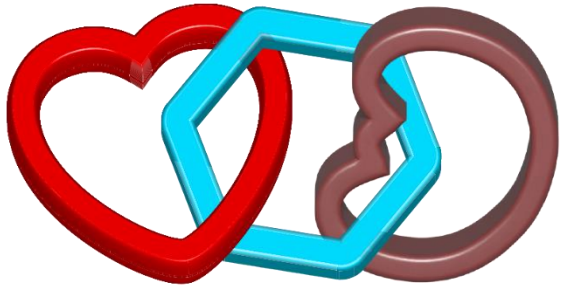
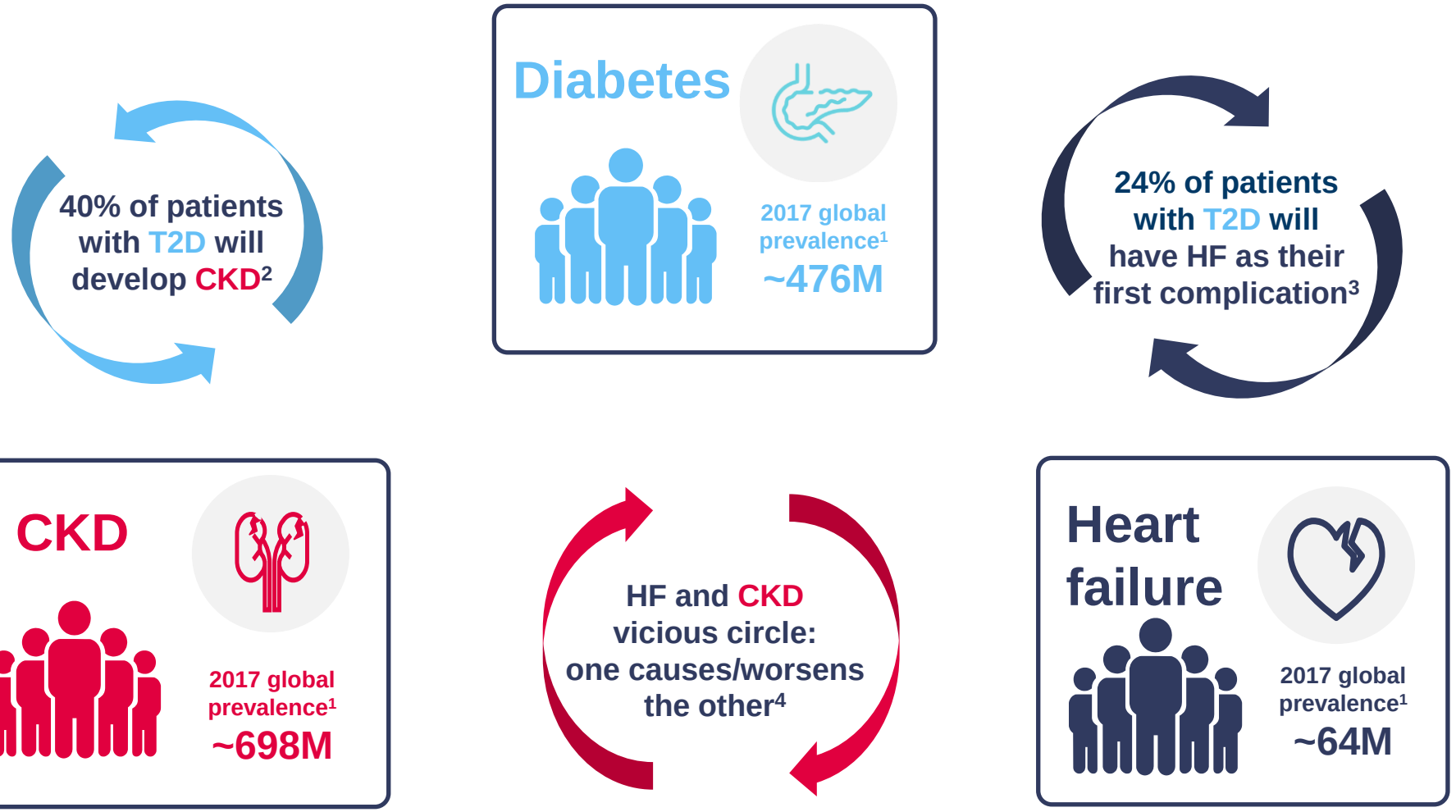


Nieuwe therapieën voor de behandeling van nierziekten

Prof. dr. Hiddo Lambers Heerspink

Klinisch farmacoloog, UMC Groningen

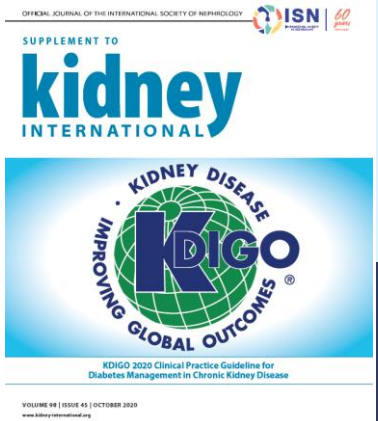
CKD, heart failure, and T2D are interrelated, leading to a vicious circle of cardiac, renal, and metabolic risk



