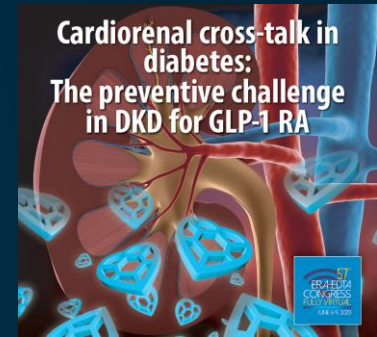


# Targeting renal outcomes in DKD: Can GLP-1 ra provide renal protection?

Prof. Johannes Mann, MD  
Munich, Germany



June 8, 2020 - Virtual ERA-EDTA



# Cardio-renal crosstalk: Preventive challenge in diabetic kidney disease for GLP-1 RA

## “ Targeting kidney outcomes in DKD: Can GLP-1 RA provide kidney protection? ”

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Germany



# “ Targeting kidney outcomes in DKD: Can GLP-1 RA provide kidney protection? ”

## Objectives:

- Summarize kidney data of large GLP-1 RA outcome trials
- Point out definitions of kidney outcomes
- Point out limitations of secondary kidney outcomes in CV outcome trials
- Why may GLP-1 RA confer benefits to the kidney

# “ Targeting kidney outcomes in DKD: Can GLP-1 RA provide kidney protection? ”

## Objectives:

- **Summarize kidney data in large outcome trials conducted with GLP-1 RA**
- Understand definitions of kidney outcomes
- Discuss limitations of secondary kidney outcomes in CV outcome trials
- Why may GLP-1 RA confer benefits to the kidney



# “ Targeting kidney outcomes in DKD: Can GLP-1 RA provide kidney protection? ”

**Trials** testing kidney outcomes as secondary:

- LEADER
- SUSTAIN-6
- REWIND

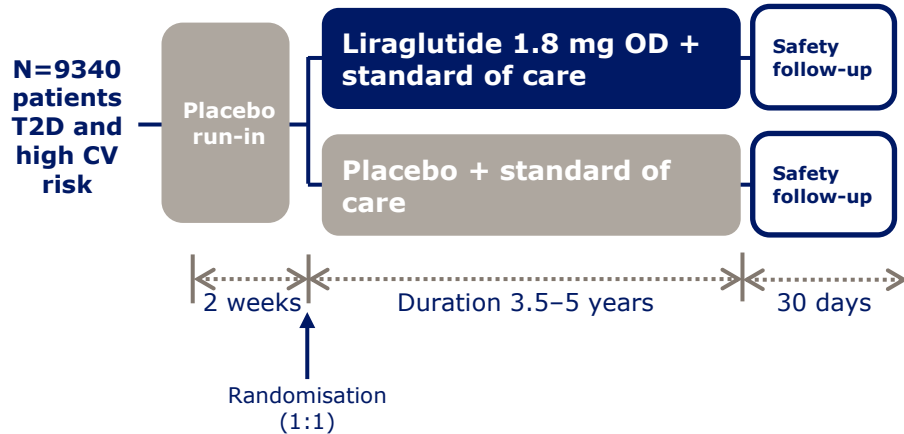
**Trials** monitoring kidney events as spontaneous reports:

- ELIXA
- EXSCEL
- HARMONY
- PIONEER-6



# LEADER and SUSTAIN 6: Study designs

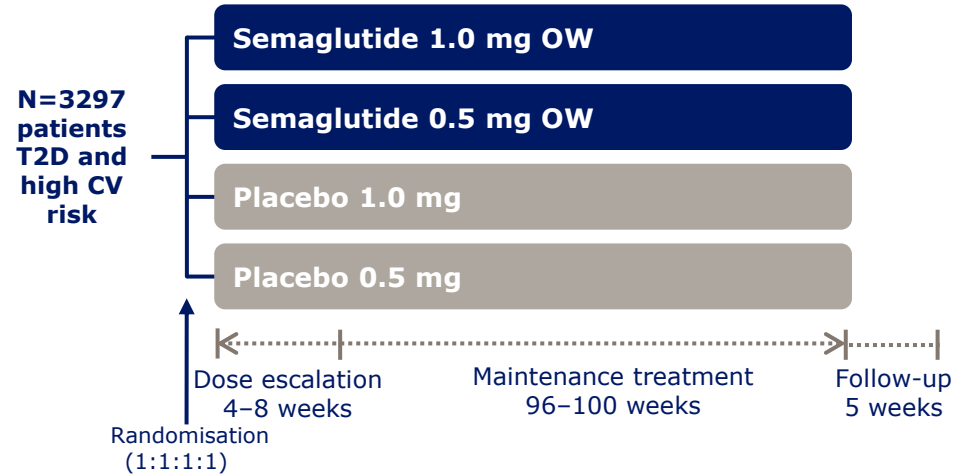
## LEADER<sup>1</sup>



### Primary outcome:

Time to first occurrence of 3-point MACE composed of: CV death, non-fatal MI and non-fatal stroke

## SUSTAIN 6<sup>2</sup>



### Key inclusion criteria

- T2D, HbA<sub>1c</sub> ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CVD or chronic renal failure or age ≥60 years and risk factors for CVD

# Renal outcomes definitions

- **LEADER & SUSTAIN 6** <sup>1,2</sup> and **REWIND\*\***: <sup>5</sup>
  - Need for continuous renal replacement therapy
  - Persistent doubling of serum creatinine and eGFR per MDRD <45 mL/min/1.73 m<sup>2</sup> \*\**Persistent eGFR decline by  $\geq 30\%$*
  - New onset of persistent macroalbuminuria
  - Death due to kidney disease

