A PANORAMA initiative: Enjoy the view
The challenge of Choosing in CVD

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A Panoramic view of the Nephrology Therapeutic Landscape

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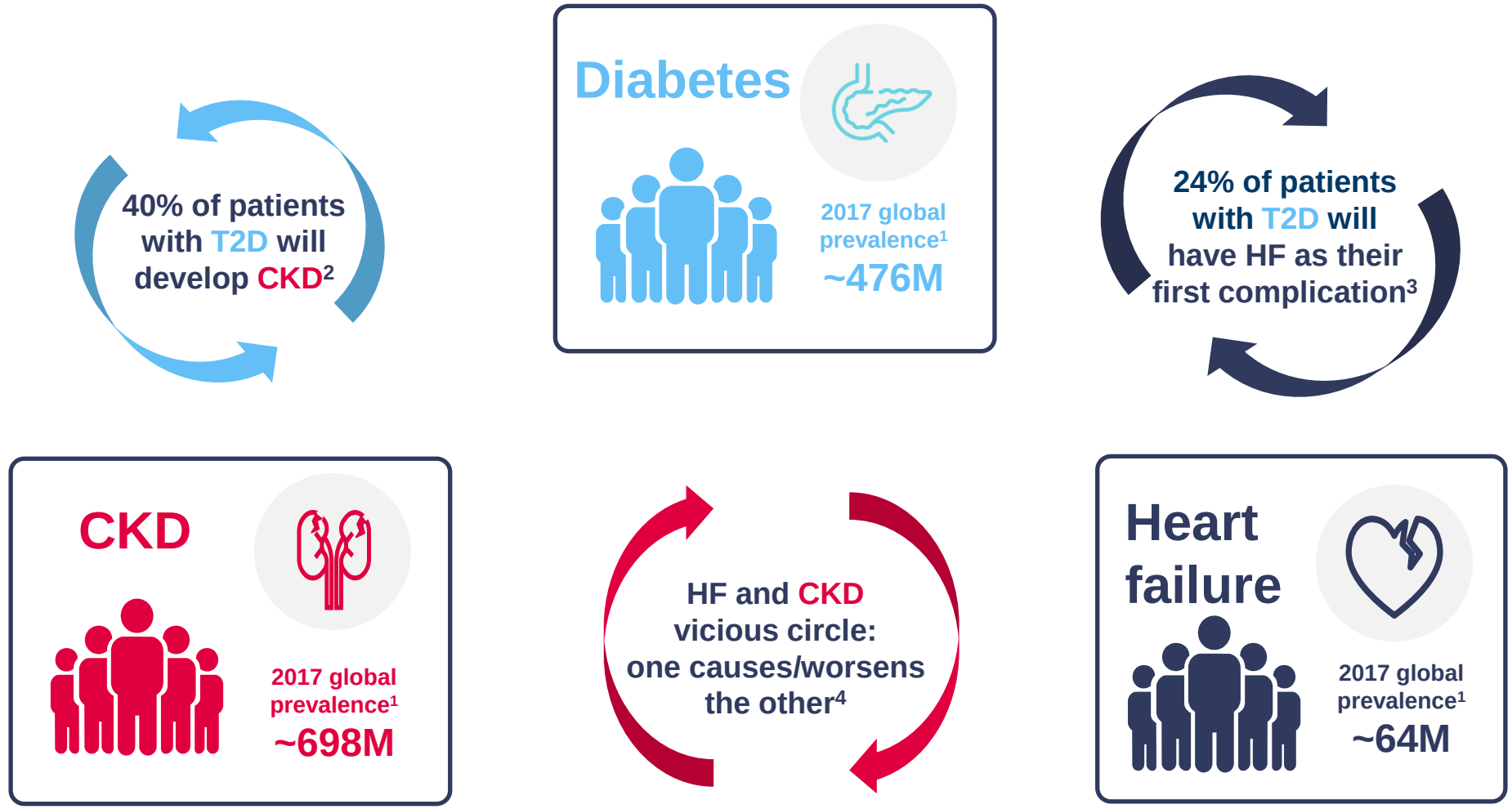
Disclosures

- HJLH is a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe, Novo Nordisk, and Retrophin
- He has received research support from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen

CKD, heart failure, and T2D are interrelated, leading to a vicious circle of cardiac, renal, and metabolic risk



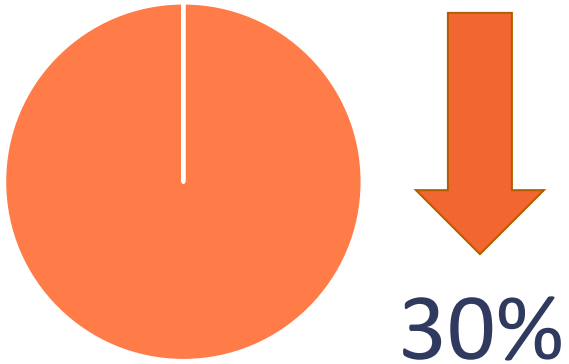
CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet* 2018;392:1789–1858; 2. Parving HH, et al. *Kidney Int* 2006;69:2057–2063;
3. Birkeland KI, et al. *Diabetes Obes Metab* 2020:22:1607–1618; 4. Ronco C, et al. *J Am Coll Cardiol* 2008;52:1527–1539

SGLT2 inhibitor trials have recruited patients with CKD with and without diabetes

CREDENCE[1]

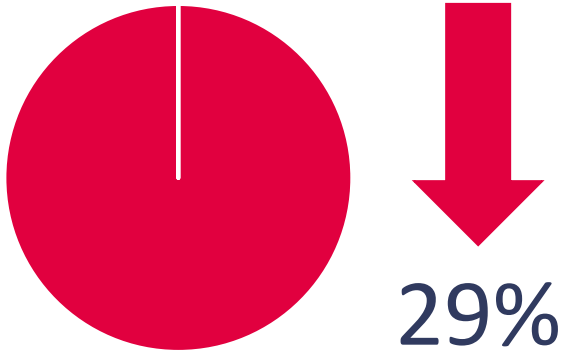
100% diabetes population



30%

SCORED[2]

