Nephro Update Europe 2017

6-7 October, Vienna

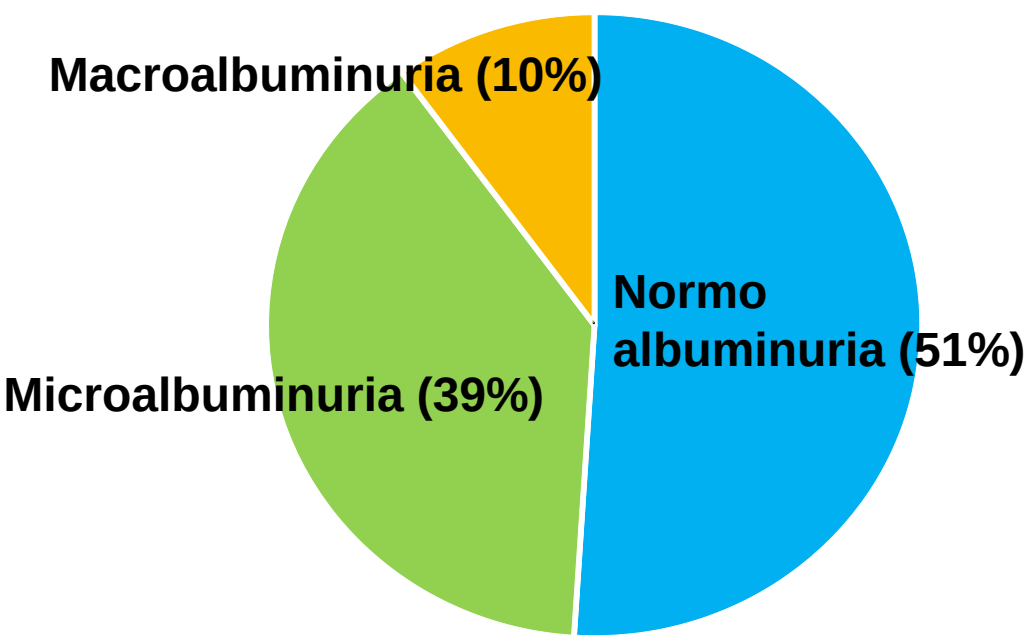
Diabetic Nephropathy

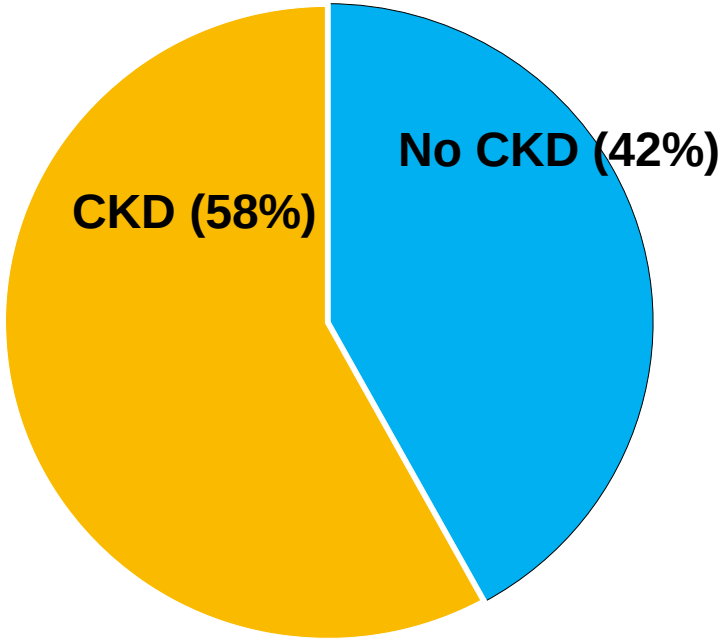
Hiddo Lambers Heerspink, Netherlands

Diabetic Kidney Disease

- *Epidemiology*
- *Pathophysiology*
- *Pharmacotherapy*

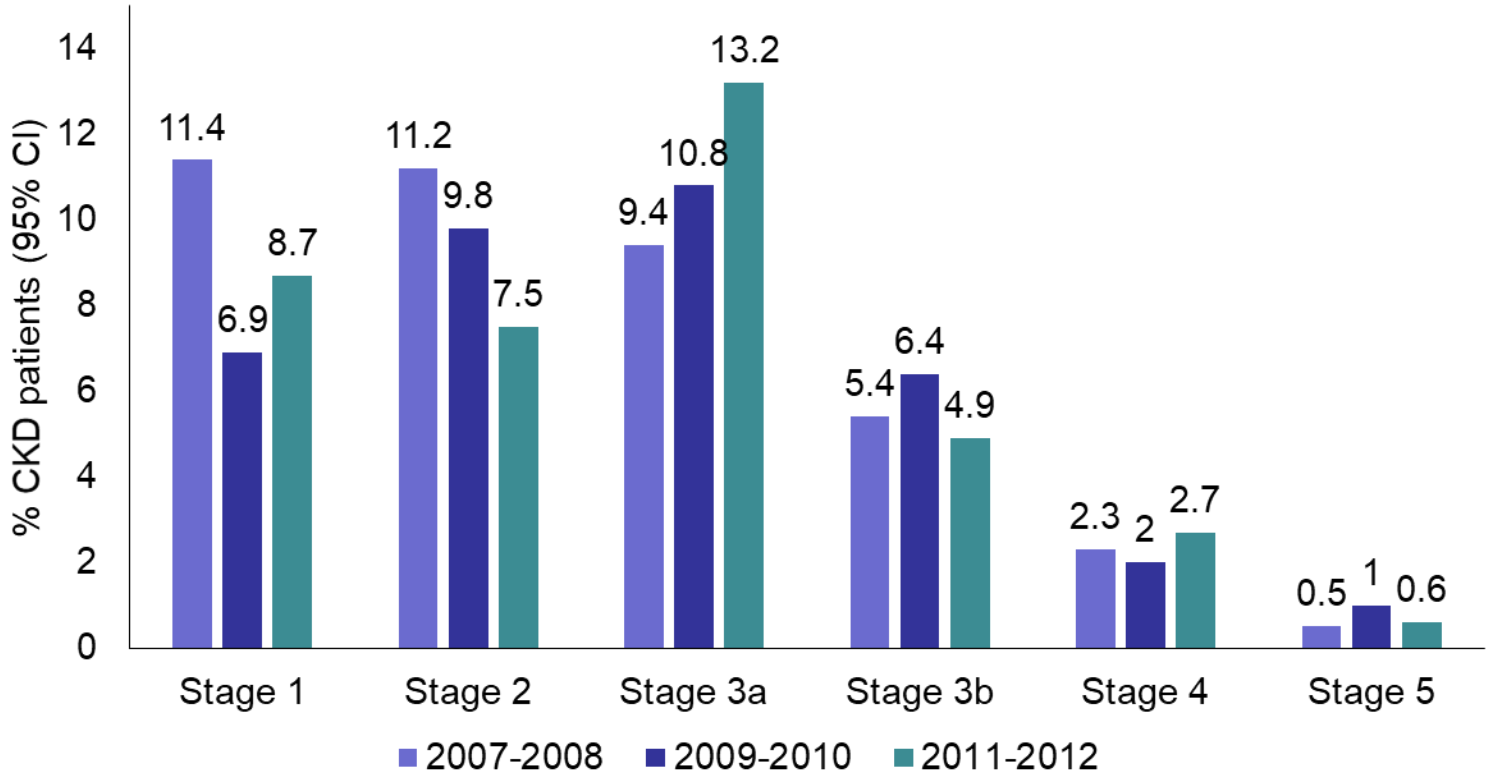
High prevalence of micro/macroalbuminuira in diabetes





Parving et al., Kidney Int 2006,69:2057-63)

NHANES: Prevalence of CKD in diabetes constant over time



Age-adjusted prevalence of CKD in T2DM: NHANES 2007-2012

2006 patients with type 2 diabetes of whom 884 had diabetes and CKD (44%)

Wu Bell BMJ open diabetes research & care. 2016;4(1):e000154

Outcomes of diabetic kidney disease

- The prevalence of kidney disease in patients with diabetes remains high
- Early detection and preventative measures are highly desired
- Mortality rates and life expectancy in early DKD are not well known

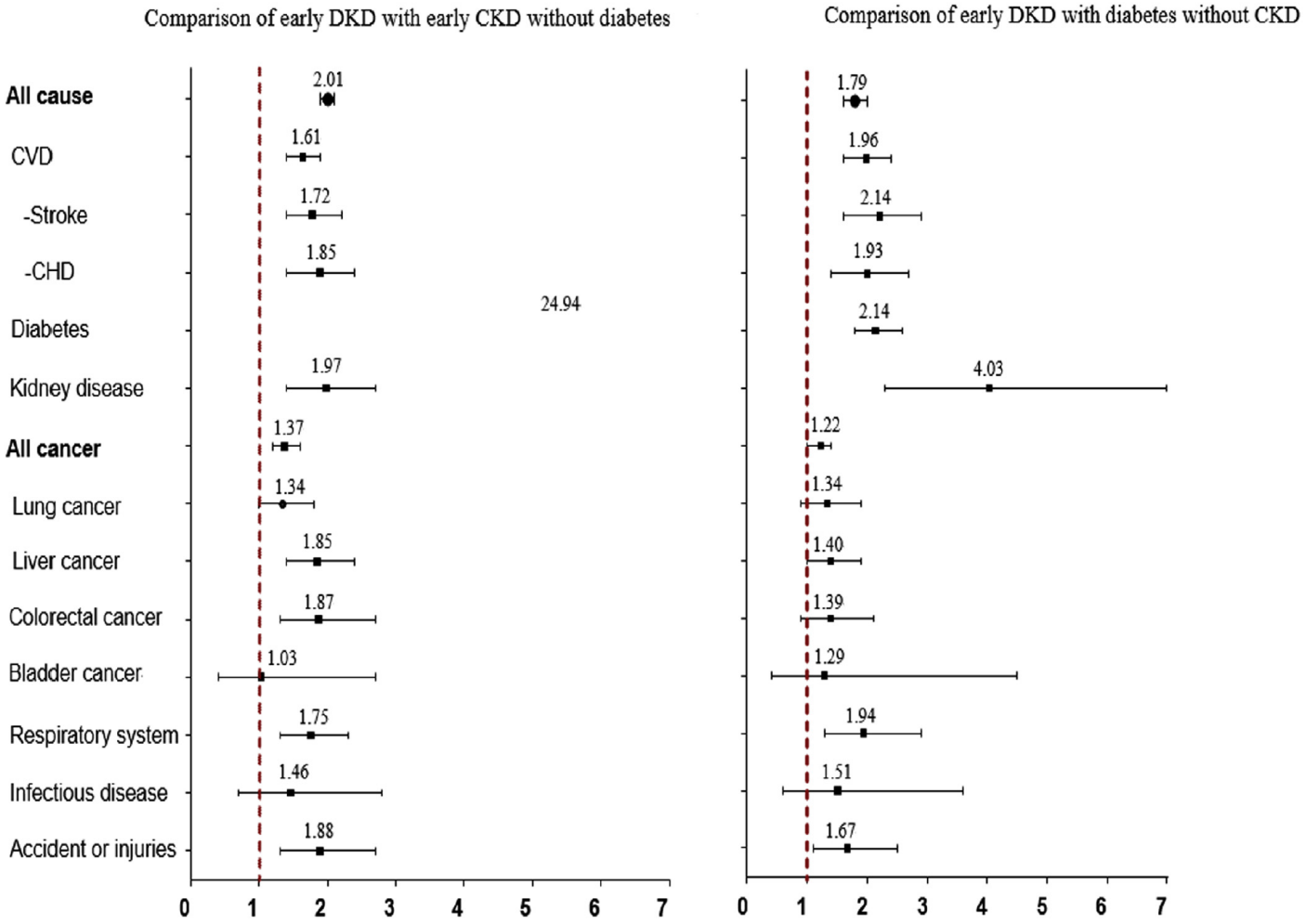
Study Design

- *Design:*

  Prospective cohort study in 543.000 individuals in Taiwan
- *Definitions:*
  - Early DKD defined as diabetes with eGFR>30 and macroalbuminuria
  - Early CKD defined as eGFR>30 and macroalbuminuria
- *Outcomes*
  - Mortality (Through national death files)
- *Comparisons*
  - Early DKD with early CKD without diabetes
  - Early DKD with diabetes without CKD

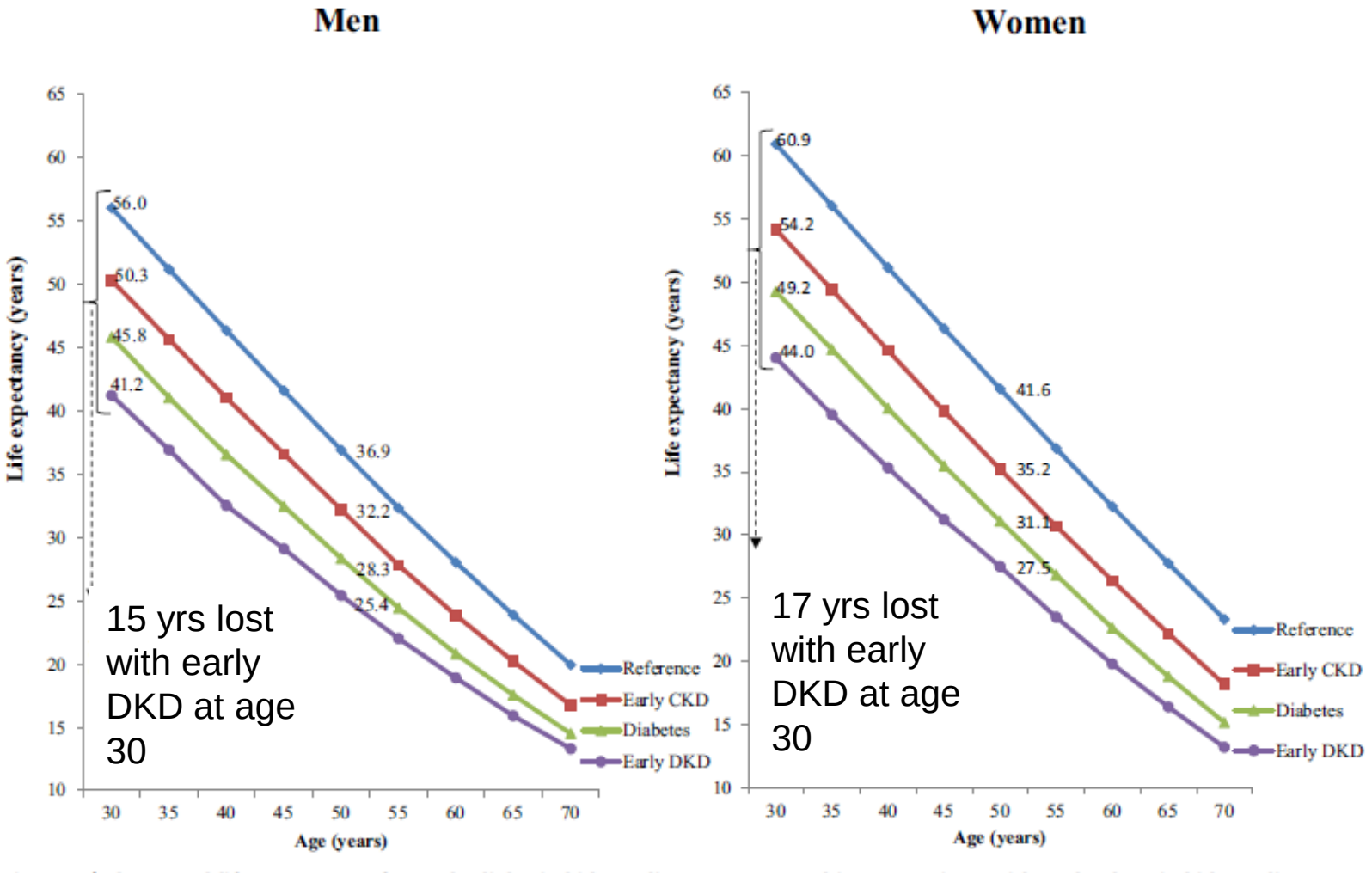
Wen et.al. Kidney International 2017: 92; 388-96