CrCl, creatinine clearance; MDRD, modification of diet in renal disease

1. Marso SP et al. *N Engl J Med* 2016;375:311–322; 2. Mann JFE et al. *N Engl J Med* 2017;377:839–848;

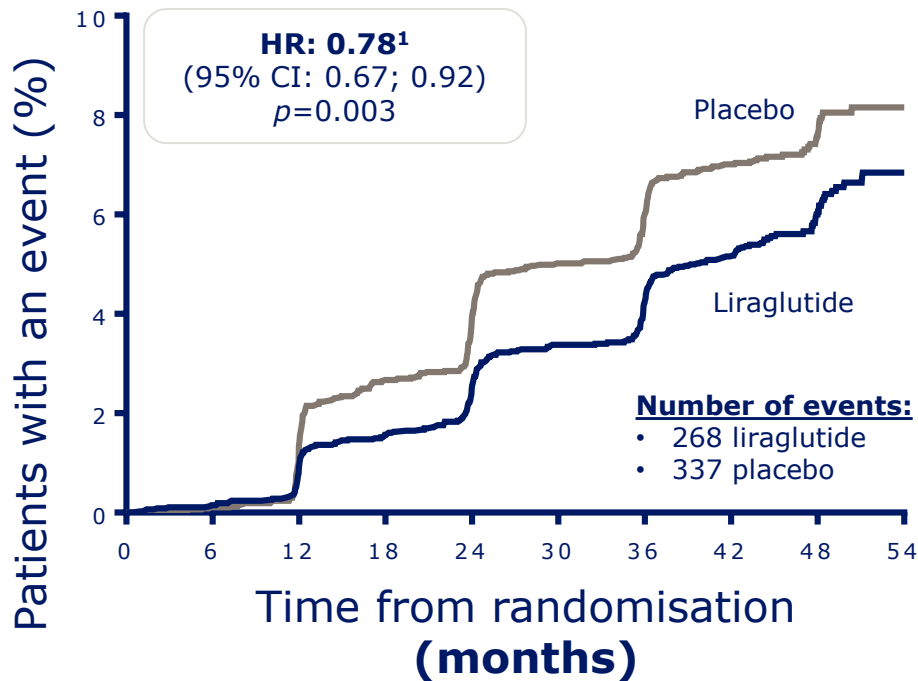
3. Holman RR et al. *N Engl J Med* 2017;377:644–657; 4. Pfeffer MA et al. *N Engl J Med* 2015;373:2247–2257; 5. Gerstein HC et al. *Lancet* 2019; DOI:10.1016/S0140-6736(19)31149-3



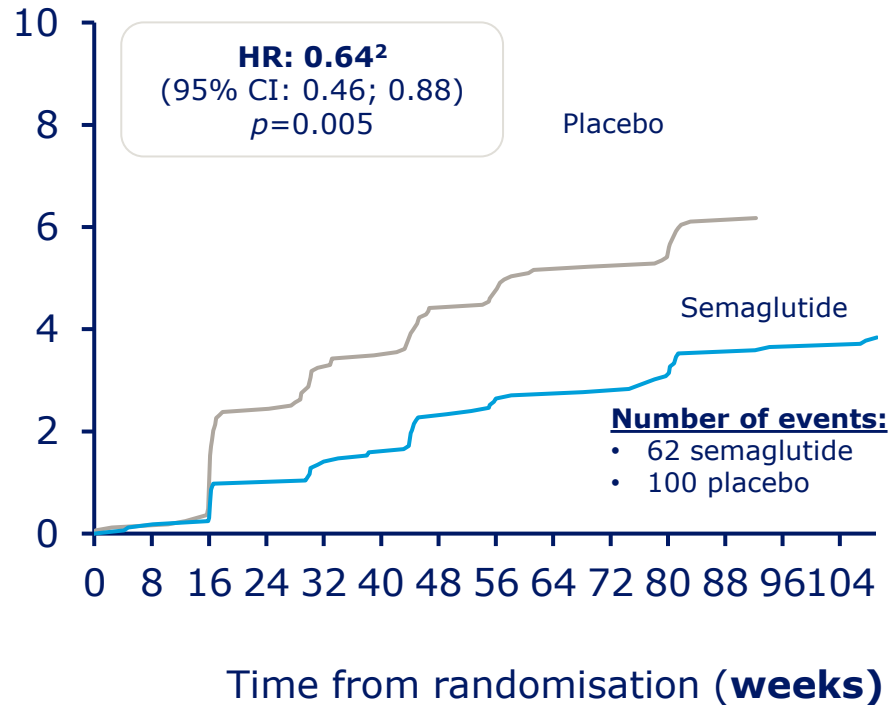
# Kidney outcomes with semaglutide & liraglutide

Macroalbuminuria, doubling of serum creatinine\*, ESRD, renal death

## LEADER<sup>1</sup>

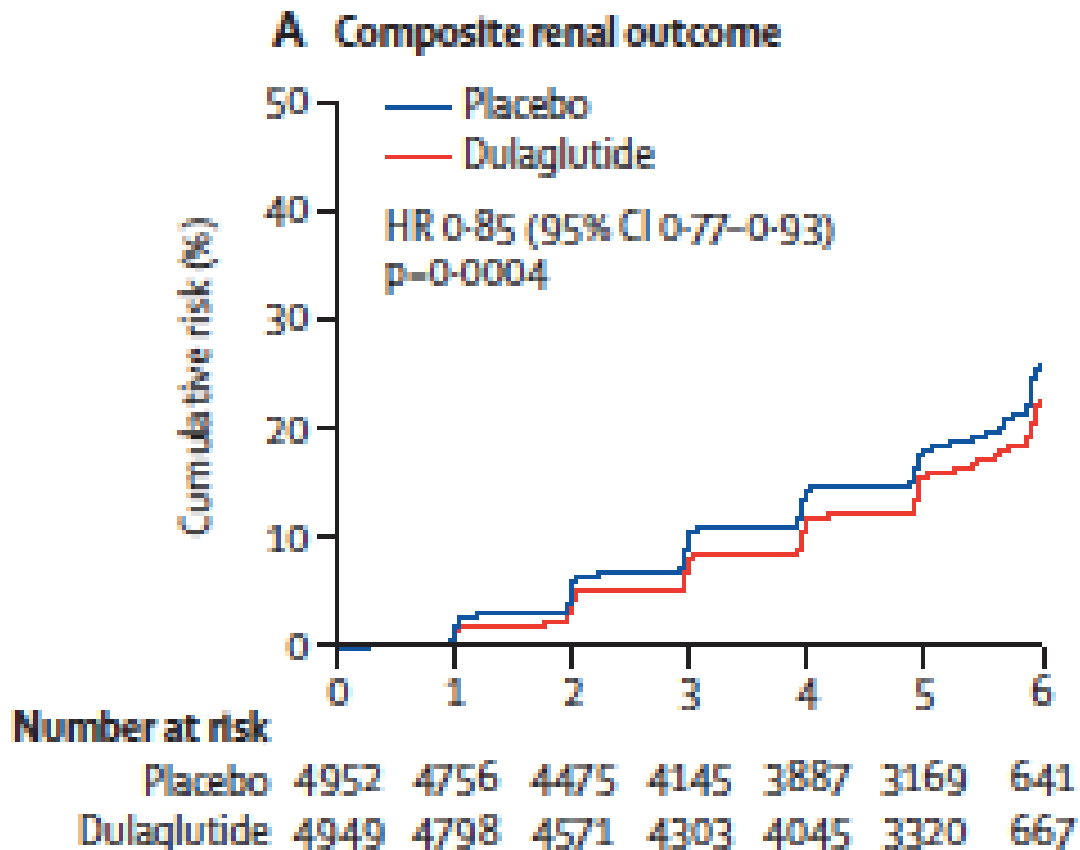


## SUSTAIN 6<sup>2</sup>





**REWIND:** kidney outcome with dulaglutide 1.5 mg/week  
Macroalbuminuria, sustained  $\geq 30\%$  decline in eGFR, or ESRD



