Prevention of microvascular complications – traditional and novel approaches

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ABCD Autumn Meeting
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Presenter disclosure information

Honoraria

Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, MSD, Novartis, Novo Nordisk, Sanofi

Grants

Eli Lilly, Roche

Advisory boards

Abbott, AbbVie, Astra Zeneca, Boehringer Ingelheim, Cebix, Eli Lilly, Janssen, Medscape, MSD, Novartis, Sanofi

Board member

Medix Laboratories

Stock/shareholder

No

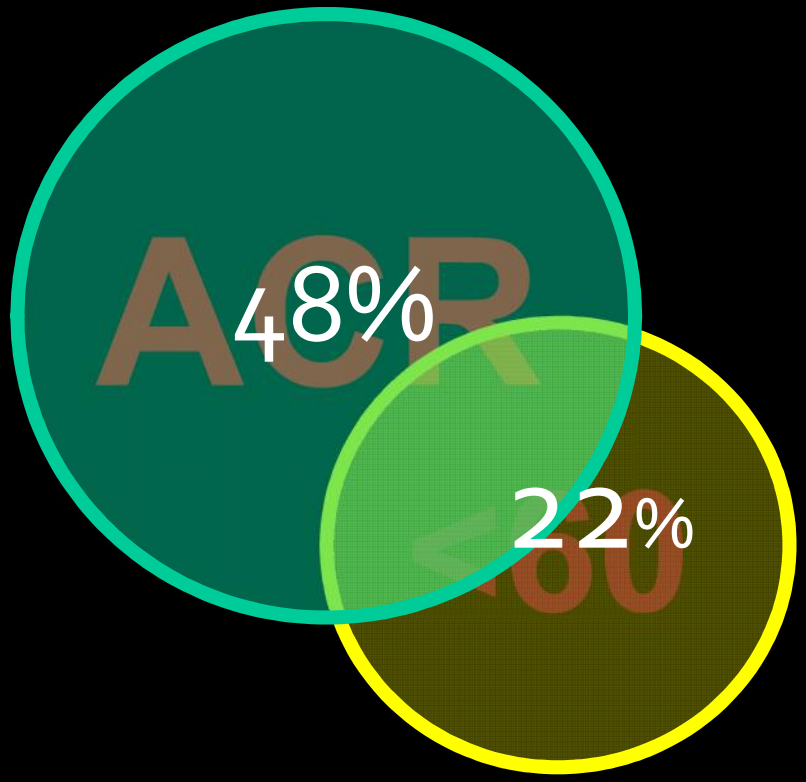
Outline of the talk

- Diabetic kidney disease epidemic
- Consequences of diabetic kidney disease
- What causes diabetic kidney disease?
- Traditional approaches for prevention
  - Glucose lowering
  - Multifactorial treatment
- Novel approaches
  - DPP4-inhibitors, GLP-1 agonists, SGLT2 inhibitors
- Why do SGLT2 inhibitors work so well?
- Take home messages

