Nephro Update Europe 2019
20 – 21 September, Prague

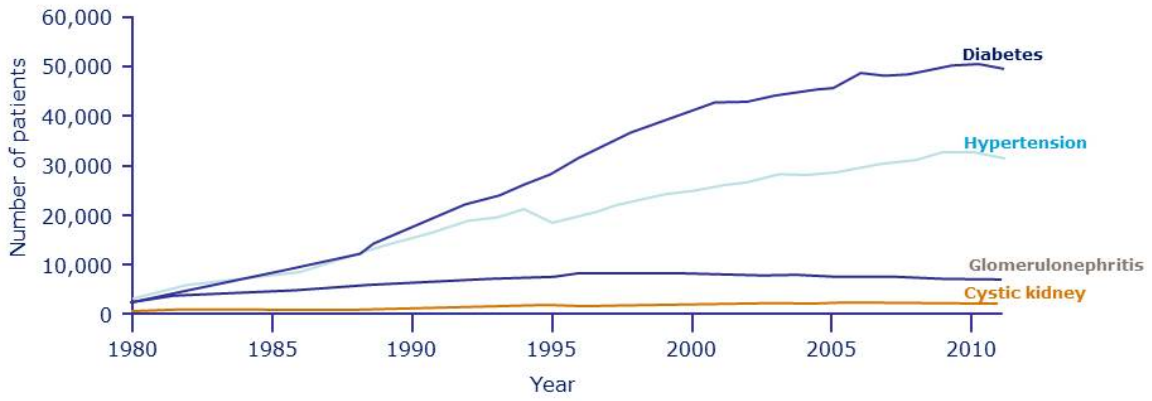
Diabetic Nephropathy

Peter Rossing, Denmark

Epidemiology

Diabetes is the leading cause of kidney failure

US DATA



United States Renal Data System. 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018. https://www.usrds.org/adr.aspx

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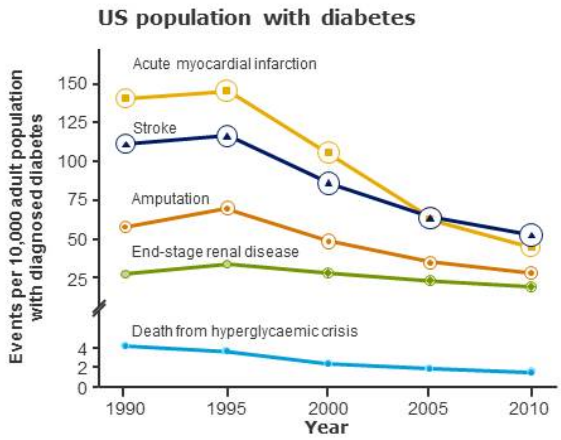
High frequency of ESRD despite reduced risk of other diabetes-related complications in the USA



Cases of end-stage renal disease in USA

Increased from around 20,000 cases in 1990 to 50,000 cases in 2010

ESRD, end-stage renal disease.
Gregg EW et al. N Engl J Med 2014;370:1514–23.

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Cumulative Risk of End-Stage Renal Disease Among Patients With Type 2 Diabetes: A Nationwide Inception Cohort Study

- Among 421,429 patients with type 2 diabetes,
- 1,516 developed ESRD and 150,524 died during 3,458,797 patient-years of follow-up.
- Cumulative risk of ESRD was 0.29% at 10 years and 0.74% at 20 years from diagnosis of diabetes.
- Risk was higher among men than among women (HR 1.93 [95% CI 1.72–2.16]),
- Decreased with older age at diagnosis (HR 0.70 [95% CI 0.60–0.81] for age 60–69 vs. 40–49 years),

P Finne et al Diabetes Care 2019;42:539–544

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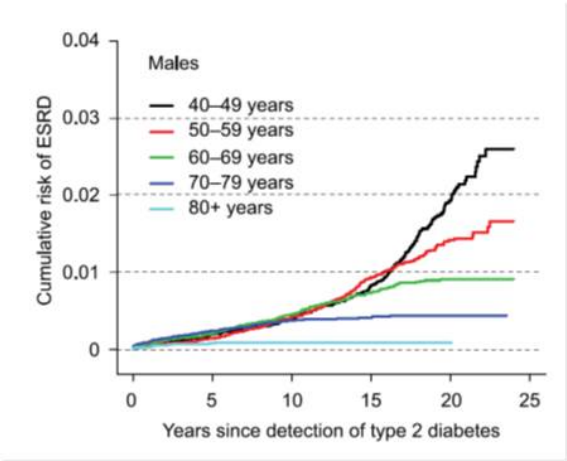
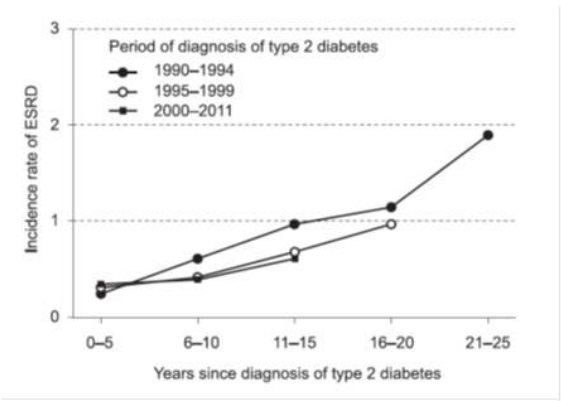
Cumulative Risk of End-Stage Renal Disease Among Patients With Type 2 Diabetes: A Nationwide Inception Cohort Study





P Finne et al Diabetes Care 2019;42:539–544

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Trends in Incidence of ESKD in People With Type 1 and Type 2 Diabetes in Australia, 2002-2013

- The number of people with diabetes and end-stage kidney disease (ESKD) is increasing worldwide, but it is unknown whether this indicates an increasing risk for ESKD in people with diabetes.
- Temporal trends in the incidence of ESKD within the Australian population with diabetes from 2002 to 2013.
- Among 1,375,877 registrants between 2002 and 2013, a total of 9,977 experienced incident ESKD, representing an overall incidence of ESKD in people with diabetes of 10.0 (95% CI, 9.8-10.2) per 10,000 person-years.

D Koye et al Am J Kidney Dis. 2018; 73(3):300-308.

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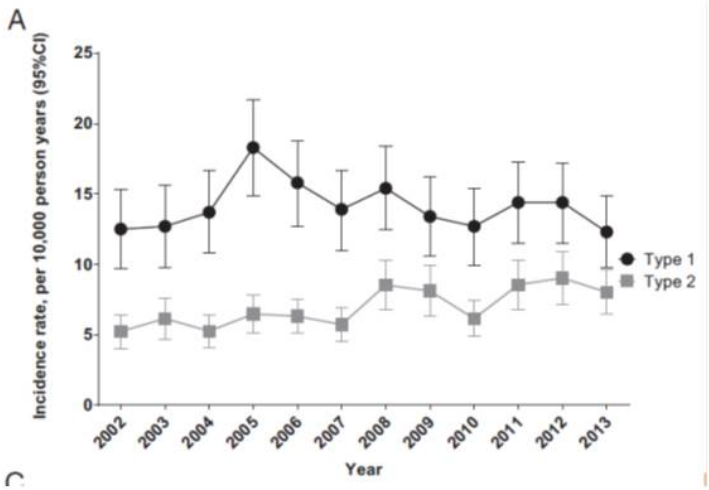
Trends in Incidence of ESKD in People With Type 1 and Type 2 Diabetes in Australia, 2002-2013



D Koye et al Am J Kidney Dis. 2018; 73(3):300-308.

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Trends in Incidence of ESKD in People With Type 1 and Type 2 Diabetes in Australia, 2002-2013

- For type 1 diabetes, the age-standardized annual incidence was stable during the study period.
- Among those with type 2 diabetes, the incidence increased in nonindigenous people (annual percentage change, 2.2%; 95% CI, 0.4%-4.1%) with the greatest increases in those younger than 50 and those older than 80 years.

