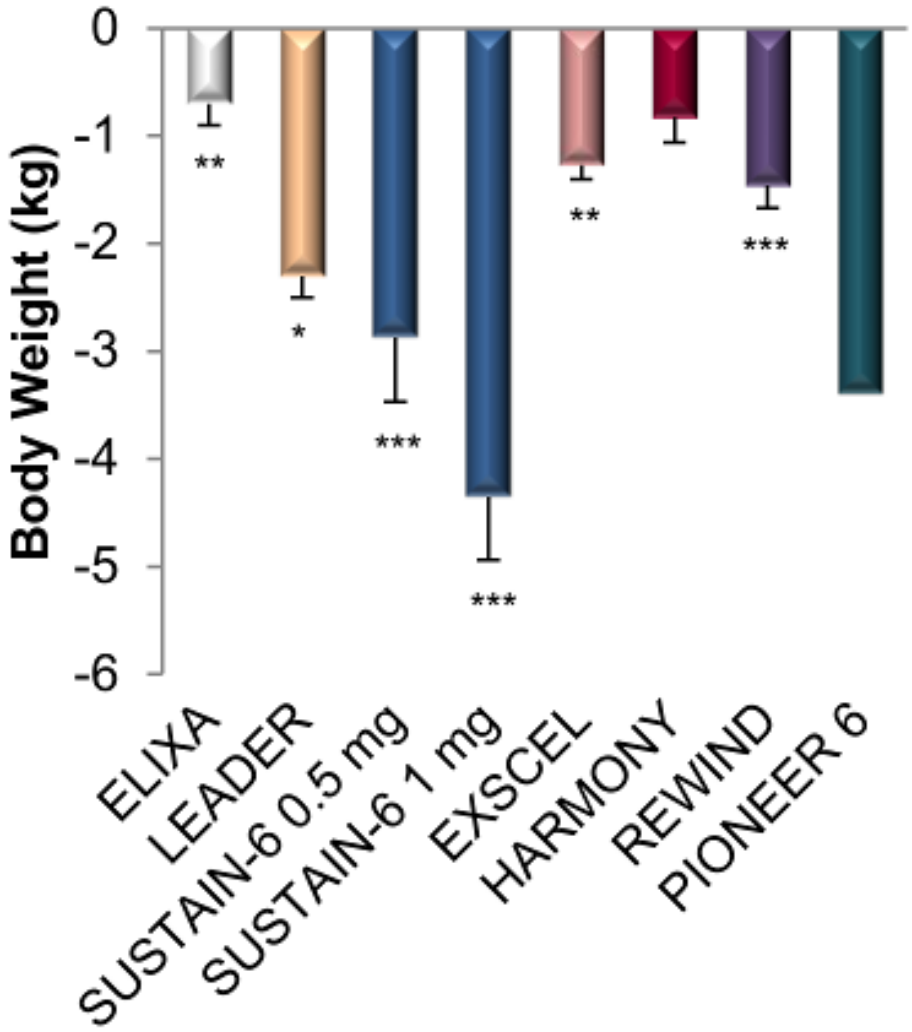
What is the contribution of correction of hyperglycaemia and control of other CV risk factors to the CV benefit?



CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; MI, myocardial infarction.

GLP-1 RA vs Usual Care: Changes in Factors Potentially Affecting CV Risk



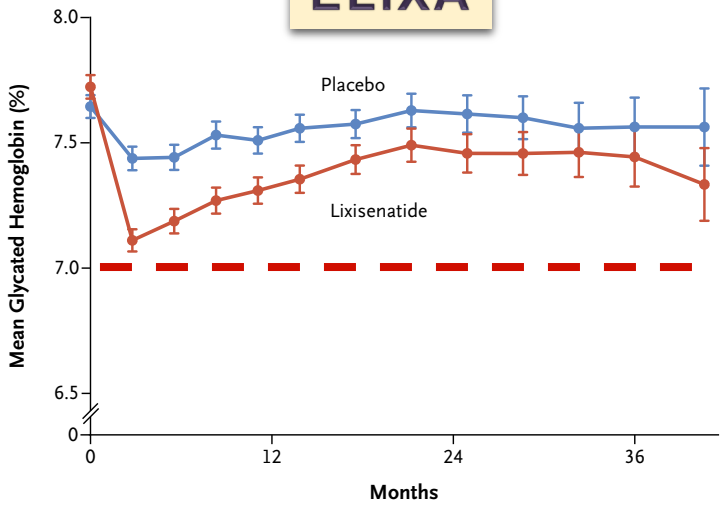


*p<0.05; **p<0.01;***p<0.001

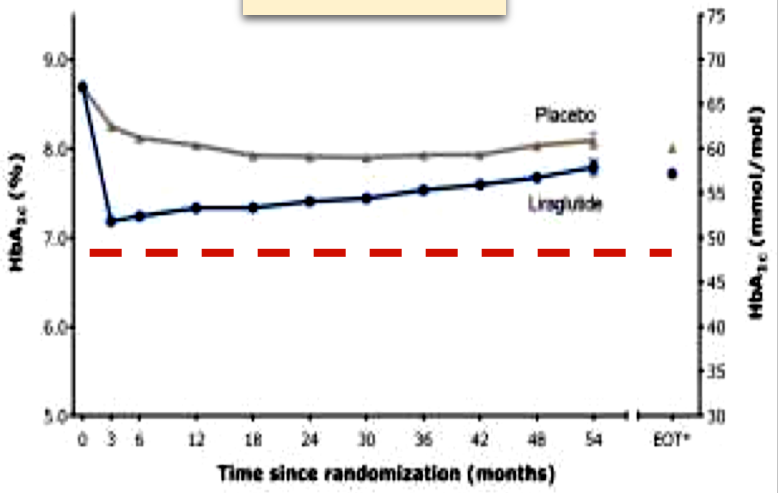
Caruso I et al., *Trends Endocrinol Metab* 2019;30(9):578-589

Change in HbA1c from Baseline throughout the Trial

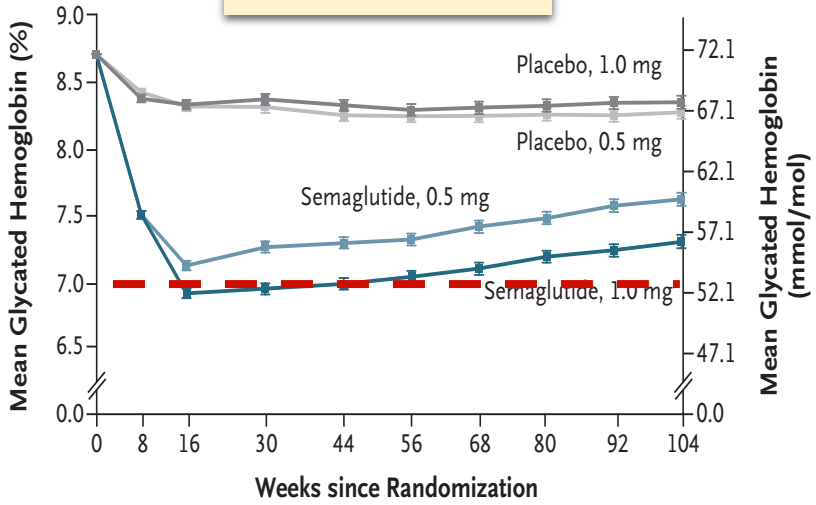
ELIXA



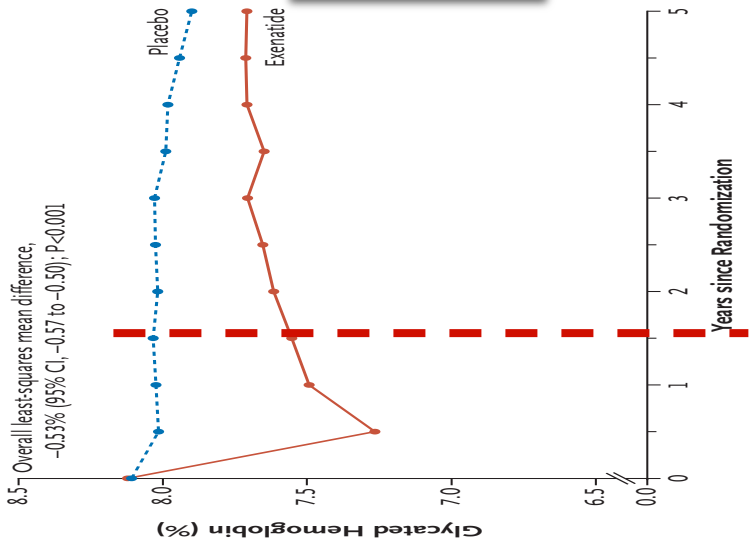
LEADER



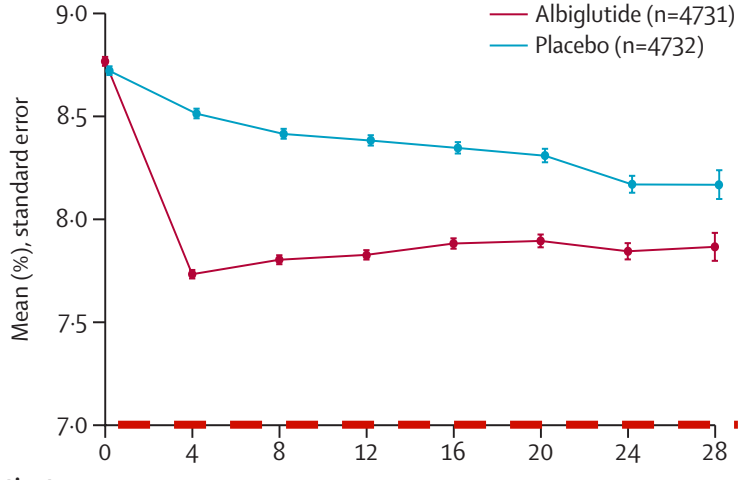
SUSTAIN-6



EXSCEL



HARMONY



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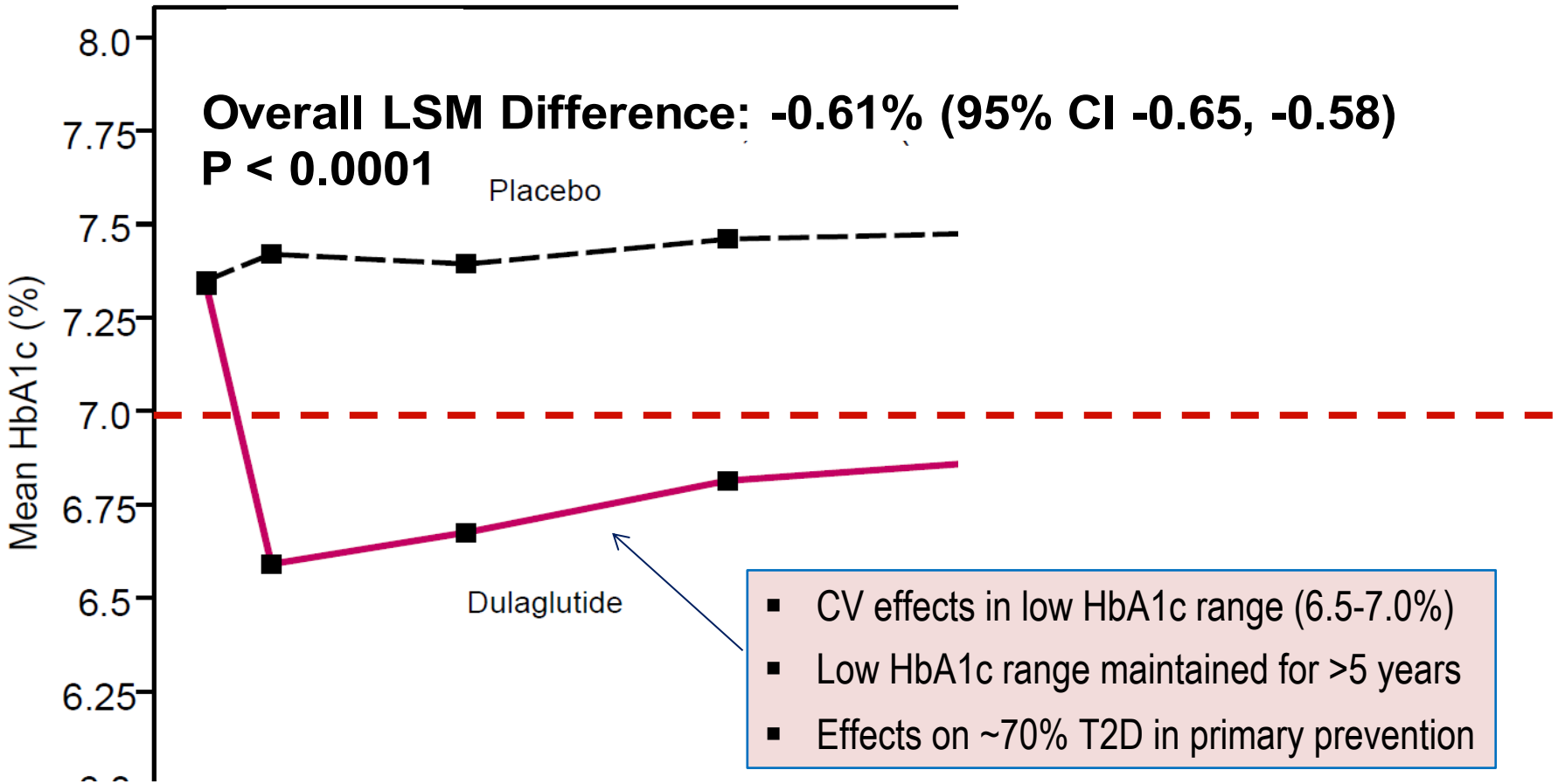
REWIND
Dulaglutide CV Outcomes Trial

Dulaglutide's Effect on HbA1c

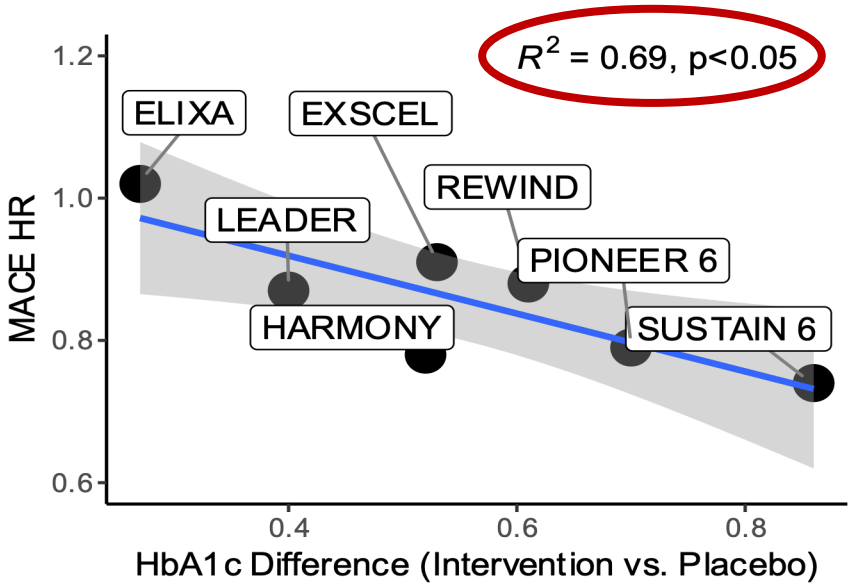
Gerstein, H.C. *et al. Lancet* (2019) .1016/S0140-6736(19)31149-3



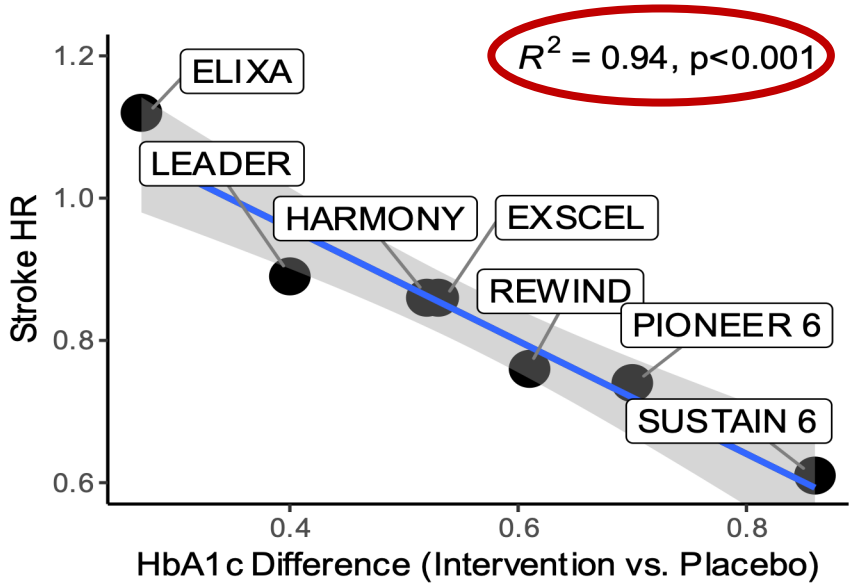
- CV effects in low HbA1c range (6.5-7.0%)
- Low HbA1c range maintained for >5 years
- Effects on ~70% T2D in primary prevention

Does Glycemia Matter?

