POSSIAMO RALLENTARE LA NEFROPATIA?

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AGENDA

- TRENDS IN DIABETIC COMPLICATIONS AND DKD
- RENAL OUTCOME FROM CARDIOVASCULAR OUTCOME TRIALS
  - CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs
  - CARDIOVASCULAR (and RENAL) OUTCOME TRIALS – SGLT2-Is
  - COMPARISON GLP-1 RAs/SGLT2-Is
- MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs AND SGLT2-Is
- GUIDELINES OF GLUCOSE-LOWERING MEDICATION IN T2DM – FOCUS ON CKD
- DOSE RECOMMENDATIONS OF GLP-1 RAs AND SGLT2-Is IN CKD
- TAKE HOME MESSAGES

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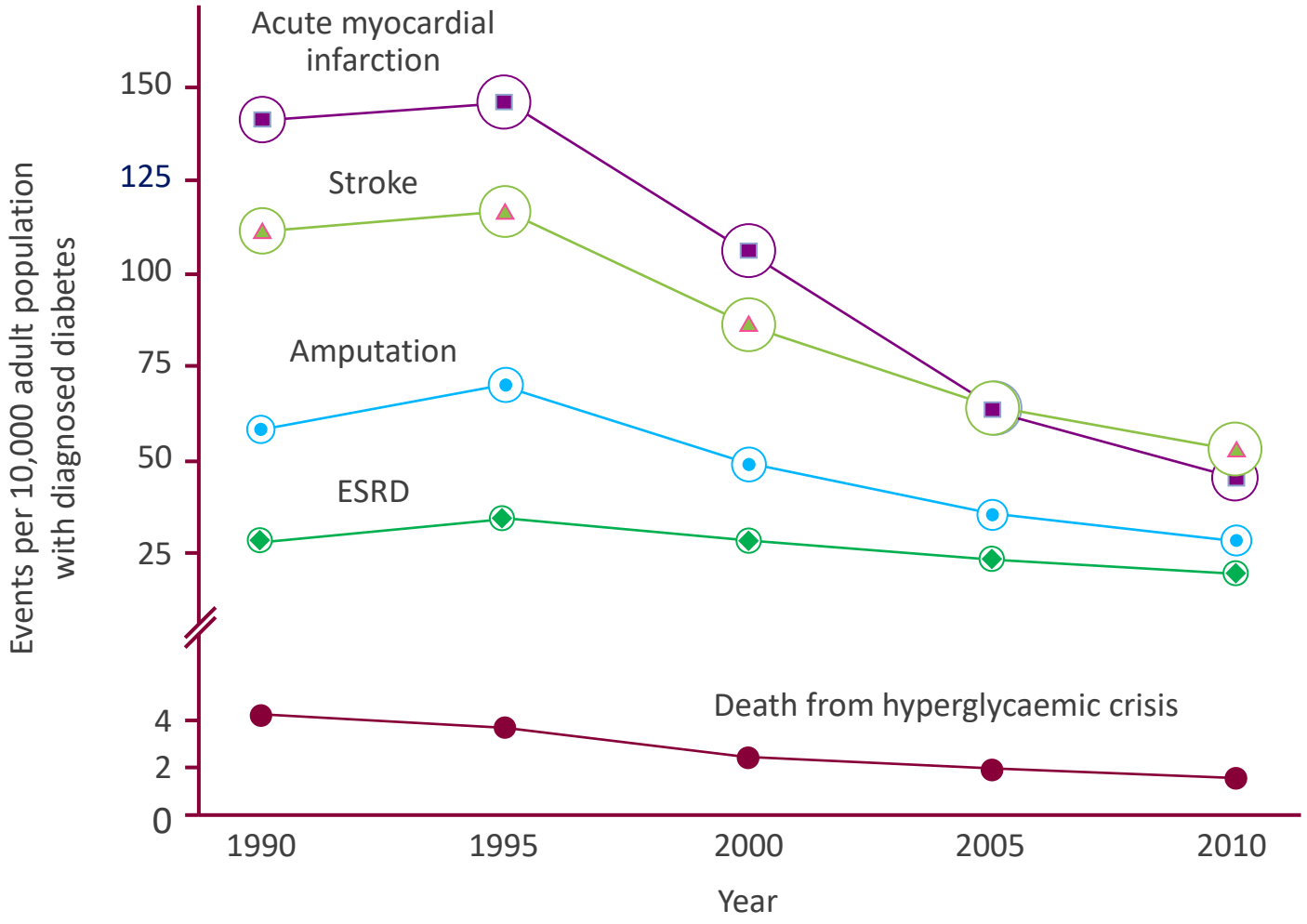
TRENDS IN DIABETIC COMPLICATIONS

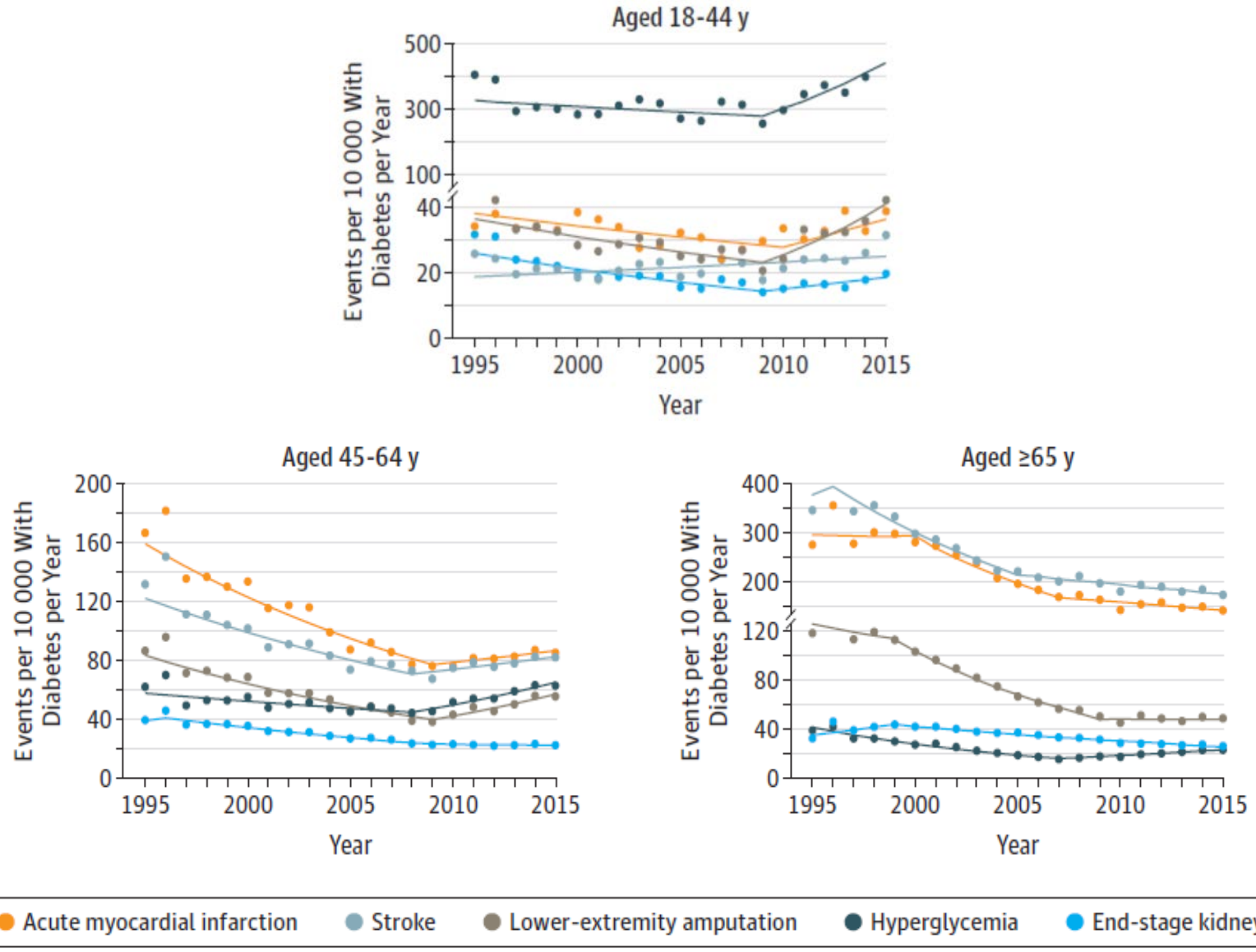
Trends in Age-Standardized Rates of Diabetes-Related Complications among U.S. Adults with Diagnosed Diabetes



Gregg EW et al. N Engl J Med 2014;370:1514–1523.

TRENDS IN DIABETIC COMPLICATIONS

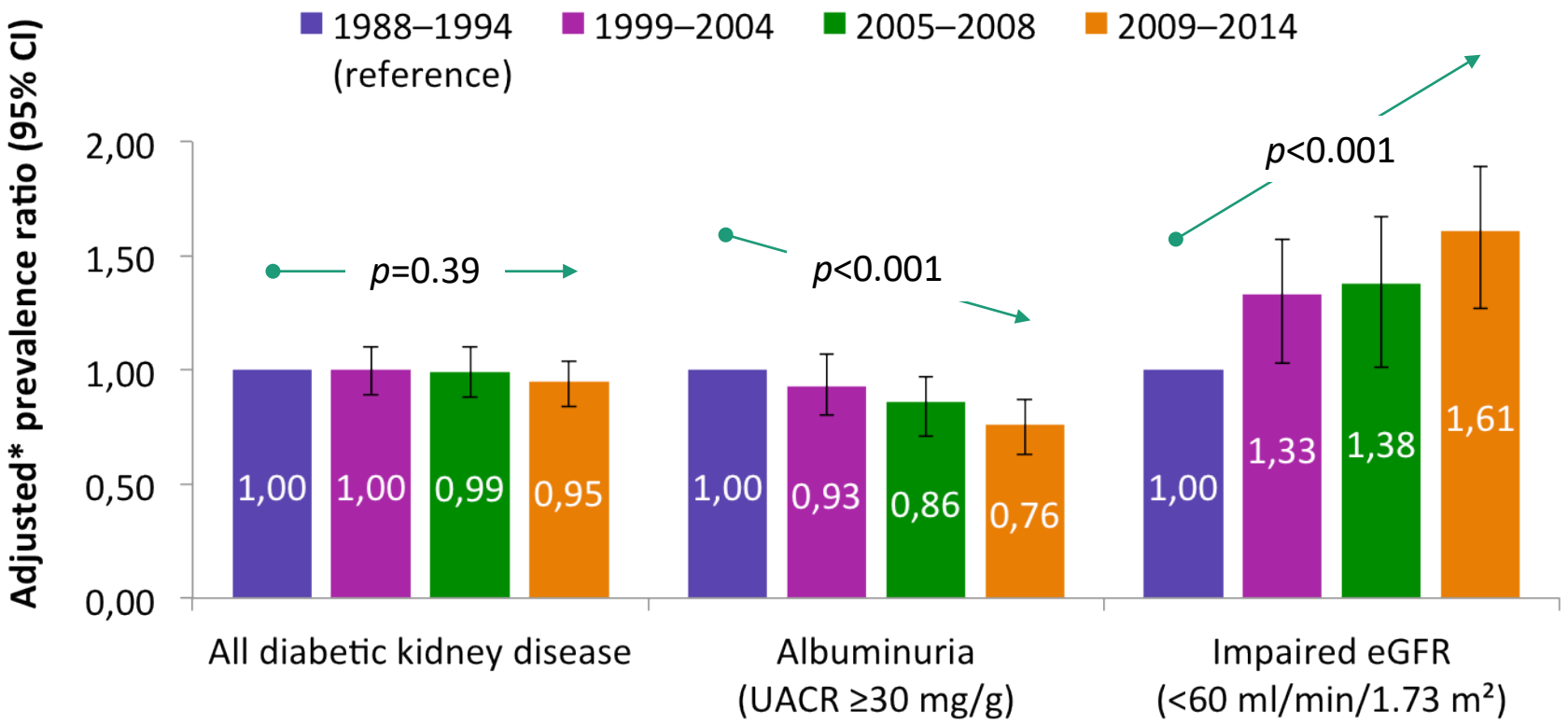
Resurgence in Diabetes-Related Complications



Gregg EW et al. JAMA 2019;321:1867–1868.

TRENDS IN DIABETIC COMPLICATIONS - DKD

Clinical Manifestations of Kidney Disease Among US Adults With Diabetes

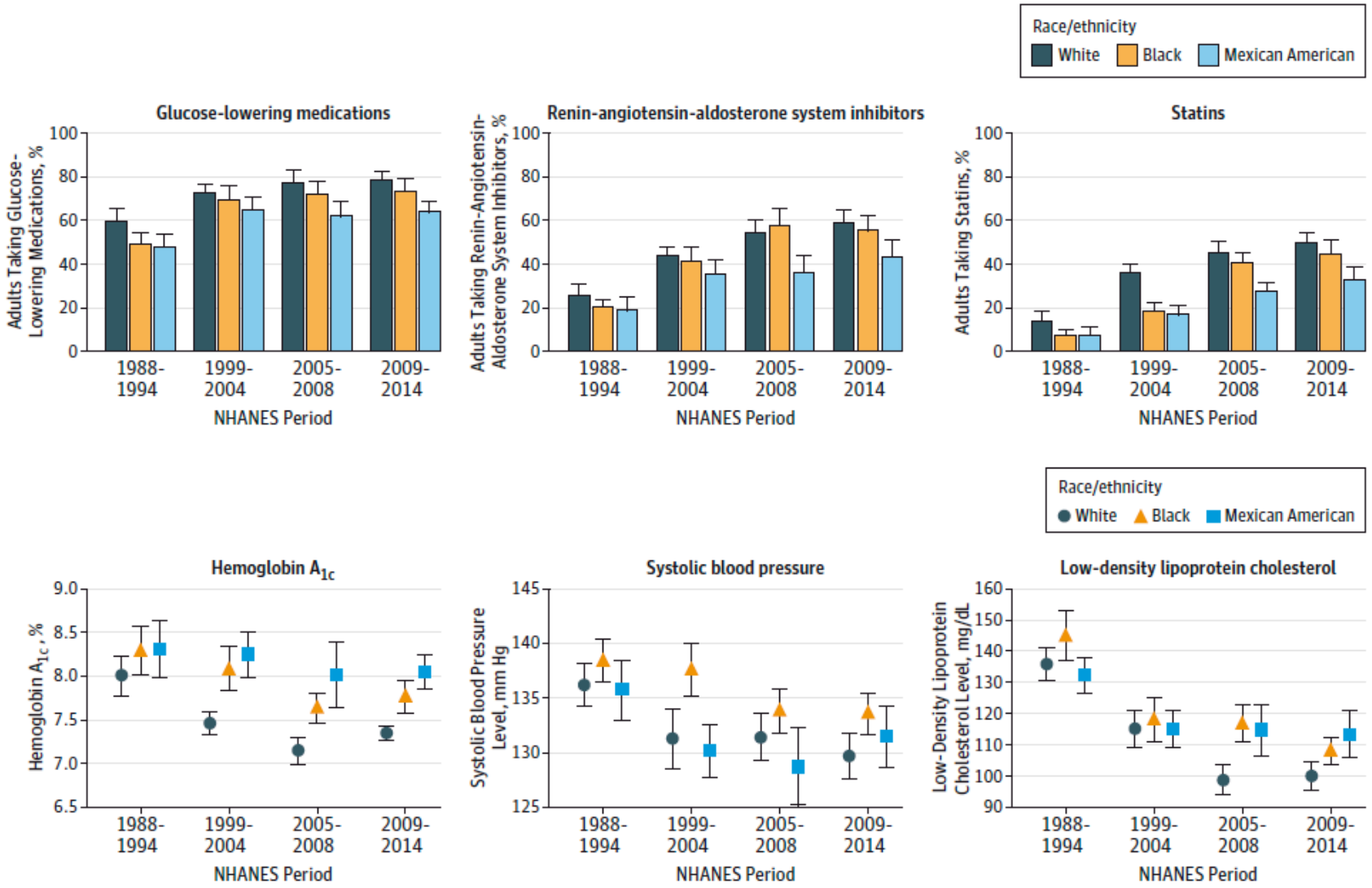


*Adjusted for age, sex, and race/ethnicity. p-values are for trend

Afkarian M et al. JAMA. 2016;316:602-610
Slide courtesy of Prof. G. Pugliese

TRENDS IN DIABETIC COMPLICATIONS - DKD

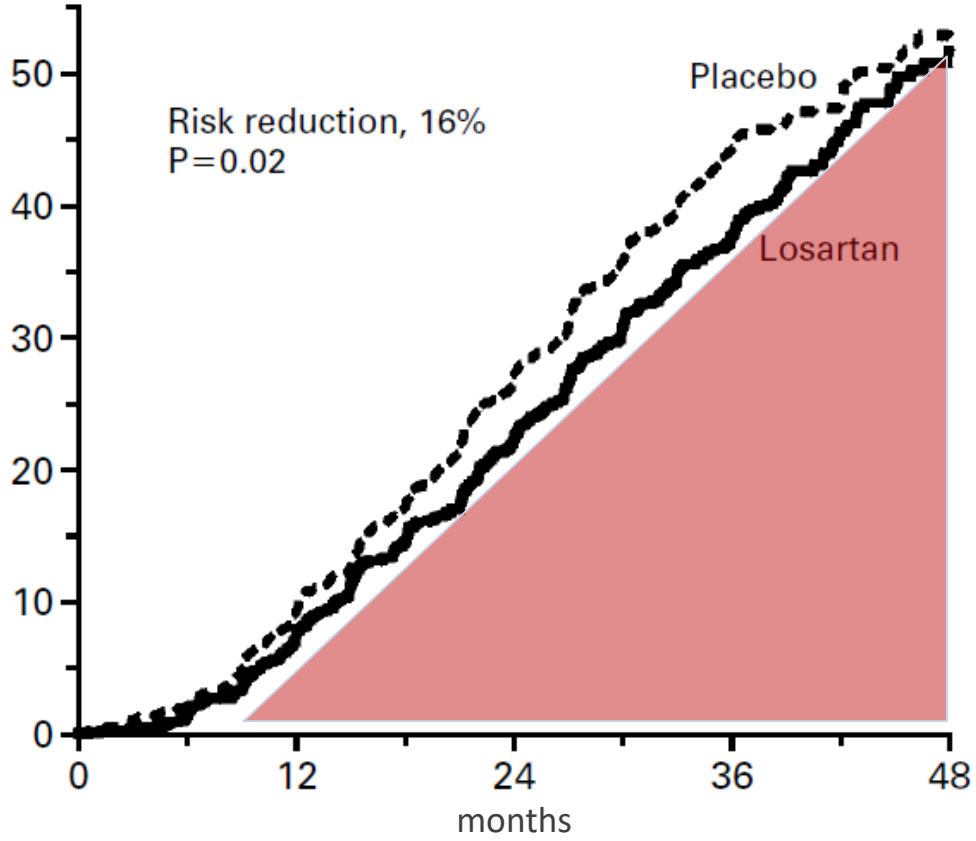
Medication Use and Trends in Clinical Targets



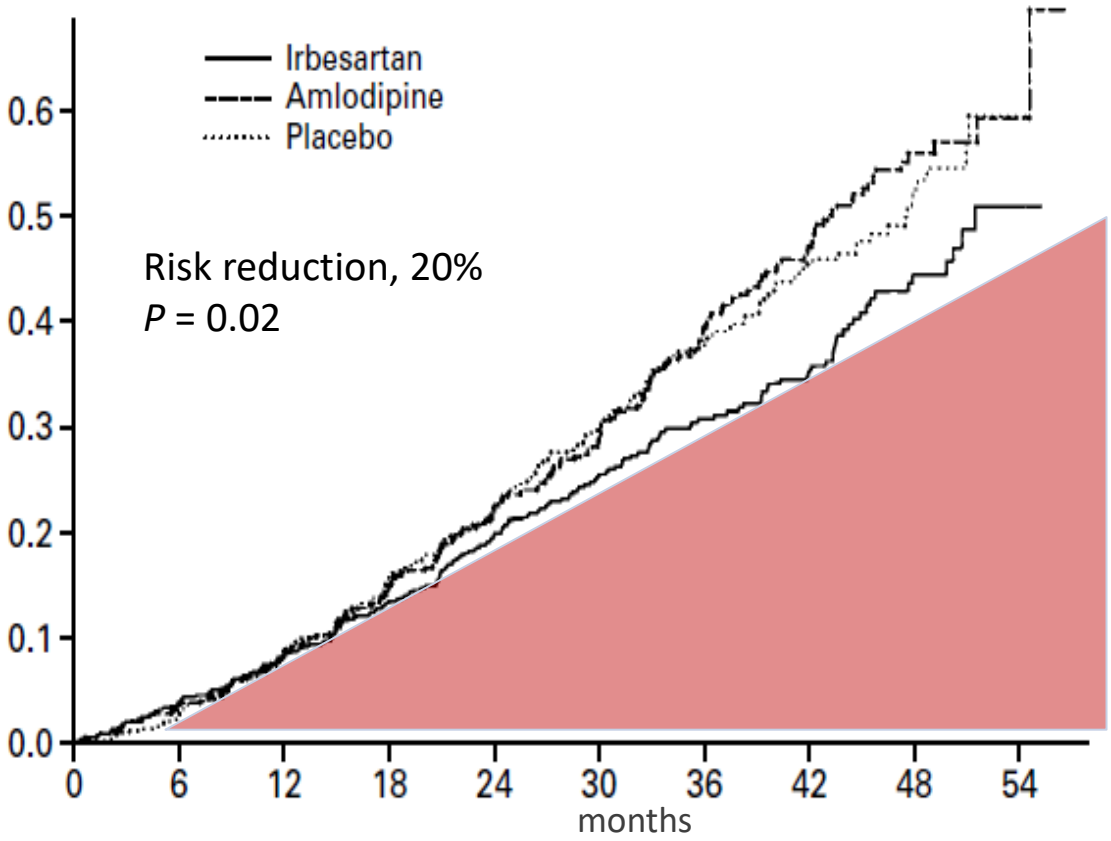
Afkarian M et al. JAMA. 2016;316:602-610

RENAL PROTECTION WITH RAS BLOCKERS

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist **Losartan** (RENAAL) Study



The **Irbesartan** Diabetic Nephropathy Trial (IDNT)



Renal composite outcome:
doubling of serum creatinine, ESRD or death

Brenner B et al. N Engl J Med. 2001;345:861-869

Lewis EJ et al. N Eng J Med. 2001;345:851-860

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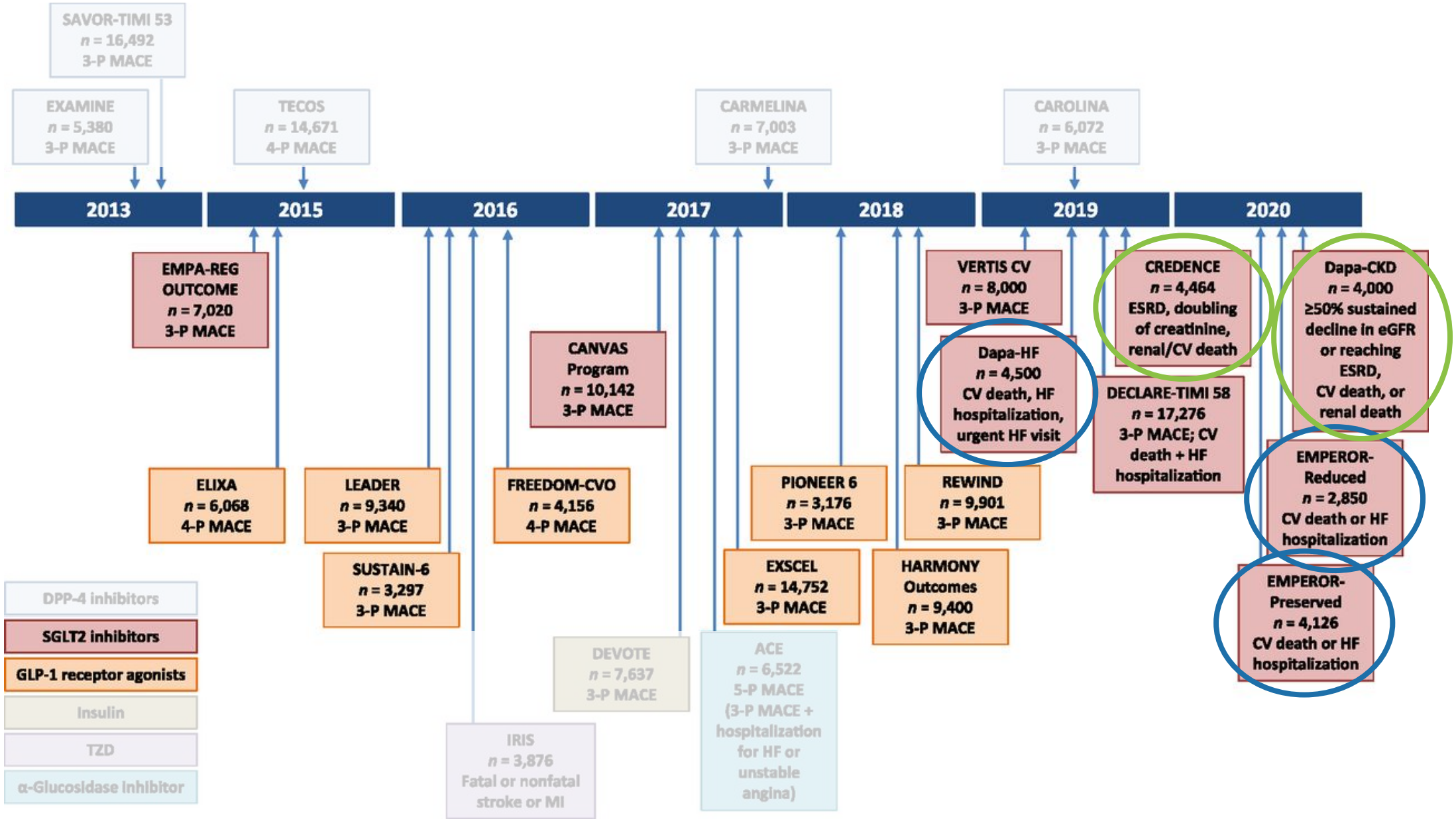
CARDIOVASCULAR OUTCOME TRIALS



Cefalu WT et al. Diabetes Care. 2018;41(1):14-31.