# “ Targeting kidney outcomes in DKD: Can GLP-1 RA provide kidney protection ”

**Trials** testing kidney outcomes as secondary:

- LEADER
- SUSTAIN-6
- REWIND

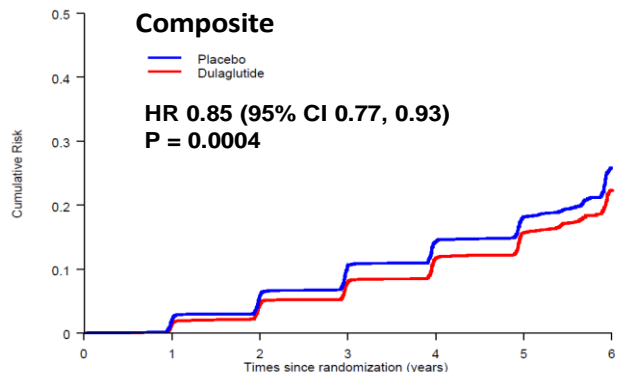
**Which composite was driving the kidney outcome ?**

**Results in subgroups with low GFR ?**

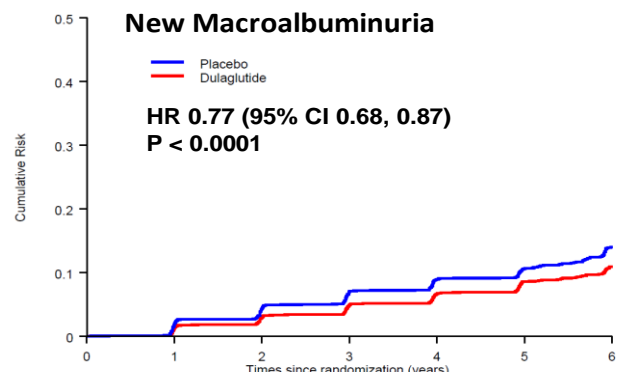


# REWIND: kidney outcome with dulaglutide 1.5 mg/week

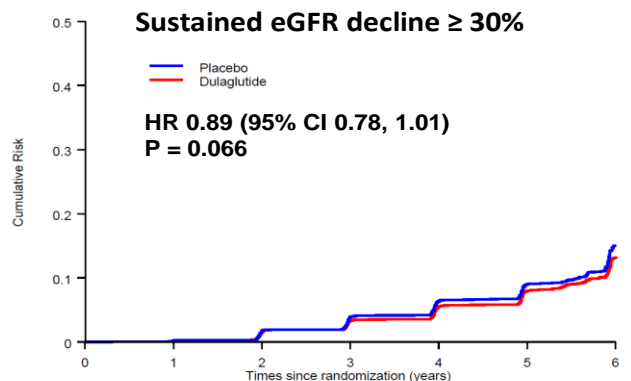
Macroalbuminuria, sustained  $\geq 30\%$  decline in eGFR, or ESRD



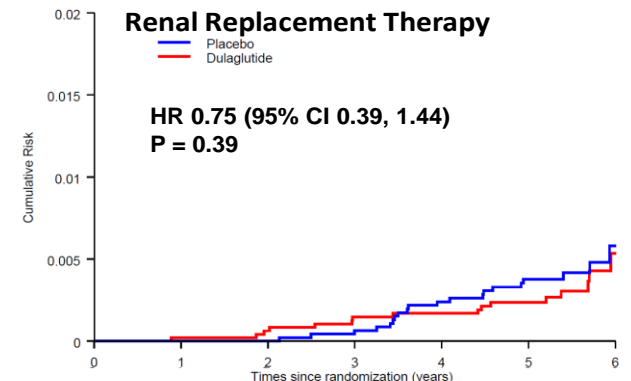
No. at Risk	4952	4756	4475	4145	3887	3169	641
Placebo	4952	4756	4475	4145	3887	3169	641
Dulaglutide	4949	4798	4571	4303	4045	3320	667



No. at Risk	4952	4762	4542	4308	4127	3440	723
Placebo	4952	4762	4542	4308	4127	3440	723
Dulaglutide	4949	4805	4636	4438	4283	3576	740



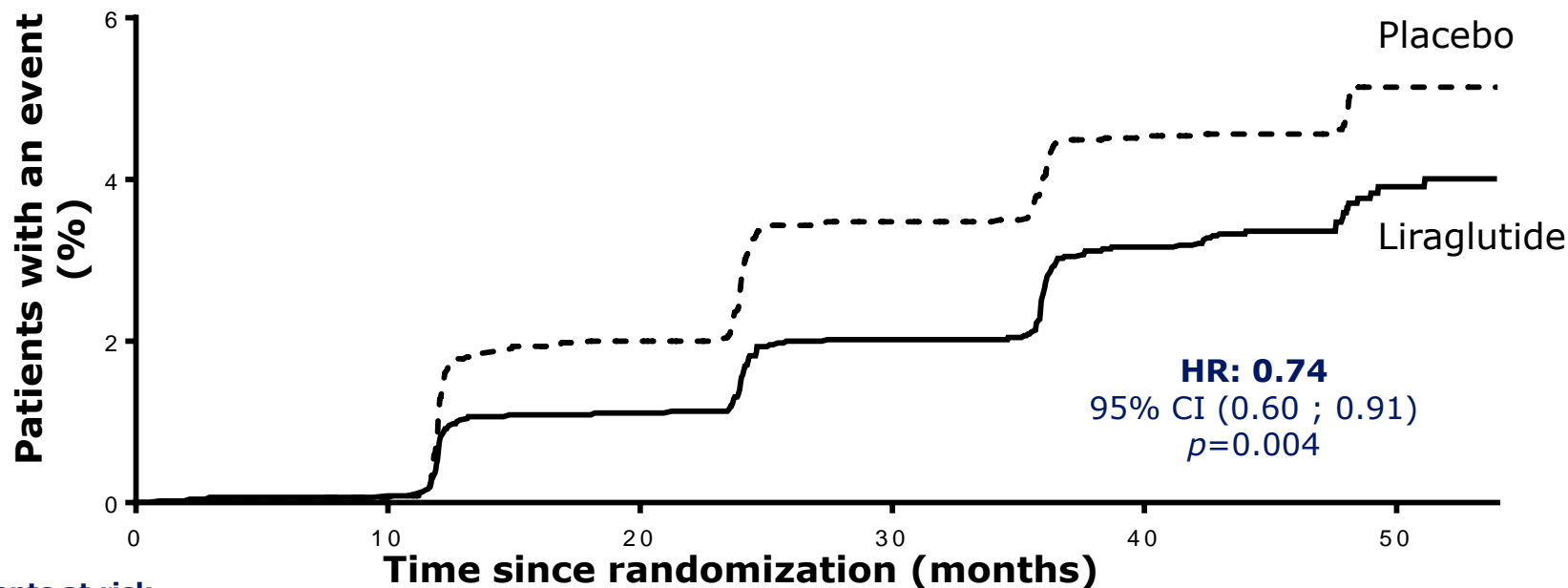
No. at Risk	4952	4848	4672	4440	4220	3489	708
Placebo	4952	4848	4672	4440	4220	3489	708
Dulaglutide	4949	4858	4707	4517	4315	3598	728