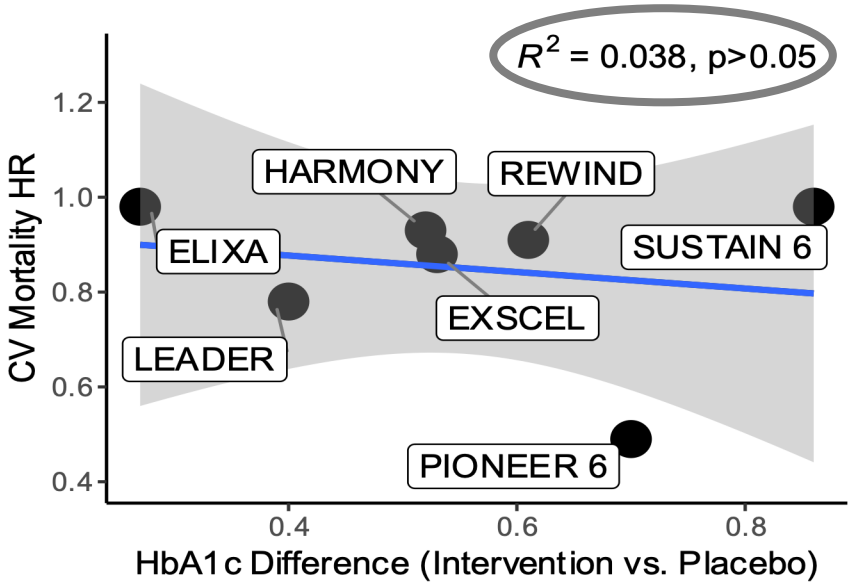
MACE



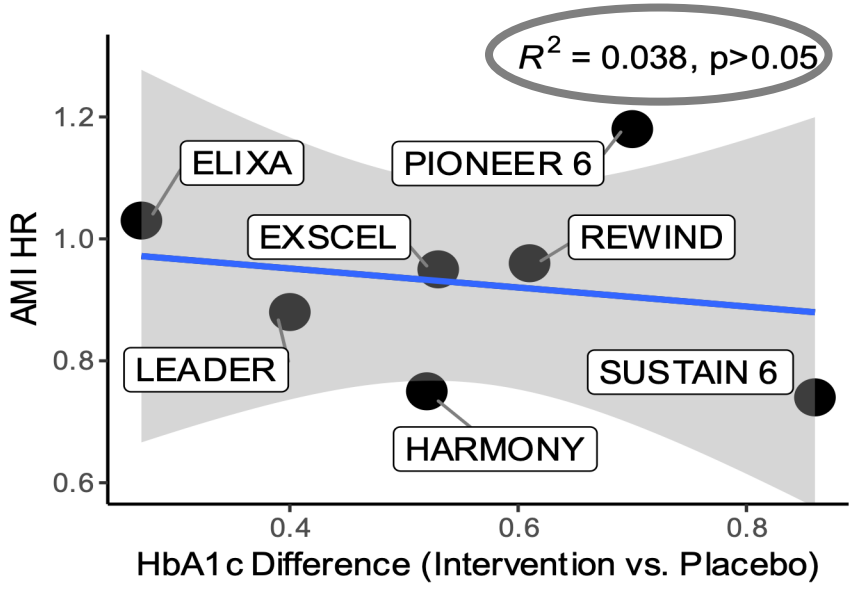
Stroke



CV death

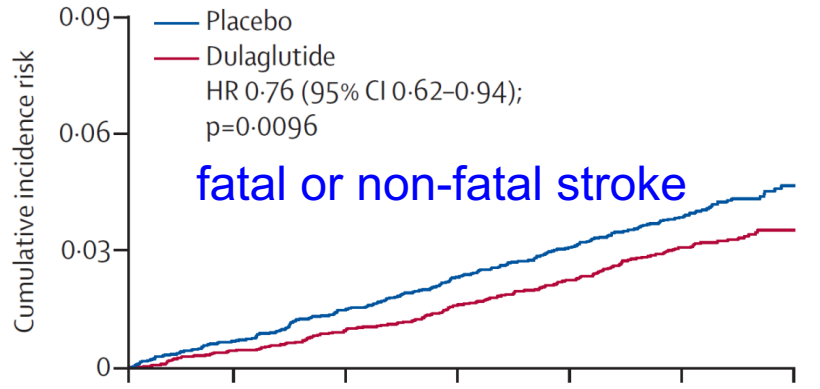


AMI



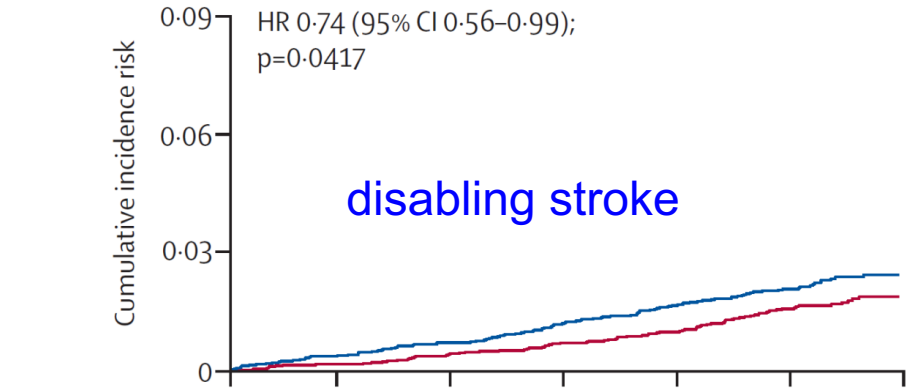
Caruso I et al., *Metabolism* 2020

REWIND: Cumulative Incidence of Stroke



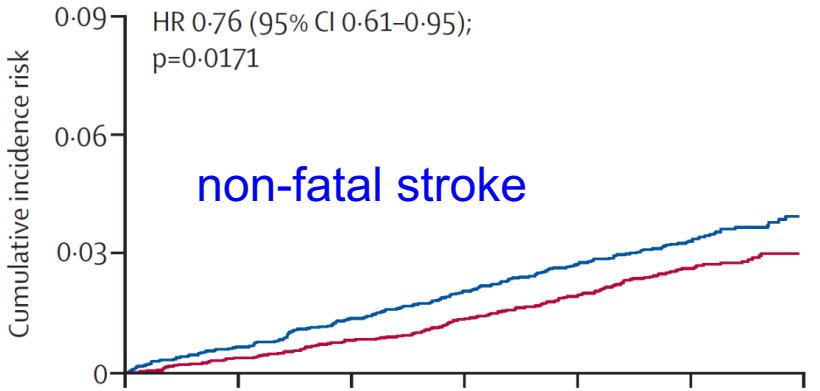
Number at risk

Placebo	4952	4826	4692	4534	4396	3710	777
Dulaglutide	4949	4847	4736	4606	4476	3796	776



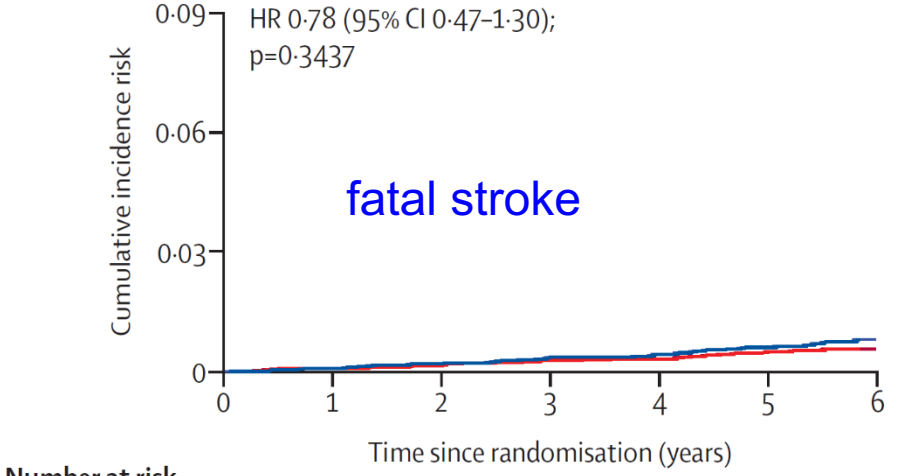
Number at risk

Placebo	4952	4843	4732	4585	4458	3777	794
Dulaglutide	4949	4862	4762	4647	4531	3854	791



Number at risk

Placebo	4952	4826	4692	4534	4396	3710	777
Dulaglutide	4949	4847	4736	4606	4476	3796	776

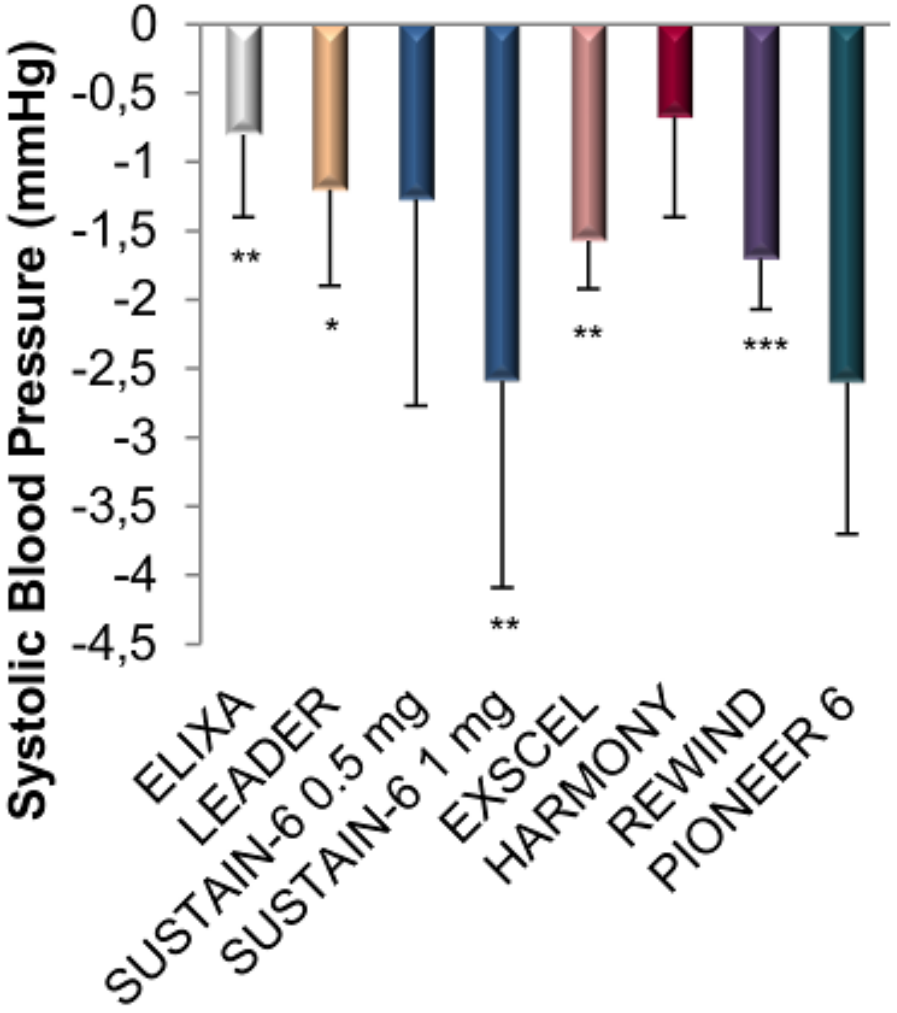


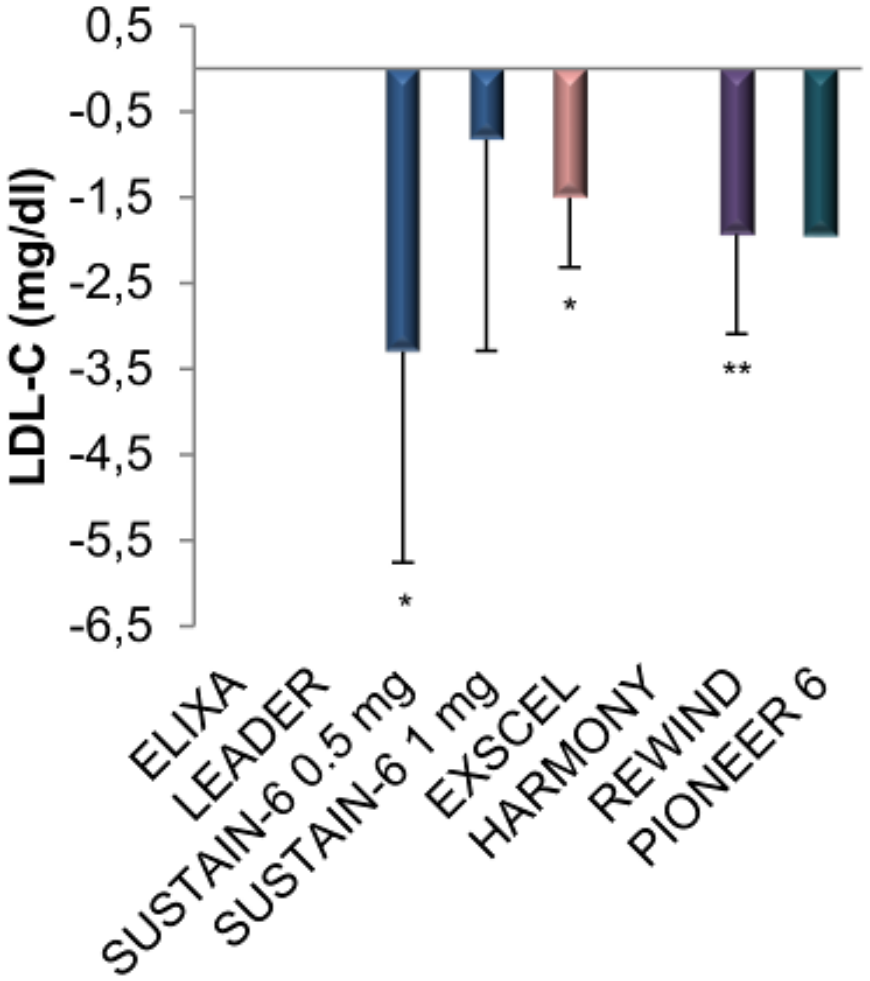
Number at risk

Placebo	4952	4854	4748	4617	4499	3813	802
Dulaglutide	4949	4866	4773	4663	4556	3887	807