D Koye et al Am J Kidney Dis. 2018; 73(3):300-308.

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Variations in Risk of End-Stage Renal Disease and Risk of Mortality in an International Study of Patients With Type 1 Diabetes and Advanced Nephropathy

During 15,685 patient-years, 505 ESRD cases (rate 32/1,000 patient-years) and 228 deaths unrelated to ESRD (rate 14/1,000 patient-years) occurred.

Risk of ESRD was associated with male sex; younger age; lower eGFR higher UACR, HbA1c, and systolic blood pressure; and smoking.

Risk of death unrelated to ESRD was associated with older age, smoking, and higher baseline eGFR.

In adjusted analysis, ESRD risk was highest in Joslin versus reference FinnDiane (hazard ratio [HR] 1.44, P = 0.003) and lowest in Steno (HR 0.54, P < 0.001). Mortality unrelated to ESRD was lowest in Joslin (HR 0.68, P = 0.003 vs. the other cohorts). Competing risk did not explain international differences in the outcomes

J Skupien et al Diabetes Care 2019;42:93–101

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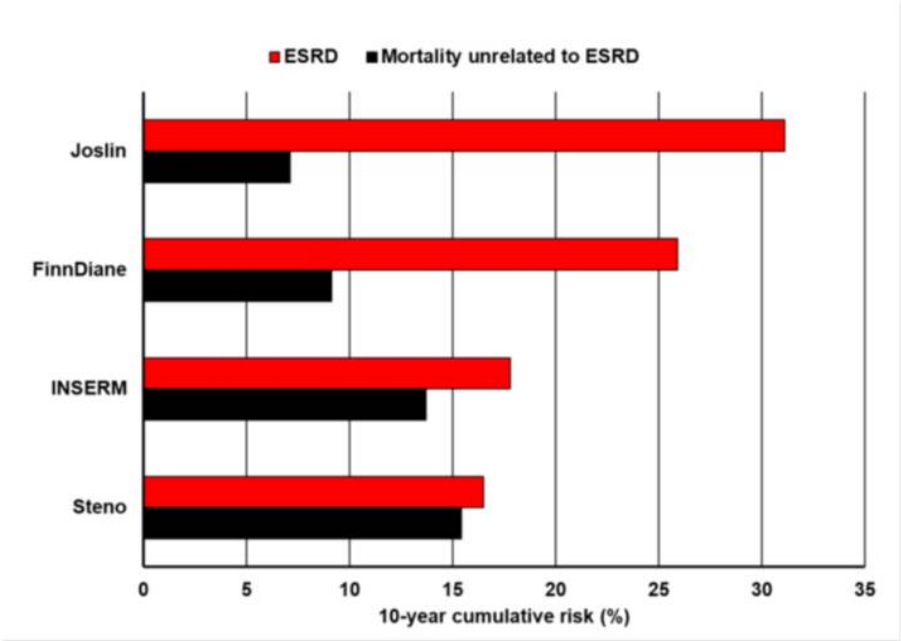
Variations in Risk of End-Stage Renal Disease and Risk of Mortality in an International Study of Patients With Type 1



J Skupien et al Diabetes Care 2019;42:93–101

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Take-Home Message

In type 2 diabetes risk for ESKD is small, but increases with younger age at onset

Number of diabetes patients is increasing, thus although treatment has improved number of ESKD patients with DM is also increasing

This is a global trend, but with variations not fully explained

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Pathophysiology

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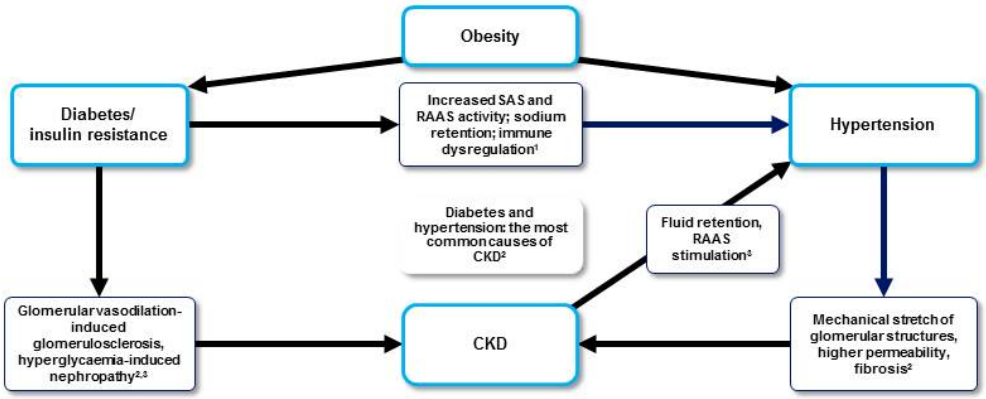
Region Hovedstaden

Diabetes increases the risk of kidney disease



CKD, chronic kidney disease; RAAS, renal-angiotensin-aldosterone system; SAS, sympathetic nervous system

1. Lastra et al. Endocrinol Metab Clin North Am 2014;43:103–22; 2. Lopez-Novoa et al. J Trans Med 2011;9:1–26;
3. Kowalski et al. Dis Mon 2015;61:378–86

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A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes

- Chronic inflammation is postulated to be involved in the development of end-stage renal disease in diabetes, but which specific circulating inflammatory proteins contribute to this risk remain unknown.
- To study this, we examined 194 circulating inflammatory proteins in subjects from three independent cohorts with type 1 and type 2 diabetes.
- A robust Kidney Risk Inflammatory Signature (KRIS), consisting of 17 proteins enriched in tumor necrosis factor-receptor superfamily members, was identified

M Niewczas et al, Nature Medicine, Vol 25; MAY 2019; 805–813

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A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes

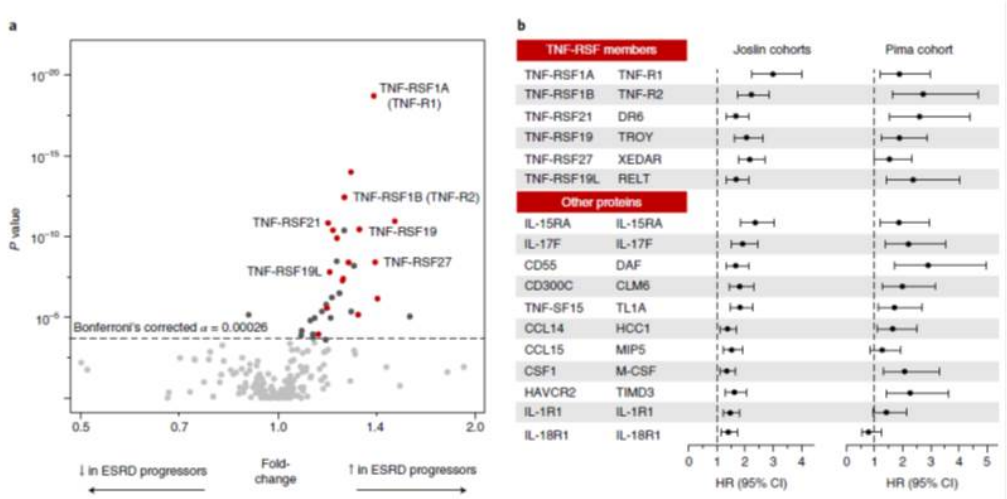

Fig. 1 | Aptamer-based proteomic discovery of circulating KRIS proteins associated with a risk of developing ESRD in three prospective cohorts.