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

2022 KDIGO treatment algorithm for patients with type 2 diabetes and CKD



Lifestyle therapy

Physical activity
Nutrition
Weight loss

First-line therapy
eGFR ≥20 mL/min/1.73m^2

Metformin
eGFR <45: reduce dose
eGFR <30 or dialysis: D/C

+

SGLT2i
eGFR <20: do not initiate
Dialysis: D/C

Additional drug therapy as needed for glycemic control

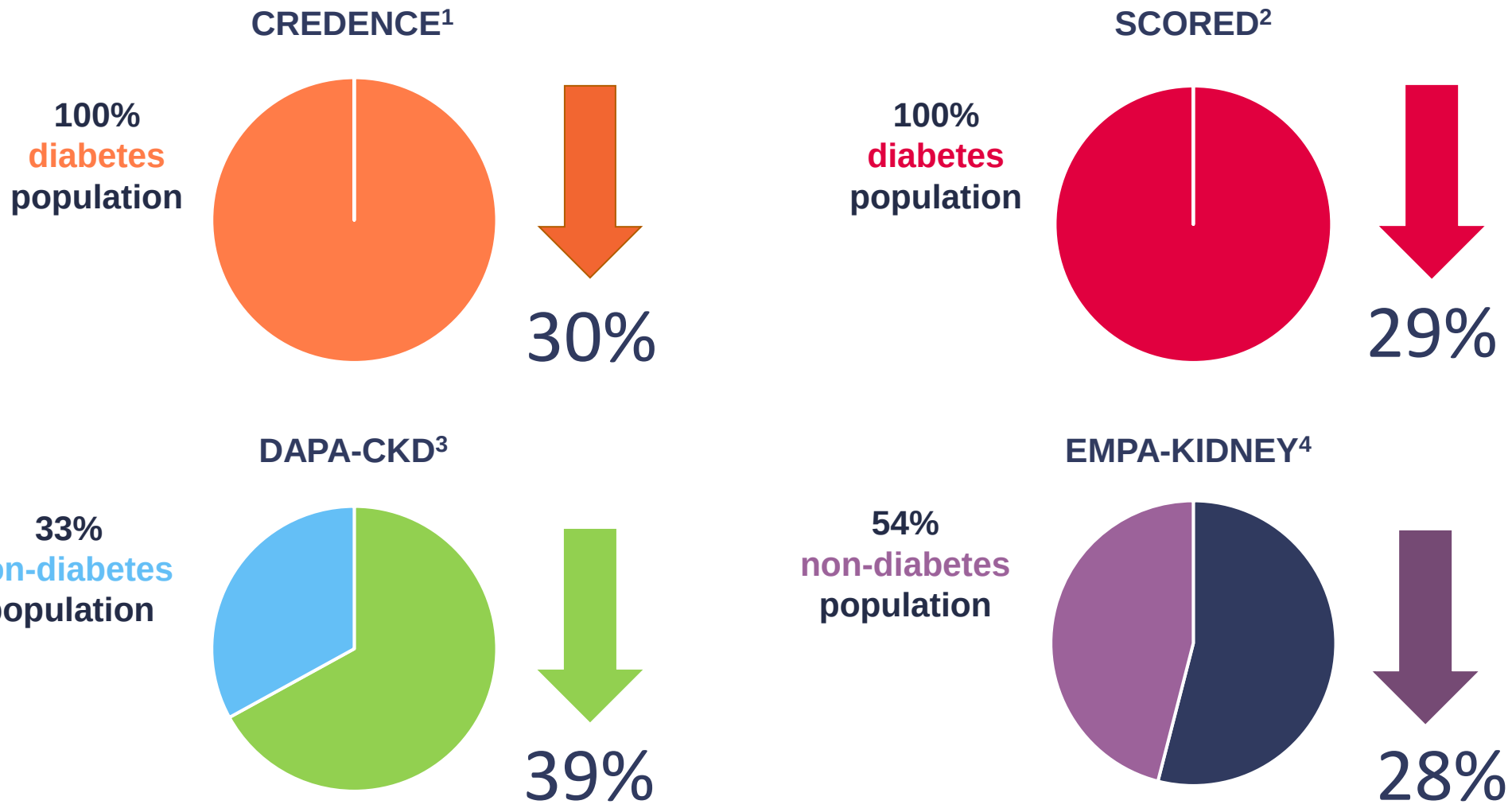
GLP-1 RA
(preferred)

DPP-4i | Insulin
SU | TZD
AGi

- Guided by patient preferences, comorbidities, eGFR and cost
- Includes patients with eGFR<30 mLmin/1.73m^2 or treated with dialysis

AGi, alpha-glucosidase inhibitor; CKD, chronic kidney disease; D/C, discontinue; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.
de Boer IH et al. *Kidney Int.* 2022; In Press.

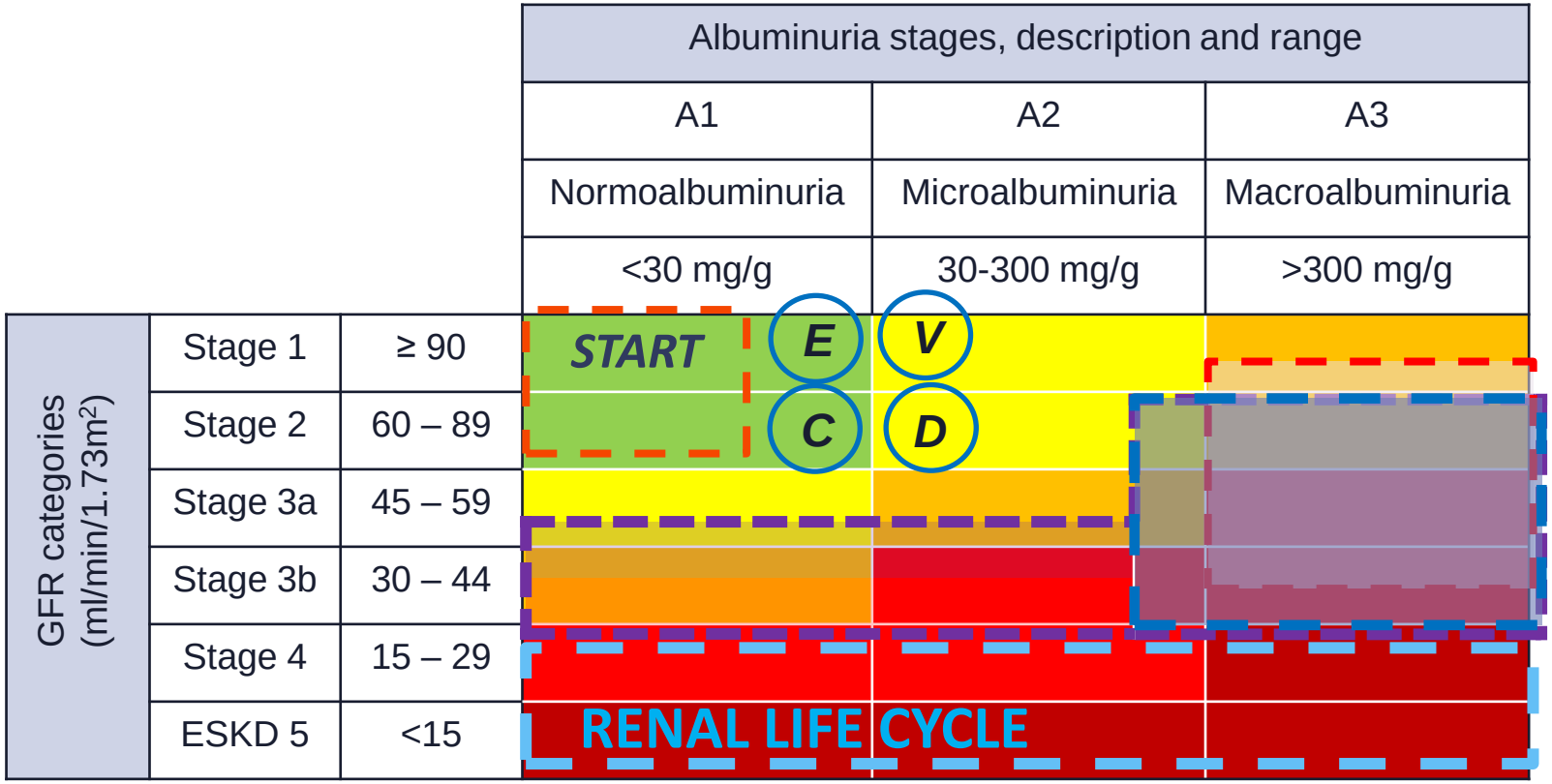
SGLT2 inhibitor trials have recruited patients with CKD with and without diabetes