Gerstein Hc et al. Lancet Diabetes Endocrinol. 2020 Jan 7. [Epub ahead of print]

GLP-1 RA vs Usual Care: Changes in Factors Potentially Affecting CV Risk



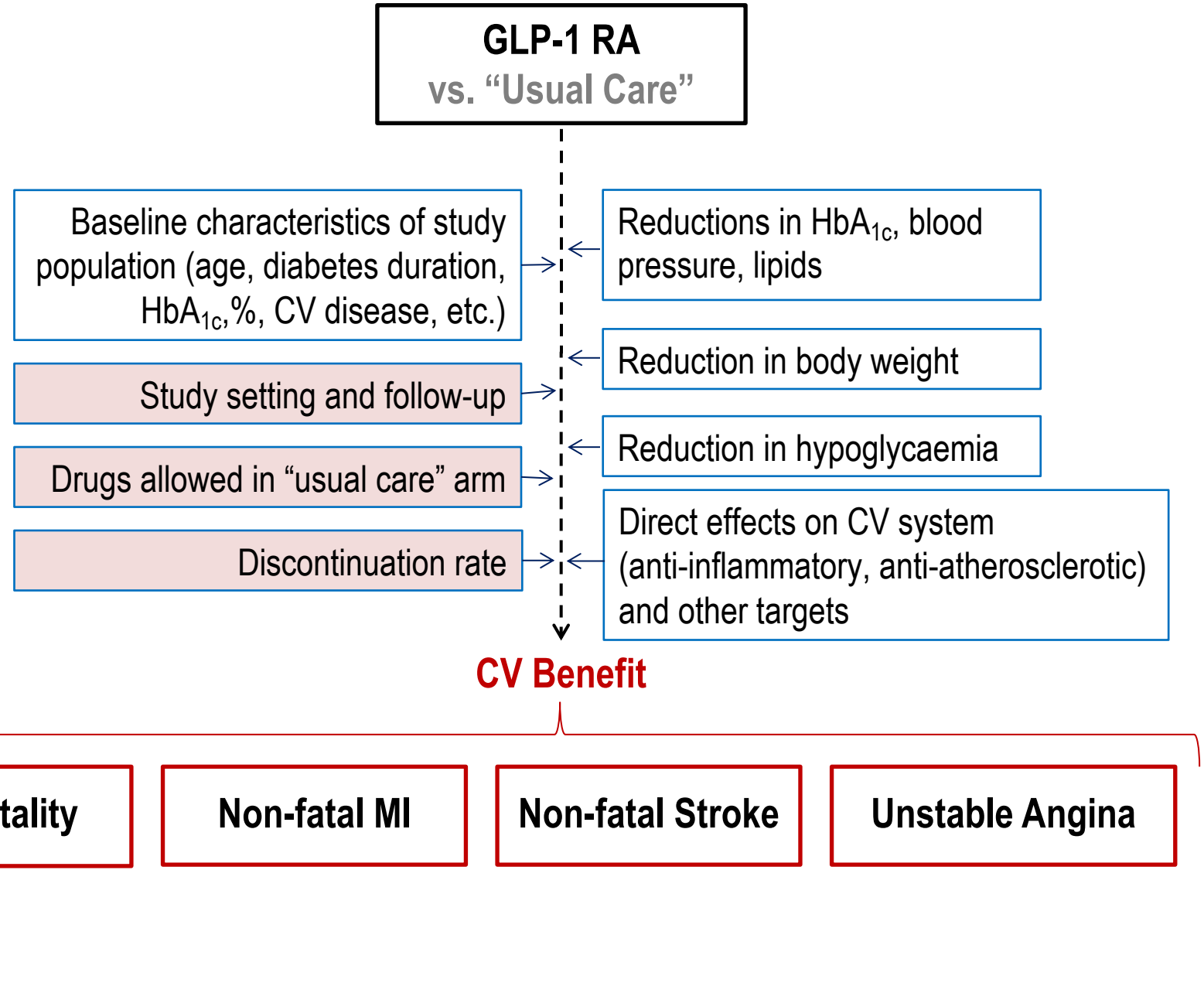


*p<0.05; **p<0.01;***p<0.001

Caruso I et al., *Trends Endocrinol Metab* 2019;30(9):578-589

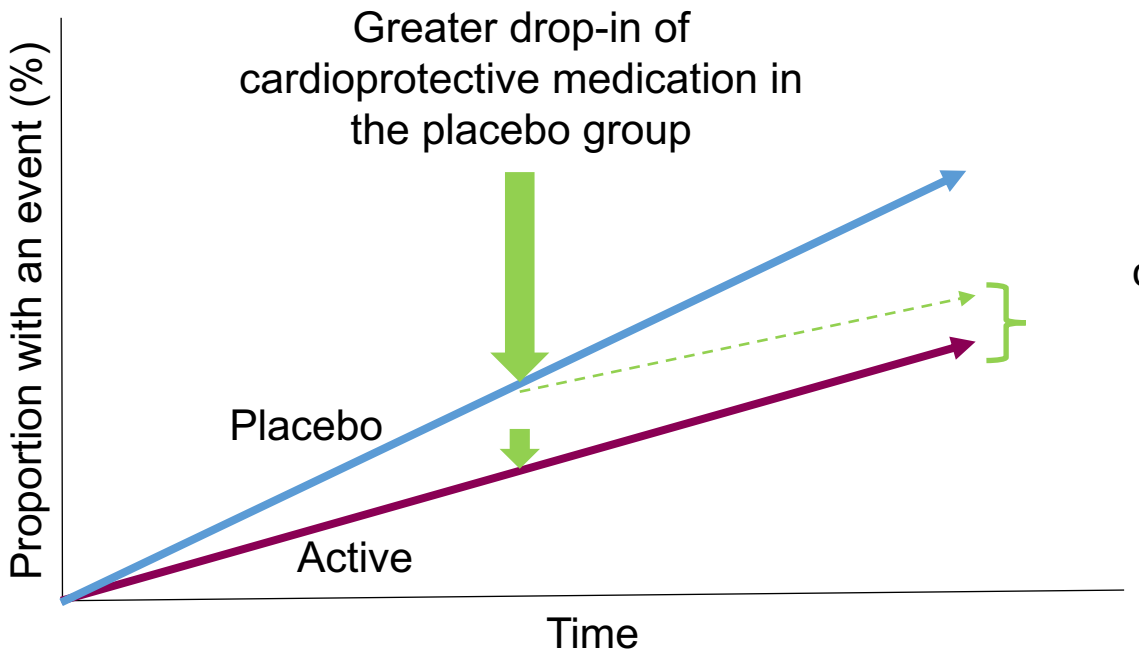
Potential Factors in CV Outcomes Trials with GLP-1 RAs

Does it matter how the study is designed and executed?



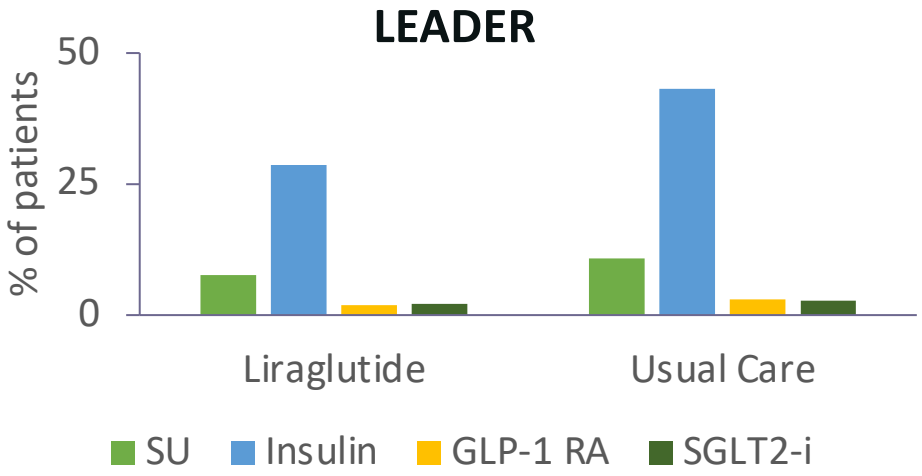
CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; MI, myocardial infarction.

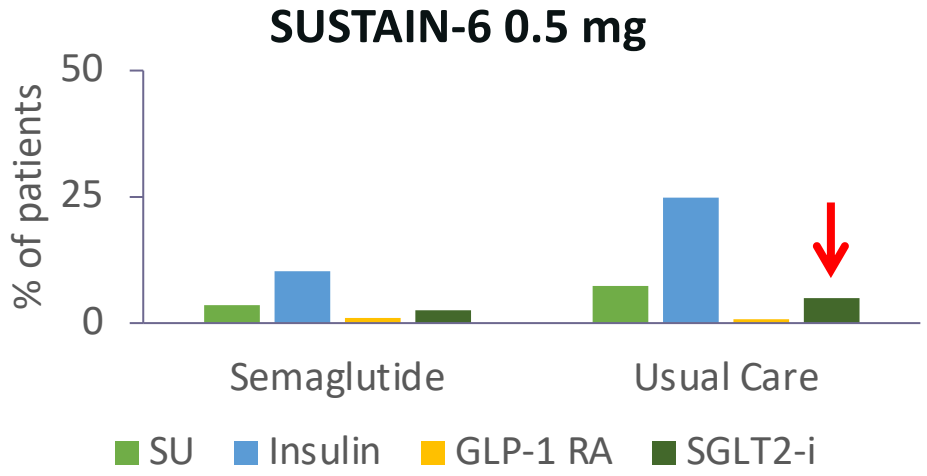
Potential Impact of Cardioprotective Drop-in Medication

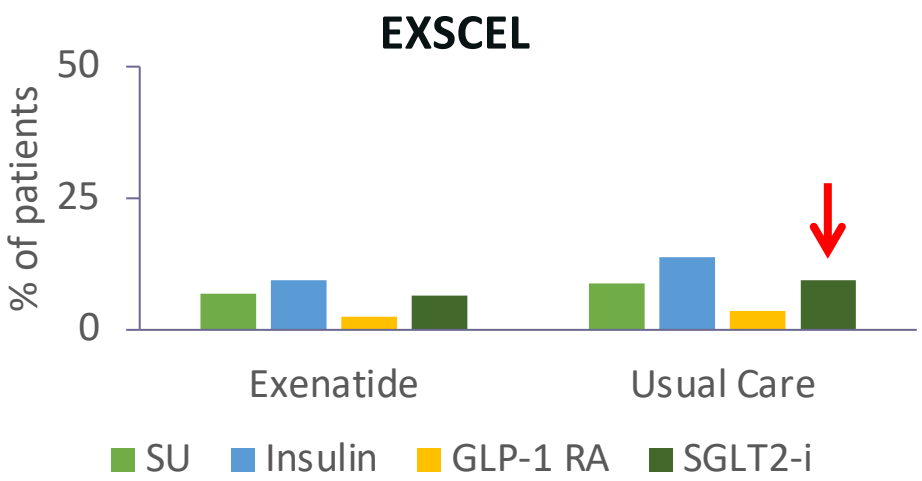


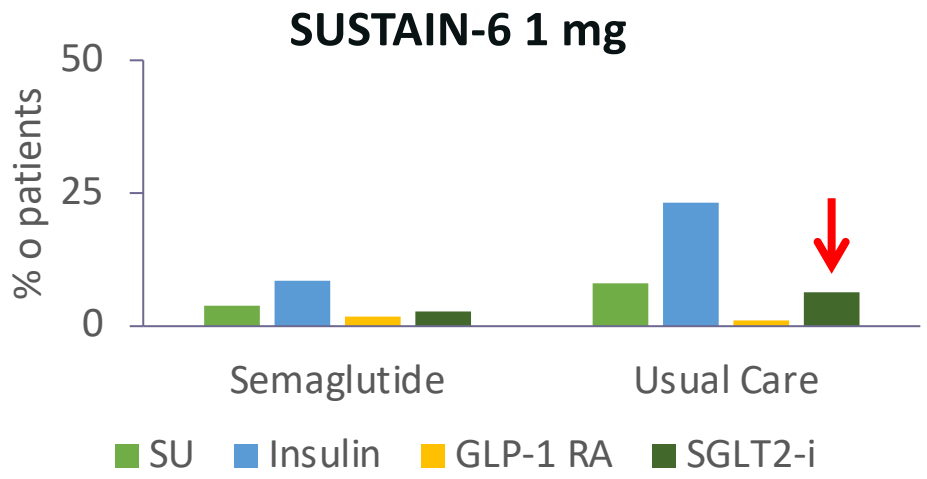
Unequal drop-in of cardioprotective medications *might reduce the detectable effect size*

Changes in Anti-Hyperglycaemic Therapy in CV Outcomes Trials with GLP-1 RA





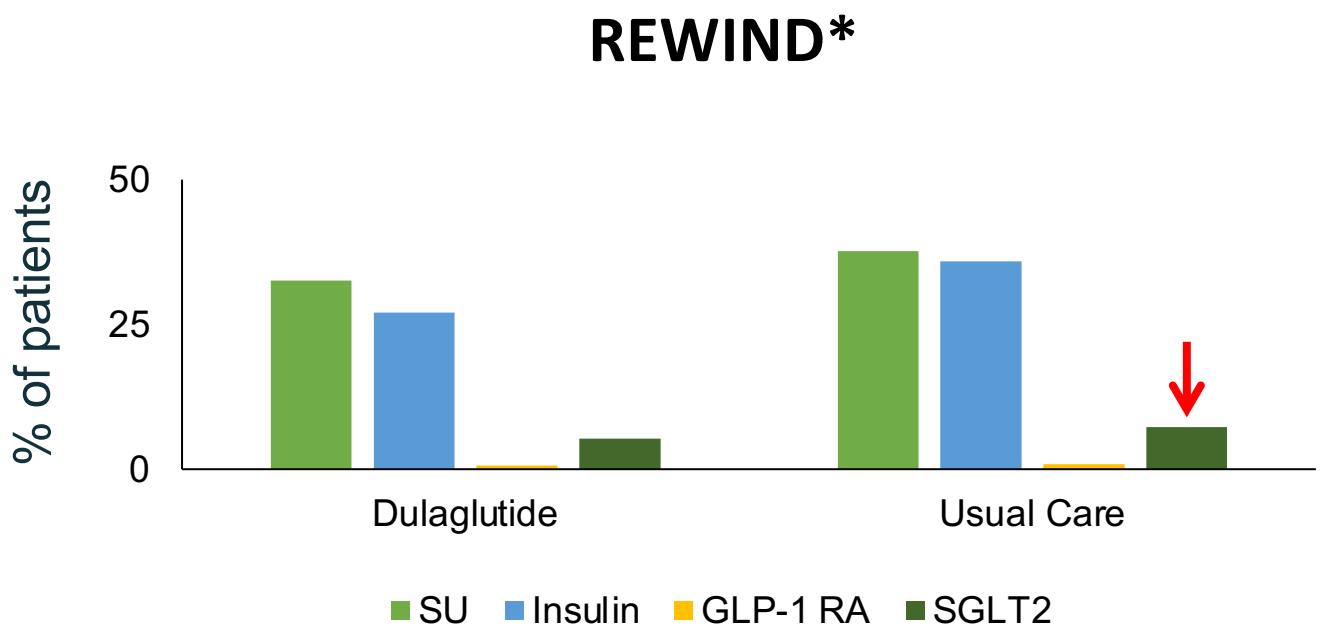




CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, SGLT-2 inhibitor; SU, sulphonylurea

Pfeffer MA, et al. *N Engl J Med.* 2015;373:2247–2257; Marso SP, et al. *N Engl J Med.* 2016;375:311–22; Marso SP, et al. *N Engl J Med.* 2016 375:1834–1844; Holman RR, et al. *N Engl J Med.* 2017;377:1228–1239.