All cause and cause specific mortality rates in Diabetic Kidney Disease



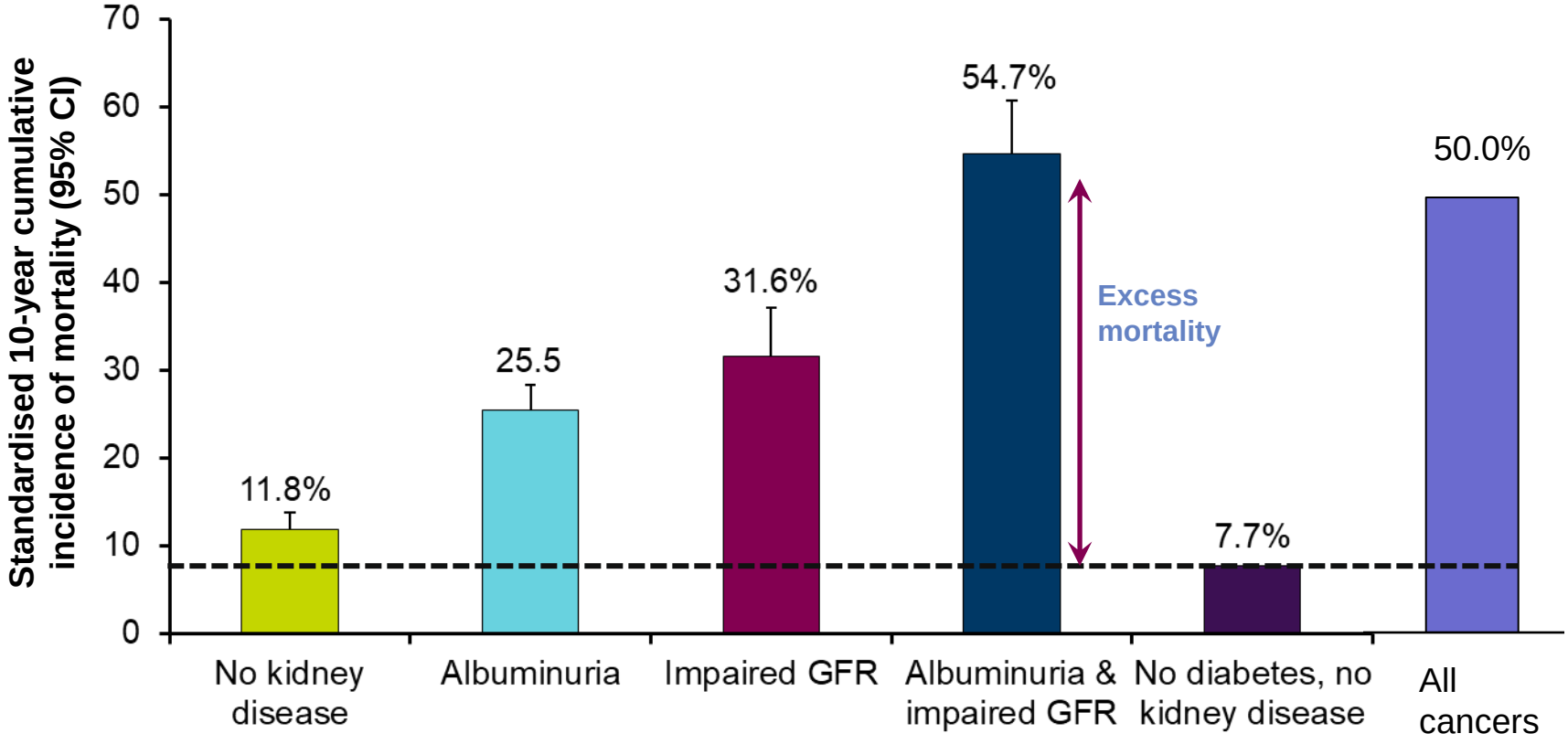
Wen et.al. Kidney International 2017: 92; 388-96

Shortened life expectancy in DKD



Wen et.al. Kidney International 2017: 92; 388-96

Mortality rates in DKD equal average cancer mortality rates



Afkarian M et al. J Am Soc Nephrol 2013;24:302
Lancet 2014 pii: S0140-6736(14)61396-9

What‘s new?

- The prevalence of DKD remains high despite increased awareness and pharmacotherapy
  - Increase in overall prevalence of type 2 diabetes
- Life expectancy in early DKD signicantly shortened
- Adequate resources to manage DKD and reduce prevalence and complications remain necessary

Diabetic Kidney Disease

- *Epidemiology*
- *Pathophysiology*
- *Pharmacotherapy*

Diabetic vs. non-diabetic kidney disease in diabetes

- Diabetic kidney disease in type 2 diabetes is heterogeneous
- Both diabetic and non-diabetic kidney disease is present
- Largest biopsy study in type 2 diabetes (N=620) revealed that:
  - 37% of biopsy specimens were consistent with DKD
  - 36% had non-diabetic CKD
  - 27% showed co-existing DKD and non-diabetic CKD
- Diabetes duration (>10 yrs) was the best clinical predictor differentiating diabetic vs non-diabetic CKD

Sharma et.al. CJASN 2013:8:1718-24

Summary of clinical features differentiating DKD vs non-DKD

Table 1. Clinical features distinguishing type 2 diabetic kidney disease (DKD) from Other Causes of Kidney Disease

Clinical Feature	Non-DKD	DKD
Onset of proteinuria	Rapid	Gradual
Progression of CKD	Rapid	Gradual
Duration of diabetes	<5 yr	>10 yr
Urinalysis	Active sediment (hematuria, pyuria, casts)	Bland sediment
Retinopathy	Absent	Present

Doshi et.al. CJASN 2017 epub ahead of print

The changing face of Diabetic Kidney Disease

Proteinuria in Type 2 Diabetic Patients with Renal Impairment: The Changing Face of Diabetic Nephropathy.

In conclusion, our results suggest that over one fifth of patients with type 2 DN and established renal impairment will have proteinuria levels below those traditionally associated with overt nephropathy. These patients will very likely be receiving ACEis, ARBs, or a combination of both. The natural history and optimal management of these patients remains to be determined.

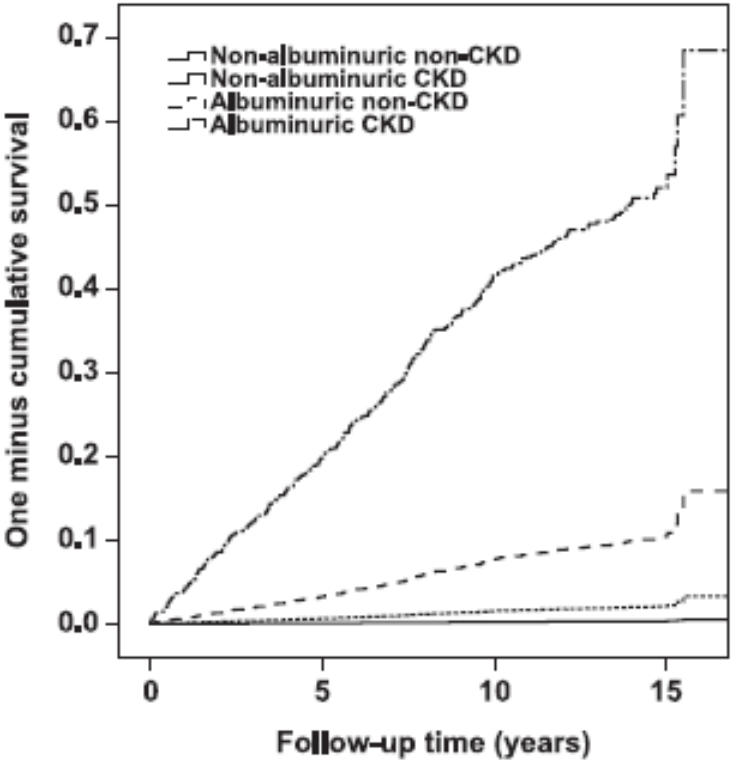
Packham et al., Nephron Clin Pract. 2011;118(4):c331-8)

Outcomes of low albuminuric CKD

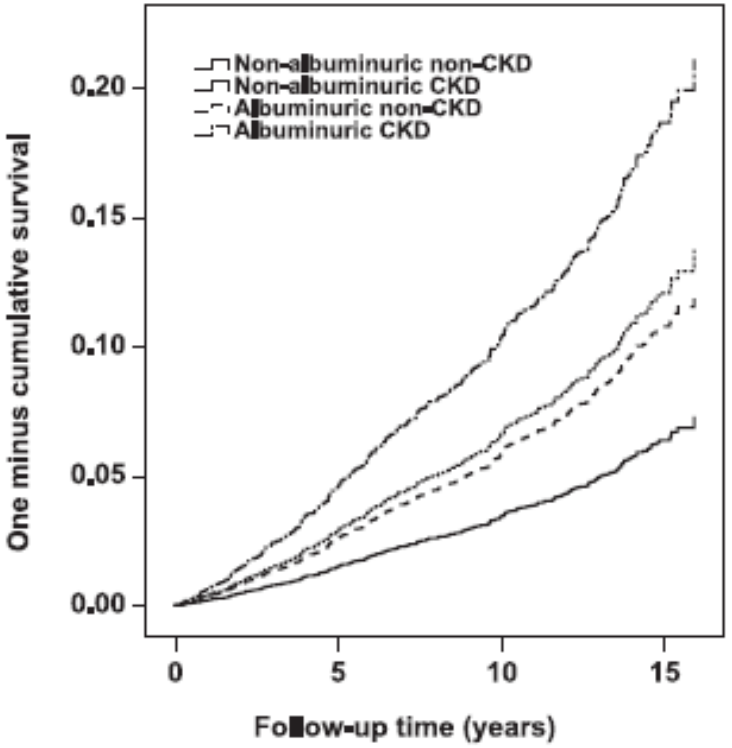
- Increase in prevalence of low/non albuminuric DKD
- Low albuminuric DKD often associated with female gender, higher age, and macrovascular disease
- Outcomes of low albuminuric CKD is less well established.

(Non)-Albuminuric DKD and renal / CV outcome

ESRD events

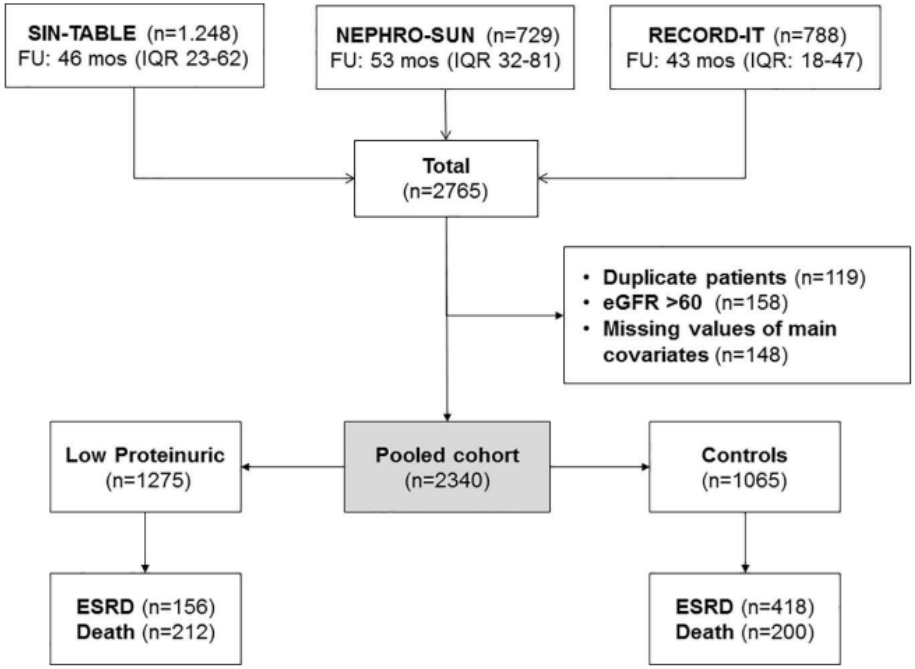


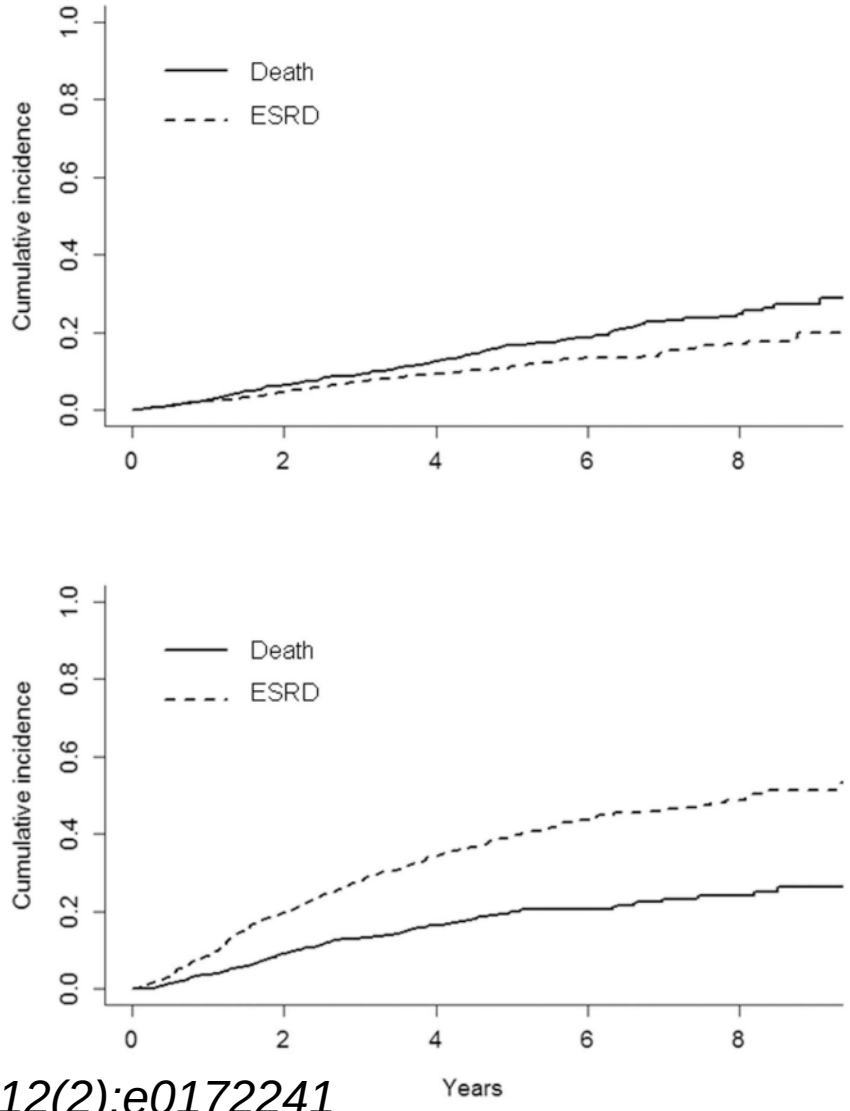
CV events



Groop et.al. Diabetes Care 2015:38;2128-33

Non-proteinuric CKD and renal/mortality outcome





Low proteinuria defiend as <0.5 g/24hr

De Nicola et.al. Plos one 2017 Feb 17;12(2):e0172241

What‘s new?

