



Congresso Regionale **SID-AMD LAZIO 2020**

IL DIABETE MELLITO DOPO IL COVID-19:
A CHE PUNTO ERAVAMO RIMASTI
E COME POSSIAMO SPINGERCI OLTRE?

9-10 OTTOBRE 2020

ROMA | NH Villa Carpegna

POSSIAMO RALLENTARE LA NEFROPATIA?

Martina Vitale

Dipartimento di Medicina Sperimentale –
Sapienza Università di Roma

UOC Medicina Specialistica Endocrino-Metabolica –
Azienda Ospedaliera Sant'Andrea, Roma

AGENDA

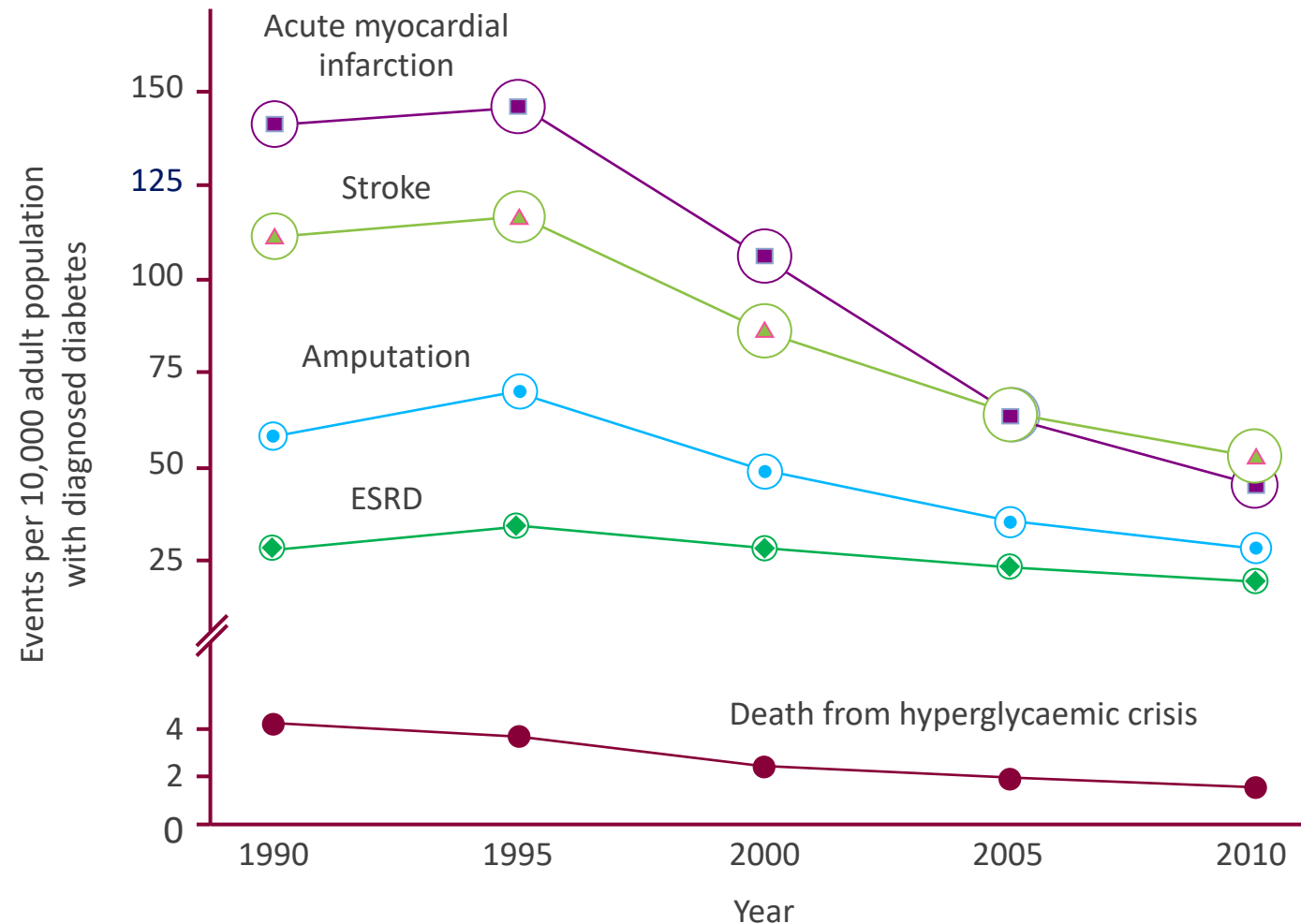
- TRENDS IN DIABETIC COMPLICATIONS AND DKD
- RENAL OUTCOME FROM CARDIOVASCULAR OUTCOME TRIALS
 - CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs
 - CARDIOVASCULAR (and RENAL) OUTCOME TRIALS – SGLT2-Is
 - COMPARISON GLP-1 RAs/SGLT2-Is
- MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs AND SGLT2-Is
- GUIDELINES OF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

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

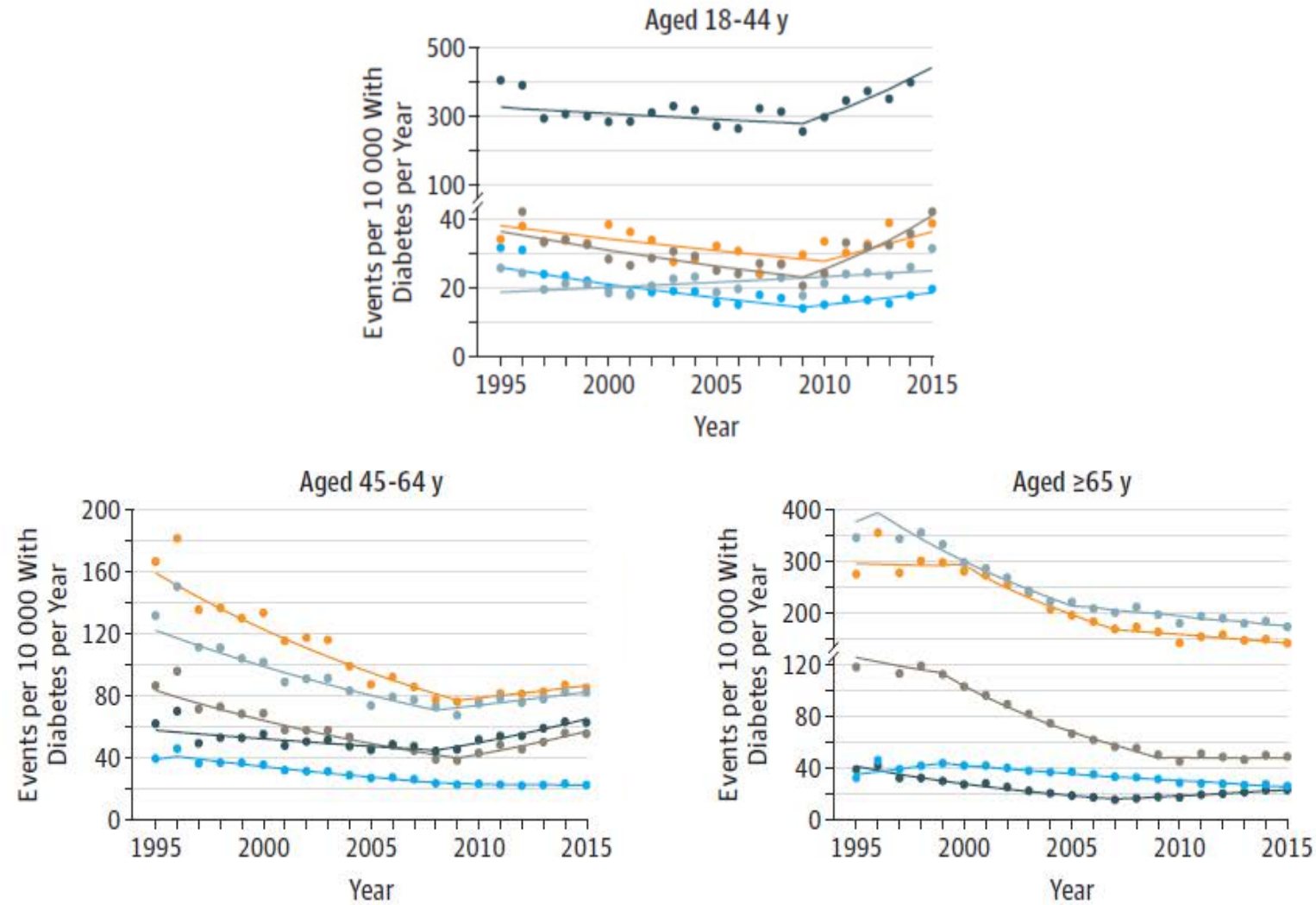
TRENDS IN DIABETIC COMPLICATIONS

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



TRENDS IN DIABETIC COMPLICATIONS

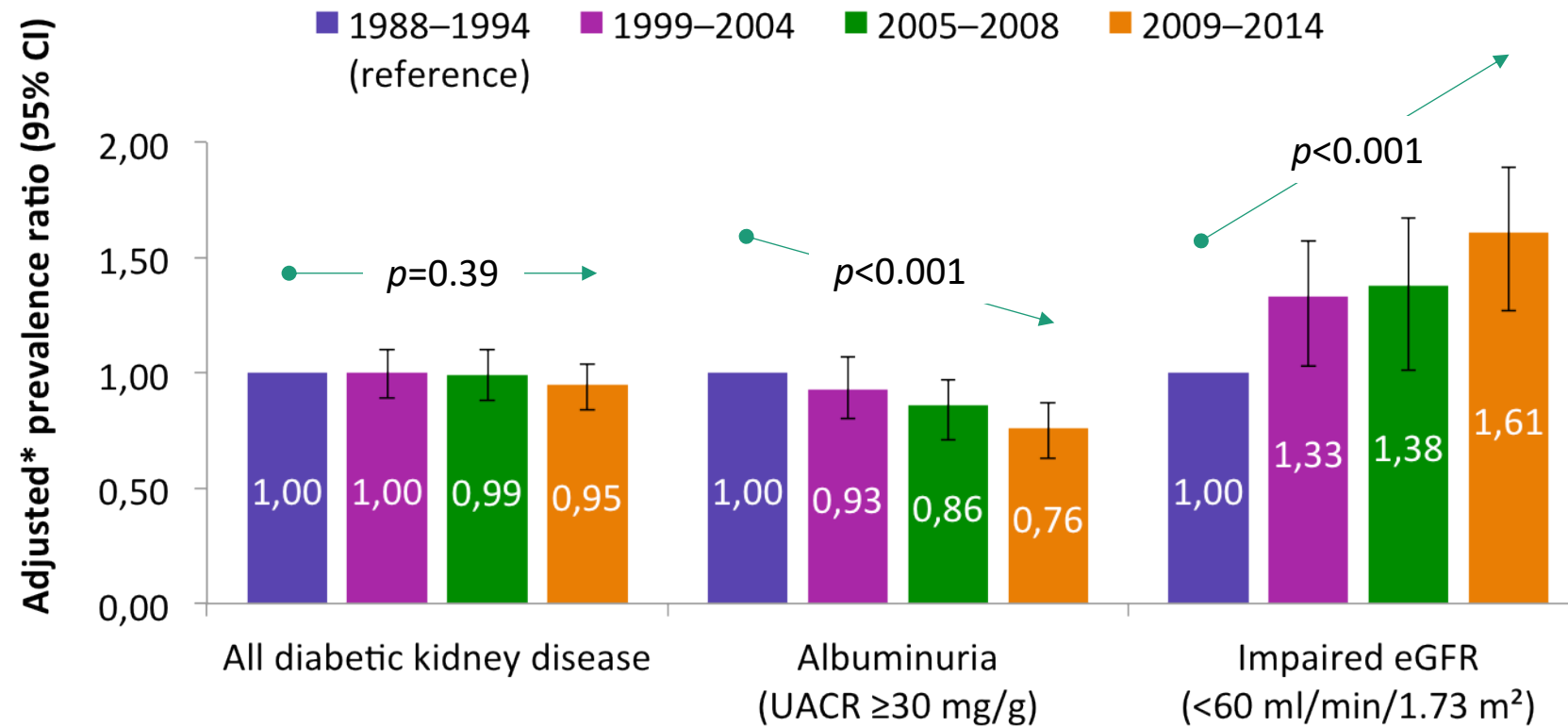
Resurgence in Diabetes-Related Complications



● Acute myocardial infarction ● Stroke ● Lower-extremity amputation ● Hyperglycemia ● End-stage kidney disease

TRENDS IN DIABETIC COMPLICATIONS - DKD

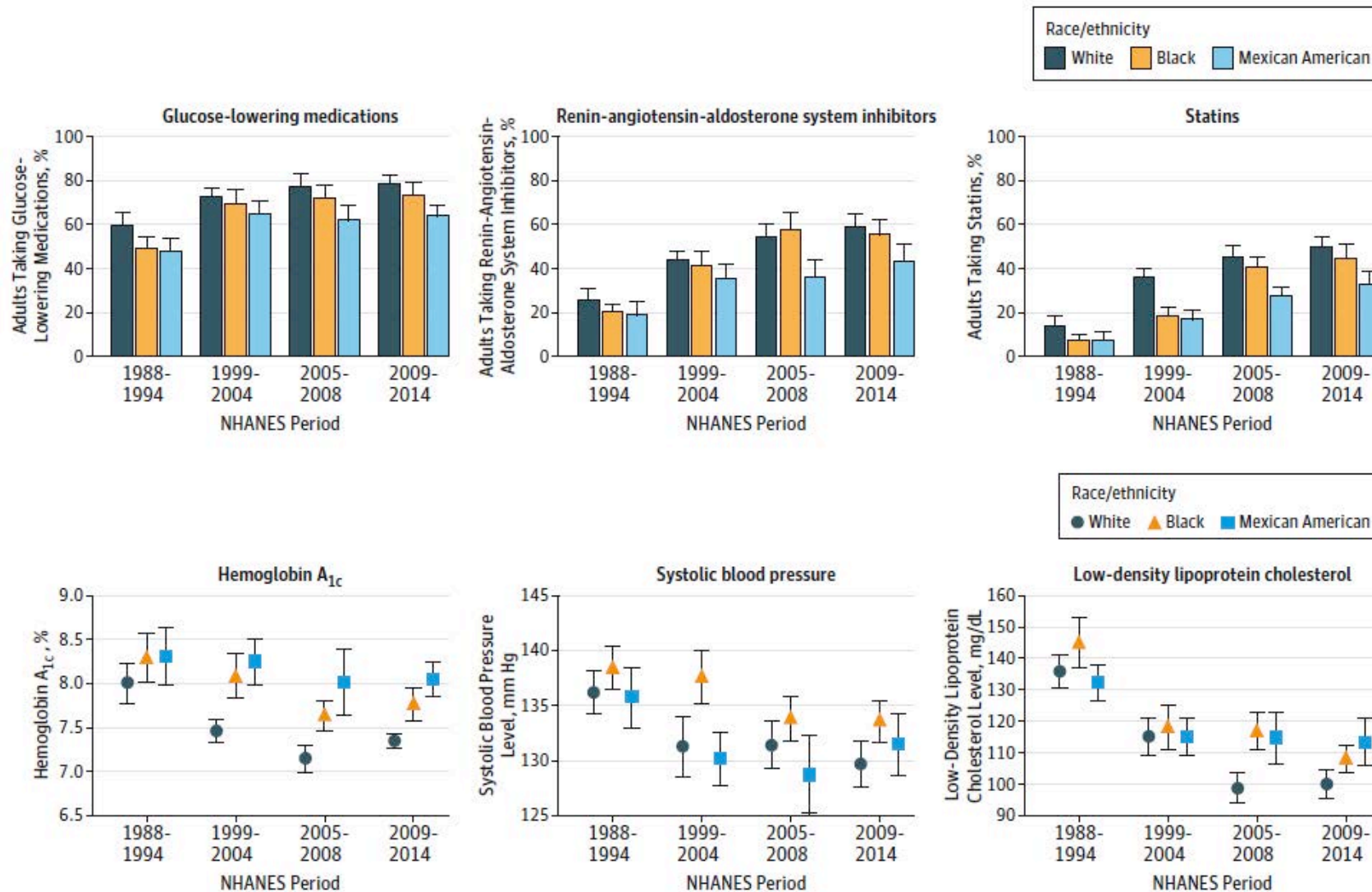
Clinical Manifestations of Kidney Disease Among US Adults With Diabetes



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

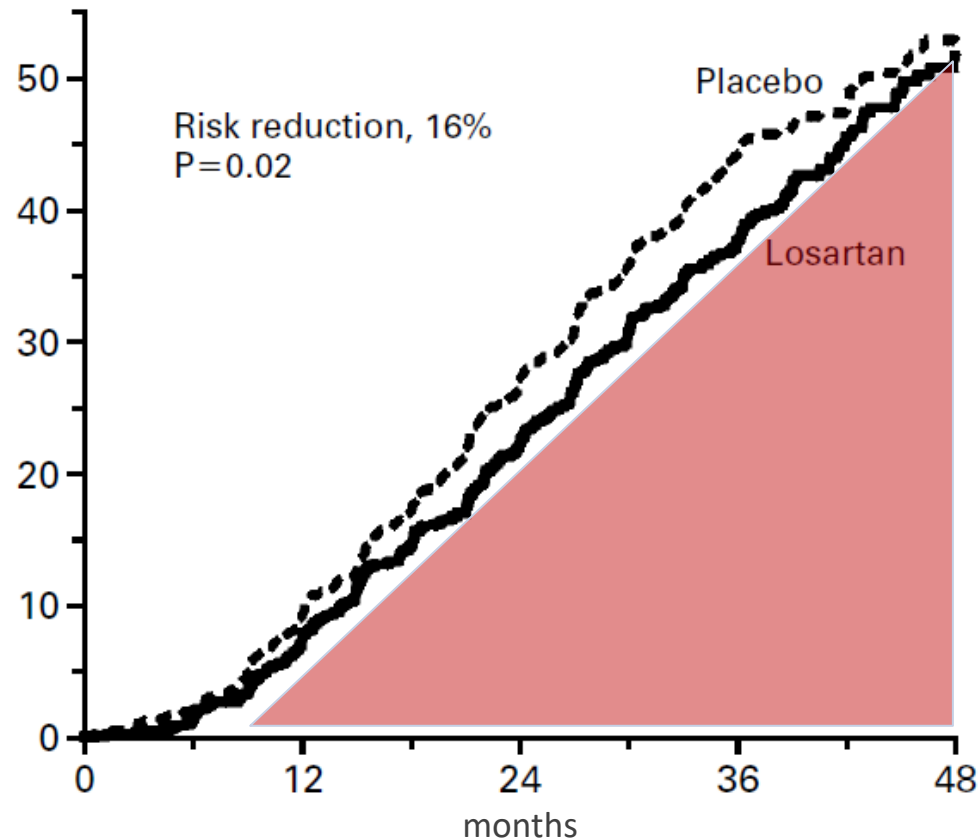
TRENDS IN DIABETIC COMPLICATIONS - DKD

Medication Use and Trends in Clinical Targets



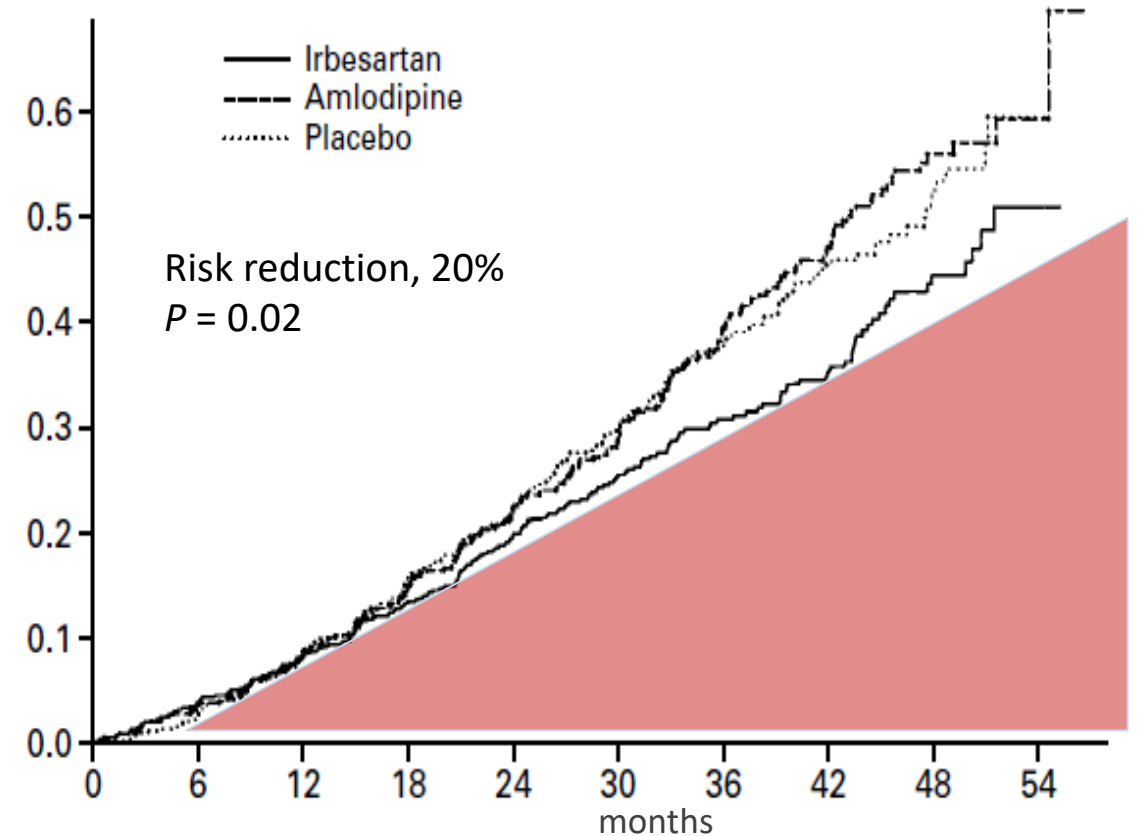
RENAL PROTECTION WITH RAS BLOCKERS

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



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

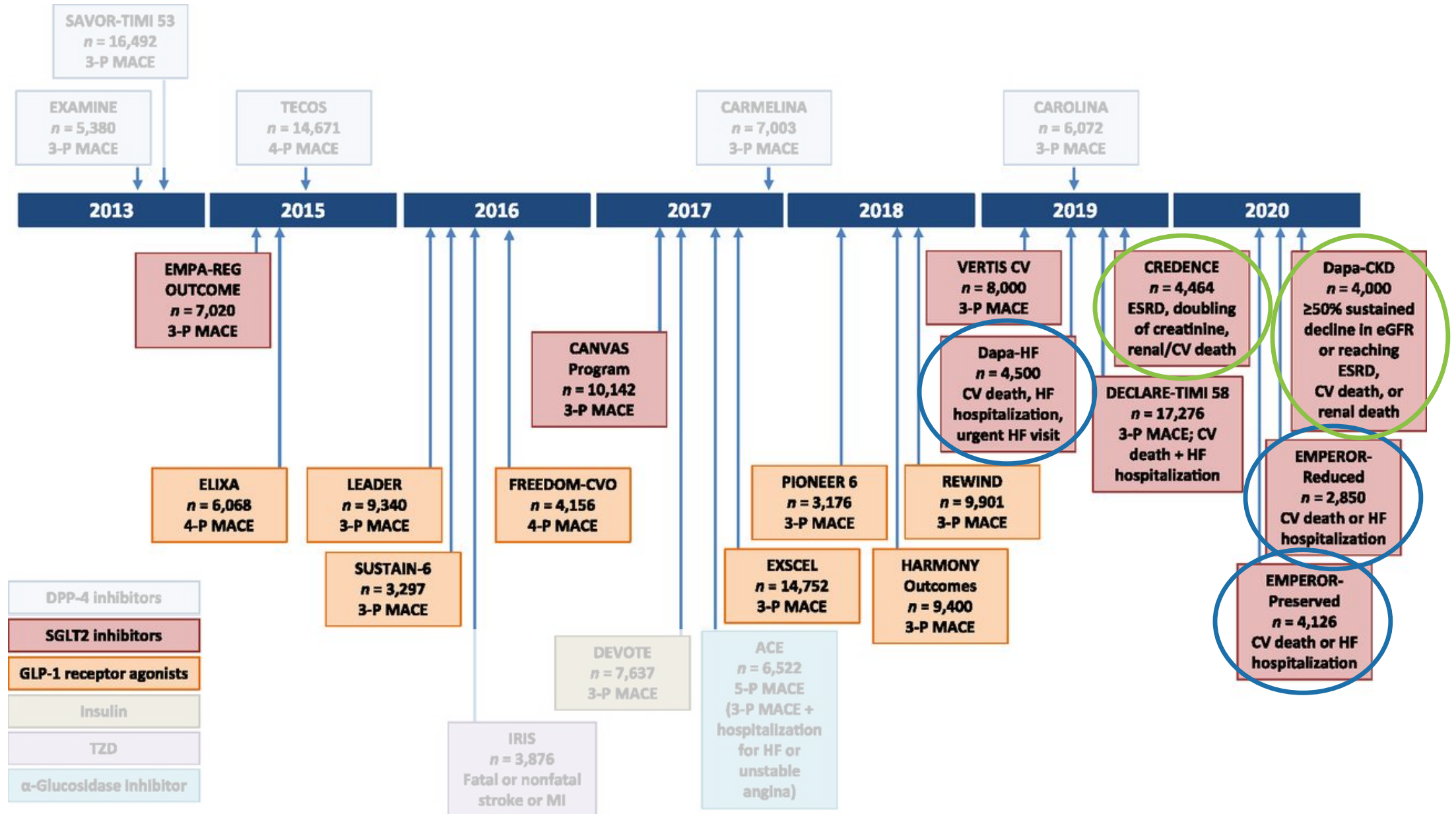
The **Irbesartan** Diabetic Nephropathy Trial (IDNT)