No. at Risk	4952	4854	4748	4614	4490	3805	797
Placebo	4952	4854	4748	4614	4490	3805	797
Dulaglutide	4949	4865	4771	4659	4552	3882	807



## Time to new onset of persistent macroalbuminuria (N= 376)

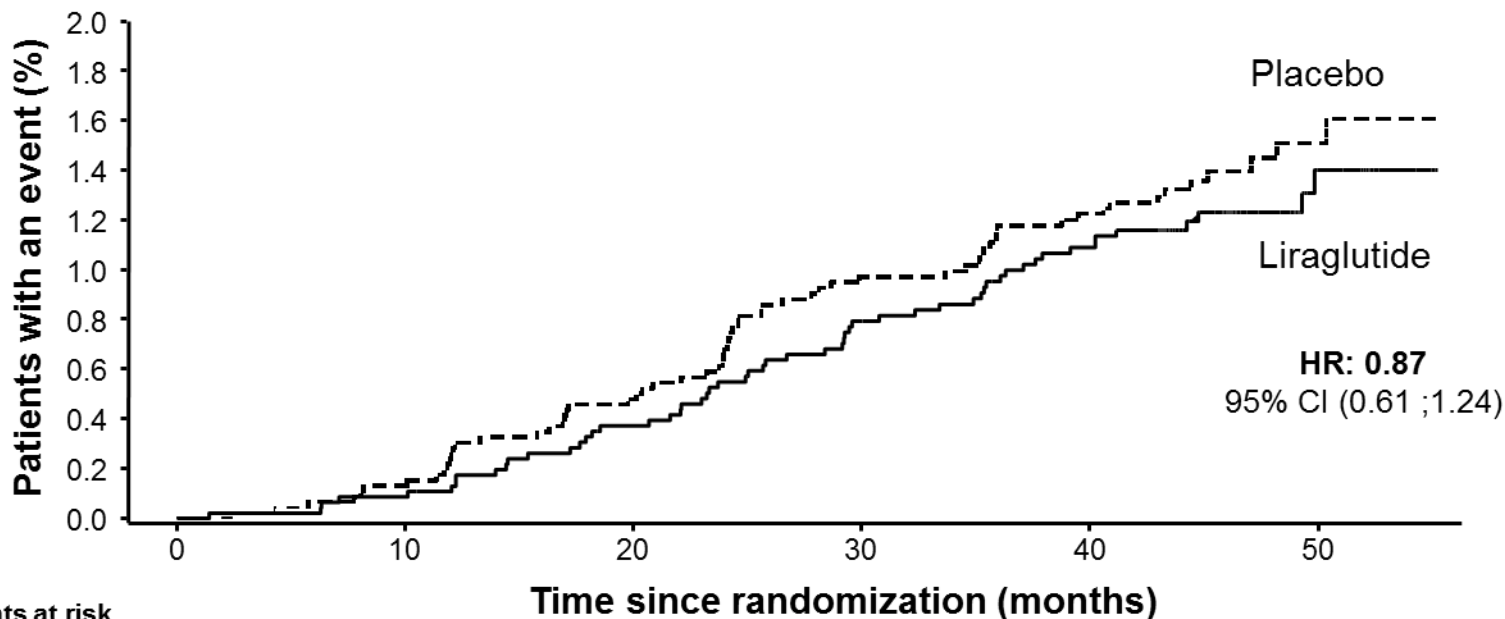


### Patients at risk

Liraglutide	4668	4606	4499	4353	4199	1006
Placebo	4672	4615	4433	4252	4094	964

Full analysis set. EAC-confirmed index events from randomization to follow-up. The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. Macroalbuminuria defined as urine albumin >300 mg/g creatinine. CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio.

# Time to ESRD N= 120



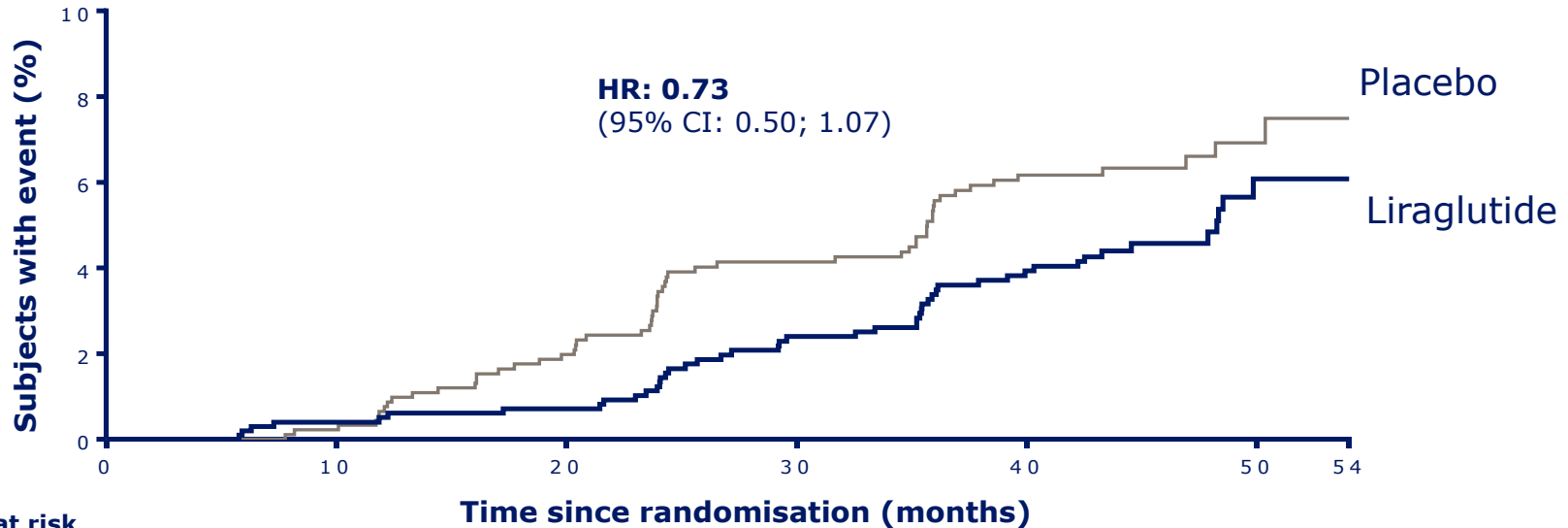
**Patients at risk**

	0	10	20	30	40	50
Liraglutide	4668	4608	4537	4416	4299	1047
Placebo	4672	4612	4506	4370	4250	1007