- Low albuminuric DKD common
  - Increase in ACEi/ARB use; intensive BP and glycemic control
- Non-albuminuric DKD likely diabetes with superimposed non-diabetic kidney disease
  - Non-albuminuric DKD often diagnosed in women of advanced age with normal BP/lipids
- Non-albuminuric DKD often associated with death
- Non-albuminuric DKD does not dismiss albuminuria as a risk factor for ESRD: If present it is associated with high risk

Diabetic Kidney Disease

- *Epidemiology*
- *Pathophysiology*
- *Pharmacotherapy*

State of the Art

HbA1c target individualised, but generally ~7%[1]

Target of <130/80 mmHg in patients with micro/macroalbuminuria /

Target of <140/90 mmHg in patients with normoalbuminuria[2]

Use ACEi or ARBs when albumin excretion ≥30 mg/g[1]

Lipid-lowering recommended to reduce risk of atherosclerotic events; statins not recommended in patients on haemodialysis[1]

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; DKD, diabetic kidney disease; HbA1c, glycated haemoglobin

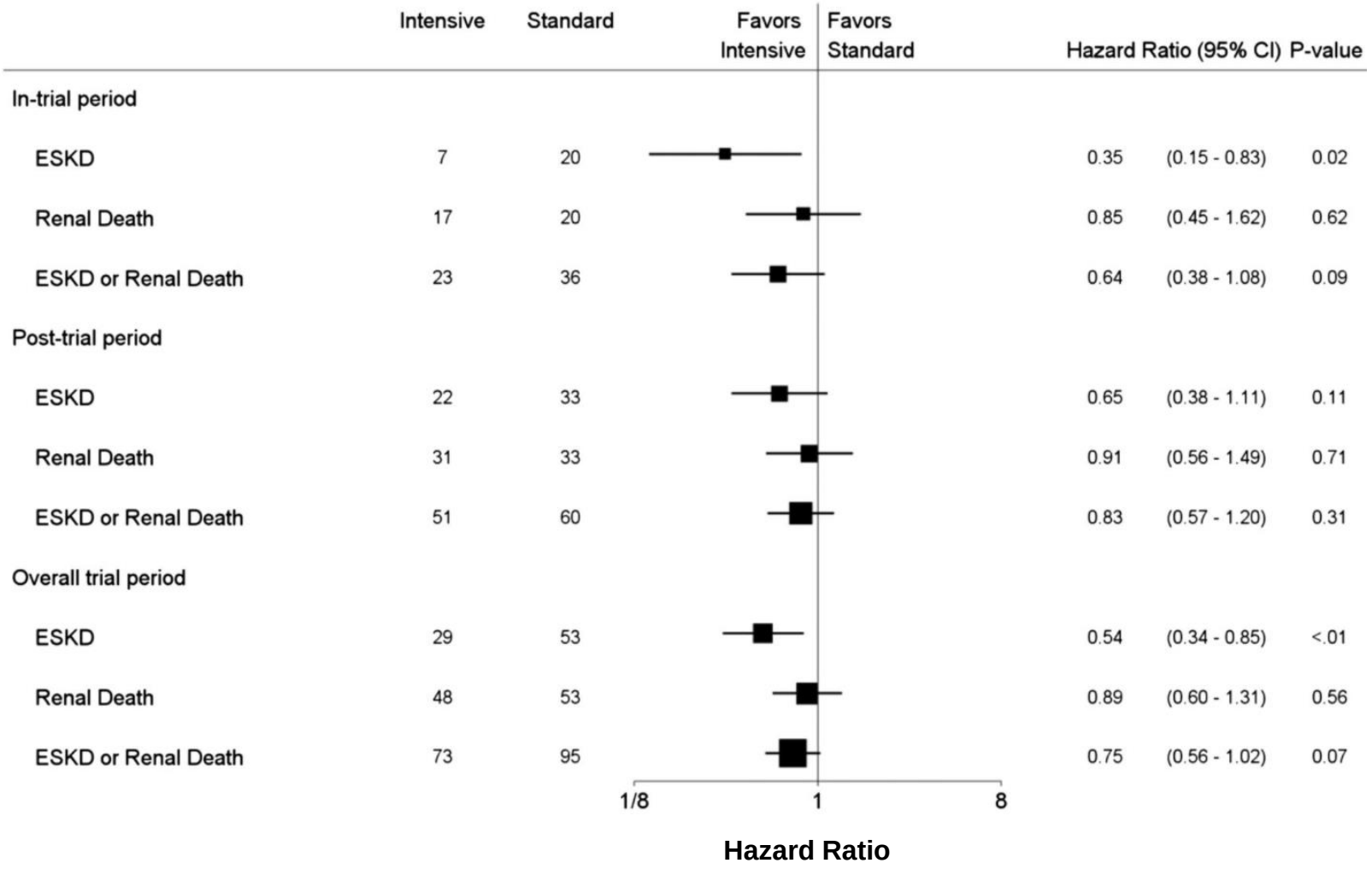
1. National Kidney Foundation. Am J Kidney Dis 2012;60:850; 2. KDIGO BP guideline

ADVANCE-ON

- *Design*
  - Observational follow-up of a RCT
- *Patients*
  - 8494 Type 2 diabetes at high CV risk
- *Follow-up*
  - 9.9 Yrs (5.4 yrs trial and 4.5 yrs observation)
- *Endpoint*
  - End-stage Kidney Disease / Death due to kidney disease

Wong et.al. Diabetes Care 2016; 39:694-700

ADVANCE-ON (in-trial and post-trial results)

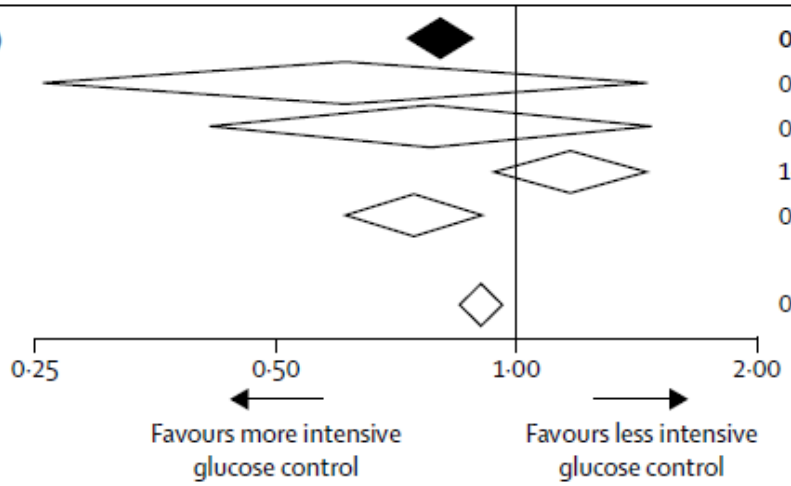


Wong et.al. Diabetes Care 2016; 39:694-700

Meta-analysis of intensive vs conventional glucose lowering therapies

A

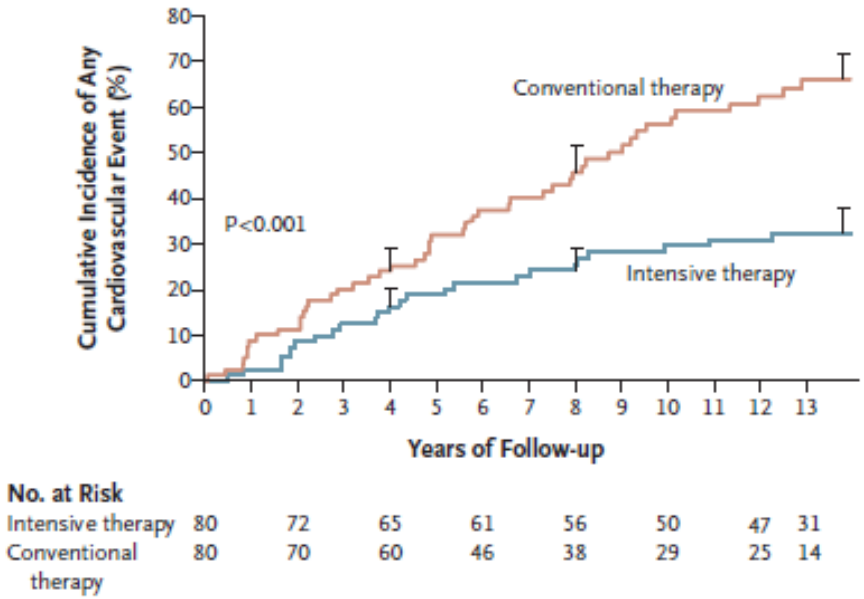
	More intensive glucose control	Less intensive glucose control	Hazard ratio (95% CI)
Primary kidney outcome	**761 (1·2%)**	**865 (1·6%)**	**0·80 (0·72–0·88)**
End-stage kidney disease	113 (0·2%)	143 (0·2%)	0·61 (0·26–1·44)
Renal death	18 (0·0%)	22 (0·1%)	0·77 (0·41–1·46)
eGFR <30 mL/min per 1·73m²	175 (0·3%)	149 (0·3%)	1·16 (0·93–1·44)
Macroalbuminuria	509 (0·9%)	603 (1·2%)	0·74 (0·61–0·90)
Secondary outcomes			
Microalbuminuria	2121 (5·2%)	2210 (6·3%)	0·90 (0·84–0·95)

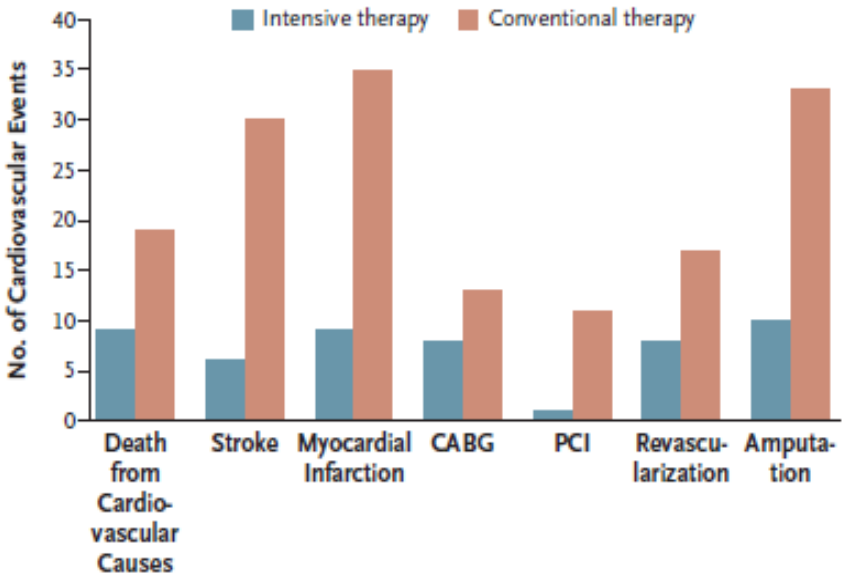


Zoungas et.al. Lancet Diabetes & Endocrinology 2017; 5:431-437

STENO: targeting multiple renal/CV risk factors

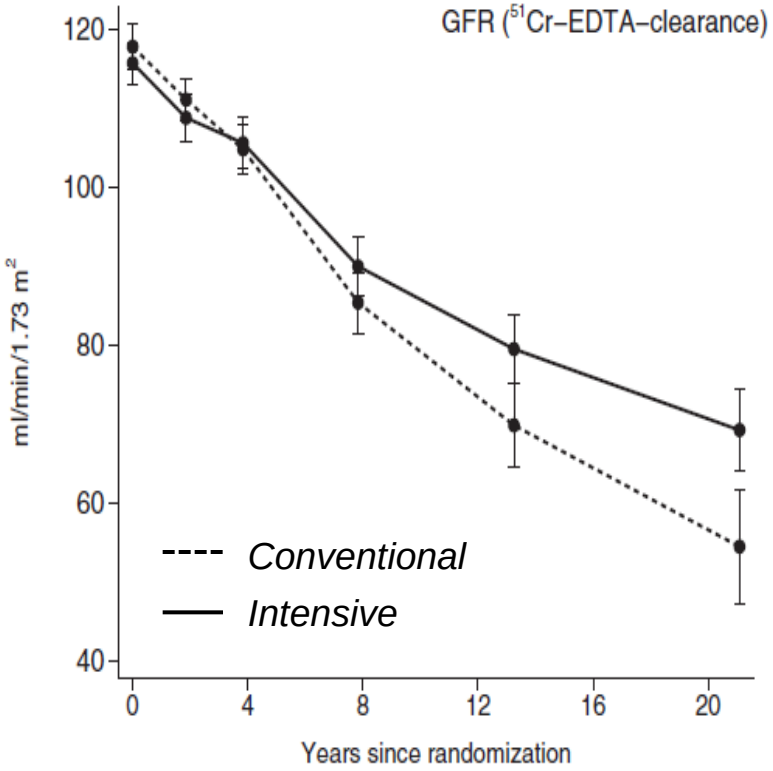
- In type 2 diabetes multiple CV / renal risk factors are elevated
- Targeting these multiple risk factors results in considerable CV protection