M Niewczas et al, Nature Medicine, Vol 25; MAY 2019; 805–813

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A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes

KRIS response to:

A Losartan

B Baricitinip

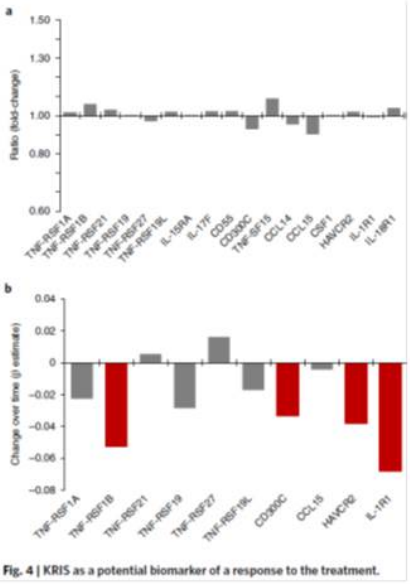

Fig. 4 | KRIS as a potential biomarker of a response to the treatment.

M Niewczas et al, Nature Medicine, Vol 25; MAY 2019; 805–813

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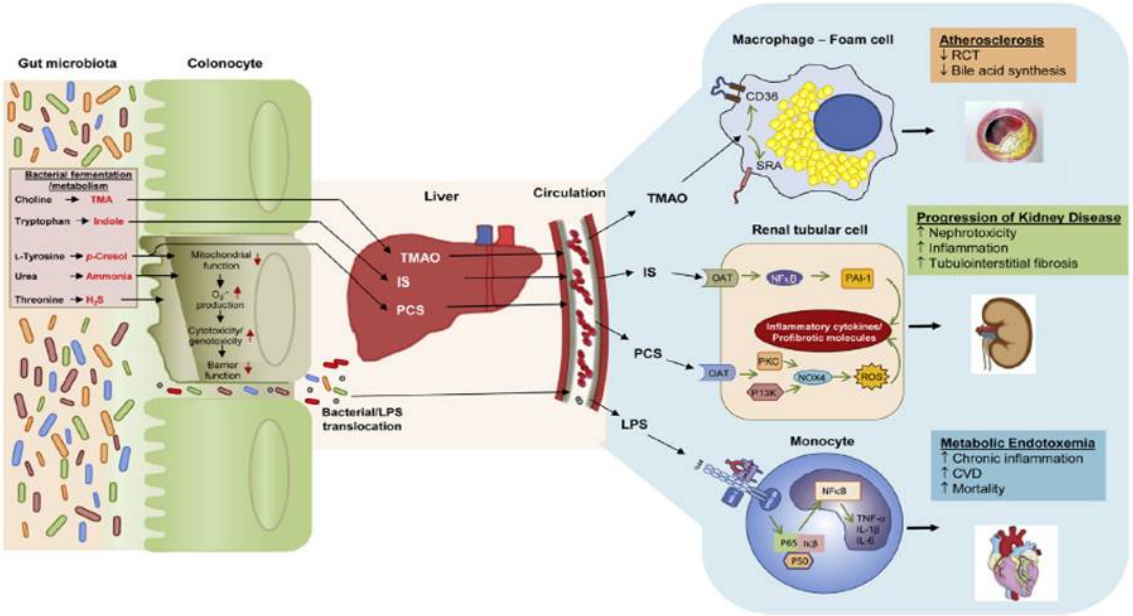
Gut Microbiome in Uremia



A Ramezani et al Am J Kid Dis 2016 Mar;67(3):483-98

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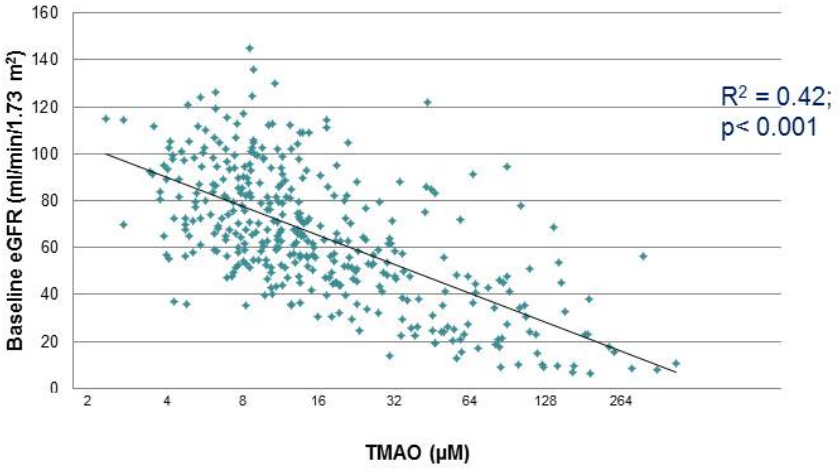
TMAO associated with baseline eGFR



S A Winther et al Diabetes Care 2019; Aug;42(8):1512-1520

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TMAO and associations with endpoints in type 1 DM

Model	ESRD (n=65)	P value	CVD events (n= 154)	P value	All-cause mortality (n=134)	P value
Model 1 (Unadjusted)	2.04 (1.73-2.41)	<0.001	1.30 (1.17-1.44)	<0.001	1.32 (1.19-1.47)	<0.001
Model 2*	2.01 (1.66-2.45)	<0.001	1.31 (1.17-1.47)	<0.001	1.30 (1.15-1.47)	<0.001
Model 3 (Model 2* + eGFR)	1.25 (0.97-1.60)	0.09	1.22 (1.05-1.41)	0.010	1.12 (0.95-1.33)	0.17

Hazard ratios (95% CI) represent risk related to a doubling of TMAO.
*Adjustment includes sex, age, systolic blood pressure, diabetes duration, cholesterol, smoking, HbA1c and urinary albumin excretion rate.

S A Winther et al Diabetes Care 2019; Aug;42(8):1512-1520

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Take-Home Message

Development of new biomarker profiles that help identify high risk individuals, and potentially provides targets has been difficult

A profile of inflammatory proteins from the TNF-R superfamily is informative across 3 cohorts

Increasing focus on gutmicrobiota in CKD unclear if it will provide markers and or targets

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Pharmacotherapy

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KDOQI guidelines for the treatment of patients with diabetes

Patient population	Recommendations
Patients with diabetes and hypertension; CKD stages 1−4	Treatment with an ACEi or an ARB, usually in combination with a diuretic, is recommended[1]
Patients with diabetes without hypertension; albuminuria; at high risk of DKD or its progression	Treatment with an ACEi or an ARB is suggested[2]
Patients with diabetes without hypertension; albumin levels normal	Do not use an ACEi or an ARB; evidence of no benefit[2]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; KDOQI, Kidney Disease Outcomes Quality Initiative

1. National Kidney Foundation. Am J Kidney Dis 2007;49(2 Suppl 2):S12−S154;
2. National Kidney Foundation. Am J Kidney Dis 2012;5:850−86

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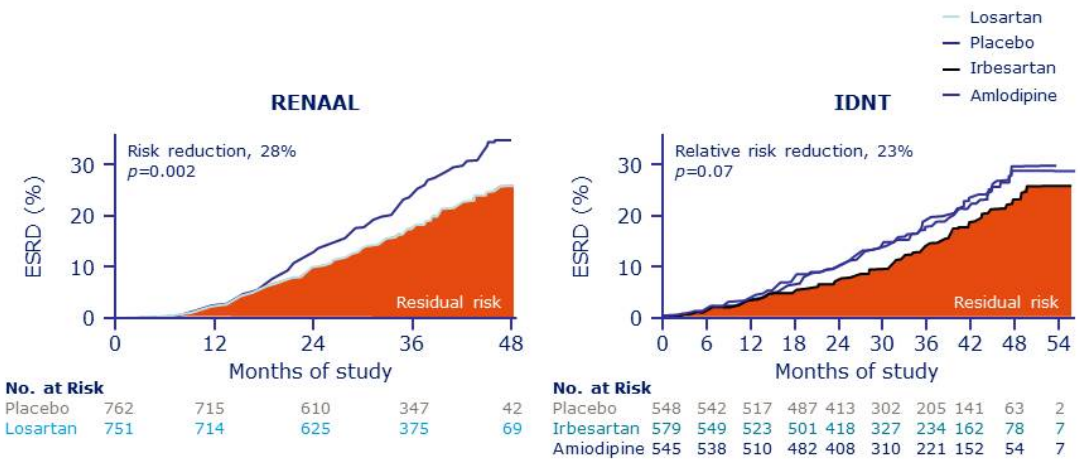
Targeting RAAS does not adequately reduce the risk of progression to ESRD



ARB, angiotensin receptor blocker; ESRD, end-stage renal disease.