Full analysis set. EAC-confirmed index events from randomization to follow-up; the cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; EAC: event adjudication committee; HR, hazard ratio

**LEADER: subjects with CKD stage 3 (N=1934):**

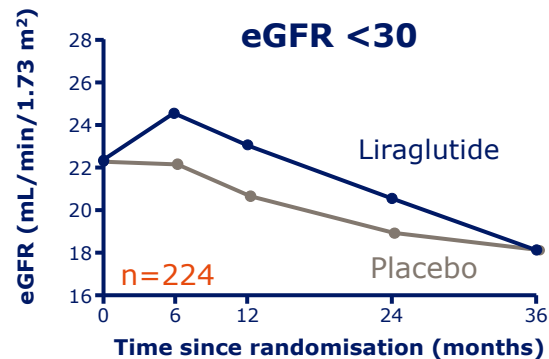
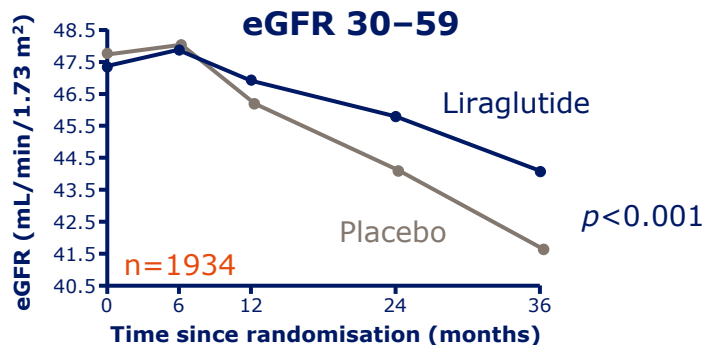
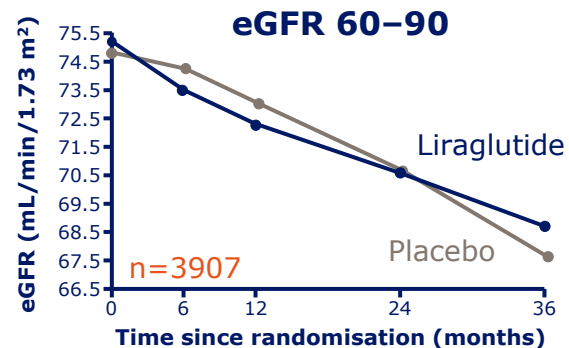
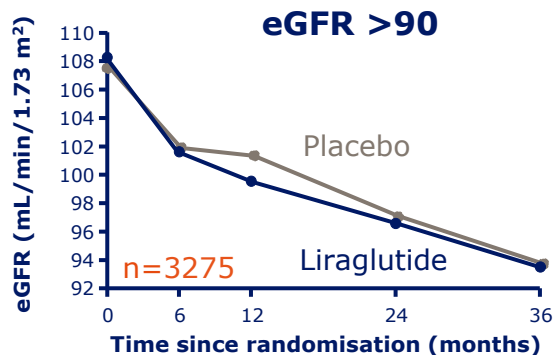
Composite outcome of “doubling of serum creatinine, ESRD or renal death”

**Subjects at risk**

Liraglutide	999	981	962	908	866	210
Placebo	935	917	875	821	765	165

Adjusted for additional covariates. Full analysis set. Kaplan–Meier plot of EAC-confirmed nephropathy event; events that occur before randomisation date are not used for defining first event; subjects without an event are censored at time of last contact (phone or visit) CI, confidence interval; CKD, chronic kidney disease; EAC, event adjudication committee; ESRD, end-stage renal disease; HR, hazard ratio

# LEADER: Change of eGFR (MDRD) by baseline eGFR



## Annual loss of eGFR in LEADER (N=9010, 3.8 years) and SUSTAIN-6 (N= 2469, 2 years)

	<b>Liraglutide 1.8 mg/day</b>	<b>Placebo</b>	<b>Semaglutide 1 mg/week</b>	<b>Placebo</b>
All	- 1.72 ml/min/y	- 1.98	- 1.05	- 1.92
Subgroup with eGFR <60ml/min*	- 1.44	- 2.11	- 0.25	- 1.87

\* N= 632 and 1873 respectively



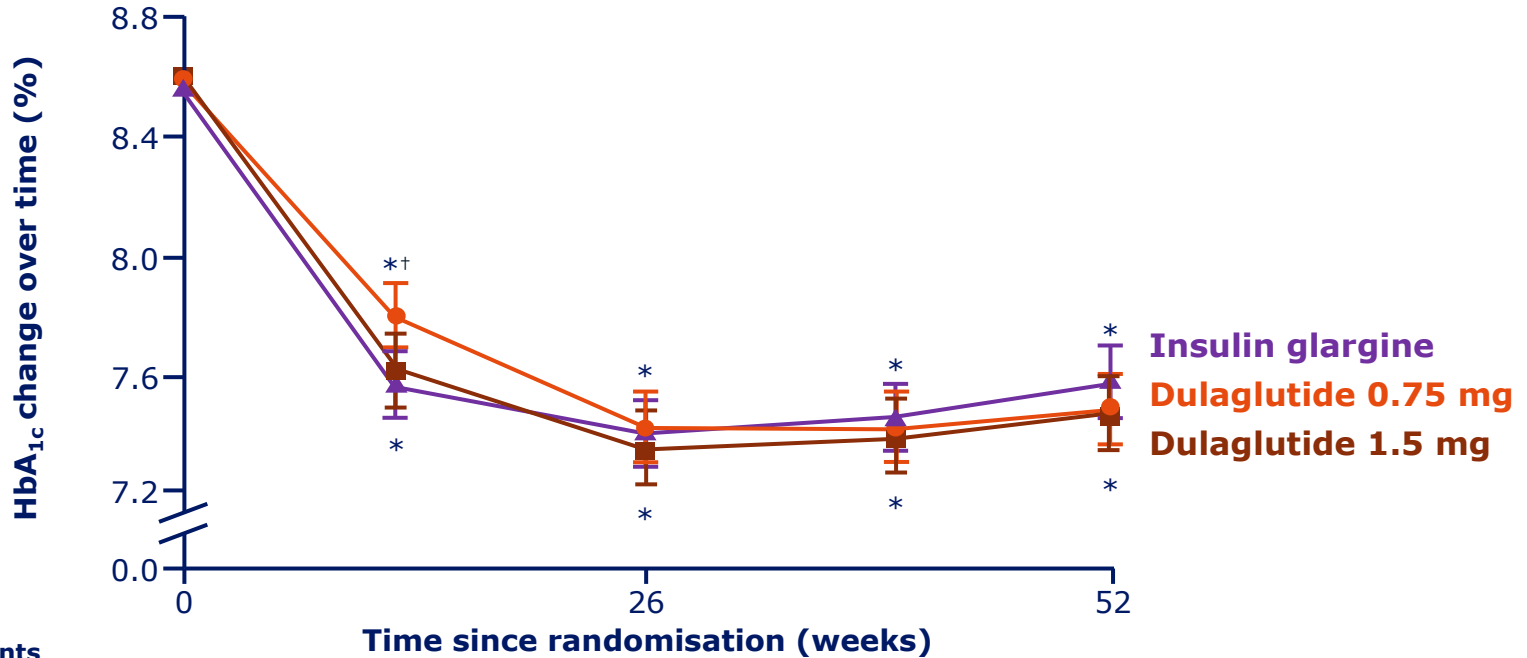
# “ Targeting kidney outcomes in DKD: Can GLP-1 RA provide kidney protection ”