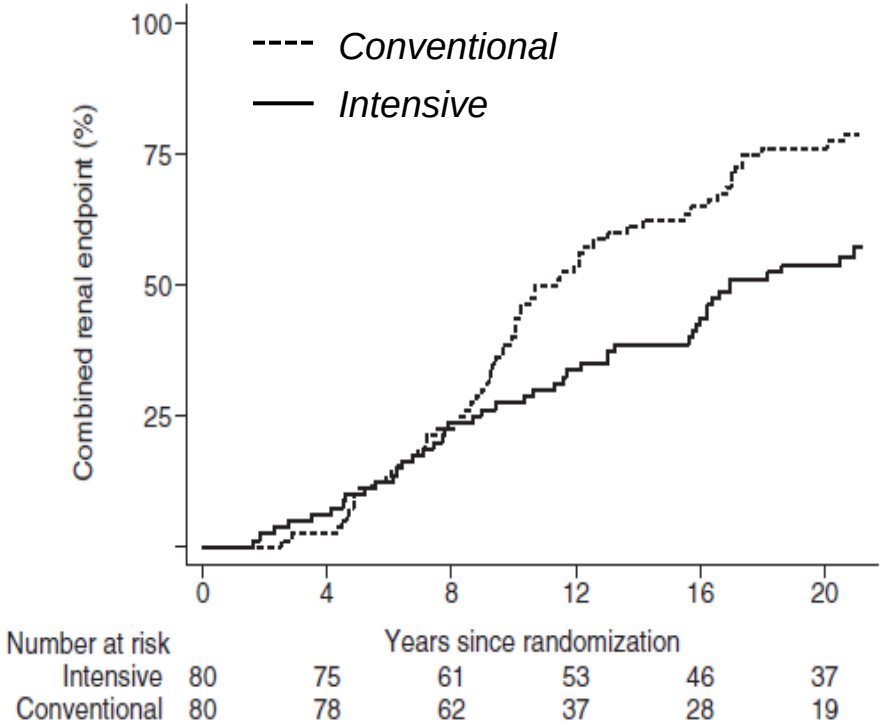




Parving et.al. New Engl J Med 2008:358;580-91

STENO: renal outcome 21 yrs follow-up





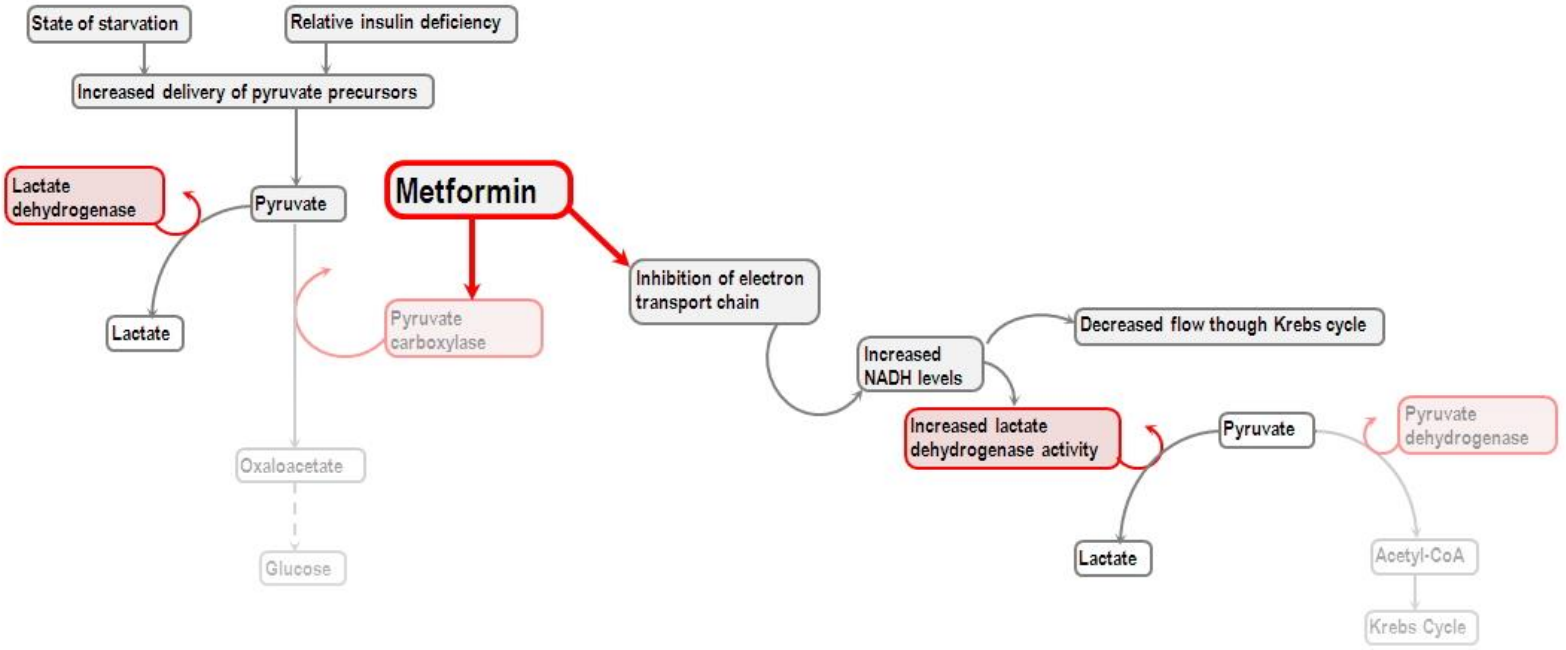
Oellgaard et.al. Kidney Int. 2017:91;982-88

What‘s new?

- Glycemic control important to manage DKD
- Glycemic targets targets should be individualized
  - Less stringent glycemic goals for patients with CKD (ADA guideline)
  - Hba1c <8.0% when GFR<60 (DKD consensus report)
- Many other risk factors important as well and they should be adequately targeted to optimize outcomes

Metformin in patients with diabetic kidney disease

- Metformin is traditionally contra-indicated in patients with diabetic kidney disease because of risk of lactate acidosis



Dembo et.al. Diabetes 1975 Vol 24; 28-35

Metformin in CKD – still contraindicated?

http://www.ema.europa.eu/ema/

FDA recommendations

Table 3. 2016 Revised recommendations for metformin use in patients with impaired renal function[37]

eGFR, ml/min per 1.73 m^2	FDA Recommendations for Metformin Use
>45	No contraindications
	Obtain eGFR at least annually
30–45	Starting metformin is not recommended
	Assess the benefits and risks of continuing treatment for patients currently receiving metformin
<30	Contraindicated
Metformin should be discontinued in patients with	History of liver disease, alcoholism, or heart failure
	Upcoming iodinated contrast imaging procedure and eGFR between 30 and 60 ml/min per 1.73 m^2 (may restart 48 h after procedure if kidney function stabilizes)
	Upcoming administration of intra-arterial iodinated contrast (may restart 48 h after procedure if kidney function stabilizes)

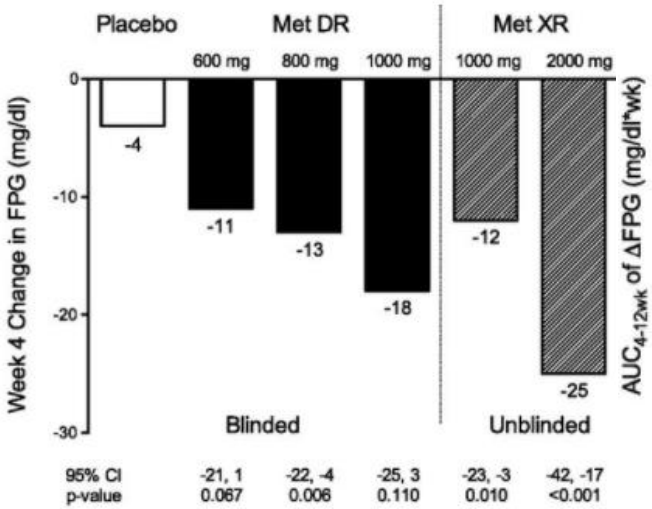
Obtain an eGFR before initiating metformin therapy.

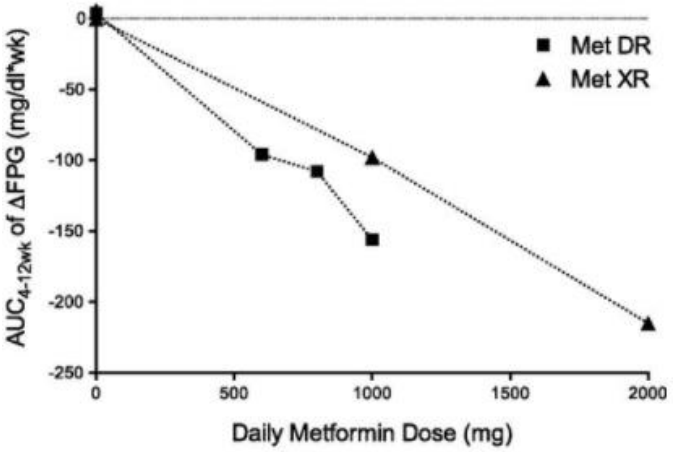
Neumiller et.al. JASN 2017:28;2263-74

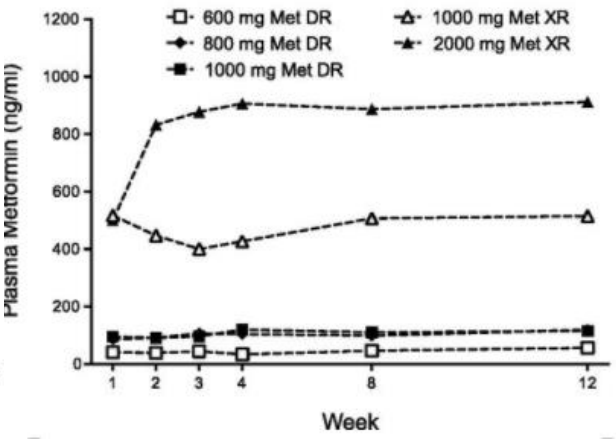
New metformin formulation which targets the small intestine

- Traditional metformin formulation target high systemic exposure
- A new formulation has been developed specifically targeting the L-cell in the small intestine (thus low systemic exposure)
- L-cells are the primary cells of several glucose regulating hormones like GLP-1

Metformin delayed release – study results

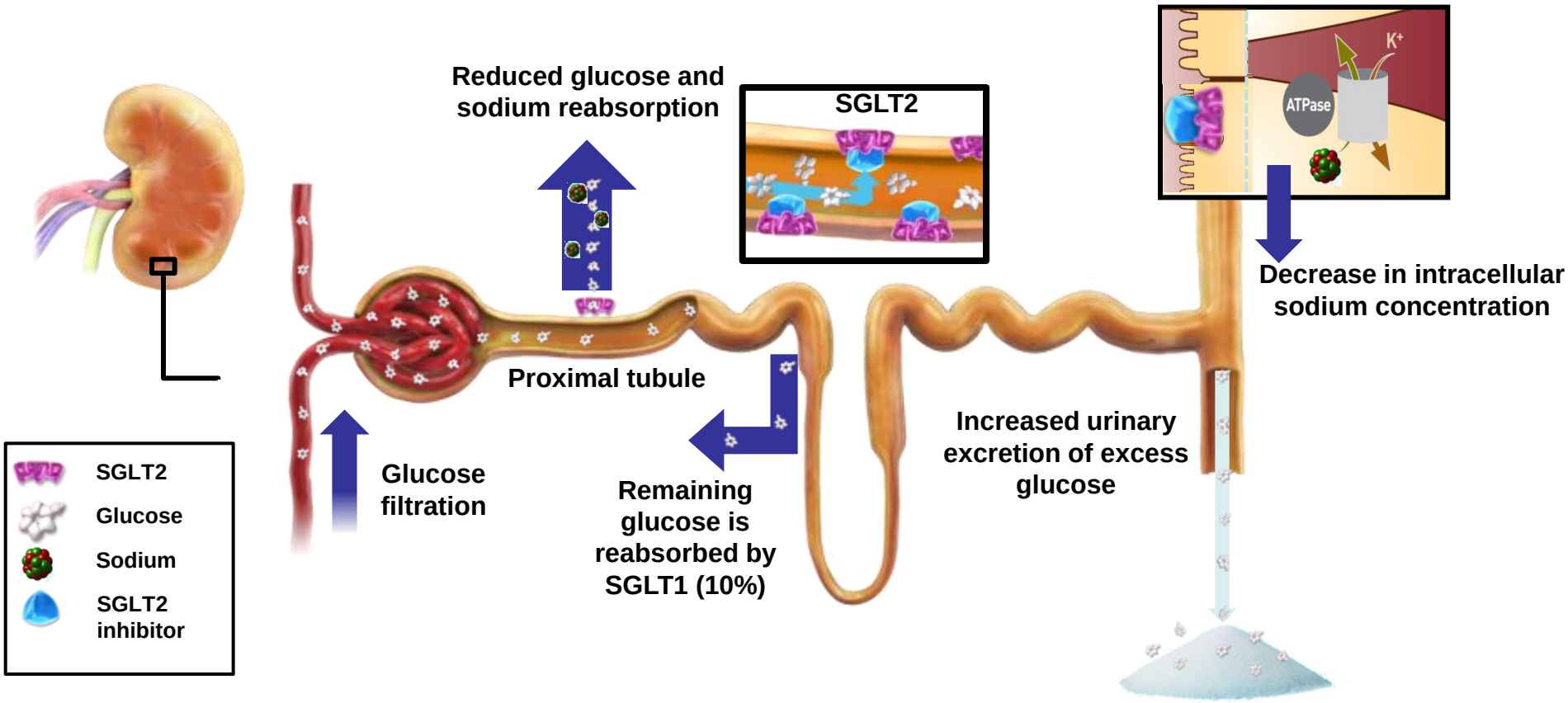




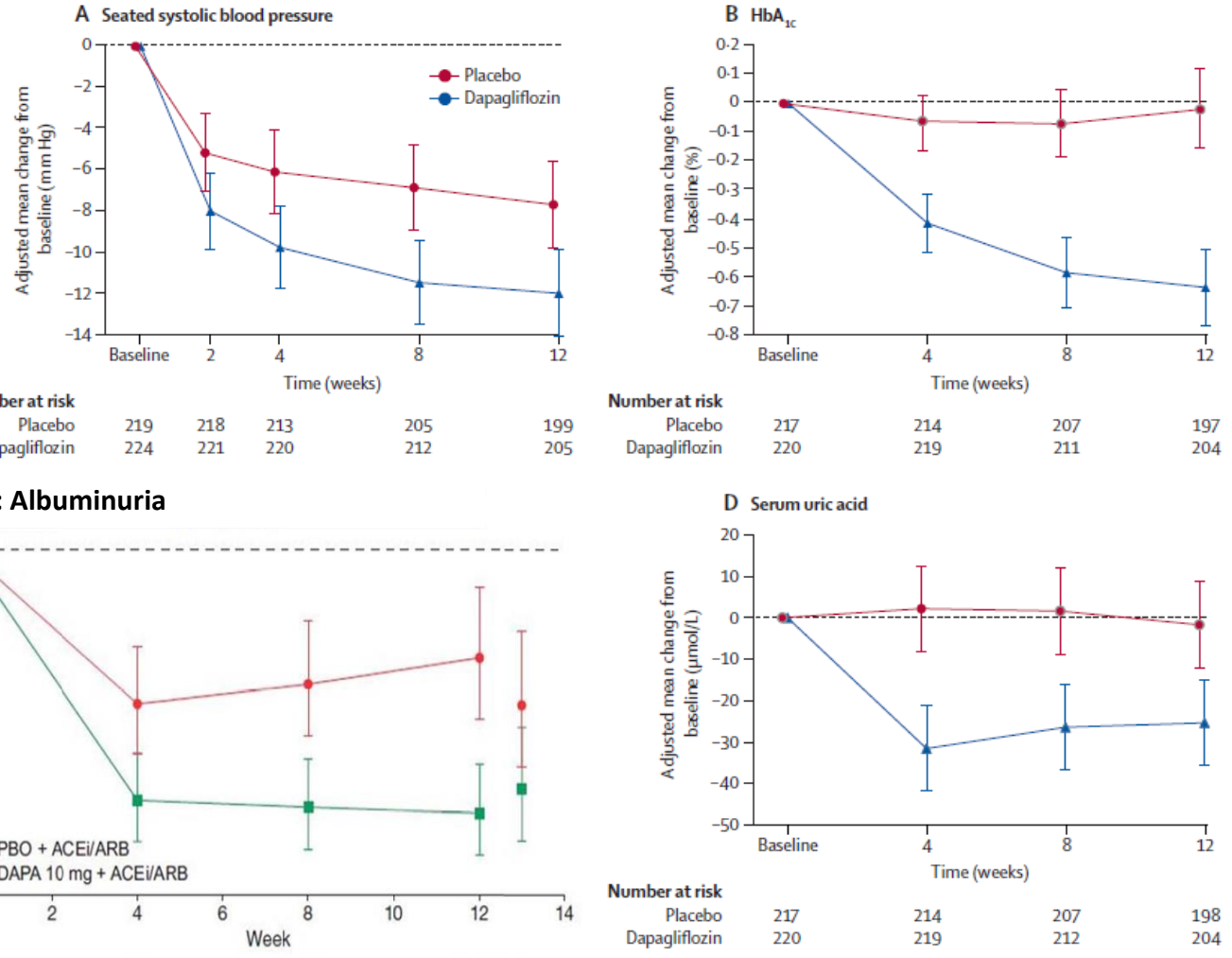


Buse et.al. Diabetes Care 2016:39;198-205

A novel avenue to protect the diabetic kidney?
Sodium glucose transporter inhibitors