Brenner BM et al. N Engl J Med 2001;345:861–869.
Lewis EJ et al. N Engl J Med 2001;345:850–860.

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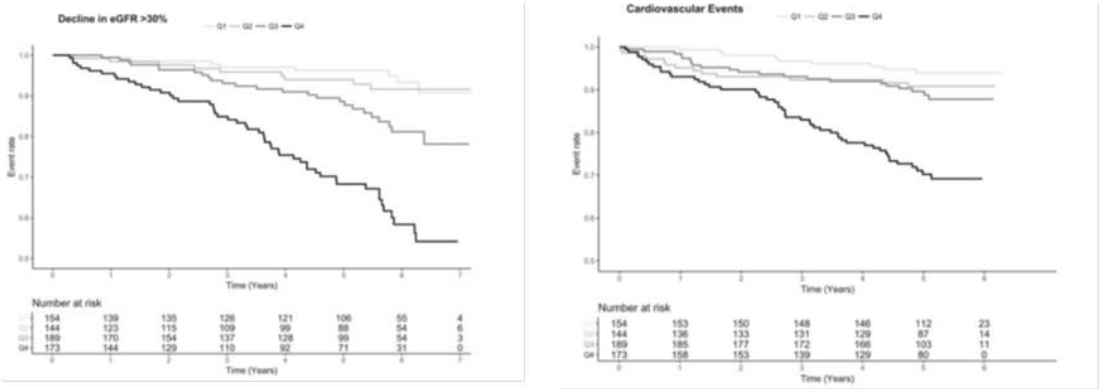
Uric acid predicts Kidney and Cardiovascular events in Type 1 DM



S Pilemann-Lyberg et al Diabetes Care 2019; Jun;42(6):1088-1094.

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Preventing Early Renal Loss in Diabetes (PERL) Study: A Randomized Double-Blinded Trial of Allopurinol Rationale, Design, and Baseline Data

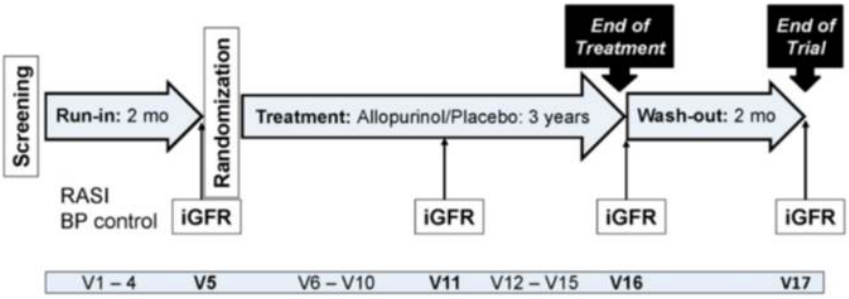

Figure 1—PERL study design. BP, blood pressure; mo, months; V, visit.

Afkarian et al Diabetes Care 2019;42:1454–1463

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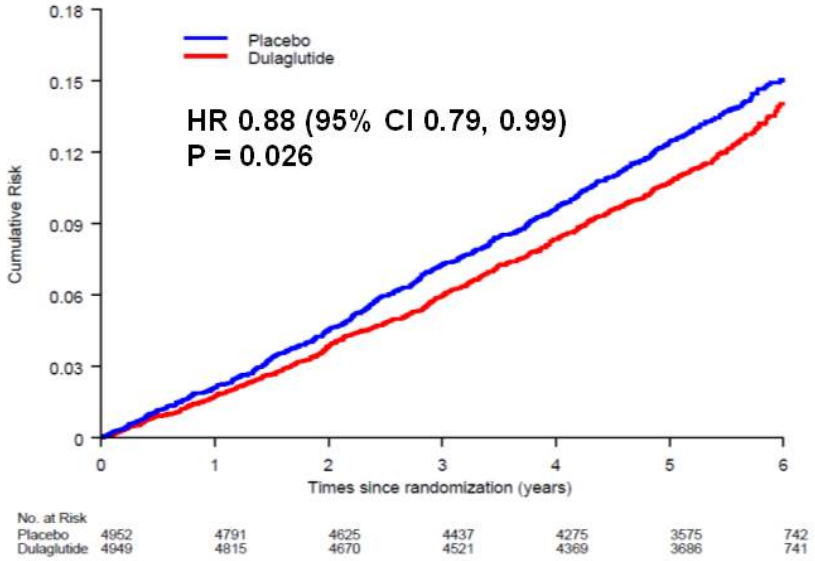
Dulaglutide's Effect on the CV Composite

Primary Outcome: 1st Occurrence of Nonfatal MI, Nonfatal Stroke, CV Death



Gerstein et al Lancet. 2019 Jul 13;394(10193):121-130

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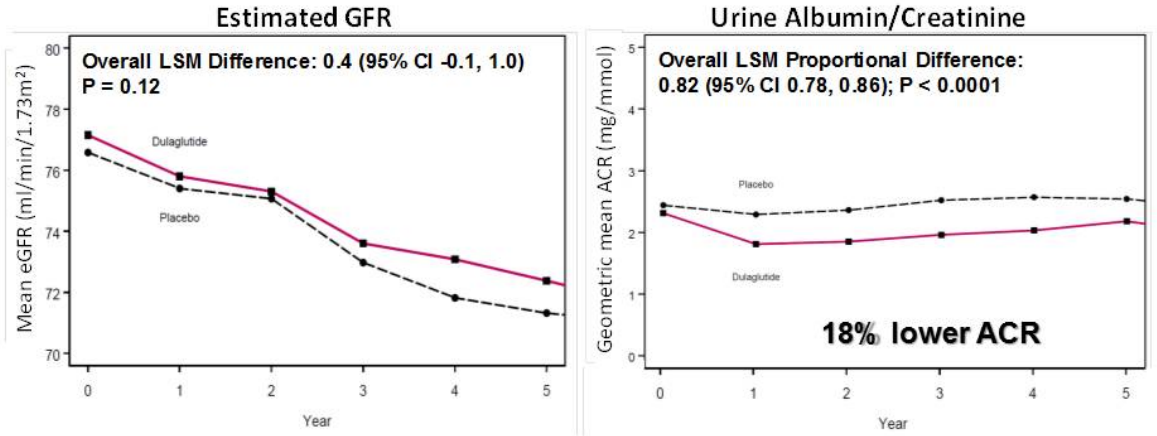
Effect on eGFR & Urine Alb/Creatinine



Gerstein et al Lancet. 2019 Jul 13;394(10193):121-130

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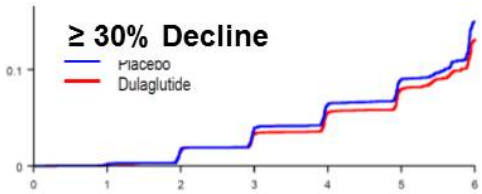
Sustained eGFR Decline ≥ 30, 40 & 50%



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

Sensitivity Analyses

Gerstein Lancet. 2019 Jul 13;394(10193):131-138

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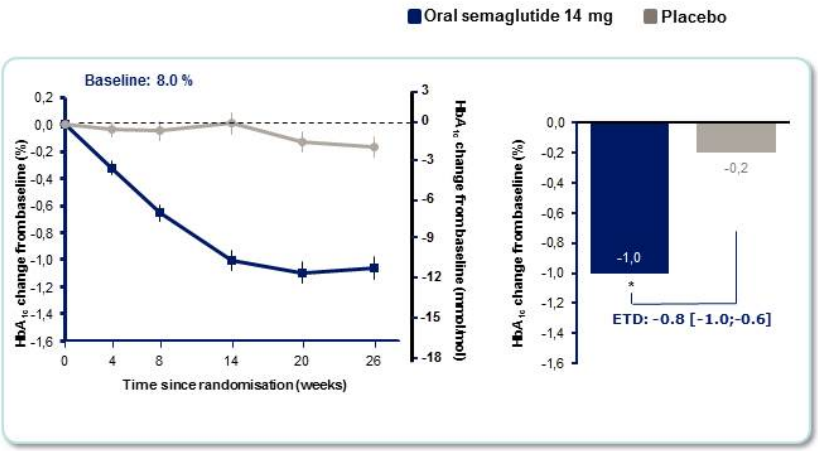
PIONEER 5
Oral semaglutide (GLP1 RA) in Type 2 DM with CKD 3
Change from baseline to week 26 in HbA_{1c}



Line graph: values are observed means ± standard error of the mean. Bar graphs: estimated mean changes from baseline to week 26.
*Statistically significant in favour of oral semaglutide compared with placebo at a 5% significance level.
ETD: Estimated treatment difference with 95% confidence interval; sema, semaglutide.