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

CARDIOVASCULAR OUTCOME TRIALS



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

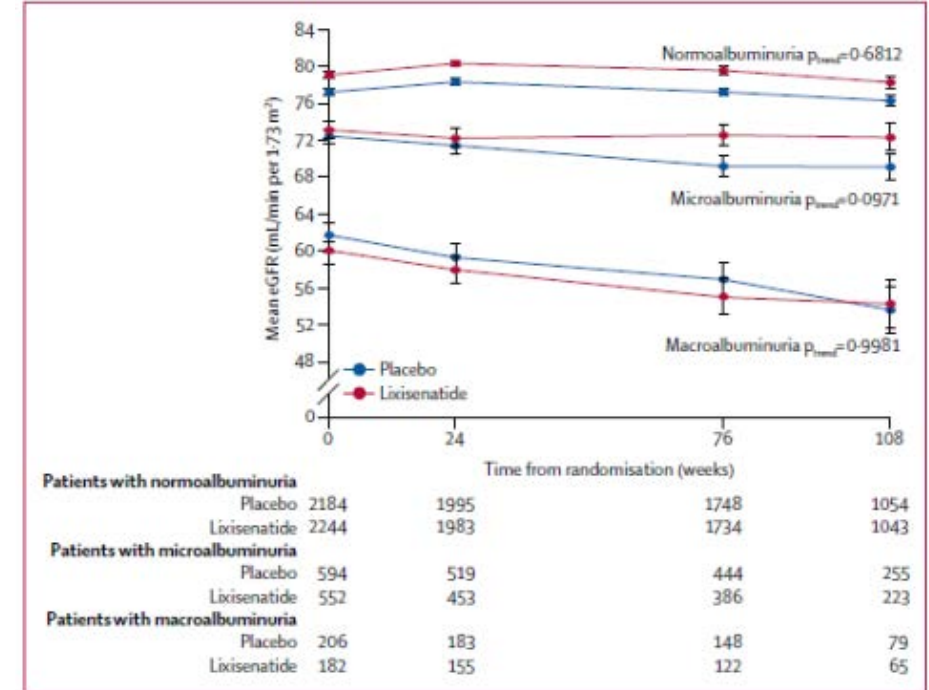
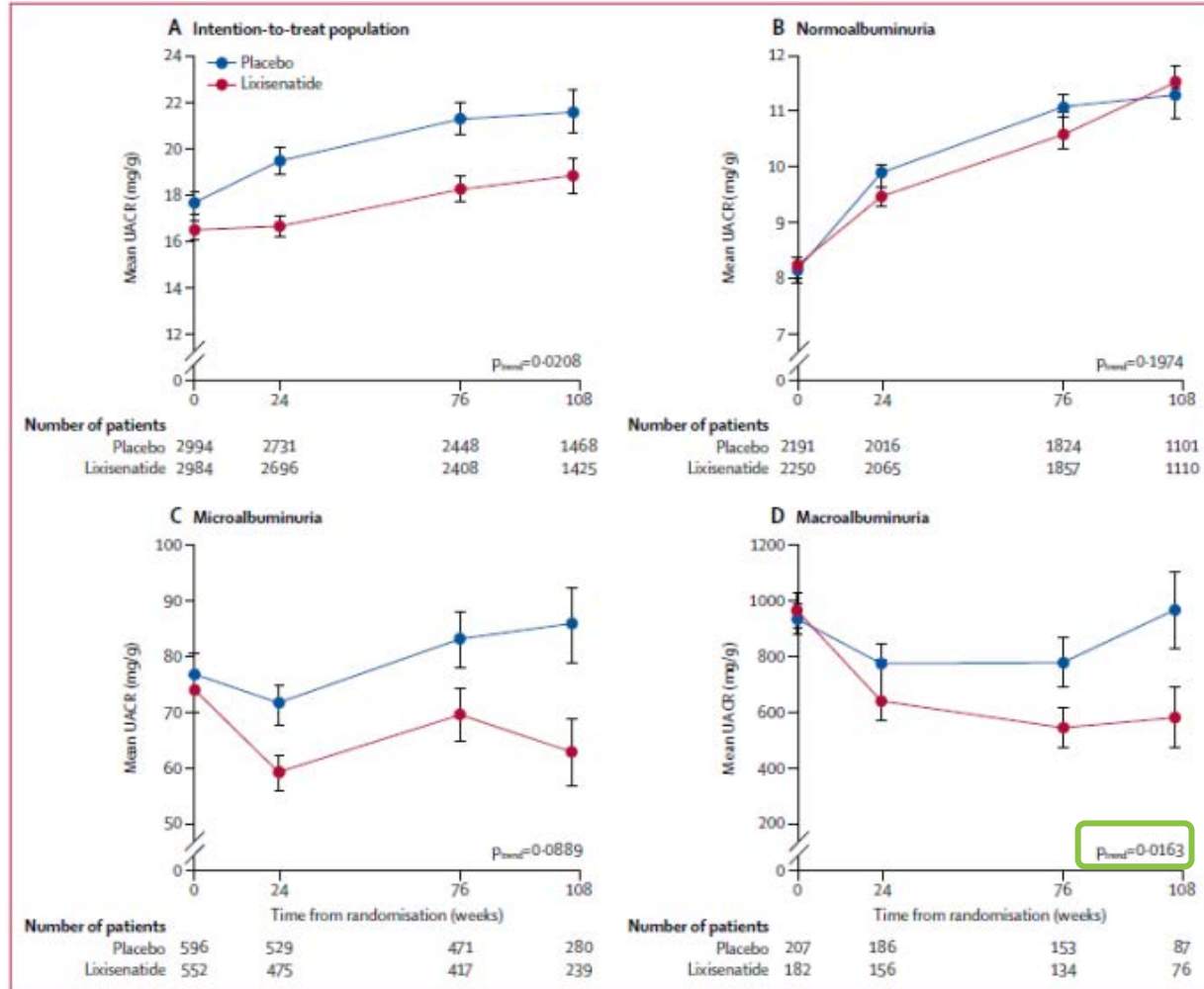
CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

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/1.73m²

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

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



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

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

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

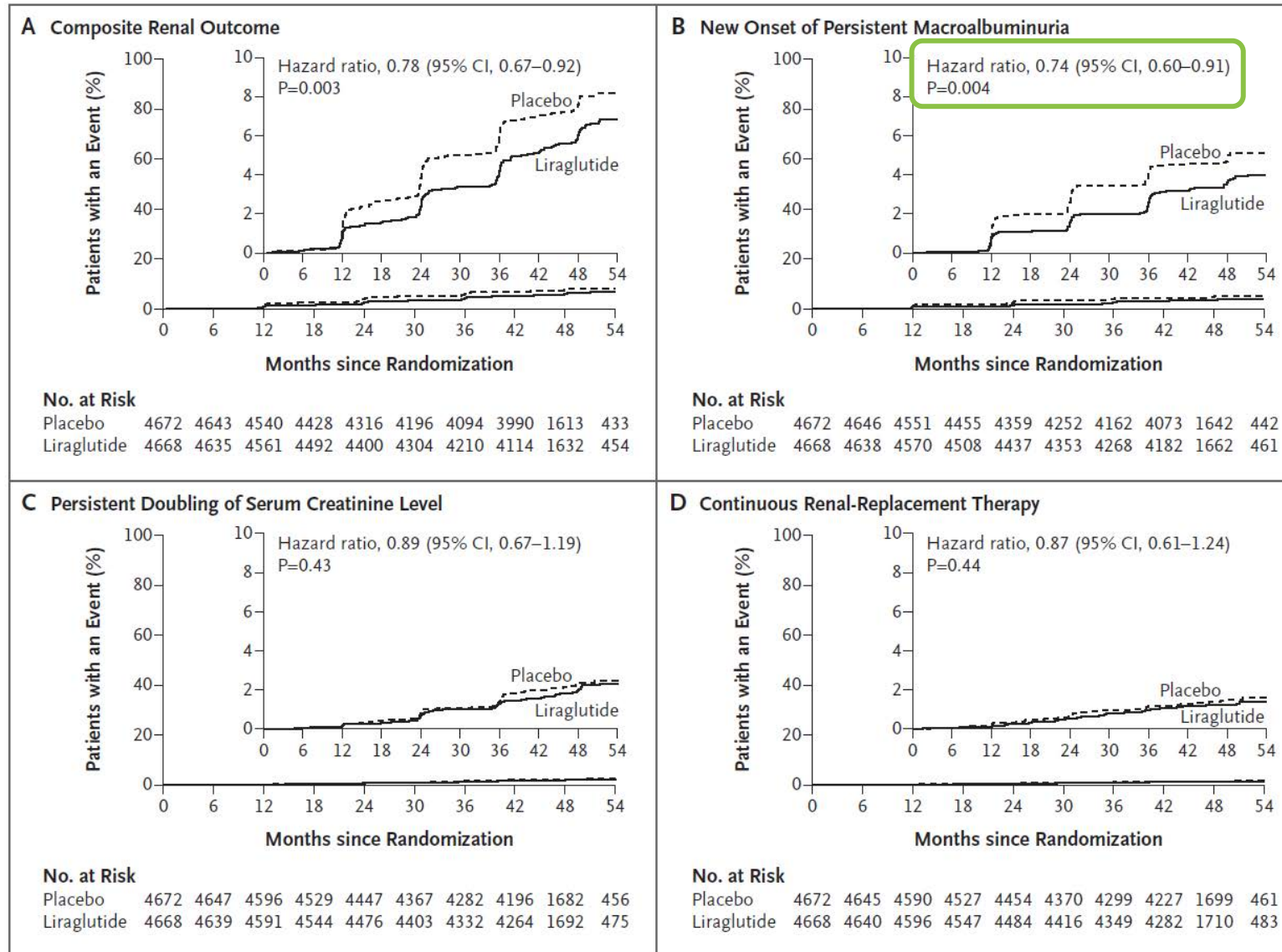
Trial	ELIXA	LEADER
Drug	Lixisenatide	Liraglutide
Participants, n (active drug/placebo)	6,068 (3,034/3,034)	9,340 (4,668/4,672)
Median follow-up, years	2.1	3.8
eGFR (ml/min/1.73m ²) (active drug/placebo)	75.2/76.7	80.2/80.6
Renal function at baseline		
Normal (eGFR ≥90)	23.3%	35%
Mild impairment (eGFR 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

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



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

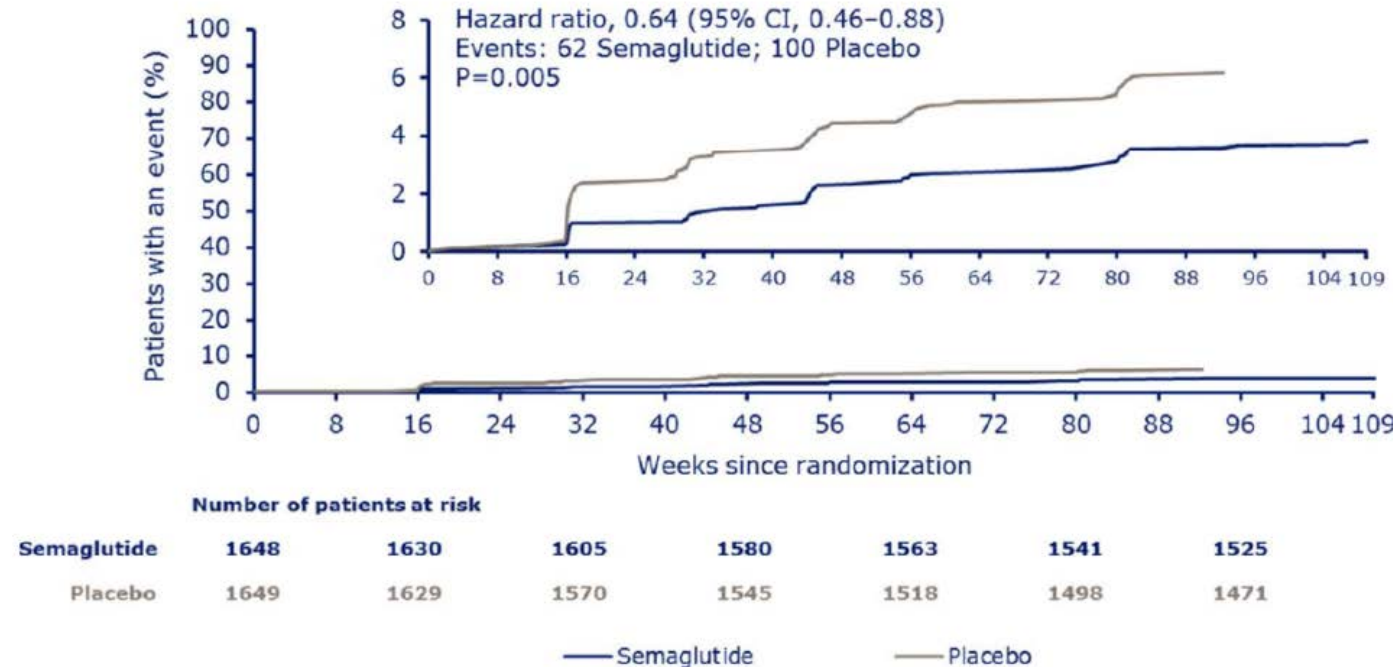
no eGFR limits

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**)



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/m²)
- ESRD

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/1.73m²) (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/1.73m²

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Exenatide Study of Cardiovascular Event Lowering (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
<i>Adjusted HR*</i>					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
<i>Adjusted HR*</i>					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.						

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

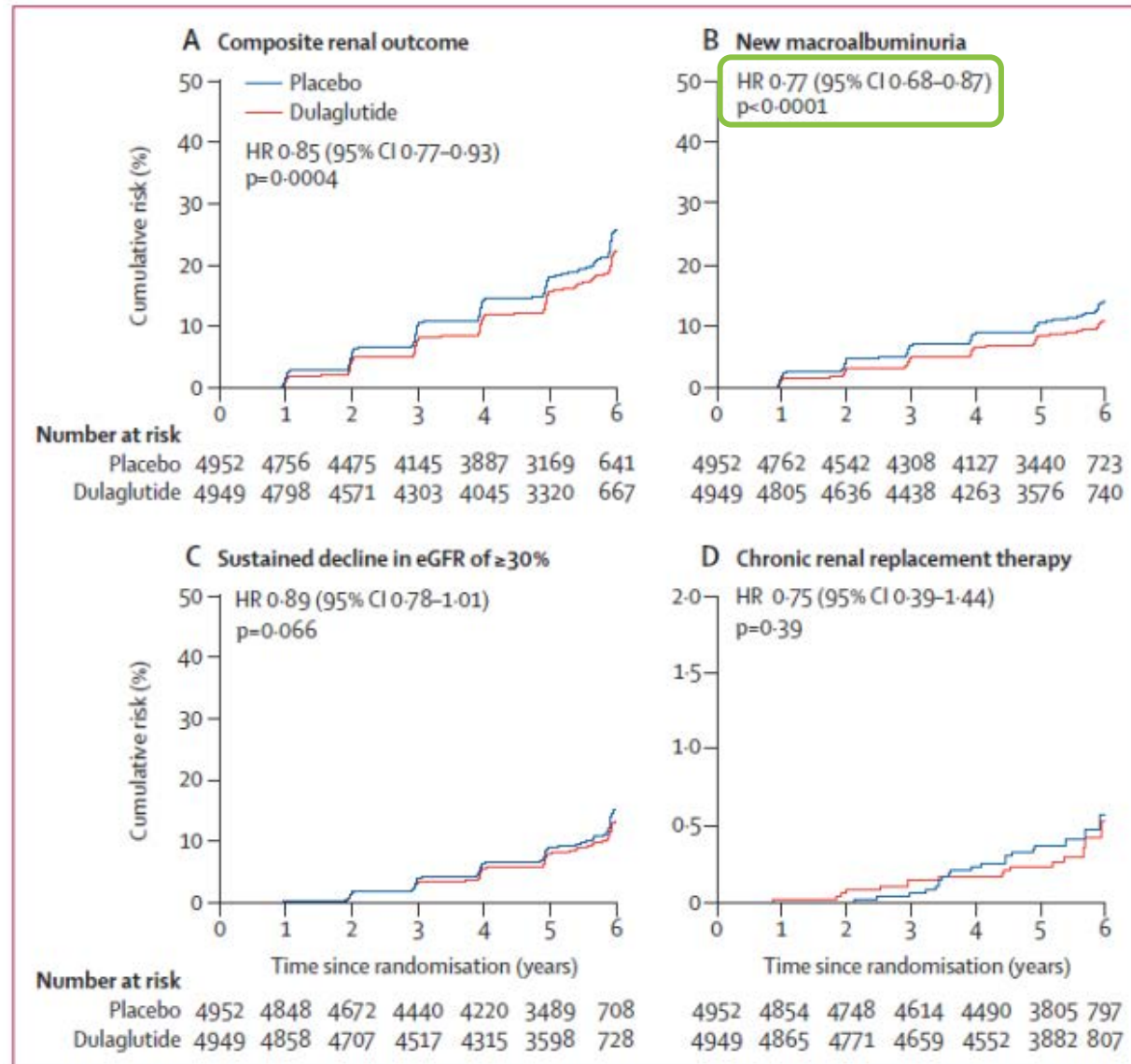
Trial	ELIXA	LEADER	SUSTAIN 6	EXSCEL	REWIND
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide ER	Dulaglutide
Participants, n (active drug/placebo)	6,068 (3,034/3,034)	9,340 (4,668/4,672)	3,297 (1,648/1,649)	14,752 (7,356/7,396)	9,901 (4,949/4,952)
Median follow-up, years	2.1	3.8	2.1	3.2	5.4
eGFR (ml/min/1.73m²) (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/1.73m²

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

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

REWIND
Dulaglutide CV Outcome Trial



CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

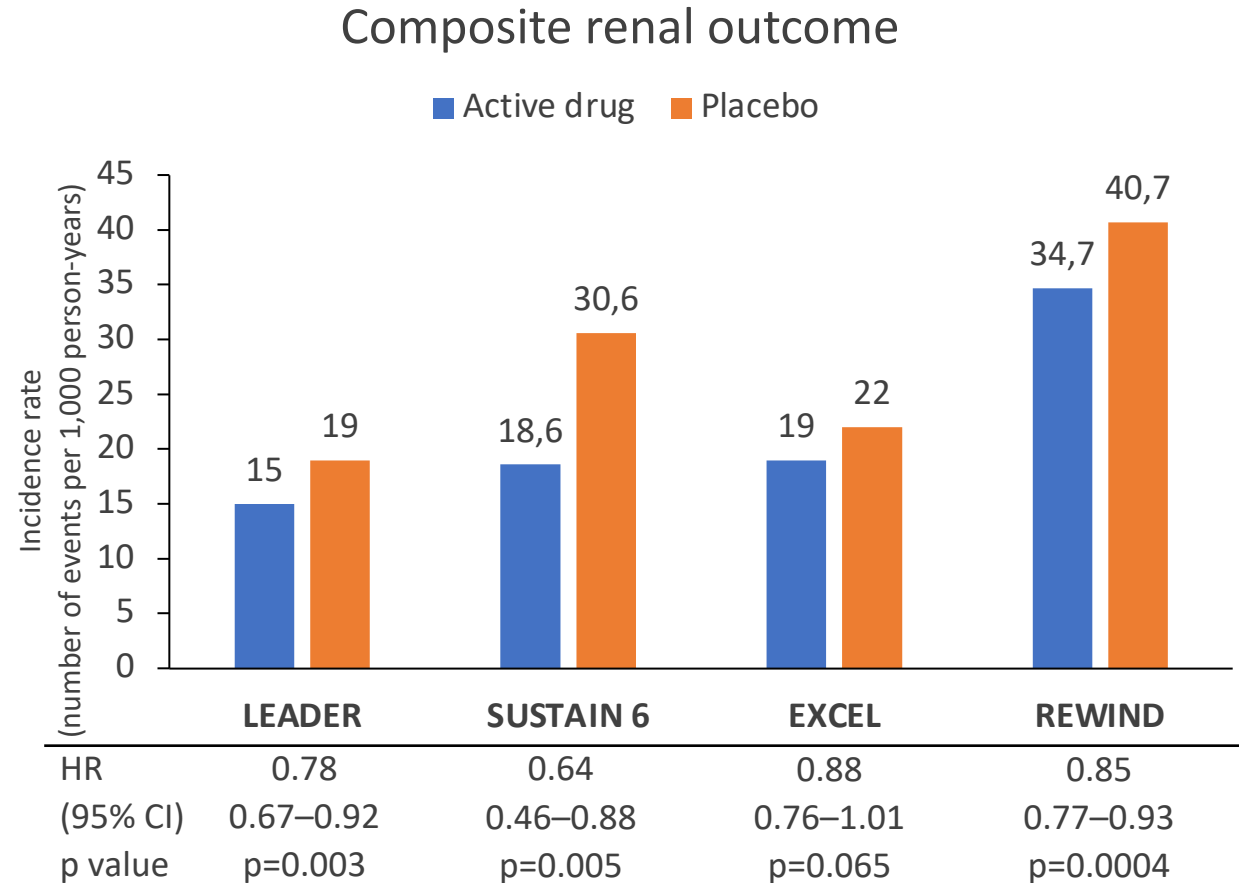
Trial	ELIXA	LEADER	SUSTAIN 6	EXSCEL	REWIND	HARMONY	PIONEER 6
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide ER	Dulaglutide	Albiglutide	Semaglutide (oral)
Participants, n (active drug/placebo)	6,068 (3,034/3,034)	9,340 (4,668/4,672)	3,297 (1,648/1,649)	14,752 (7,356/7,396)	9,901 (4,949/4,952)	9,463 (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%		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%	NR	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%		67%
Microalbuminuria	19%	26.3%	NR	NR	27%	NR	33%
Macroalbuminuria	7%	10.3%	NR	NR	8%		(micro+macro)