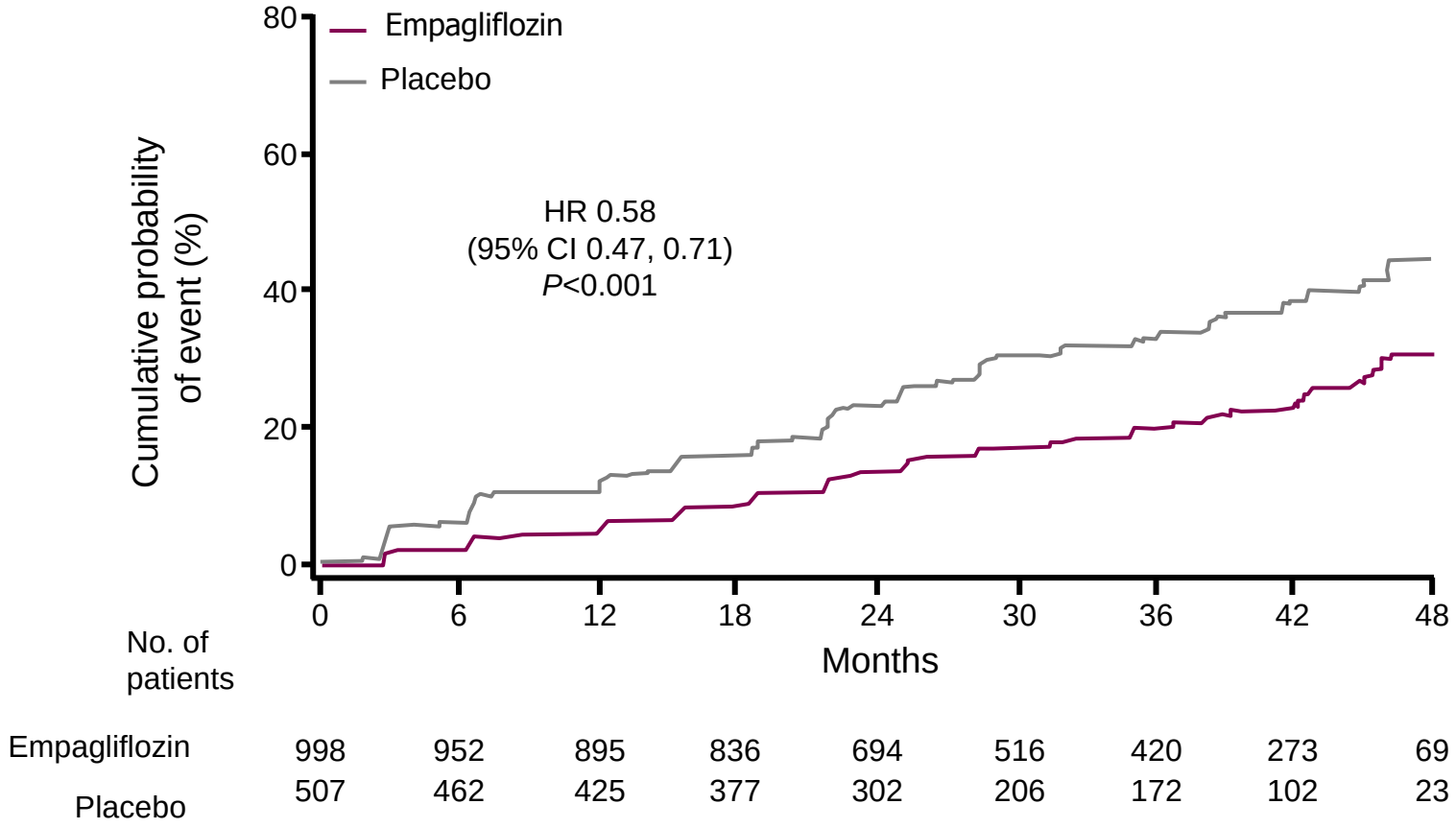


Multiple effects SGLT2



Weber et.al. Lancet Diabetes & Endocrinology 2016:4;211-20

EMPAREG: Effects of Empagliflozin on kidney end points



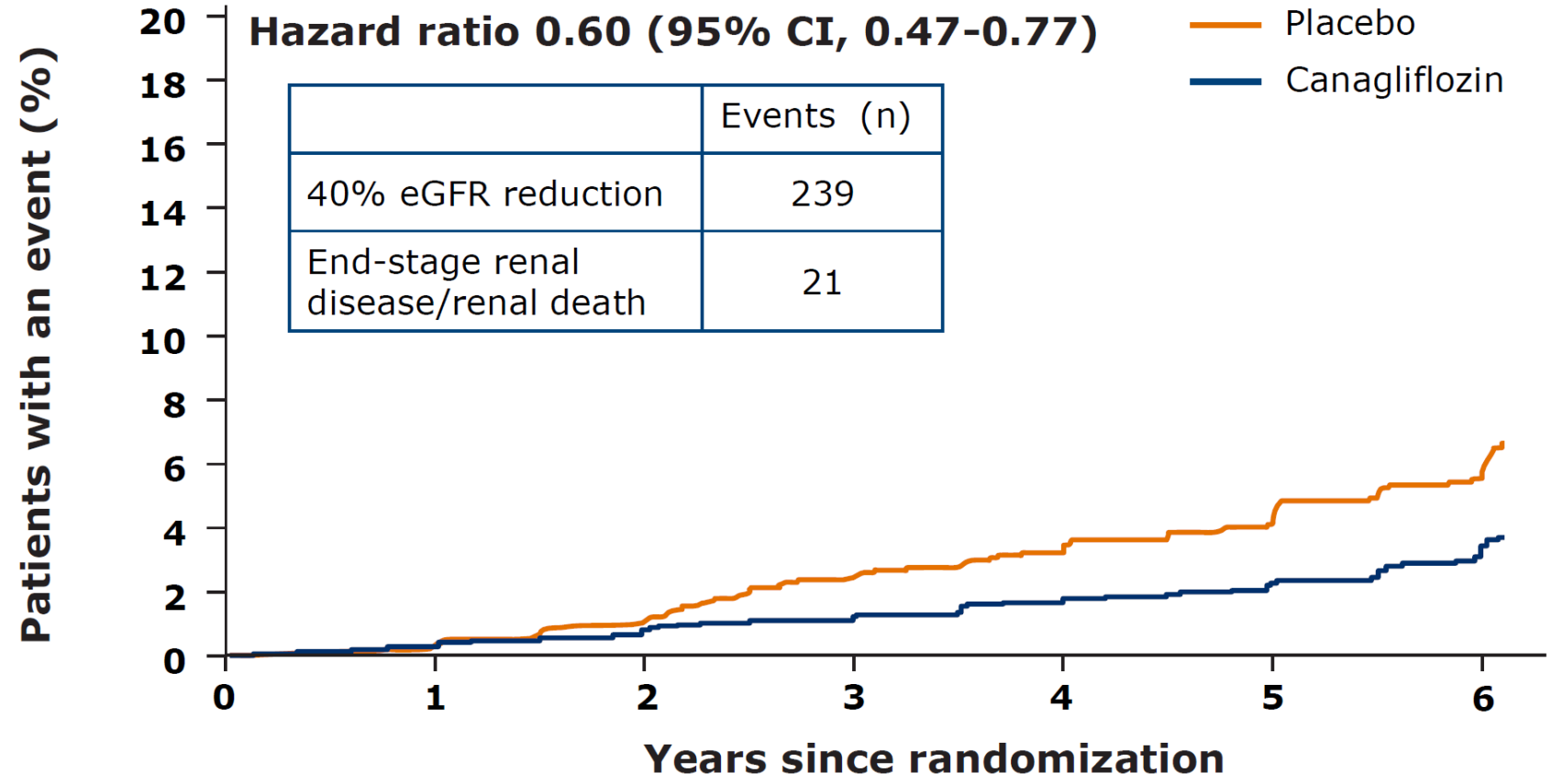
Wanner C et.al. N Engl J Med. 2016 Jul 28;375(4):323-34

CANVAS population

	Canagliflozin (N=5795)	Placebo (4347)
Age (Yr)	63	63
Female Gender (%)	35	37
Duration of Diabetes (Yr)	14	14
CV Disease history	65	67
HbA1c (%)	8.2	8.2
Systolic BP (mmHg)	136	136
Metformin (%)	77	78
Insulin (%)	50	51

Neal et.al. NEJM 2017;377(7):644-657

CANVAS: Renal outcome

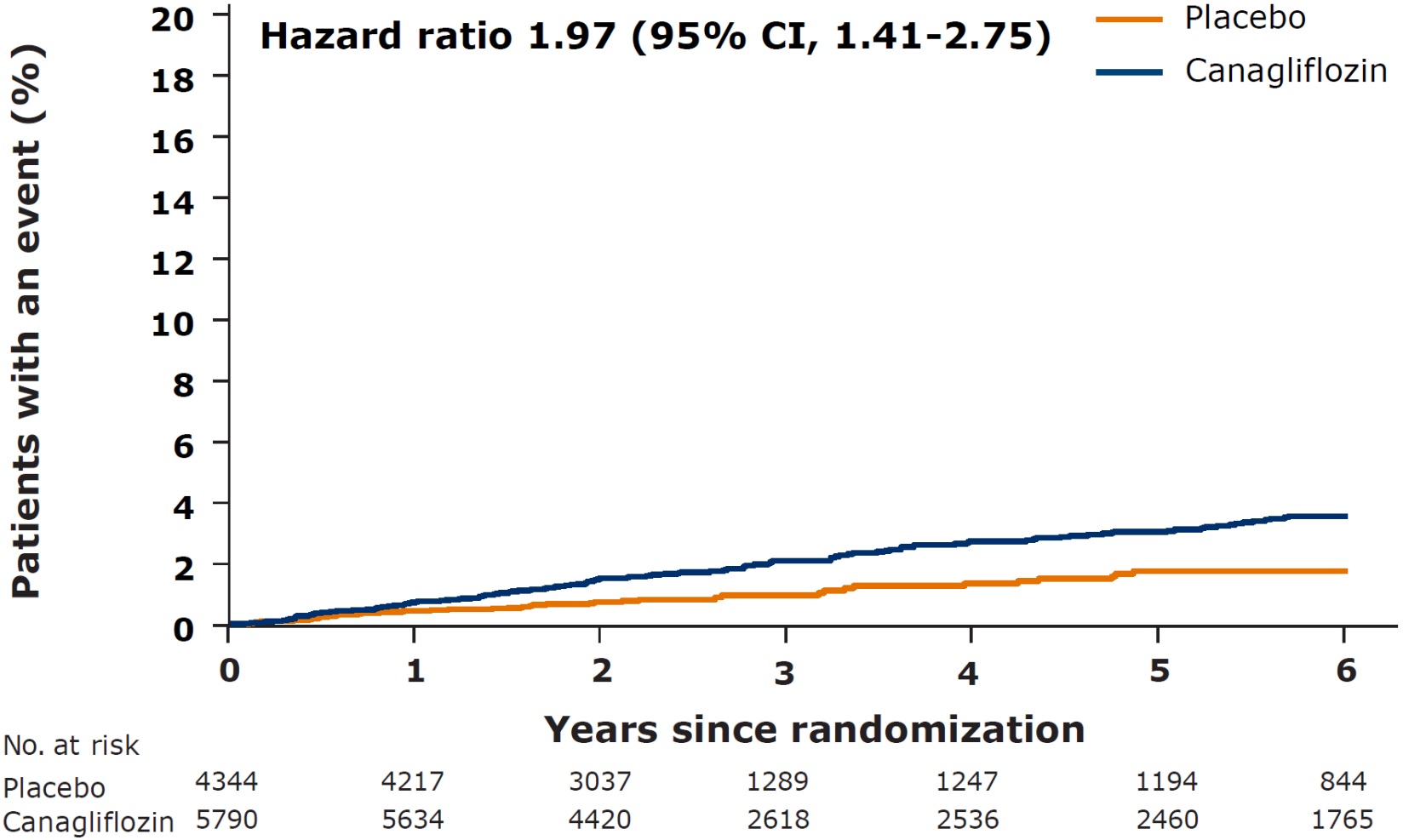


	Events (n)
40% eGFR reduction	239
End-stage renal disease/renal death	21

No. of patients							
Placebo	4347	4227	3029	1274	1229	1173	819
Canagliflozin	5795	5664	4454	2654	2576	2495	1781

Neal et.al. NEJM 2017;377(7):644-657

CANVAS: Lower extremity amputations



Neal et.al. NEJM 2017;377(7):644-657

Can SGLT2 inhibitors be used in DKD?

Dapagliflozin

Use in patients with renal impairment

The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension,

Canagliflozin

Renal impairment

For patients with an eGFR 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2 or CrCl 60 mL/min to < 90 mL/min, no dose adjustment is needed.

Canagliflozin should not be initiated in patients with an eGFR < 60 mL/min/1.73 m^2 or CrCl < 60 mL/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m^2 or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl persistently below 45 mL/min (see sections 4.4, 4.8, 5.1, and 5.2).

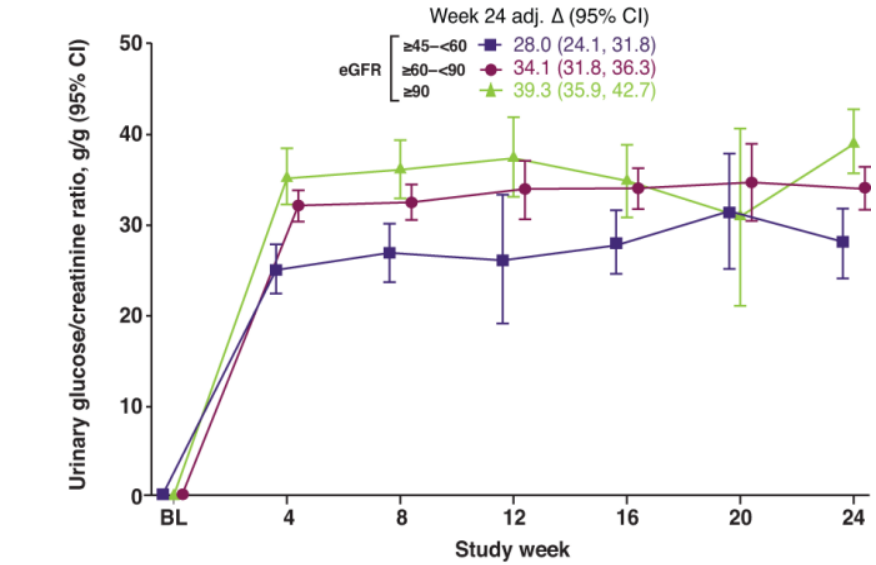
Empagliflozin

Jardiance should not be initiated in patients with an eGFR below 60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR is persistently below 60 ml/min/1.73 m^2 or CrCl <60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below

SUMMARY OF PRODUCT CHARACTERISTICS www.ema.europa.eu

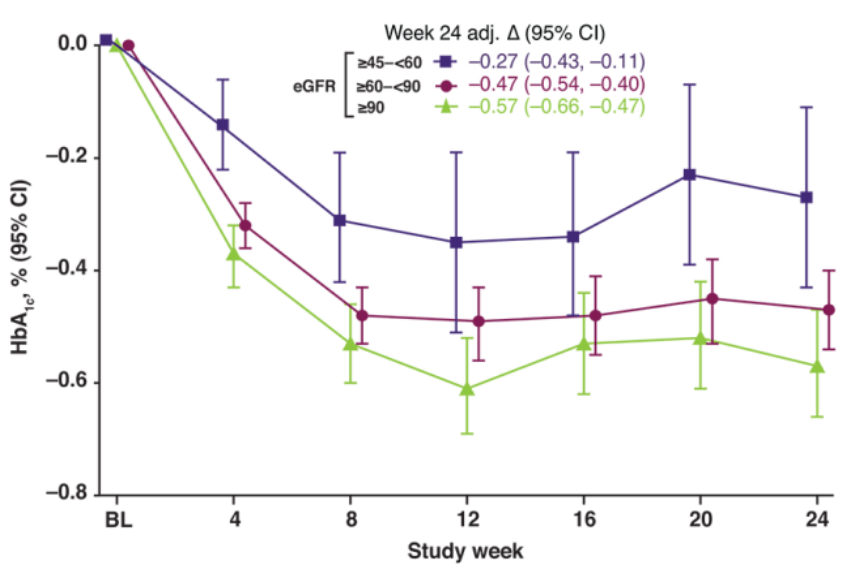
Glycemic effects of SGLT2i are blunted in DKD

Placebo-adjusted change from baseline over time with dapagliflozin in HbA1c in the overall population



Patients per timepoint

eGFR	BL	4	8	12	16	20	24
≥45–<60	192	158	150	26	130	20	147
≥60–<90	1128	831	806	265	683	150	986
≥90	649	419	417	171	320	80	574