Mosenzon et al Lancet Diabetes Endocrinol. 2019 Jul;7(7):515-527.

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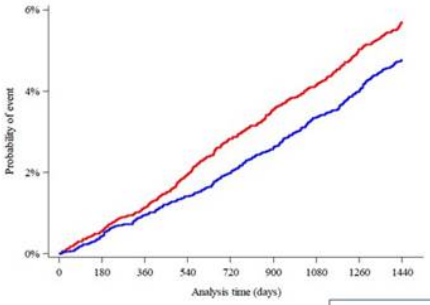
Primary Endpoints

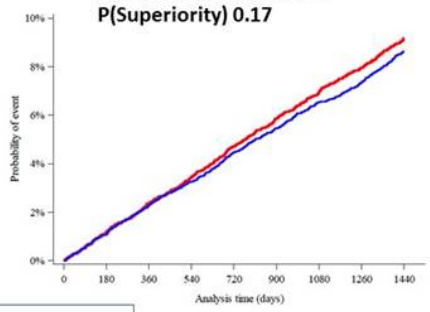
CVD/HHF

4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005



MACE

8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17



Dapagliflozin
Placebo

S Wiviott et al N Engl J Med. 2019 Jan 24;380(4):347-357

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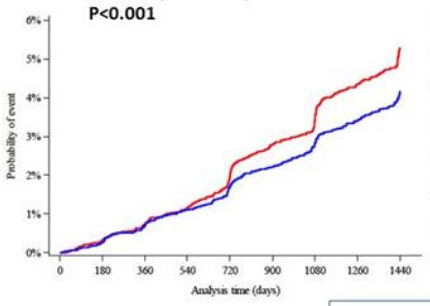
Secondary Endpoints

Renal Composite EP

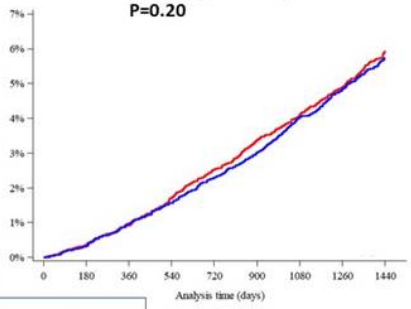
40%↓ eGFR, ESRD, Renal or CV death

4.3% vs. 5.6%
HR 0.76 (0.67-0.87)
P<0.001



All-Cause Mortality

6.2% vs 6.6%
HR 0.93 (0.82-1.04)
P=0.20



Dapagliflozin
Placebo

S Wiviott et al N Engl J Med. 2019 Jan 24;380(4):347-357

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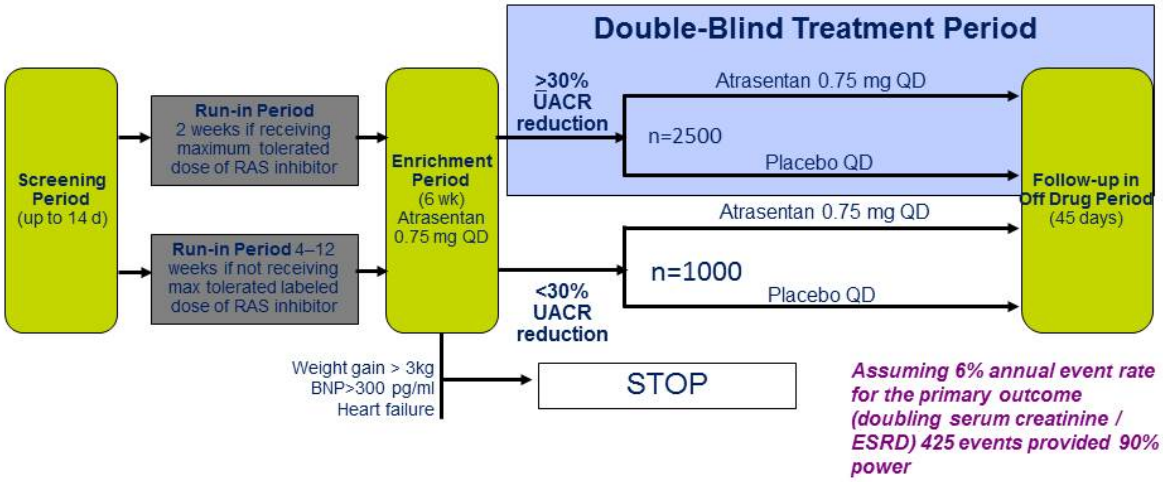
SONAR Trial scheme



Assuming 6% annual event rate for the primary outcome (doubling serum creatinine / ESRD) 425 events provided 90% power

Heerspink et al; Diabetes Obesity Metab 2018: 20(6):1369-1376

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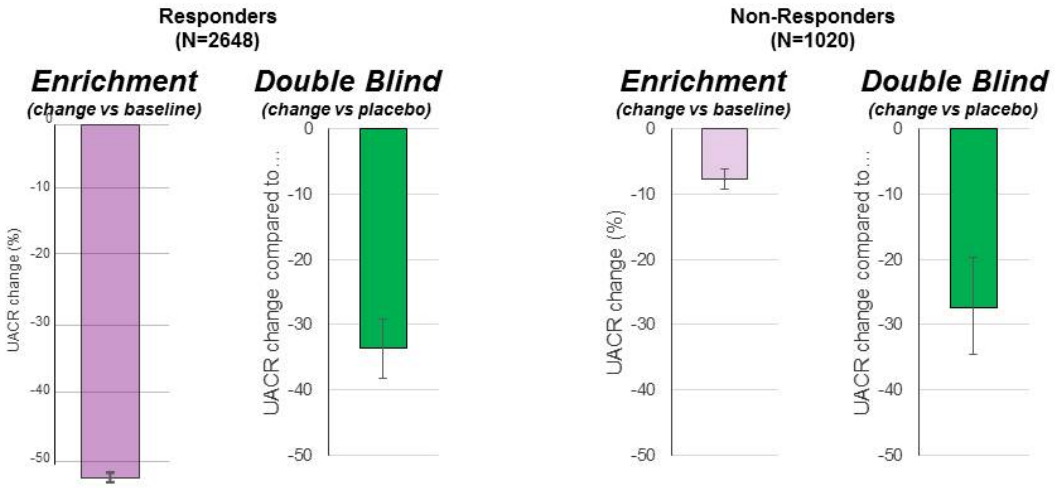
Albuminuria lowering effect of atrasentan during enrichment versus double blind treatment