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

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



LEADER: new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level (and eGFR <45 mL/min/m²), ESRD, renal death

SUSTAIN 6: new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level (and eGFR <45 mL/min/m²), ESRD

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

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

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

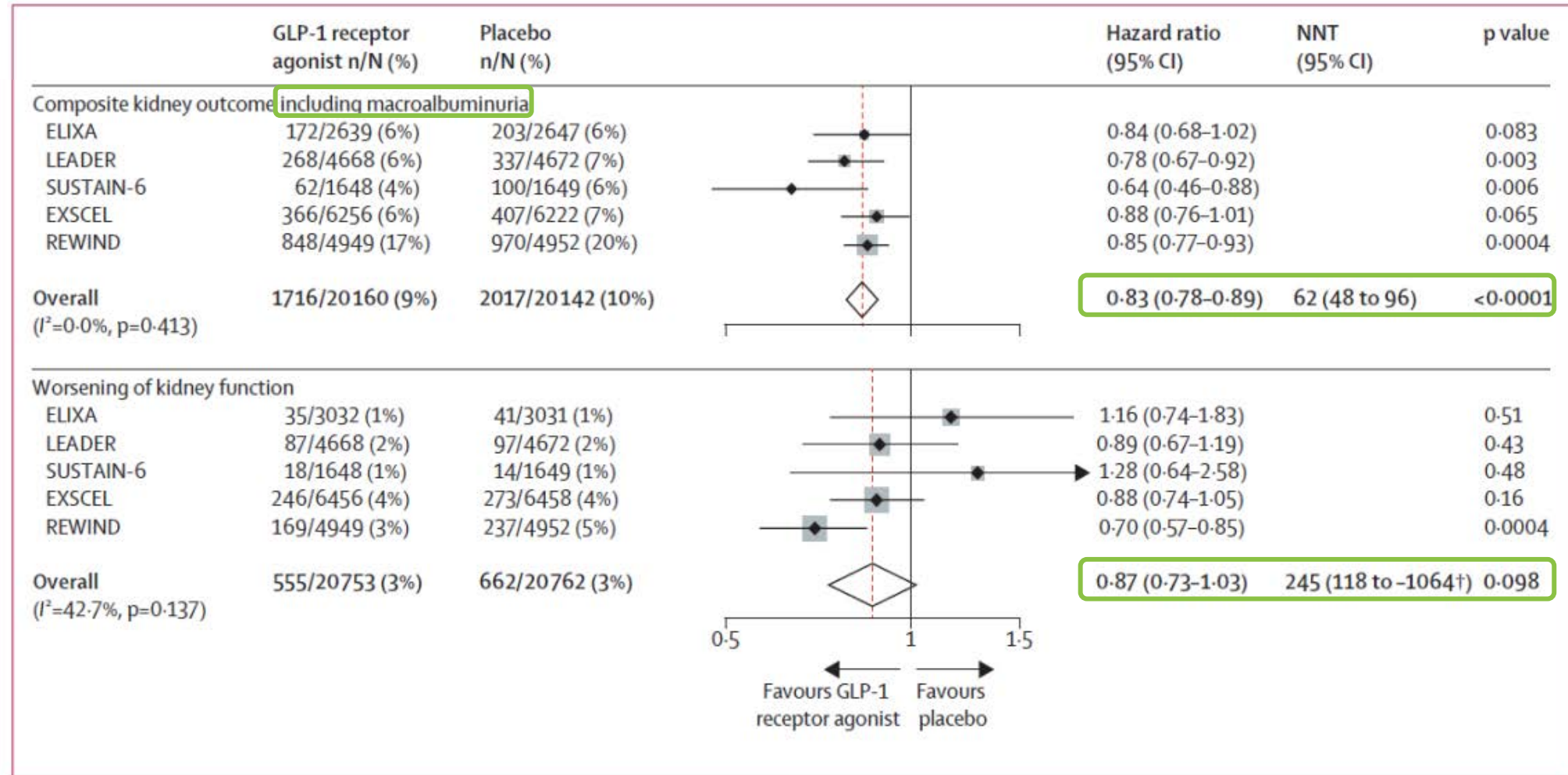
Data are reported as hazard ratios with 95% confidence intervals and p value.

Doubling of serum creatinine level and eGFR <45 mL/min/m².

ER = extended release; eGFR = estimated glomerular filtration rate; ESRD: end-stage renal disease; NR: not reported; NA: not assessed.

CARDIOVASCULAR OUTCOME TRIALS – GLP-1 RAs

Systematic review and meta-analysis of cardiovascular outcome trials



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

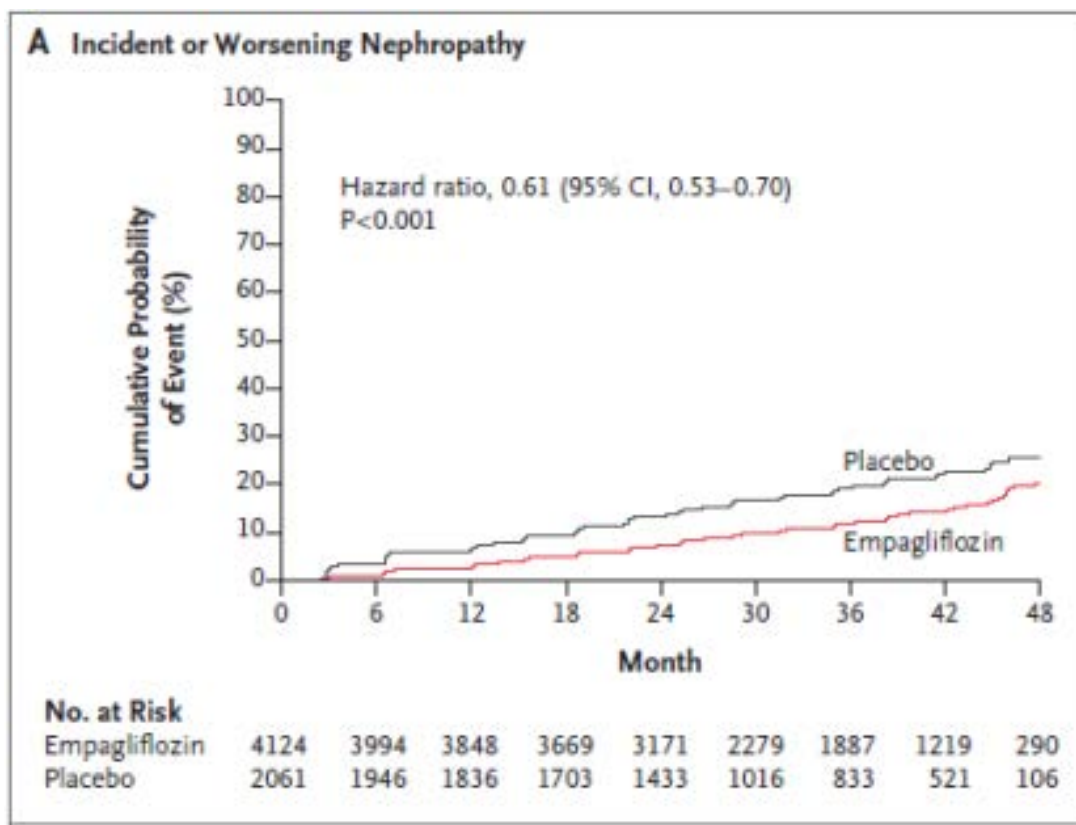
CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

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/1.73m²) (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%

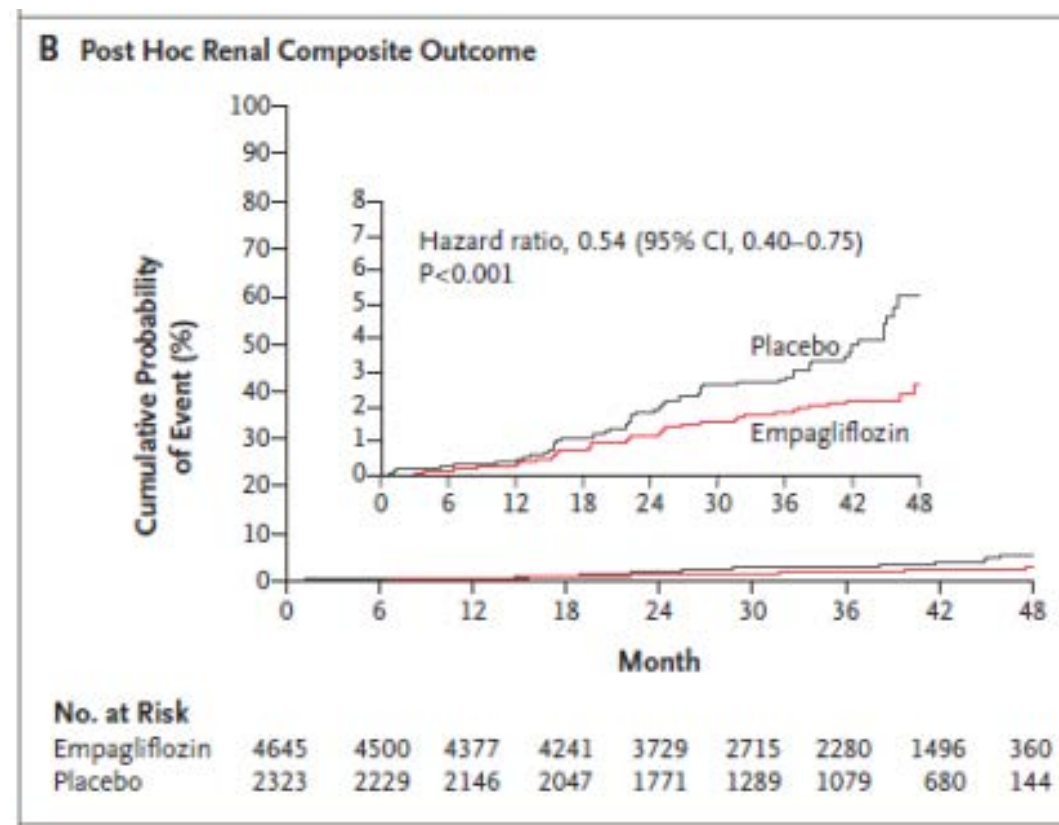
EXCL CRITERION:
eGFR <30
ml/min/1.73m²

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

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



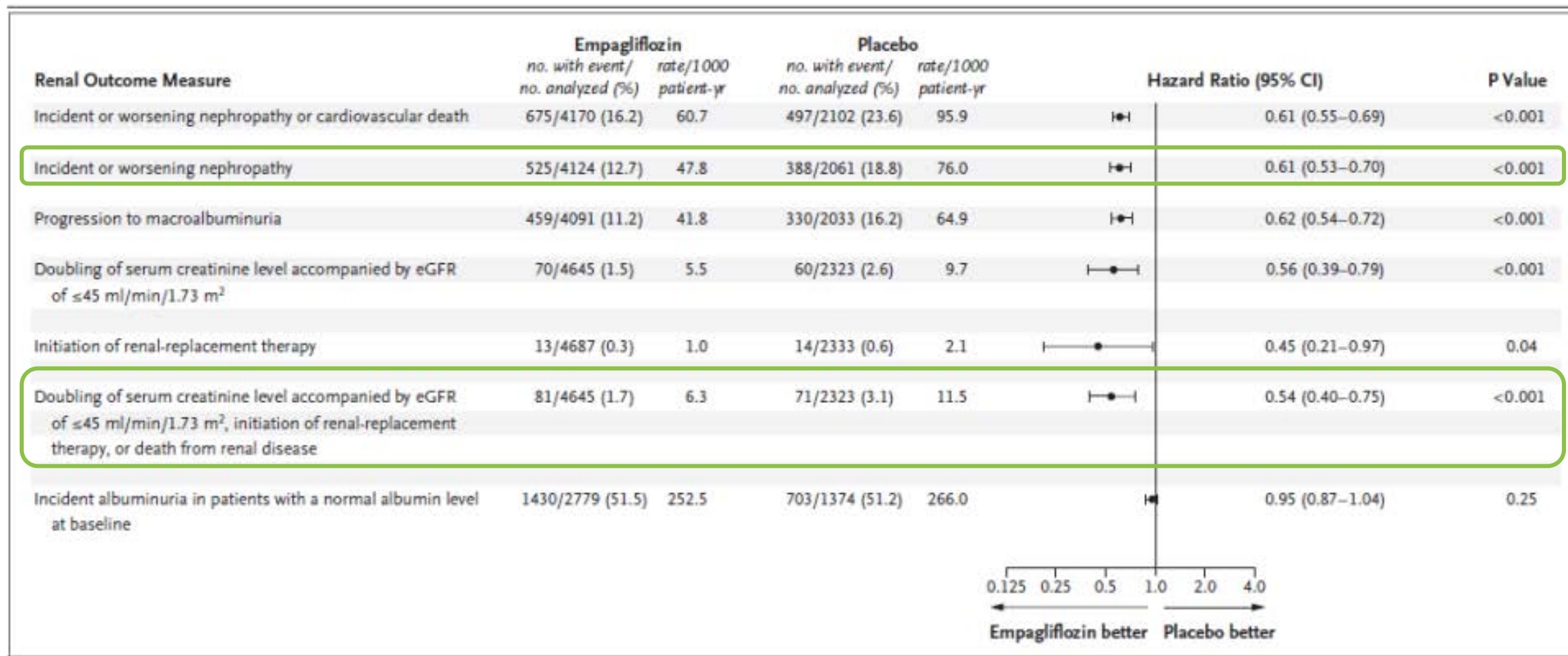
Progression to macroalbuminuria, doubling of serum creatinine level accompanied by eGFR of ≤ 45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease



Doubling of serum creatinine level accompanied by eGFR of ≤ 45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease

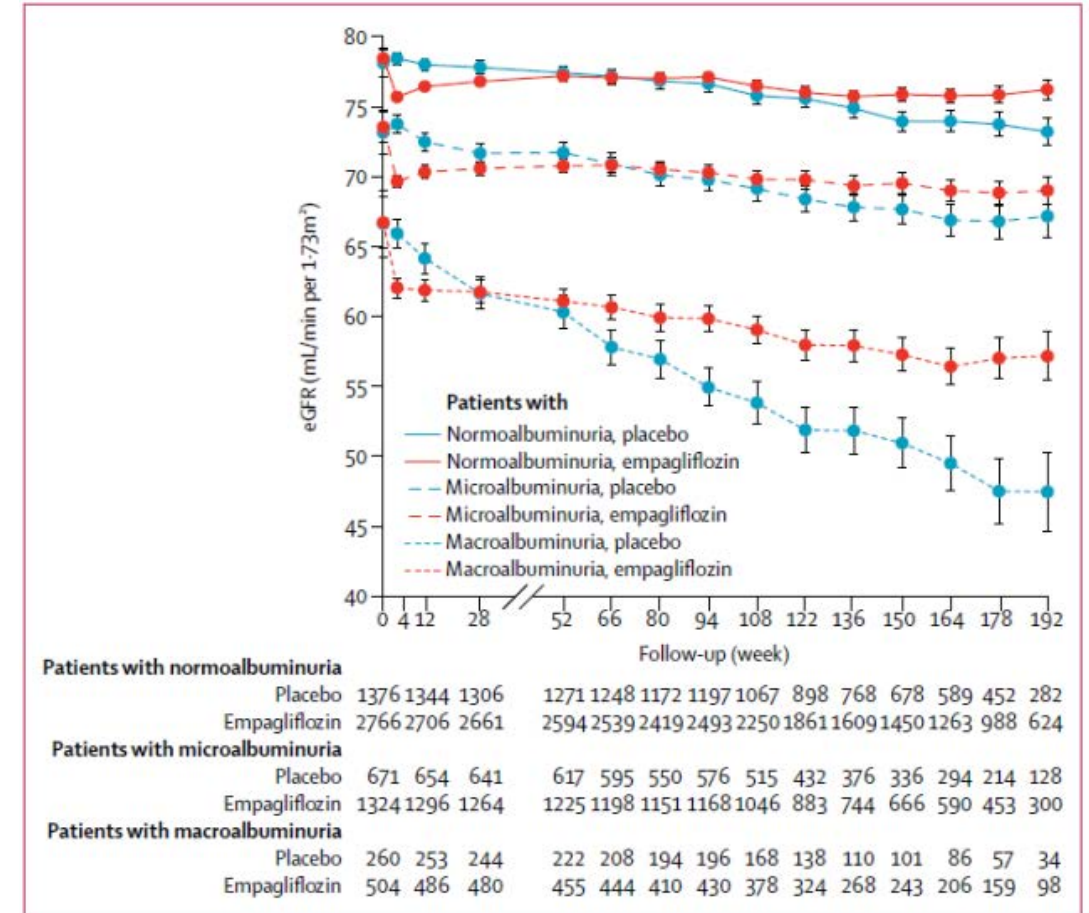
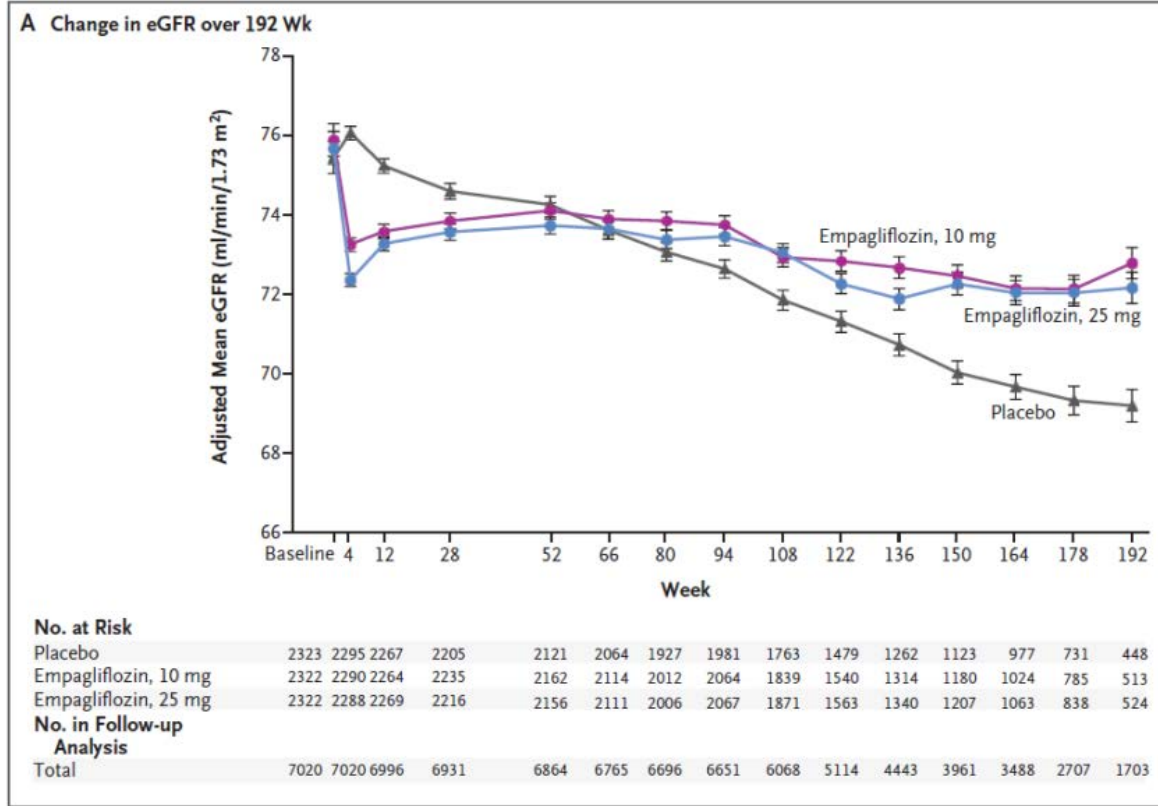
CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