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CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

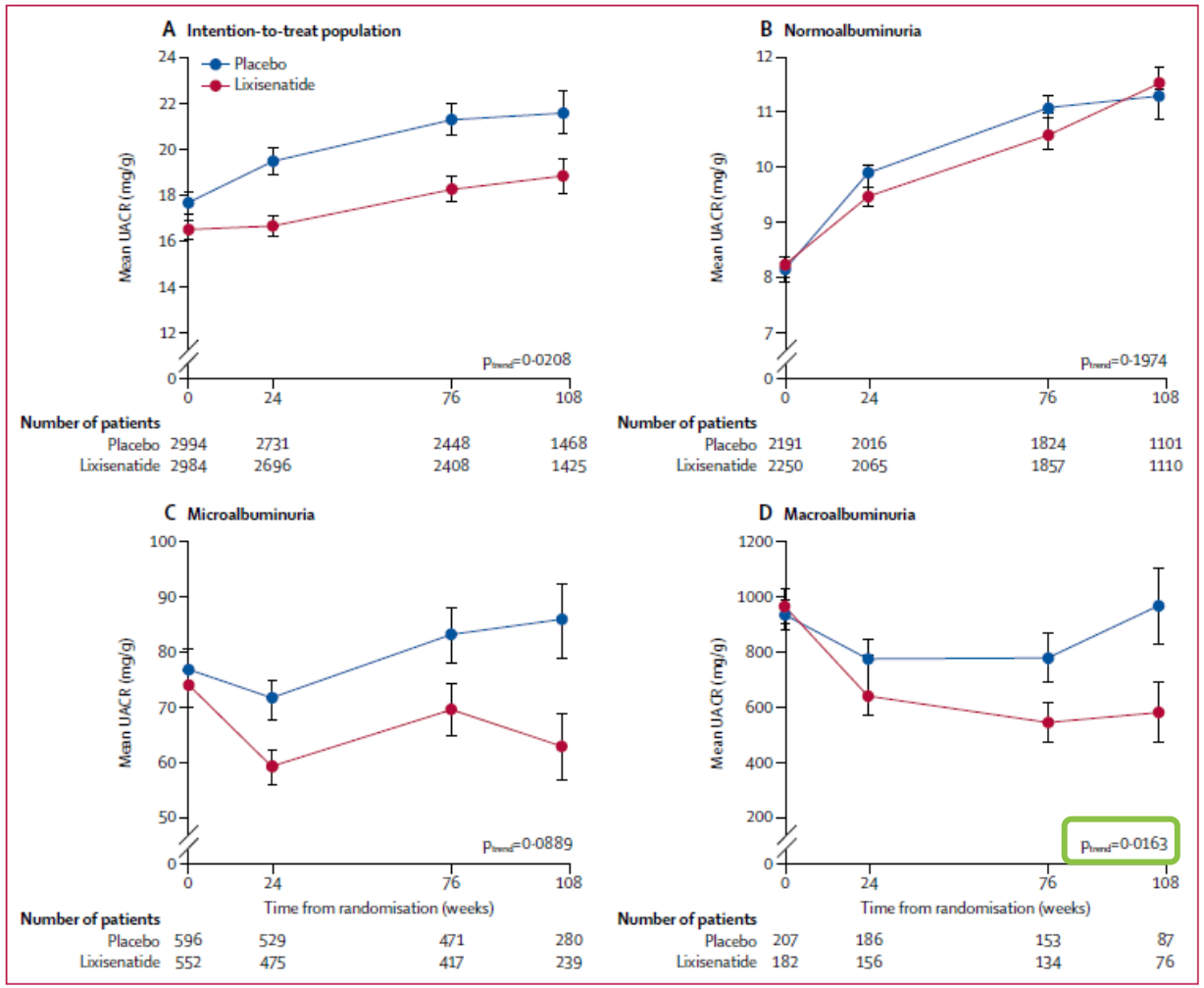
Trial	ELIXA
Drug	Lixisenatide
Participants, n (active drug/placebo)	6,068 (3,034/3,034)
Median follow-up, years	2.1
eGFR (ml/min/1.73m^2) (active drug/placebo)	75.2/76.7
Renal function at baseline	
Normal (eGFR ≥90)	23.3%
Mild impairment (eGFR 60-89)	53.5%
Moderate impairment (eGFR 30-59)	23.1%
Severe impairment (eGFR<30)	0.1%
Albuminuria at baseline	
Normoalbuminuria	74%
Microalbuminuria	19%
Macroalbuminuria	7%

EXCL CRITERION:
eGFR <30
ml/min/1.73m^2

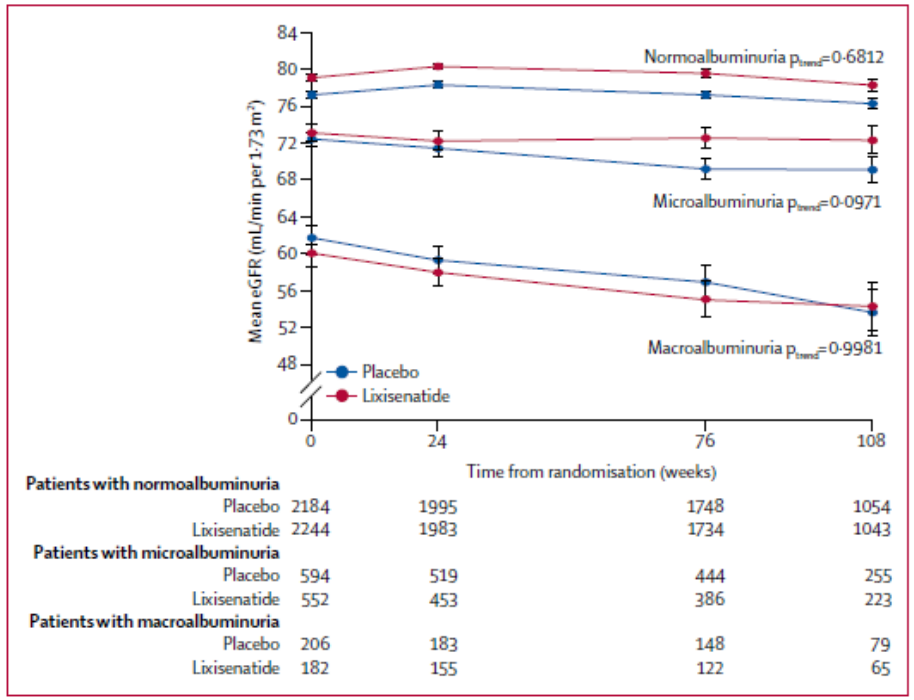
Pfeffer MA et al. N Engl J Med. 2015;373;2247–2257

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

The Evaluation of **Lixisenatide** in Acute Coronary Syndrome (ELIXA) trial



New-onset macroalbuminuria:
HR, 0.84; 95% CI, 0.68–1.02; P=0.083



Doubling of serum creatinine:
HR, 1.16; 95% CI, 0.74–1.83; P=0.51

Muskiet MHA et al. Lancet Diabetes Endocrinol 2018;6: 859–69

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Trial	ELIXA	LEADER
Drug	Lixisenatide	Liraglutide
Participants, n (active drug/placebo)	6,068 (3,034/3,034)	9,340 (4,668/4,672)
Median follow-up, years	2.1	3.8
eGFR (ml/min/1.73m²) (active drug/placebo)	75.2/76.7	80.2/80.6
Renal function at baseline		
Normal (eGFR ≥90)	23.3%	35%
Mild impairment (eGFR 60-89)	53.5%	41.9%
Moderate impairment (eGFR 30-59)	23.1%	20.7%
Severe impairment (eGFR<30)	0.1%	2.4%
Albuminuria at baseline		
Normoalbuminuria	74%	63.4%
Microalbuminuria	19%	26.3%
Macroalbuminuria	7%	10.3%

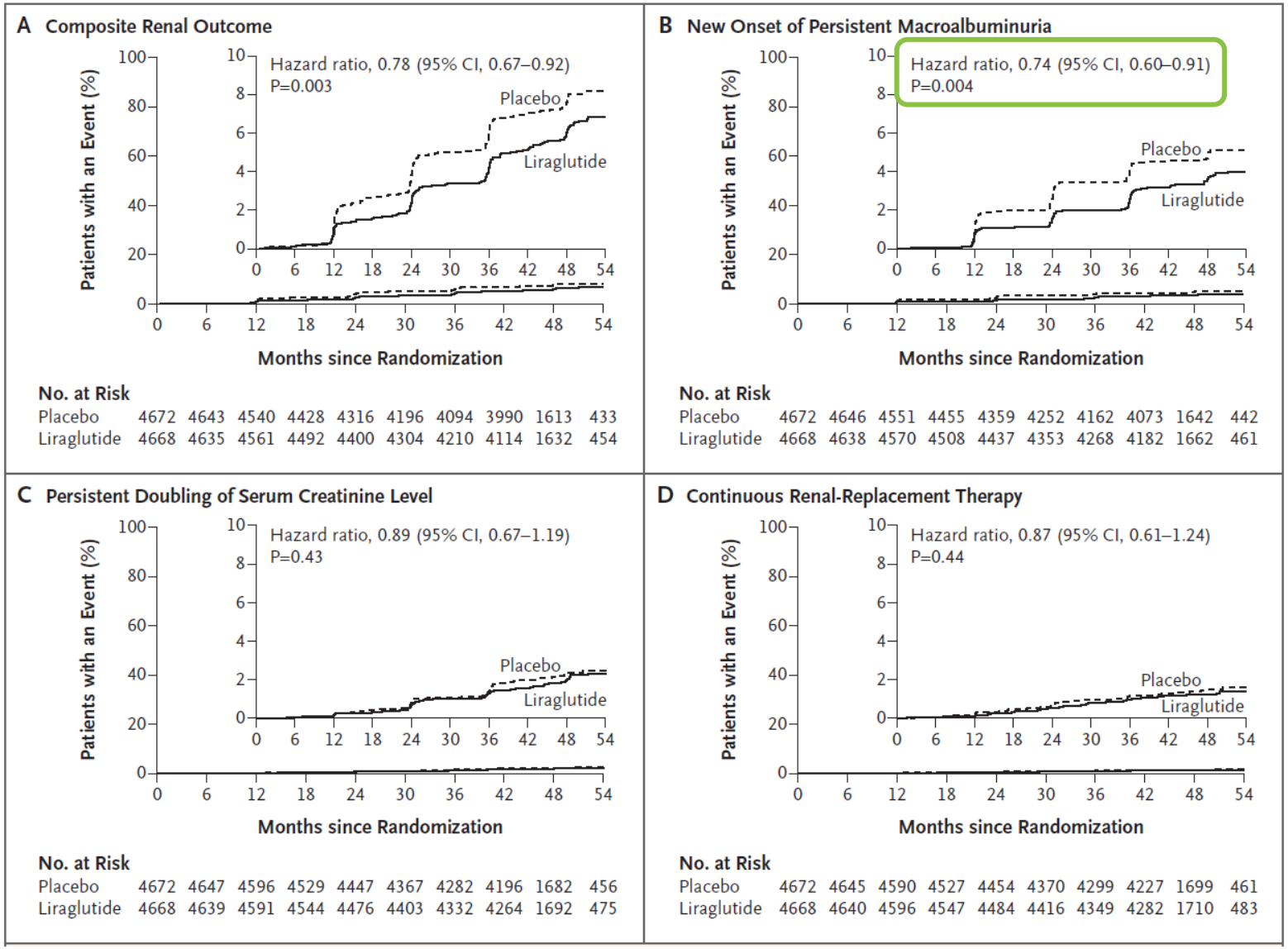
no eGFR limits

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

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

The **Liraglutide** Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) Trial

LEADER® Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results



Mann JFE et al. N Engl J Med. 2017;377:839-848

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Trial	ELIXA	LEADER	SUSTAIN 6
Drug	Lixisenatide	Liraglutide	Semaglutide
Participants, n (active drug/placebo)	6,068 (3,034/3,034)	9,340 (4,668/4,672)	3,297 (1,648/1,649)
Median follow-up, years	2.1	3.8	2.1
eGFR (ml/min/1.73m²) (active drug/placebo)	75.2/76.7	80.2/80.6	NR
Renal function at baseline			
Normal (eGFR ≥90)	23.3%	35%	30.1%
Mild impairment (eGFR 60-89)	53.5%	41.9%	41.5%
Moderate impairment (eGFR 30-59)	23.1%	20.7%	25.2%
Severe impairment (eGFR<30)	0.1%	2.4%	3.2%
Albuminuria at baseline			
Normoalbuminuria	74%	63.4%	NR
Microalbuminuria	19%	26.3%	NR
Macroalbuminuria	7%	10.3%	NR

no eGFR limits

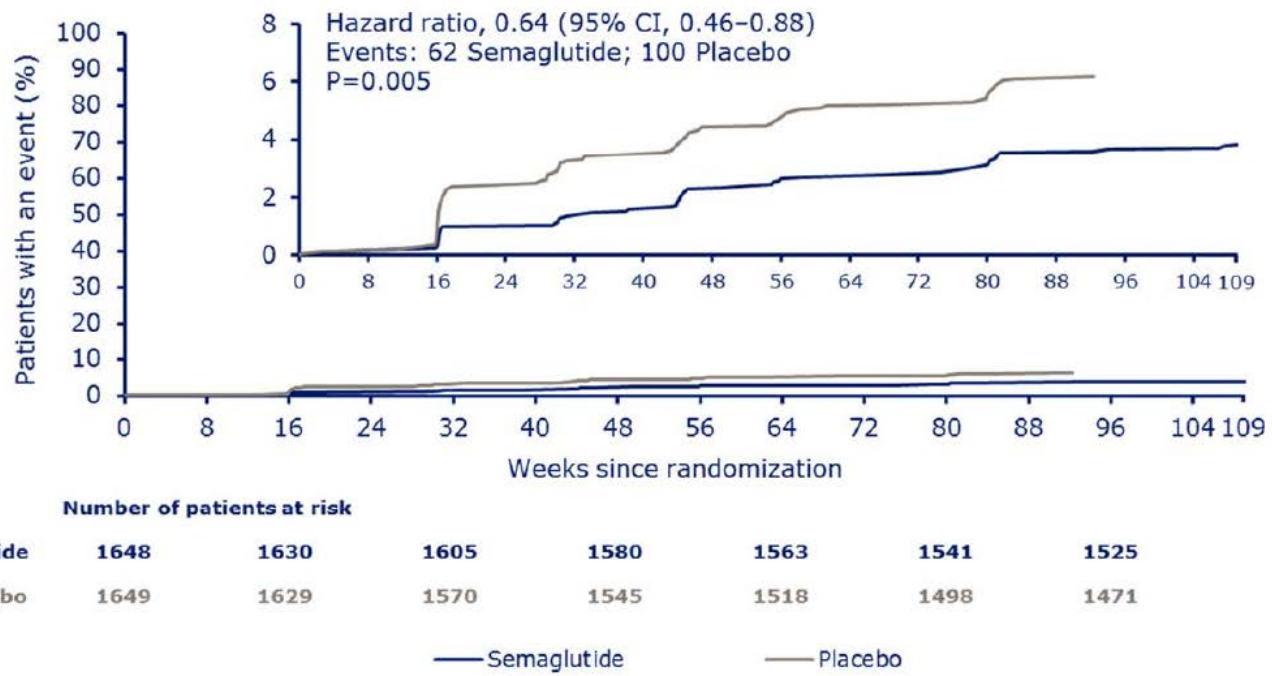
Marso SP et al. N Engl J Med. 2016;375;1834–1844

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Trial to Evaluate Cardiovascular and Other Long-term Outcomes with **Semaglutide** in Subjects with Type 2 Diabetes (SUSTAIN-6)

SUSTAIN™
SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

B. New or worsening nephropathy



- new-onset persistent macroalbuminuria → HR, 0.54; 95% CI, 0.37–0.77; P=0.001
- persistent doubling of serum creatinine level (and eGFR <45 mL/min/m^2)
- ESRD

Marso SP et al. N Engl J Med. 2016;375;1834–1844

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Trial	ELIXA	LEADER	SUSTAIN 6	EXSCEL
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide ER
Participants, n (active drug/placebo)	6,068 (3,034/3,034)	9,340 (4,668/4,672)	3,297 (1,648/1,649)	14,752 (7,356/7,396)
Median follow-up, years	2.1	3.8	2.1	3.2
eGFR (ml/min/1.73m^2) (active drug/placebo)	75.2/76.7	80.2/80.6	NR	76.6/76
Renal function at baseline				
Normal (eGFR ≥90)	23.3%	35%	30.1%	29%
Mild impairment (eGFR 60-89)	53.5%	41.9%	41.5%	49.3%
Moderate impairment (eGFR 30-59)	23.1%	20.7%	25.2%	21.6%
Severe impairment (eGFR<30)	0.1%	2.4%	3.2%	0.1%
Albuminuria at baseline				
Normoalbuminuria	74%	63.4%	NR	NR
Microalbuminuria	19%	26.3%	NR	NR
Macroalbuminuria	7%	10.3%	NR	NR

EXCL CRITERION: eGFR <30 ml/min/1.73m^2

Holman RR et al. N Engl J Med. 2017;377;1228–1239

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Exenatide Study of Cardiovascular Event Lowering (EXSCEL)

EXSCEL

	Exenatide		Placebo		HR (95% CI)	p
	# with event, n/N (%)	Incidence/ 100 pyr	# with event, n/N (%)	Incidence/ 100 pyr		
Renal composite 1	246/6456 (3.8%)	1.2	273/6458 (4.2%)	1.4	0.88 (0.74, 1.05)	0.164
*Adjusted HR**					0.87 (0.73, 1.04)	0.128
40% eGFR decline	239		266			
Renal replacement	7		7			
Renal death	0		0			
Renal composite 2	366/6256 (5.8%)	1.9	407/6222 (6.5%)	2.2	0.88 (0.76, 1.01)	0.065
*Adjusted HR**					0.85 (0.73, 0.98)	0.027
40% eGFR decline	216		228			
Renal replacement	7		6			
Renal death	0		0			
New macroalbuminuria	143		173			

*Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline HbA1c, eGFR, and BMI.

Bethel MA et al. Diabetes 2018, 67:522-P.

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Trial	ELIXA	LEADER	SUSTAIN 6	EXSCEL	REWIND
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide ER	Dulaglutide
Participants, n (active drug/placebo)	6,068 (3,034/3,034)	9,340 (4,668/4,672)	3,297 (1,648/1,649)	14,752 (7,356/7,396)	9,901 (4,949/4,952)
Median follow-up, years	2.1	3.8	2.1	3.2	5.4
eGFR (ml/min/1.73m^2) (active drug/placebo)	75.2/76.7	80.2/80.6	NR	76.6/76	77.2/76.6
Renal function at baseline					
Normal (eGFR ≥90)	23.3%	35%	30.1%	29%	25.6%
Mild impairment (eGFR 60-89)	53.5%	41.9%	41.5%	49.3%	49.5%
Moderate impairment (eGFR 30-59)	23.1%	20.7%	25.2%	21.6%	21.2%
Severe impairment (eGFR<30)	0.1%	2.4%	3.2%	0.1%	1.1% (2.6% missing)
Albuminuria at baseline					
Normoalbuminuria	74%	63.4%	NR	NR	65%
Microalbuminuria	19%	26.3%	NR	NR	27%
Macroalbuminuria	7%	10.3%	NR	NR	8%

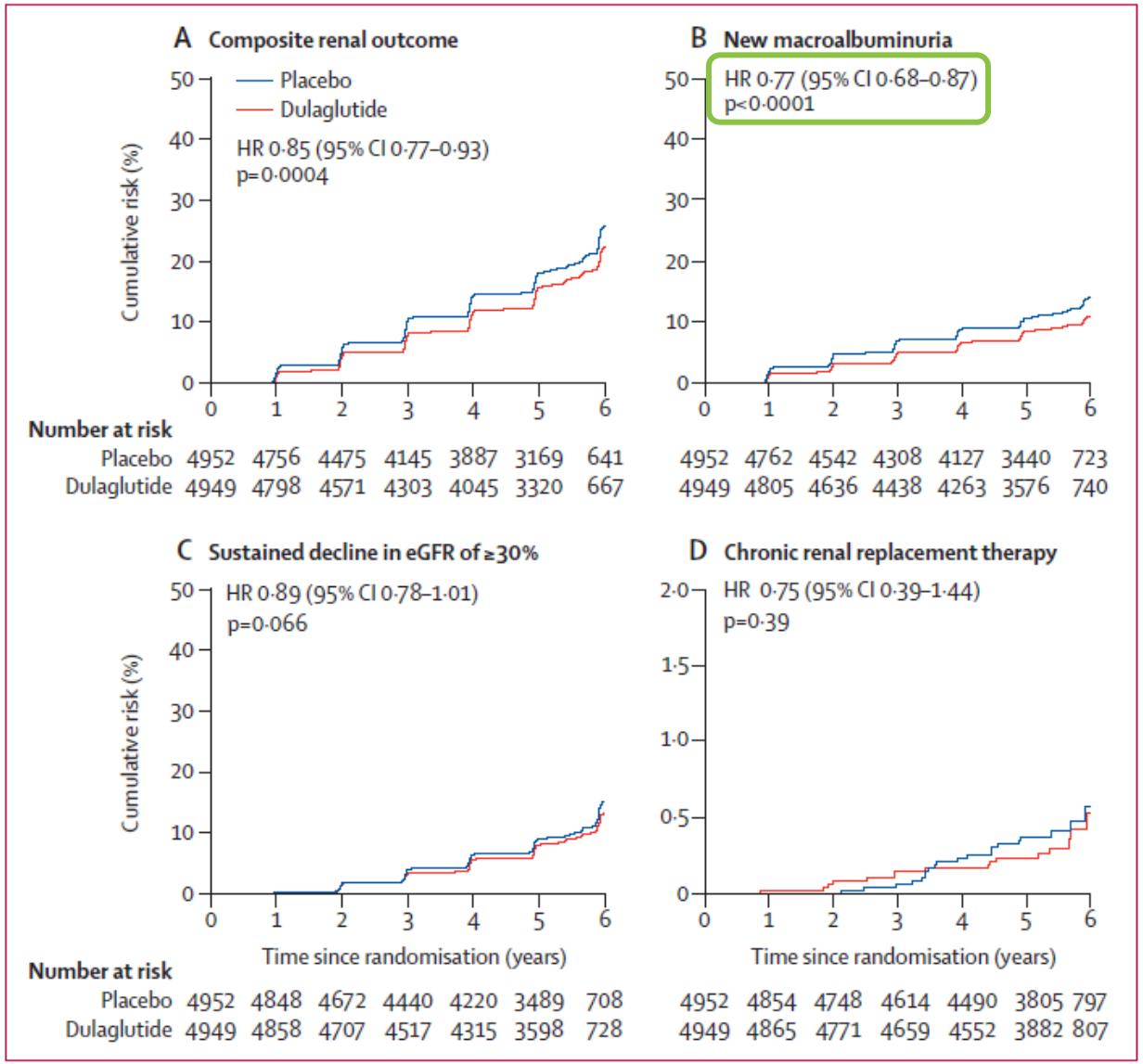
EXCL CRITERION: eGFR <15 ml/min/1.73m^2

Gerstein H et al. Lancet. 2019;394:121–130

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial

REWIND
Dulaglutide CV Outcome Trial



Gerstein H et al. Lancet. 2019;394:131–138

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Trial	ELIXA	LEADER	SUSTAIN 6	EXSCEL	REWIND	HARMONY	PIONEER 6
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide ER	Dulaglutide	Albiglutide	Semaglutide (oral)
Participants, n (active drug/placebo)	6,068 (3,034/3,034)	9,340 (4,668/4,672)	3,297 (1,648/1,649)	14,752 (7,356/7,396)	9,901 (4,949/4,952)	9,463 (4,731/4,732)	3,183 (1,591/1,592)
Median follow-up, years	2.1	3.8	2.1	3.2	5.4	1.6	1.3
eGFR (ml/min/1.73m²) (active drug/placebo)	75.2/76.7	80.2/80.6	NR	76.6/76	77.2/76.6	79.1/78.9	74/74
Renal function at baseline							
Normal (eGFR ≥90)	23.3%	35%	30.1%	29%	25.6%	NR	28.9%
Mild impairment (eGFR 60-89)	53.5%	41.9%	41.5%	49.3%	49.5%		43.6%
Moderate impairment (eGFR 30-59)	23.1%	20.7%	25.2%	21.6%	21.2%		26%
Severe impairment (eGFR<30)	0.1%	2.4%	3.2%	0.1%	1.1% (2.6% missing)		0.9% (0.6% missing)
Albuminuria at baseline							
Normoalbuminuria	74%	63.4%	NR	NR	65%	NR	67%
Microalbuminuria	19%	26.3%	NR	NR	27%		33% (micro+macro)
Macroalbuminuria	7%	10.3%	NR	NR	8%		

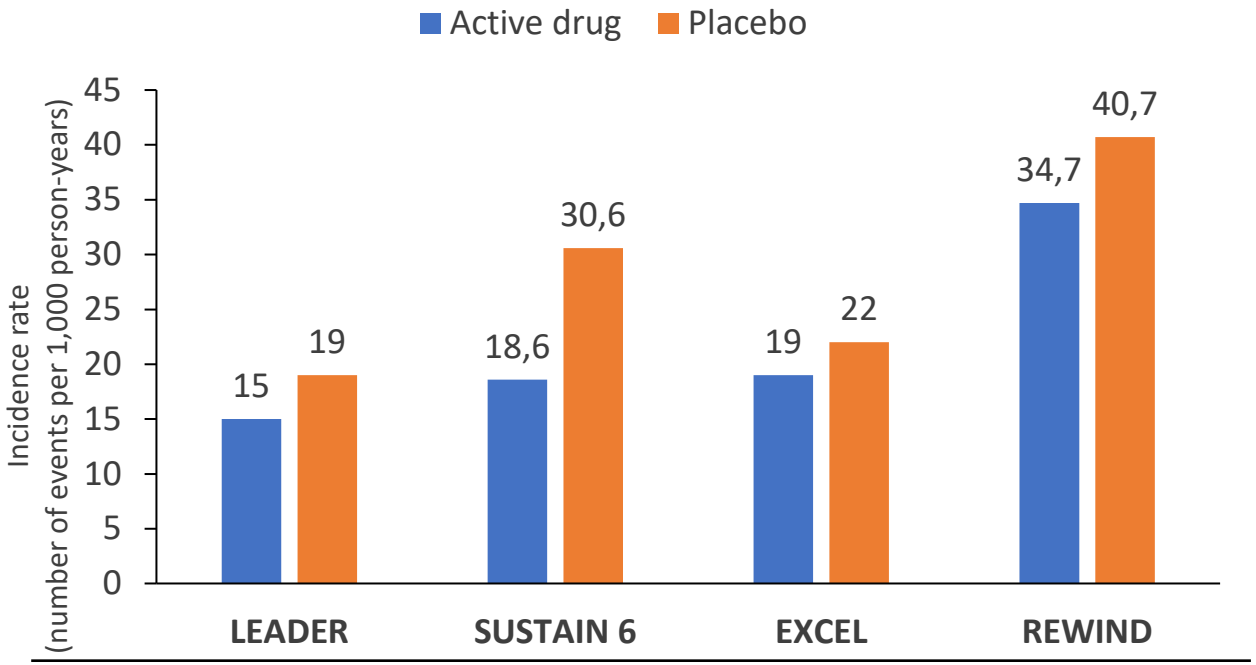
ER = extended release; eGFR = estimated glomerular filtration rate; NR = not reported.