Heerspink et al Lancet. 2019 May 11;393(10184):1937-1947

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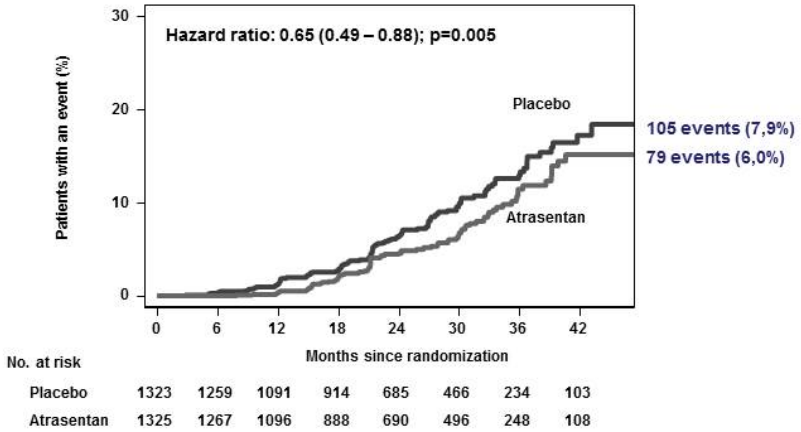
Results
Primary outcome (Doubling serum creatinine or ESRD)*



* ESRD: defined as eGFR < 15 ml/min/1.73 m^2 confirmed at 90 days, receiving chronic dialysis, renal transplantation or renal death

Heerspink et al Lancet. 2019 May 11;393(10184):1937-1947

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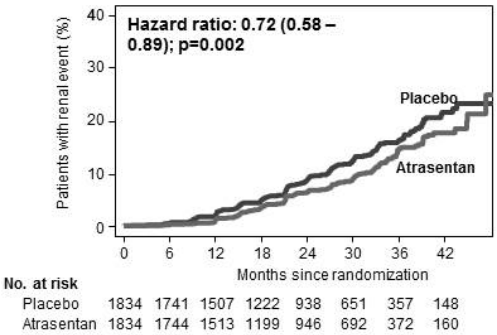
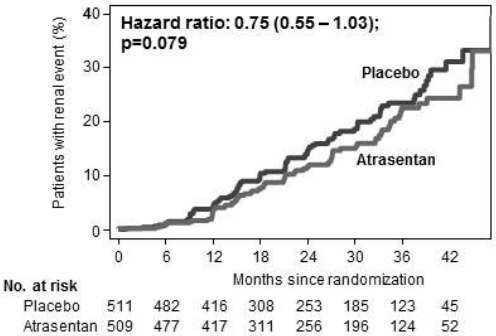
Results
Primary outcome total group (responders and non-responders)

Responders and non-responders



Non-Responders



Heerspink et al Lancet. 2019 May 11;393(10184):1937-1947

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CREDENCE: Study Design

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m²
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K^+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

2-week placebo run-in → R (Double-blind randomization (1:1)) → Canagliflozin 100 mg / Placebo

Follow-up at Weeks 3, 13, and 26 (F2F) then every 13 weeks (alternating phone/F2F)

Participants continued treatment if eGFR was <30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred.

Jardine MJ, et al. Am J Nephrol. 2017;46(6):462-472.

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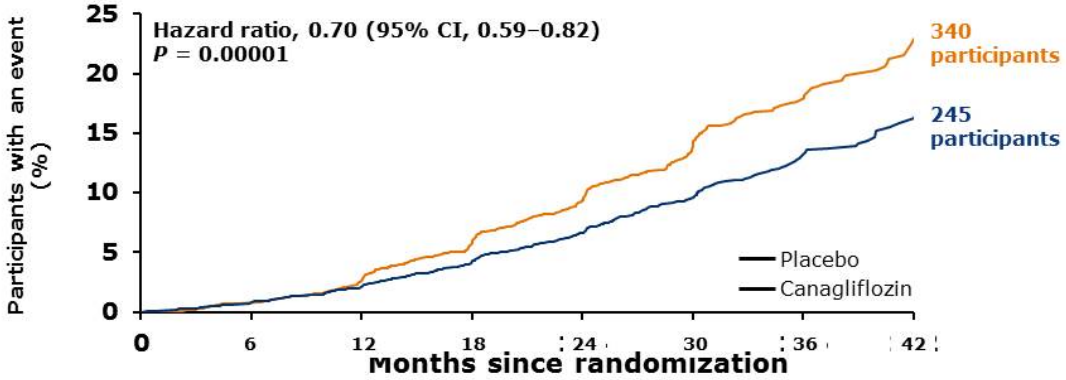
Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

V Perkovic et al N Engl J Med. 2019 Jun 13;380(24):2295-2306

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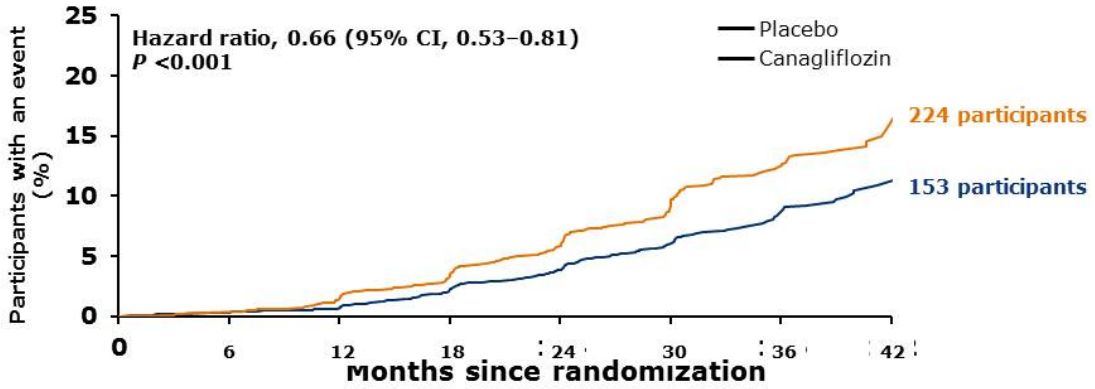
ESKD, Doubling of Serum Creatinine, or Renal Death



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Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

V Perkovic et al N Engl J Med. 2019 Jun 13;380(24):2295-2306

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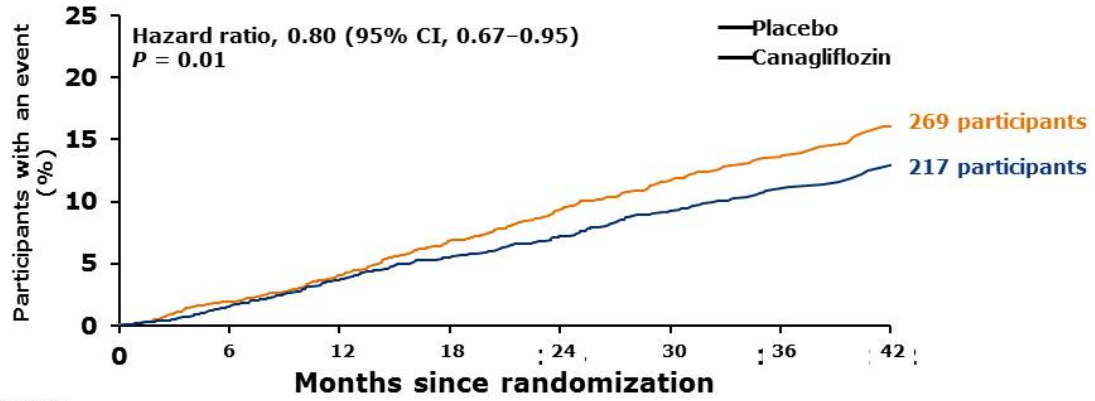
Major Cardiovascular Events: CV Death, MI, or Stroke



No. at risk								
Placebo	2199	2152	2100	2022	1717	1143	635	168
Canagliflozin	2202	2163	2106	2047	1756	1196	642	198