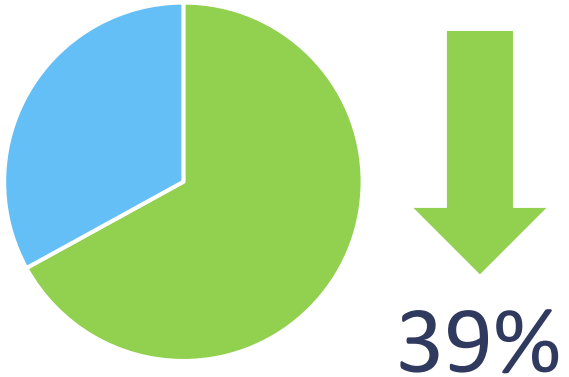
100% diabetes population



29%

DAPA-CKD[3]

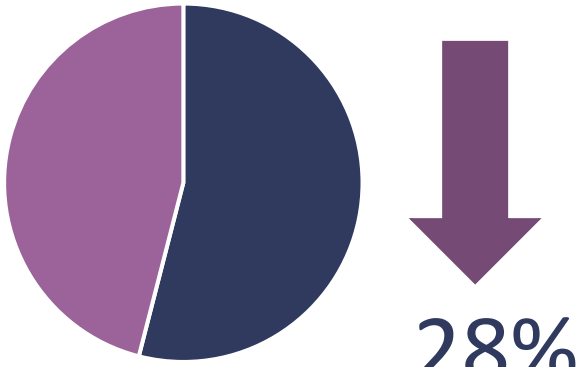
33% non-diabetes population



39%

EMPA-KIDNEY[4]

54% non-diabetes population

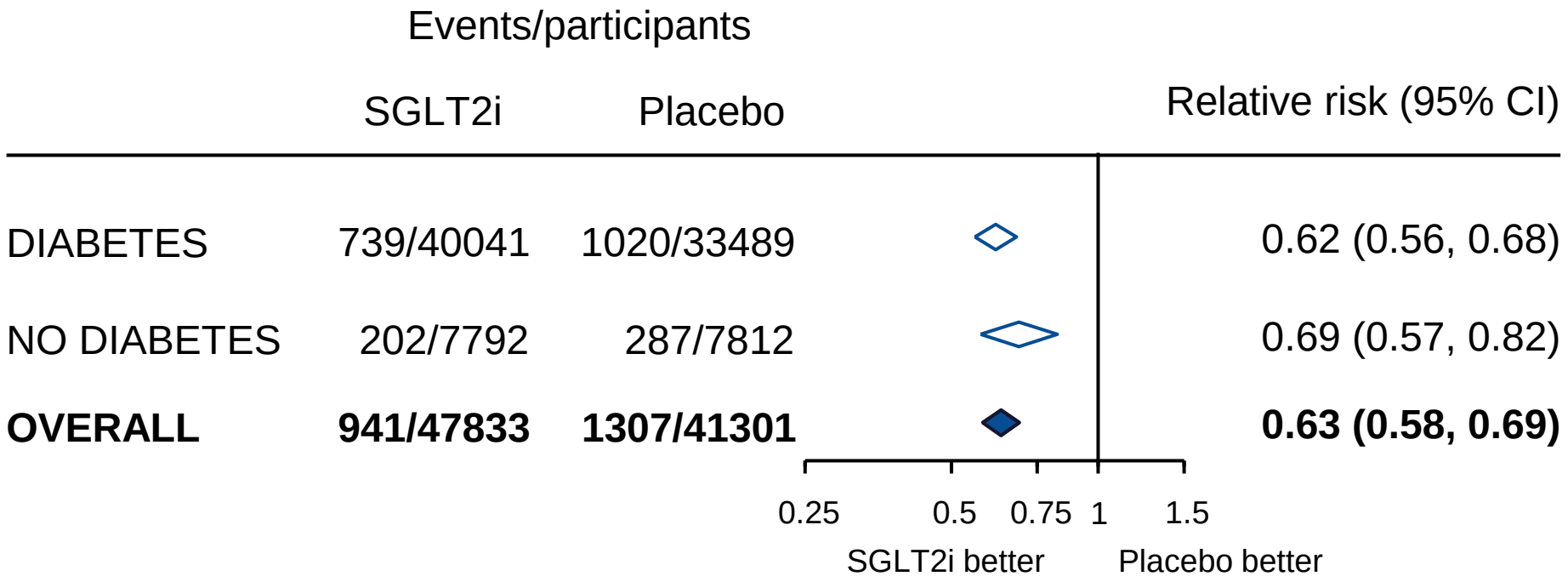


28%

CKD, chronic kidney disease

1. Perkovic V, et al. *N Engl J Med* 2019;380:2295–306; 2. Bhatt DL, et al. *N Engl J Med* 2021;384:129–139;
3. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446; 4.EMPA-KIDNEY Collaborative Group. *N Engl J Med* Nov 4. doi: 10.1056/NEJMoa2204233

The Benefit of SGLT2 Inhibitors to Delay CKD Progression are Consistent in Patients with and without Type 2 Diabetes