## Objectives:

- Learn about kidney data in large outcome trials conducted with GLP-1 RA
- Understand definitions of kidney outcomes
- Emphasise limitations of secondary kidney outcomes in CV outcome trials
- **Why may GLP-1 RA confer benefits to the kidney**



# AWARD 7: Change in HbA<sub>1c</sub> with dulaglutide and insulin glargine



**No. of patients**

Dulaglutide 1.5 mg  
 Dulaglutide 0.75mg  
 Insulin glargine

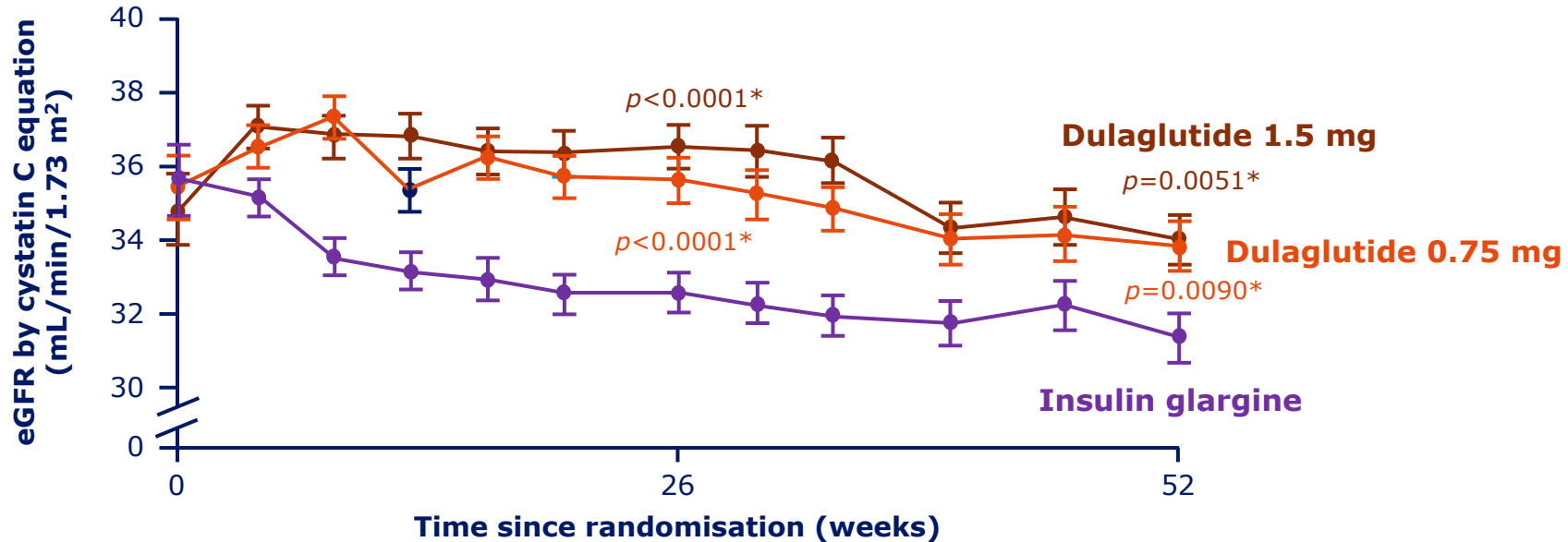
183  
 180  
 186

138  
 149  
 175

130  
 132  
 153

\* $p < 0.0001$  versus baseline; † $p < 0.05$  versus insulin glargine  
 HbA<sub>1c</sub>, glycosylated haemoglobin  
 Tuttle KR et al. *Lancet Diabetes Endocrinol* 2018;6:605–617

# AWARD 7: Change in eGFR with dulaglutide and insulin glargine



**No. of patients**

Dulaglutide 1.5 mg	192	163	157
Dulaglutide 0.75mg	190	167	160
Insulin glargine	194	174	164

\*Versus baseline  
 eGFR, estimated glomerular filtration rate  
 Tuttle KR et al. *Lancet Diabetes Endocrinol* 2018;6:605–617



# Summary

- Semaglutide, liraglutide & dulaglutide reduce composite kidney outcomes, driven by less macroalbuminuria
- Semaglutide & liraglutide slow the decline in eGFR in T2D with CKD stages 3–4; no data yet for dulaglutide
- The beneficial effects of these 3 GLP-1RAs on the kidney appear to be independent, at least in part, of improved HbA<sub>1c</sub>
- These 3 GLP-1RAs are safe in patients with CKD and elimination via the kidney is negligible
- (GLP-1RAs reduce CV outcomes, particularly in patients with T2D and CKD)