Vitale M et al. Curr Opin Pharmacol. 2020, 54:91–101

Hernandez HF et al. Lancet. 2018;392:1519–1529
Husain M et al. N Engl J Med 2019;381:841–851

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Composite renal outcome



	LEADER	SUSTAIN 6	EXCEL	REWIND
HR	0.78	0.64	0.88	0.85
(95% CI)	0.67–0.92	0.46–0.88	0.76–1.01	0.77–0.93
p value	p=0.003	p=0.005	p=0.065	p=0.0004

LEADER: new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level (and eGFR <45 mL/min/m^2), ESRD, renal death

SUSTAIN 6: new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level (and eGFR <45 mL/min/m^2), ESRD

EXCEL: new-onset persistent macroalbuminuria, ≥40% worsening of eGFR, ESRD, renal death

REWIND: new-onset persistent macroalbuminuria, ≥30% worsening of eGFR, ESRD

Vitale M et al. Curr Opin Pharmacol. 2020, 54:91–101

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Post-hoc individual renal endpoints

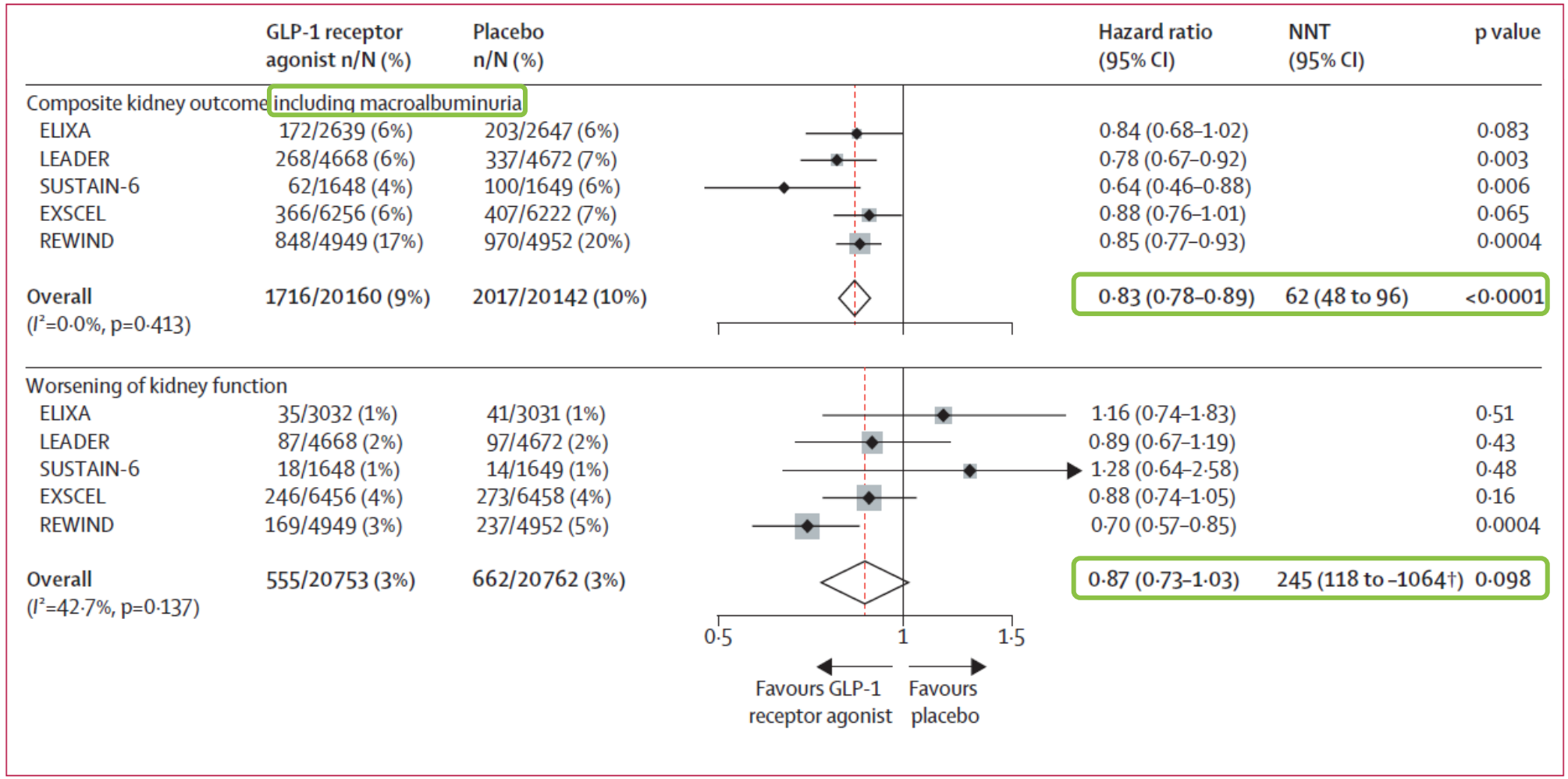
Trial	ELIXA	LEADER	SUSTAIN 6	EXSCEL	REWIND
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide ER	Dulaglutide
New-onset persistent macroalbuminuria	0.84 (0.68–1.02) p=0.083	0.74 (0.60–0.91) p=0.004	0.54 (0.37–0.77) p=0.001	NR p=0.19	0.77 (0.68–0.87) p<0.0001
Persistent doubling of serum creatinine	1.16 (0.74–1.83) p=0.51	0.89 (0.67–1.19)* p=0.43	1.28 (0.64–2.58)* p=0.48	NA	NA
≥30% worsening of eGFR	NA	NA	NA	NA	0.89 (0.78–1.01) p=0.066
≥40% worsening of eGFR	NA	NA	NA	NA	0.70 (0.57–0.85) p=0.0004
≥50% worsening of eGFR	NA	NA	NA	NA	0.56 (0.41–0.76) p=0.0002
ESRD	NA	0.87 (0.61-1.24) p=0.44	0.91 (0.40-2.07) p=0.83	NA	0.75 (0.39–1.44) p=0.39
Death due to renal disease	NA	1.59 (0.52-4.87) p=0.41	NA	NA	NA

Data are reported as hazard ratios with 95% confidence intervals and p value.
Doubling of serum creatinine level and eGFR <45 mL/min/m^2.
ER = extended release; eGFR = estimated glomerular filtration rate; ESRD: end-stage renal disease; NR: not reported; NA: not assessed.

Vitale M et al. Curr Opin Pharmacol. 2020, 54:91–101

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Systematic review and meta-analysis of cardiovascular outcome trials



Kristensen SL et al. Lancet Diabetes Endocrinol 2019;7: 776–85

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CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

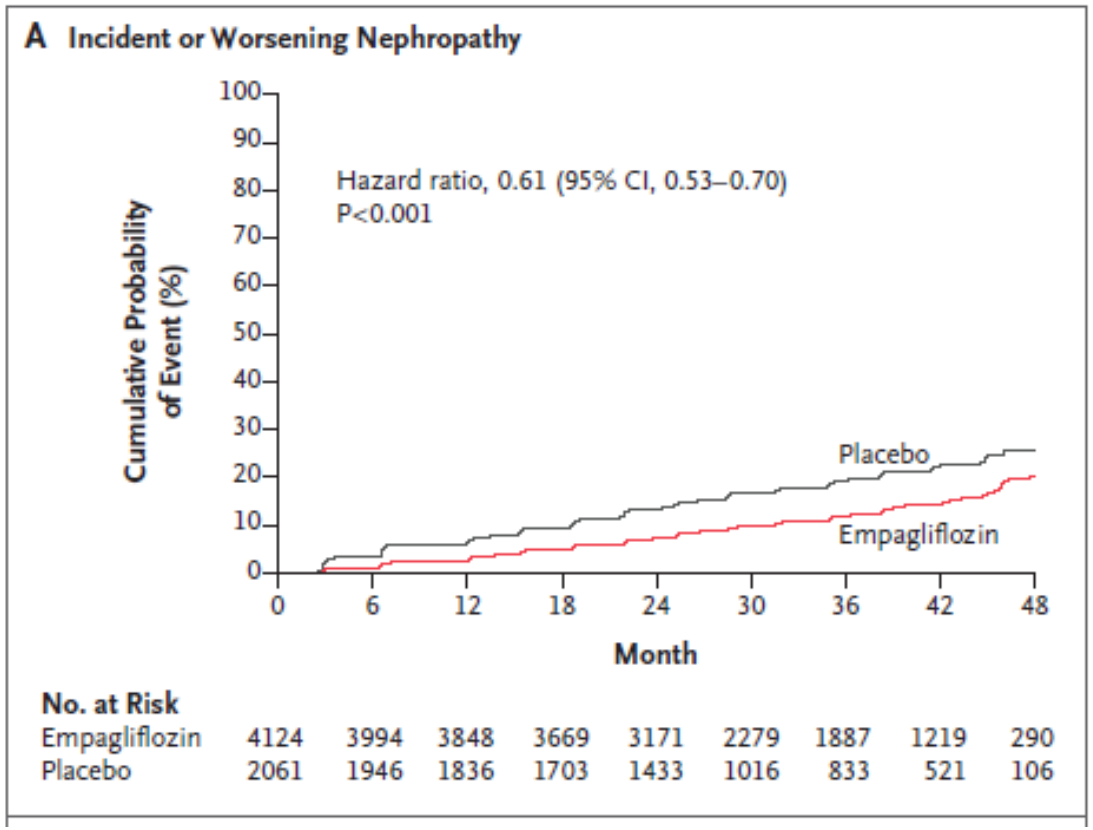
Trial	EMPA-REG OUTCOME
Drug	Empagliflozin
Participants, n (active drug/placebo)	7,020 (4,687/2,333)
Median follow-up, years	3.1
eGFR (ml/min/1.73m^2) (active drug/placebo)	73.8/74.2
Renal function at baseline	
Normal (eGFR ≥90)	21.9%
Mild impairment (eGFR 60-89)	52.2%
Moderate impairment (eGFR 30-59)	25.9%
Severe impairment (eGFR<30)	-
Albuminuria at baseline	
Normoalbuminuria	60.0%
Microalbuminuria	29.0%
Macroalbuminuria	11.0%

EXCL CRITERION:
eGFR <30
ml/min/1.73m^2

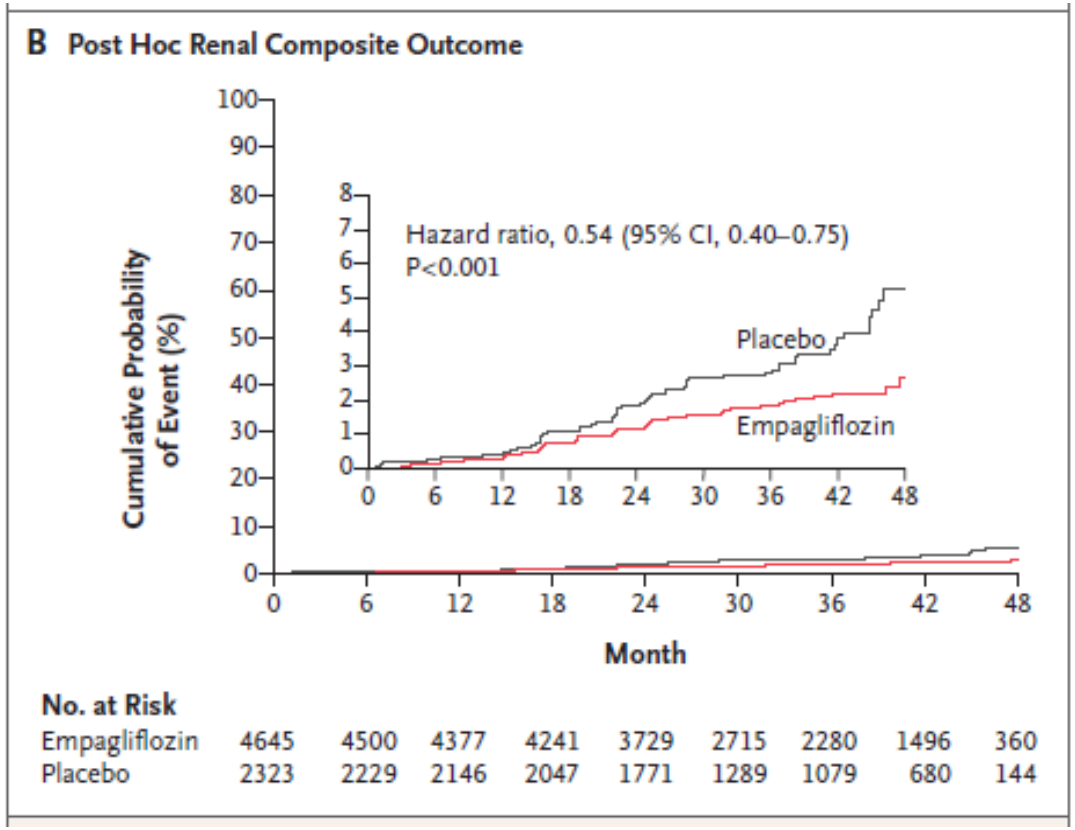
Zinman B et al. N Engl J Med. 2015;373:2117–2128

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)



Progression to macroalbuminuria, doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease



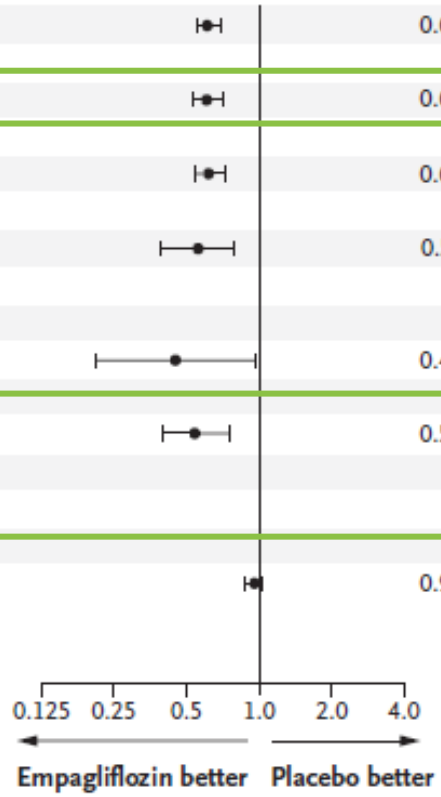
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease

Wanner C et al. N Engl J Med. 2016;375:323-334

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)

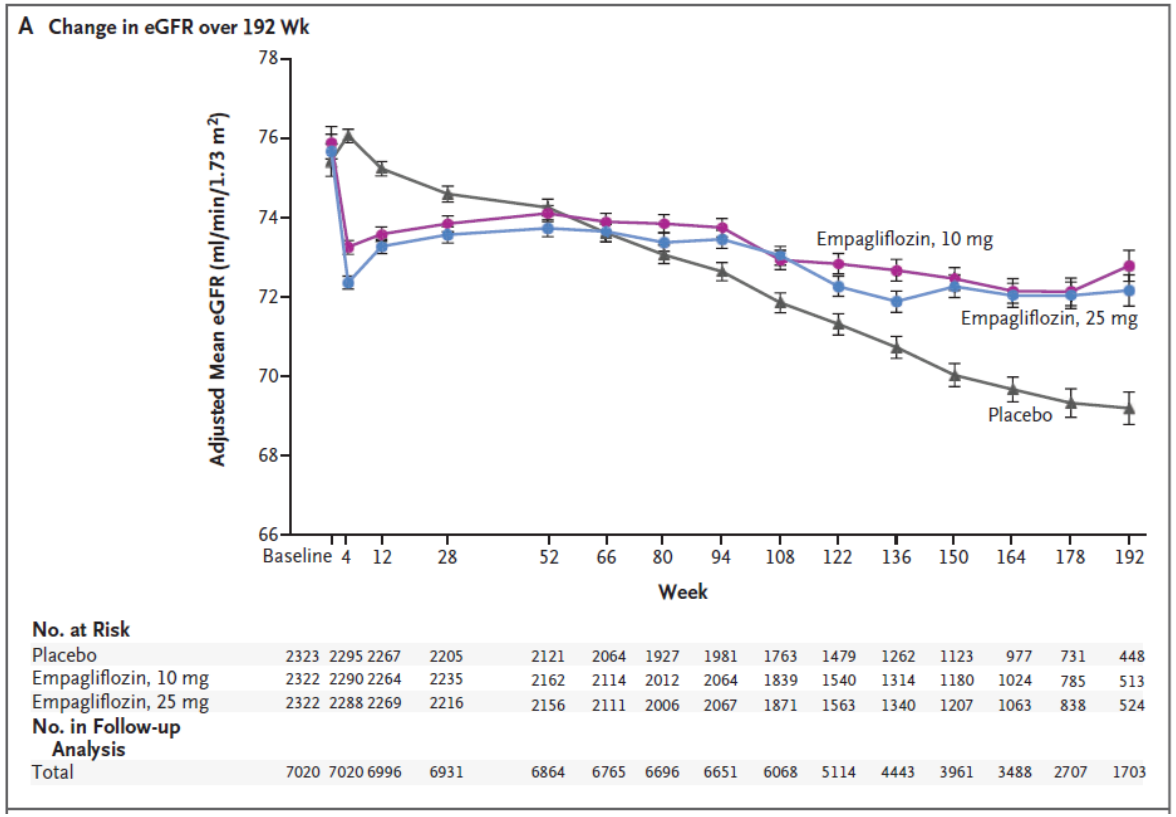
Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



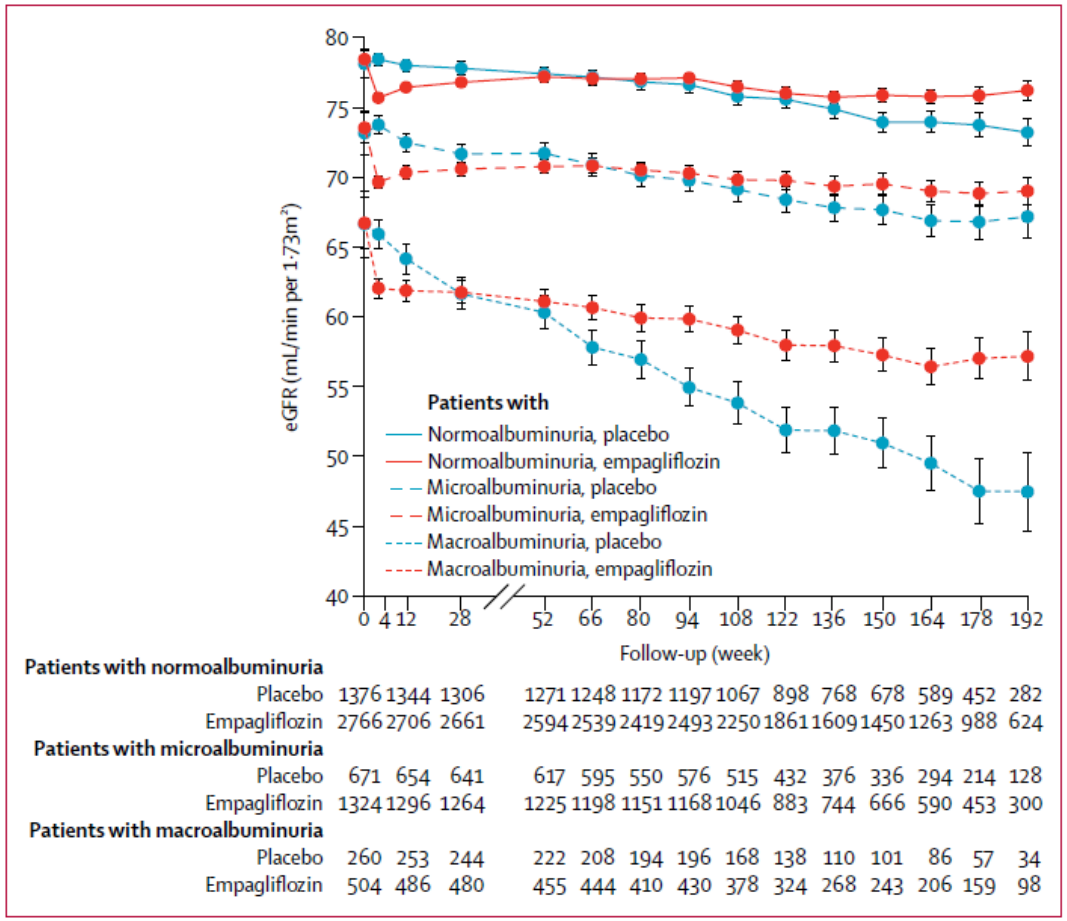
Wanner C et al. N Engl J Med. 2016;375:323-334

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703



Patients with normoalbuminuria															
Placebo	1376	1344	1306	1271	1248	1172	1197	1067	898	768	678	589	452	282	
Empagliflozin	2766	2706	2661	2594	2539	2419	2493	2250	1861	1609	1450	1263	988	624	
Patients with microalbuminuria															
Placebo	671	654	641	617	595	550	576	515	432	376	336	294	214	128	
Empagliflozin	1324	1296	1264	1225	1198	1151	1168	1046	883	744	666	590	453	300	
Patients with macroalbuminuria															
Placebo	260	253	244	222	208	194	196	168	138	110	101	86	57	34	
Empagliflozin	504	486	480	455	444	410	430	378	324	268	243	206	159	98	

Wanner C et al. N Engl J Med. 2016;375:323-334
Cherney DZI et al. Lancet Diabetes Endocrinol. 2017;5:610–621

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Trial	EMPA-REG OUTCOME	CANVAS Program
Drug	Empagliflozin	Canagliflozin
Participants, n (active drug/placebo)	7,020 (4,687/2,333)	10,142 (5,795/4,347)
Median follow-up, years	3.1	2.4
eGFR (ml/min/1.73m^2) (active drug/placebo)	73.8/74.2	76.7/76.2
Renal function at baseline		
Normal (eGFR ≥90)	21.9%	24.4%
Mild impairment (eGFR 60-89)	52.2%	55.5%
Moderate impairment (eGFR 30-59)	25.9%	20.1%
Severe impairment (eGFR<30)	-	-
Albuminuria at baseline		
Normoalbuminuria	60.0%	69.8%
Microalbuminuria	29.0%	22.6%
Macroalbuminuria	11.0%	7.6%

EXCL CRITERION:
eGFR <30
ml/min/1.73m^2

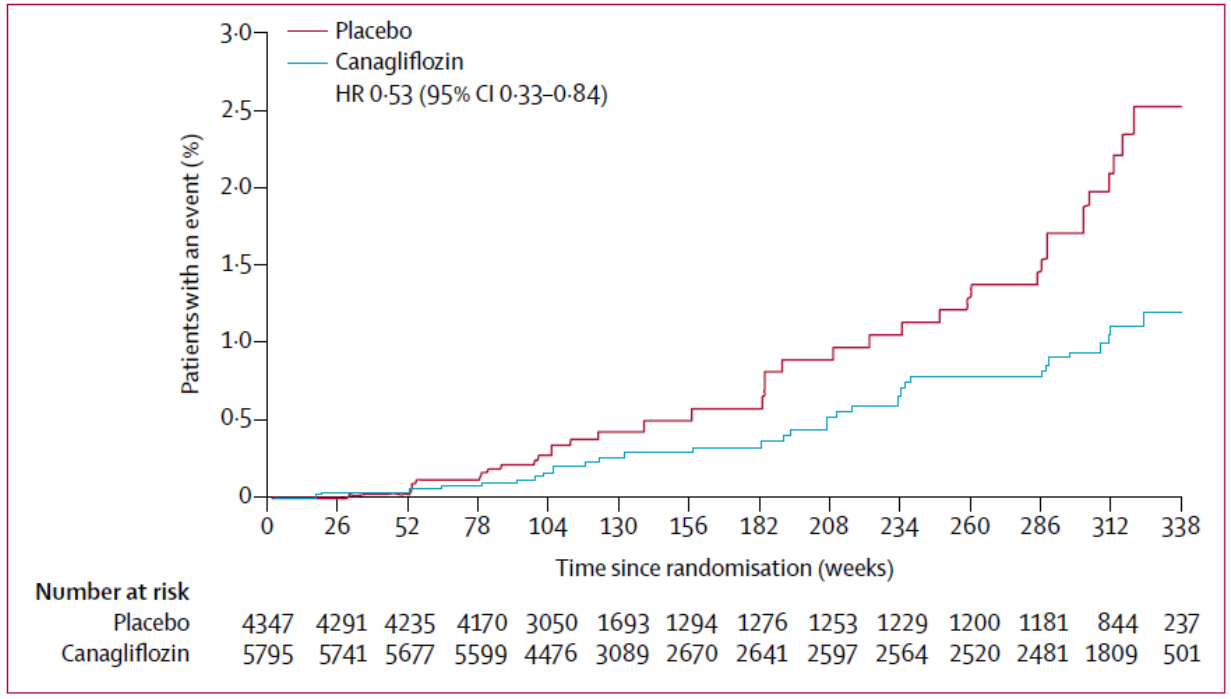
Neal B et al. N Engl J Med 2017;377:644-57.