Diabetic kidney disease epidemic

Global perspective

N=24.151

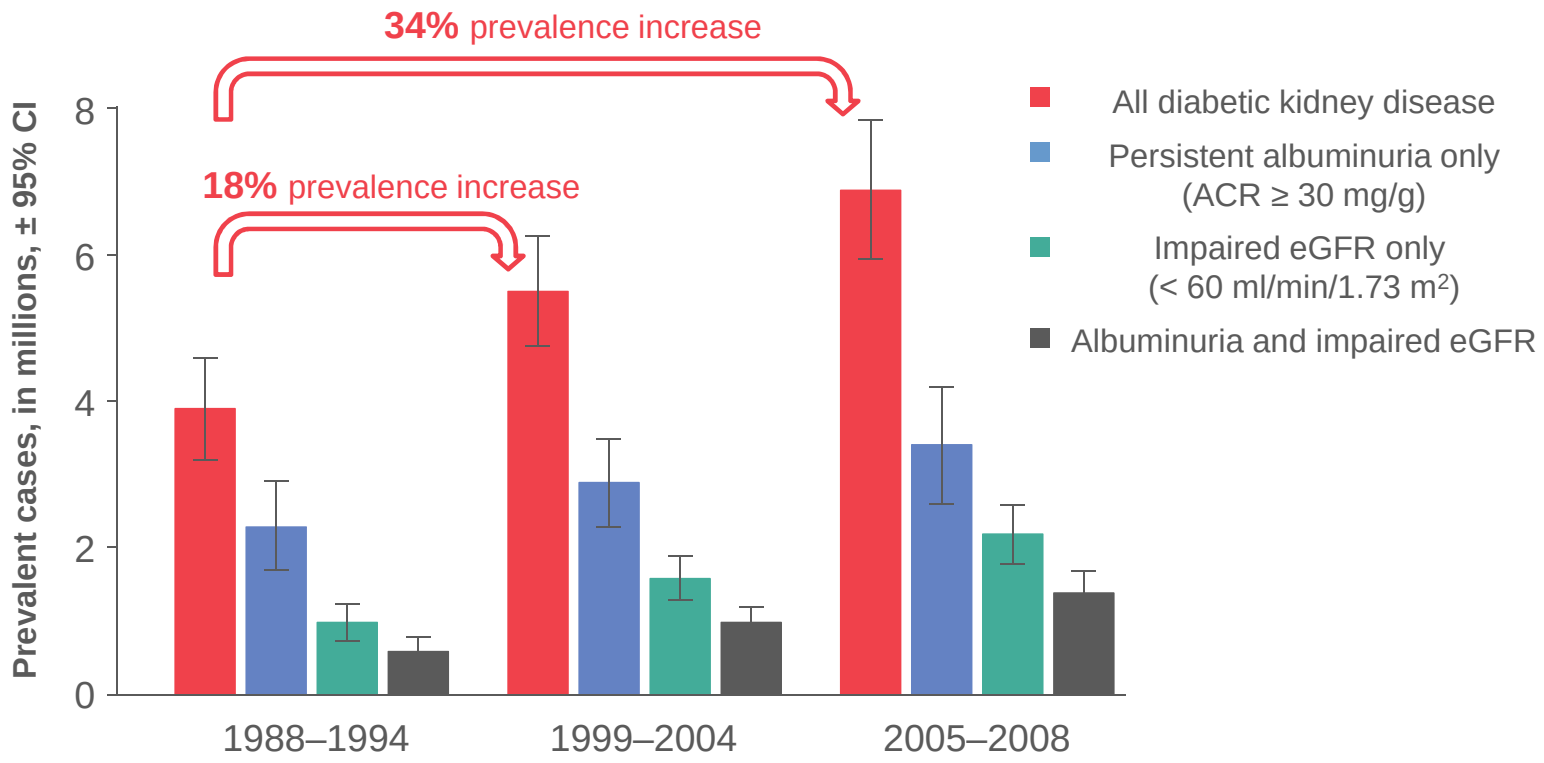


= 56%

Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND)

Parving HH et al. *Kidney Int* 2006;69(11):2057-63.