Changes in Anti-Hyperglycaemic Therapy in CV Outcomes Trials with GLP-1 RA (continued)

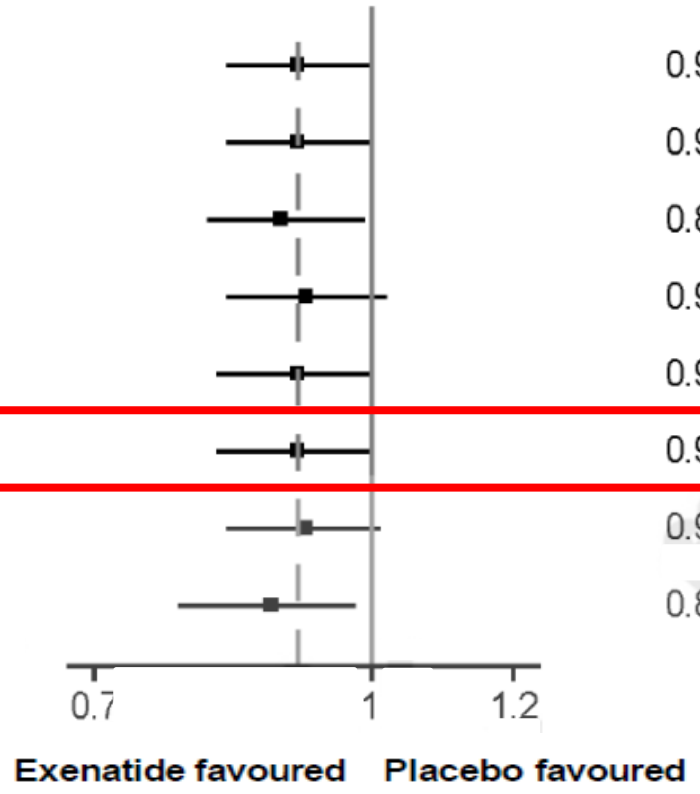


*Medications used at the last study visit.
CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, SGLT-2 inhibitor; SU, sulphonylurea

Gerstein HC, et al. *Lancet*. 2019;394:121-130.

EXSCEL Study Censoring Analysis – MACE-3 Endpoint

Censored medication	# Uncensored Exenatide / Placebo	Total events Exenatide / Placebo	Hazard Ratio (95% CI)	P-value
None	7356 / 7396	839 / 905	0.91 (0.83, 1.00)	0.061
Metformin	7038 / 7004	792 / 852	0.91 (0.83, 1.00)	0.055
Sulfonylurea	6903 / 6820	758 / 821	0.89 (0.81, 0.99)	0.025
DPP-4i	6887 / 6711	763 / 799	0.92 (0.83, 1.02)	0.107
Insulin	6793 / 6515	770 / 803	0.91 (0.82, 1.00)	0.060
SGLT-2i	6896 / 6755	759 / 816	0.91 (0.82, 1.00)	0.060
GLP-1 RA	7215 / 7177	766 / 819	0.92 (0.83, 1.01)	0.080
Any	5373 / 4742	638 / 648	0.88 (0.78, 0.98)	0.017



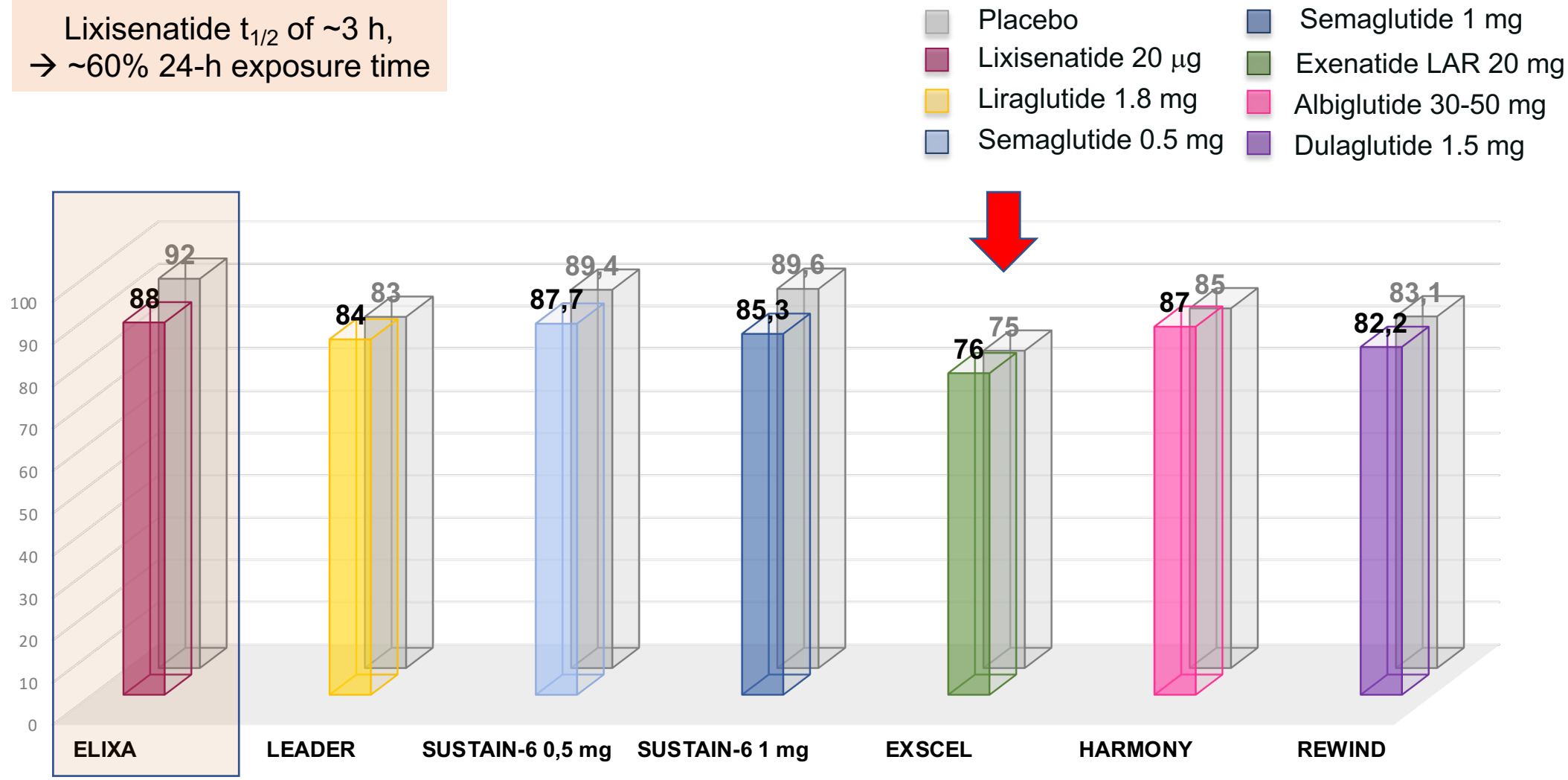
After censoring events on “drop-in” of concomitant medications, the HR effect size was consistent with the main EXSCEL results and ranged from 0.87 to 0.92.

[a]Patients starting concomitant medications post randomization were censored at the time of drop-in.
CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Bethel A et al. Circulation 2020

Mean Percentage of Time That Participants Received the Trial Regimen

Lixisenatide $t_{1/2}$ of ~3 h,
→ ~60% 24-h exposure time

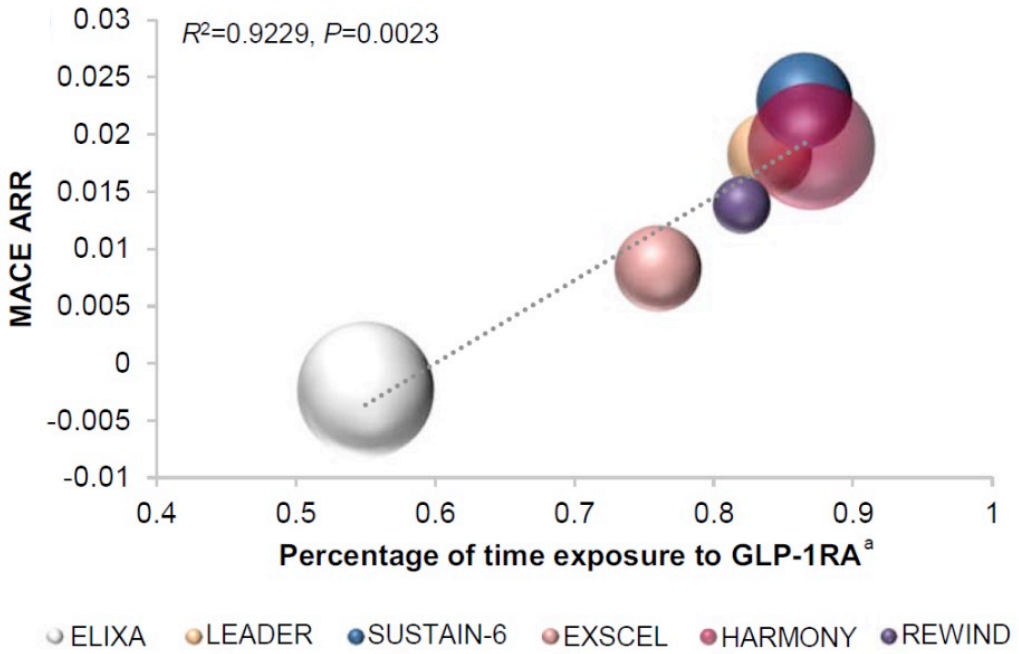


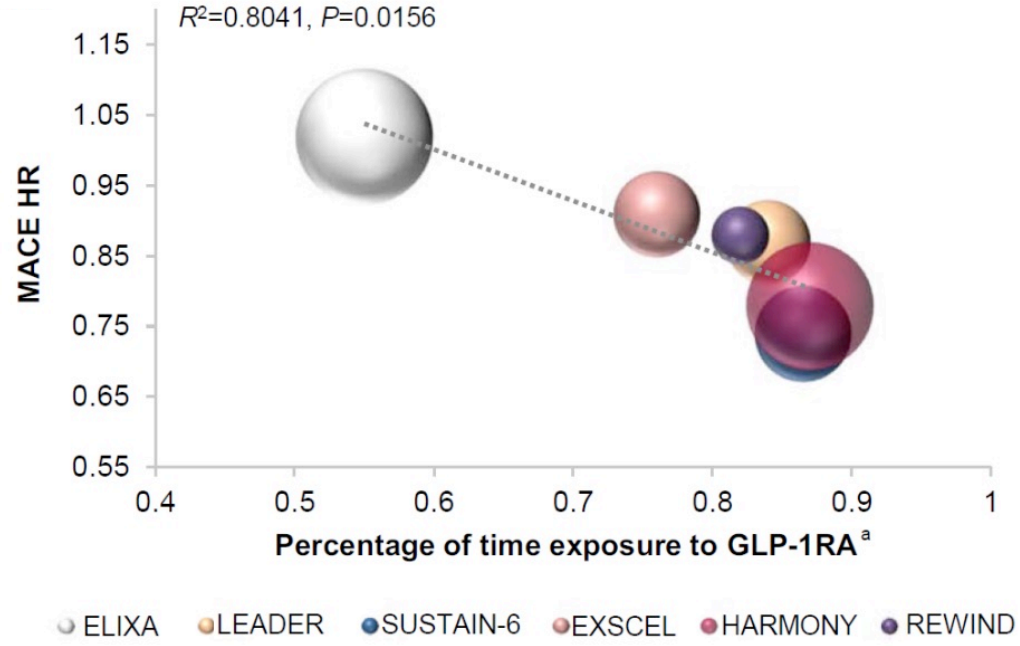
H, hours; LAR, long-acting release; $t_{½}$, elimination half-life.

Adapted from: Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247–2257; Marso SP, et al. *N Engl J Med*. 2016;375:311–22; Marso SP, et al. *N Engl J Med*. 2016 375:1834–1844; Holman RR, et al. *N Engl J Med*. 2017;377:1228–1239; Hernandez AF, et al. *Lancet*. 2018;392(10157):1519–1529; Gerstein HC, et al. *Lancet*. 2019 Jun 7. pii: S0140-6736(19)31149-3.

Correlation between Percentage of Time Exposure to Study Drug and MACE ARR and HR

- **Time of exposure to the investigational GLP-1 RA is positively correlated with the MACE ARR and, accordingly, negatively correlated with the MACE HR.** (Actual exposure to lixisenatide in ELIXA is estimated to be approximately 56%)
- **Baseline CV risk level does not seem to be related to changes in CV outcomes.** (Sphere size represents the baseline CV risk of the study population, expressed as MACE incidence rate in the control arm [# events per 100 patient-year])



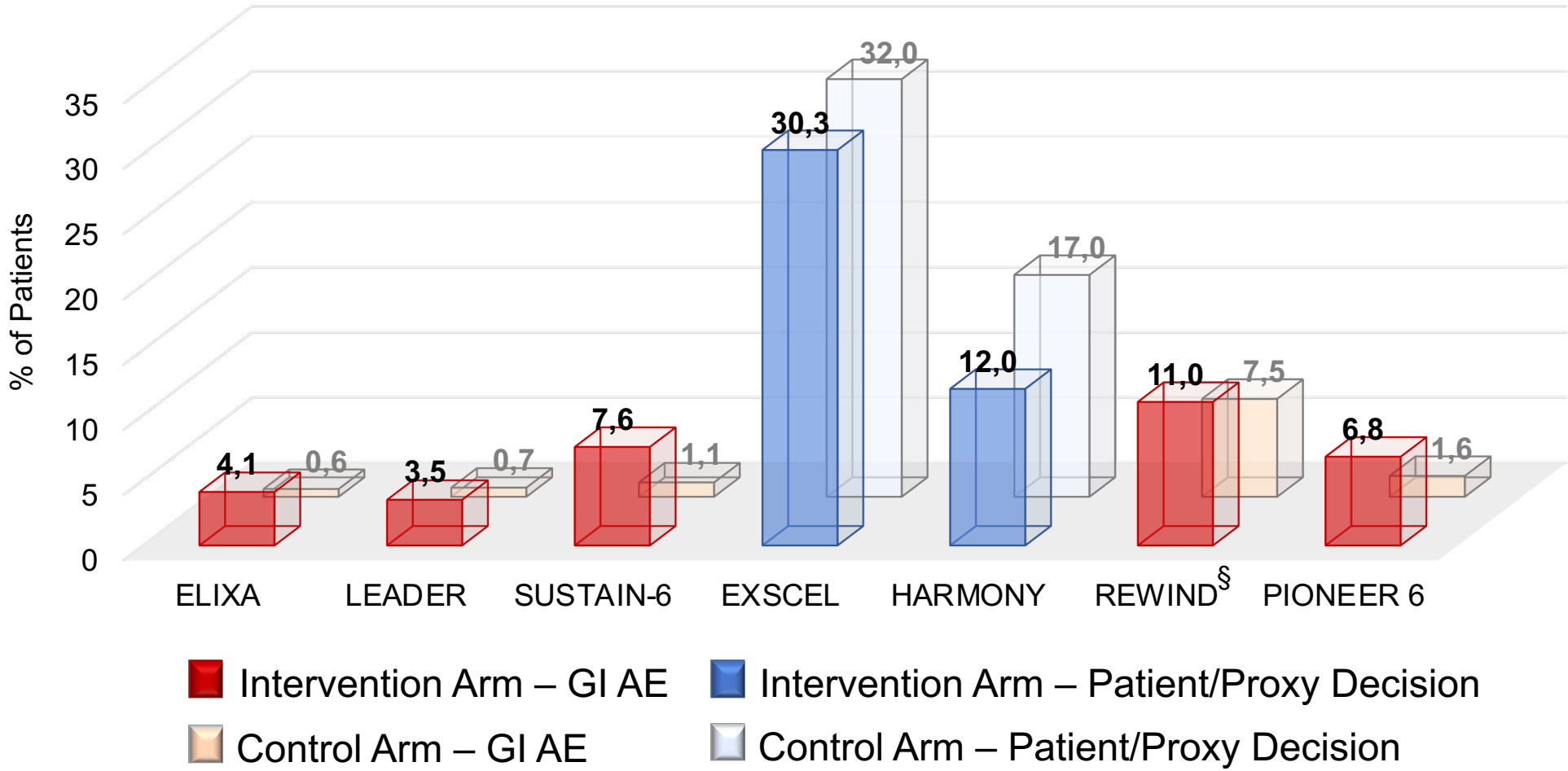


[a] The percentage of time exposure to study drug is expressed as median in ELIXA, HARMONY Outcomes and REWIND, and as mean in LEADER, SUSTAIN–6 and EXSCEL

ARR, absolute risk reduction; CV; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event.