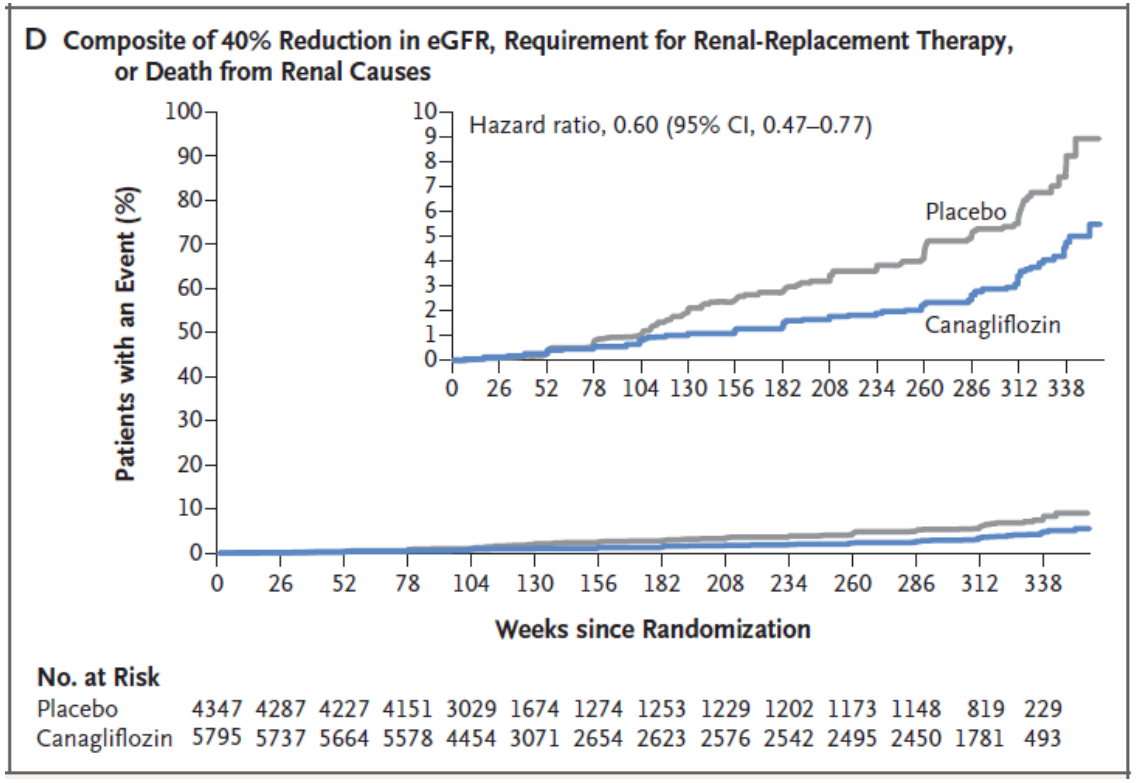
CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

CANagliflozin cardioVascular Assessment Study (CANVAS)

CANVAS Program

Composite outcome of doubling of serum creatinine, ESKD, or death from renal causes





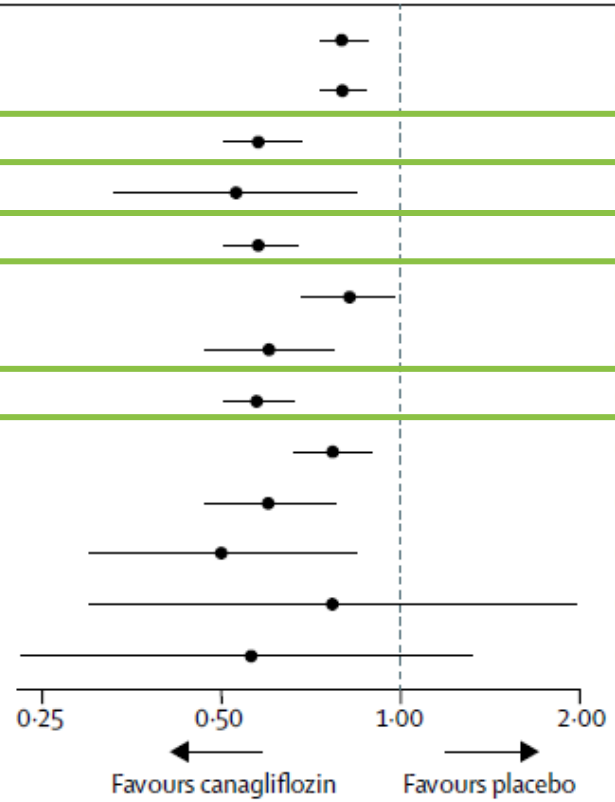
Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704
Neal B et al. N Engl J Med 2017;377:644-57.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

CANagliflozin cardioVascular Assessment Study (CANVAS)

CANVAS Program

	Number of participants with an event	Canagliflozin participants with an event per 1000 patient-years	Placebo participants with an event per 1000 patient-years	Hazard ratio (95% CI)
New-onset albuminuria	1990	100·4	130·8	0·80 (0·73–0·88)
New-onset microalbuminuria	1935	96·7	127·3	0·80 (0·73–0·87)
New-onset macroalbuminuria	636	15·1	27·6	0·58 (0·50–0·68)
dSCr, ESKD, or death from renal causes	73	1·5	2·8	0·53 (0·33–0·84)
dSCr, ESKD, death from renal causes, or new-onset macroalbuminuria	698	15·1	27·4	0·58 (0·50–0·67)
dSCr, ESKD, or death from renal or cardiovascular causes	518	13·2	15·8	0·82 (0·68–0·97)
40% reduction in eGFR, ESKD, or death from renal causes	249	5·5	9·0	0·60 (0·47–0·77)
40% reduction in eGFR, ESKD, death from renal causes, or new-onset macroalbuminuria	847	18·6	33·3	0·57 (0·50–0·66)
40% reduction in eGFR, ESKD, or death from renal or cardiovascular causes	679	16·9	21·6	0·77 (0·66–0·89)
40% eGFR reduction	239	5·3	8·7	0·60 (0·47–0·78)
dSCr	60	1·2	2·4	0·50 (0·30–0·84)
ESKD	18	0·4	0·6	0·77 (0·30–1·97)
ESKD or death from renal causes	21	0·4	0·8	0·56 (0·23–1·32)

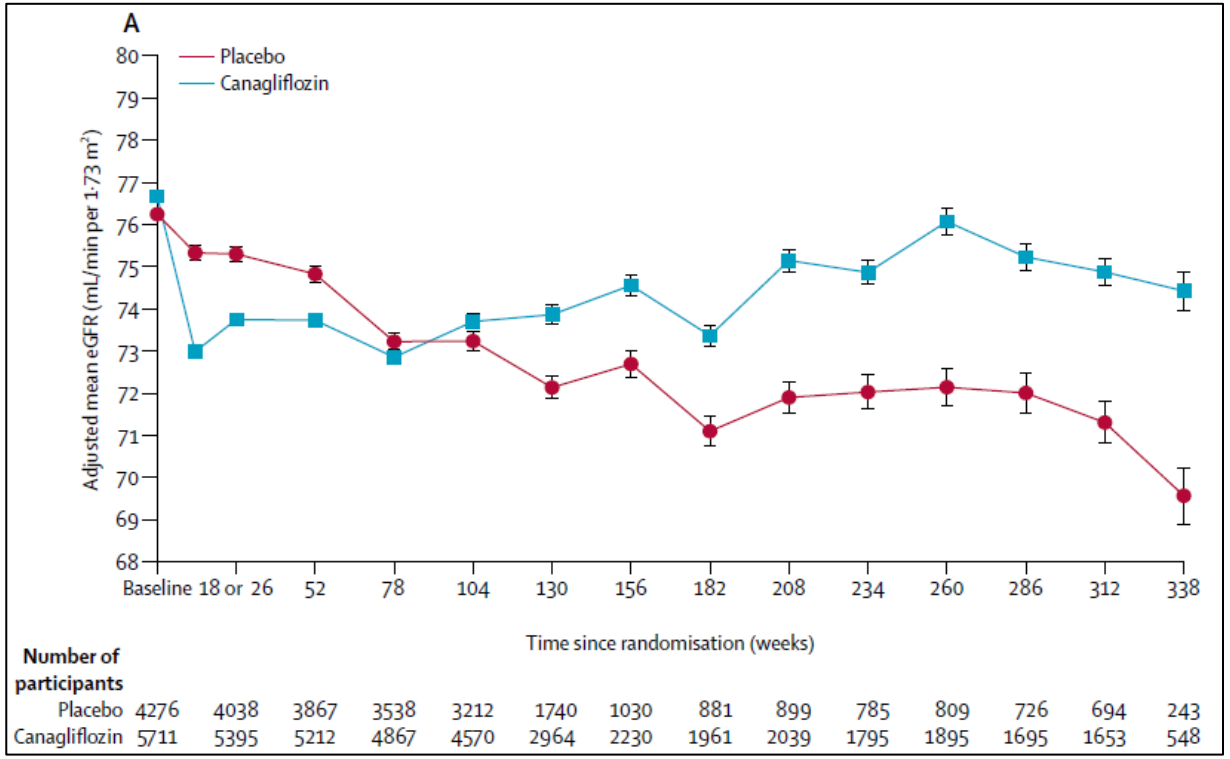


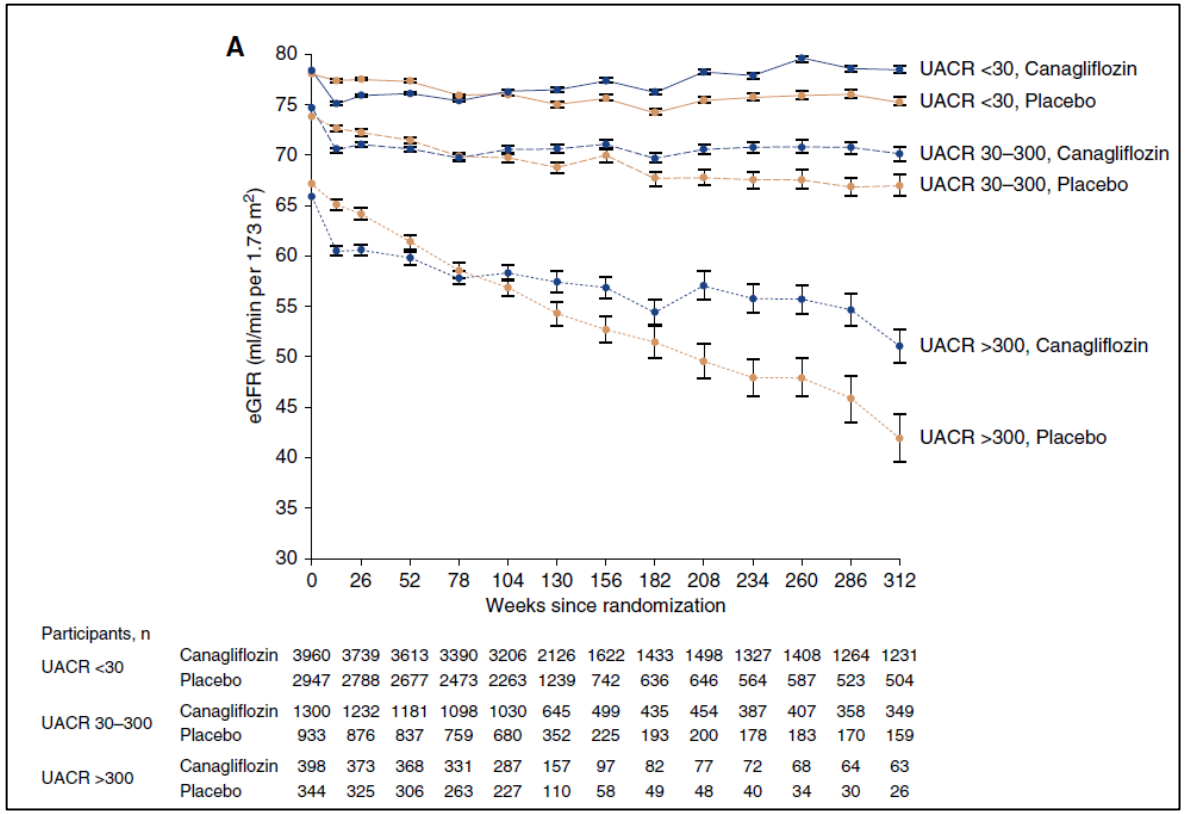
Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

CANagliflozin cardioVascular Assessment Study (CANVAS)

CANVAS Program





Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704
Neuen BL et al. JASN. 2019 Nov;30(11):2229-2242.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

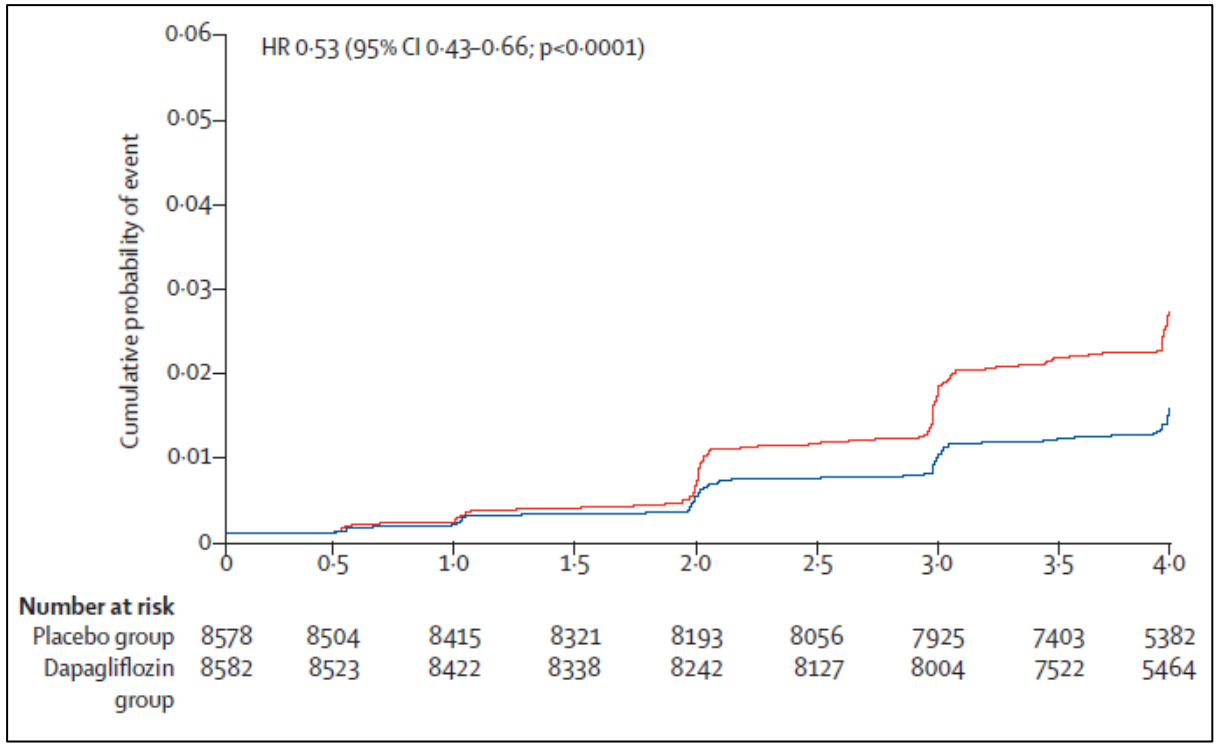
Trial	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Participants, n (active drug/placebo)	7,020 (4,687/2,333)	10,142 (5,795/4,347)	17,160 (8,582/8,578)
Median follow-up, years	3.1	2.4	4.2
eGFR (ml/min/1.73m^2) (active drug/placebo)	73.8/74.2	76.7/76.2	85.4/85.1
Renal function at baseline			
Normal (eGFR ≥90)	21.9%	24.4%	47.6%
Mild impairment (eGFR 60-89)	52.2%	55.5%	45.0%
Moderate impairment (eGFR 30-59)	25.9%	20.1%	7.4%
Severe impairment (eGFR<30)	-	-	-
Albuminuria at baseline			
Normoalbuminuria	60.0%	69.8%	69.1%
Microalbuminuria	29.0%	22.6%	23.9%
Macroalbuminuria	11.0%	7.6%	7.0%

EXCL CRITERION:
eGFR <60 ml/min/1.73m^2

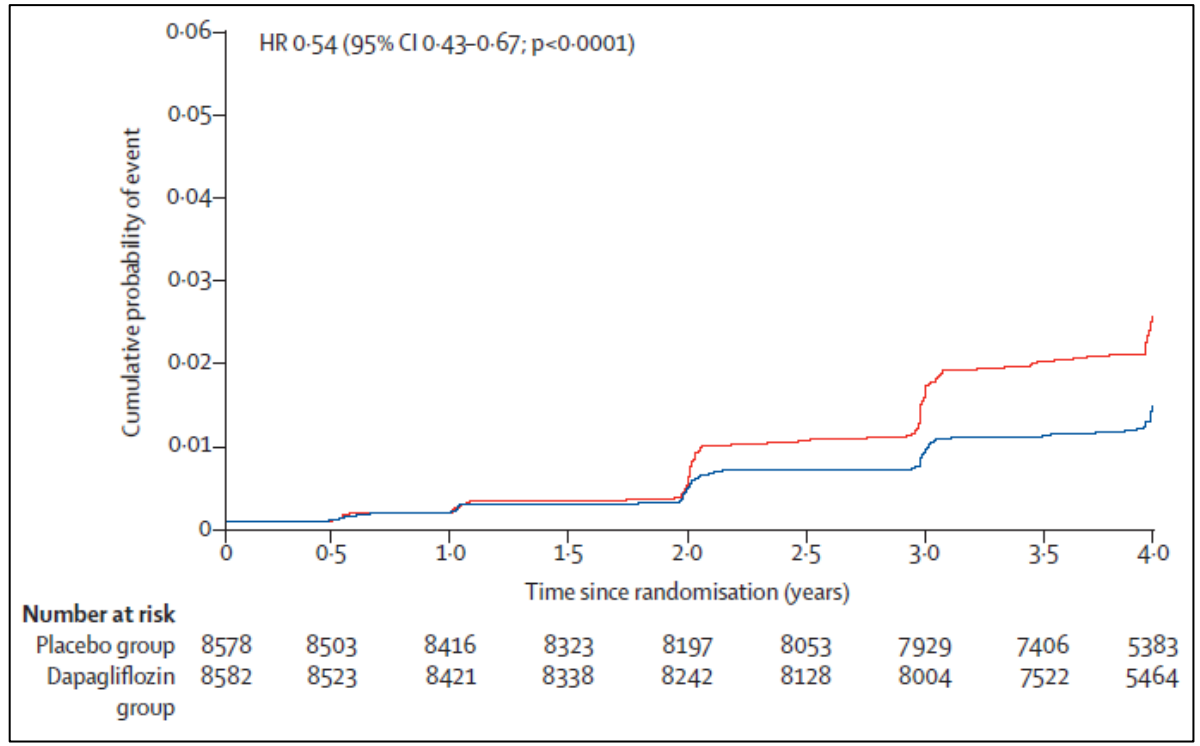
Wiviott SD et al. N Engl J Med 2019;380:347-57.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

The **Dapagliflozin** Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial



Composite renal outcome: ≥40% decrease in eGFR, ESRD, renal death



Sustained eGFR decrease ≥40%

Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:606-617

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

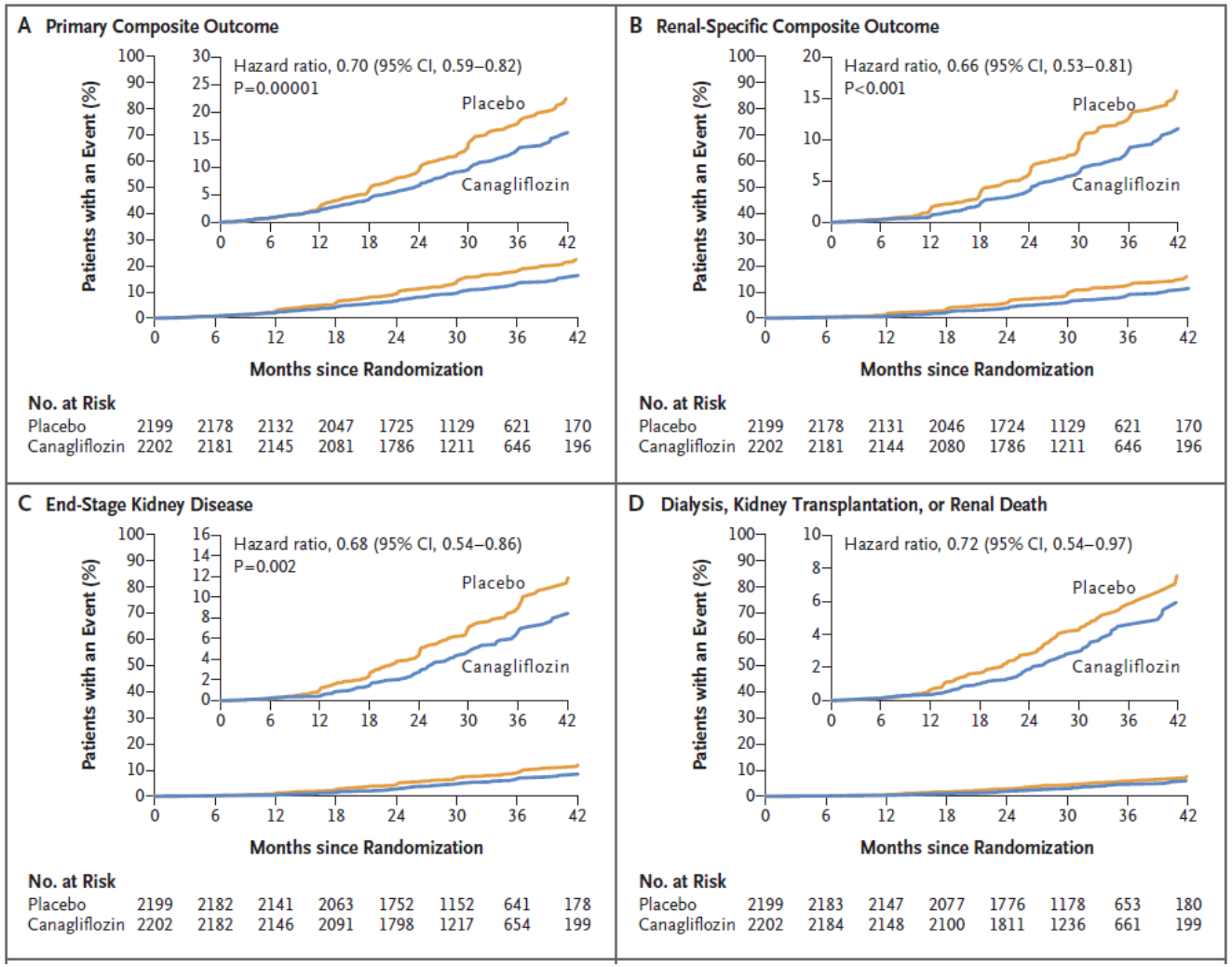
Trial	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	CREDENCE
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Participants, n (active drug/placebo)	7,020 (4,687/2,333)	10,142 (5,795/4,347)	17,160 (8,582/8,578)	4,401 (2,202/2,199)
Median follow-up, years	3.1	2.4	4.2	2.6
eGFR (ml/min/1.73m^2) (active drug/placebo)	73.8/74.2	76.7/76.2	85.4/85.1	56.3/56.0
Renal function at baseline				
Normal (eGFR ≥90)	21.9%	24.4%	47.6%	4.8%
Mild impairment (eGFR 60-89)	52.2%	55.5%	45.0%	35.4%
Moderate impairment (eGFR 30-59)	25.9%	20.1%	7.4%	55.9%
Severe impairment (eGFR<30)	-	-	-	3.9%
Albuminuria at baseline				
Normoalbuminuria	60.0%	69.8%	69.1%	0.7%
Microalbuminuria	29.0%	22.6%	23.9%	11.3%
Macroalbuminuria	11.0%	7.6%	7.0%	88.0%

INCL CRITERIA:
eGFR 30-90 ml/min/m^2
UACR >300 mg/g

Perkovic V et al. N Engl J Med 2019;380:2295-306.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Evaluation of the Effects of **Canagliflozin** on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE)



Perkovic V et al. N Engl J Med 2019;380:2295-306.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Evaluation of the Effects of **Canagliflozin** on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE)

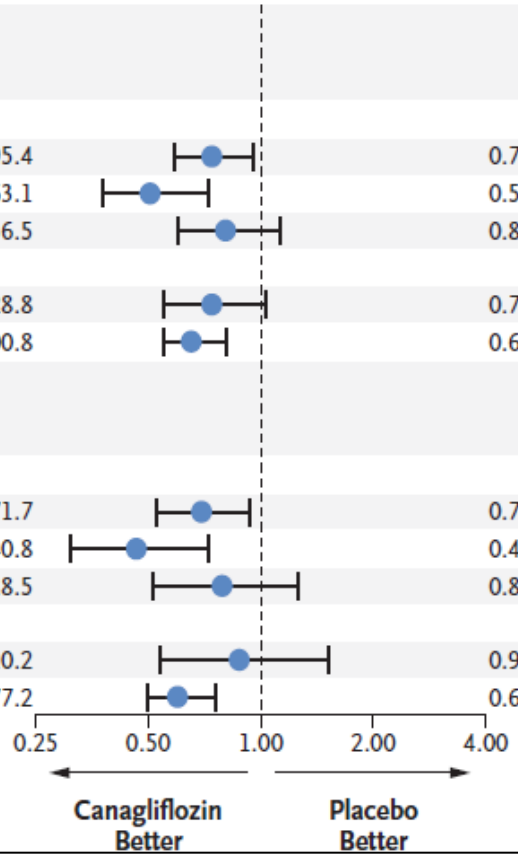
Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		*events/ 1000 patient-yr*			
Efficacy						
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine level	118/2202	188/2199	20.7	33.8	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	116/2202	165/2199	20.4	29.4	0.68 (0.54–0.86)	0.002
Estimated GFR <15 ml/min/1.73 m^2	78/2202	125/2199	13.6	22.2	0.60 (0.45–0.80)	NA
Dialysis initiated or kidney transplantation	76/2202	100/2199	13.3	17.7	0.74 (0.55–1.00)	NA
Renal death	2/2202	5/2199	0.3	0.9	NA	NA
Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61–1.00)	0.05
Secondary outcomes						
Cardiovascular death or hospitalization for heart failure	179/2202	253/2199	31.5	45.4	0.69 (0.57–0.83)	<0.001
Cardiovascular death, myocardial infarction, or stroke	217/2202	269/2199	38.7	48.7	0.80 (0.67–0.95)	0.01
Hospitalization for heart failure	89/2202	141/2199	15.7	25.3	0.61 (0.47–0.80)	<0.001
End-stage kidney disease, doubling of serum creatinine level, or renal death	153/2202	224/2199	27.0	40.4	0.66 (0.53–0.81)	<0.001
Death from any cause	168/2202	201/2199	29.0	35.0	0.83 (0.68–1.02)	NA
Cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina	273/2202	361/2199	49.4	66.9	0.74 (0.63–0.86)	NA
End-stage kidney disease, renal death, or cardiovascular death†	214/2202	287/2199	37.6	51.2	0.73 (0.61–0.87)	NA
Dialysis, kidney transplantation, or renal death†	78/2202	105/2199	13.6	18.6	0.72 (0.54–0.97)	NA