# GLP1-R agonist: effects on the kidney

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

Knock-out of the  
GLP-1 Receptor  
enhances renal  
damage in diabetic  
mice

Mesangial  
Expansion

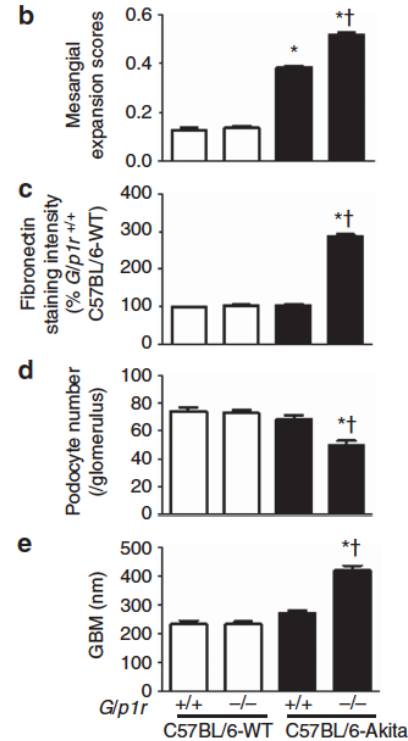
Fibronectin

Number of  
podocytes

GBM width

Mice without diabetes  
GLP1-Receptor + or -

Mice with diabetes  
GLP1-Receptor + or -



# GLP1-R agonist: effects on the kidney

Fujita et al., Kidney Int 2014;85:579

Liraglutid reduces renal damage in diabetic mice

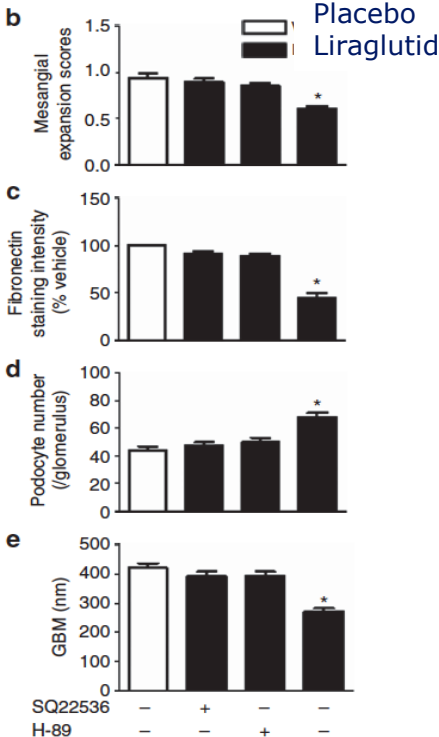
SQ: Inhibitor of cAMP  
H-89: Inhibitor of proteinkinase

Mesangial Expansion

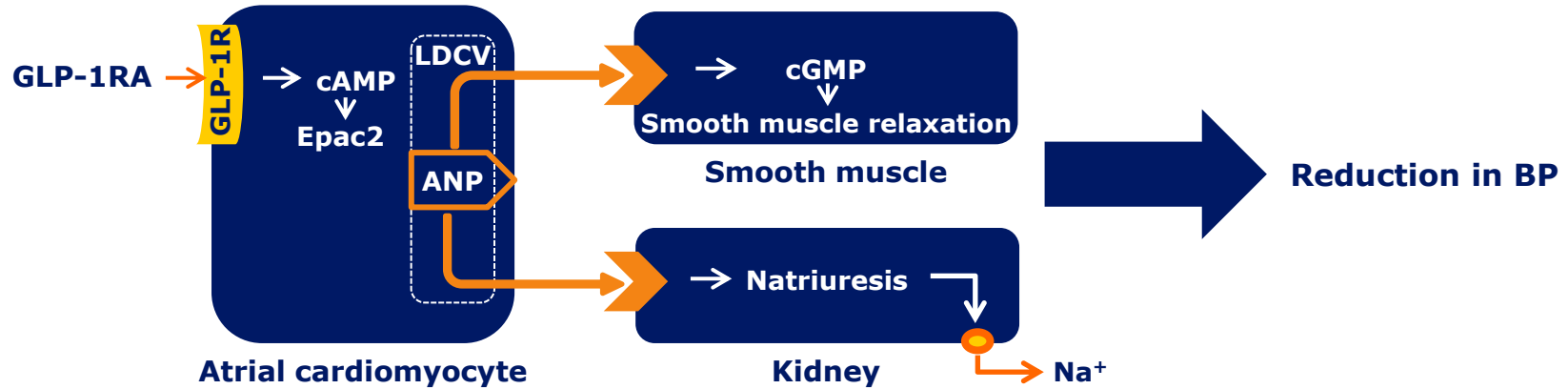
Fibronectin

Number of podocytes

GBM width



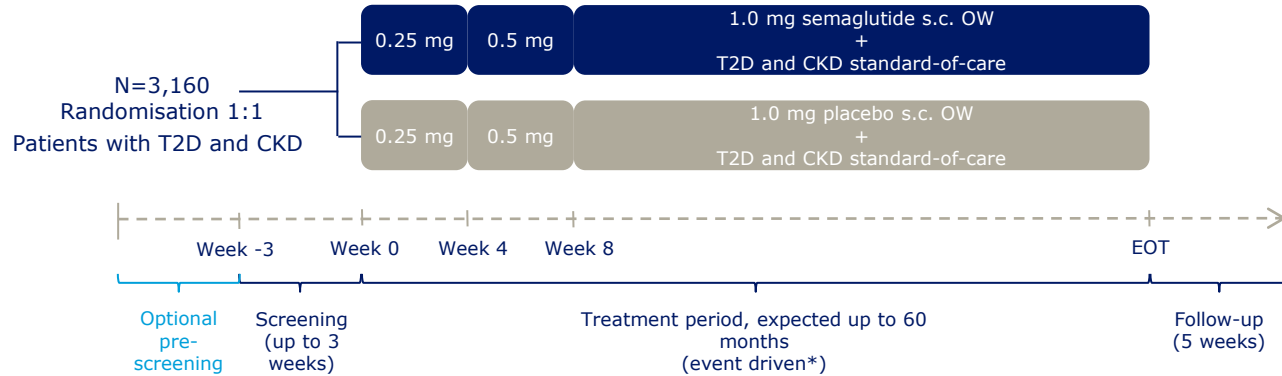
# Hypothesised mechanism of GLP-1 regulation of arteriolar function



1. Activation of atrial cardiomyocyte GLP-1R with GLP-1R agonists
2. Increased amounts of cAMP promote Epac2 membrane translocation
3. Epac2 increases ANP levels in LDCV
4. ANP induces cGMP-mediated smooth muscle relaxation and natriuresis
5. BP reduced

ANP, atrial natriuretic peptide; BP, blood pressure; cAMP, cyclic adenosine monophosphate; Epac2, exchange protein activated by cAMP; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; cGMP, cyclic guanosine monophosphate; LDCV, large dense core vesicle

# FLOW: does semaglutide prevent “ESRD, 50% decrease in eGFR or CV death” in T2D with CKD



## Trial information

- Randomised, double-blind, placebo-controlled
- Expected annual event rate 8.5% and HR=0.8; power 90%
- Stratify by baseline SGLT-2i use
- Interim testing for efficacy

## Primary objective

- To demonstrate that semaglutide delays progression of renal impairment and lowers the risk of renal and CV mortality vs. placebo in patients with T2D and CKD