Caruso I et al., *Trends Endocrinol Metab* 2019

Main Reason for Investigational Product Discontinuation



§% of premature discontinuation due to AE, mostly GI

Pfeffer MA et al., *N Engl J Med* 2015; Marso SP, et al., *N Engl J Med* 2016; Marso SP, et al., *N Engl J Med* 2016; Holman RR et al., *N Engl J Med* 2017; Hernandez AF et al., *Lancet* 2018; Gerstein HC et al., *Lancet* 2019; Husain M et al., *N Engl J Med* 2019.

REWIND: Follow up time, Retention, Adherence

- Median follow-up period: 5.4 years (IQR 5.1, 5.9)
- Person years of follow-up: 51820
- Retention: 97.1%
- Vital Status: 99.7%
- Adherence (F/U time on drug): 82.2% dulaglutide; 83.1% placebo
- Stopped due to adverse event: 11% dulaglutide; 7.5% placebo

F/U = follow-up

Gerstein HC, et al. *Lancet.* 2019;394(10193):121-130.

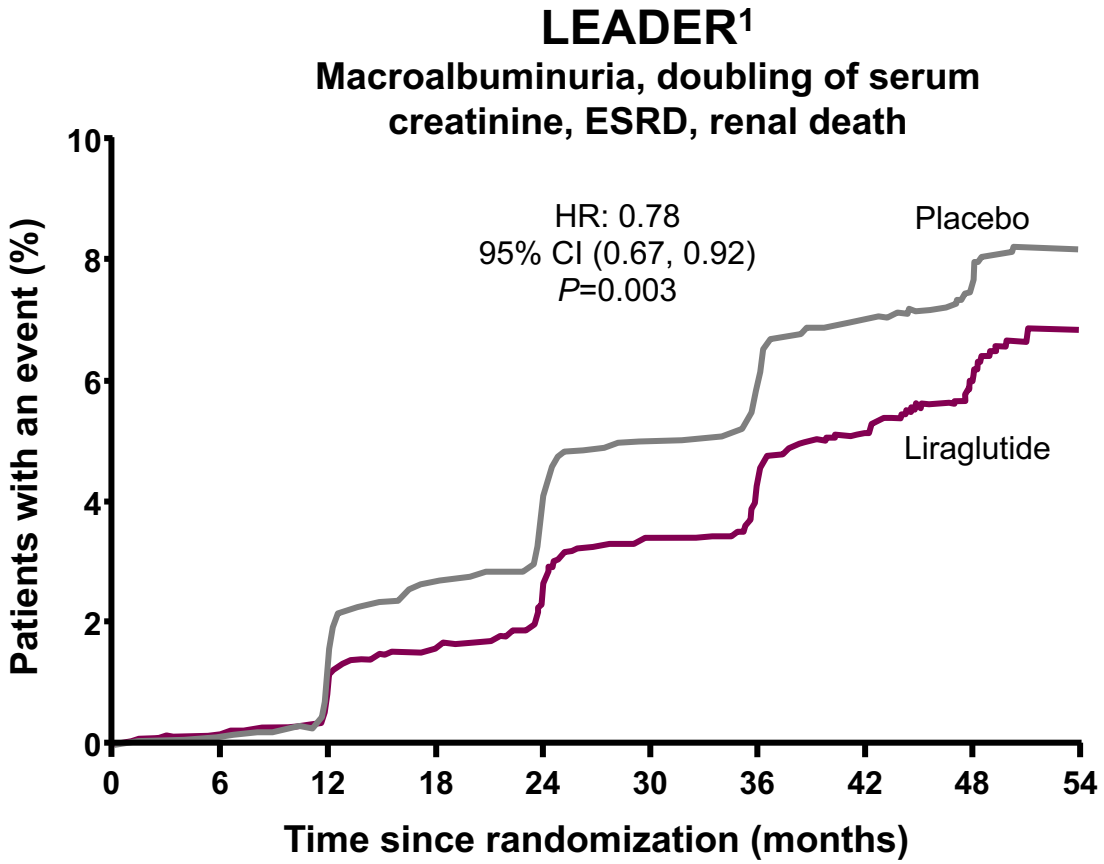
REWIND
Dulaglutide CV Outcomes Trial

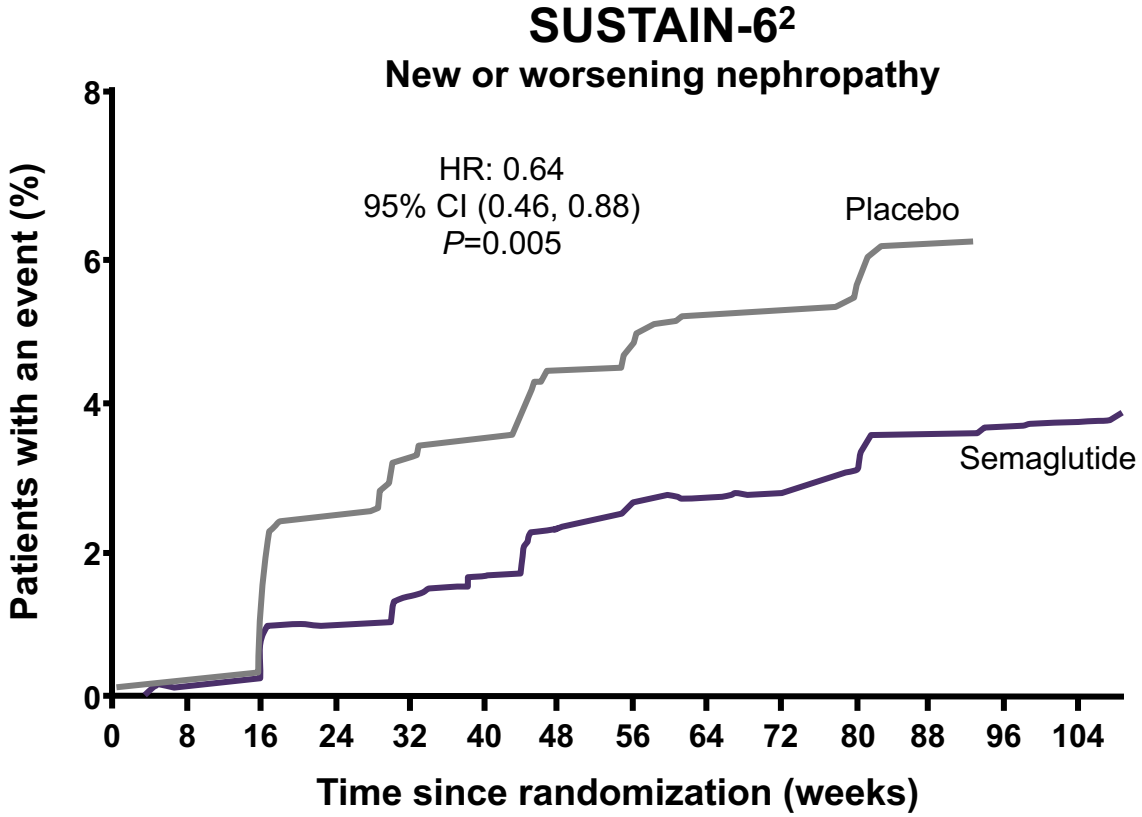
GLP-1 RA and cardiovascular benefit: conclusions

1. CV risk level of the exposed T2D population may not influence the benefit: CV benefit was not seen in ELIXA (ACS patients) but was evident in HARMONY (100% with CVD) and in the lower-risk patients of REWIND.
2. Exendin-4-based and GLP-1-based agonists have the potential to differ in signalling and biological effects. However, they seem to not differ qualitatively in their direct positive effects on cardiovascular cells and tissues, supporting the hypothesis of a «class effect».
3. It is unclear whether differences in HbA_{1c} and weight, or in hypoglycaemia may explain heterogeneity in the results. HbA1c reduction may contribute to stroke prevention by GLP-1RA (see REWIND and SUSTAIN-6).
4. The time of drug exposure during the trial appears to be the most important factor for CV benefit. High adherence and persistence to GLP-1 RA treatment (resulting from frequent follow-up and/or ease of drug administration) are important to achieve CV protection.

ACS, acute coronary syndrome; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; T2D, type 2 diabetes mellitus.

GLP-1 RAs demonstrate significant improvement in renal outcomes versus placebo …





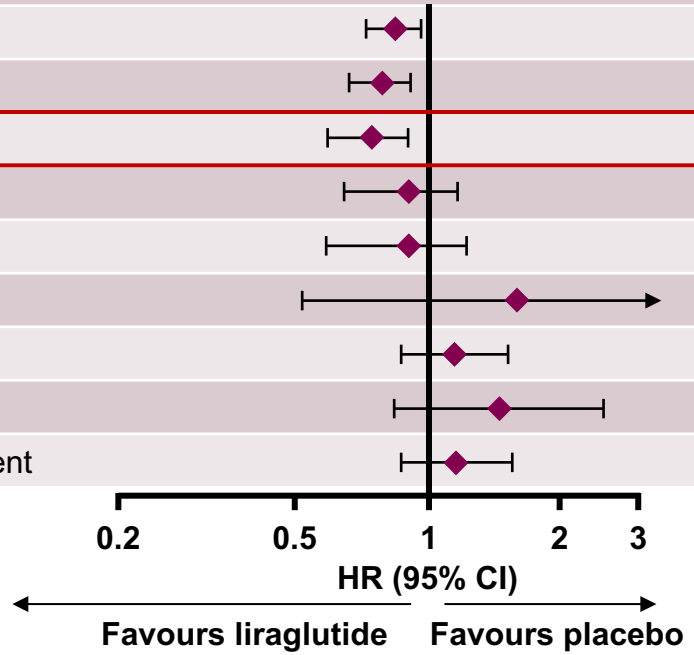
LEADER: Cumulative incidences were estimated with the Kaplan–Meier method, and the HRs with the Cox proportional-hazard regression model; the data analyses are truncated at 54 months because <10% of the patients had an observation time beyond 54 months

CI, confidence interval; ESRD, end-stage renal disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio

[1]Marso SP, et al. *N Engl J Med.* 2016;375:311–322; [2]Vilsbøll T. Presented at 52nd European Association for the Study of Diabetes Annual Meeting; 16th September 2016; Munich, Germany; OP S35.3

LEADER: time to first microvascular endpoints

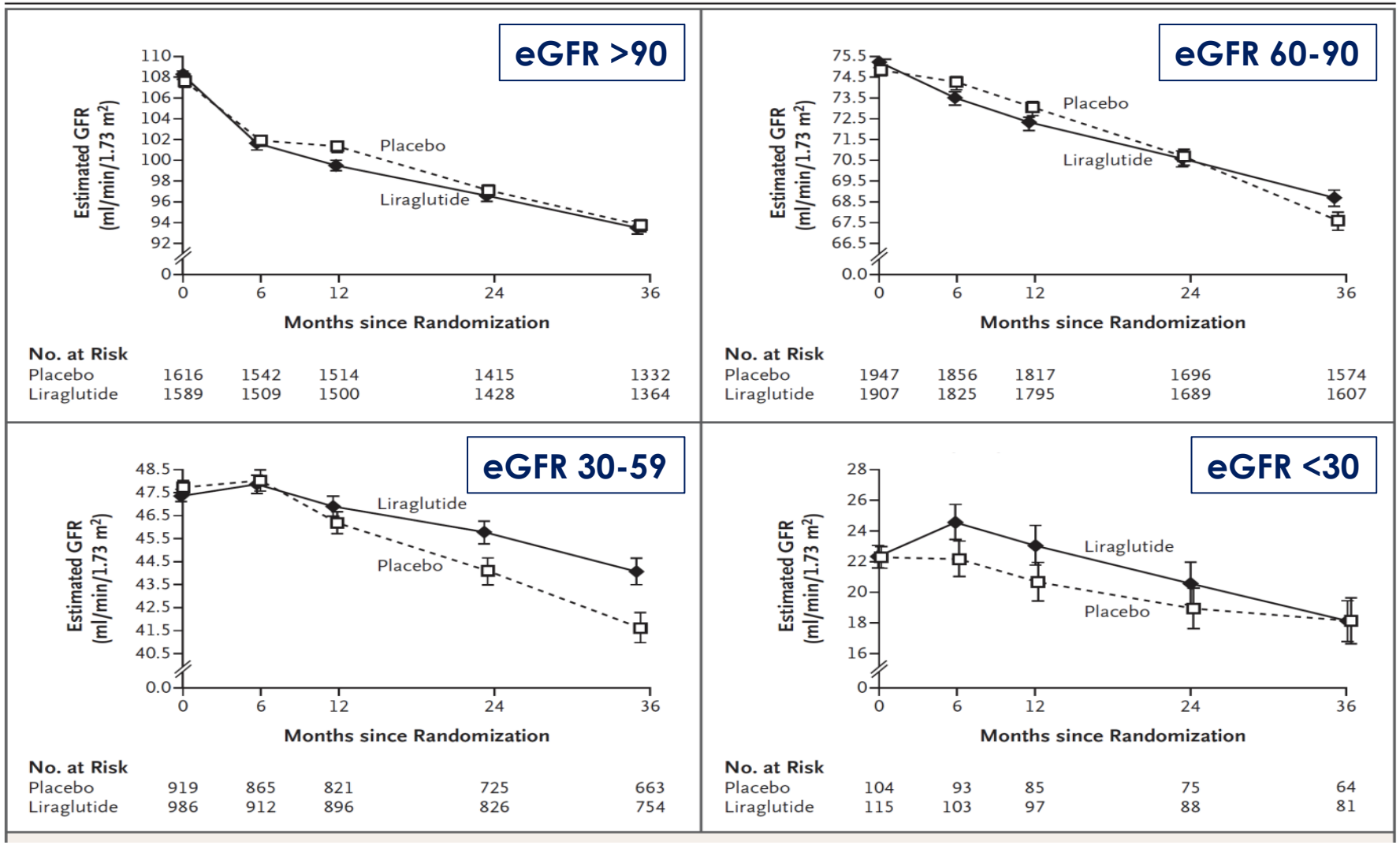
	HR (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
Number of patients		**4668**	**100**	**4672**	**100**
Microvascular endpoint	**0.84 (0.73, 0.97)**	**355**	**7.6**	**416**	**8.9**
Renal event	**0.78 (0.67, 0.92)**	**268**	**5.7**	**337**	**7.2**
New onset of persistent macroalbuminuria[a]	0.74 (0.60, 0.91)	161	3.4	215	4.6
Persistent doubling of serum creatinine[b]	0.88 (0.66, 1.18)	87	1.9	97	2.1
Need for continuous renal replacement therapy	0.87 (0.61, 1.24)	56	1.2	64	1.4
Death due to renal disease	1.59 (0.52, 4.87)	8	0.2	5	0.1
Eye event	**1.15 (0.87, 1.52)**	**106**	**2.3**	**92**	**2.0**
Vitreous haemorrhage	1.45 (0.84, 2.50)	32	0.7	22	0.5
Treatment with photocoagulation or intravitreal agent	1.16 (0.87, 1.55)	100	2.1	86	1.8