Perkovic V et al. N Engl J Med 2019;380:2295-306.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Evaluation of the Effects of **Canagliflozin** on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE)

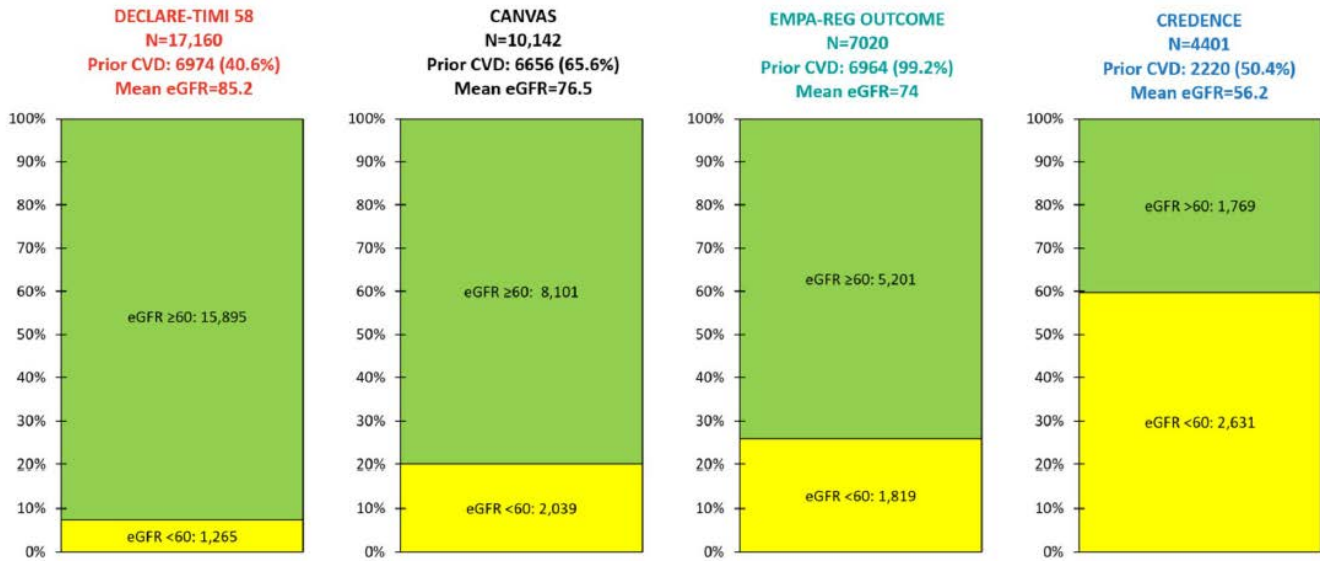
Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m²	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m²	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m²	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m²	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m²	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m²	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	

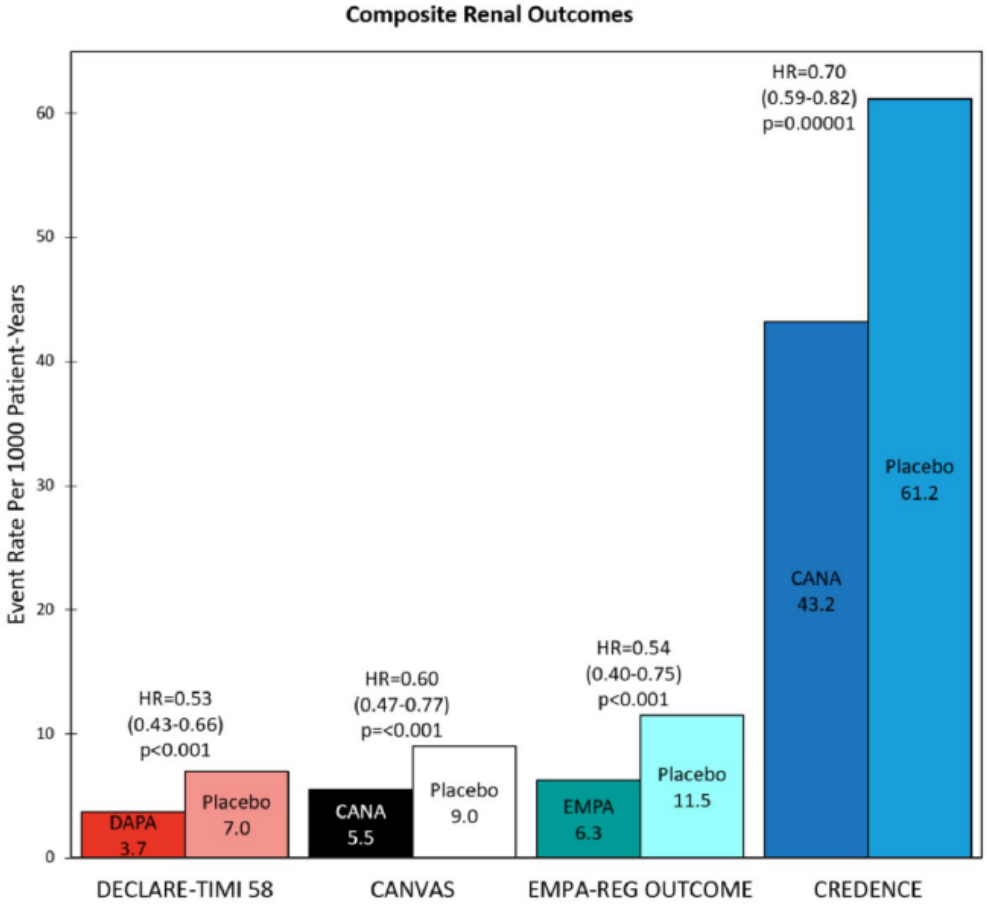


Perkovic V et al. N Engl J Med 2019;380:2295-306.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Class effects of SGLT2 inhibitors on cardiorenal outcomes

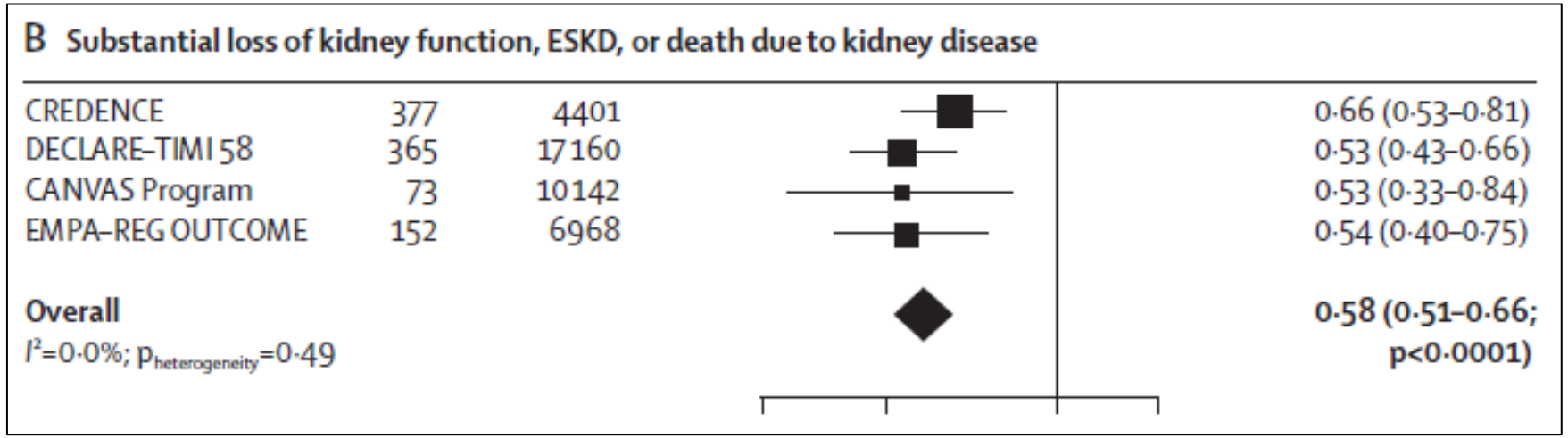




Kluger AJ te al. Cardiovasc Diabetol. 2019;18:99

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Meta-analysis on hard renal endpoints



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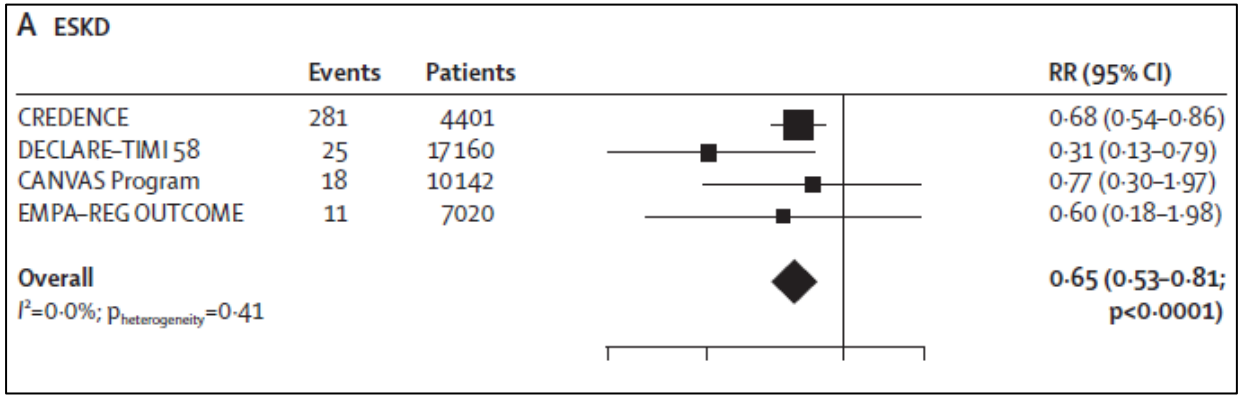

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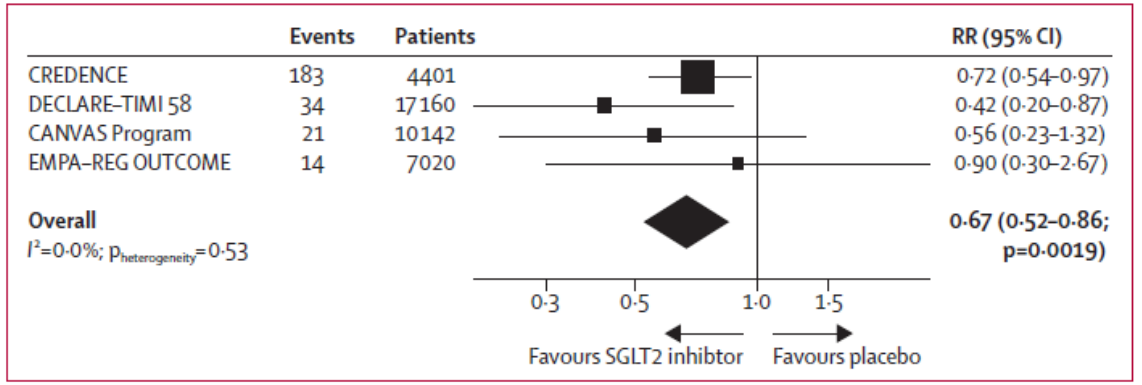


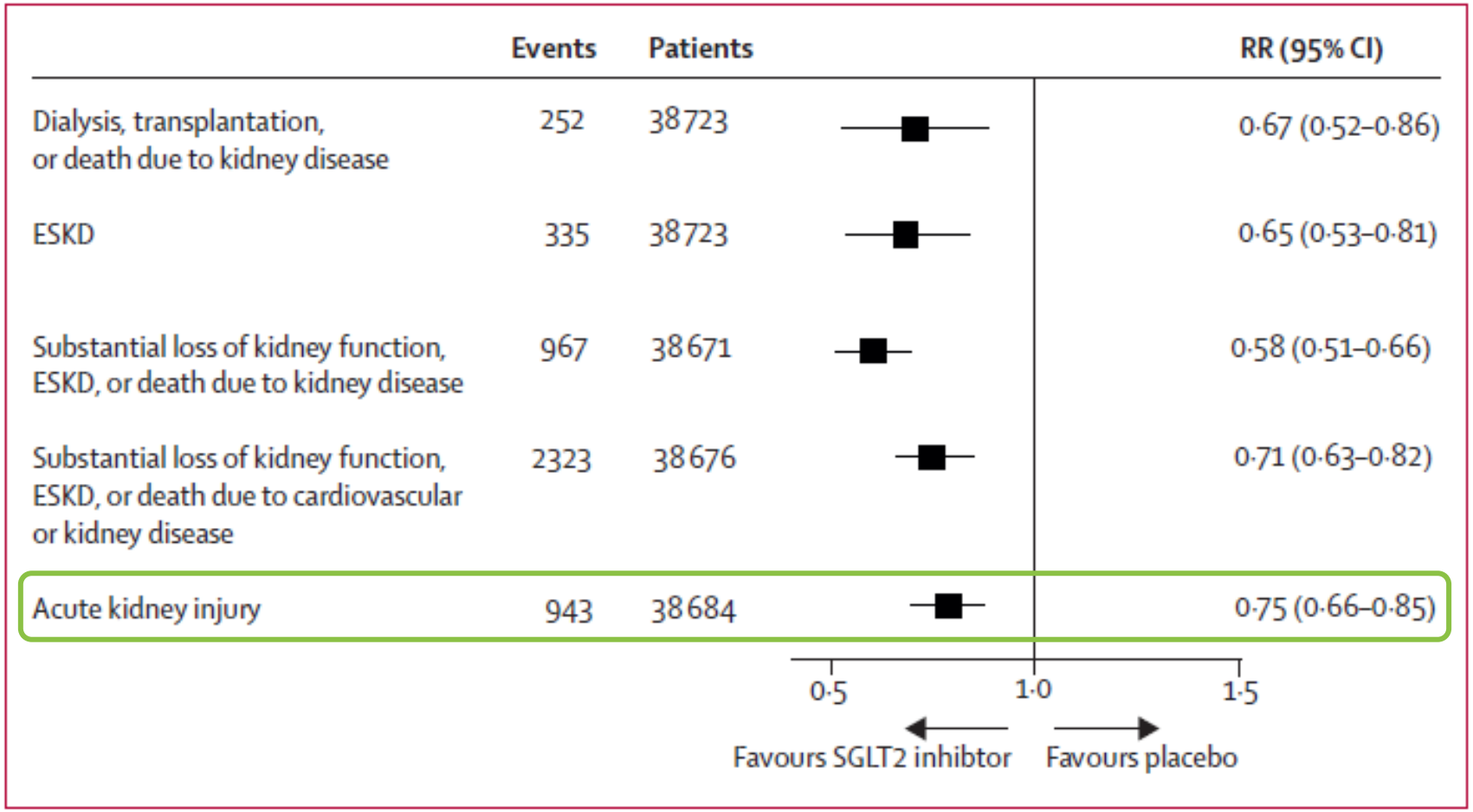
Figure 1: Effect of SGLT2 inhibitors on dialysis, transplantation, or death due to kidney disease

- 33%

Neuen BL et al. Lancet Diabetes Endocrinol. 2019;7:845–854

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

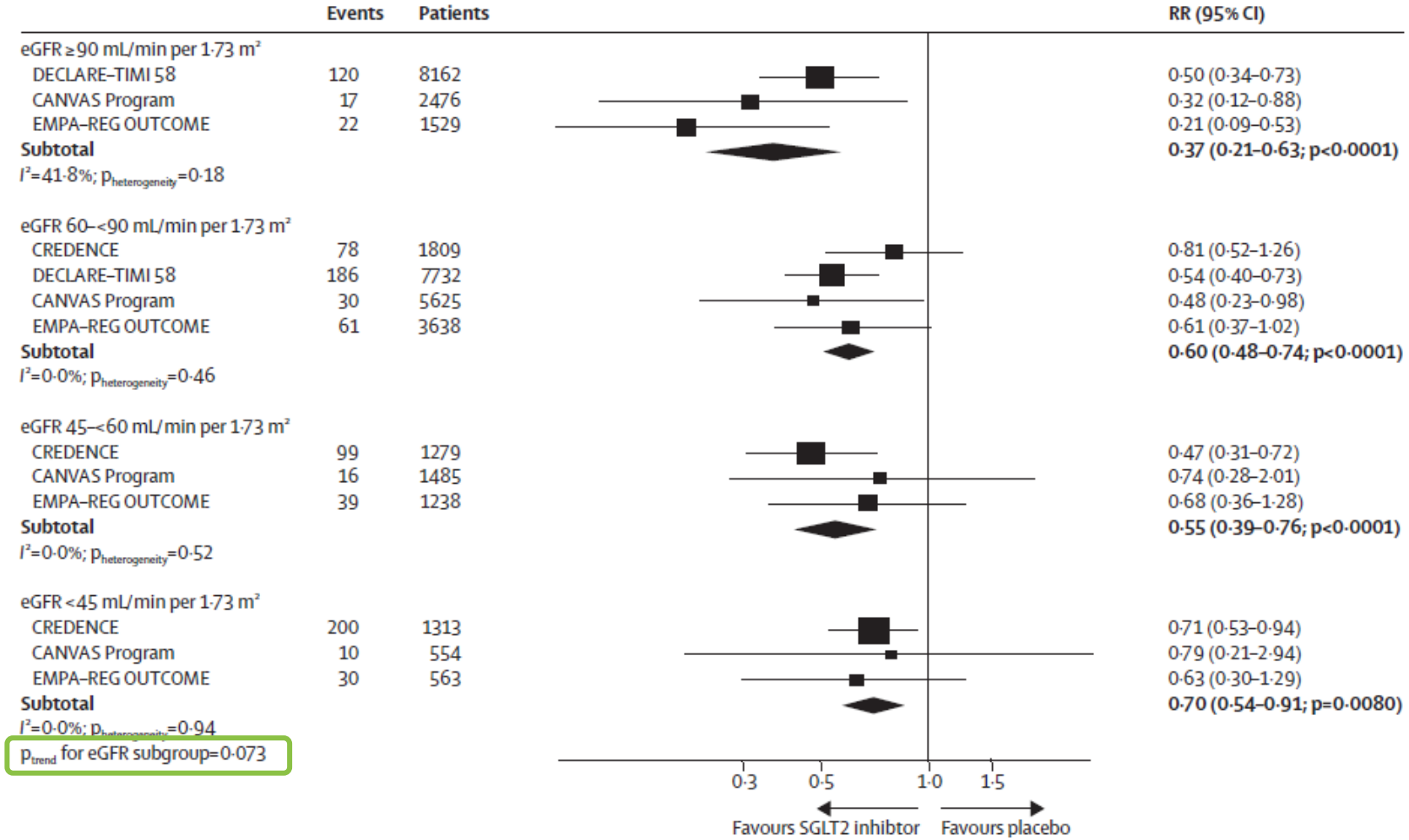
Summary of the effects of SGLT2 inhibition on major kidney outcomes



Neuen BL et al. Lancet Diabetes Endocrinol. 2019;7:845–854

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Effect of SGLT2-Is on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by baseline eGFR



- Effect across UACR subgroups: p_{trend}=0.66
- Effect between users and non-users of RAS-Is: $p_{heterogeneity}$=0.31

Neuen BL et al. Lancet Diabetes Endocrinol. 2019;7:845–854

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Trial	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	CREDENCE	DAPA-CKD
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin
Participants, n (active drug/placebo)	7,020 (4,687/2,333)	10,142 (5,795/4,347)	17,160 (8,582/8,578)	4,401 (2,202/2,199)	4,304 (2,152/2,152)
Median follow-up, years	3.1	2.4	4.2	2.6	2.4
eGFR (ml/min/1.73m^2) (active drug/placebo)	73.8/74.2	76.7/76.2	85.4/85.1	56.3/56.0	43.2/43.0
Renal function at baseline					
Normal (eGFR ≥90)	21.9%	24.4%	47.6%	4.8%	
Mild impairment (eGFR 60-89)	52.2%	55.5%	45.0%	35.4%	10.5%
Moderate impairment (eGFR 30-59)	25.9%	20.1%	7.4%	55.9%	75.0%
Severe impairment (eGFR<30)	-	-	-	3.9%	14.5%
Albuminuria at baseline					
Normoalbuminuria	60.0%	69.8%	69.1%	0.7%	-
Microalbuminuria	29.0%	22.6%	23.9%	11.3%	10.3%
Macroalbuminuria	11.0%	7.6%	7.0%	88.0%	89.7 %

67.5% with T2DM

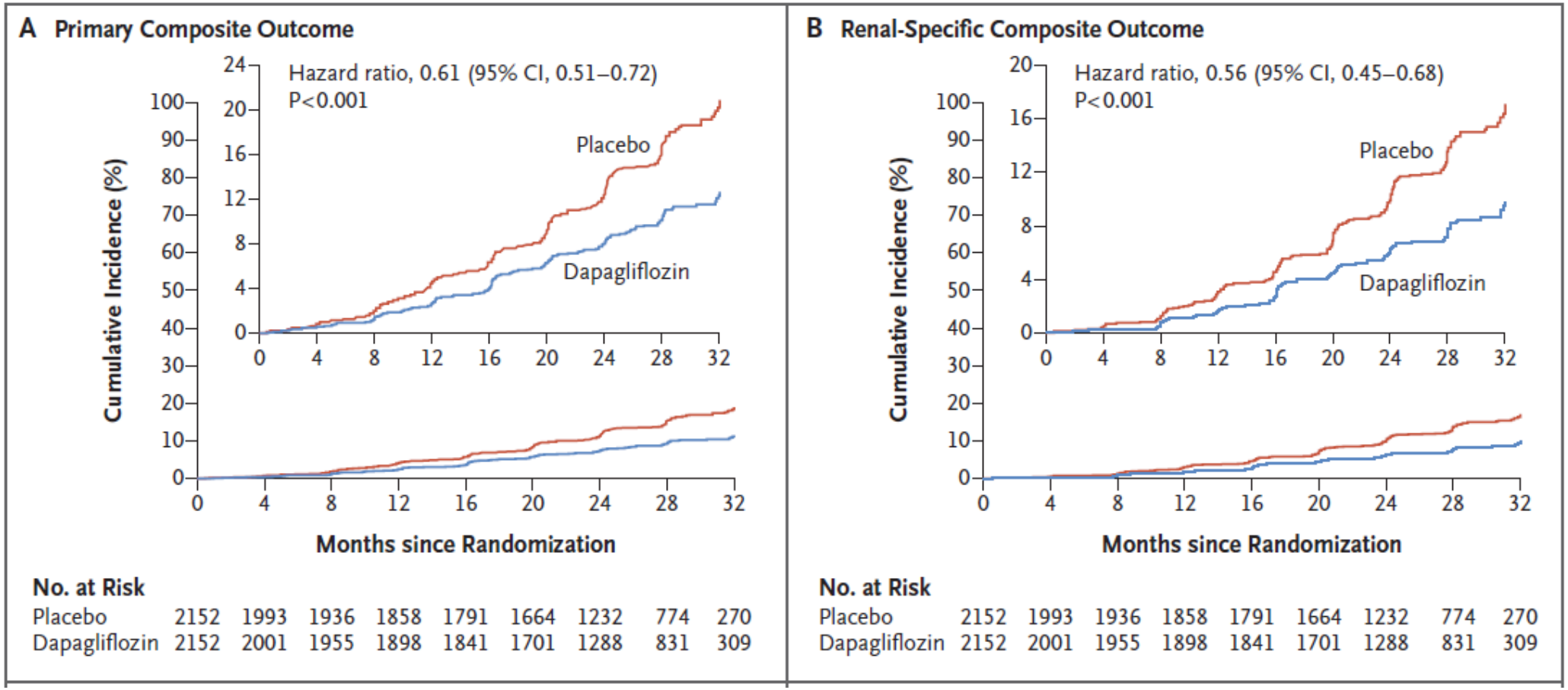
INCL CRITERIA:
eGFR 25-75 ml/min/m^2
UACR 200-5000 mg/g

Heerspink HJL et al. N Engl J Med. 2020 Sep 24.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

A Study to Evaluate the Effect of **Dapagliflozin** on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD)

DAPACKD



Sustained decline in eGFR ≥50%, ESRD, or death from renal or cardiovascular causes

Sustained decline in eGFR ≥50%, ESRD, or death from renal causes

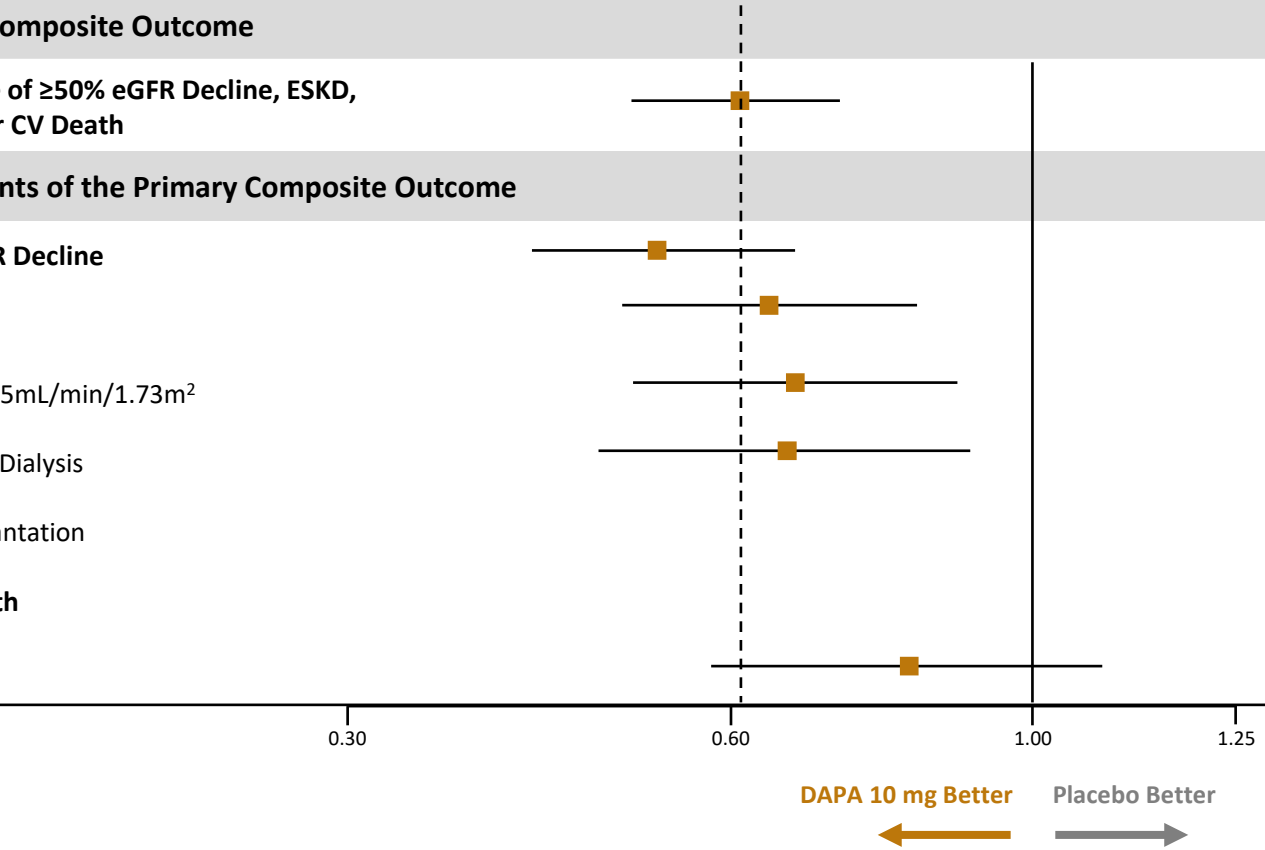
Heerspink HJL et al. N Engl J Med. 2020 Sep 24.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