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

Kidney outcome trials with SGLT2 inhibitors address the spectrum of CKD



E=EMPAREG-Outcome; C=CANVAS; D=DECLARE TIMI-58

CREDENCE (DKD only)
eGFR ≥30 to <90 ml/min/1.73m²
and UACR ≥300 mg/g

DAPA-CKD (CKD)
eGFR ≥25 to <75 ml/min/1.73m²
and UACR ≥200 mg/g

EMPA-KIDNEY (CKD)
eGFR ≥45 to <75 ml/min/1.73m²
and UACR ≥200 mg/g
OR
eGFR ≥20 to <4 ml/min/1.73m²

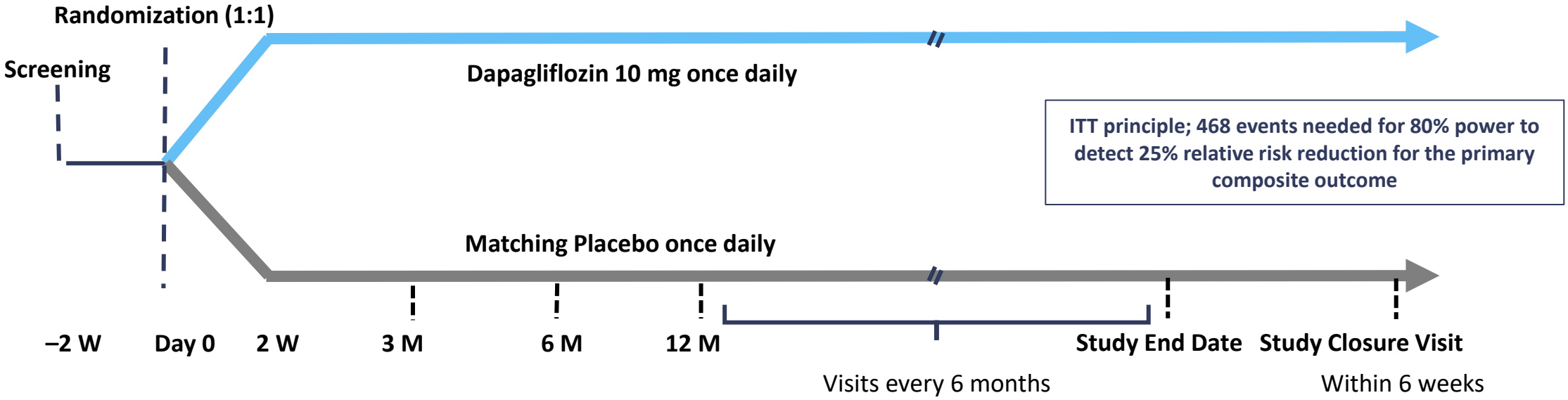
RENAL LIFE CYCLE (CKD)
eGFR ≤25 mL/min/1.73m²
Kidney Transplantation
Peritoneal or Hemodialysis

CKD, chronic kidney disease; DKD, diabetic kidney disease, eGFR, glomerular filtration rate; GFR, glomerular filtration rate
Heerspink HJL, et.al. *Nephrol Dial Transplant* 2020;35:274–282

RENAL LIFE CYCLE Trial

Key inclusion criteria:
- ≥18 years of age
- Three main patient groups:
  - eGFR ≤25 mL/min/1.73m^2
  - Kidney Transplantation and eGFR ≤ 45 mL/min/1.73m^2
  - Peritoneal or hemodialysis (residual diuresis > 500 mL/24hr)

Key exclusion criteria:
- Type 1 diabetes
- Life expectancy < 6 months
- Concurrent treatment with SGLT2 inhibitor
- Scheduled start dialysis or kidney transplantation < 6 months
- Known severe hepatic impairment