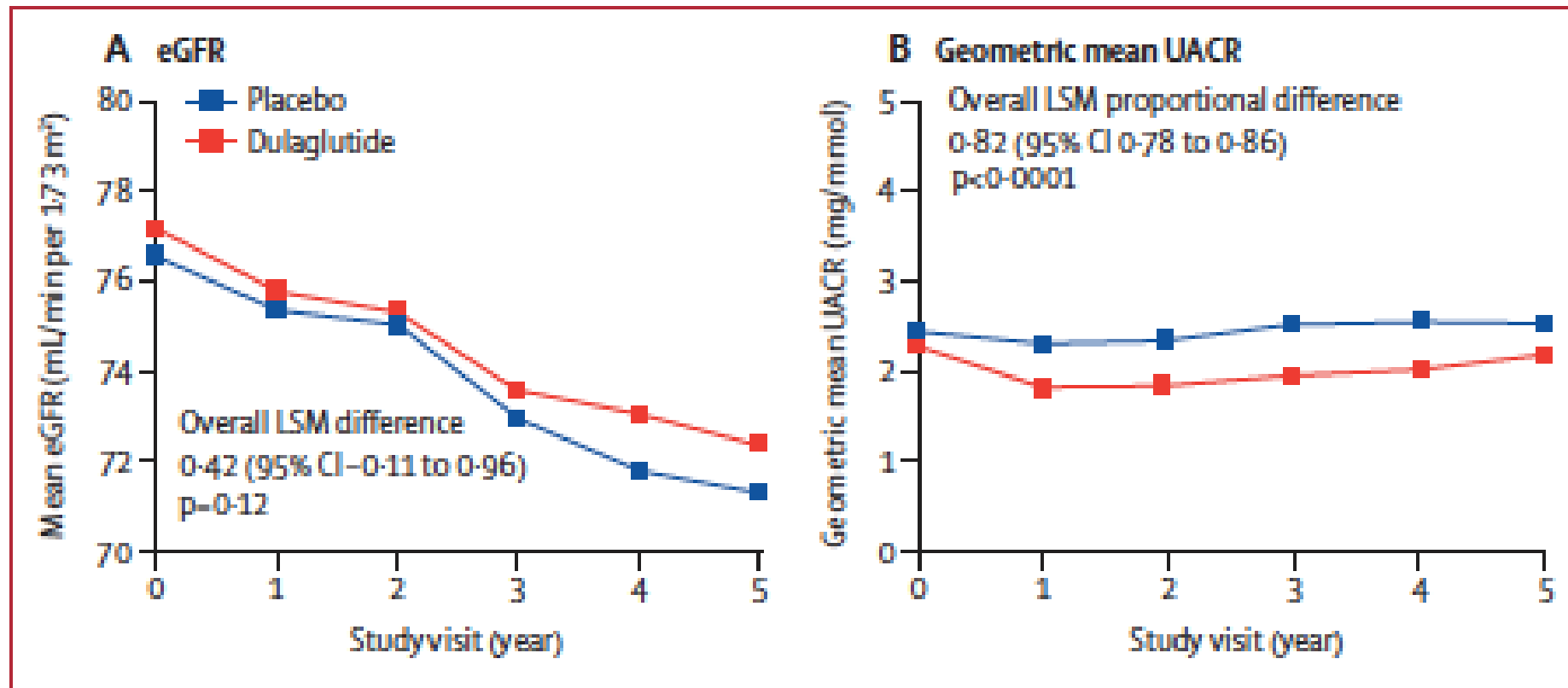
## Secondary objective:

- To assess the effect of semaglutide vs placebo on CV morbidity, PAD, glycaemic control, body weight, blood pressure and safety in patients with T2D and CKD

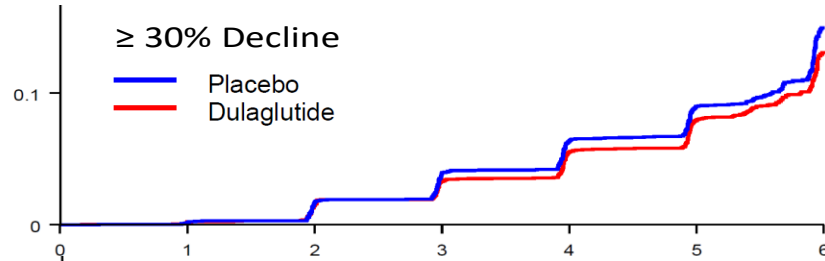
CKD, chronic kidney disease; CV, cardiovascular; HbA1c, glycosylated haemoglobin; PAD, peripheral artery disease; s.c., subcutaneous; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SoC, standard of care; T2D, type 2 diabetes

\* 854 primary events; including minimum 515 primary renal events



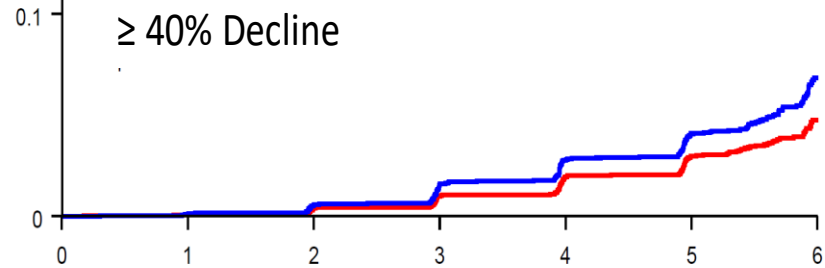
**REWIND:** eGFR & UACR with dulaglutide 1.5 mg/week

# REWIND: Decline in eGFR with dulaglutide 1.5 mg/week



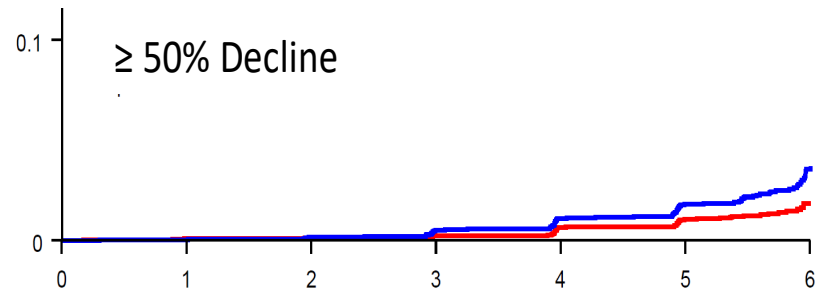
Sustained  
eGFR  
decline ≥  
30%

HR 0.89 (0.78, 1.01) 0.066



Sustained  
eGFR decline ≥  
40%

HR 0.70 (0.57, 0.85) 0.0004



Sustained  
eGFR decline ≥  
50%

HR 0.56 (0.41, 0.76) 0.0002