A Study to Evaluate the Effect of **Dapagliflozin** on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD)

DAPACKD

	Number of Events				
	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value
Primary Composite Outcome					
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death	197	312	0.61	(0.51, 0.72)	0.000000028
Components of the Primary Composite Outcome					
≥50% eGFR Decline	112	201	0.53	(0.42, 0.67)	<0.0001
ESKD	109	161	0.64	(0.50, 0.82)	0.0004
eGFR <15mL/min/1.73m^2	84	120	0.67	(0.51, 0.88)	0.0045
Chronic Dialysis	68	99	0.66	(0.48, 0.90)	0.0080
Transplantation	3	8	NC		
Renal Death	2	6	NC		
CV Death	65	80	0.81	(0.58, 1.12)	0.2029



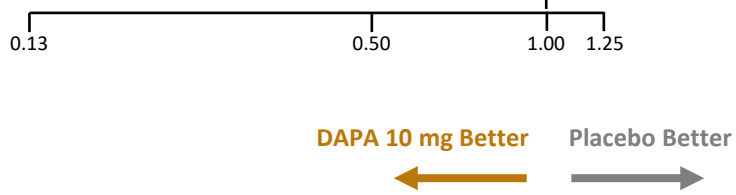
Heerspink HJL et al. N Engl J Med. 2020 Sep 24.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

A Study to Evaluate the Effect of **Dapagliflozin** on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD)

DAPACKD

	Number of Events				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					0.52
≤1000	44	84	0.54	(0.37, 0.77)	
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m^2) at Baseline					0.22
<45	152	217	0.63	(0.51, 0.78)	
≥45	45	95	0.49	(0.34, 0.69)	



Heerspink HJL et al. N Engl J Med. 2020 Sep 24.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Trial	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	CREDENCE	DAPA-CKD	VERTIS CV
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Participants, n (active drug/placebo)	7,020 (4,687/2,333)	10,142 (5,795/4,347)	17,160 (8,582/8,578)	4,401 (2,202/2,199)	4,304 (2,152/2,152)	8,246 (5,499/2,747)
Median follow-up, years	3.1	2.4	4.2	2.6	2.4	3.0
eGFR (ml/min/1.73m^2) (active drug/placebo)	73.8/74.2	76.7/76.2	85.4/85.1	56.3/56.0	43.2/43.0	76.1/75.7
Renal function at baseline						
Normal (eGFR ≥90)	21.9%	24.4%	47.6%	4.8%		
Mild impairment (eGFR 60-89)	52.2%	55.5%	45.0%	35.4%	10.5%	78.1%
Moderate impairment (eGFR 30-59)	25.9%	20.1%	7.4%	55.9%	75.0%	21.9%
Severe impairment (eGFR<30)	-	-	-	3.9%	14.5%	-
Albuminuria at baseline						
Normoalbuminuria	60.0%	69.8%	69.1%	0.7%	-	NR
Microalbuminuria	29.0%	22.6%	23.9%	11.3%	10.3%	NR
Macroalbuminuria	11.0%	7.6%	7.0%	88.0%	89.7 %	NR

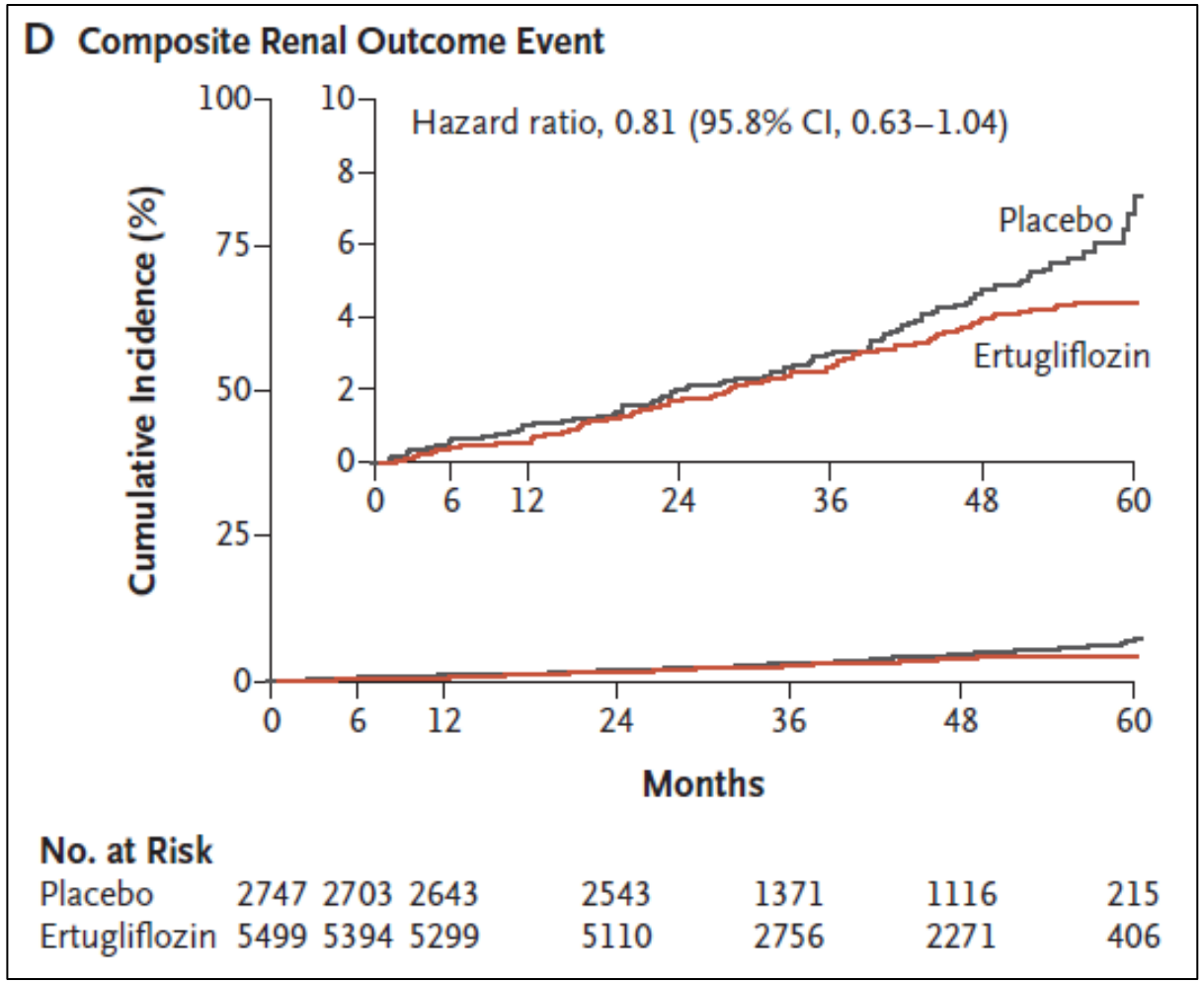
EXCL CRITERION: eGFR <30 ml/min/1.73m^2

Cannon CP et al. N Engl J Med. 2020 Sep 23.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Cardiovascular Outcomes Following **Ertugliflozin** Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease
The VERTIS CV Study

VERTIS CV



Death from renal causes, renal replacement therapy, or doubling of the serum creatinine level

Cannon CP et al. N Engl J Med. 2020 Sep 23.

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Cardiovascular Outcomes Following **Ertugliflozin** Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease
The VERTIS CV Study

VERTIS CV

- **Sustained 40% reduction in eGFR, chronic kidney dialysis/transplant or renal death:** HR 0.66 (0.50-0.88), p<0.01 (similar across CKD stage and level of UACR)
- **Sustained 40% reduction in eGFR:** HR 0.65 (0.49-0.87), p<0.01
- **Progression of albuminuria:** HR 0.79 (0.72-0.86), p<0.01
- **Regression of albuminuria:** HR 1.23 (1.10-1.36), p<0.01
- **Mean UACR:** difference relative to placebo at month 60 → -16.2%
- **Mean eGFR:** difference in LSM relative to placebo at month 60 → -2.55 ml/min/1.73 m^2
  → -5.80 ml/min/1.73 m^2 in macroalbuminuria group

Cherney DZI, presented at 56° annual meeting EASD, 23 sep 2020

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Trial	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	CREDENCE	DAPA-CKD	VERTIS CV	DAPA-HF	EMPEROR-Reduced
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	42% and 50% with T2DM	rtugliflozin	Dapagliflozin	Empagliflozin
Participants, n (active drug/placebo)	7,020 (4,687/2,333)	10,142 (5,795/4,347)	17,160 (8,582/8,578)	4,401 (2,202/2,199)	(2,152/2,152)	8,246 (5,499/2,747)	4,744 (2,373/2,371)	3,730 (1,863/1,867)
Median follow-up, years	3.1	2.4	4.2	2.6	2.4	3.0	1.5	1.3
eGFR (ml/min/1.73m²) (active drug/placebo)	73.8/74.2	76.7/76.2	85.4/85.1	56.3/56.0	43.2/43.0	76.1/75.7	66.0/65.5	61,8/62,2
Renal function at baseline					EXCL CRITERION: eGFR <30 or <20 ml/min/1.73m²			
Normal (eGFR ≥90)	21.9%	24.4%	47.6%	4.8%				
Mild impairment (eGFR 60-89)	52.2%	55.5%	45.0%	35.4%		78.1%	59.4%	51.7%
Moderate impairment (eGFR 30-59)	25.9%	20.1%	7.4%	55.9%		21.9%	40.6%	48.3%
Severe impairment (eGFR<30)	-	-	-	3.9%	14.5%	-	-	
Albuminuria at baseline								
Normoalbuminuria	60.0%	69.8%	69.1%	0.7%	-	NR	NR	NR
Microalbuminuria	29.0%	22.6%	23.9%	11.3%	10.3%	NR	NR	NR
Macroalbuminuria	11.0%	7.6%	7.0%	88.0%	89.7 %	NR	NR	NR

McMurray JJV et al. N Engl J Med 2019;381:1995-2008.
Packer M et al. N Engl J Med. 2020 Aug 29.

ONGOING TRIALS IN CKD PATIENTS

EMPA-KIDNEY: The Study of Heart and Kidney Protection With **Empagliflozin**

EMPA-KIDNEY
The study of heart and kidney protection with empagliflozin

INCLUSION CRITERIA:
w and w/o T2DM

eGFR ≥20 to <45 mL/min/1.73m²
eGFR ≥45 to <90 mL/min/1.73m²
and **UACR** ≥200 mg/g

Composite primary outcome:

kidney disease progression or cardiovascular death

A Research Study to See How **Semaglutide** Works Compared to Placebo in People With T2D and CKD (FLOW)

FLOW
semaglutide | renal outcomes trial

INCLUSION CRITERIA:
w T2DM

eGFR ≤75 to ≥50 ml/min/1.73 m²
and **UACR** >300 to <5000 mg/g
eGFR <50 to ≥25 ml/min/1.73 m²
and **UACR** >100 to <5000 mg/g

Composite primary outcome:

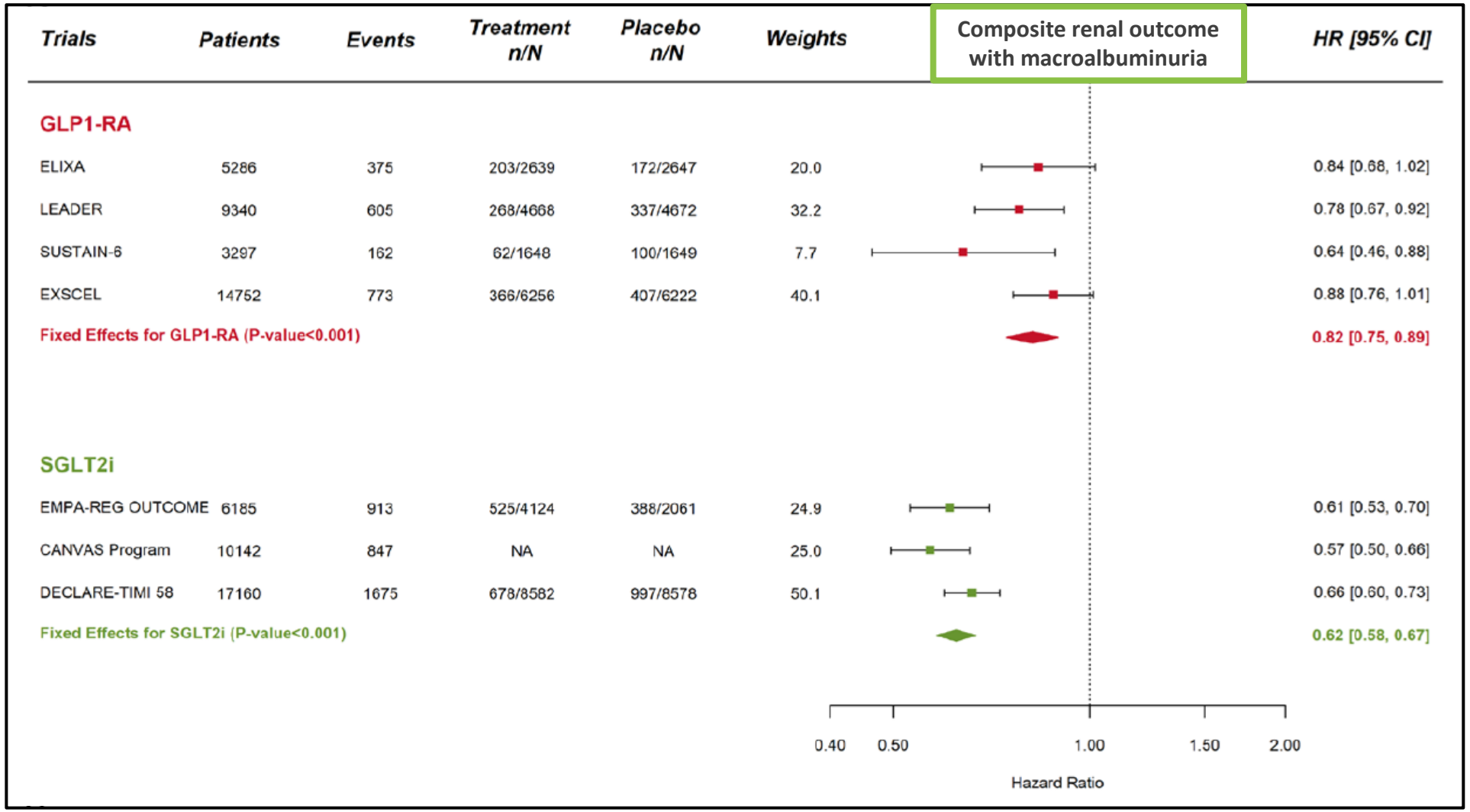
kidney disease progression or cardiovascular death

AGENDA

- TRENDS IN DIABETIC COMPLICATIONS AND DKD
- RENAL OUTCOME FROM CARDIOVASCULAR OUTCOME TRIALS
  - CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs
  - CARDIOVASCULAR (and RENAL) OUTCOME TRIALS – SGLT2-Is
  - COMPARISON GLP-1 RAs/SGLT2-Is
- MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs AND SGLT2-Is
- GUIDELINES OF GLUCOSE-LOWERING MEDICATION IN T2DM – FOCUS ON CKD
- DOSE RECOMMENDATIONS OF GLP-1 RAs AND SGLT2-Is IN CKD
- TAKE HOME MESSAGES

COMPARISON GLP-1 RAs/SGLT2-Is

Comparison of the Effects of GLP-1 RAs and SGLT2-Is for Prevention of Renal Outcomes in Type 2 Diabetes Mellitus



Zelniker TA et al. Circulation. 2019;139:2022–2031

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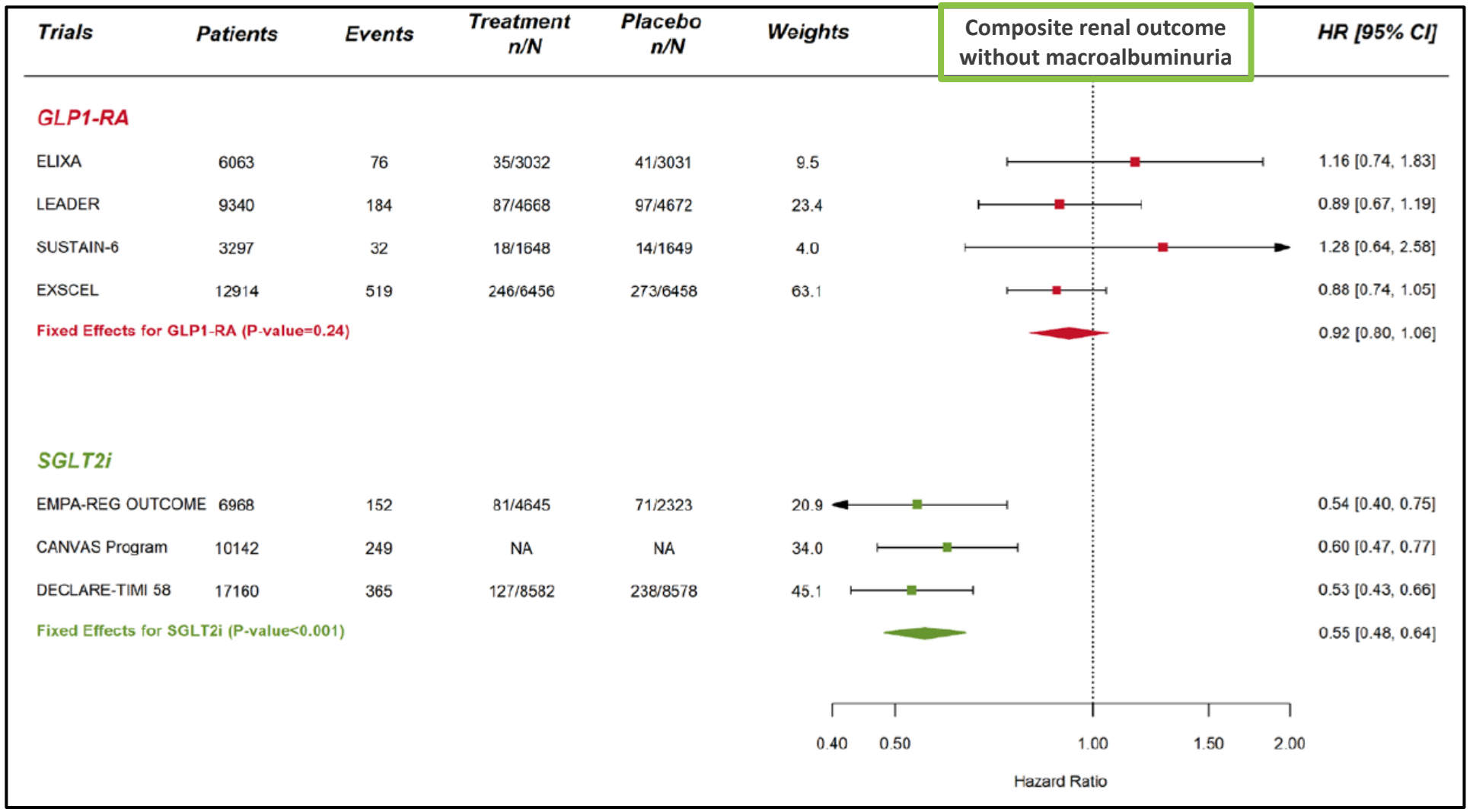
Comparison of the Effects of GLP-1 RAs and SGLT2-Isvfor Prevention of Renal Outcomes in Type 2 Diabetes Mellitus



Zelniker TA et al. Circulation. 2019;139:2022–2031

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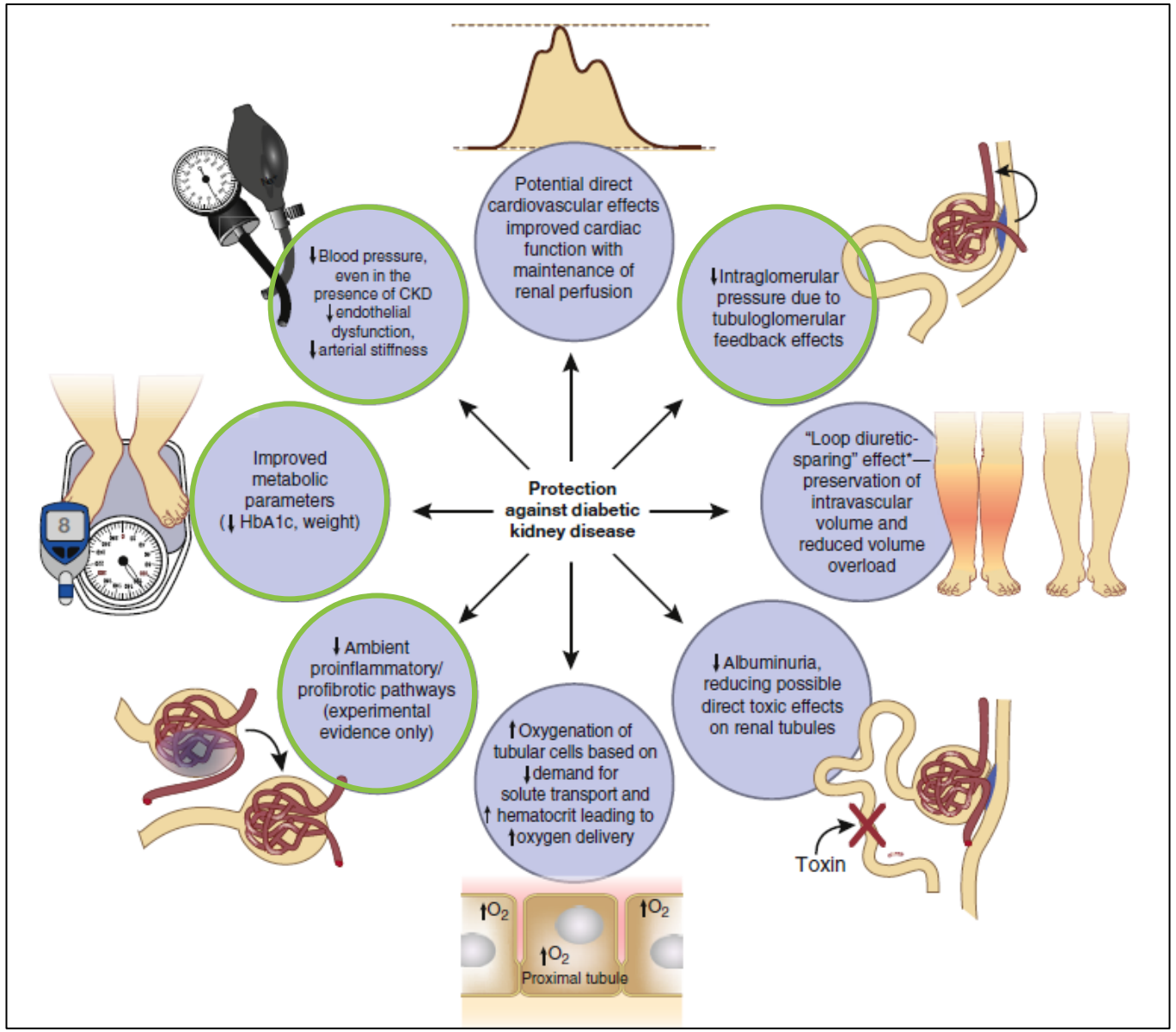
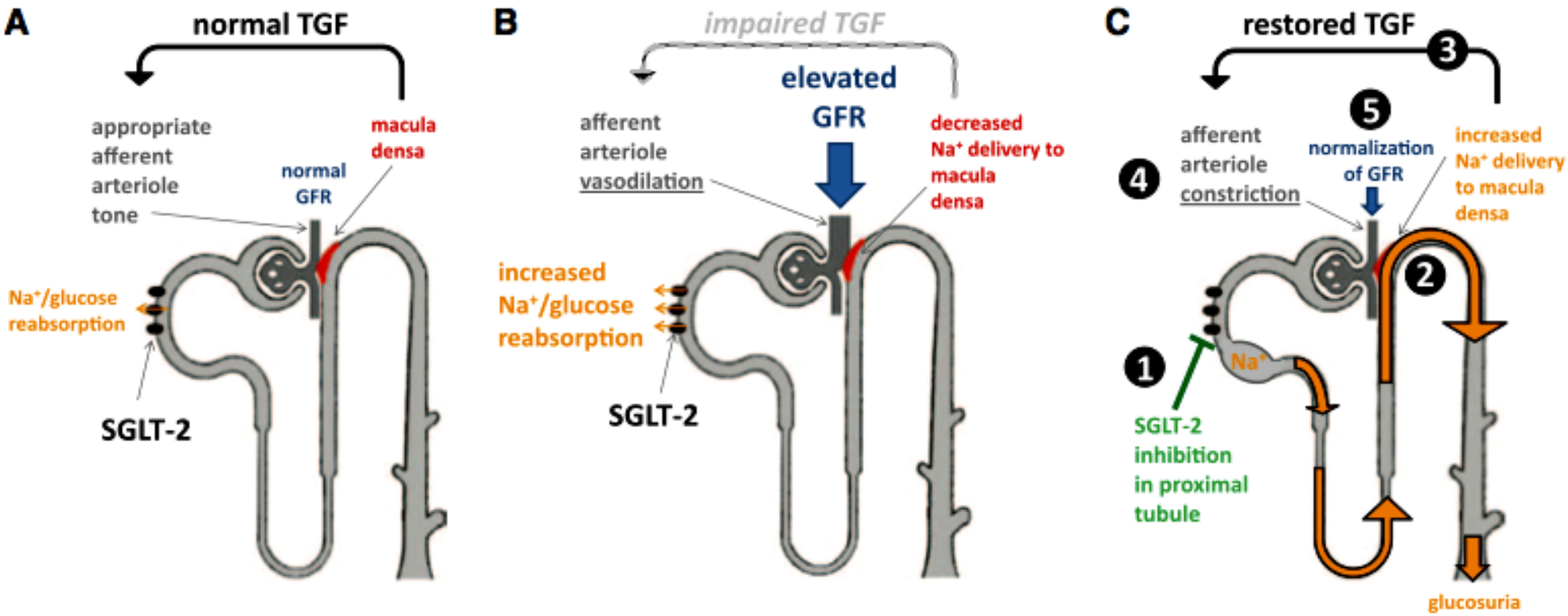
- TAKE HOME MESSAGES

MECHANISMS OF RENAL PROTECTION BY SGLT2-Is



Heerspink HJL et al. Kidney Int. 2018;94(1):26-39.