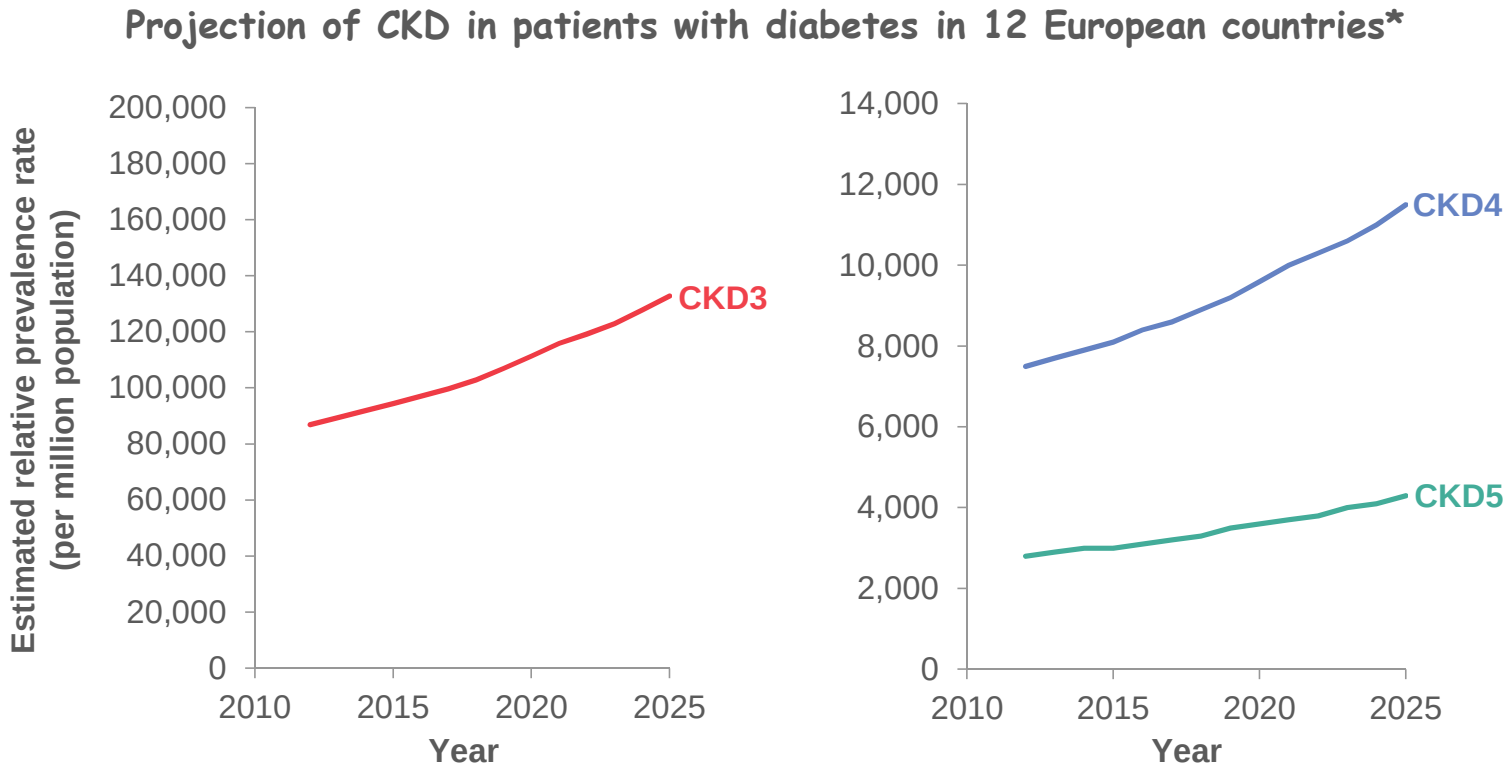
Diabetic kidney disease is common



ACR, albumin-to-creatinine ratio

De Boer IH et al. JAMA 2011;305:2532

Prevalence of diabetic kidney disease is projected to increase



CKD3, CKD stage 3; CKD4, CKD stage 4; CKD5, CKD stage 5

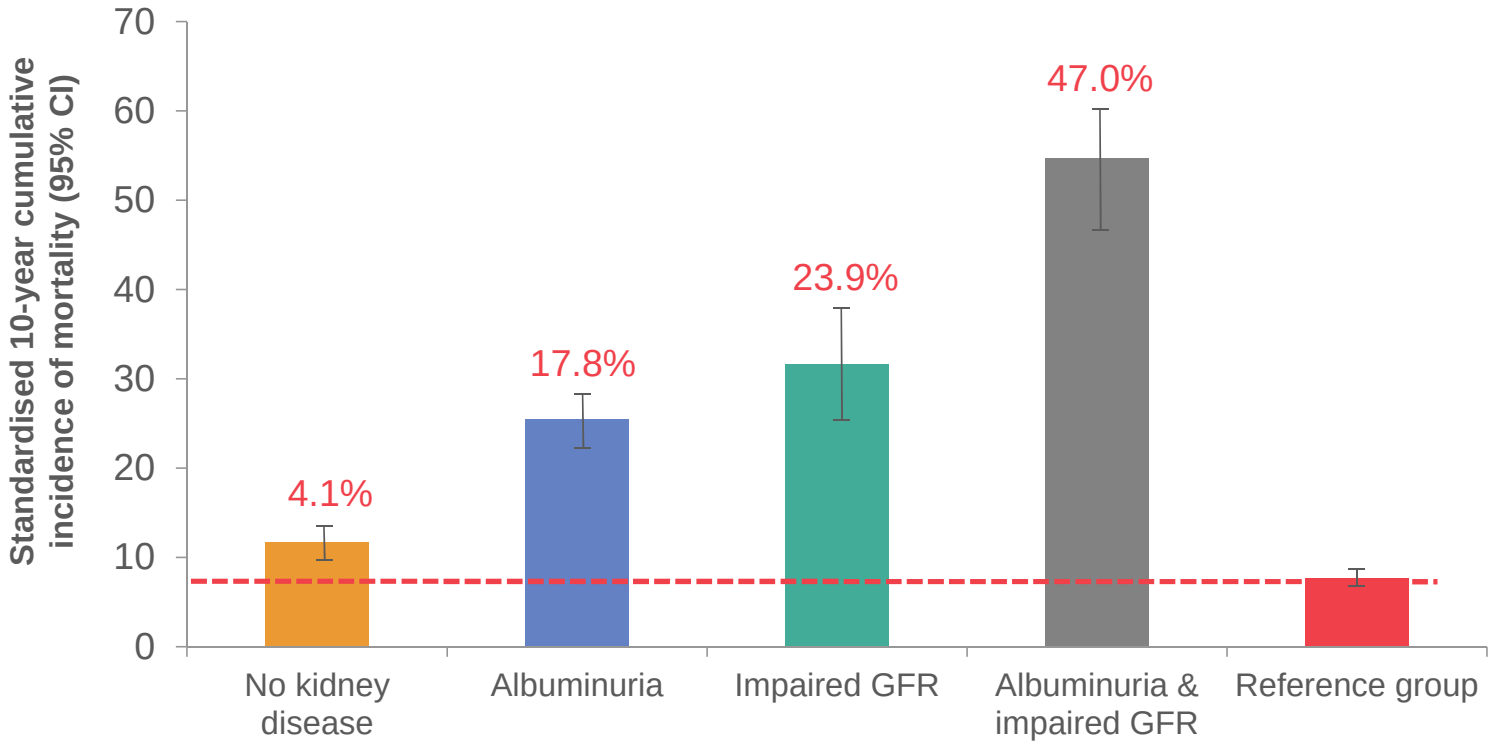
*Austria, Belgium, Denmark, Finland, Greece, Iceland, Italy, Netherlands, Norway, Spain, Sweden, UK

Kainz A et al. Nephrol Dial Transplant 2015

ACROSS T2D

Consequences of diabetic kidney disease

Patients with T2D and kidney disease have a higher mortality rate than those without kidney disease