V Perkovic et al N Engl J Med. 2019 Jun 13;380(24):2295-2306

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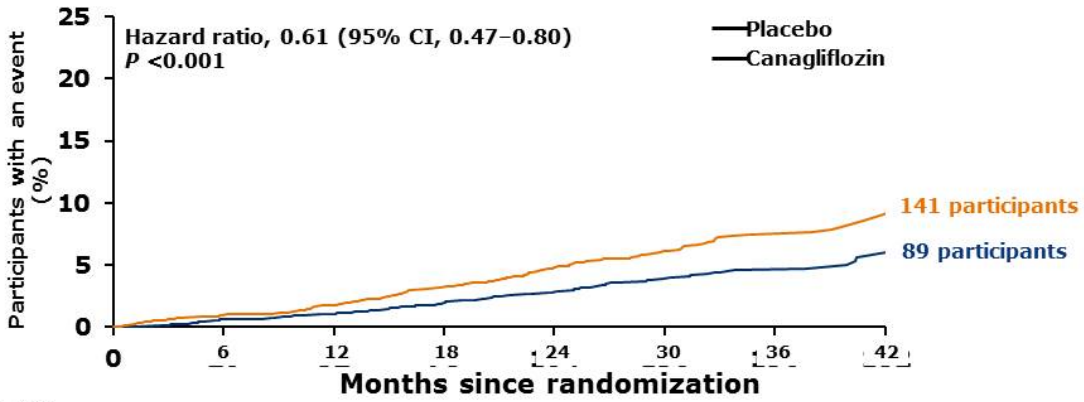
Hospitalization for Heart Failure



No. at risk								
Placebo	2199	2165	2122	2043	1735	1147	638	170
Canagliflozin	2202	2171	2131	2076	1789	1226	668	199

V Perkovic et al N Engl J Med. 2019 Jun 13;380(24):2295-2306

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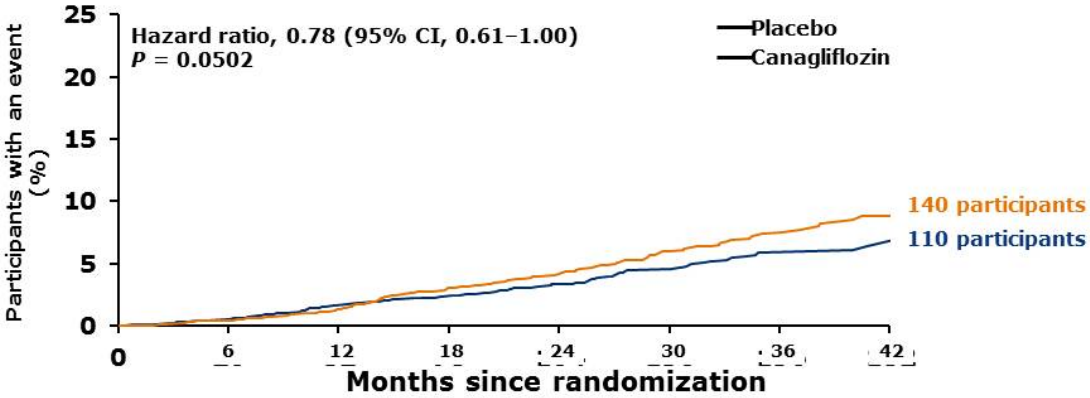
CV Death



No. at risk								
Placebo	2199	2185	2160	2106	1818	1220	688	189
Canagliflozin	2202	2187	2155	2120	1835	1263	687	212

V Perkovic et al N Engl J Med. 2019 Jun 13;380(24):2295-2306

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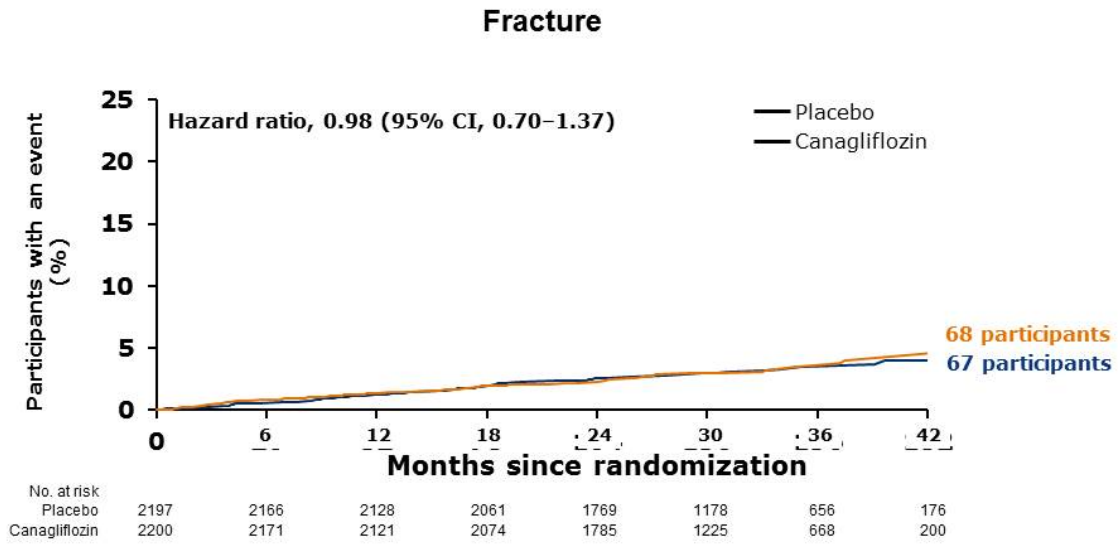

V Perkovic et al N Engl J Med. 2019 Jun 13;380(24):2295-2306

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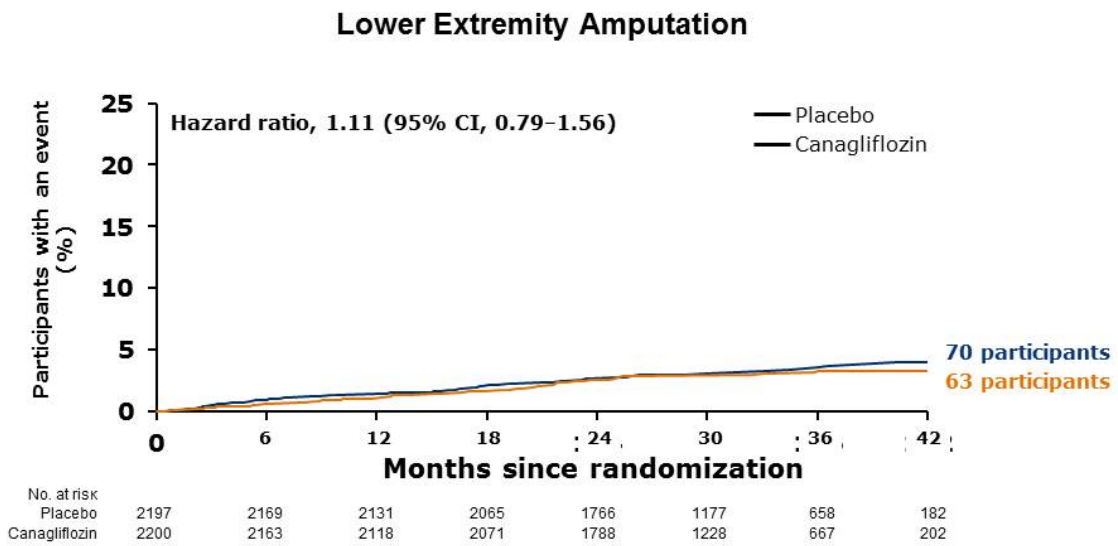