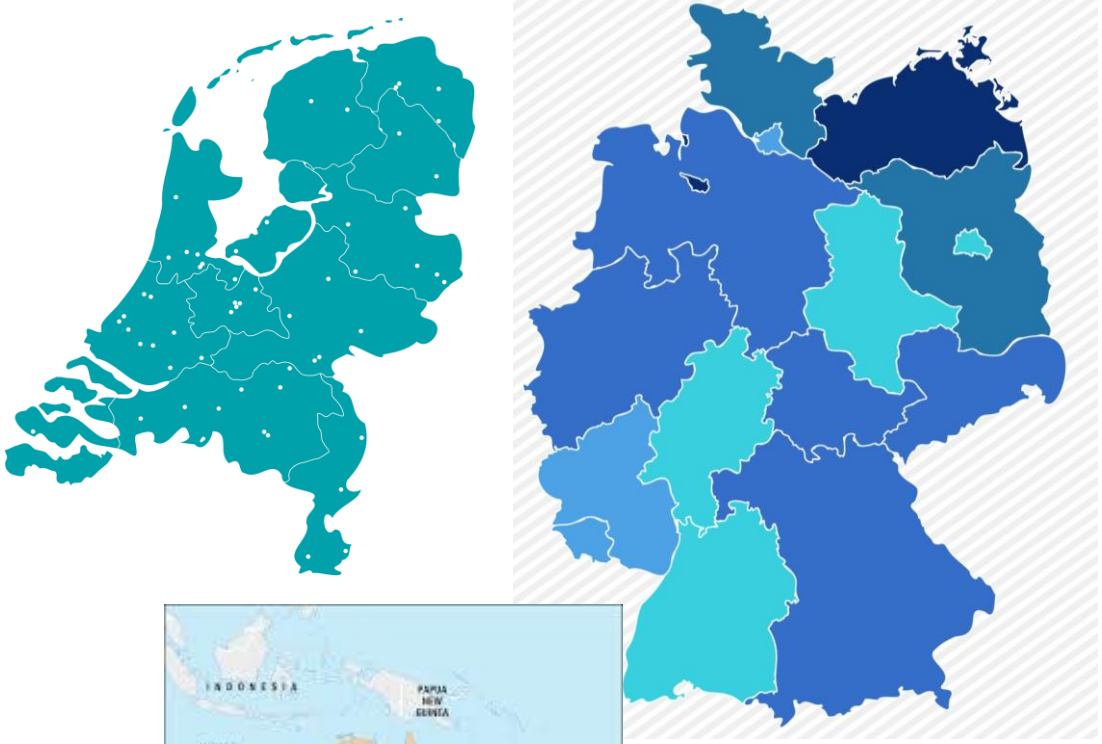


- Primary outcome: All cause mortality; heart failure hospitalization; dialysis or kidney transplantation (in pre-dialysis stratum)
- Outcome analysis based on Cox proportional hazard model stratified by subgroup and type 2 diabetes status

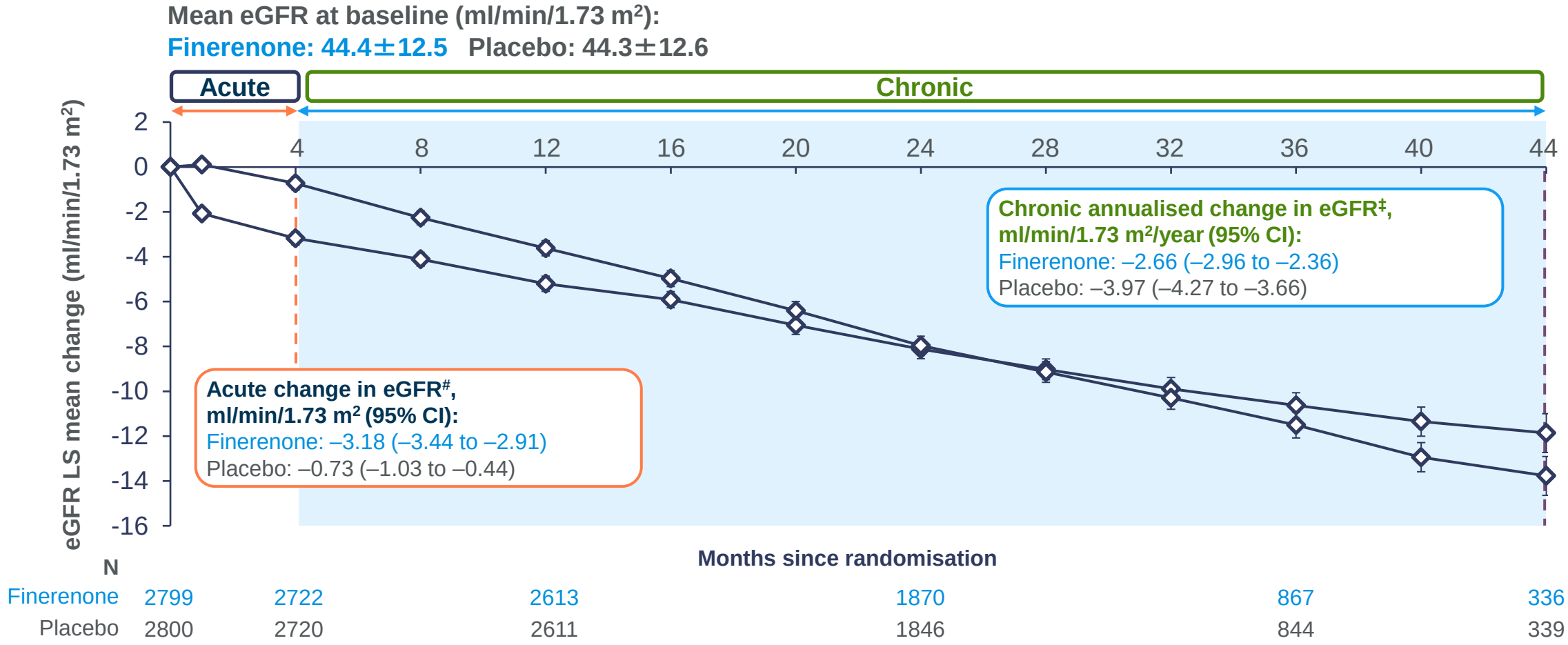
eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; UACR, urinary albumin-to-creatinine ratio

Renal Life Cycle: A joint Dutch-German-Australian effort

- An investigator initiated Randomized Placebo-Controlled Trial (Coordination Center Groningen)
- 90 Peripheral and Academic hospitals in the Netherlands, Germany and Australia
- First patient enrolled in October 2022