Full analysis set. EAC-confirmed microvascular events including events with onset between date of randomisation and date of follow-up; Cox proportional hazard model adjusted for treatment; development of diabetes-related blindness was not analysed as an individual component because only one event was observed; [a]new onset of persistent macroalbuminuria: urine albumin ≥300 mg/g creatinine; [b]persistent doubling of serum creatinine level and eGFR ≤45 mL/min/1.73 m^2 per MDRD
CI, confidence interval; EAC, event adjudication committee; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, modification of diet in renal disease

Marso SP, et al. *N Engl J Med.* 2016;375:311–322

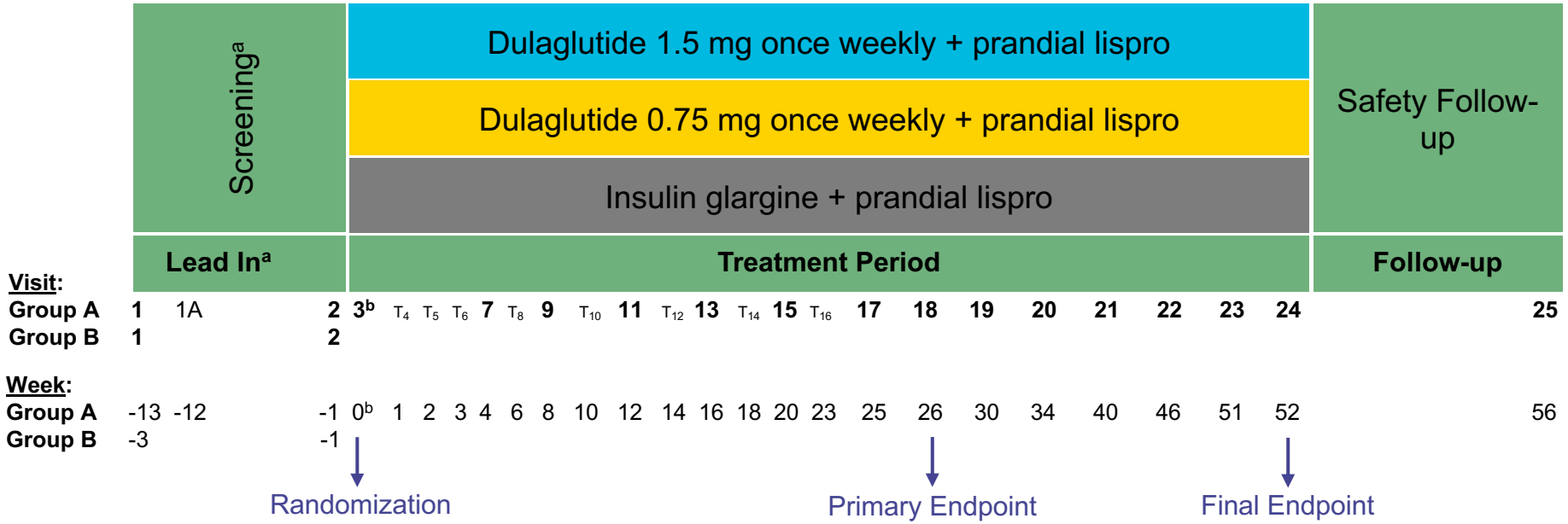
LEADER: change in eGFR during the trial in subgroups stratified according to eGFR at baseline



eGFR, estimated glomerular filtration rate, ml/min/1.73m^2

Mann JFE, et al. *N Engl J Med.* 2017;377:839–848

AWARD-7: Study Design



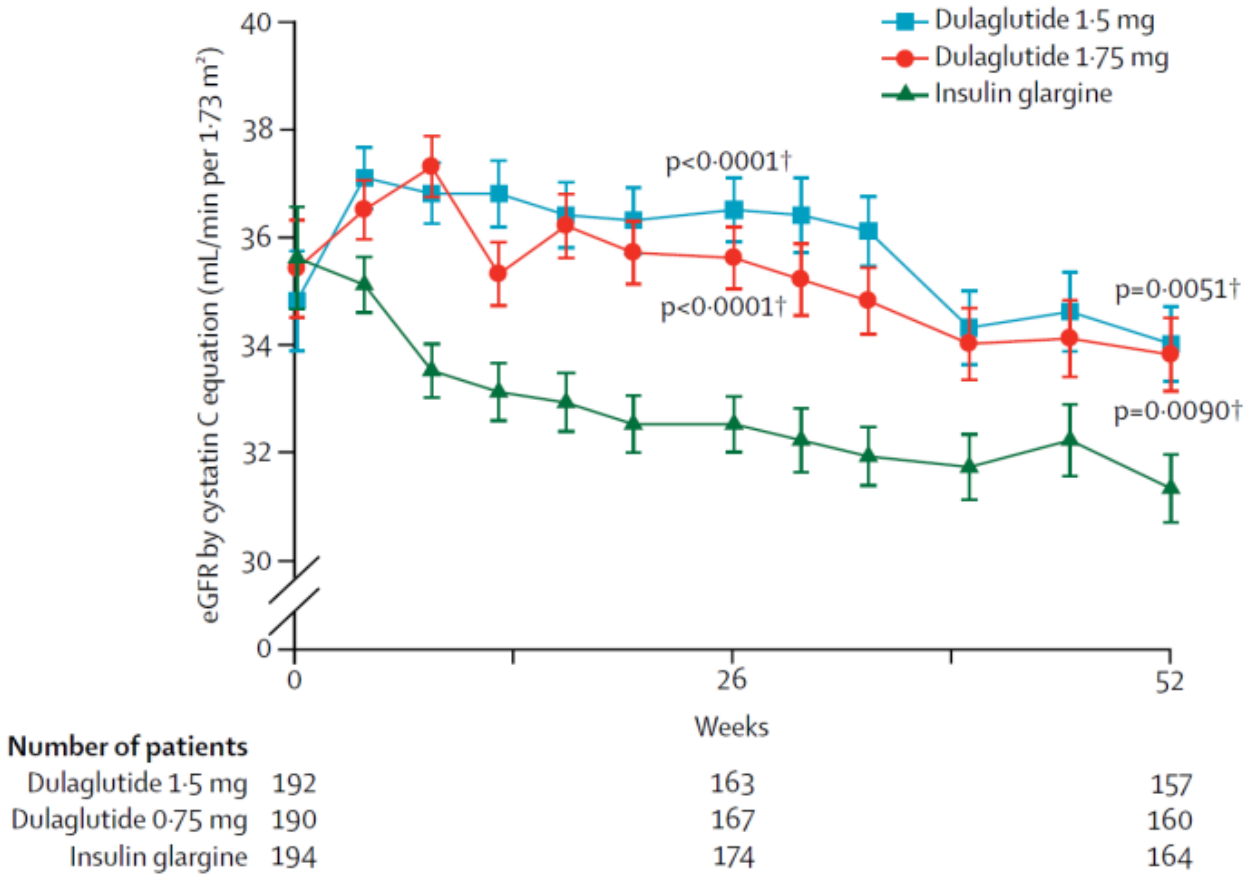
Multicenter, parallel-arm, randomized, 52-week clinical trial assessing the efficacy and safety of dulaglutide at two dose levels compared to insulin glargine in people with type 2 diabetes and moderate or severe chronic kidney disease

Key inclusion criteria: adults with T2D, eGFR of <60 to ≥15 mL/min/1.73 m^2, BMI 23-45 kg/m^2, A1c ≥7.5% and ≤10.5% for patients receiving insulin + OAM(s) and/or pramlintide or only insulin prior to screening

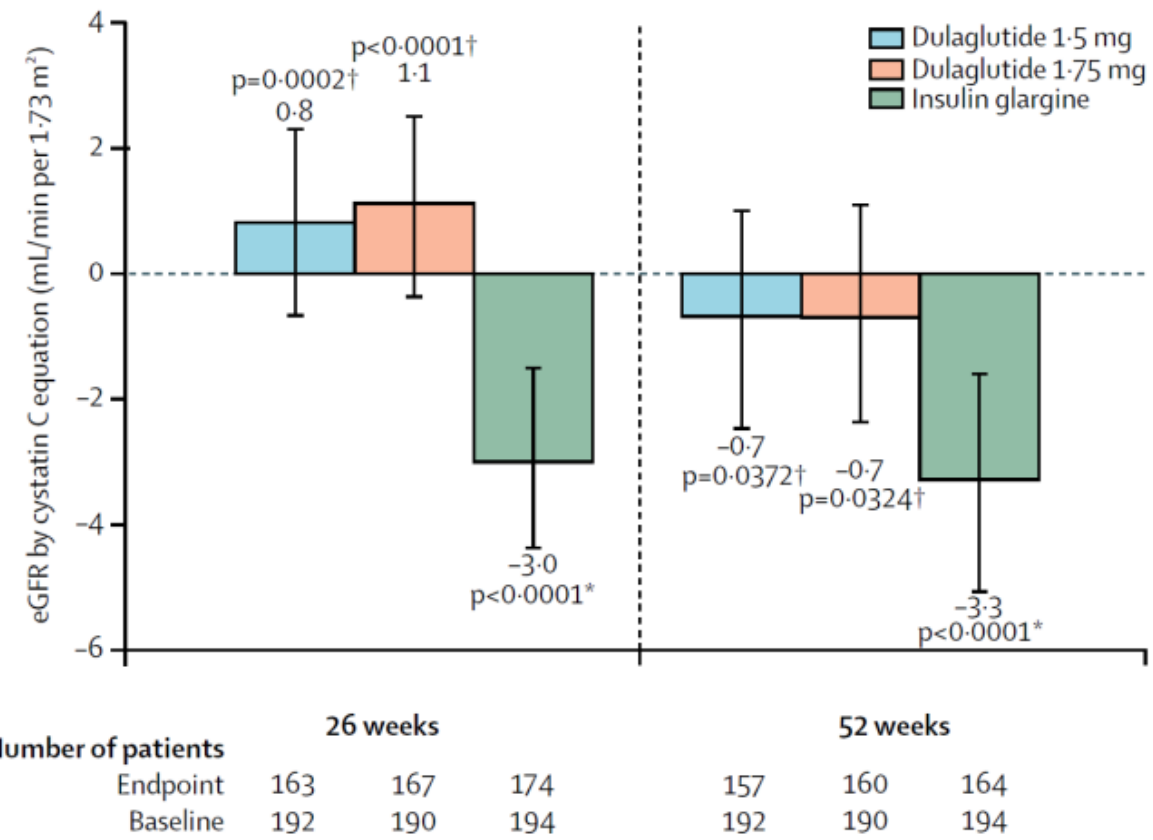
[a]Group A: patients who were taking oral antihyperglycemic medication(s) ± pramlintide in addition to insulin at Screening had a 13-week Screening/Lead-in Period; Group B: patients who only take insulin at screening had a 3-week Screening/Lead-In Period; [b]Once patients are randomized, there is no distinction between Groups A and B. Insulin glargine dose was adjusted to target fasting plasma glucose (PG) values between 100-150 mg/dL, and insulin lispro doses were adjusted to target pre-prandial PG values between 120-180 mg/dL
BMI, body mass index; eGFR, estimated glomerular filtration rate; OAM, oral antidiabetic medication; PG, plasma glucose

Tuttle KR, et al. *Lancet Diabetes Endocrinol* 2018;6:605–17

AWARD-7: Changes in eGFR



Number of patients			
Dulaglutide 1·5 mg	192	163	157
Dulaglutide 0·75 mg	190	167	160
Insulin glargine	194	174	164

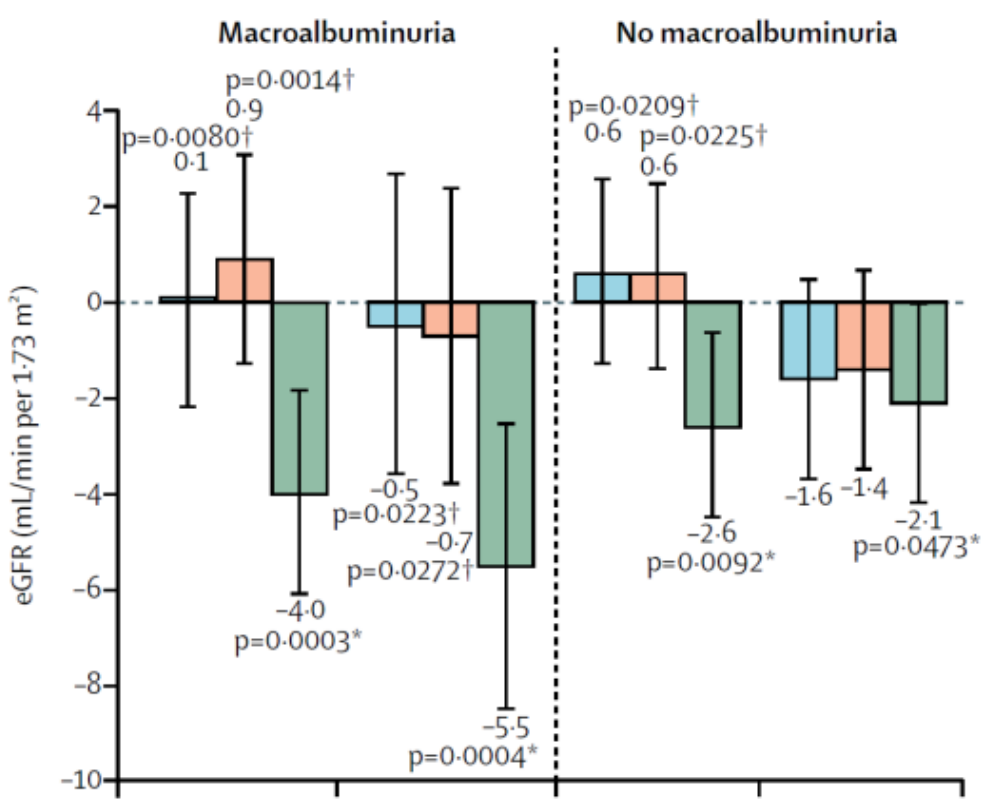


Number of patients						
Endpoint	163	167	174	157	160	164
Baseline	192	190	194	192	190	194