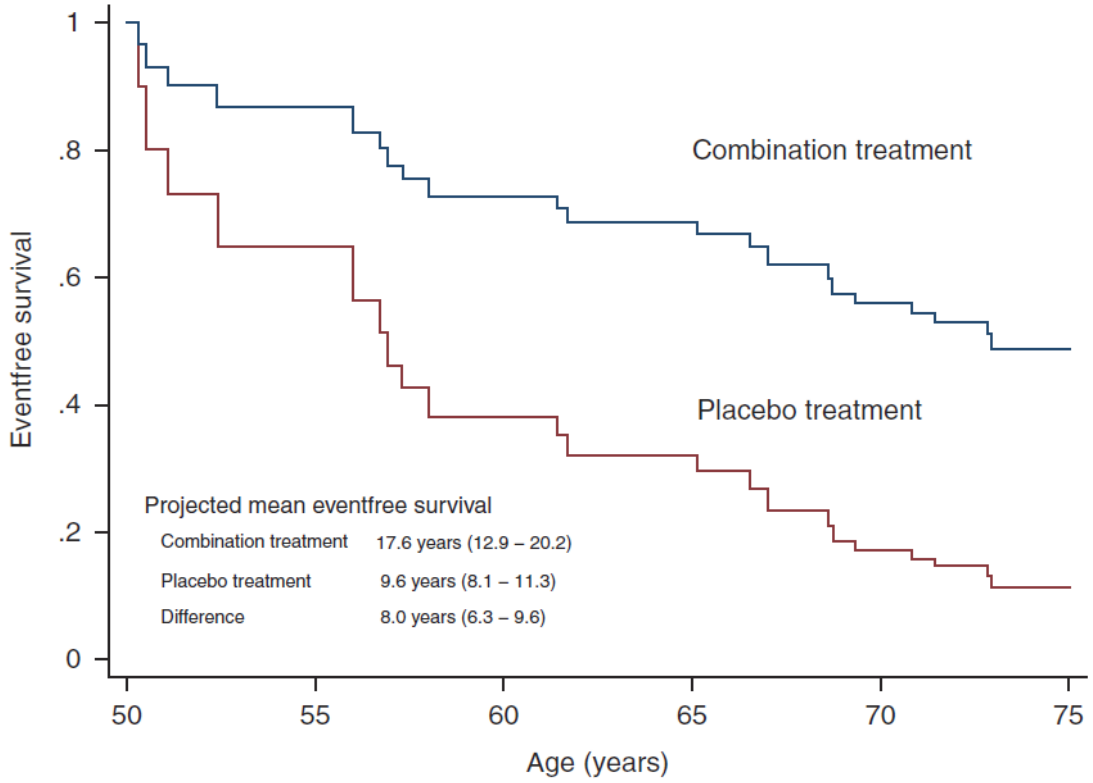
Heterogeneity by diabetes status: p=0.31

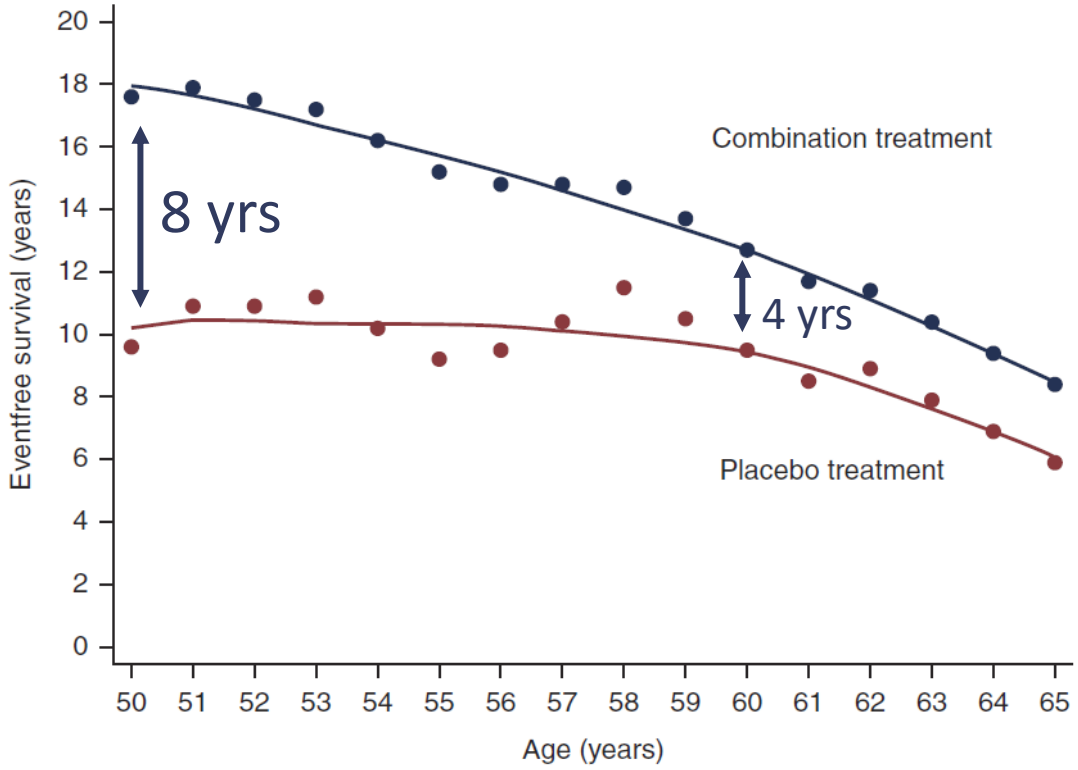
SMART-C

SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium.Lancet. 2022 Nov 19;400(10365):1788-1801