V Perkovic et al N Engl J Med. 2019 Jun 13;380(24):2295-2306

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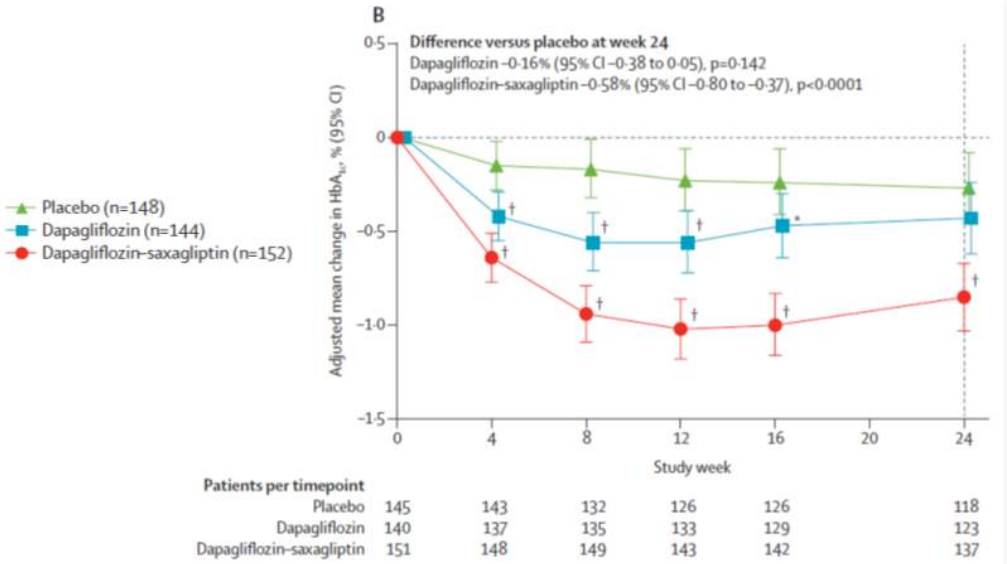
Combination of SGLT2i+DPP4 inhibitor in Type 2 diabetes with albuminuria and impaired GFR



C Pollock et al Lancet Diabetes Endocrinol 2019; 7: 429–41

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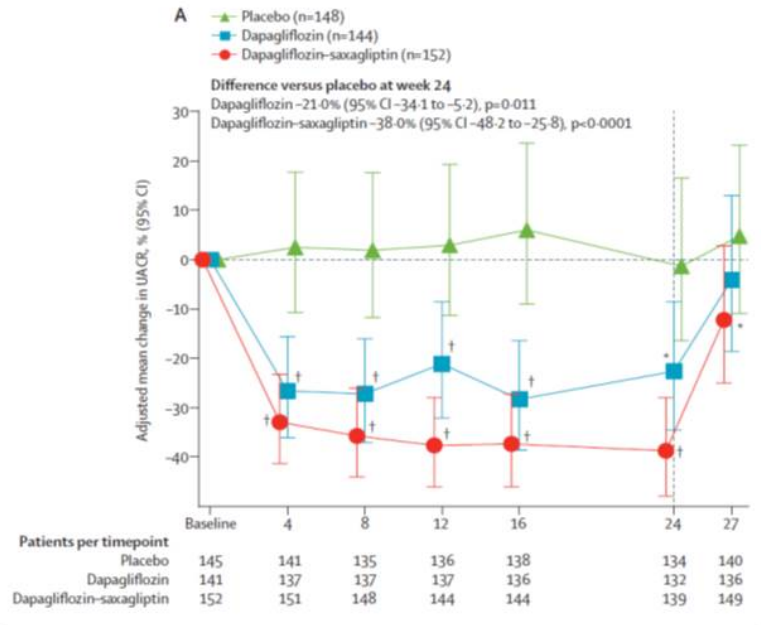
Combination of SGLT2i+DPP4 inhibitor in Type 2 diabetes with albuminuria and impaired GFR



C Pollock et al Lancet Diabetes Endocrinol 2019; 7: 429–41

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Take-Home Message

- It is important for CV and renal risk how glucose is lowered in type 2 DM
- GLP1 RA's have shown benefit mostly on albuminuria progression but also eGFR as secondary outcomes in CVOT
- SGLT2 inhibitors demonstrated similar data, more convincing on GFR endpoints
- Credence was a dedicated renal trial in type 2 DM with albuminuria >300 mg/g and eGFR 30-90 with positive outcomes
- Additional options may be atrasentan, also with positive renal outcome data, but not available, and non significant HF
- The right combination may provide even better results

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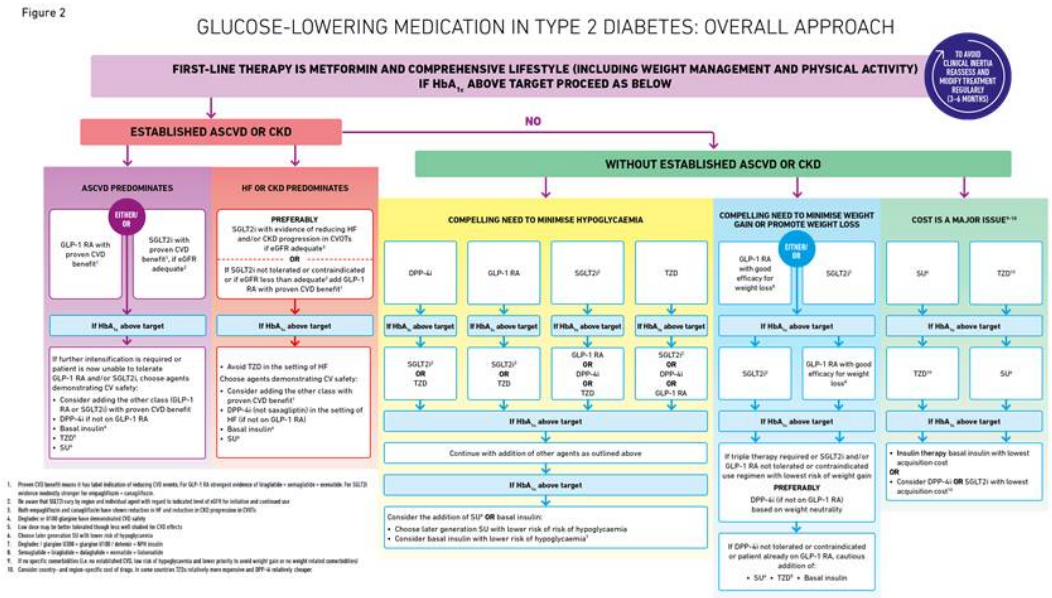

M Davies et al Diabetes Care. 2018 Dec;41(12):2669-2701

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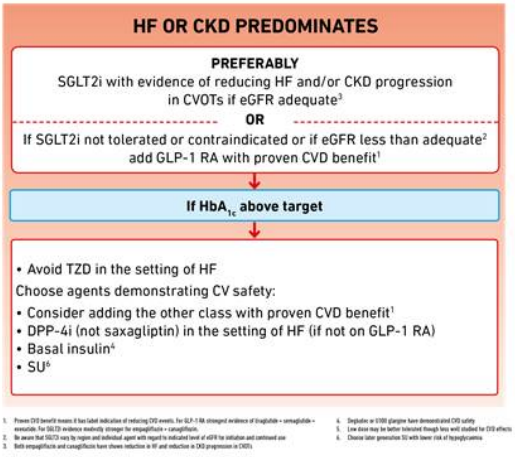
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED HF OR CKD



M Davies et al Diabetes Care. 2018 Dec;41(12):2669-2701

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List of Abbreviations

- ACEi, angiotensin-converting enzyme inhibitor;
- ARB, angiotensin receptor blocker
- CI confidence interval
- CKD, chronic kidney disease;
- CVD cardiovascular disease
- CVOT, cardiovascular outcome trial
- DM, diabetes mellitus
- DPP4 dipeptidyl peptidase 4
- eGFR, estimated glomerular filtration rate
- ESKD end stage kidney disease
- ESRD end stage renal disease
- GLP1 RA glucagon like peptide 1 receptor agonist
- HF heart failure
- HHF hospitalisation for heart failure
- HR, hazard ratio
- KDOQI, Kidney Disease Outcomes Quality Initiative
- LPS lipopolysaccharide
- MACE major cardiovascular events
- RAAS, renal-angiotensin-aldosterone system;
- SAS, sympathetic nervous system
- TMAO, Trimethylamine N-Oxide

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