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



CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

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



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%

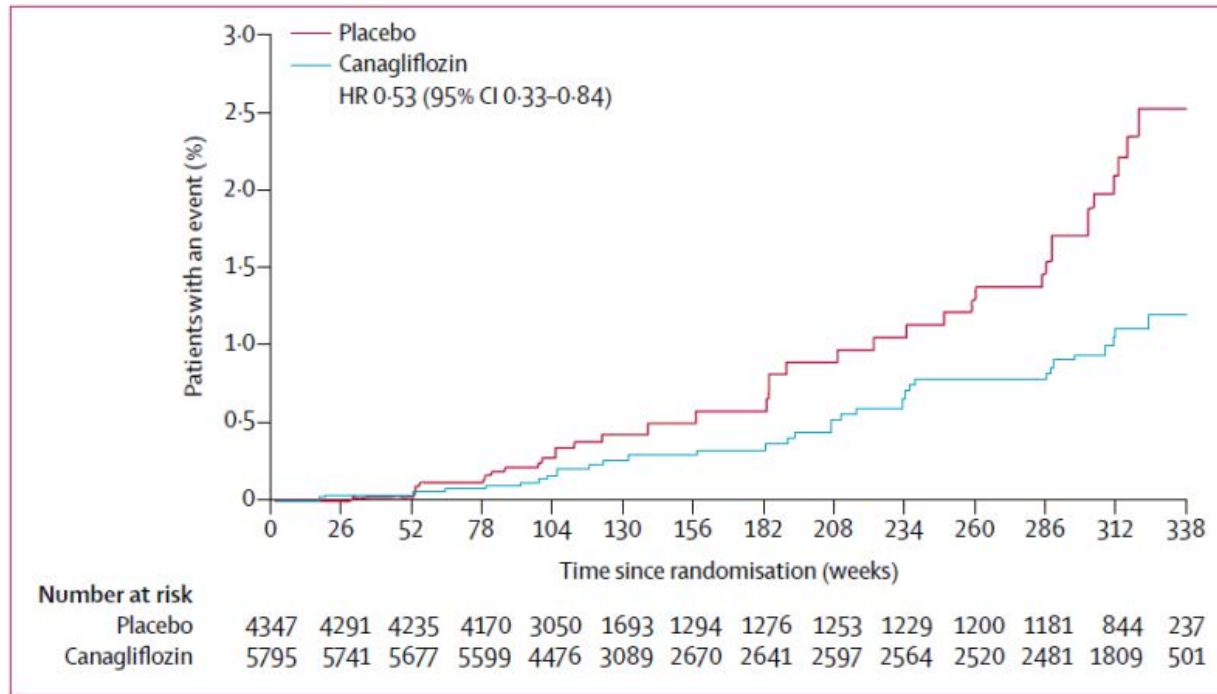
EXCL CRITERION:
eGFR <30
ml/min/1.73m²

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

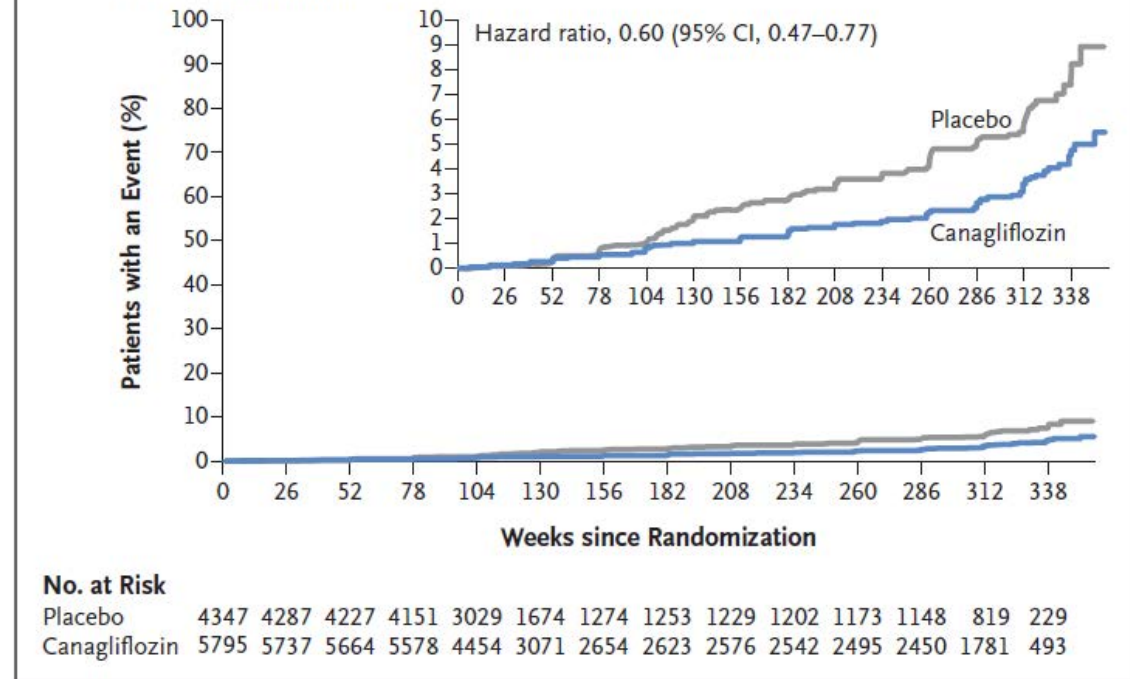
CANagliflozin cardioVascular Assessment Study (CANVAS)



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

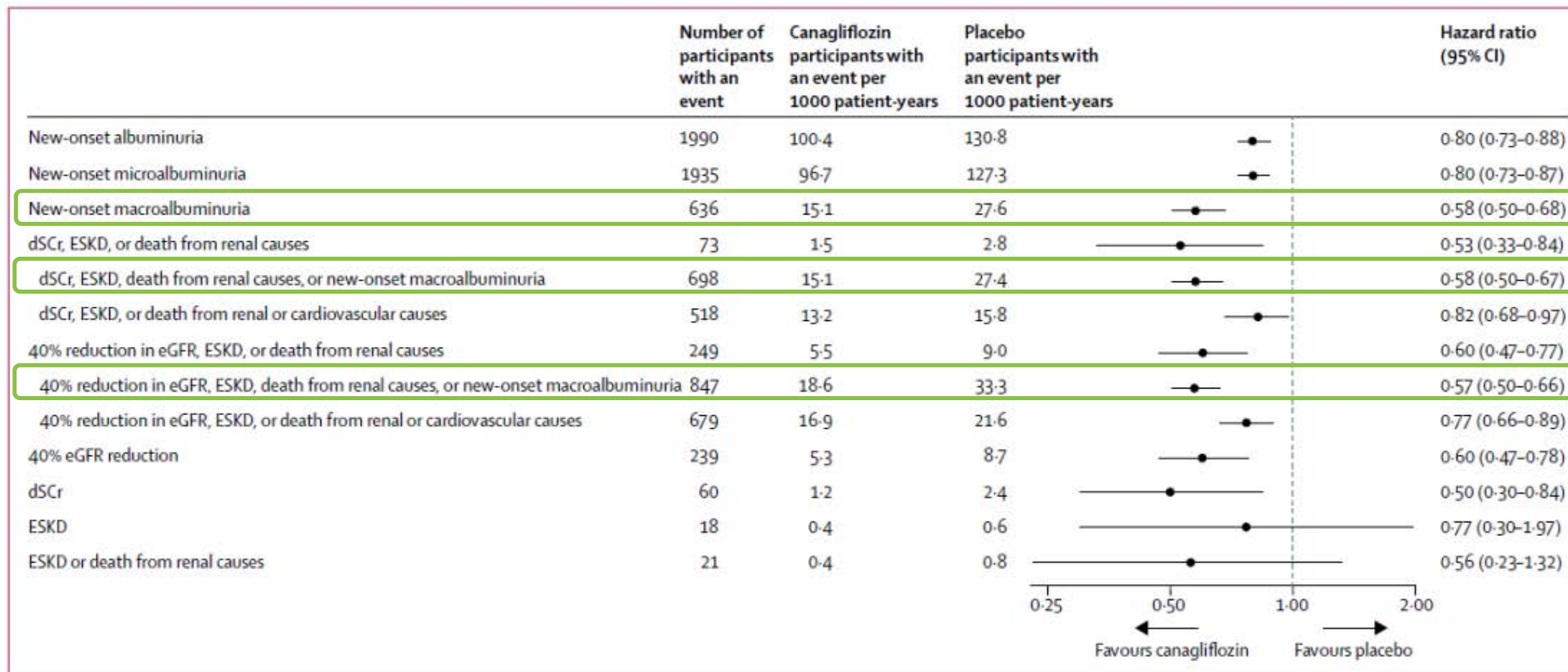


D Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes



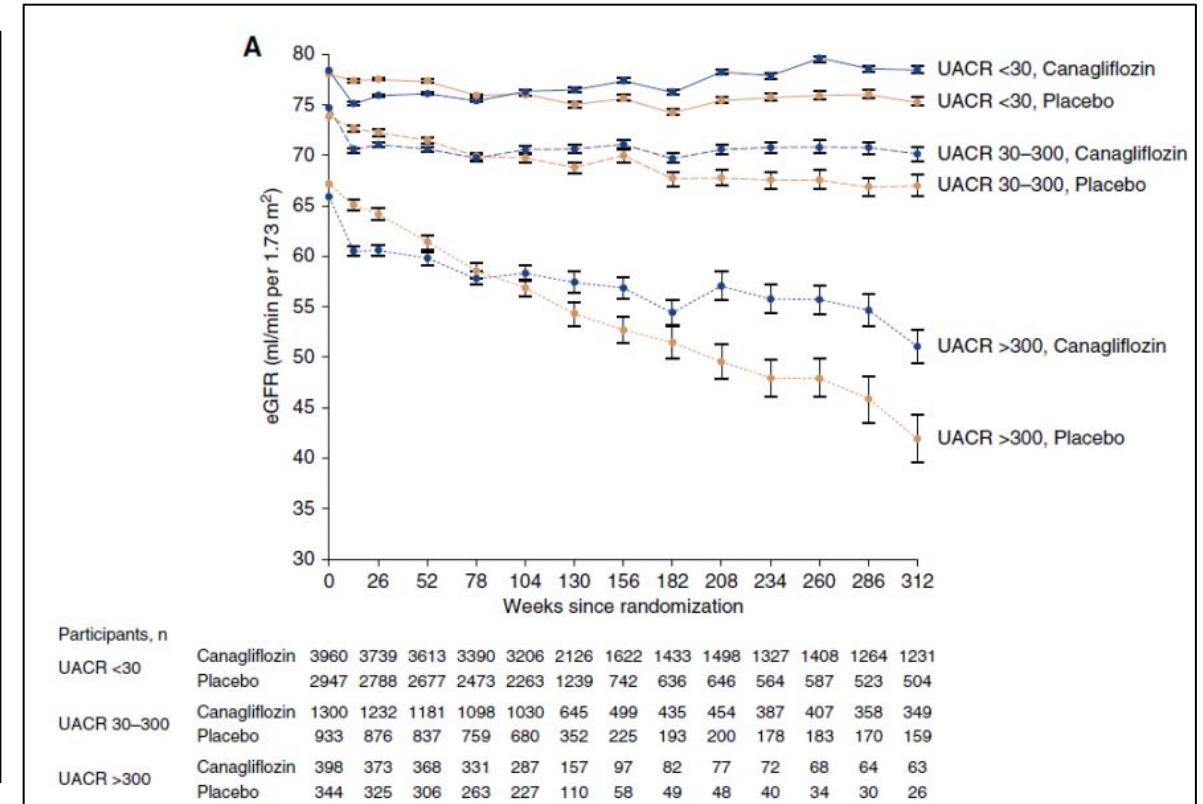
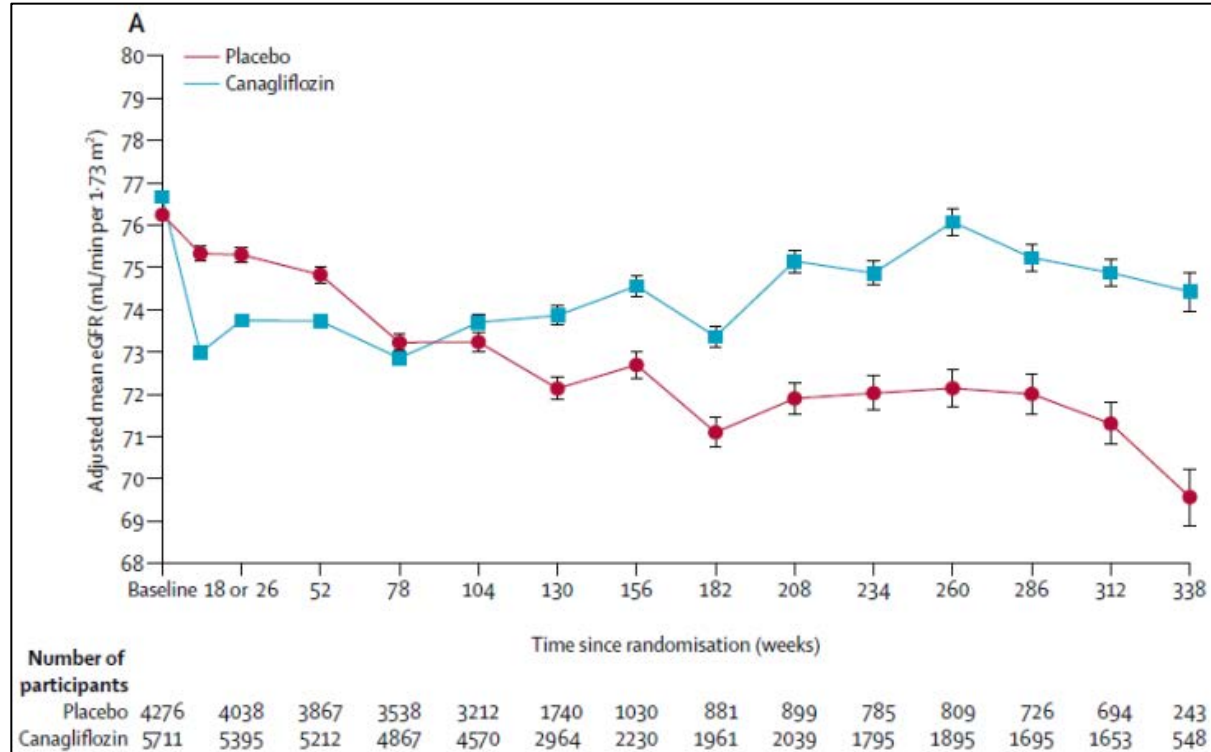
CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

CANagliflozin cardioVascular Assessment Study (CANVAS)



CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

CANagliflozin cardioVascular Assessment Study (CANVAS)



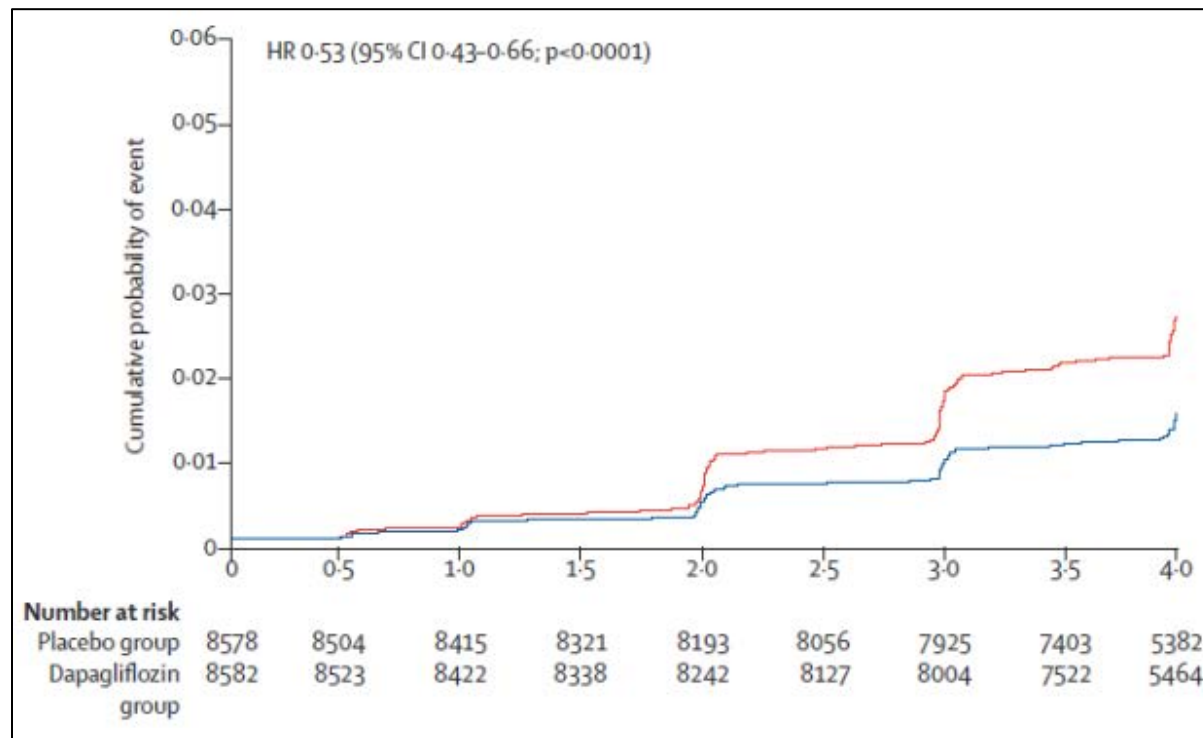
CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

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/1.73m²) (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%

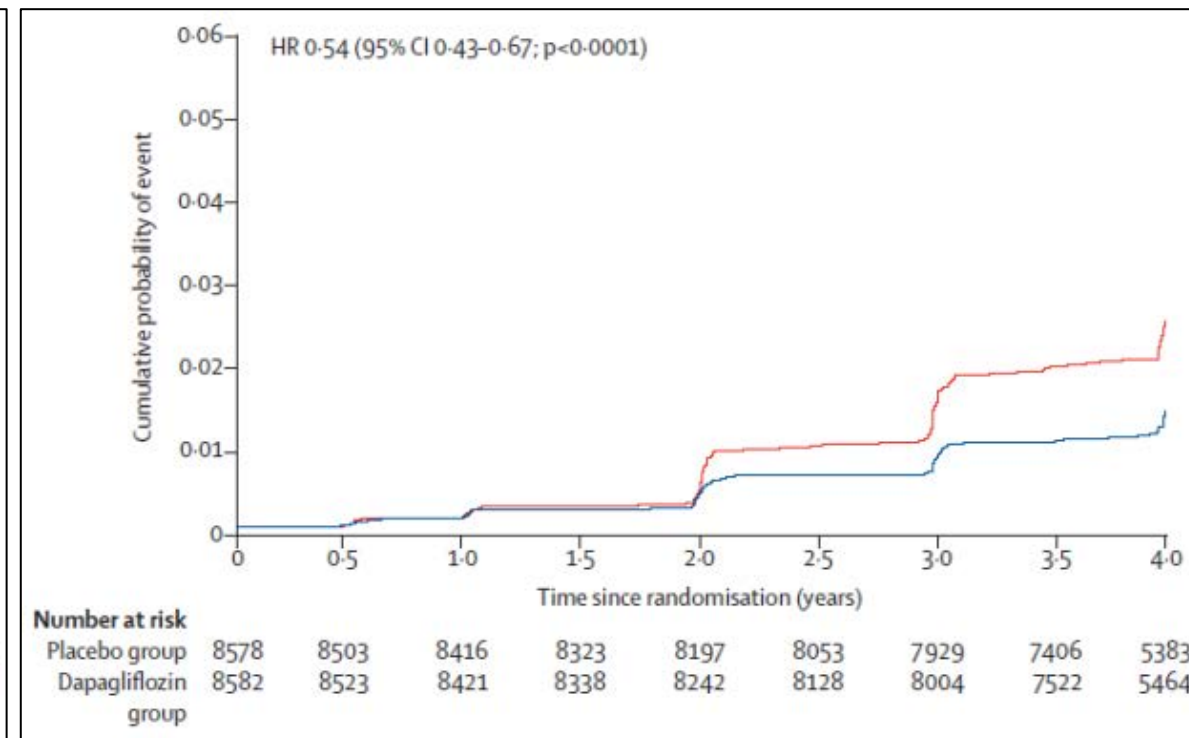
EXCL CRITERION:
eGFR <60
ml/min/1.73m²

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%

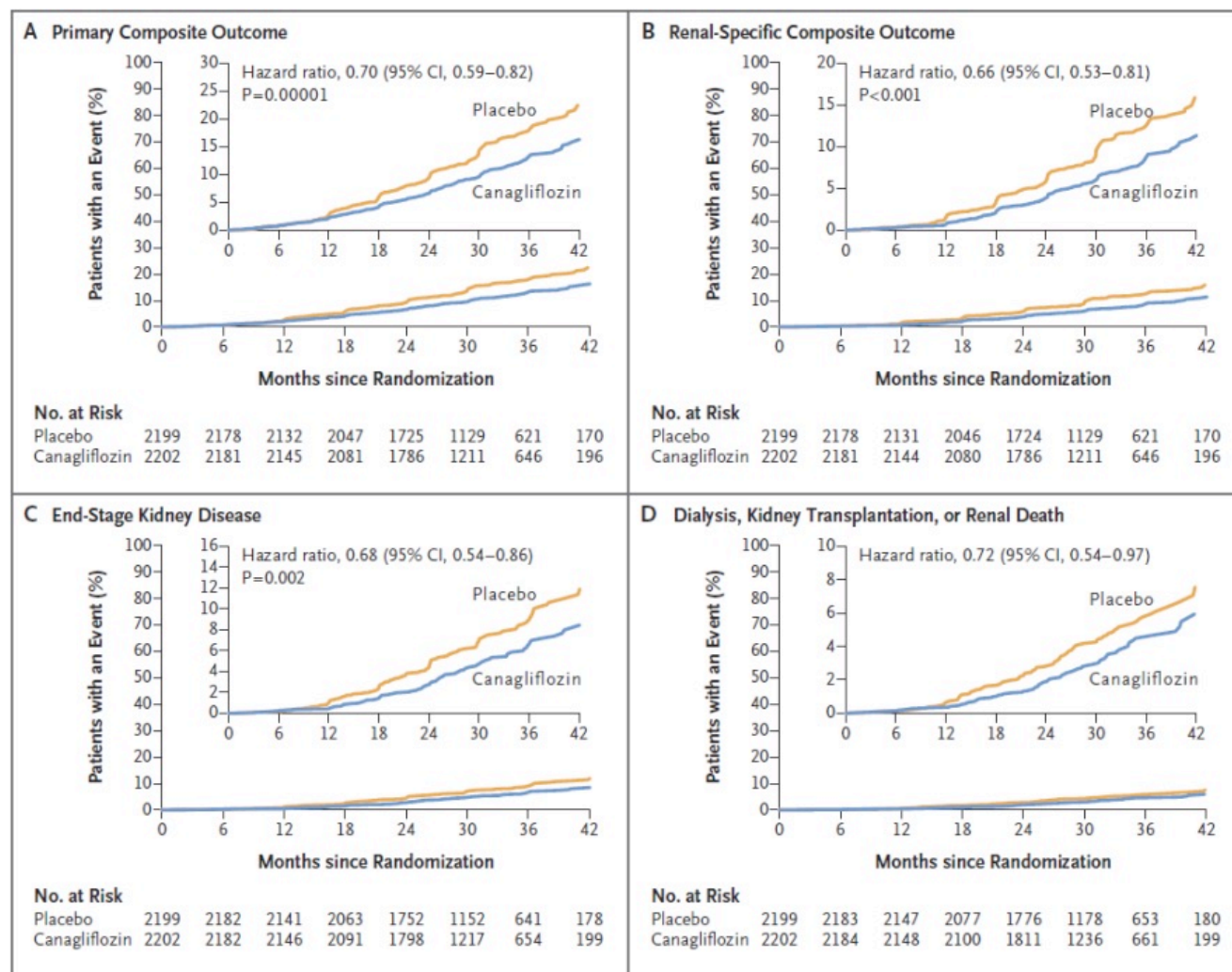
CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