Lifetime benefit of combined treatment ACEi and SGLT2i

Combination vs no treatment delays dialysis by 8 years



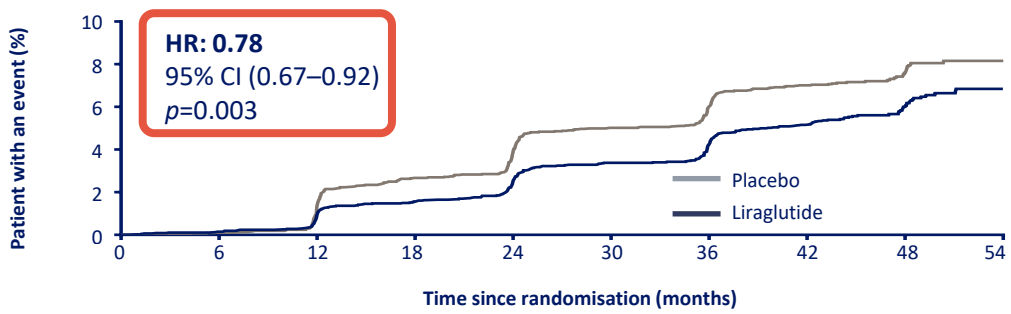


Vart et.al. Clin J Am Soc 2022

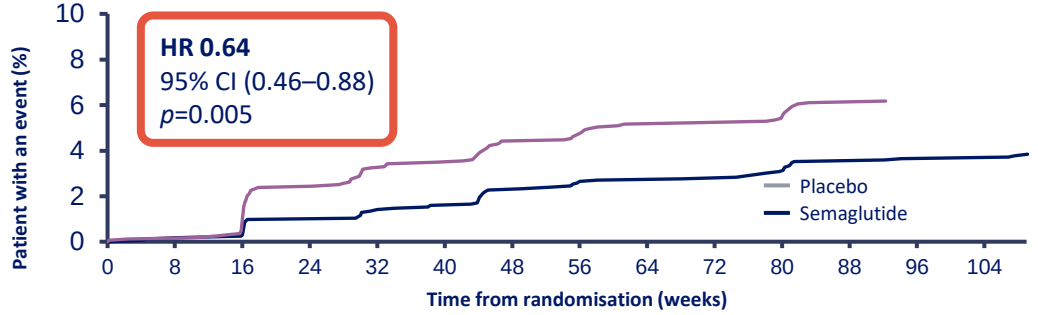
Renal outcomes from CVOTs

REWIND, LEADER, SUSTAIN 6 and AMPLITUDE-O

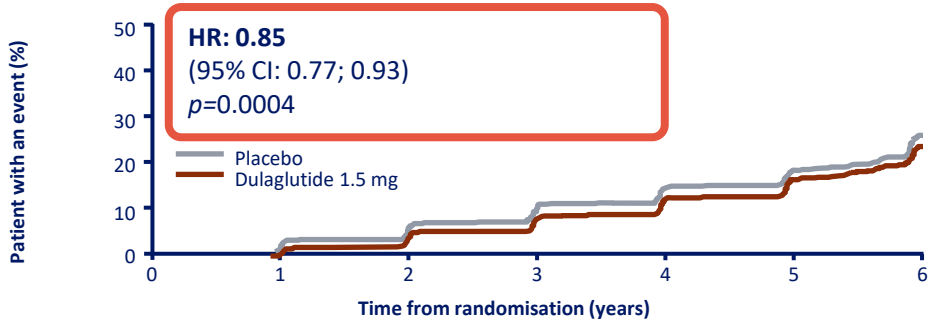
LEADER (Liraglutide)[1]: Composite kidney outcome
Macroalbuminuria, doubling of serum creatinine, ESRD or renal death



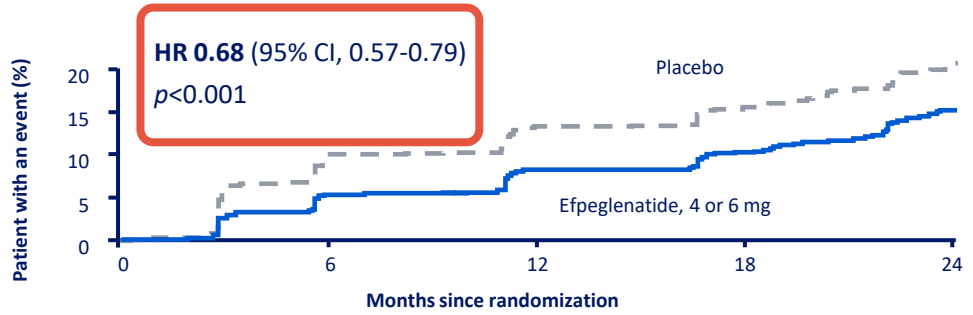
SUSTAIN 6 (Semaglutide)[2]: Composite kidney outcome
Macroalbuminuria, doubling of serum creatinine or ESRD



REWIND (Dulaglutide)[3]: Composite kidney outcome
Macroalbuminuria, sustained ≥30% decline in eGFR, or new chronic RRT*



Amplitude-O (Efpeglenatide)[4]: Composite kidney outcome#



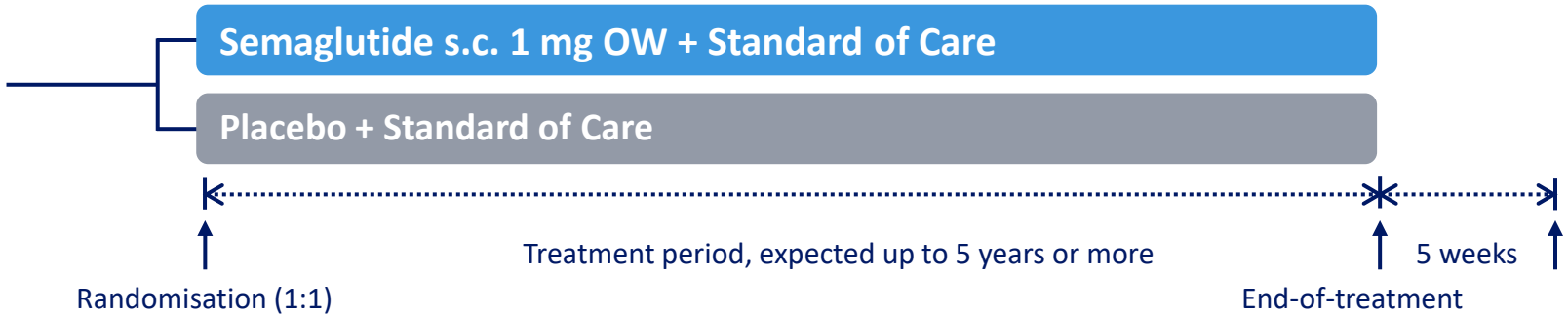
Composite renal outcome: New macroalbuminuria (ACR > 300 mg/g) and ≥ 30% rise from baseline decrease in eGFR by ≥ 40% from baseline for ≥ 30 days, or end-stage kidney disease

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease

1. Mann JFE et al. N Engl J Med 2017; 377(9):839–848; 2. Marso SP et al. N Engl J Med 2016; 375:1834-1844; 3. Gerstein HC et al. Lancet 2019; 394(10193):131–138; 4. Gerstein HC et al. N Engl J Med. 2021; 385:896-907

FLOW: Study Design

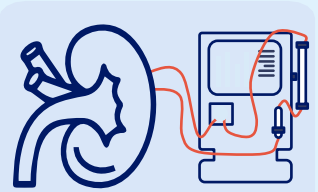
3508 patients
- T2D, HbA_{1c} ≤10%
- eGFR ≤75 to ≥50* and UACR >300 to <5000 mg/g *OR* eGFR <50 to ≥25* and UACR >100 to <5000 mg/g
- RAAS blocker



Time to first occurrence of a composite endpoint consisting of:

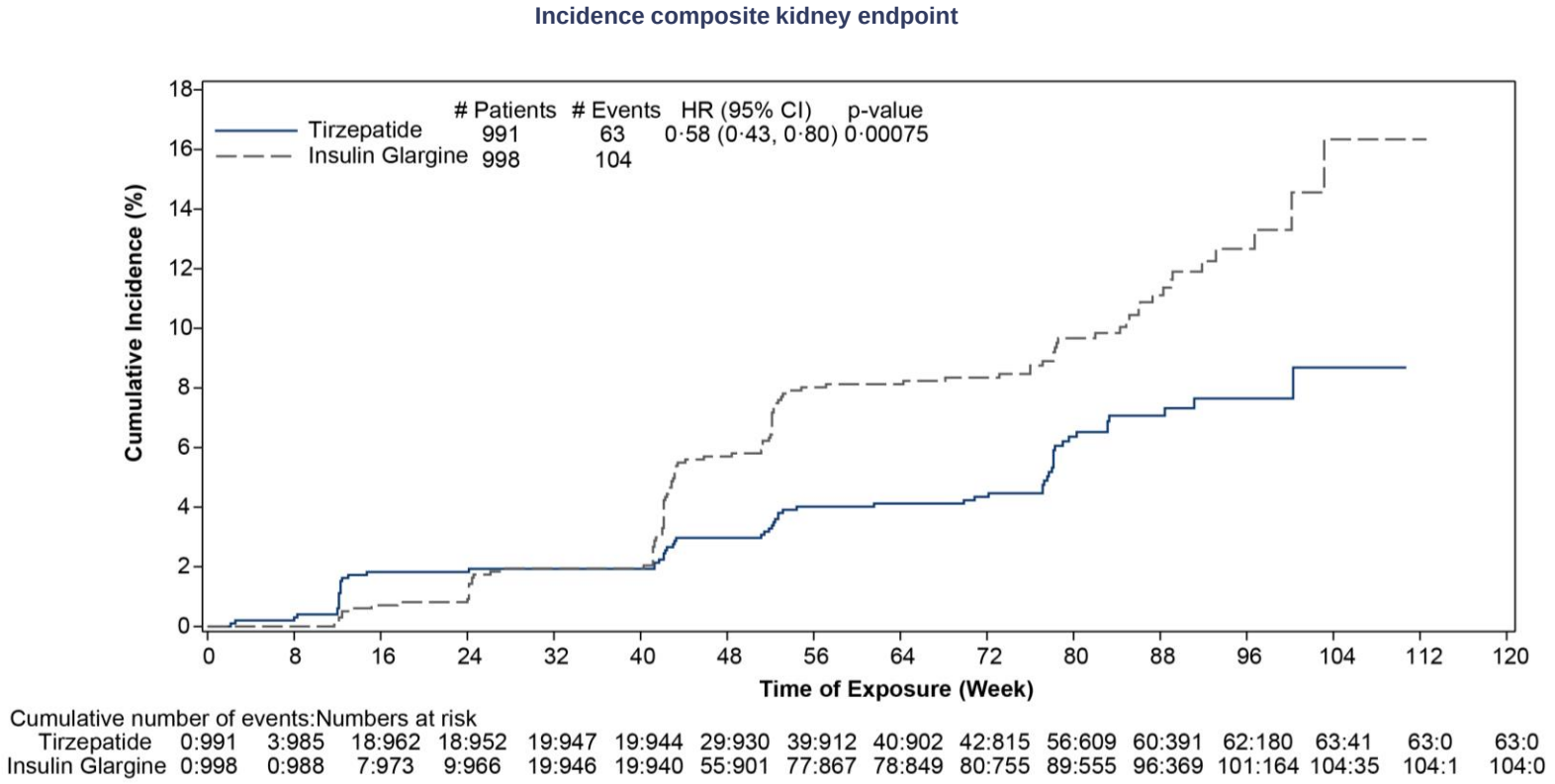
Onset of persistent* **≥50% eGFR reduction** (CKD-EPI) compared with baseline

Onset of persistent* eGFR <15mL/min /1.73 m^2 or **Renal replacement therapy****



Cardiovascular or renal death

Tirzepatide Reduces the Risk of the Composite Kidney Endpoint (Macroalbuminuria, 40% eGFR Decline, ESKD, Renal Death)