MECHANISMS OF RENAL PROTECTION BY SGLT2-Is



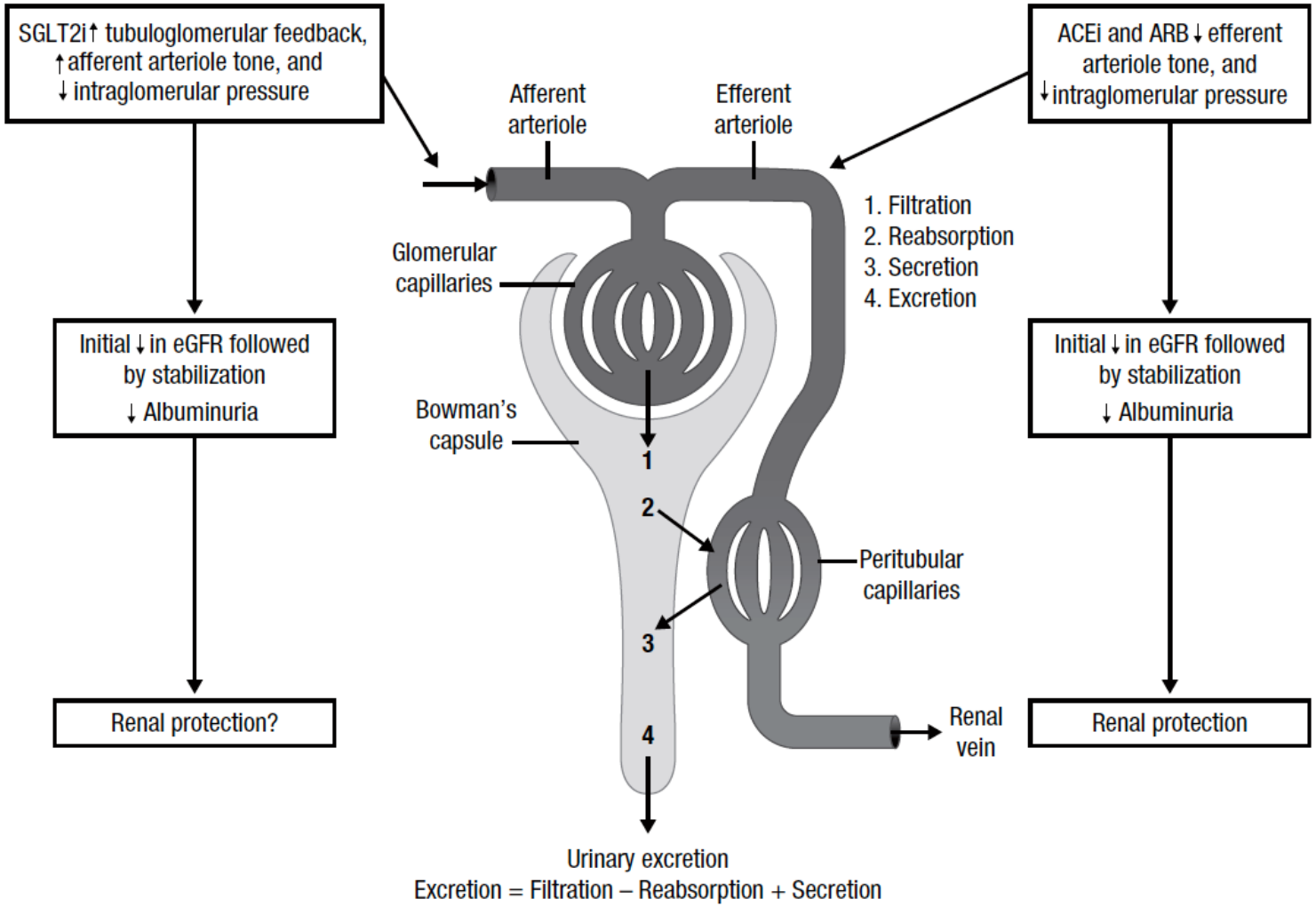
Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

SGLT-2 inhibition reduces hyperfiltration via TGF

Cherney D et al. Circulation. 2014; 129:587-597

MECHANISMS OF RENAL PROTECTION BY SGLT2-Is

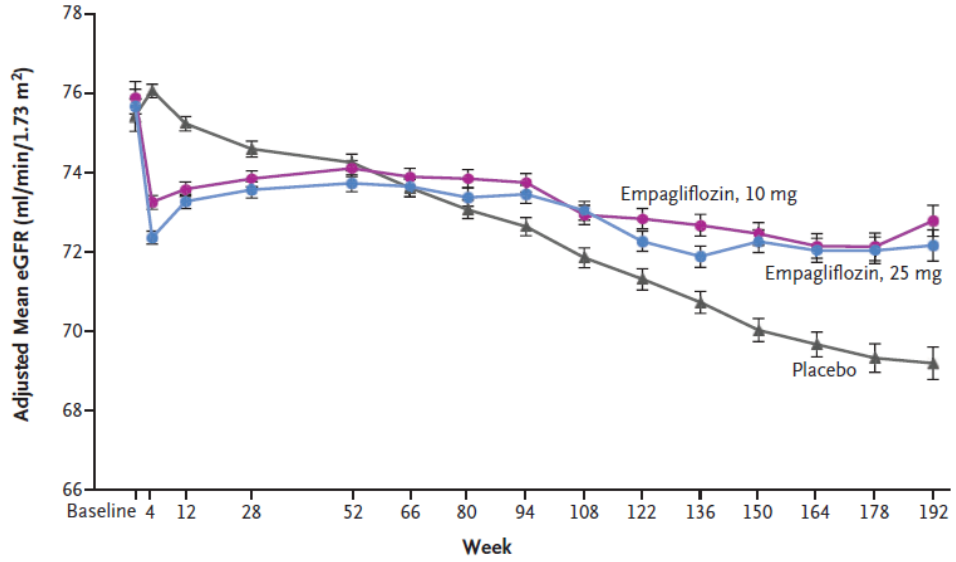


Perkovic V et al. Curr Med Res Opin. 2015; 12:2219-2231

MECHANISMS OF RENAL PROTECTION BY SGLT2-Is

EMPA-REG OUTCOME®

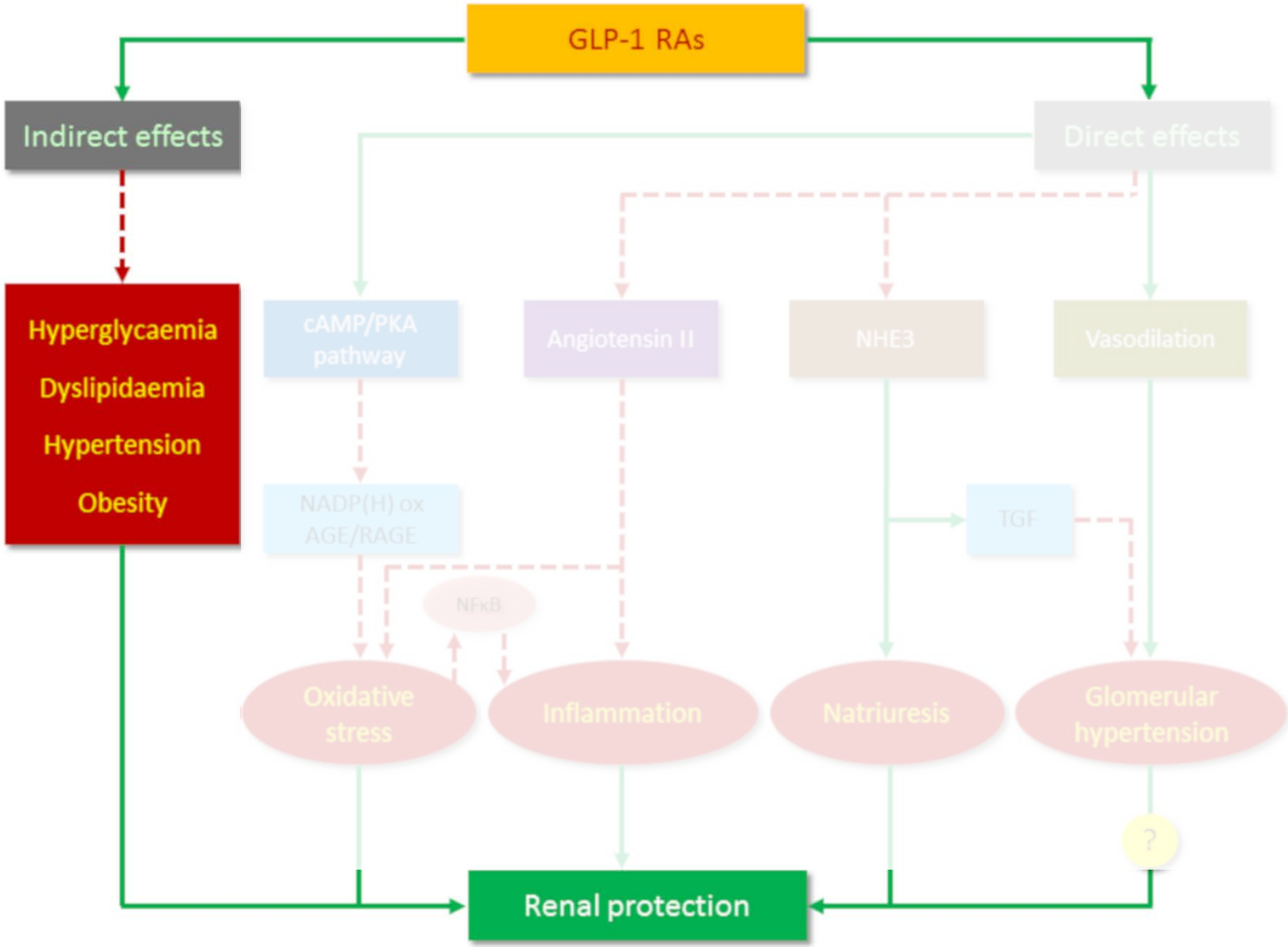
A Change in eGFR over 192 Wk



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

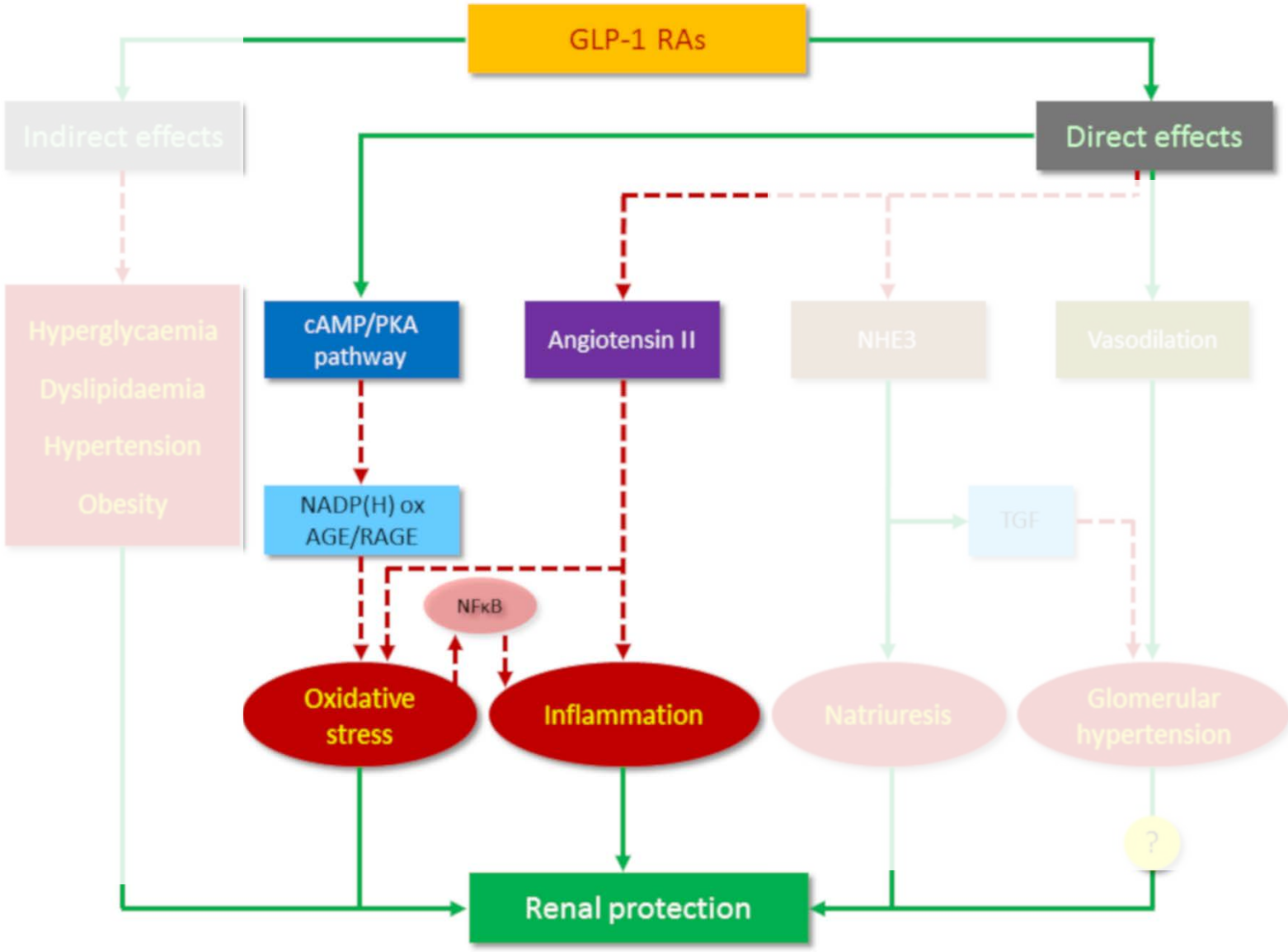
Wanner C et al. N Engl J Med. 2016;375:323-334

MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs



Vitale M et al. Curr Opin Pharmacol. 2020, 54:91–101

MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs



Vitale M et al. Curr Opin Pharmacol. 2020, 54:91–101

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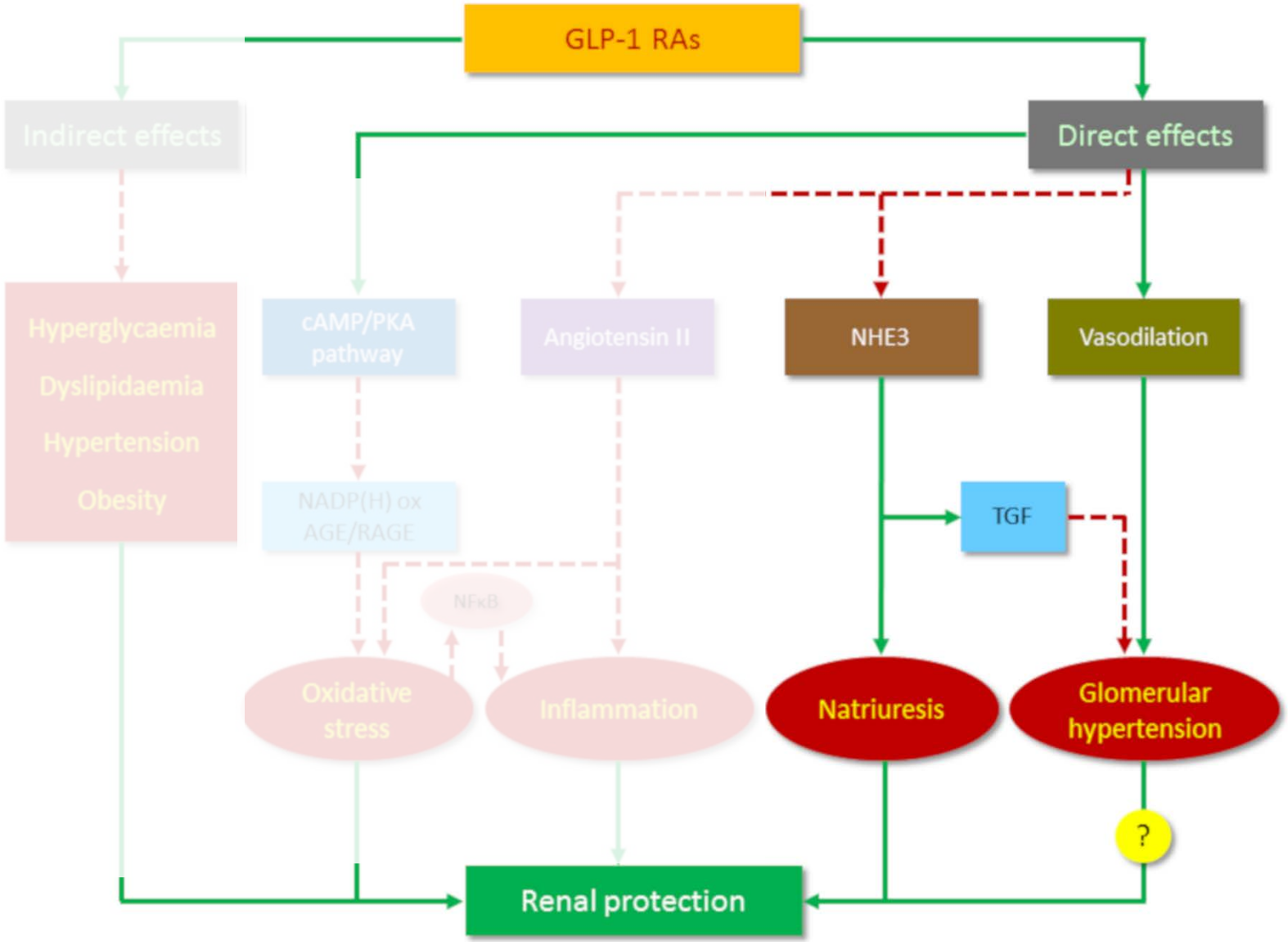
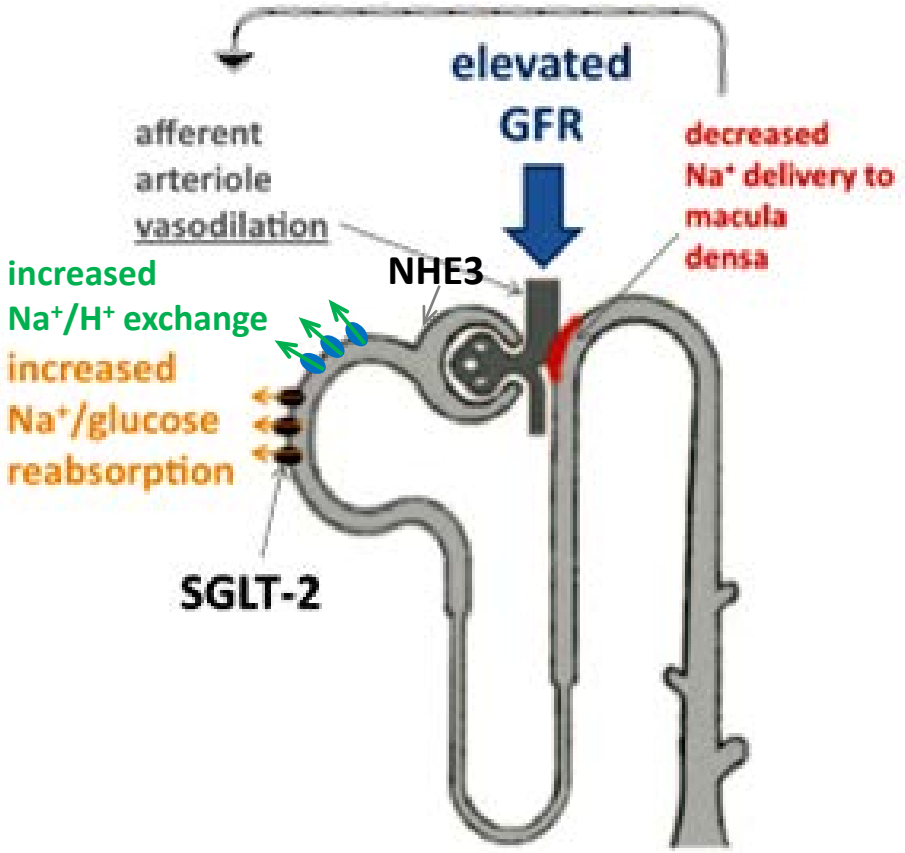


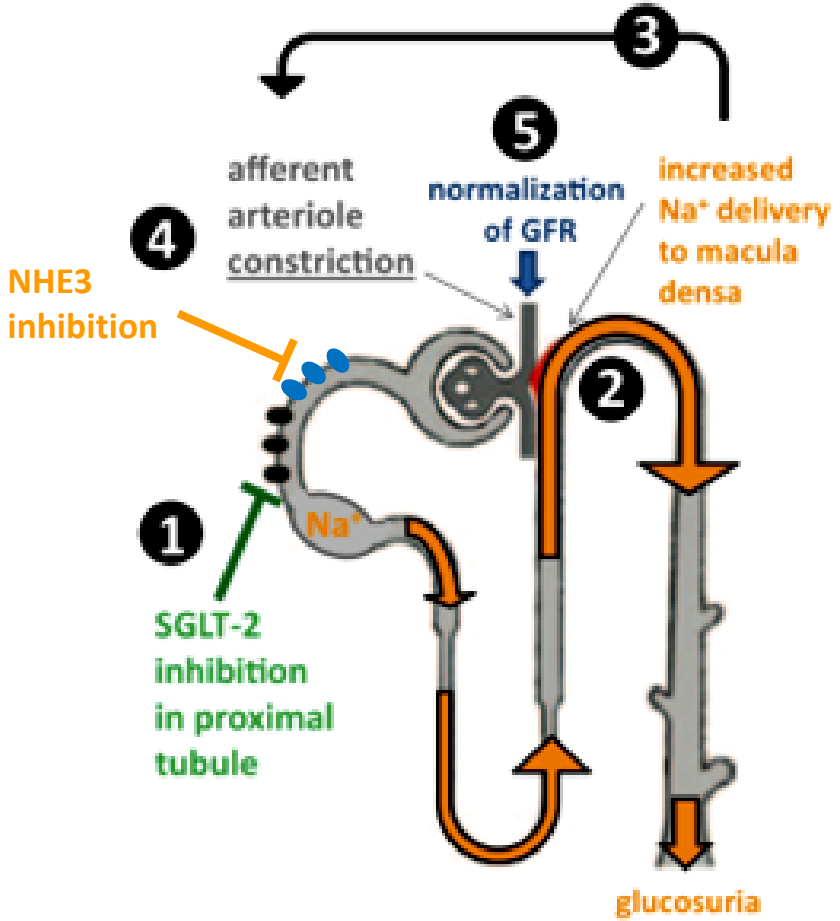
Vitale M et al. Curr Opin Pharmacol. 2020, 54:91–101

MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs

Impaired TGF



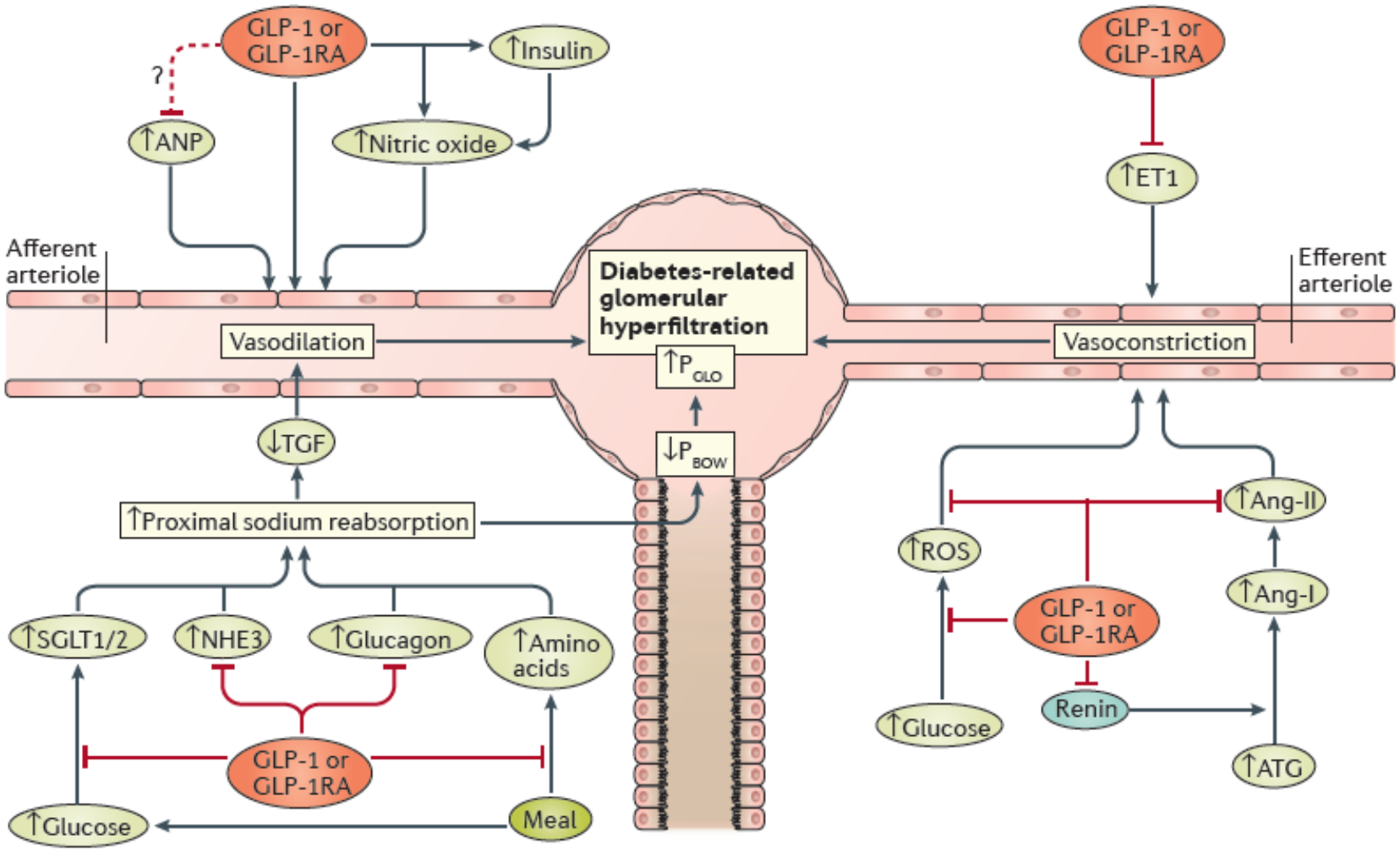
Restored TGF



Modified from Cherney DZ et al. Circulation. 2014;129:587–597
Slide courtesy of Prof. G. Pugliese

MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs

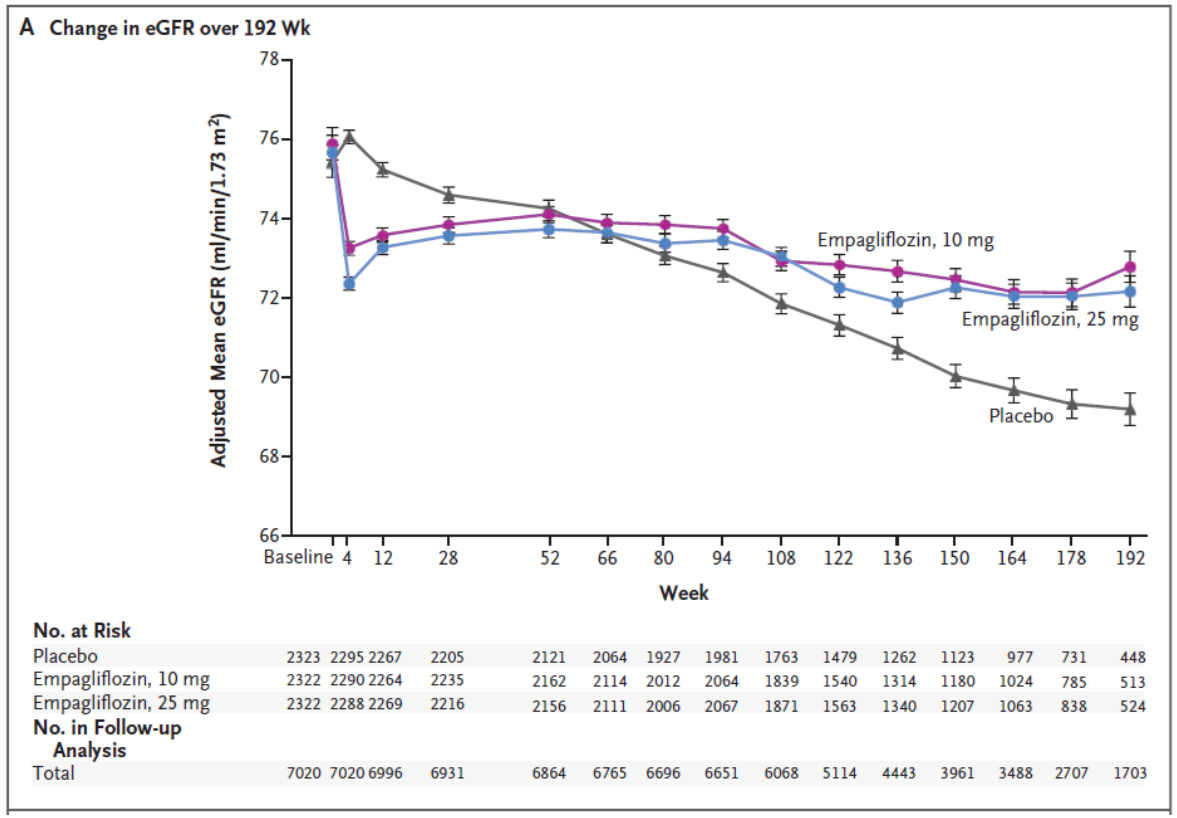
Effects of GLP-1 and GLP-1RAs on renal haemodynamics in diabetes mellitus



Muskiet MHA et al. Nat Rev Nephrol. 2017;13:605-628

MECHANISMS OF RENAL PROTECTION BY SGLT2-Is

EMPA-REG OUTCOME®



No. at Risk															
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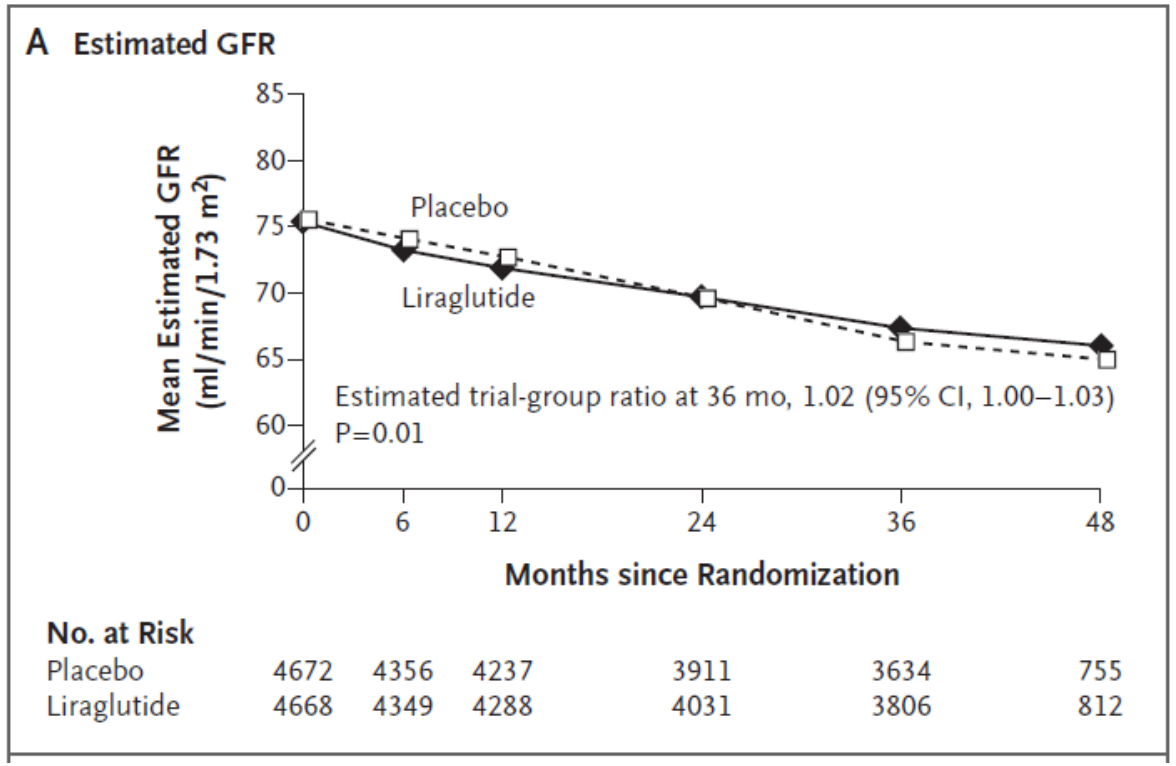
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results



No. at Risk						
Placebo	4672	4356	4237	3911	3634	755
Liraglutide	4668	4349	4288	4031	3806	812

Wanner C et al. N Engl J Med. 2016;375:323-334
Mann JFE et al. N Engl J Med. 2017;377:839-848

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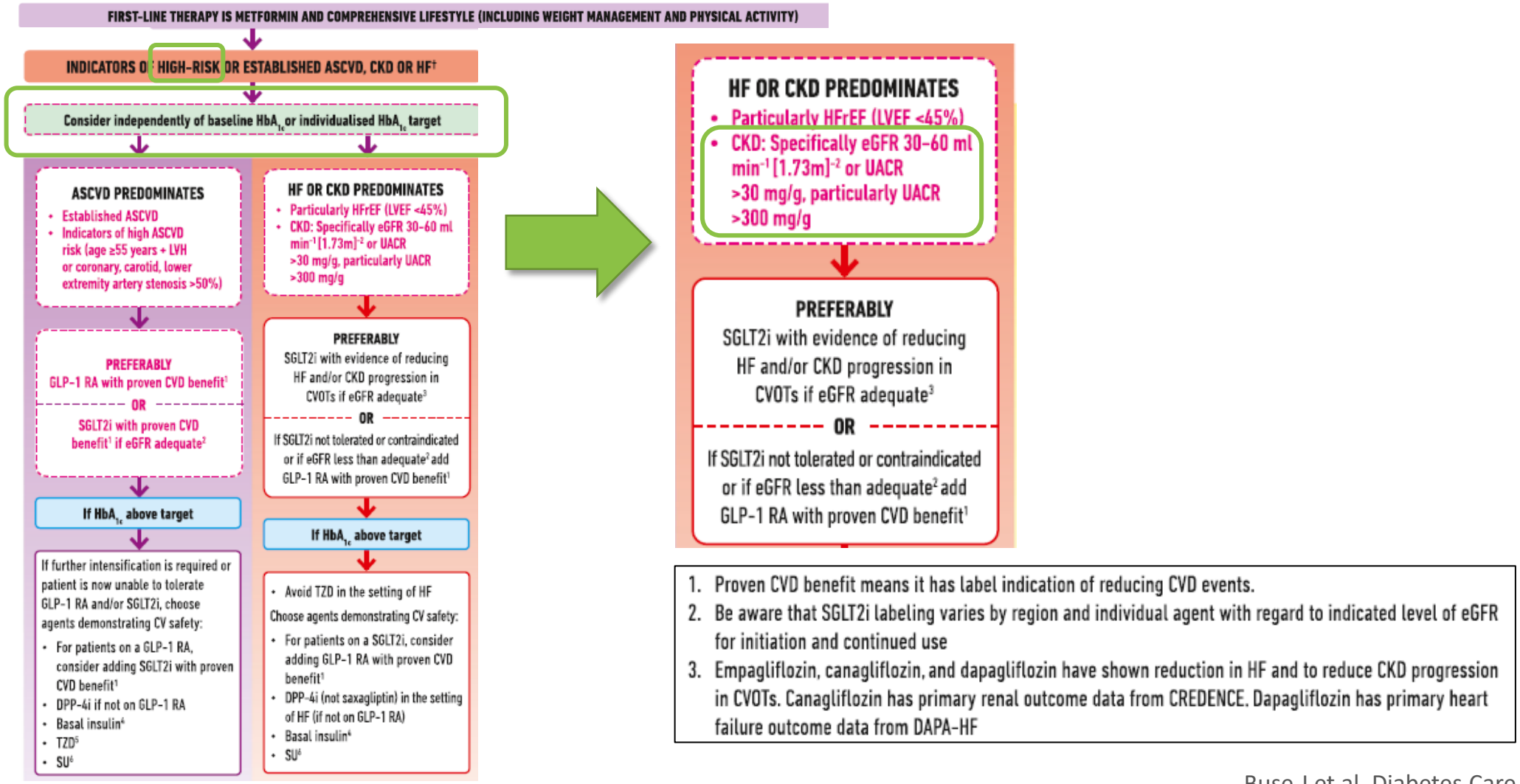
GUIDELINES OF GLUCOSE-LOWERING MEDICATION IN T2DM – FOCUS ON CKD

2019 update to the 2018 consensus report by
the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

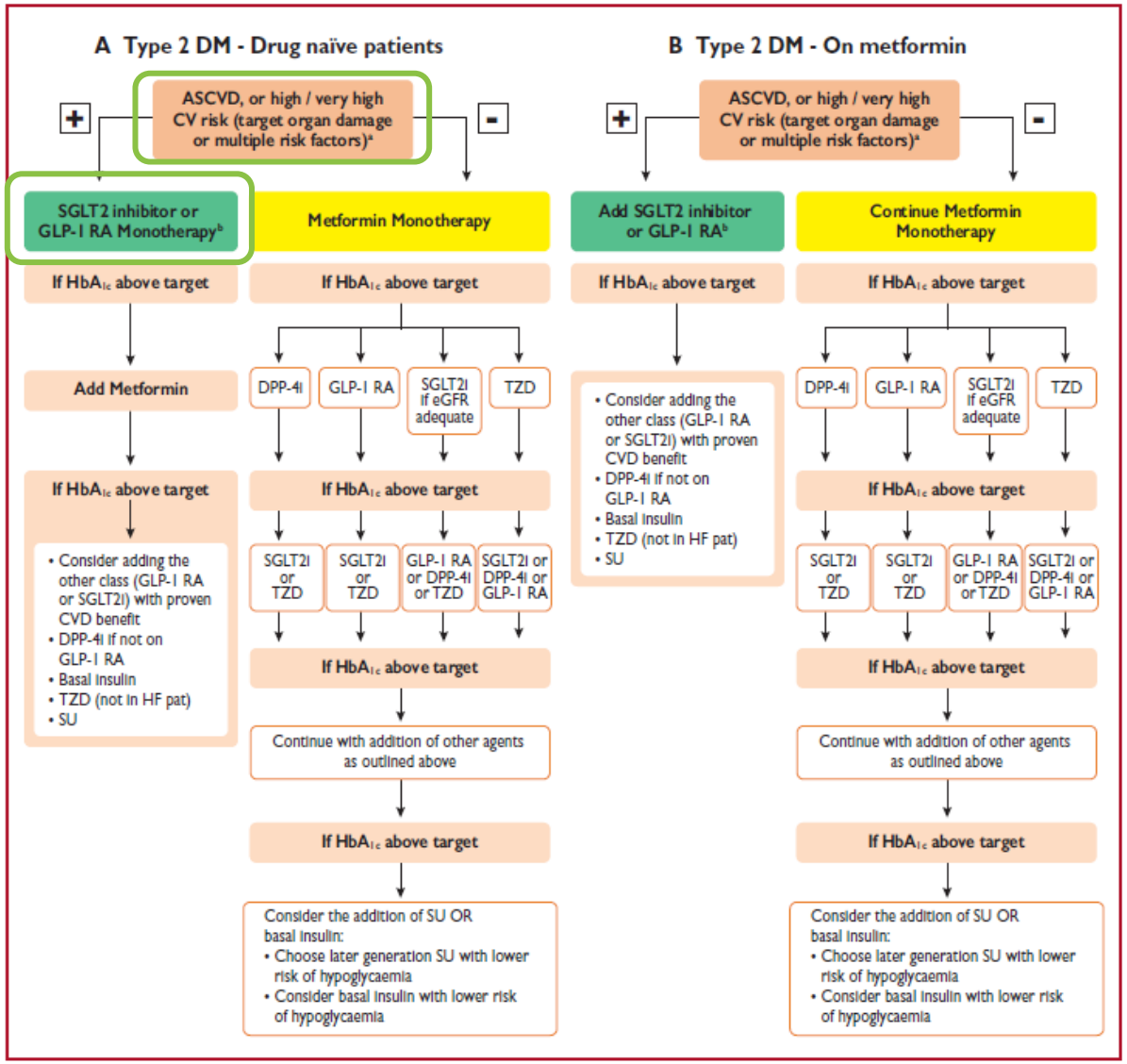


1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labeling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF

Buse J et al. Diabetes Care. 2020;43:487–493

GUIDELINES OF GLUCOSE-LOWERING MEDICATION IN T2DM – FOCUS ON CKD

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD



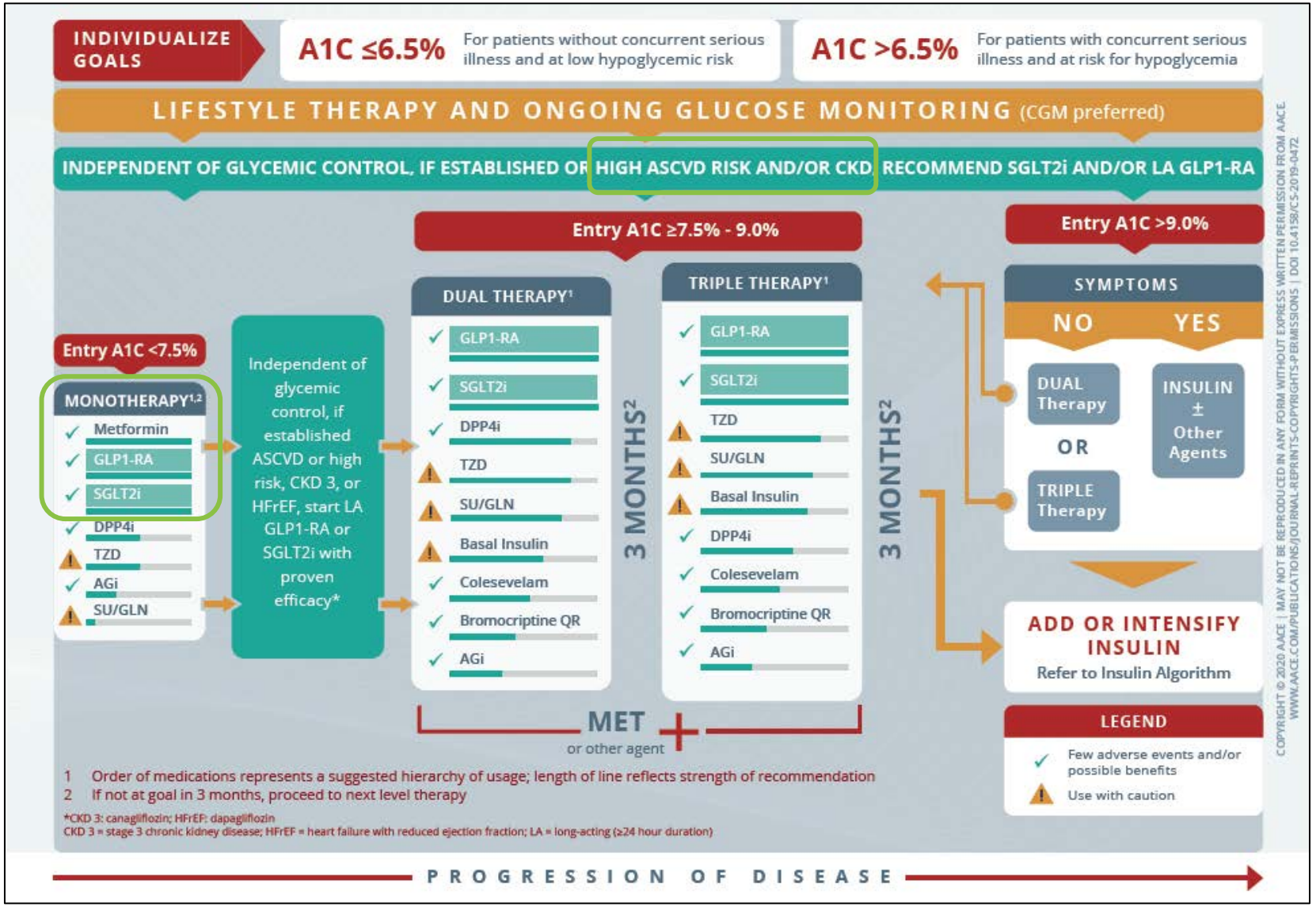
Recommendations for the prevention and management of chronic kidney disease in patients with diabetes

Recommendations	Class[a]	Level[b]
Treatment with an SGLT2 inhibitor (empagliflozin, canagliflozin, or dapagliflozin) is associated with a lower risk of renal endpoints and is recommended if eGFR is 30 to <90 mL/min/1.73 m^2). [306,311,313,496]	I	B
Treatment with the GLP1-RAs liraglutide and semaglutide is associated with a lower risk of renal endpoints, and should be considered for DM treatment if eGFR is >30 mL/min/1.73m^2. [176,299]	IIa	B

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

GUIDELINES OF GLUCOSE-LOWERING MEDICATION IN T2DM – FOCUS ON CKD

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2020 Guidelines



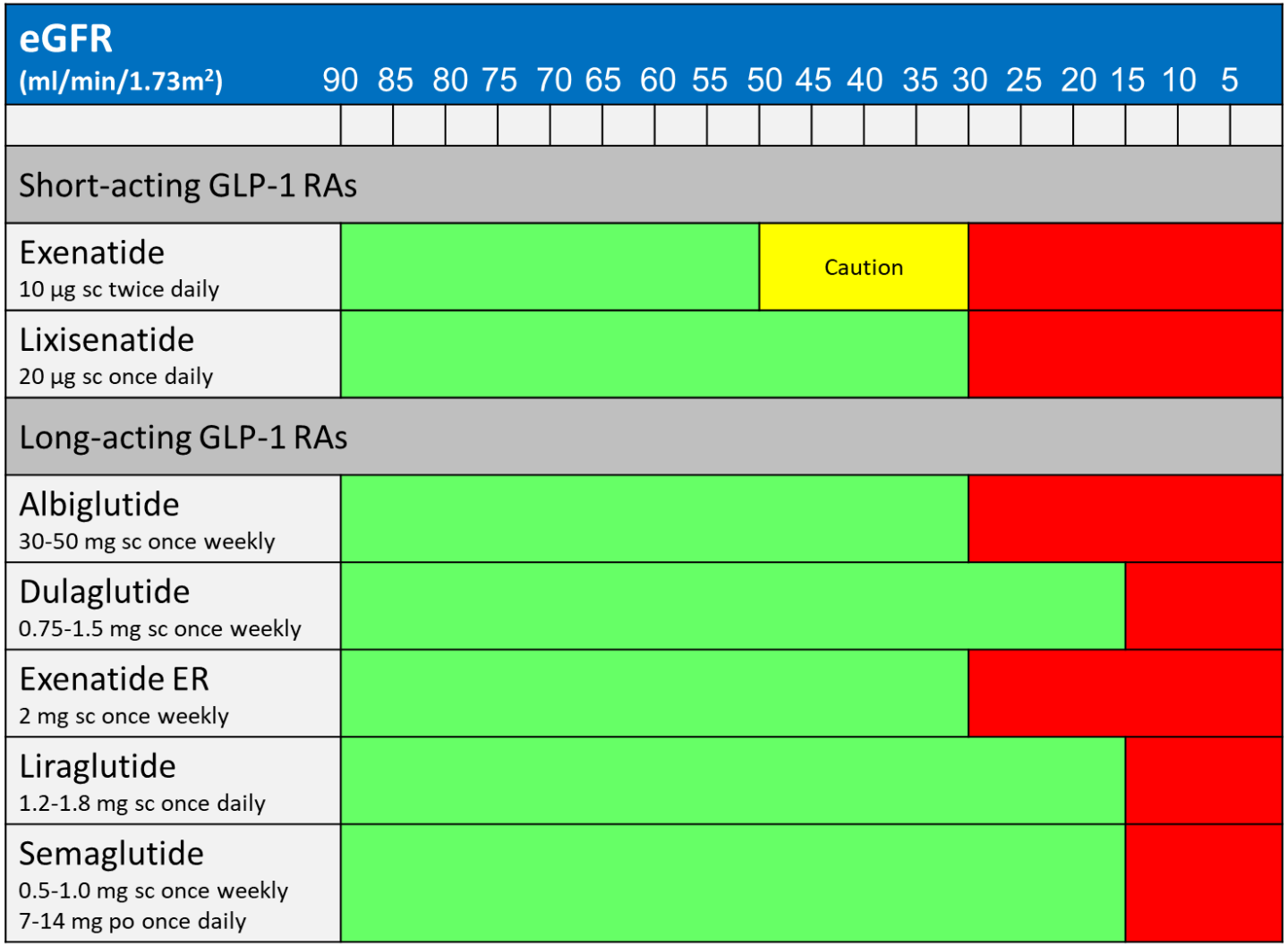
Garber AJ et al. Endocr Pract. 2020;26:107–139

AGENDA

- TRENDS IN DIABETIC COMPLICATIONS AND DKD
- RENAL OUTCOME FROM CARDIOVASCULAR OUTCOME TRIALS
  - CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs
  - CARDIOVASCULAR (and RENAL) OUTCOME TRIALS – SGLT2-Is
  - COMPARISON GLP-1 RAs/SGLT2-Is
- MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs AND SGLT2-Is
- GUIDELINES OF GLUCOSE-LOWERING MEDICATION IN T2DM – FOCUS ON CKD
- DOSE RECOMMENDATIONS OF GLP-1 RAs AND SGLT2-Is IN CKD
- TAKE HOME MESSAGES

DOSE RECOMMENDATIONS OF GLP-1 RAs AND SGLT2-Is IN CKD

GLP-1 RAs



Vitale M et al. Curr Opin Pharmacol. 2020; in press

DOSE RECOMMENDATIONS OF GLP-1 RAs AND SGLT2-Is IN CKD

SGLT2-Is

eGFR (ml/min/1.73m²)	90 85 80 75	70 65 60	55 50 45	40 35 30 25 20 15 10 5
SGLT2 inhibitors				
Dapagliflozin 10 mg po once daily	10 mg	Do not initiate		
	10 mg	10 mg		
Canagliflozin 100-300 mg po once daily	100 mg	Do not initiate		
	↑ 300 mg	↓ 100 mg		
Empagliflozin 10-25 mg po once daily	10 mg	Do not initiate		
	↑ 25 mg	↓ 10 mg		
Ertugliflozin 5-15 mg po once daily	5 mg	Do not initiate		
	↑ 15 mg	↓ 5 mg		

Modified from Pugliese G et al. Nutr Metab Cardiovasc Dis 2019;29:1127–1150

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TAKE HOME MESSAGES

- Strong evidence from cardiovascular outcome trials support a significant renal protection in diabetic patients, with both GLP-1 RAs and SGLT2-Is, despite different nephroprotection profiles

  - GLP-1 RAs act mostly in terms of reduced onset of new macroalbuminuria, while their role on hard renal endpoints seems to be less clear

  - SGLT2-Is significantly reduce both albuminuria and loss of renal function

- Most recent data on SGLT2-Is in patients with chronic kidney disease confirm their great renal protective effects, that extend also to non diabetic patients, suggesting mechanisms independent of their blood glucose–lowering effects

TAKE HOME MESSAGES

- International guidelines recommend early use of GLP-1 RAs and SGLT2-Is in high risk patients, independent of glycemic control, also in monotherapy

- Efficacy and safety profile that came from these trials reassure about the use of these drugs also in patients with severe renal impairment

POSSIAMO RALLENTARE LA NEFROPATIA?