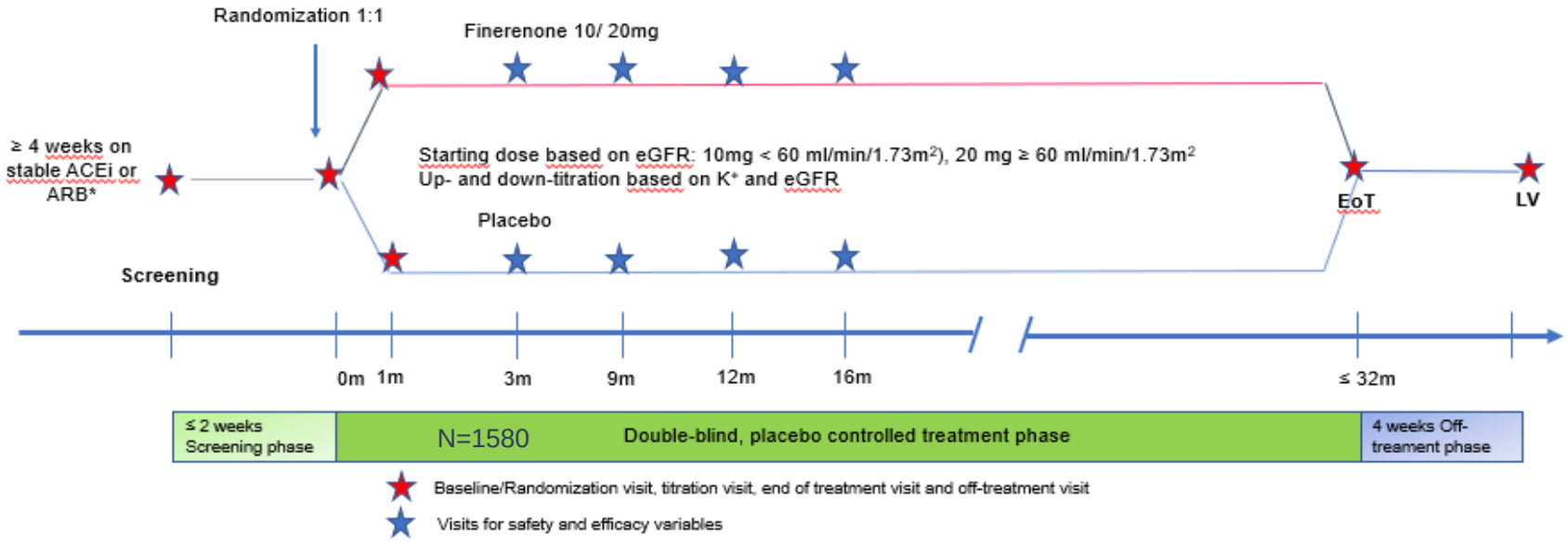


FIDELIO-DKD: The MRA finerenone reduces the rate of eGFR decline over time in Type 2 Diabetes and CKD



*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

FIND-CKD: finerenone in Non-Diabetic CKD



Innovative ph3 design

- eGFR slope is a valid endpoint from a clinical and increasingly from regulatory perspective
- Full decentralized clinical trial approach (pilot for Bayer)

Study Endpoints

Primary Endpoint

- **Total eGFR slope difference**

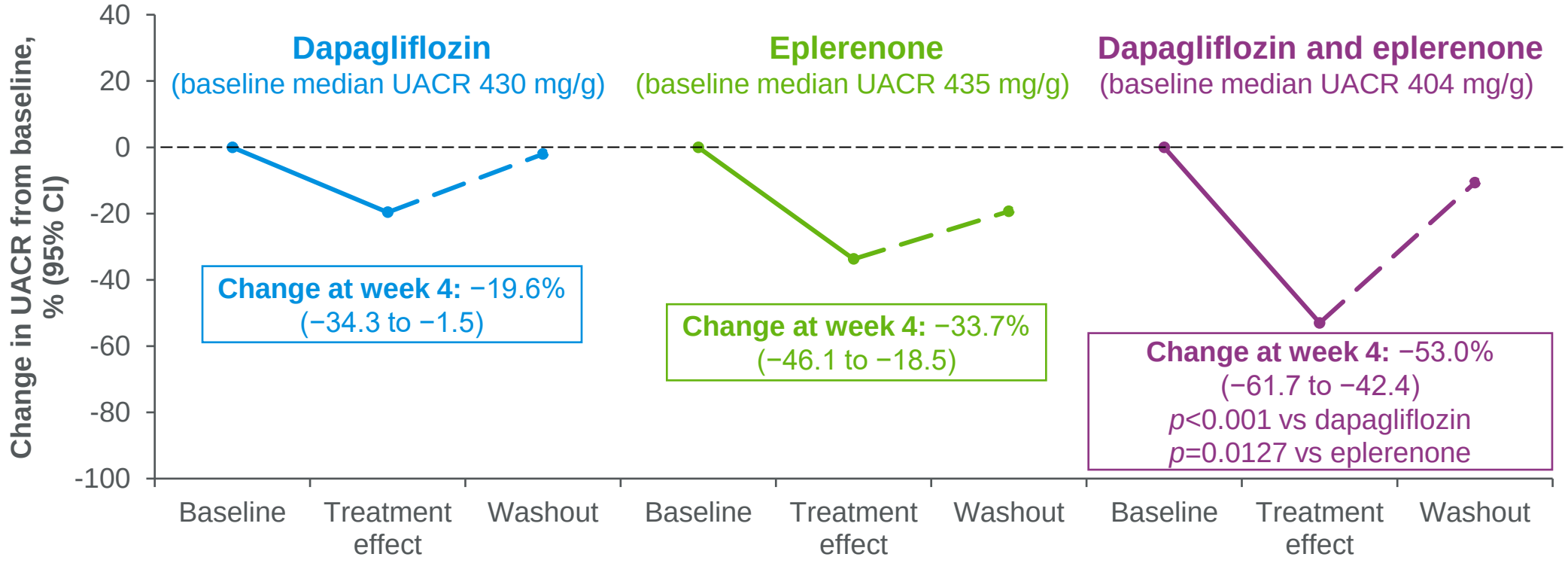
Supportive evidence

- Chronic eGFR slope
- eGFR change from baseline to 1 month off-treatment
- ≥ 30% UACR reduction at month 6