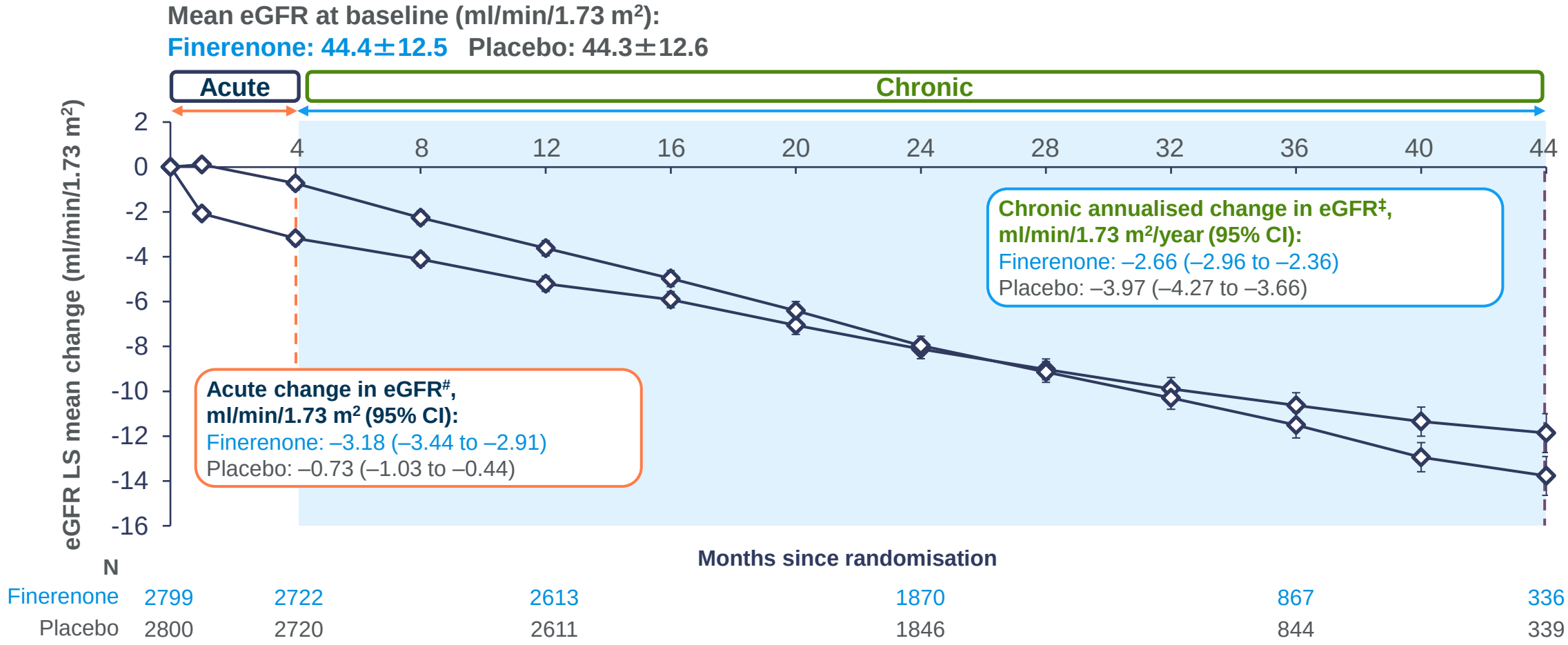


Component	Treatment	N (%)	HR (95%CI)
eGFR decline ≥40% from baseline	TZP	38 (3.8%)	0.87 (0.56,1.33)
	iGLAR	45 (4.5%)	
Renal death	TZP	0	-
	iGLAR	0	
Progression to ESKD	TZP	0	-
	iGLAR	5 (0.5%)	
New onset macroalbuminuria[a]	TZP	25 (2.5%)	**0.41 (0.26,0.66) ***
	iGLAR	61 (6.1%)	

Cumulative incidence of time to renal composite endpoint 1. HR, CI, and p-value are derived from a Cox proportional-hazards model with treatment (tirzepatide vs. insulin glargine) as a fixed effect. Heerspink et.al. Lancet Diabetes & Endocrinology

HR estimate with CI is not calculated when either the TZP or iGLAR arm has no event. [a]UACR ≥30 mg/g. *P<.05 versus iGLAR.

FIDELIO-DKD: The MRA Finerenone Reduces the Rate of eGFR Decline Over Time in Type 2 Diabetes and CKD



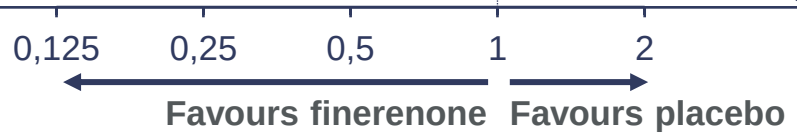
*Mixed model analysis of eGFR over time. Full analysis set; #LS mean change in eGFR slope from baseline to month 4; ‡LS mean change in eGFR slope from month 4 to the permanent discontinuation or end-of-study visit

CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least-squares

Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229

CV and kidney benefits of finerenone were consistent among patients treated with and without an SGLT-2i at baseline

Endpoint	Finerenone n/N (n/100 PY)	Placebo n/N (n/100 PY)	Hazard ratio (95% CI)	Adjusted HR (95% CI)*	*p*-value for interaction
CV composite[#]					
No SGLT-2i	786/6081 (4.4)	887/6068 (5.1)		0.87 (0.79–0.96)	0.46
SGLT-2i	39/438 (3.0)	52/439 (4.1)		0.67 (0.42–1.07)	
HHF					
No SGLT-2i	246/6081 (1.4)	303/6068 (1.7)		0.80 (0.68–0.95)	0.29
SGLT-2i	10/438 (0.7)	22/439 (1.7)		0.44 (0.19–0.99)	
eGFR 57% kidney composite[‡]					
No SGLT-2i	351/6081 (2.1)	448/6068 (2.6)		0.80 (0.69–0.92)	0.29
SGLT-2i	9/438 (0.7)	17/439 (1.4)		0.42 (0.16–1.08)	
eGFR 40% kidney composite[§]					
No SGLT-2i	818/6081 (5.0)	961/6068 (5.9)		0.84 (0.76–0.92)	0.59
SGLT-2i	36/438 (2.9)	34/439 (2.8)		0.70 (0.41–1.21)	