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/m²
UACR >300 mg/g

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

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



CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

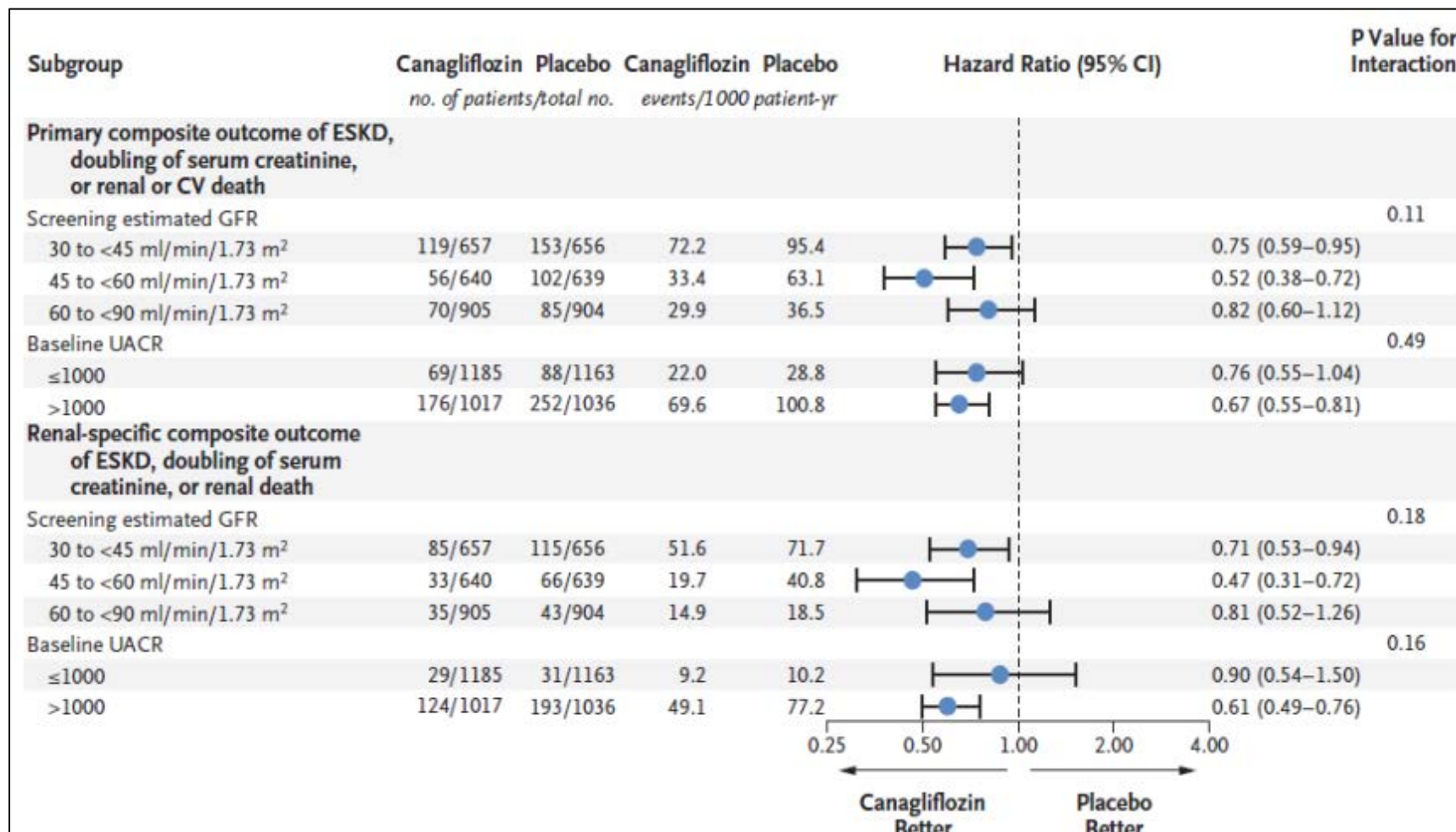
Evaluation of the Effects of **Canagliflozin** on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (**CREDENCE**)



Variable	Canagliflozin <i>no./total no.</i>	Placebo	Canagliflozin <i>events/ 1000 patient-yr</i>	Placebo	Hazard Ratio (95% CI)	P Value
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

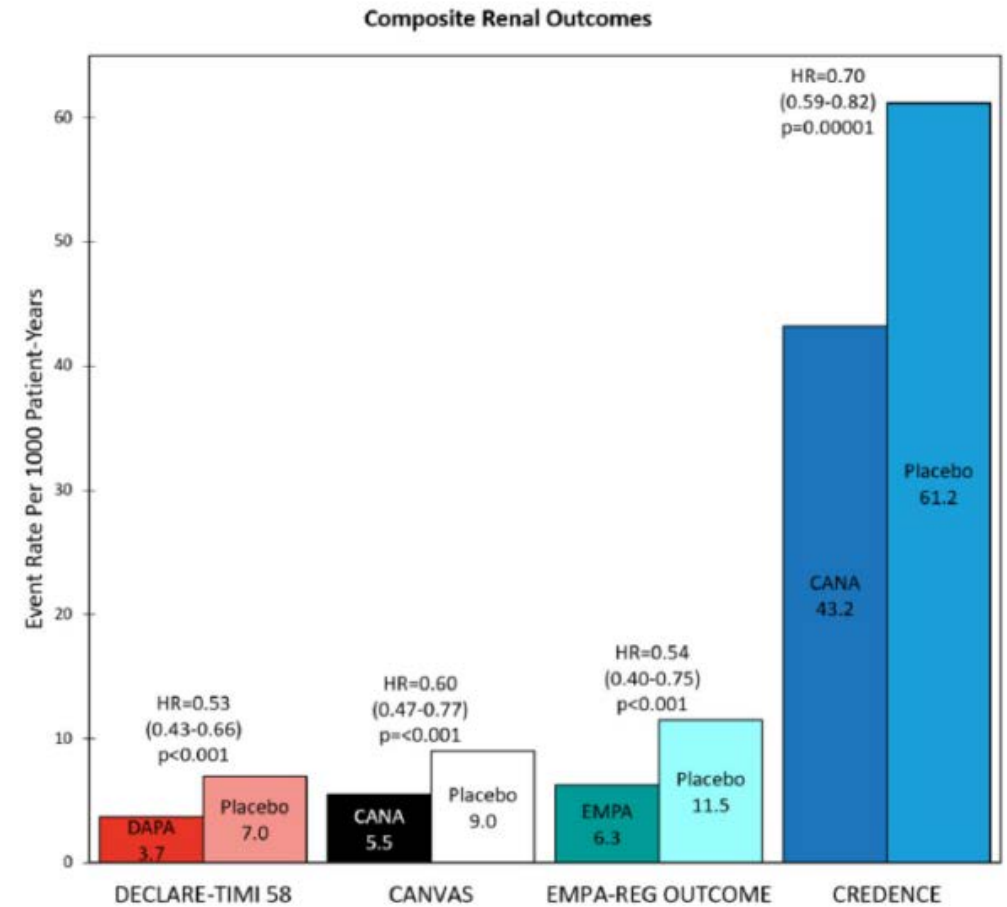
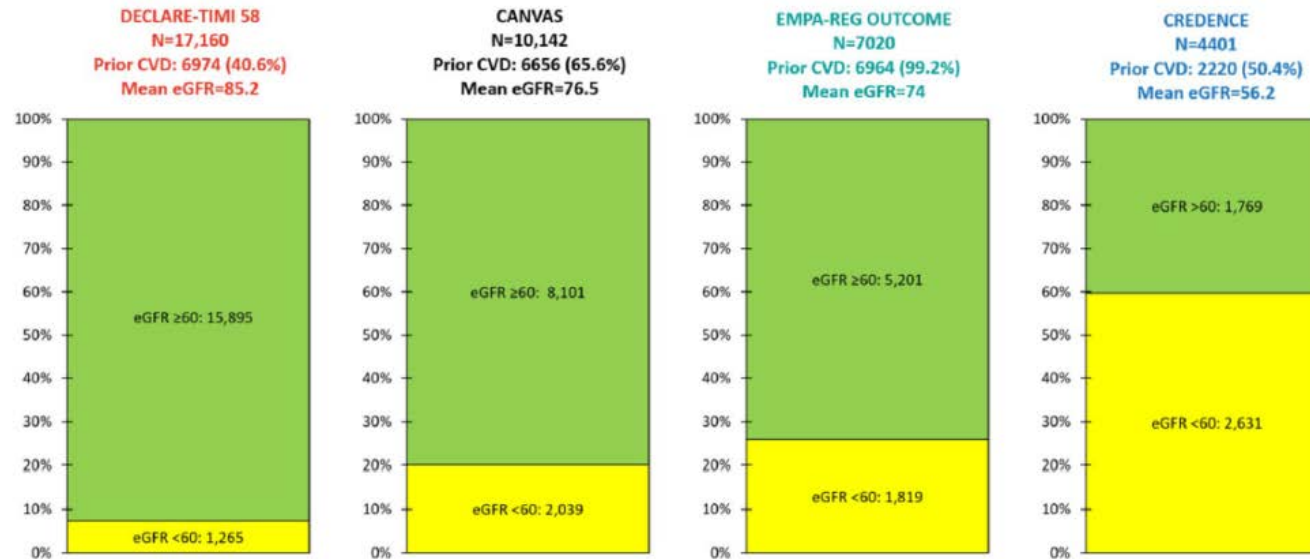
CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

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



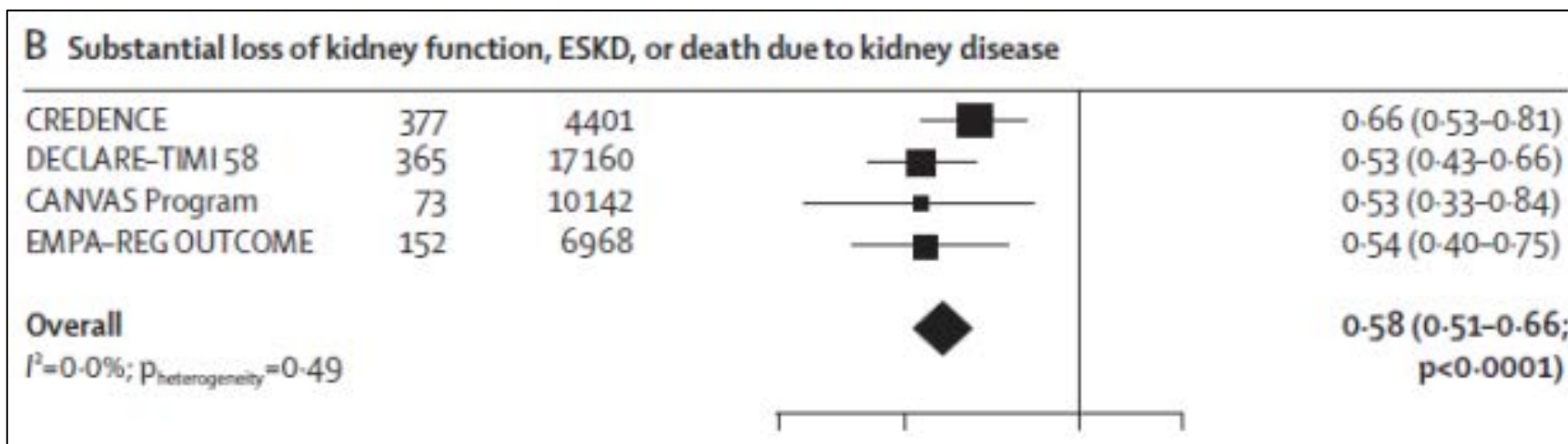
CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Class effects of SGLT2 inhibitors on cardiorenal outcomes

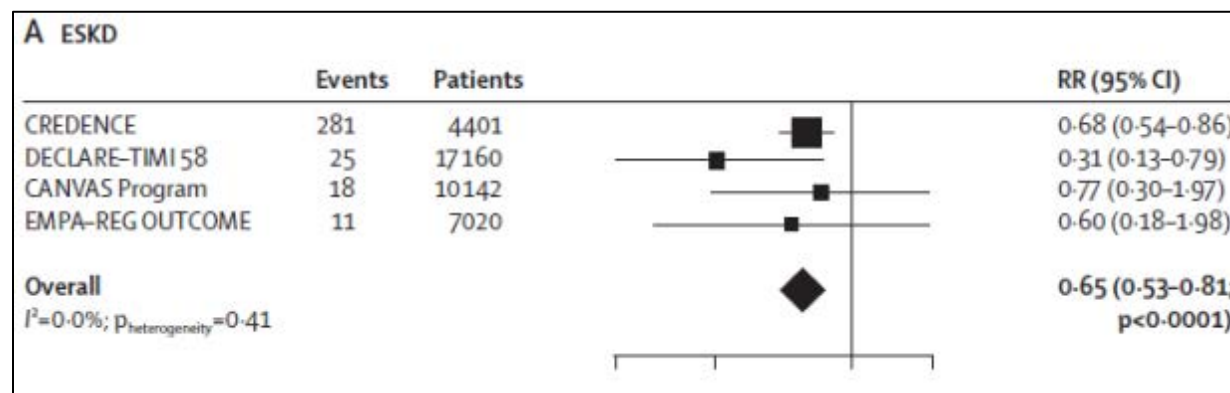


CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

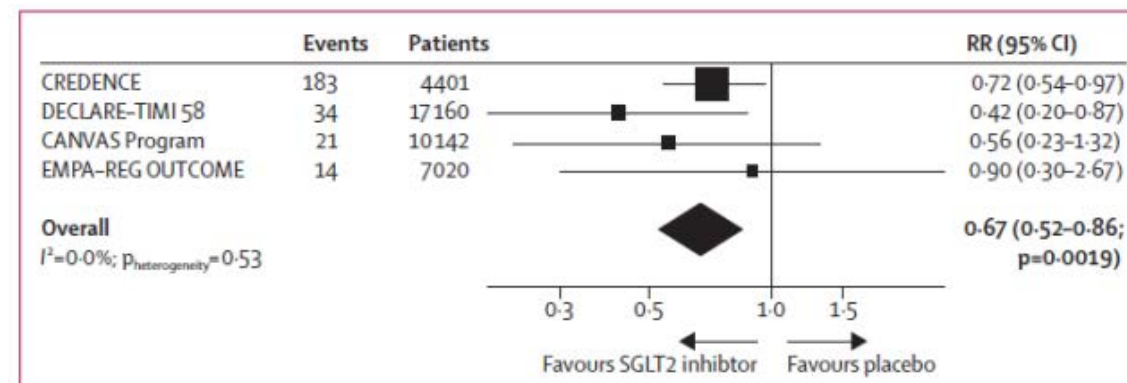
Meta-analysis on hard renal endpoints



- 42%



- 35%

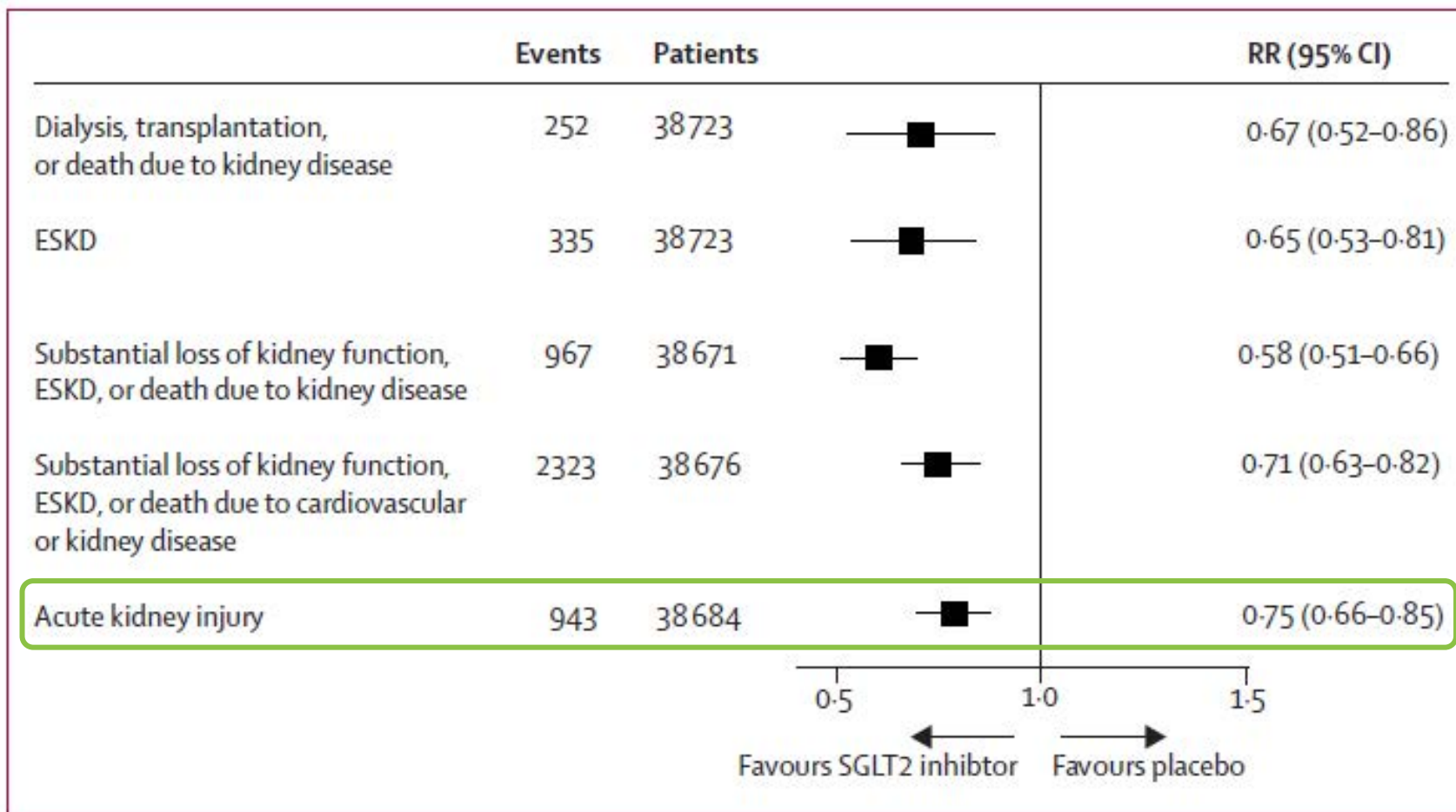


- 33%

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

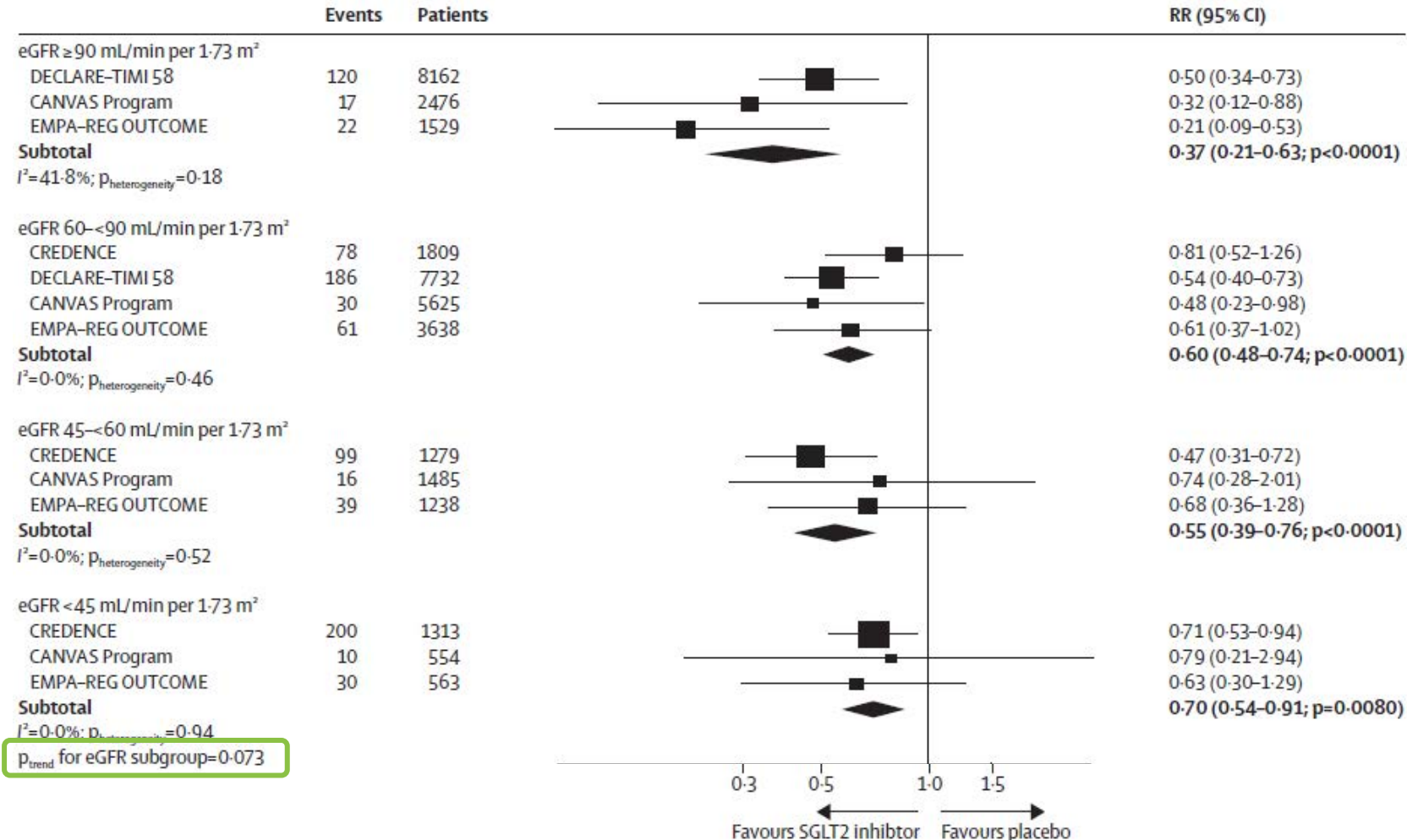
CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

Summary of the effects of SGLT2 inhibition on major kidney outcomes



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: $p_{\text{trend}}=0.66$
- Effect between users and non-users of RAS-Is: $p_{\text{heterogeneity}}=0.31$