Secondary Endpoints

- Time to the composite of confirmed eGFR decline of ≥57%, kidney failure, HHF and CV death
- Time to the composite of confirmed eGFR decline of ≥57%, kidney failure
- Time to HHF or CV death

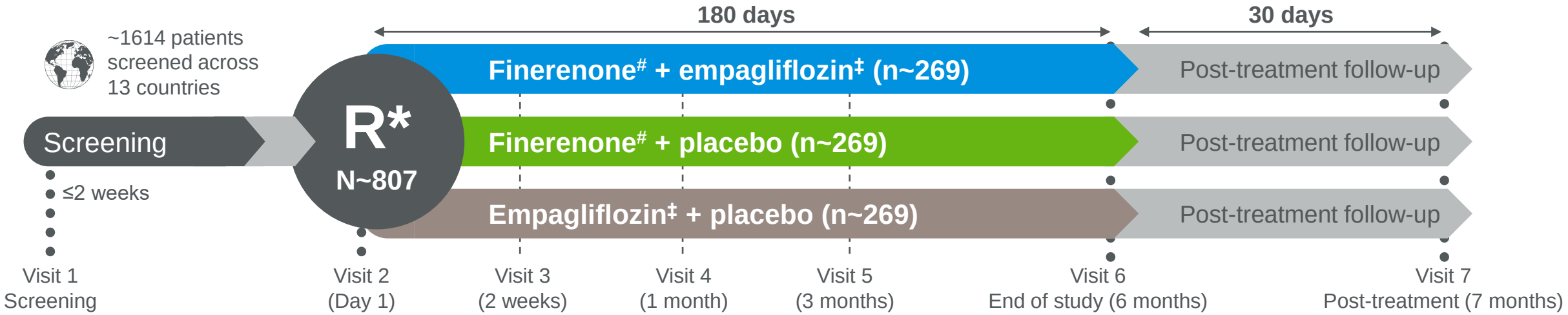
ROTATE-3: additive kidney benefit of SGLT2i and MRA



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

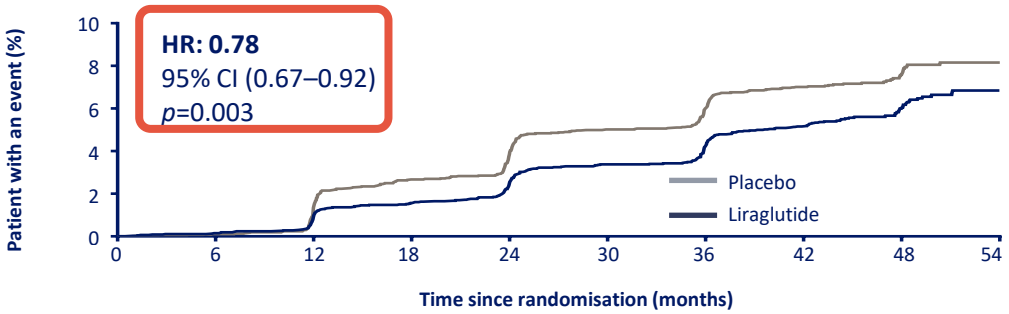
Bayer. https://www.clinicaltrials.gov/ct2/show/NCT05254002 [accessed 23 Aug 2022]

CONFIDENCE

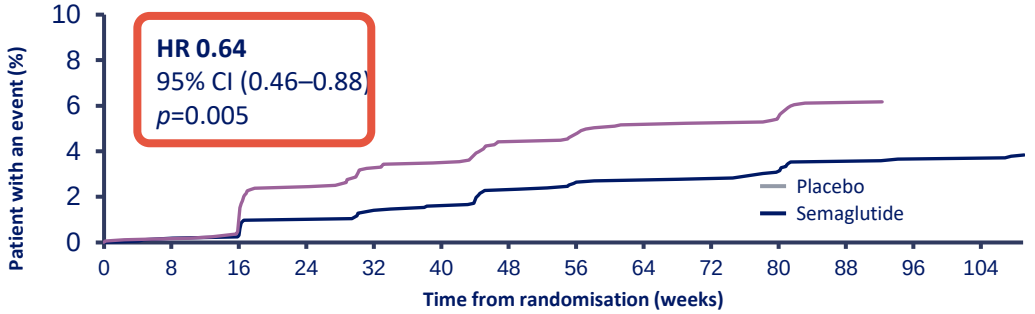
Renal outcomes from CVOTs

REWIND, LEADER, SUSTAIN 6 and AMPLITUDE-O

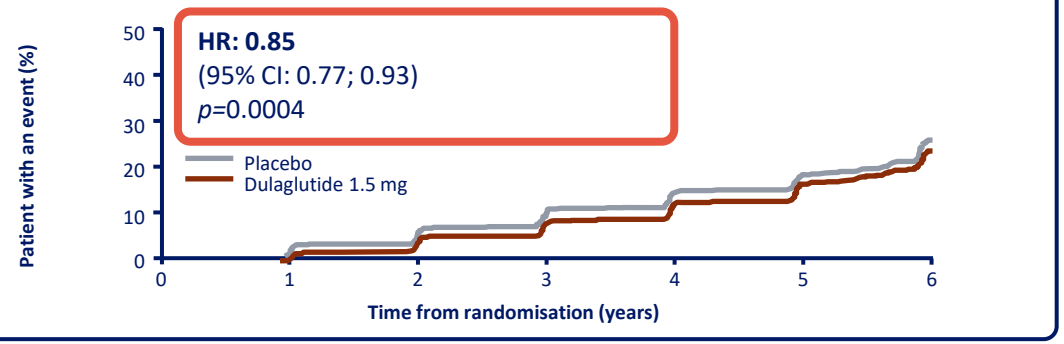
LEADER (Liraglutide)[1]: Composite kidney outcome
Macroalbuminuria, doubling of serum creatinine, ESRD or renal death