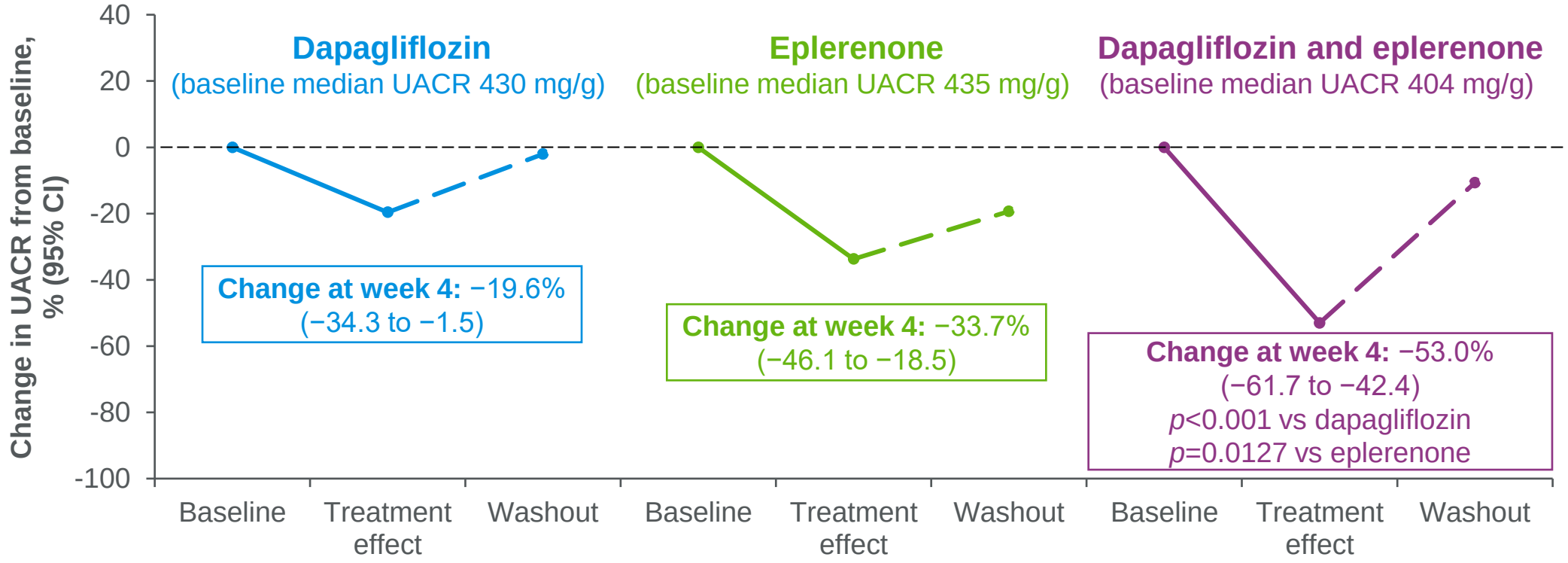


*Adjusted HR for HbA1c, SBP, UACR at baseline (log-transformed), eGFR at baseline; [#]composite of CV death, nonfatal MI, nonfatal stroke or HHF; [‡]eGFR 57% kidney composite outcome defined as kidney failure (ESKD or eGFR <15 ml/min/1.73 m^2), a sustained ≥57% decrease in eGFR from baseline (equivalent to a doubling of serum creatinine) for ≥4 weeks, or renal death; [§]eGFR 40% kidney composite outcome defined as kidney failure (ESKD or eGFR <15 ml/min/1.73 m^2), a sustained ≥40% decrease in eGFR from baseline maintained for ≥4 weeks, or renal death
HbA1c, glycated haemoglobin; PY, patient-years

1. Rossing P, *et al. Diabetes Care* 2022; doi: 10.2337/dc22-0294; 2. Rossing P, *et al. ASN.* 2021. Presentation

FIDELITY
Finerenone in chronic kidney disease and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis

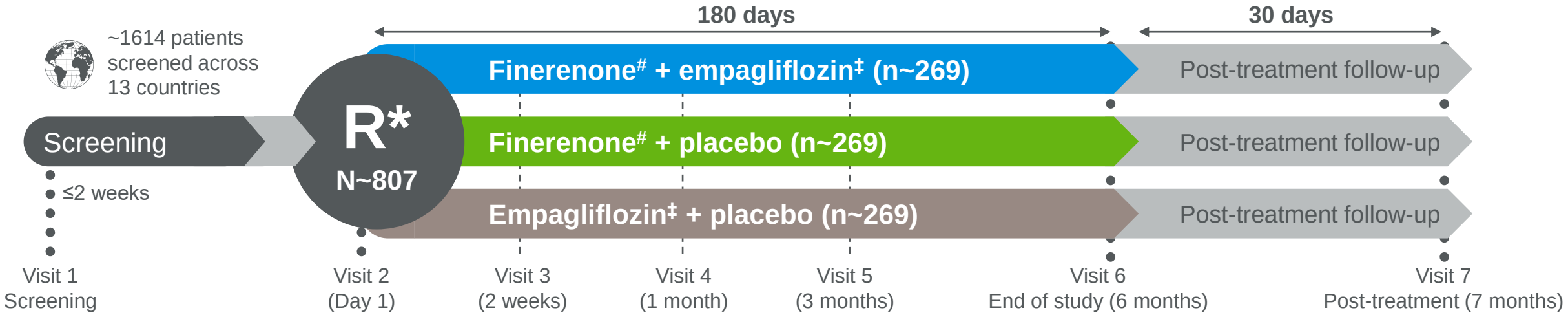
ROTATE-3: Additive kidney benefit of SGLT2i and MRA



Significant fewer hyperkalemia with combination treatment (4.3%) vs. eplerenone (17.4%) vs dapagliflozin (0%)

Provenzano M, *et al*. *J Am Soc Nephrol* 2022;33:1569–1580

CONFIDENCE is a phase II, randomised, double-blind, multicentre, prospective trial



Primary endpoints

Relative change in UACR from baseline to 180 days for:

Finerenone + empagliflozin combination vs **empagliflozin** OR **Finerenone + empagliflozin combination** vs **finerenone**

Key safety endpoints

- Change in eGFR from baseline to 30 days
- Change in eGFR from 30 days to 180 and 210 days
- eGFR decline >30% from baseline to 30 days
- Incidences (n, %) of: AKI, hyperkalaemia, severe hypoglycaemia, symptomatic hypotension, and genital mycotic events
- Monitoring of AEs, ECG, laboratory and vital signs

*Randomised patients stratified by eGFR (<60 and ≥60 ml/min/1.73 m²) and UACR (≤850 mg/g and >850 mg/g); #10 to 20 mg od based on serum [K^+] and eGFR. Up-titration to target dose of 20 mg od allowed from visit 4 onwards. Down-titration allowed at any time during the study for safety reasons; ‡10 mg od

AKI, acute kidney injury; ECG, electrocardiogram; [K^+], potassium concentration

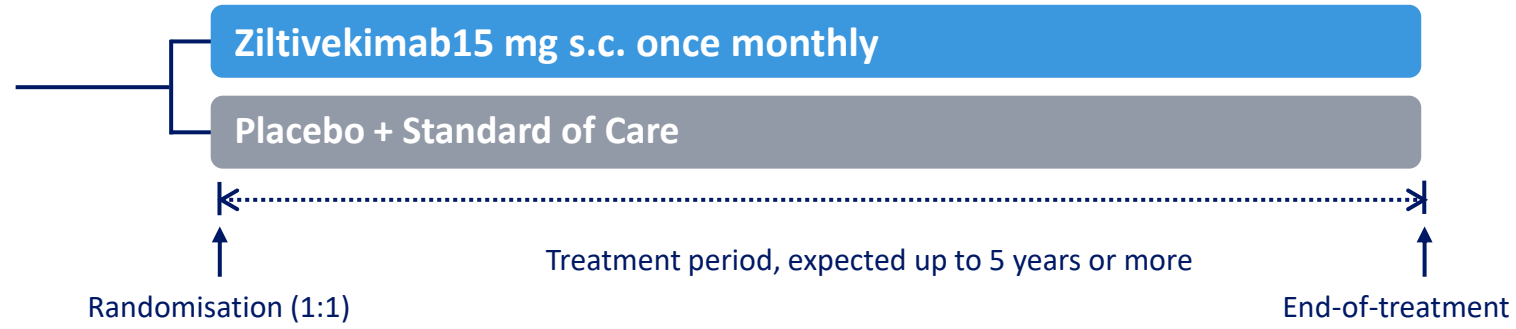
Bayer. https://www.clinicaltrials.gov/ct2/show/NCT05254002 [accessed 23 Aug 2022]