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

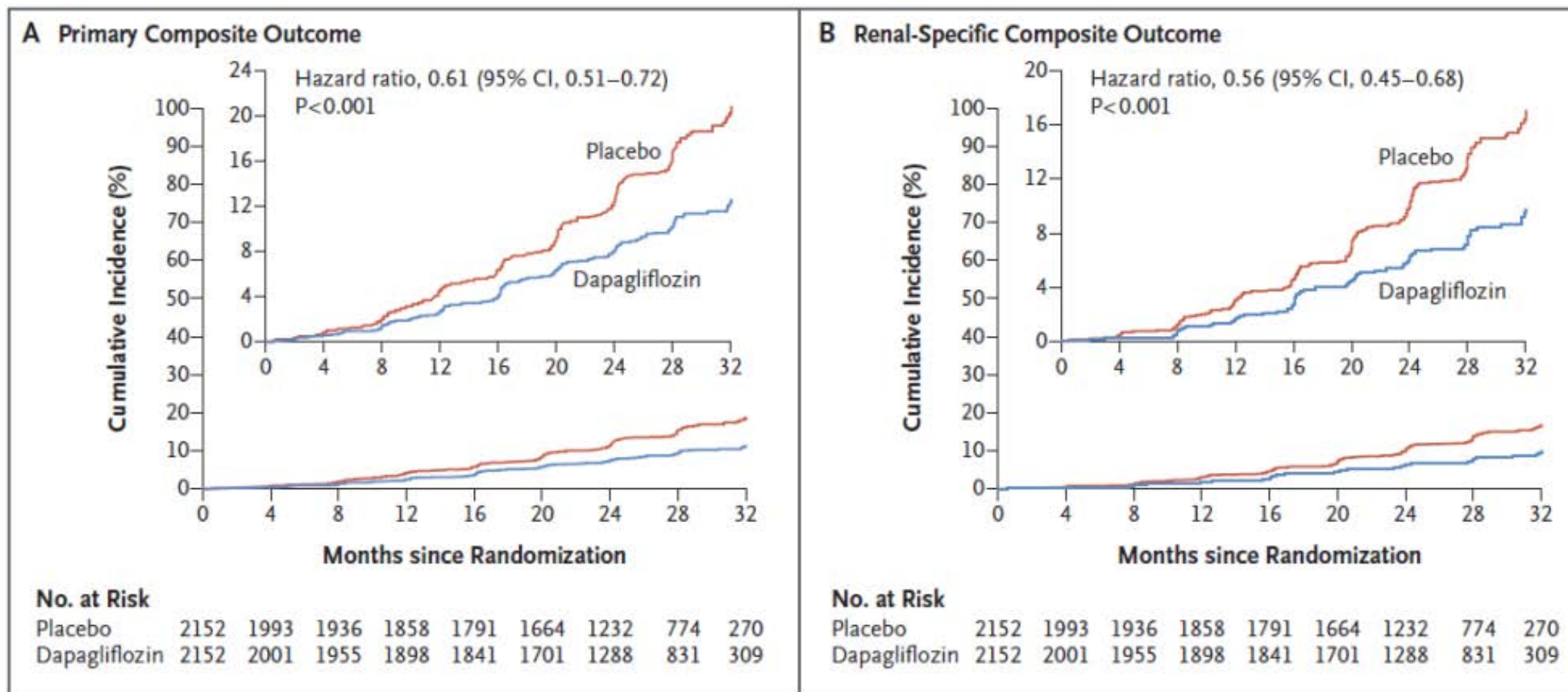
Trial	EMPA-REG OUTCOME	CANVAS Program	DECLARE- TIMI 58	CREDENCE	DAPA-CKD
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin
Participants, n (active drug/placebo)	7,020 (4,687/2,333)	10,142 (5,795/4,347)	17,160 (8,582/8,578)	4,401 (2,202/2,199)	4,304 (2,152/2,152)
Median follow-up, 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/m²
UACR 200-5000 mg/g

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**)



Sustained decline in eGFR $\geq 50\%$, ESRD, or death from renal or cardiovascular causes

Sustained decline in eGFR $\geq 50\%$, ESRD, or death from renal causes

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**)



	Number of Events				
	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value
Primary Composite Outcome					
Composite of $\geq 50\%$ eGFR Decline, ESKD, or Renal or CV Death	197	312	0.61	(0.51, 0.72)	0.000000028
Components of the Primary Composite Outcome					
$\geq 50\%$ 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

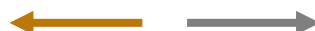
0.30

0.60

1.00

1.25

DAPA 10 mg Better Placebo Better



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**)



HR (95% CI)	Number of Events				
	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					
Yes	152	229	0.64	(0.52, 0.79)	0.24
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					
≤1000	44	84	0.54	(0.37, 0.77)	0.52
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m²) at Baseline					
<45	152	217	0.63	(0.51, 0.78)	0.22
≥45	45	95	0.49	(0.34, 0.69)	

0.13 0.50 1.00 1.25

DAPA 10 mg Better ← → Placebo Better

CARDIOVASCULAR and RENAL OUTCOME TRIALS – SGLT2-Is

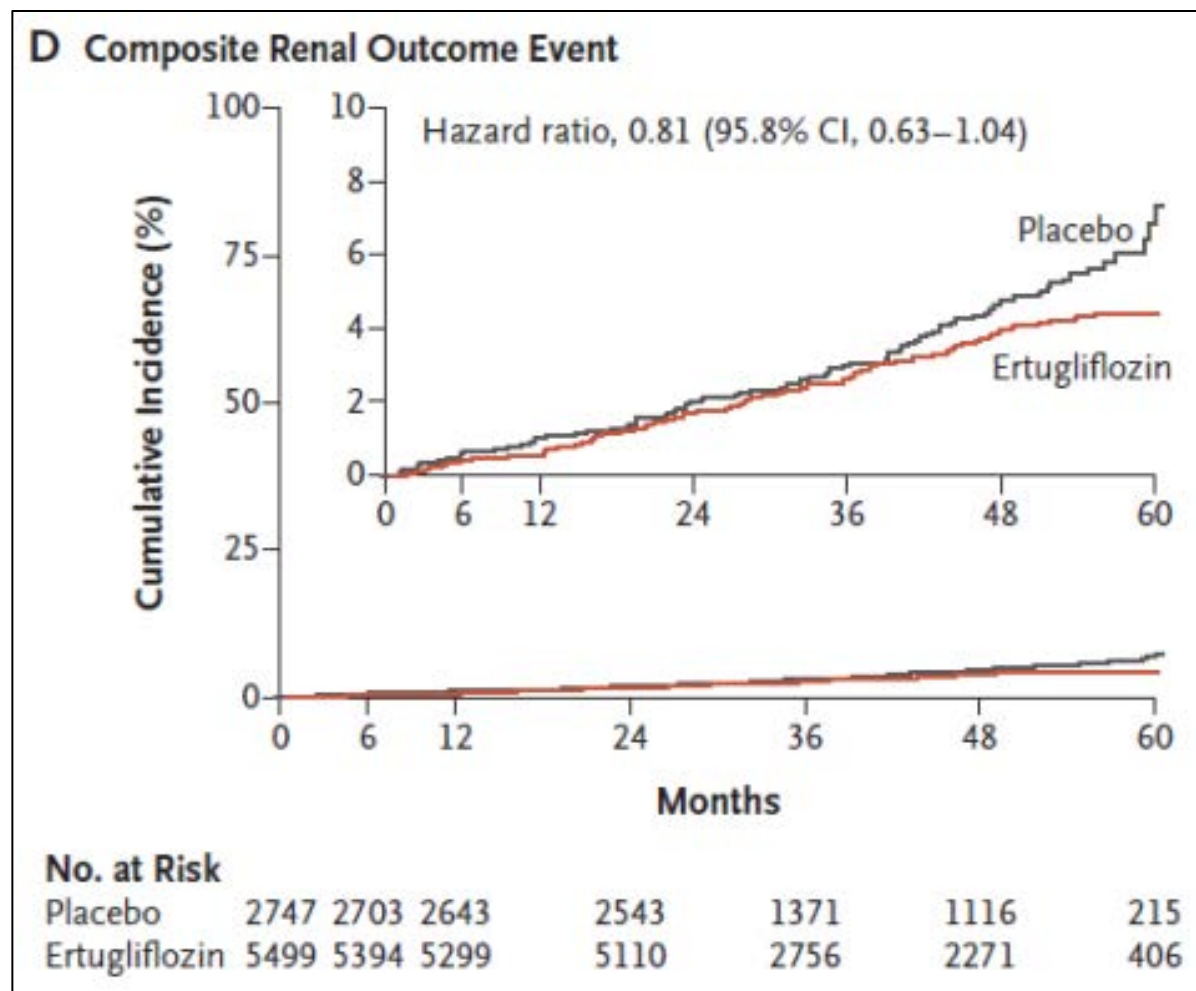
Trial	EMPA-REG OUTCOME	CANVAS Program	DECLARE- TIMI 58	CREDENCE	DAPA-CKD	VERTIS CV
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Participants, n (active drug/placebo)	7,020 (4,687/2,333)	10,142 (5,795/4,347)	17,160 (8,582/8,578)	4,401 (2,202/2,199)	4,304 (2,152/2,152)	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/1.73m²

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

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



- **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 m²
→ -5.80 ml/min/1.73 m² in macroalbuminuria group

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	Dapagliflozin	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)	4,738 (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/1.73m 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	66.0/65.5	61.8/62.2
Renal function at baseline					EXCL CRITERION: eGFR <30 or <20 ml/min/1.73m ²			
Normal (eGFR ≥90)	21.9%	24.4%	47.6%	4.8%	4.8%	78.1%	59.4%	51.7%
Mild impairment (eGFR 60-89)	52.2%	55.5%	45.0%	35.4%	35.4%	21.9%	40.6%	48.3%
Moderate impairment (eGFR 30-59)	25.9%	20.1%	7.4%	55.9%	75.8%	-	-	-
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**



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**)



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:

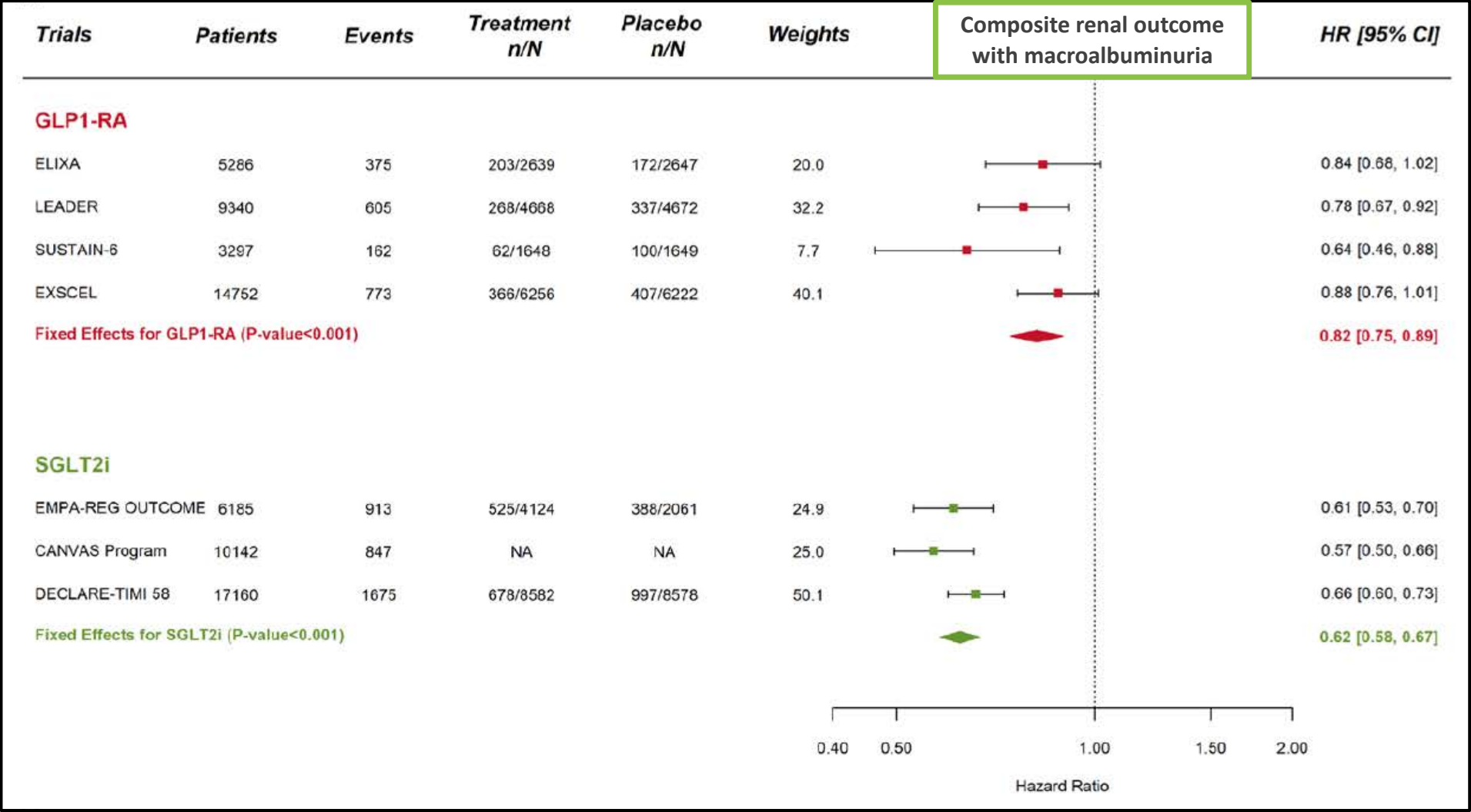
kidney disease progression or
cardiovascular death

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

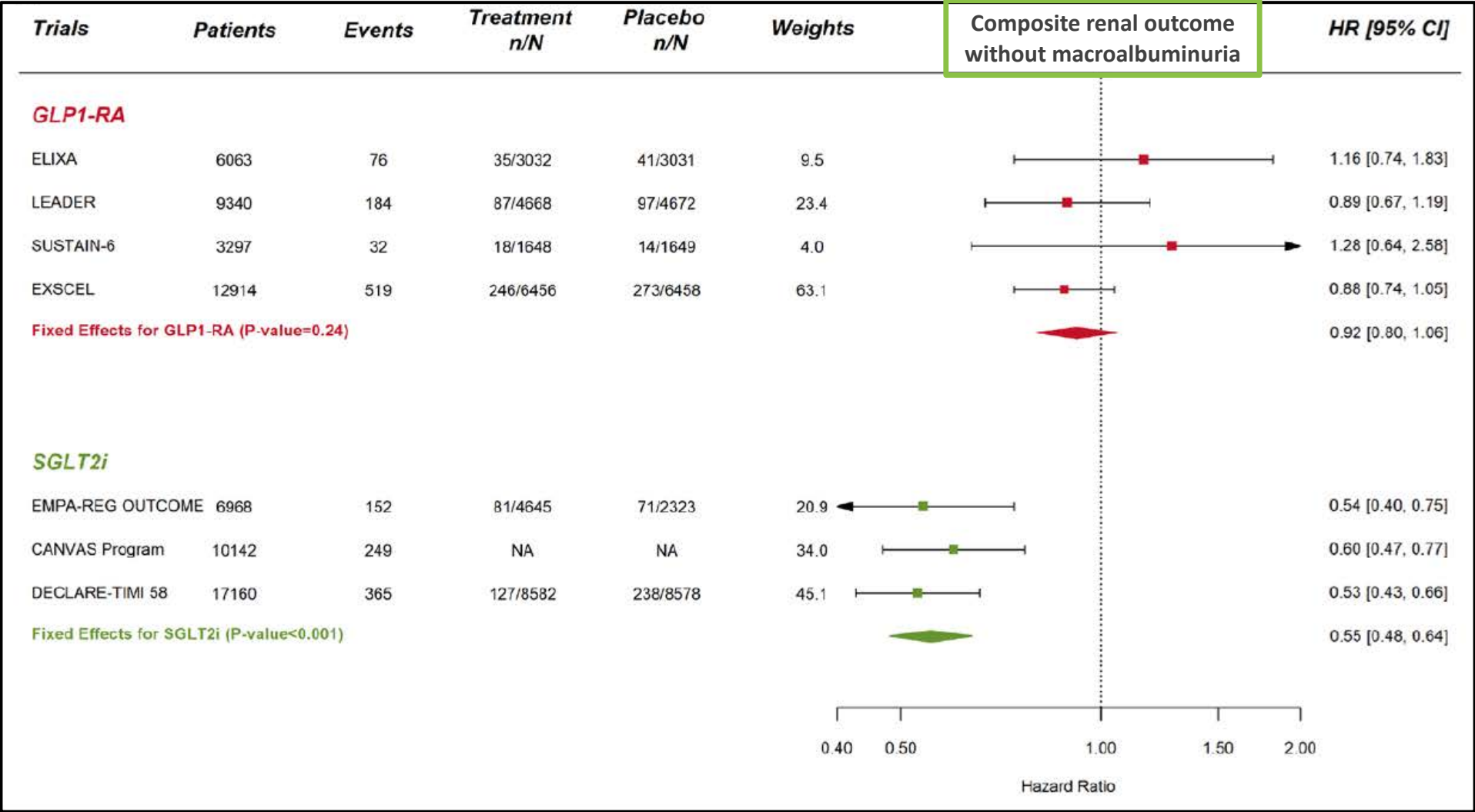
COMPARISON GLP-1 RAs/SGLT2-Is

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



COMPARISON GLP-1 RAs/SGLT2-Is

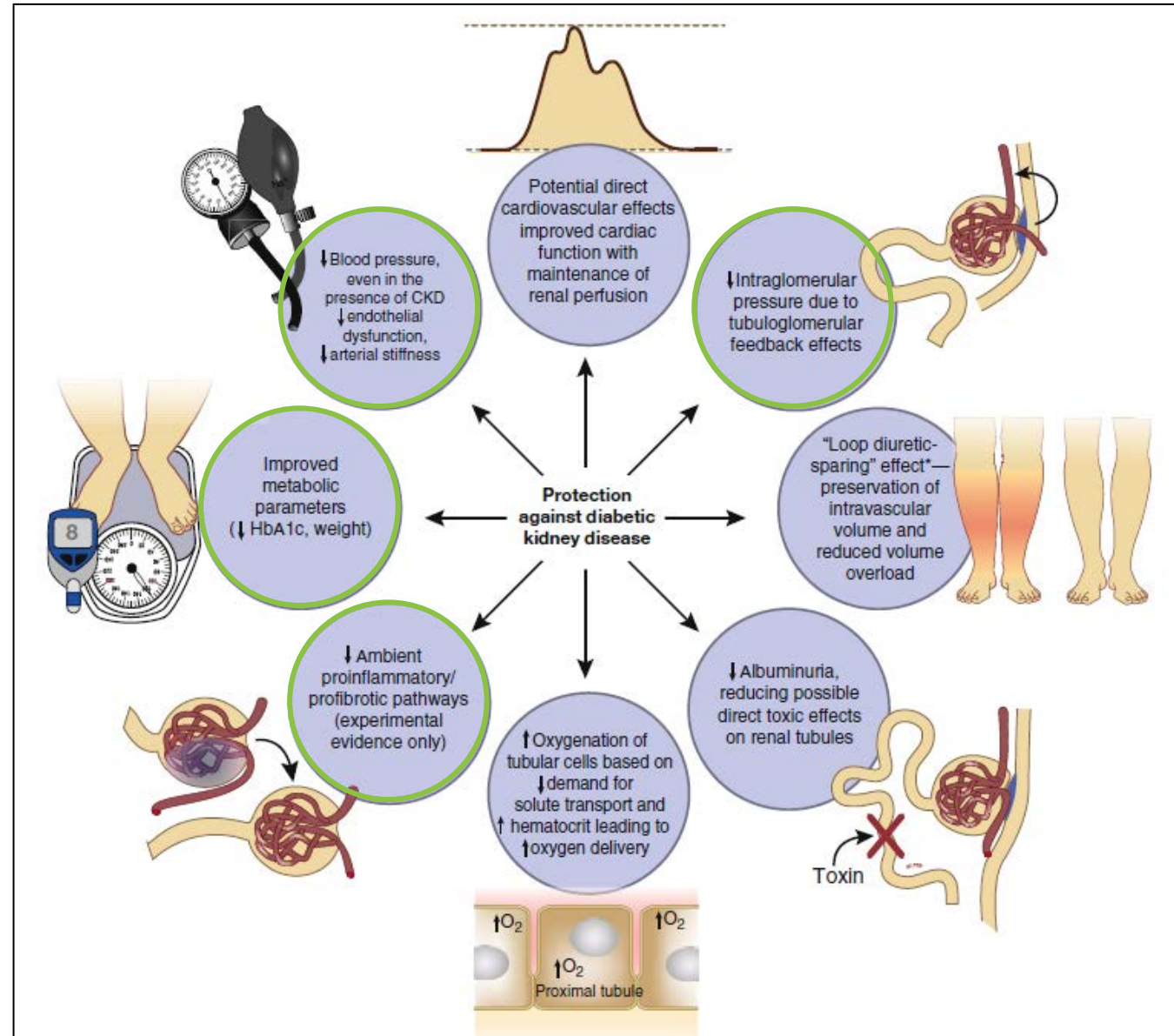
Comparison of the Effects of GLP-1 RAs and SGLT2-Is for Prevention of Renal Outcomes in Type 2 Diabetes Mellitus