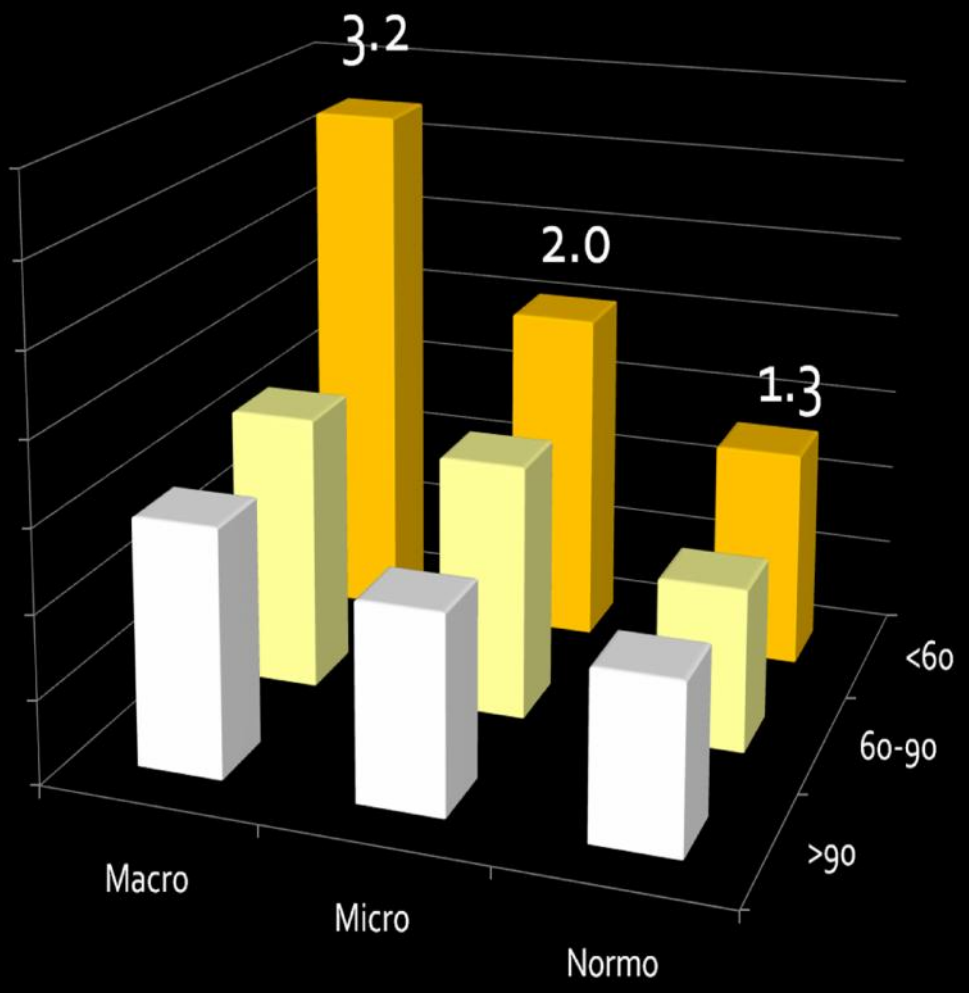


Percentages indicate excess mortality above the reference group (individuals with no diabetes or kidney disease)