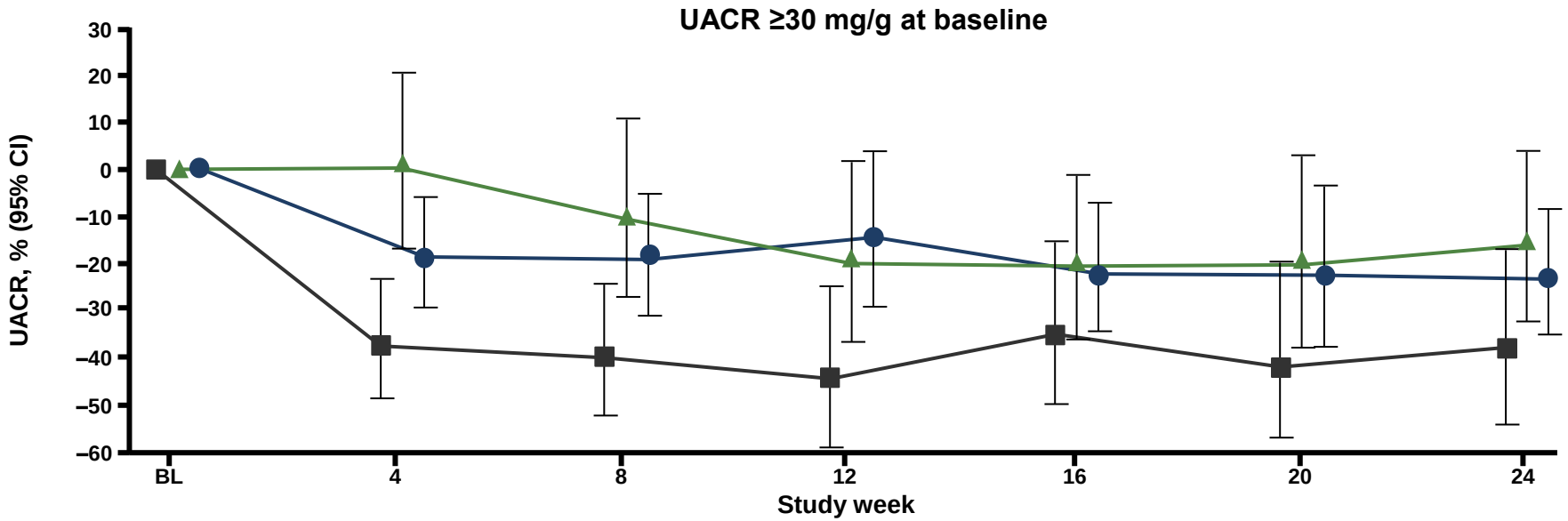
Patients per timepoint

eGFR	BL	4	8	12	16	20	24
≥45–<60	238	232	227	99	204	83	190
≥60–<90	1213	1149	1169	596	970	458	1050
≥90	697	650	673	428	531	311	612

Excludes data after rescue. Adj., adjusted; BL, baseline; CI, confidence interval.

Petrykiv et.al. CJASN 2017: 8:751-759

Non-glycemic effects of SGLT2i persist in DKD

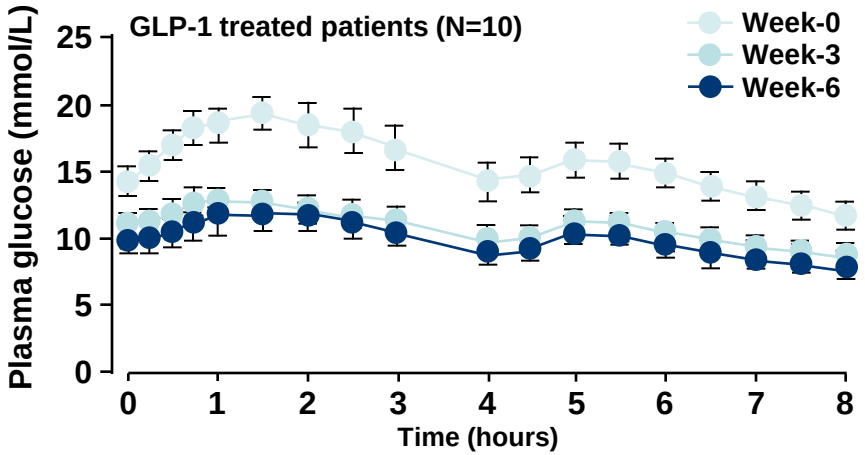


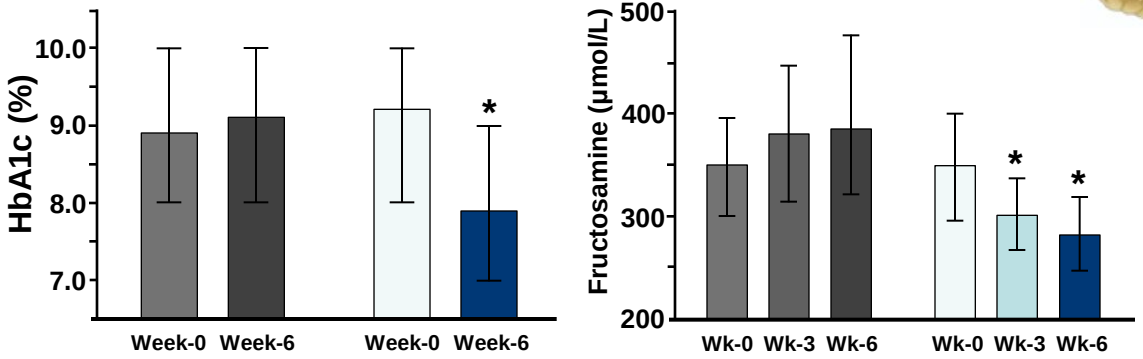
eGFR							
≥45–<60, n	90	88	82	40	74	36	71
≥60–<90, n	310	306	293	126	269	105	261
≥90, n	175	173	168	94	145	77	150

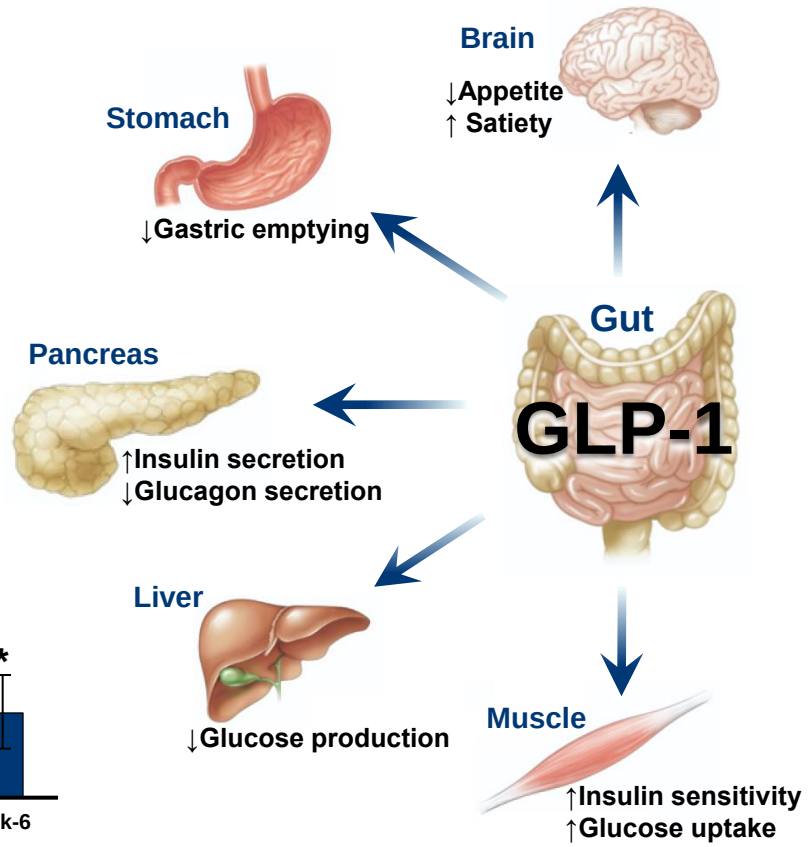
eGFR subgroup (mL/min/1.73 m²)	Mean UACR		
	Baseline (SD)	Week 24 adjusted Δ (%)	95% CI
≥45–<60	211 (370)	–38.3	–54.4, –16.6
≥60–<90	206 (350	–23.3	–35.5, –8.7
≥90	170 (248)	–16.1	–32.3, 3.8

Petrykiv et.al. CJASN 2017: 8:751-759

Native GLP-1 infusion in type 2 diabetes patients improves glycemic control through various mechanisms

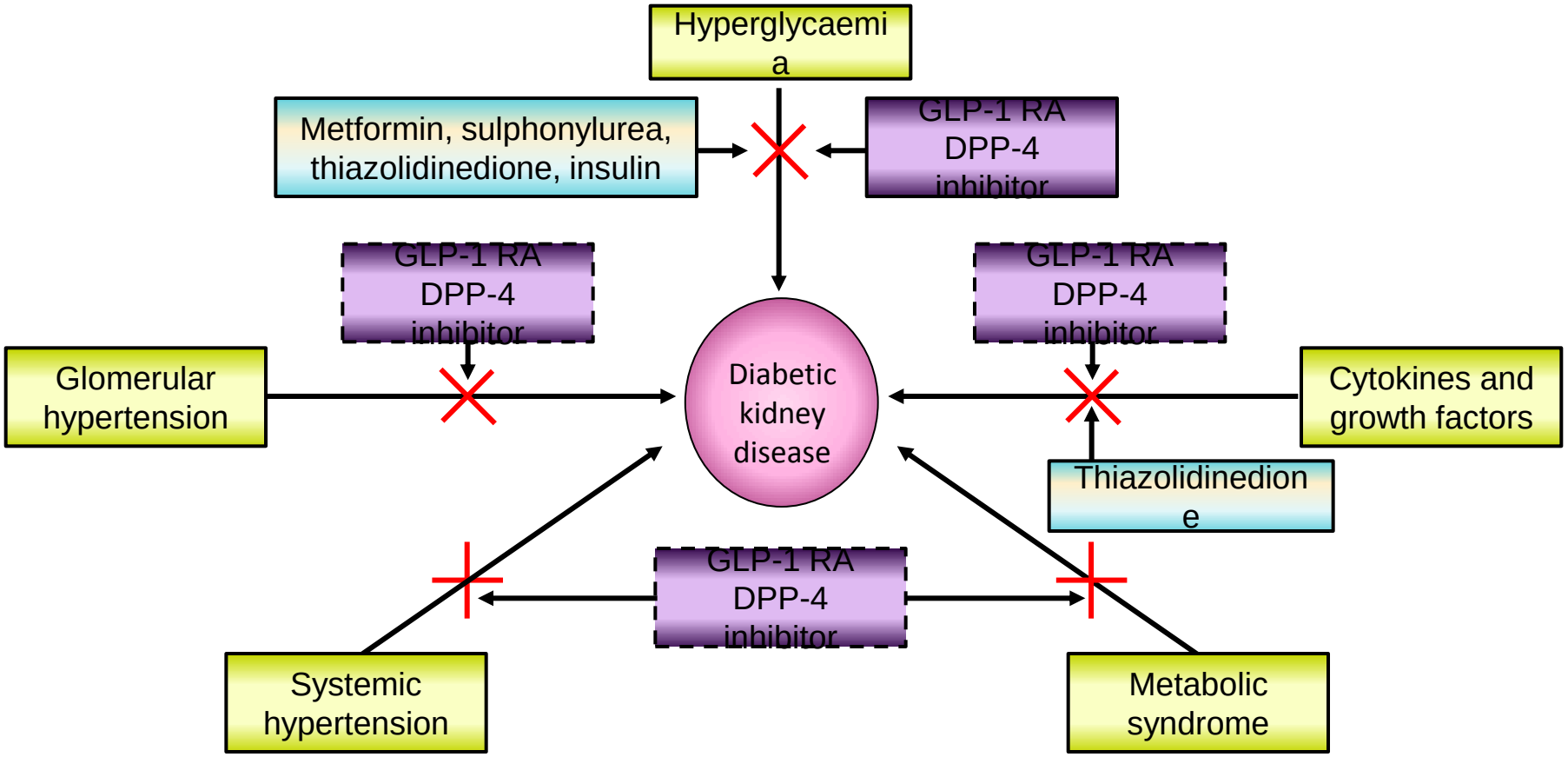






Zander M. Lancet 2002;359(9309):824-30.

Incretins may protect the kidney via multiple pathways



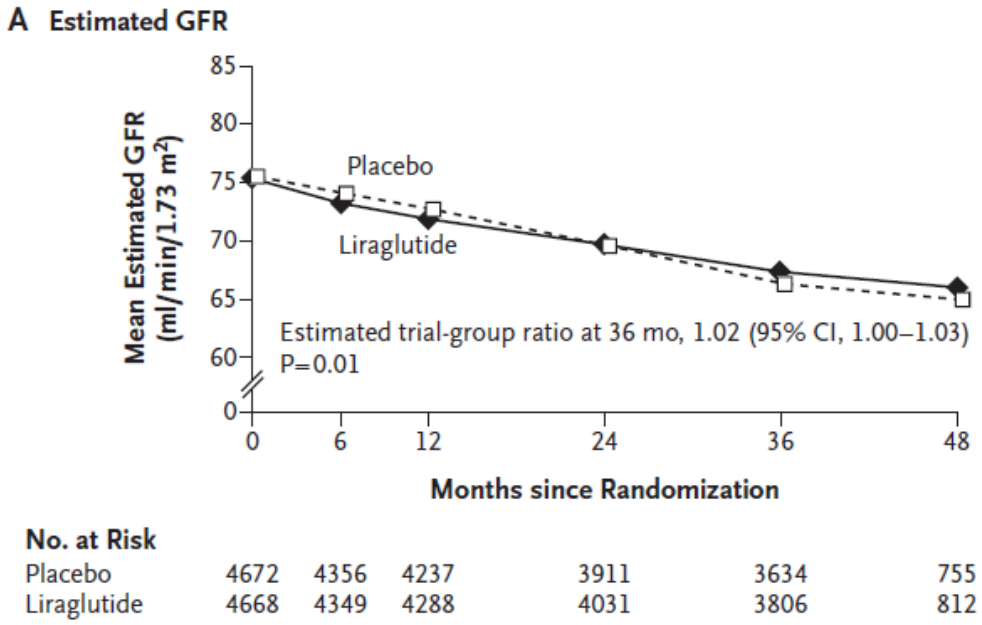
Muskiet et.al. Nature Reviews Nephrology 2017; 13(10):605-628