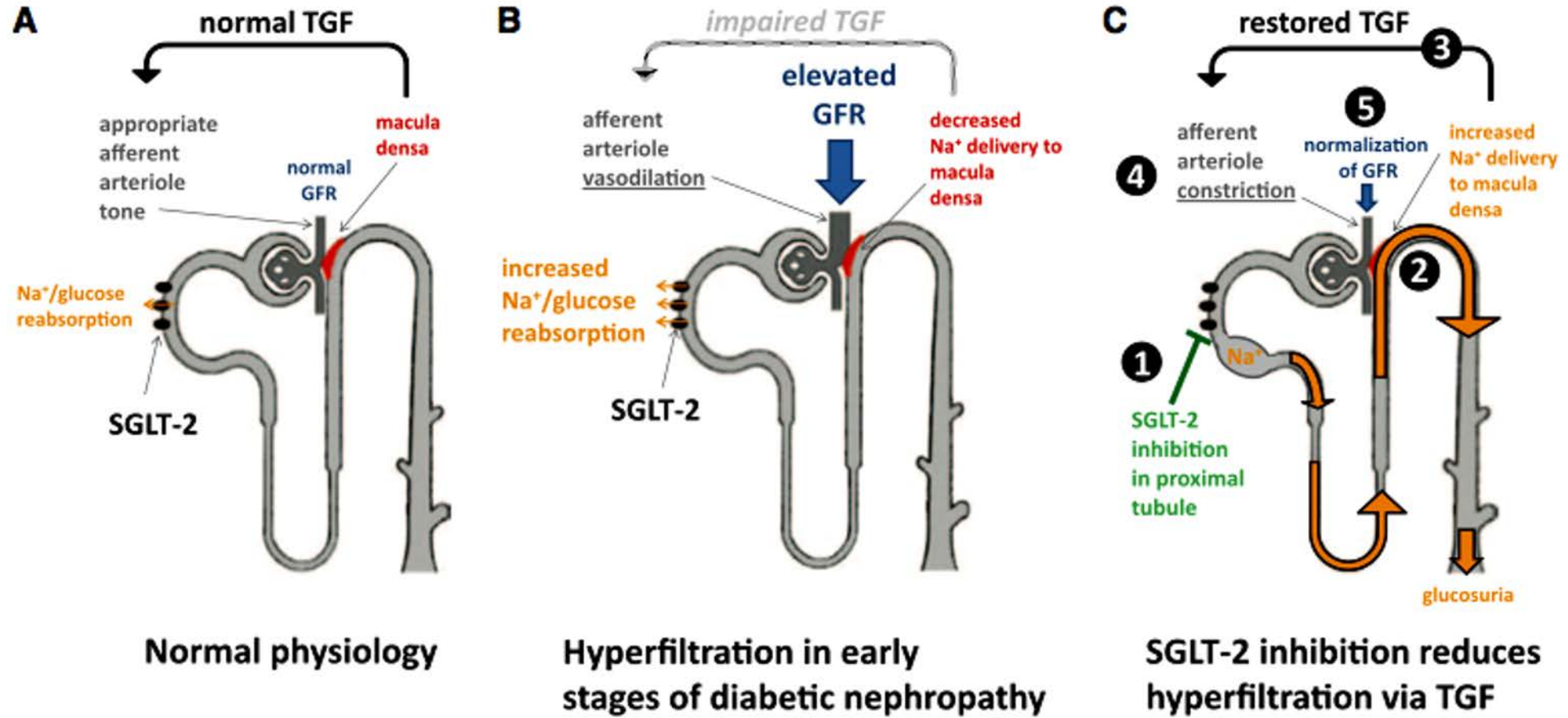
AGENDA

- 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

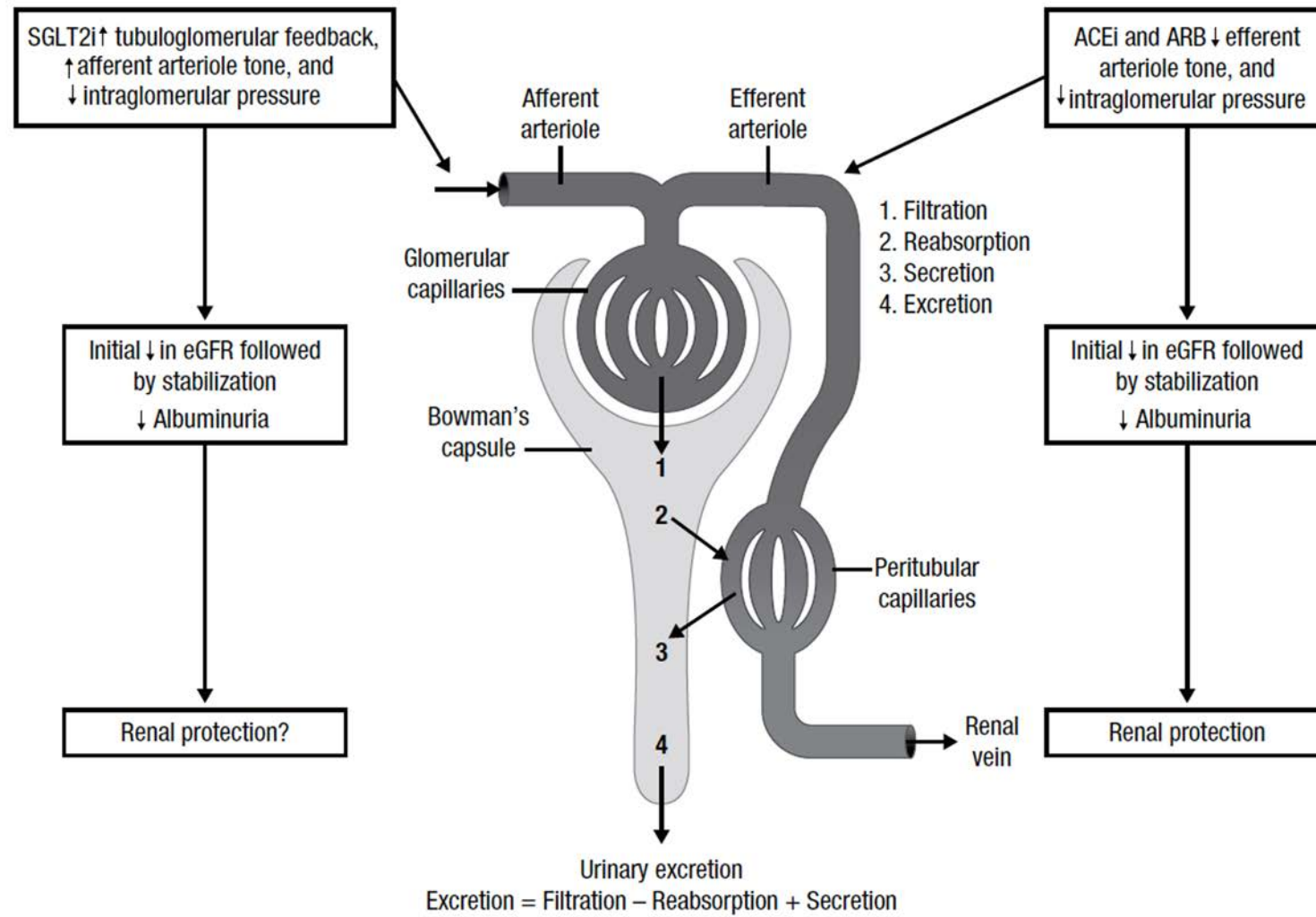
MECHANISMS OF RENAL PROTECTION BY SGLT2-Is



MECHANISMS OF RENAL PROTECTION BY SGLT2-Is



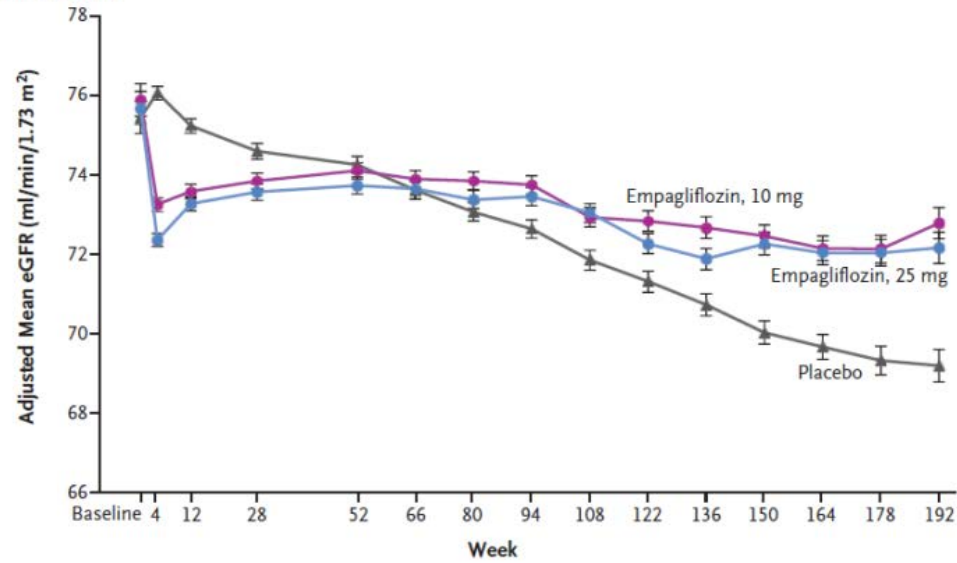
MECHANISMS OF RENAL PROTECTION BY SGLT2-Is



MECHANISMS OF RENAL PROTECTION BY SGLT2-Is



A Change in eGFR over 192 Wk



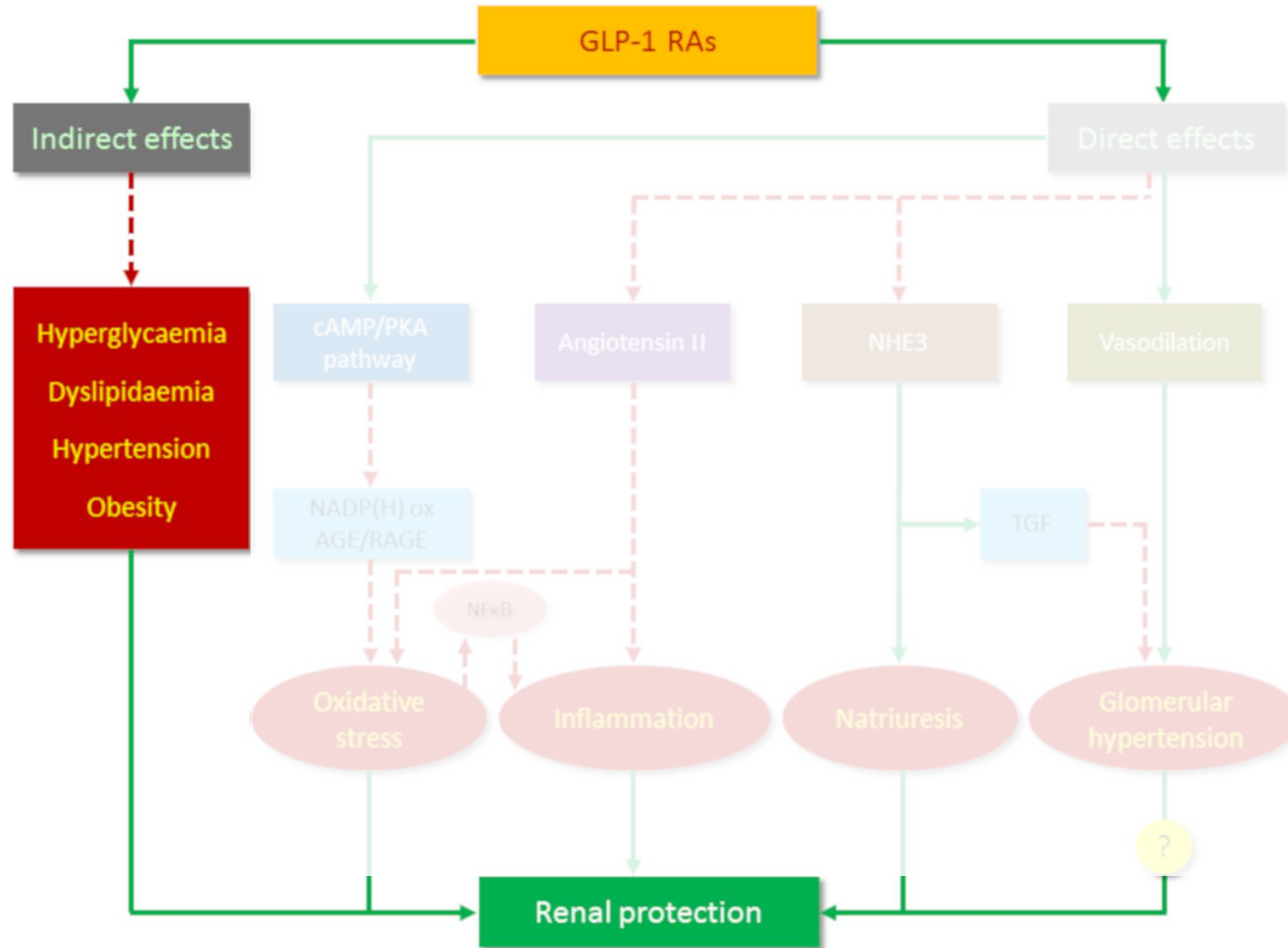
No. at Risk

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

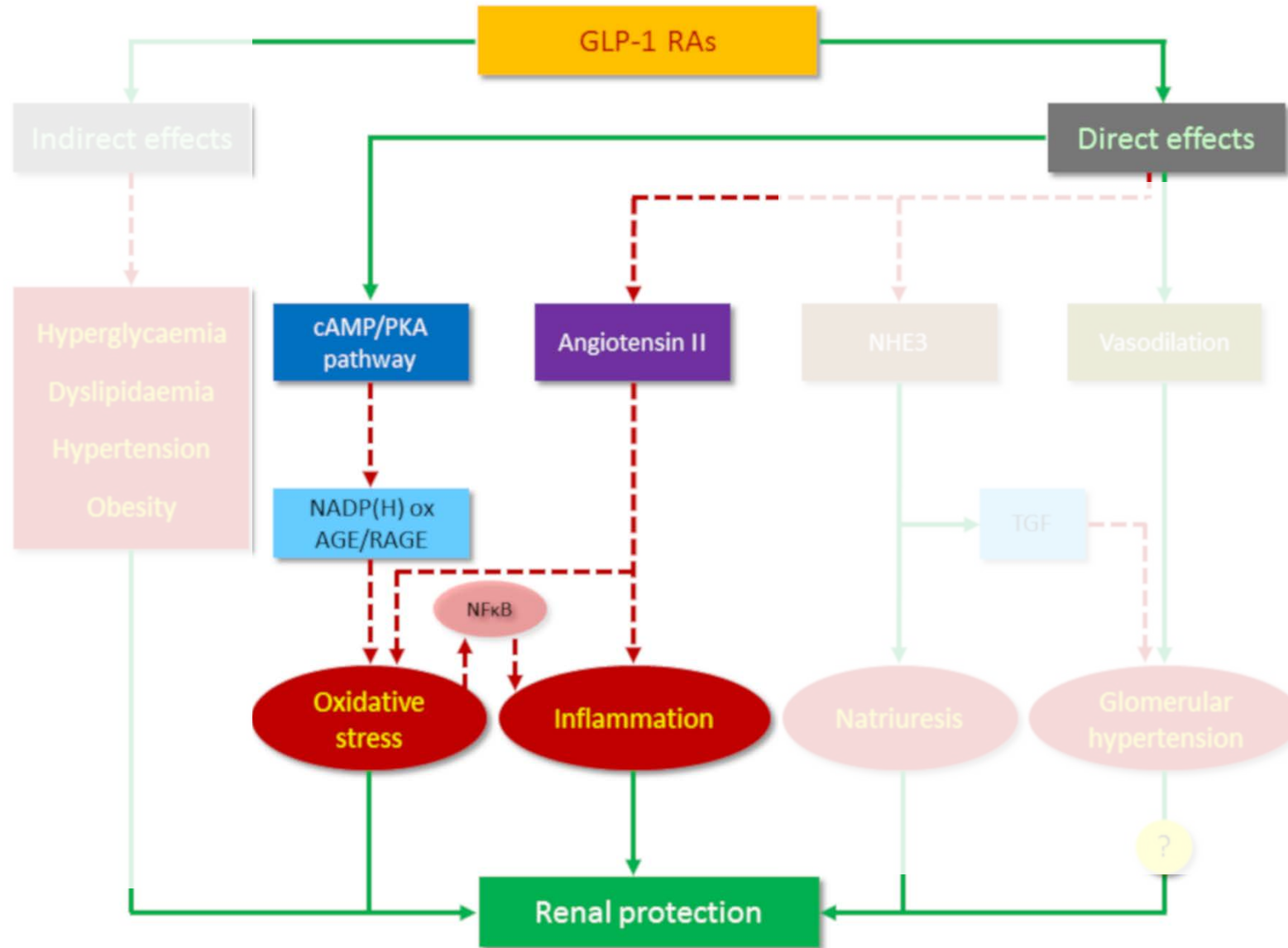
No. in Follow-up Analysis

Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703
-------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------

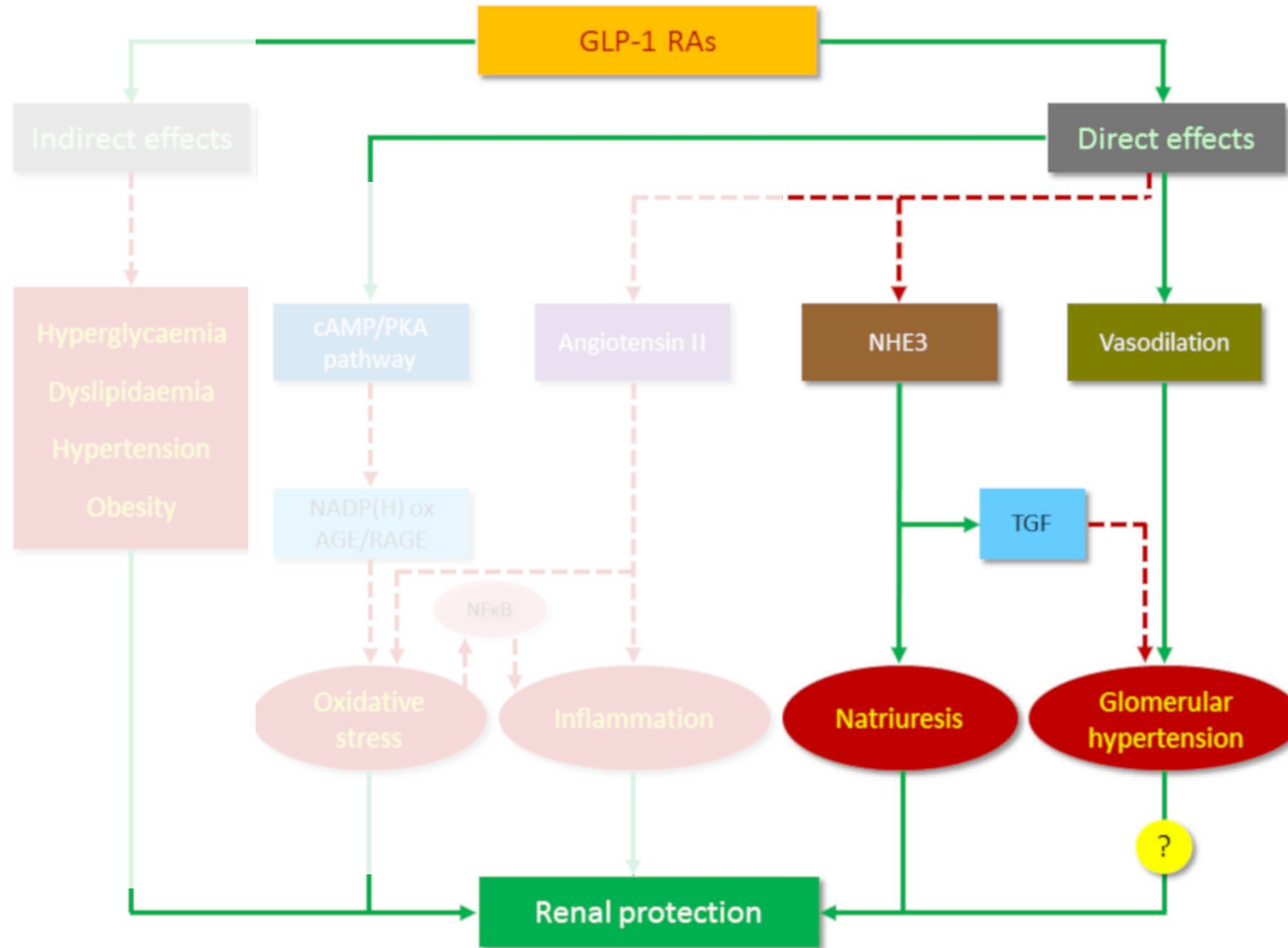
MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs



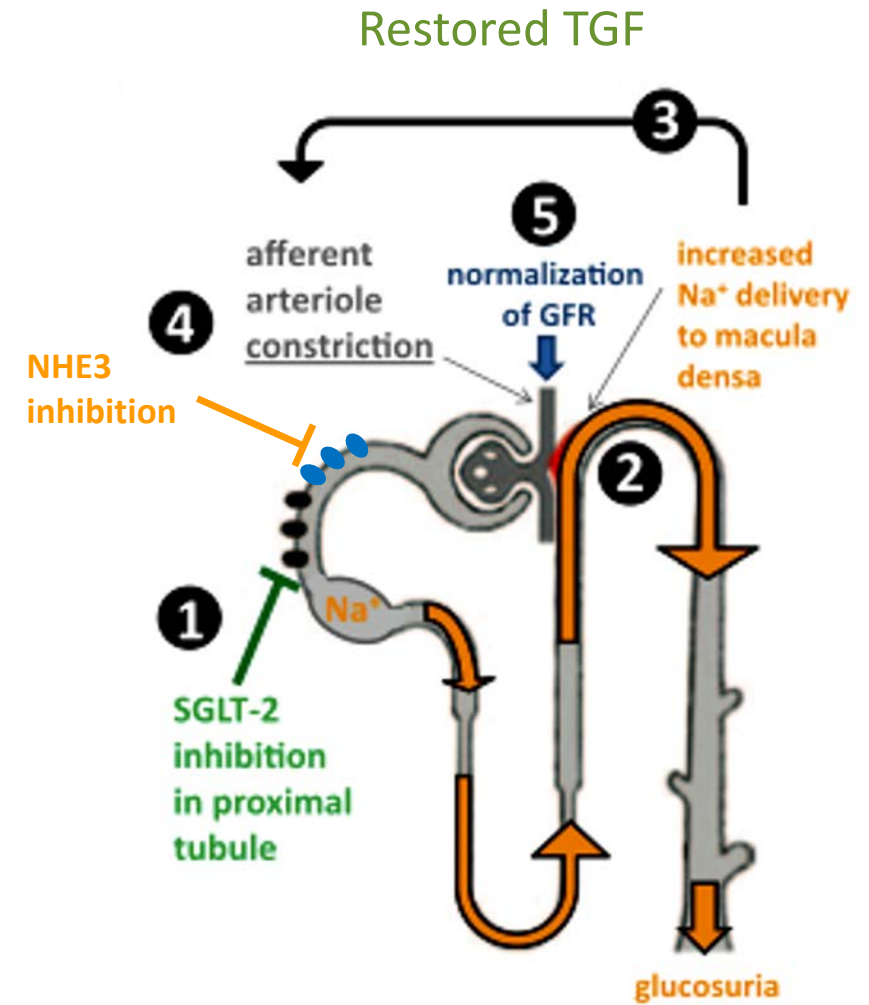
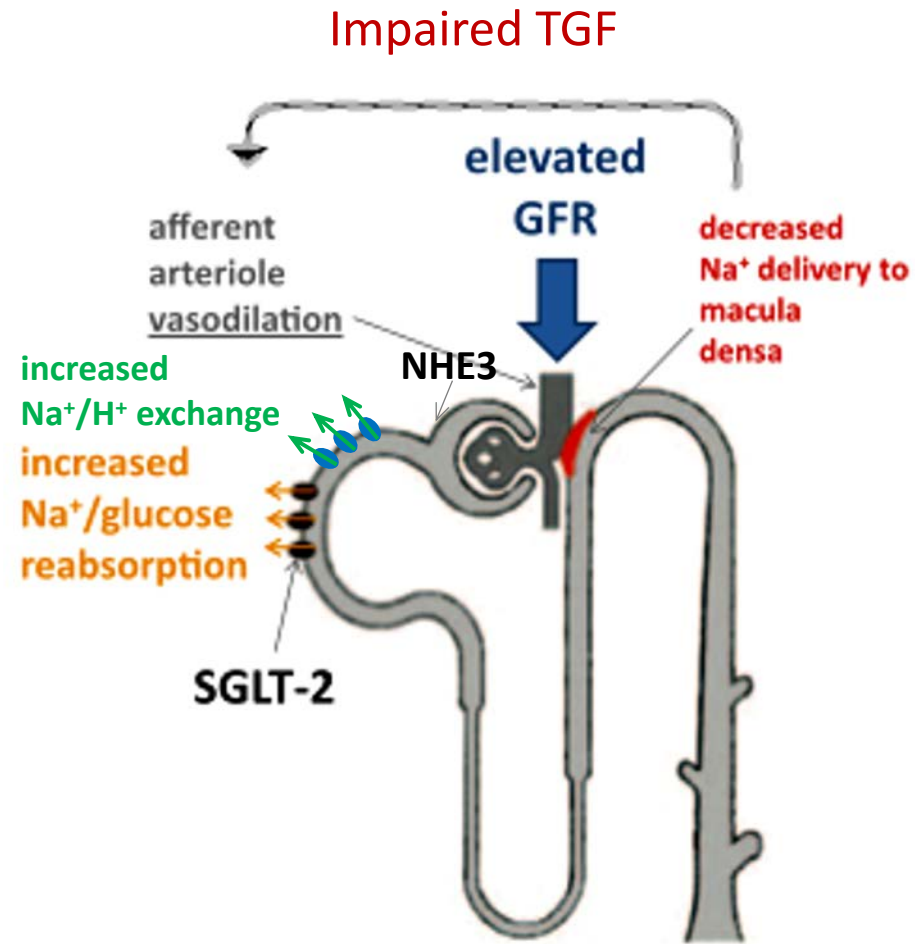
MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs



MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs

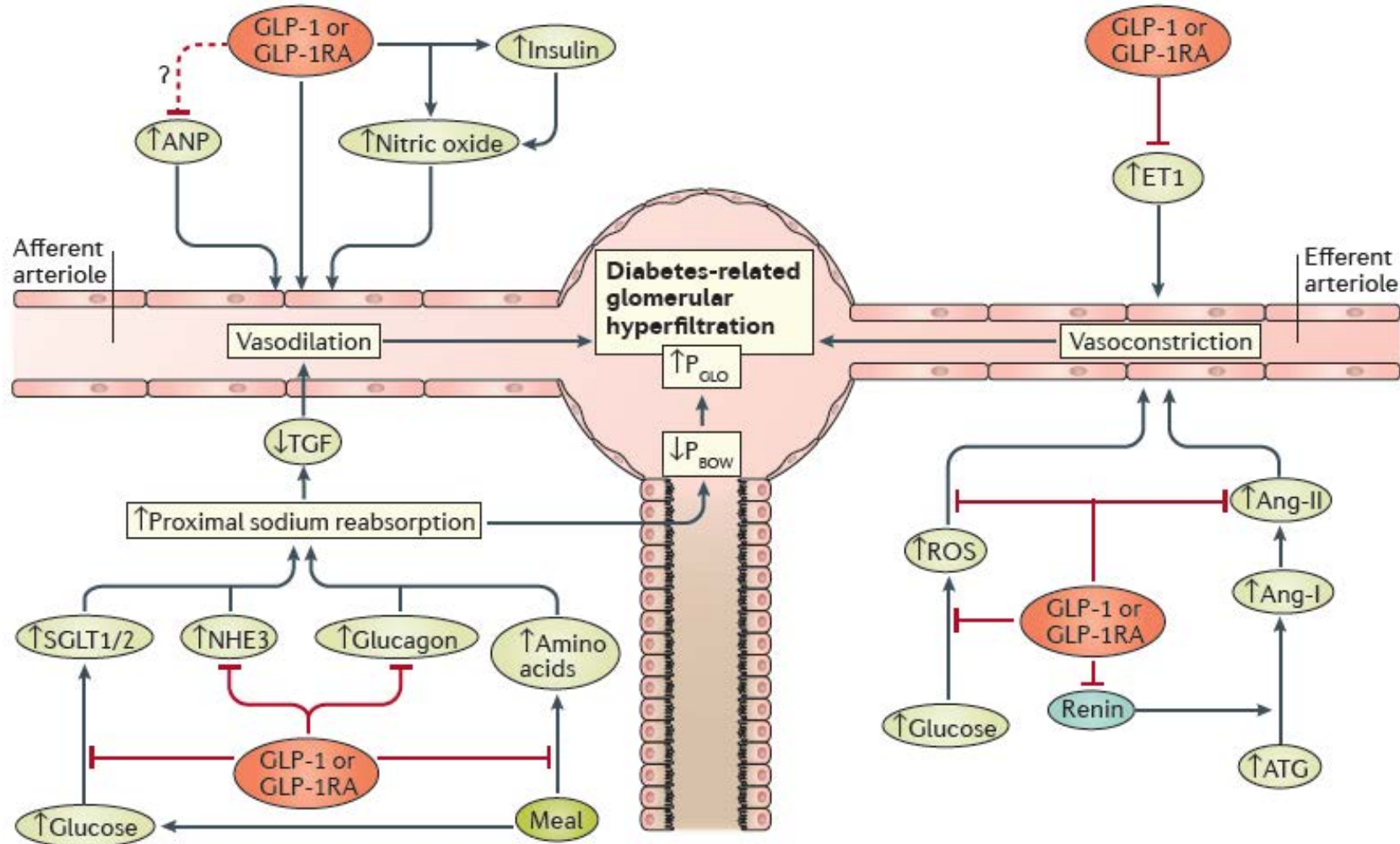


MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs

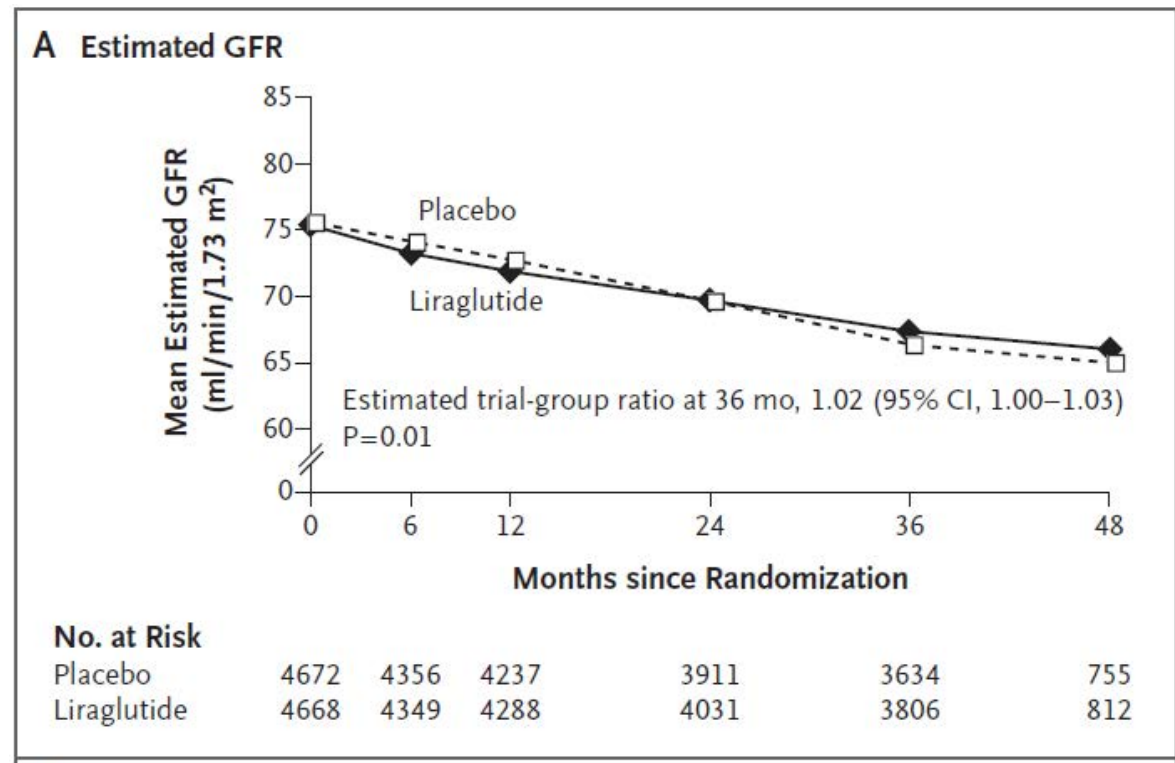
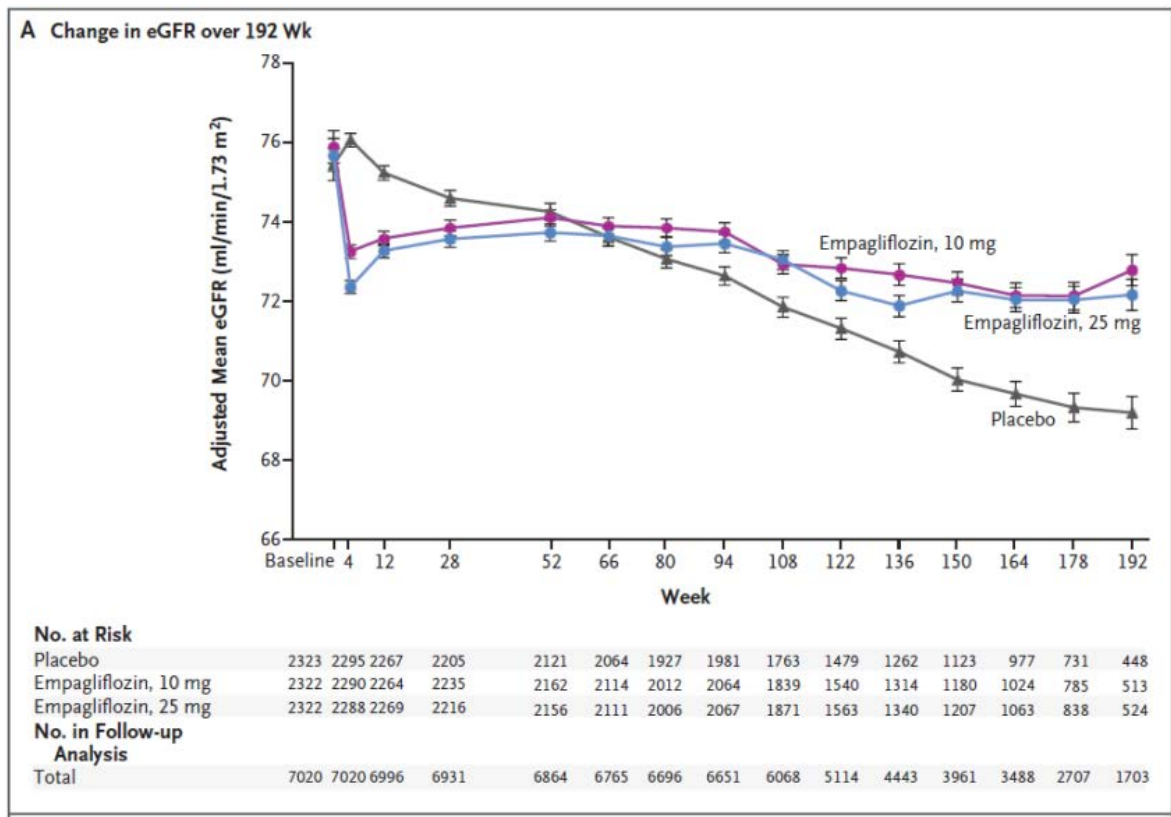


MECHANISMS OF RENAL PROTECTION BY GLP-1 RAs

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



MECHANISMS OF RENAL PROTECTION BY SGLT2-Is

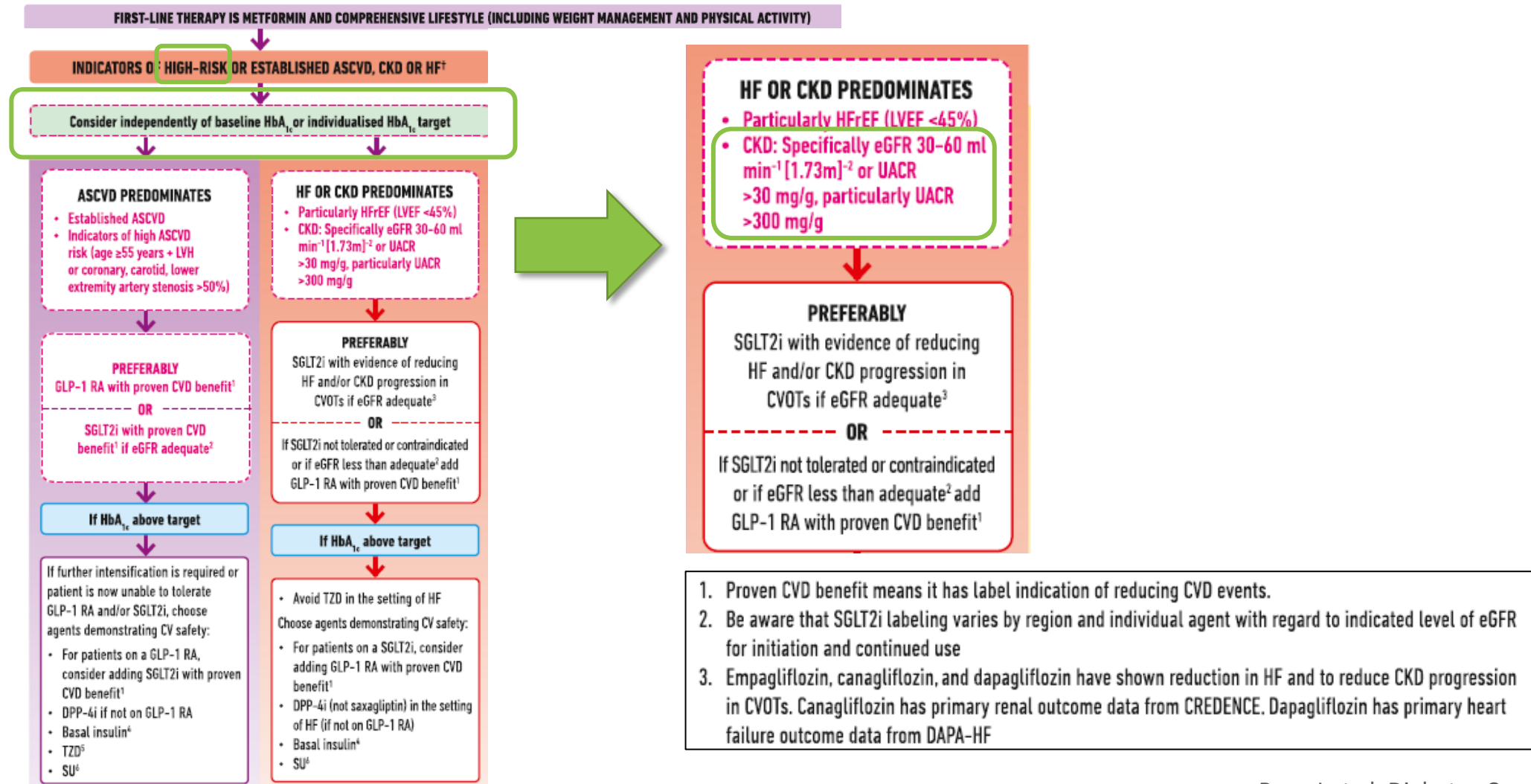


AGENDA

- 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

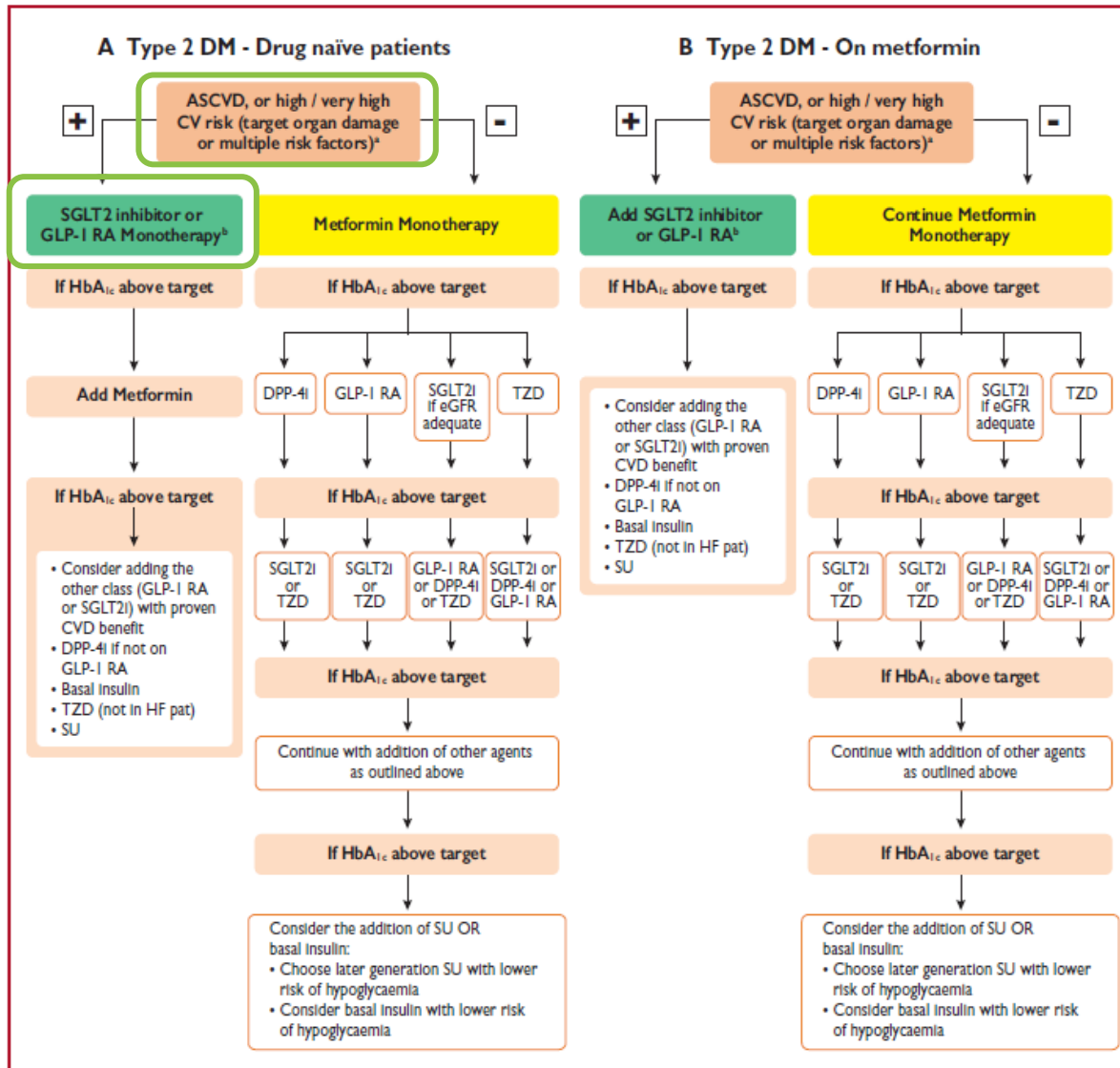
GUIDELINES OF GLUCOSE-LOWERING MEDICATION IN T2DM – FOCUS ON CKD

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



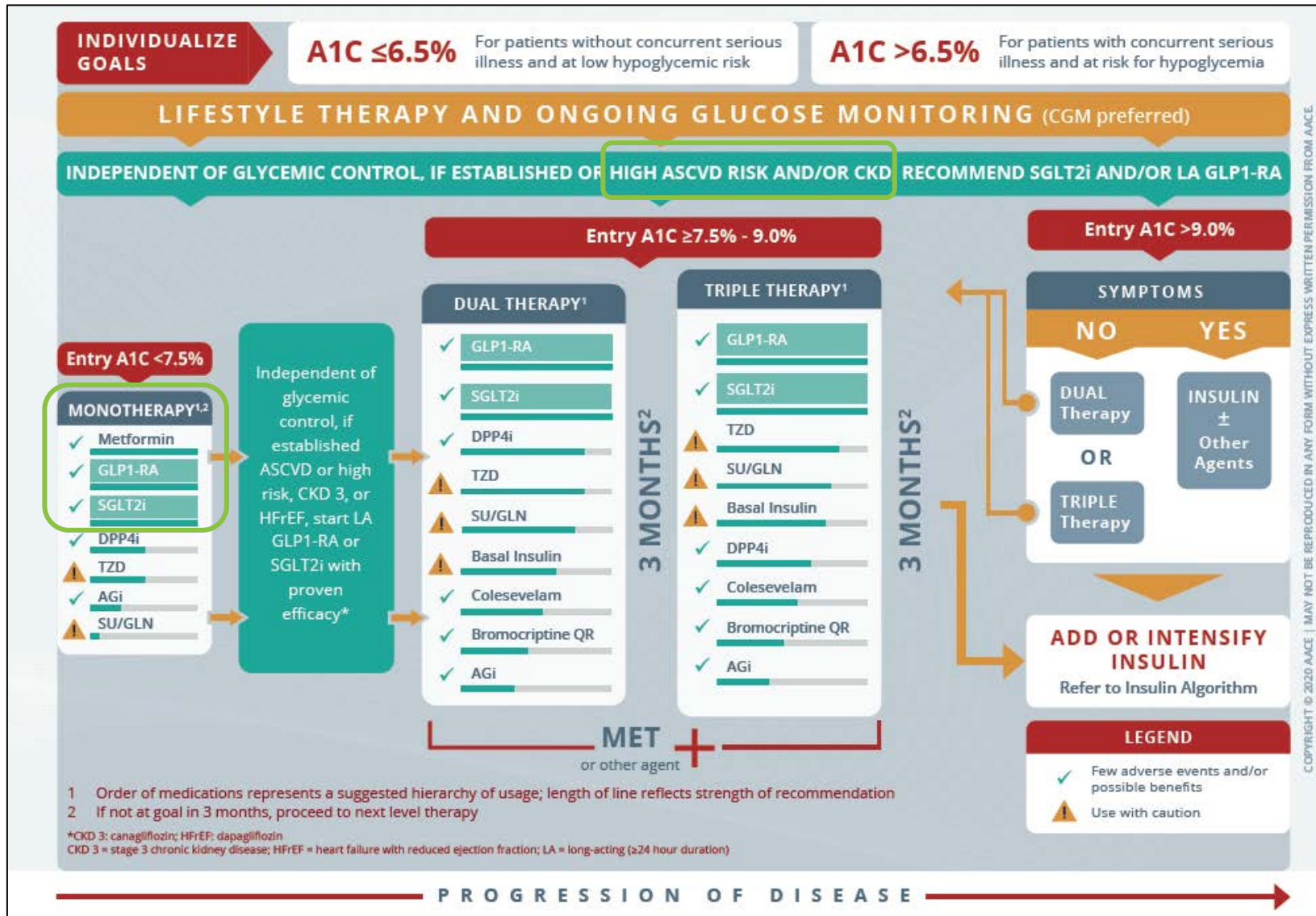
GUIDELINES OF GLUCOSE-LOWERING MEDICATION IN T2DM – FOCUS ON CKD

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



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

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



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

eGFR (ml/min/1.73m ²)	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5
Short-acting GLP-1 RAs																		
Exenatide 10 µg sc twice daily													Caution					
Lixisenatide 20 µg sc once daily																		
Long-acting GLP-1 RAs																		
Albiglutide 30-50 mg sc once weekly																		
Dulaglutide 0.75-1.5 mg sc once weekly																		
Exenatide ER 2 mg sc once weekly																		
Liraglutide 1.2-1.8 mg sc once daily																		
Semaglutide 0.5-1.0 mg sc once weekly 7-14 mg po once daily																		

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

SGLT2-Is

eGFR (ml/min/1.73m ²)																		
	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												

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

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?

A graphic of a notepad with horizontal lines and small circular icons at the corners. The word "yes!!" is written in a large, black, handwritten font in the center of the notepad.

yes!!