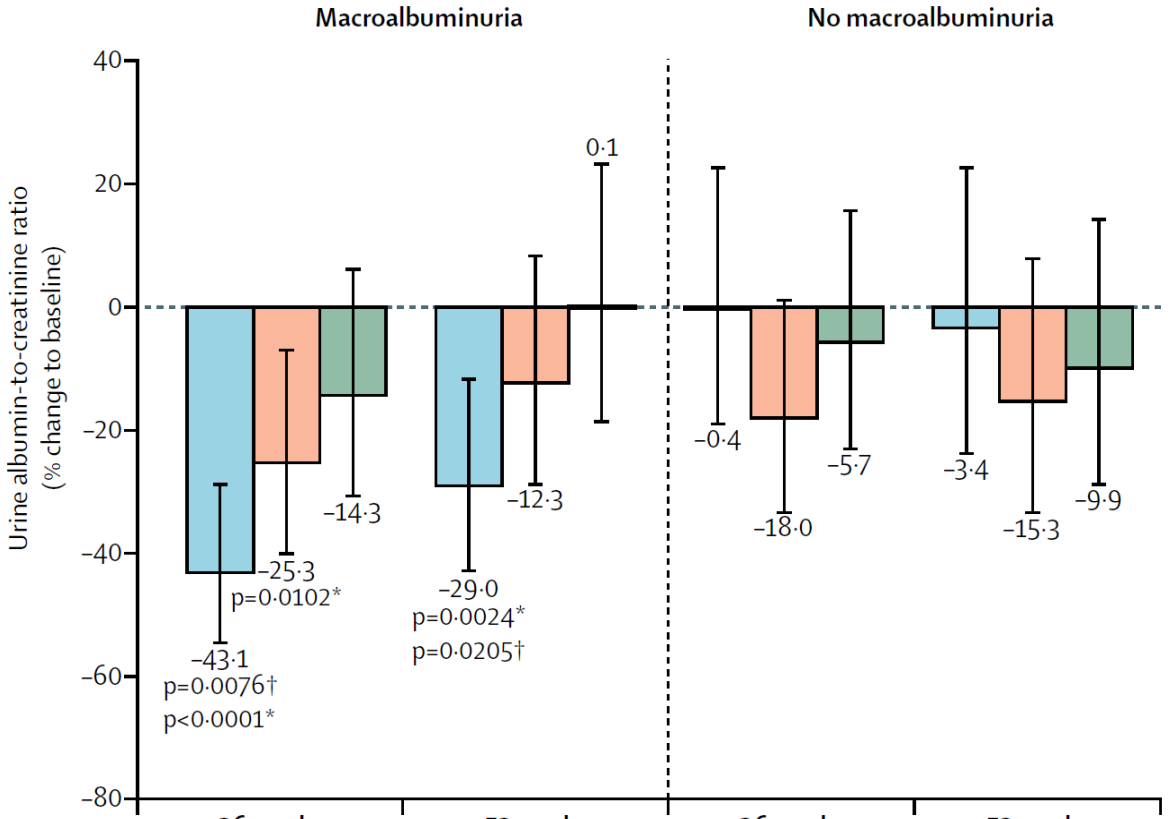
eGFR, estimated glomerular filtration rate

Tuttle KR, et al. *Lancet Diabetes Endocrinol* 2018;6:605–17

AWARD-7: Changes in eGFR and Albuminuria by Macroalbuminuria Status at Baseline



Number of patients	26 weeks			52 weeks			26 weeks			52 weeks		
Endpoint	70	71	77	64	67	69	93	96	97	93	93	95
Baseline	84	84	90	84	84	90	108	106	104	108	106	104

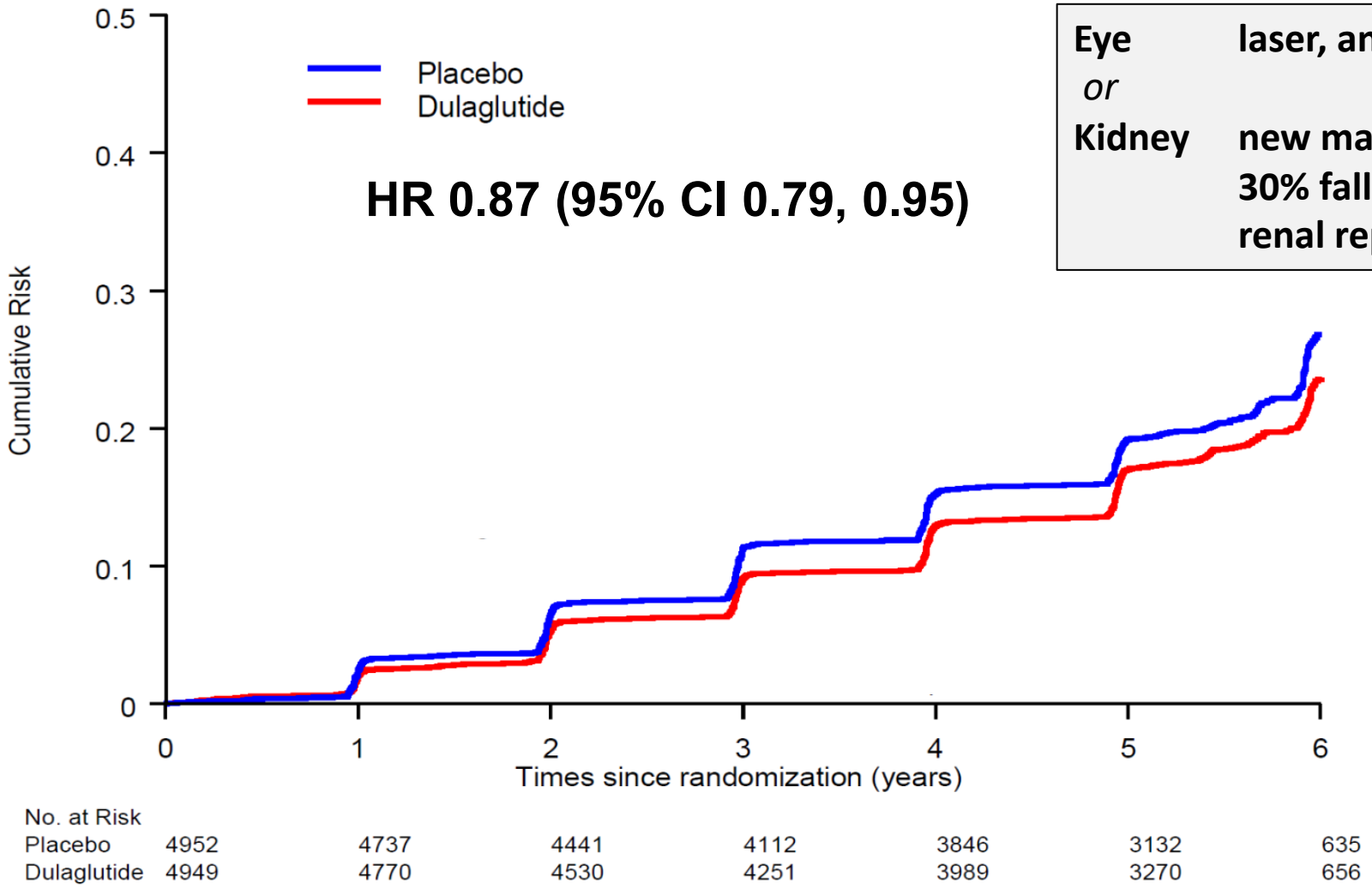


Number of patients	26 weeks			52 weeks			26 weeks			52 weeks		
Endpoint	75	76	80	65	70	71	100	99	101	94	92	94
Baseline	84	84	90	84	84	90	108	105	104	108	105	104

eGFR, estimated glomerular filtration rate

Tuttle KR, et al. *Lancet Diabetes Endocrinol* 2018;6:605–17

REWIND: Microvascular Composite Outcome



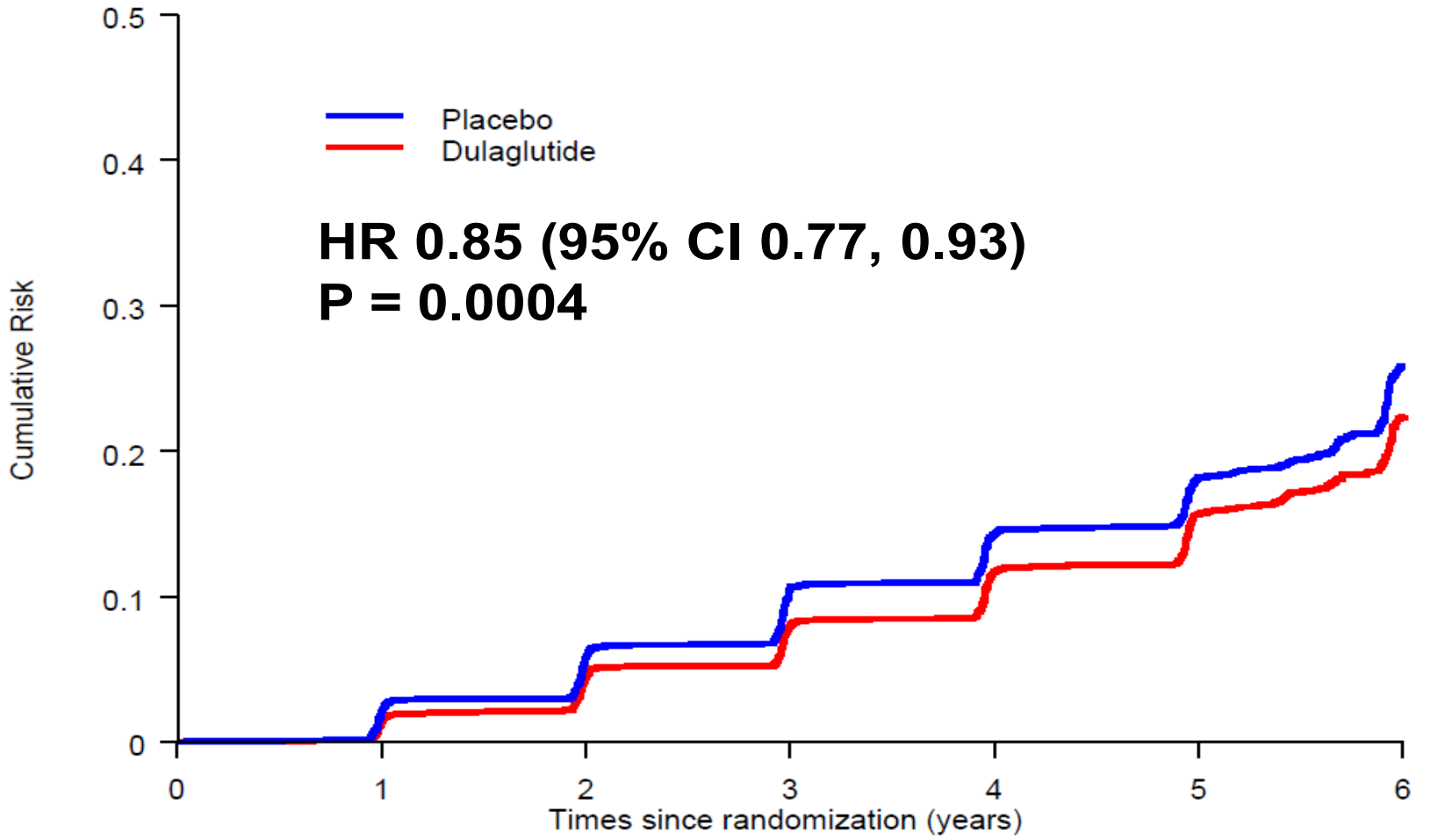
Eye	**laser, anti VEGF, vitrectomy**
or	
Kidney	**new macroalbuminuria,** *or* **30% fall in eGFR,** *or* **renal replacement Rx**

Gerstein HC, et al. *Lancet.* 2019;394(10193):121-130.

REWIND
Dulaglutide CV Outcomes Trial

REWIND: Renal Composite Outcome

New Macroalbuminuria, 30% fall in eGFR, or Renal Replacement Rx

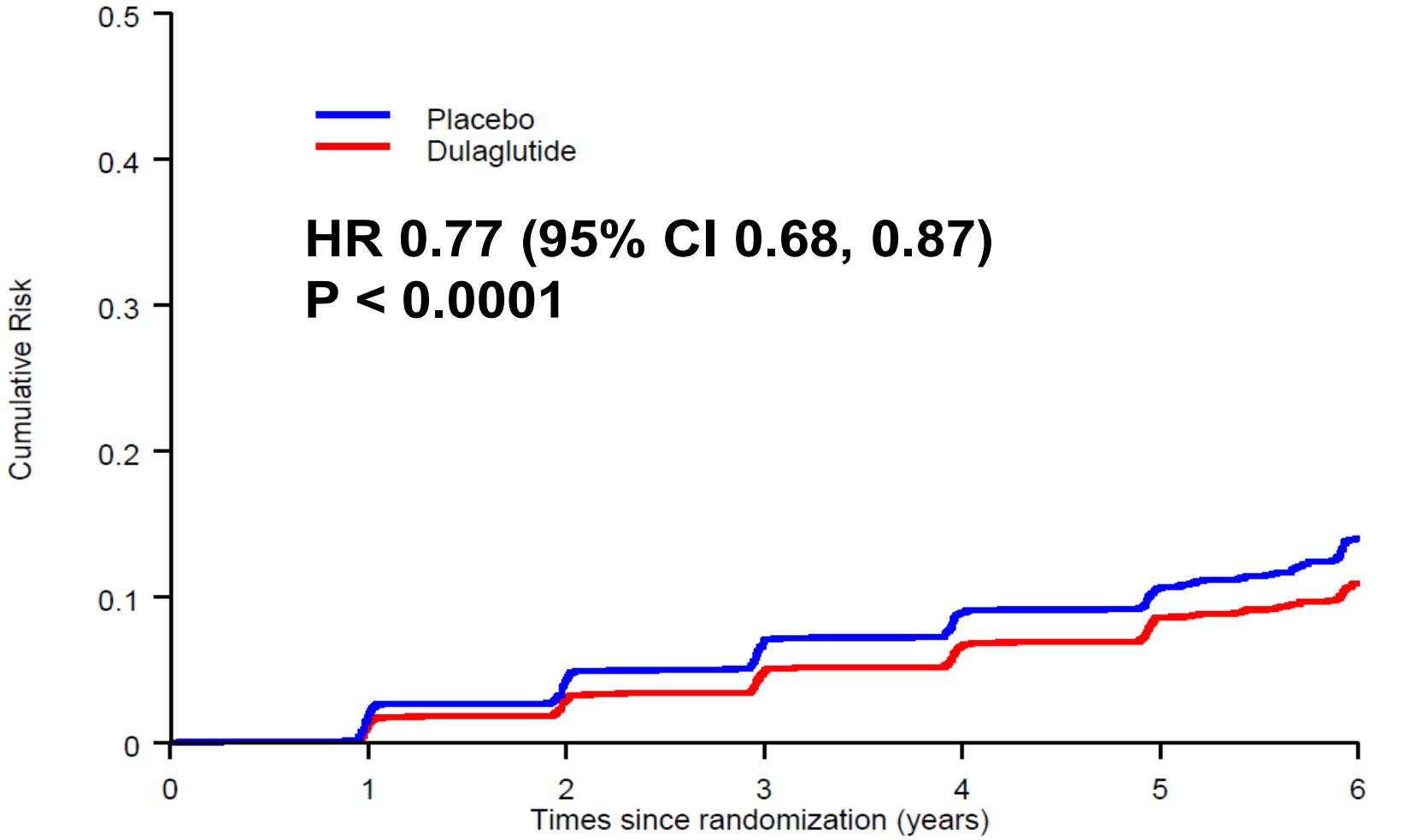


No. at Risk							
Placebo	4952	4756	4475	4145	3887	3169	641
Dulaglutide	4949	4798	4571	4303	4045	3320	667