LEADER baseline characteristics

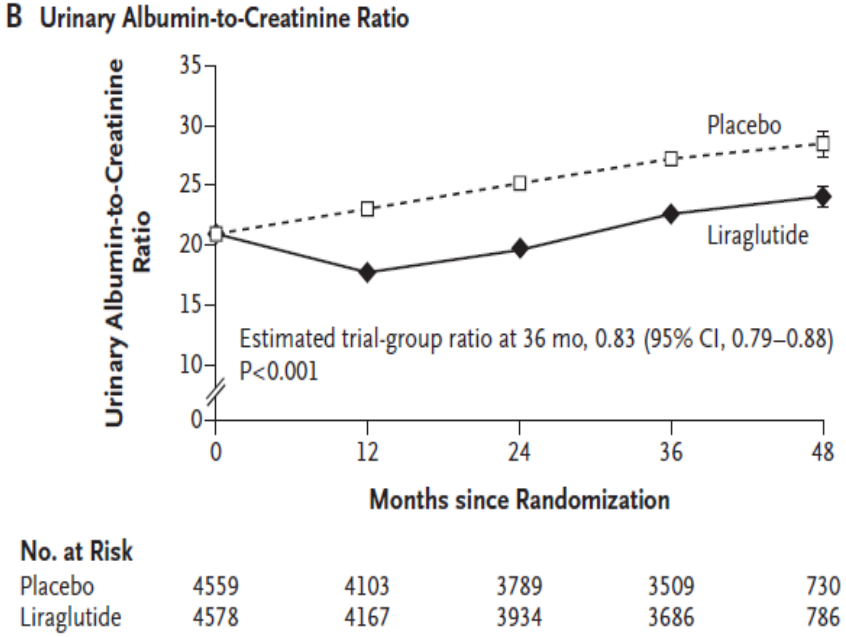
	Liraglutide (N=4,668)	Placebo (N=4,672)
Male sex	3011 (64.5)	2992 (64.0)
Age, years	64.2 ±7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Geographic region		
Europe	1639 (35.1)	1657 (35.5)
North America	1401 (30.0)	1446 (31.0)
Asia	360 (7.7)	351 (7.5)
Rest of the world	1268 (27.2)	1218 (26.1)
Glycated hemoglobin, %	8.7 ± 1.6	8.7 ± 1.5
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.3
Body weight, kg	91.9 ± 21.2	91.6 ± 20.8
Systolic blood pressure, mm Hg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mm Hg	77.2 ± 10.3	77.0 ± 10.1
Renal function		
Normal (eGFR ≥90)	1620 (34.7)	1655 (35.4)
Mild impairment (eGFR 60–89)	1932 (41.4)	1975 (42.3)
Moderate impairment (eGFR 30–59)	999 (21.4)	935 (20.0)
Severe impairment (eGFR <30)	117 (2.5)	107 (2.3)

Mann JF et.al. New Engl. J. Med 2017 Aug 31;377(9):839-848

LEADER: Effects on eGFR and albuminuria



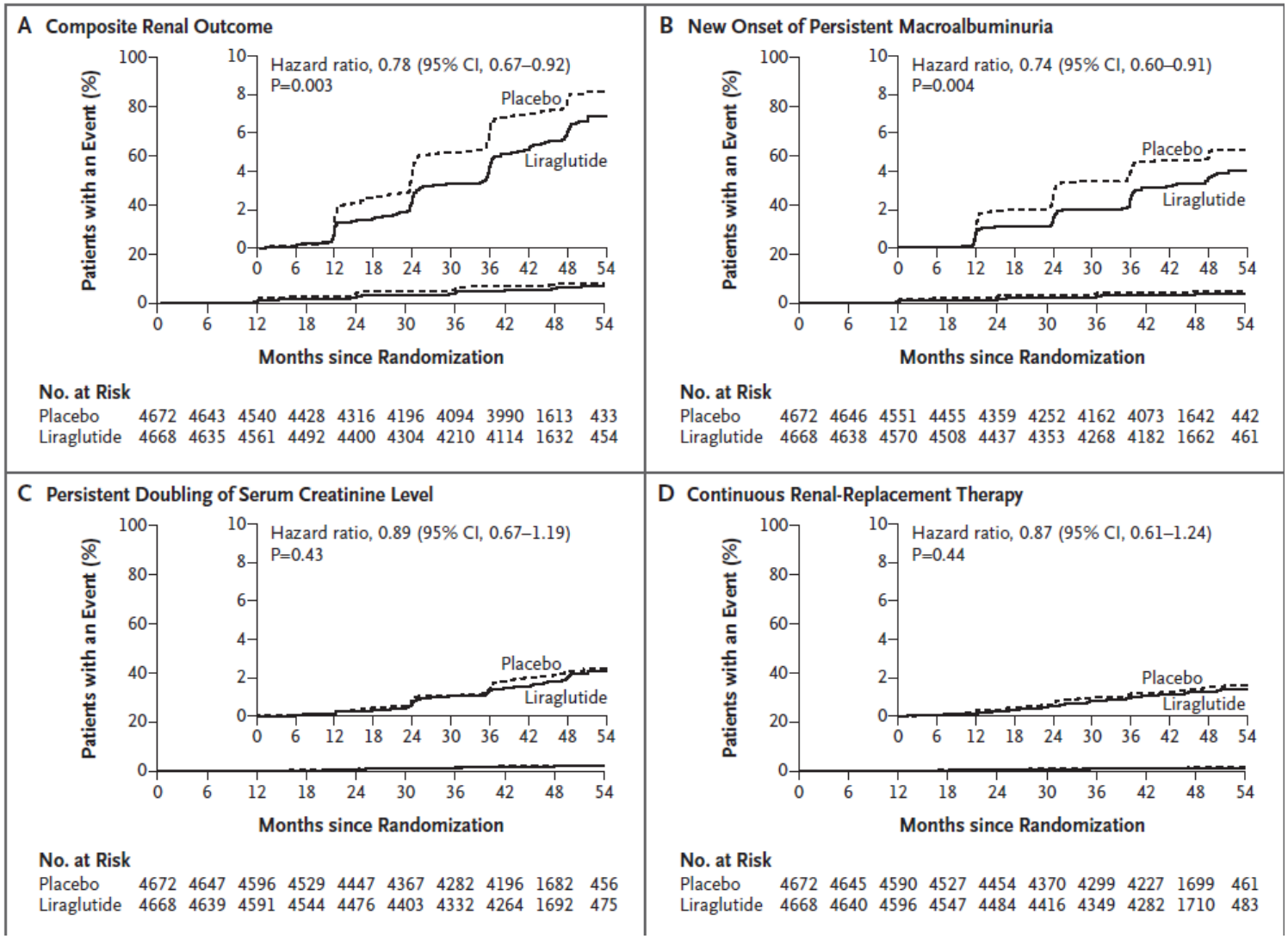
No. at Risk						
Placebo	4672	4356	4237	3911	3634	755
Liraglutide	4668	4349	4288	4031	3806	812



No. at Risk						
Placebo	4559	4103	3789	3509	730	
Liraglutide	4578	4167	3934	3686	786	

Mann JF et.al. New Engl. J. Med 2017 Aug 31;377(9):839-848

LEADER renal outcome

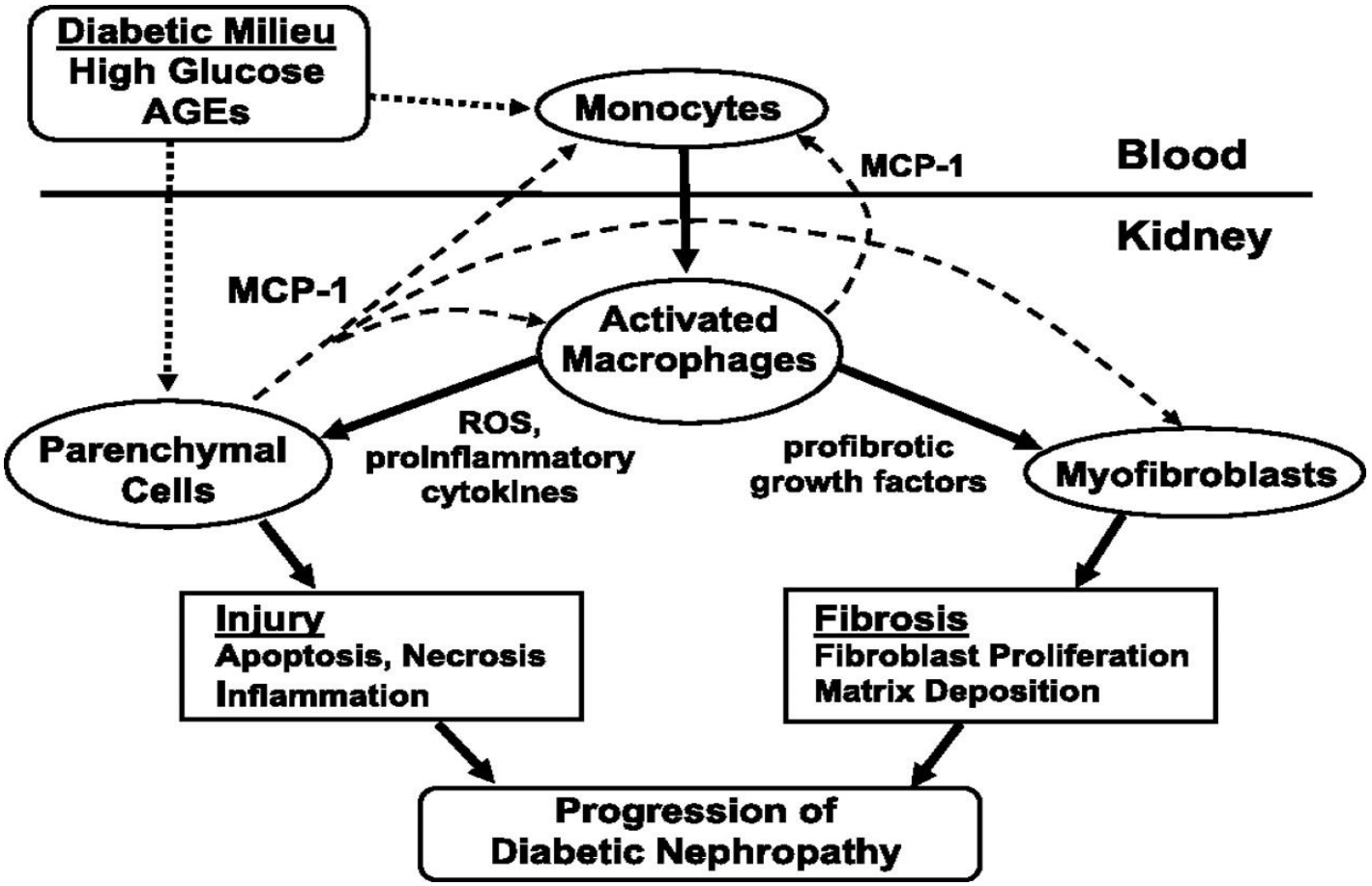


Mann JF et.al. New Engl. J. Med 2017 Aug 31;377(9):839-848

What‘s new?

- Many pharmacotherapeutic developments
  - Existing drugs new formulations (metformin)
  - New interventions
    - SGLT-2 inhibitors
    - GLP-1 analogues?
- SGLT2 inhibitors appear to be very promising to slow progression of DKD.
- Ongoing trials (CREDENCE / DAPA-CKD) provide definitive evidence in the near future

Inflammation drives progression of diabetic kidney disease



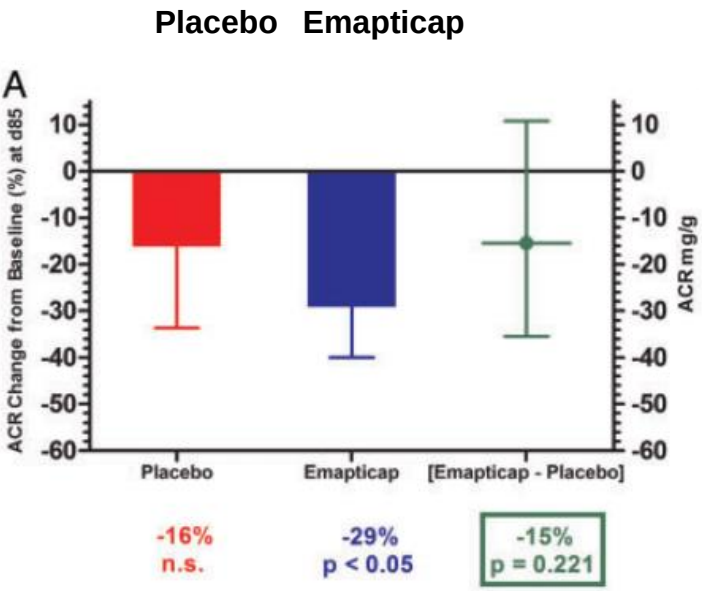
Tesch GH: American Journal of Physiology - Renal Physiology 2008;294(4):F697-F701

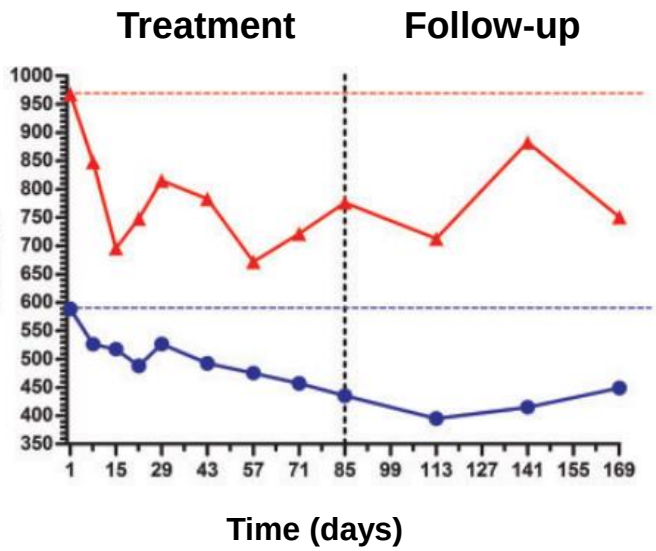
Emapticap (MCP-1 inhibitor) exploratory phase 2 study

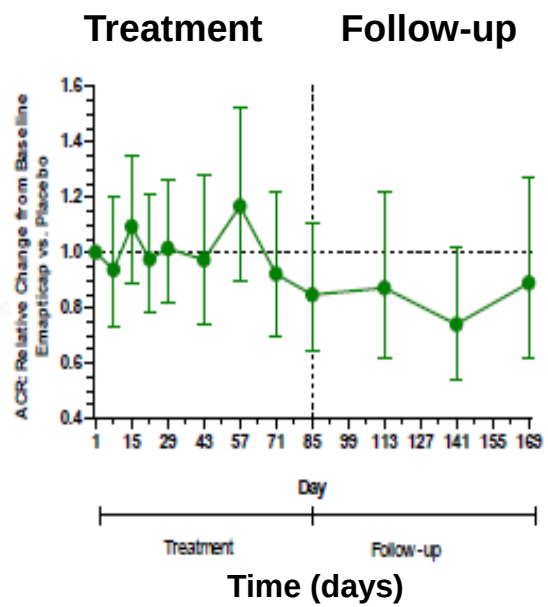
- *Design*
  - Randomized placebo controlled trial
- *Patients*
  - 76 patients with type 2 diabetes and ACR > 100 mg/g
- *Follow-up*
  - 19 wks (7 on treatment / 12 off treatment
- *Intervention*
  - Emapticap 0.5 mg/kg s.c. twice weekly