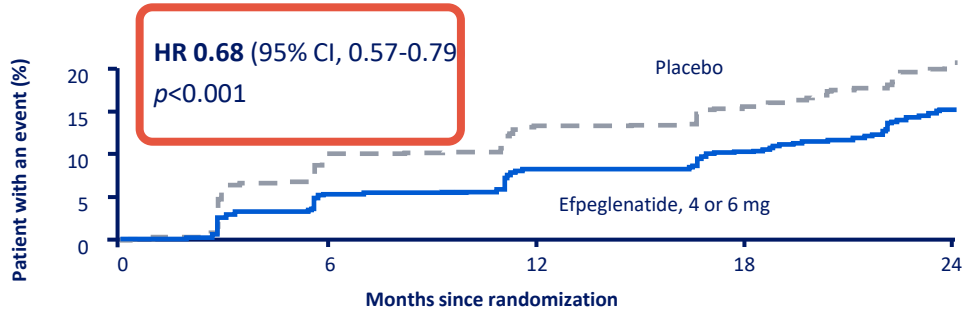
SUSTAIN 6 (Semaglutide)[2]: Composite kidney outcome
Macroalbuminuria, doubling of serum creatinine or ESRD



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



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



*RRT is defined as either dialysis or renal transplantation; #Composite renal outcome defined by one or more of new macroalbuminuria (ACR > 300 mg/g) and ≥ 30% rise from baseline decrease in eGFR by ≥ 40% from baseline for ≥ 30 days, Kidney replacement therapy for ≥ 90 days, eGFR < 15 ml/min/1.73 m² for ≥ 30 days
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

Semaglutide s.c. 1 mg OW + Standard of Care

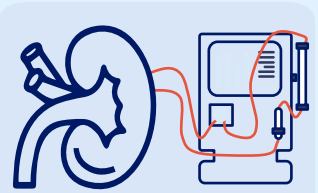
Placebo + Standard of Care

Randomisation (1:1) — Treatment period, expected up to 5 years or more — 5 weeks — End-of-treatment

Time to first occurrence of a composite endpoint consisting of:

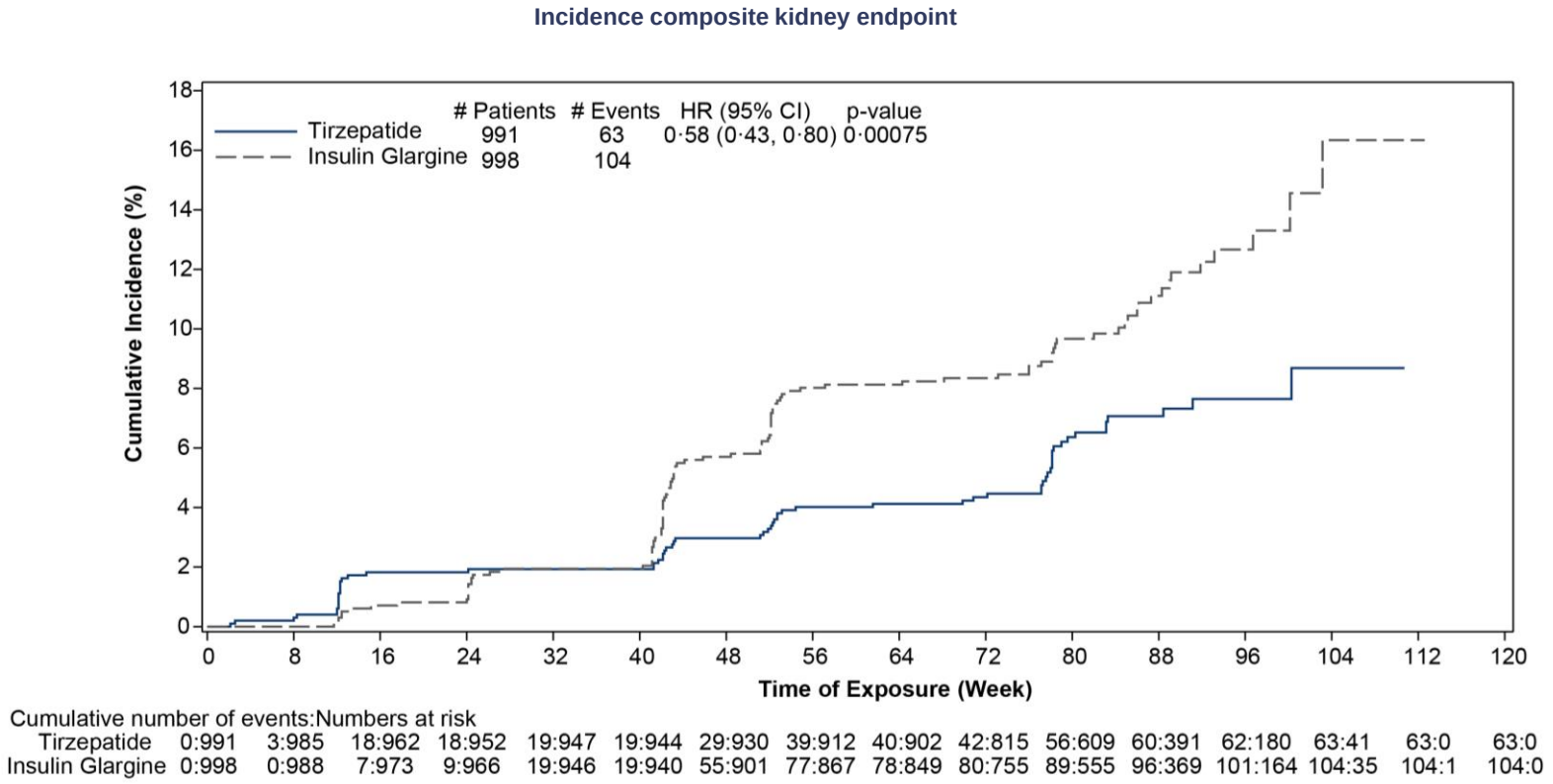
Onset of persistent* **≥50% eGFR reduction** (CKD-EPI) compared with baseline

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)