Gerstein, H.C. *et al.* Lancet 2019

REWIND: Development of New Macroalbuminuria

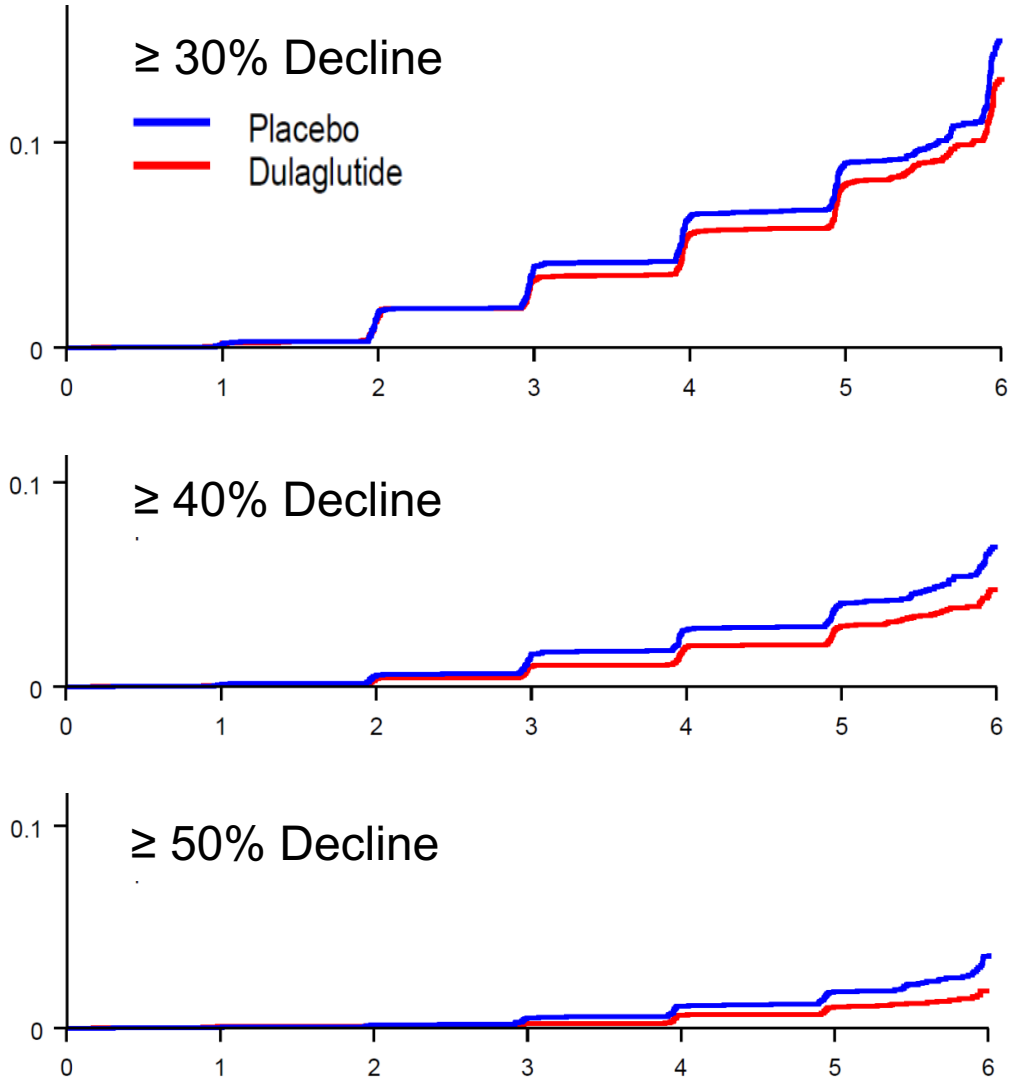
New Urine Albumin/Creatinine > 33.9 mg/mmol (300 mg/g)



No. at Risk							
Placebo	4952	4762	4542	4308	4127	3440	723
Dulaglutide	4949	4805	4636	4438	4263	3576	740

Gerstein, H.C. *et al.* Lancet 2019

REWIND: Sustained eGFR Decline ≥ 30, 40 & 50%

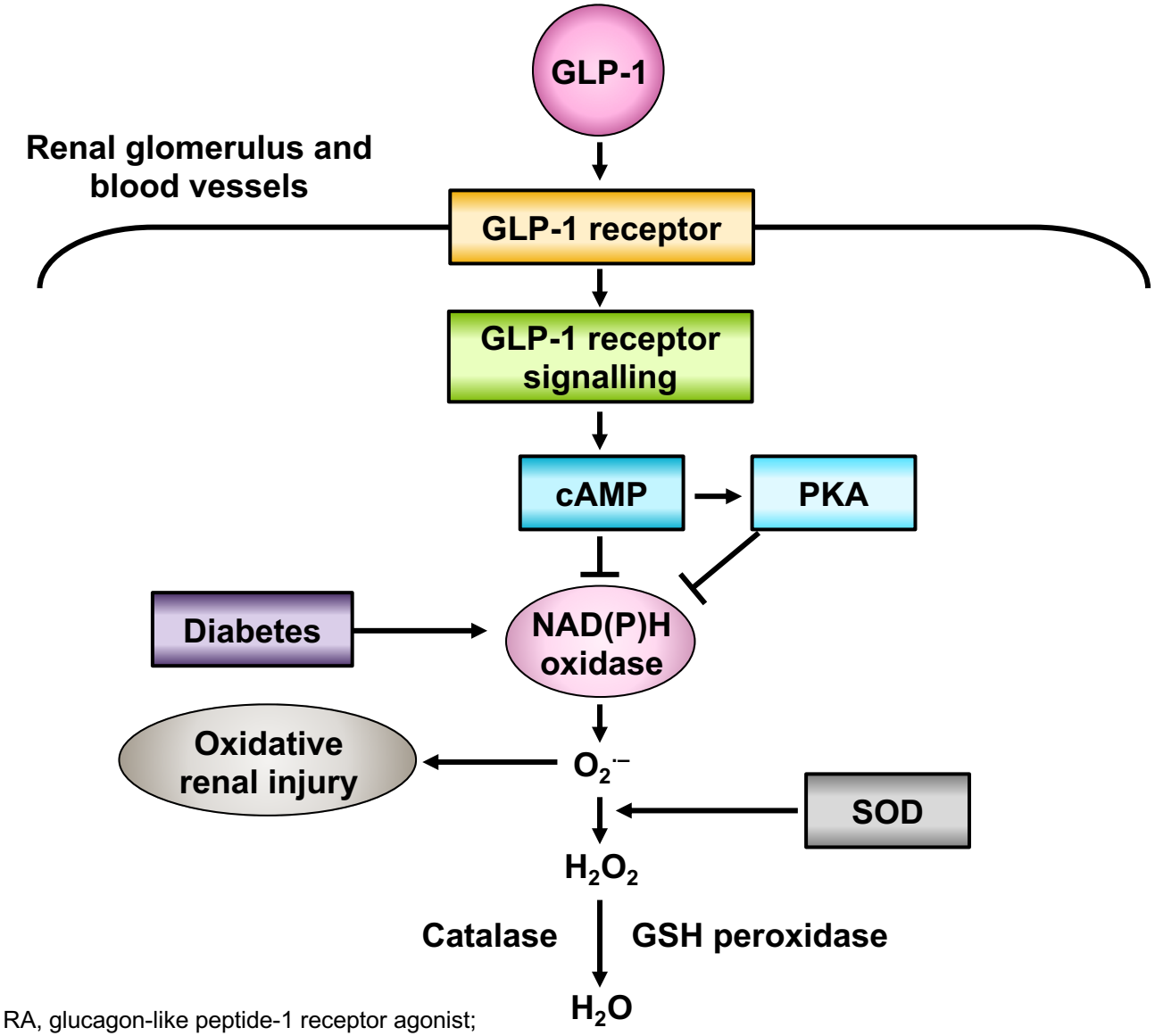


Sensitivity Analyses

Sustained eGFR decline ≥ 30%	HR 0.89 (0.78, 1.01)	0.066
Sustained eGFR decline ≥ 40%	HR 0.70 (0.57, 0.85)	0.0004
Sustained eGFR decline ≥ 50%	HR 0.56 (0.41, 0.76)	0.0002

Gerstein, H.C. *et al.* Lancet 2019

The Protective Roles of GLP-1 RA in Diabetic Kidney Disease



cAMP, cyclic adenosine monophosphate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GSH, glutathione; NADPH, nicotinamide adenine dinucleotide phosphate; PKA, protein kinase A;SOD, superoxide dismutase

Fujita H, et al. *Kidney Int* 2014;85:579–89

ADA/EASD and ADA recommend that the choice of second-line therapy should be based on assessment of ASCVD, HF or CKD

FIRST-LINE therapy is **metformin** and comprehensive lifestyle change

↓

Indicators of high-risk or established ASCVD, HF or CKD*

↓

Consider independently of baseline HbA1c

If ASCVD predominates

Preferably
GLP-1 receptor agonist with **proven CV benefit**
OR
SGLT2 inhibitor with **proven CV benefit**†

If HF or CKD predominates

Preferably
SGLT2 inhibitor with **evidence of reducing HF and/or CKD progression**
OR
(if can't use SGLT2i) GLP-1 receptor agonist with **proven CV benefit**‡

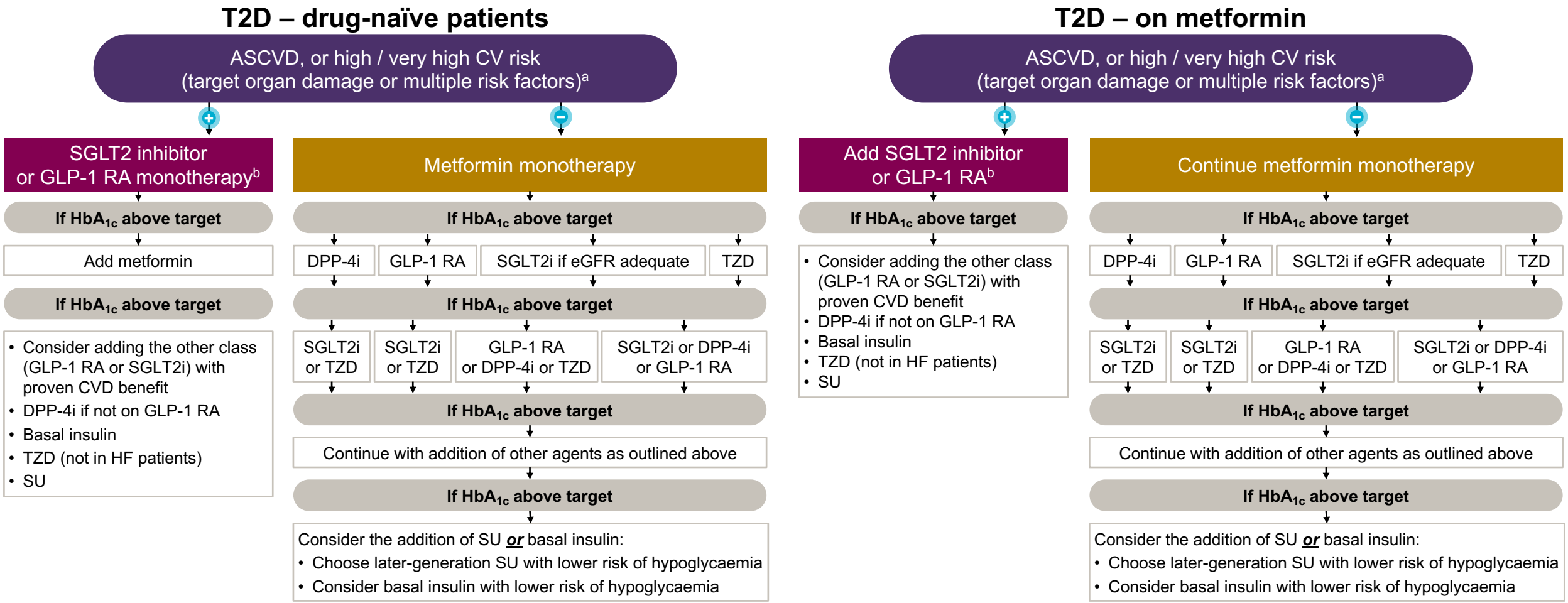
	ADA level of evidence	T2D patient population	Treatment recommendation
10.43a SGLT2 inhibitor[2]	A	ASCVD, ASCVD risk factors or DKD	To reduce the risk of MACE and HHF
10.43b GLP-1 receptor agonist[2]	A	ASCVD or ASCVD risk factors	To reduce the risk of MACE

*Action whenever these become new clinical observations, regardless of background glucose-lowering medication; †If eGFR adequate; ‡If SGLT2 inhibitor not tolerated or contraindicated or if eGFR less than adequate

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HF, heart failure; HHF, hospitalisation for heart failure; MACE, major adverse cardiovascular events; SGLT2, sodium-glucose co-transporter-2

1. Buse JB *et al. Diabetes Care* 2020;43:487; 2. American Diabetes Association. *Diabetes Care* 2020;43:S1

2019 ESC/EASD guidelines recommend SGLT2 inhibitors or GLP-1 RA as first line therapy in drug naïve T2D patients with ASCVD or high CV risk



[a]Very high risk was defined as: patients with diabetes and established CVD; or proteinuria, eGFR <30 mL/min/1.73 m^2, left ventircular hypertrophy, or retinopathy; or three or more of age, hypertension, dyslipidemia, smoking or obesity; or early onset T1D for >20 years. High risk was defined as: patients with diabetes ≥10 years without target organ damage plus any other additional risk factor. Moderate risk was defined as: T1D patients aged <35 years or T2D patients aged <50 years with diabetes duration <10 years, without other risk factors; [b]Use drugs with proven CV benefit

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HF, heart failure; SGLT2i, sodium–glucose co-transporter 2 inhibitor; SU, sulfonylurea; T1D, Type 1 diabetes;T2D, Type 2 diabetes; TZD, thiazolidinedione

Cosentino F, et al. *Eur Heart J* 2020;41:255–323

Patient Phenotypes for SGLT-2i vs. GLP-1RA

T2DM and ASCVD or HF

Prefer GLP-1RA	Prefer SGLT-2i	Choose GLP-1RA if SGLT-2i not suitable due to
eGFR 60-15 mL/min/m^2 (any albuminuria)	eGFR>60 mL/min/m2 (any albuminuria)	eGFR <60 mL/min/1.73 m^2
Overweight/obesity (semaglutide > dulaglutide/liraglutide)		Previous amputations or history of peripheral artery disease (canagliflozin)
Risk of stroke		High susceptibility to genital infections
NASH		Elderly on loop diuretics
PAD, diabetic foot ulcers, previous amputations (liraglutide)		Severe carbohydrate restriction, severe illness
High fracture risk		
High risk of volume depletion (elderly, loop diuretics)		

Giorgino F et al., *Metabolism* 2020