Menne et.al. Nephrol Dial Transpl 2017:32;307-15

Results







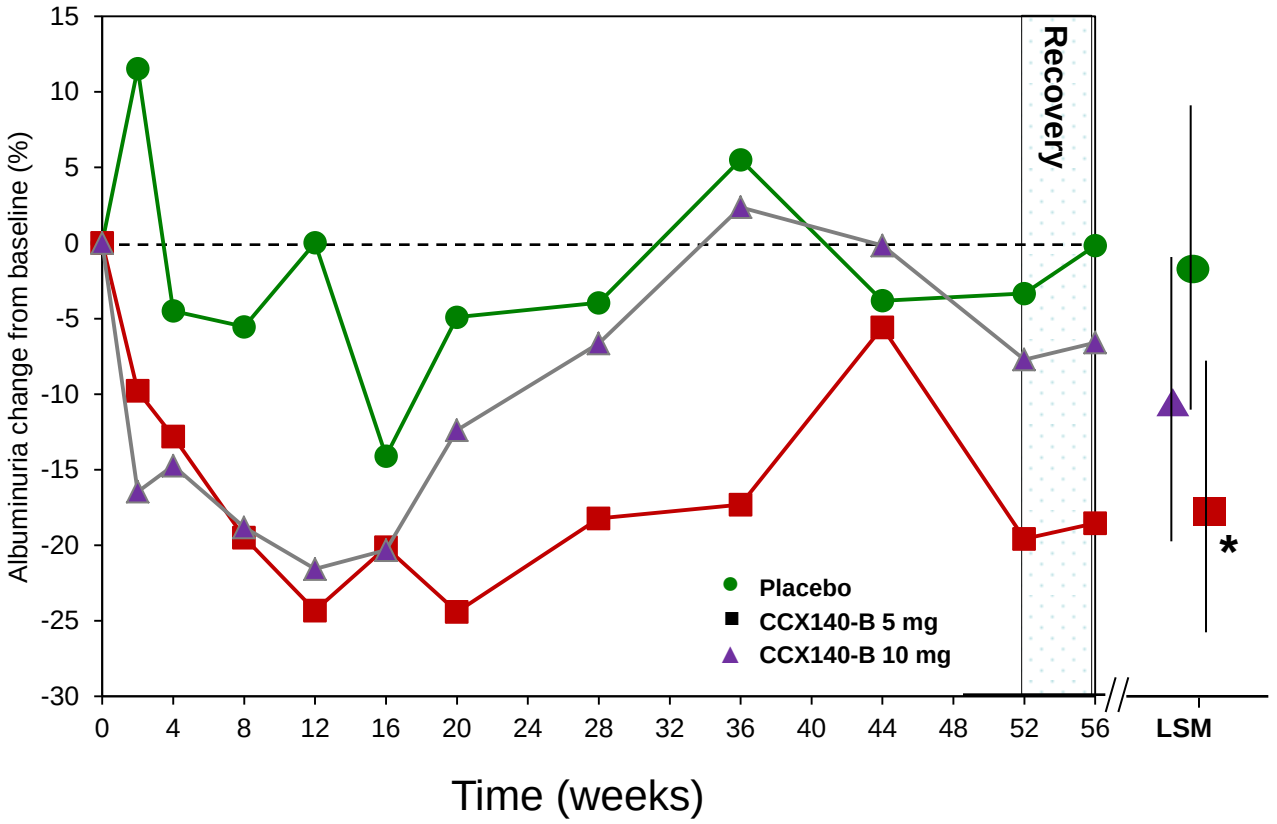
Menne et.al. Nephrol Dial Transpl 2017:32;307-15

CCX140-B: An MCP-1 receptor antagonist

- MCP-1 (CCL2) is a ligand for the CCR2 receptor
- MCP-1 promotes monocyte and macrophage activation
- CCRX140B is an antagonist of the CCR2 receptor and inhibits monocyte activation
- Phase 2 study in 332 subjects for 12 weeks; 192 completed week 52 follow-up
- Patients with type 2 diabetes; UACR > 100 mg/g; eGFR>25

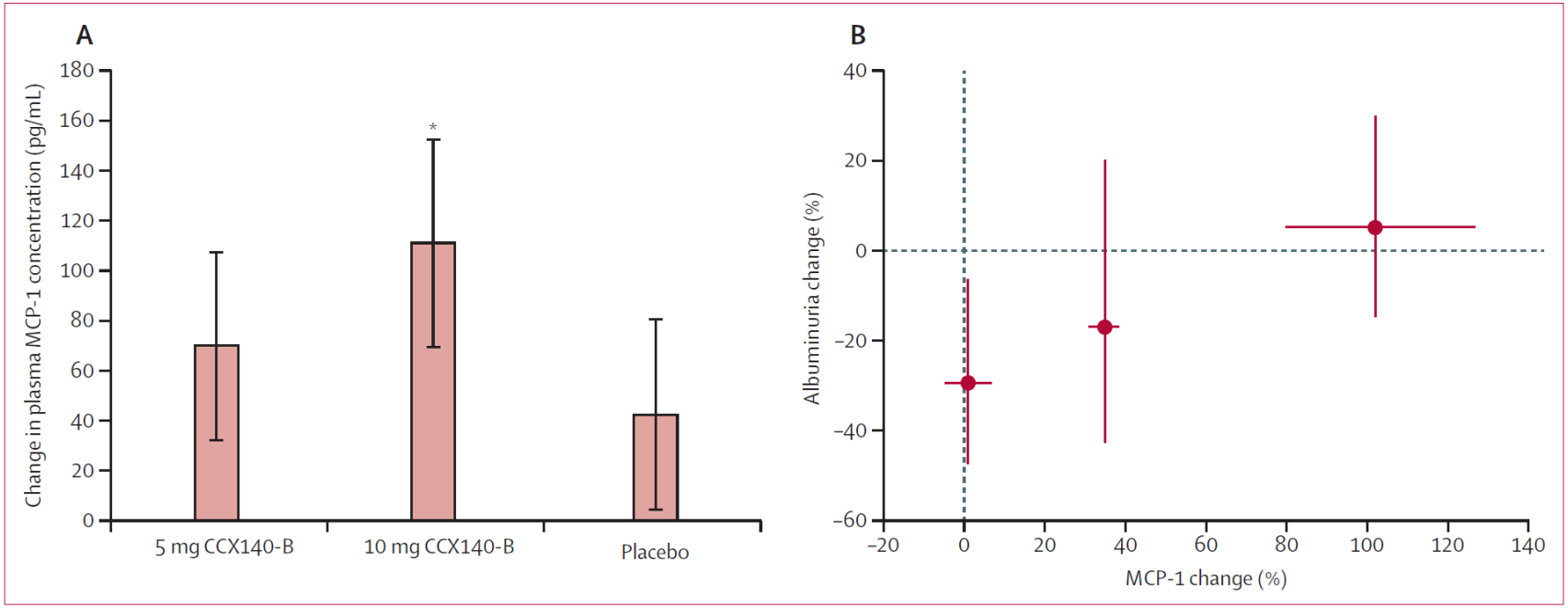
De Zeeuw et.al. Lancet Diabetes & Endo. 2015;3(9):687-96

Results phase 2 study



De Zeeuw et.al. Lancet Diabetes & Endo. 2015;3(9):687-96

MCP-1 increases during CCX140-B treatment and is associated with blunted albuminuria response



De Zeeuw et.al. Lancet Diabetes & Endo. 2015;3(9):687-96

Does targeting of growth factors help to slow progession of DKD?

- TGF- β has been shown to be upregulated in DKD
- Renal fibrosis has been associated with increased β expression
- Voelker et.al. tested the hypothesis that anti-TGF-β therapy is renoprotective in a RCT of 417 patients with DKD
- Endpoint was change in creatinine

Attisona et.al. Science 2002:1646-47
Voelker et.al. JASN 2017:28;953-62

Anti-TGF beta therapy does not slow progression of kidney function decline

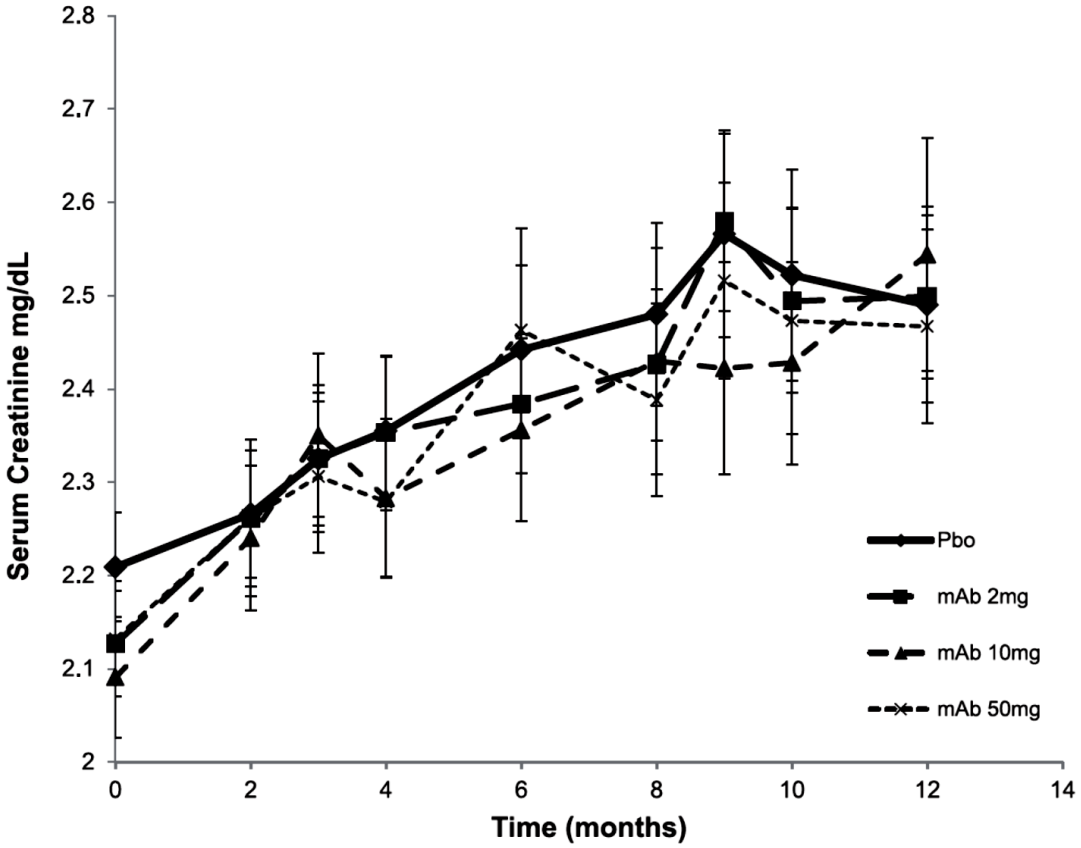


Figure 2. Effect of TGF-β1 mAb on SCr levels measured over time. Pbo, placebo.

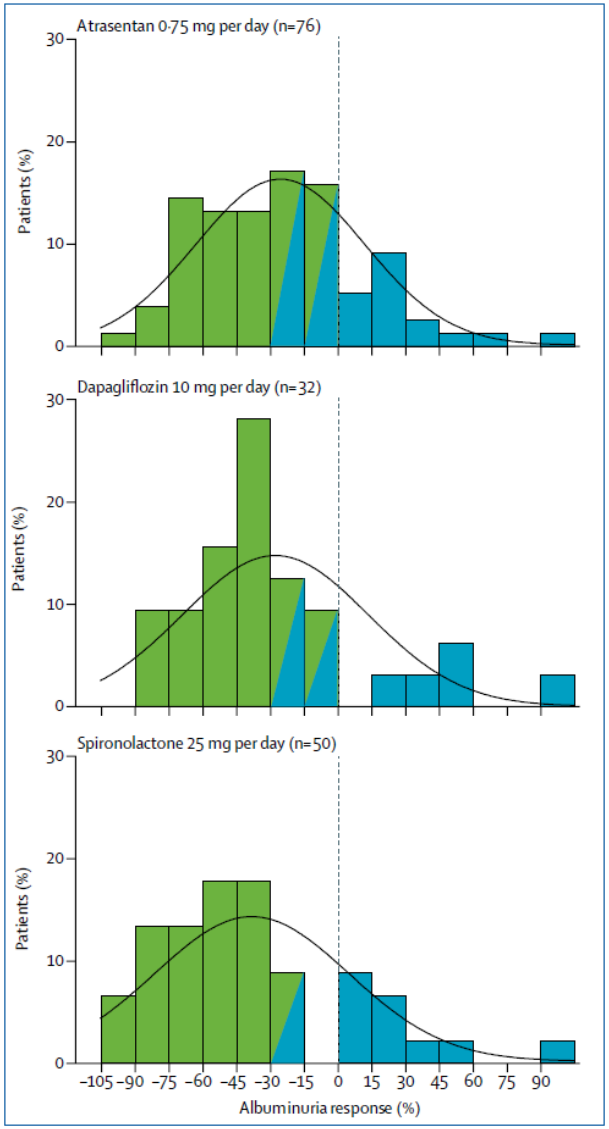
Voelker et.al. JASN 2017:28;953-62

What‘s new?

- Inflammation is involved in DKD
- Many different anti-inflammatory approaches are tested.
- Althought effective in animal models, they have not been very effective to date in lowering albuminuria / eGFR decline

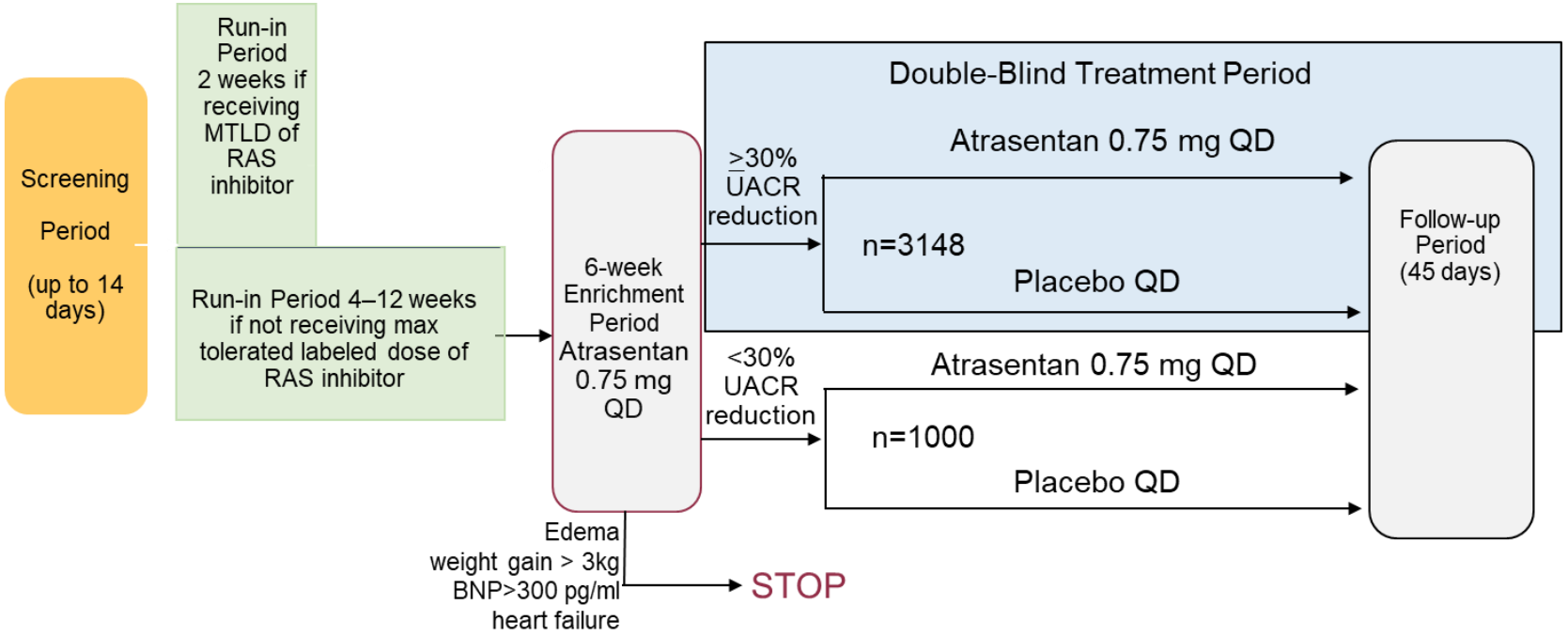
How does the future look like?

- In all trials with different drugs large variation in drug response
- Current trials are designed with one-size fits all approach
- More focus on how individual patient respond to drugs i.e. precision medicine
  - Investigate underlying mechanisms
  - Change clinical trial design
  - Change drug registration / clinical practice guidelines



De Zeeuw et.al. Lancet D&E 2017 Aug 7; epub ahead of print

SONAR: First response enrichment trial



- Primary endpoint
  Time to first occurrence of composite renal endpoint: doubling of serum creatinine or onset of ESRD (needing chronic dialysis or renal transplantation or renal death)
- Study completion
  425 distinct primary renal events have occurred (adjudicated) in the responder population

Lambers Heerspink et.al. Submitted

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