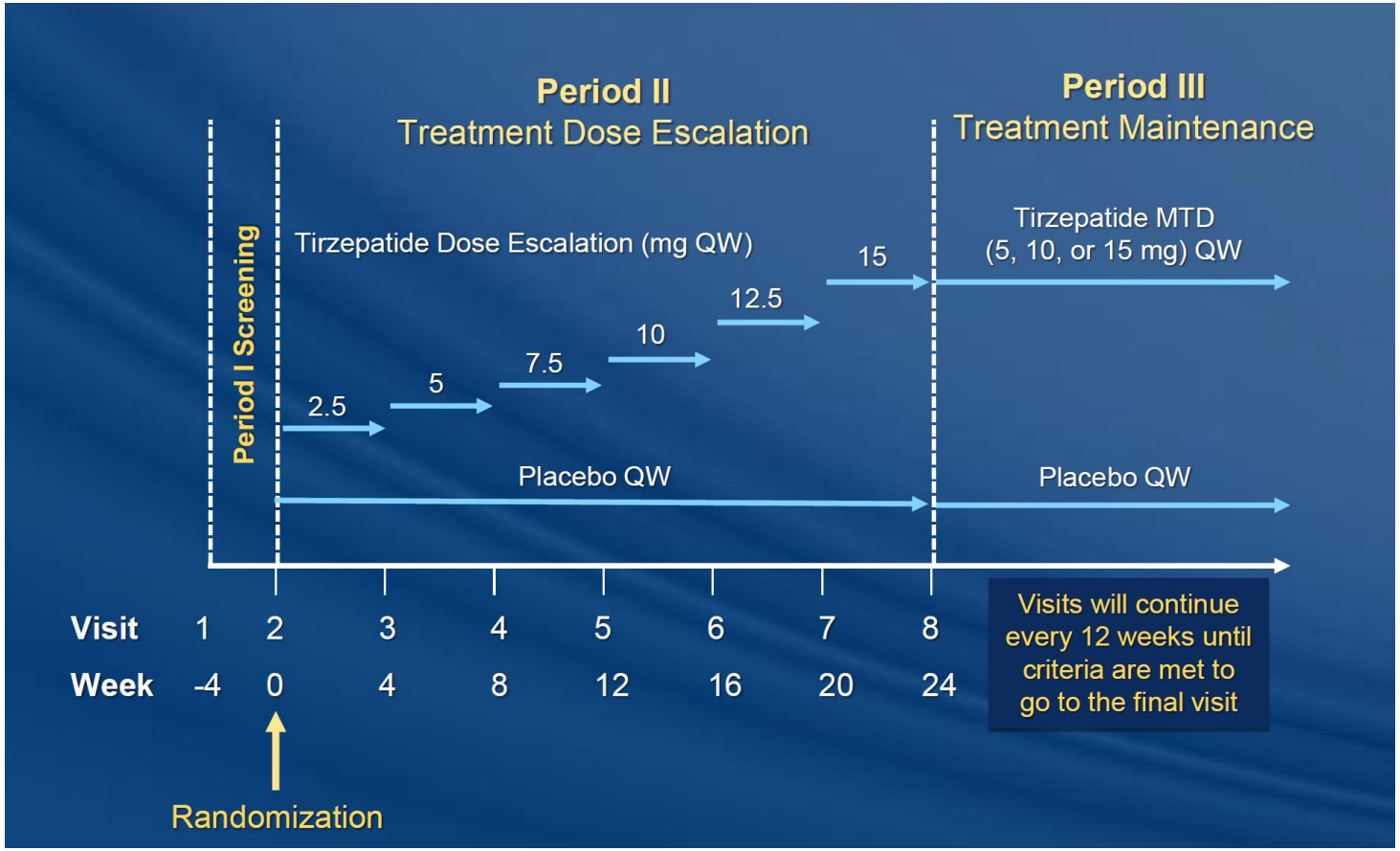


Component	Treatment	N (%)	HR (95%CI)
eGFR decline ≥40% from baseline	TZP	38 (3.8%)	0.87 (0.56,1.33)
	iGLAR	45 (4.5%)	
Renal death	TZP	0	-
	iGLAR	0	
Progression to ESKD	TZP	0	-
	iGLAR	5 (0.5%)	
New onset macroalbuminuria[a]	TZP	25 (2.5%)	**0.41 (0.26,0.66) ***
	iGLAR	61 (6.1%)	

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.

SURMOUNT-MMO



Endpoint:

Primary

- Time to CV composite

Secondary

- Time to new-onset diabetes
- Renal endpoint (Win-ratio)

Population:

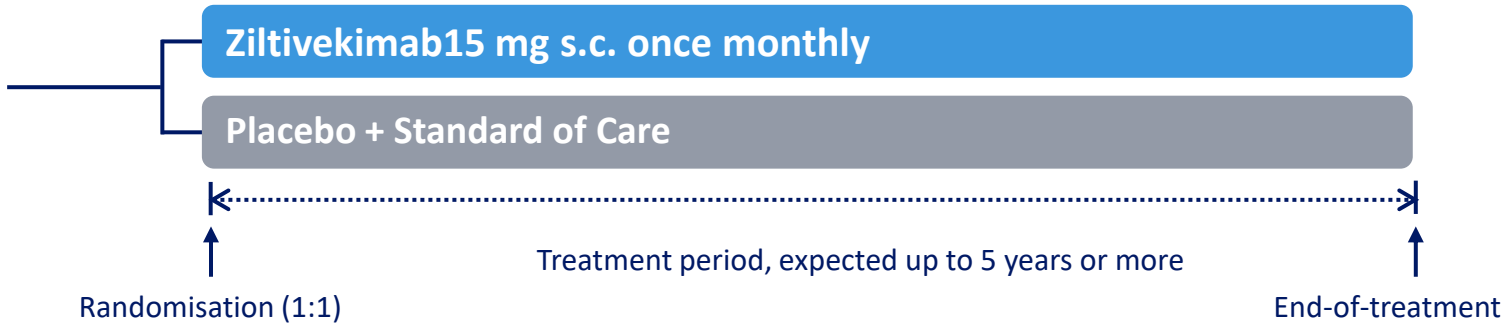
- Obese individuals with CV disease or CV risk factors

- Pre-specified number of patients with established CKD

Nissen et.al

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