CONFIDENCE

ZEUS trial: Ziltivekimab in chronic kidney disease

6200 patients

- T2D, HbA_{1c} ≤10%
- eGFR 15 -60
- hsCRP > 2mg/L
- Evidence of CV disease

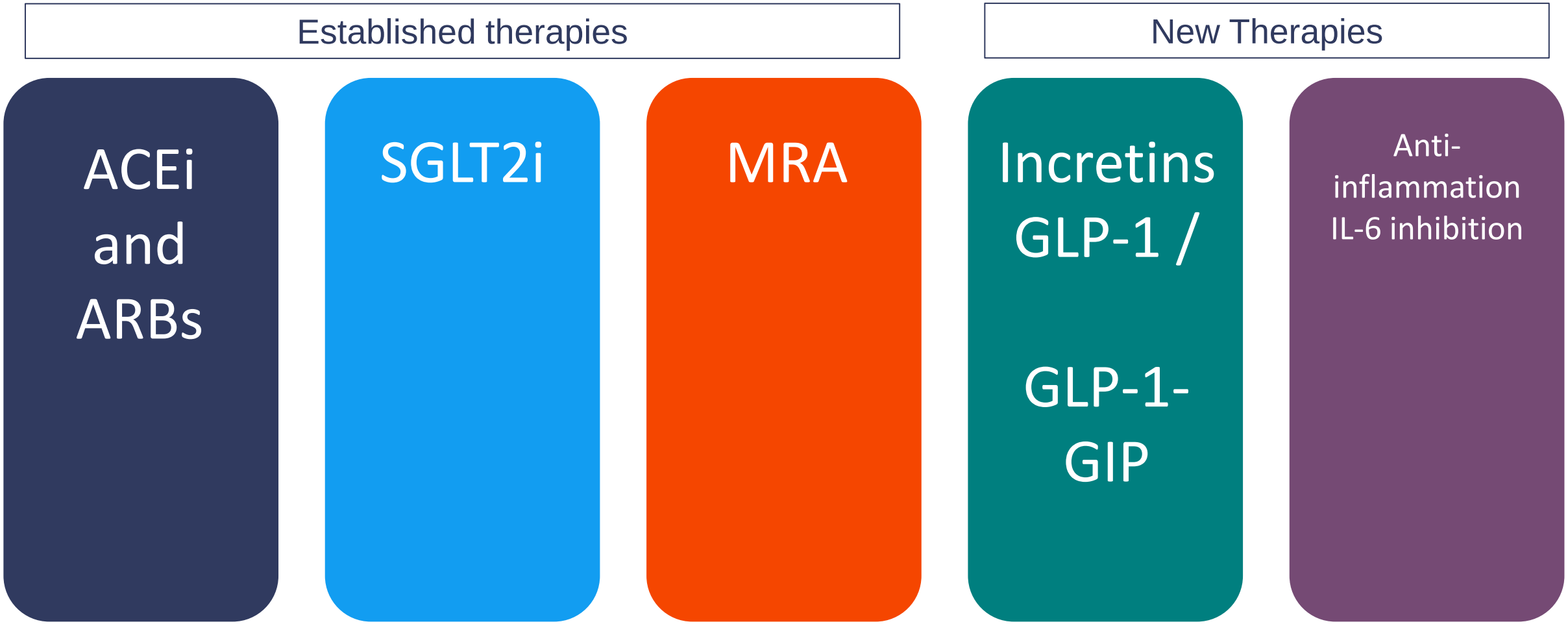


Time to first occurrence of a composite endpoint consisting of:

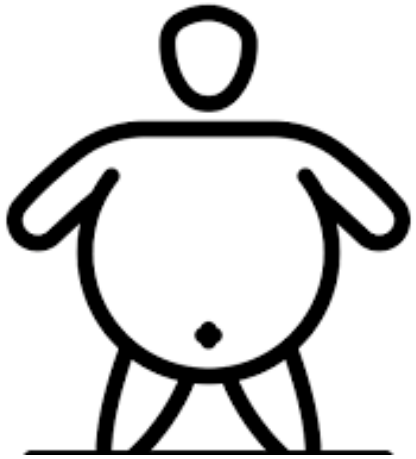
Primary: Cardiovascular (CV) death, non-fatal Myocardial Infarction (MI) and non-fatal stroke. [Time Frame: From randomisation (month 0) to end-of-study (up to 48 months)]

Secondary: eGFR decline

Current and new treatment strategies for patients with CKD



Algorithm to personalize treatment

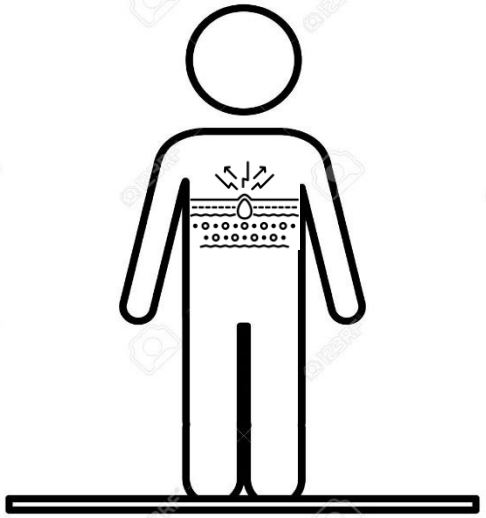


Obese individual
Hba1c 9.1%
eGFR 46 ml/min
UACR 52 mg/mmol

SGLT2i + GLP1-RA

NTproBNP 850 pg/mL
Heart Failure NYHA class III
Hba1c 7.1%
eGFR 53 ml/min
UACR 109 mg/mmol
BMI 19 kg/m^2

SGLT2i + MRA



Hba1c 8.0%
CRP>2mg/L
eGFR 46 ml/min
UACR 52 mg/mmol

SGLT2i + IL-6 mAB