Afkarian M *et al. J Am Soc Nephrol* 2013;24:302

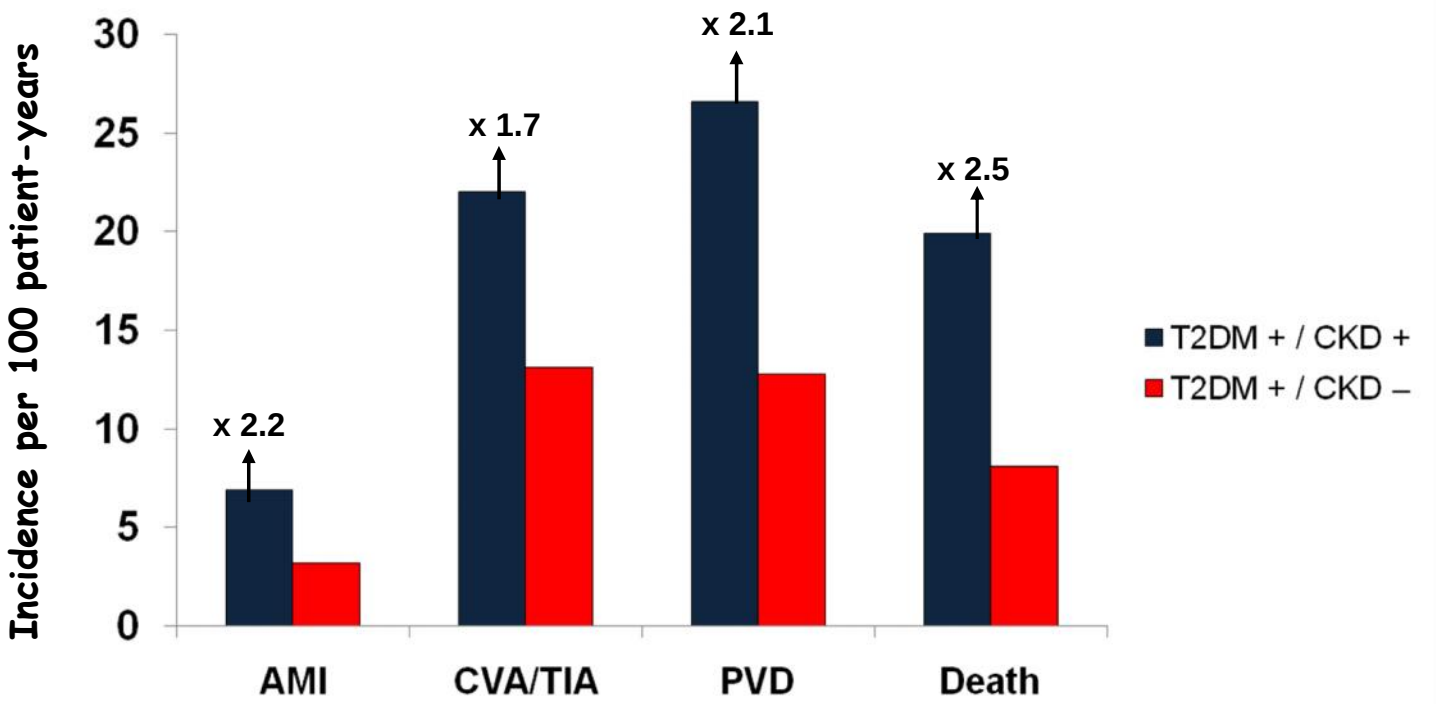
ACROSS T2D

ADVANCE: Cardiovascular events



Ninomiya et al. J Am Soc Nephrol 2009;20:1813-21

Cardiovascular risk is greatest when both diabetes and CKD are present



Among patients with diabetes and CKD, the rate of cardiovascular events is more than twice that among patients with diabetes only

Foley et al. J Am Soc Nephrol. 2005, 16,489–495

Impaired kidney function may directly contribute to adverse outcomes

- Hypertension
- Oxidative stress
- Insulin resistance
- Arterial calcification
- Inflammation/immunity
- Accumulation of uraemic toxins
- Left ventricular hypertrophy
- Endothelial dysfunction
- Activation of the RAAS
- Activation of the SNS
- Anaemia

RAAS = renin-angiotensin aldosterone system; SNS = sympathetic nervous system

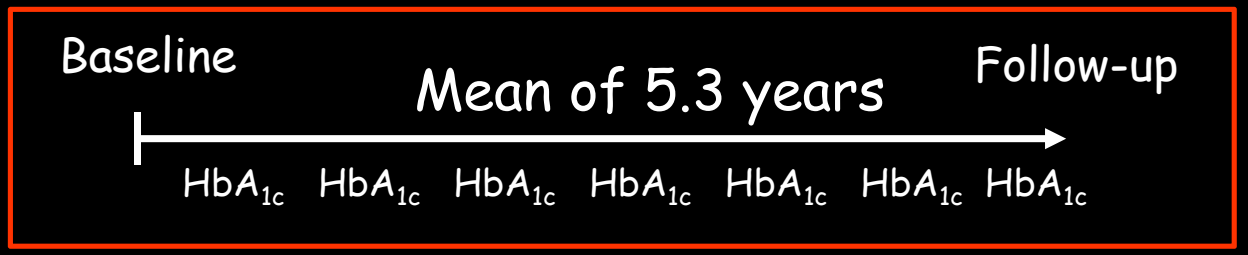
What causes diabetic kidney disease?

1. Exposure to glucose
2. Smoking
3. Lack of intensive physical exercise
4. Obesity

1. Long-term exposure to high glucose

Johan Wadén

HbA_{1c} variability based on serial measurements in the FinnDiane study



- 2107 patients with serial data on HbA_{1c}
- 71% of patients with follow-up data on renal status
- Median of 13 measurements per patient
- i.e. 2.3 measurements/year

Wadén et al. Diabetes 58, 2649-2655, 2009

HbA_{1c} variability is associated with progression of diabetic nephropathy in patients with type 1 diabetes

	Non-progressors			Progressors			P-values		
	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV
Renal status (N=1893/214)	8.5	0.76	0.09	9.2	1.01	0.11	<0.001	<0.001	<0.001
Normo->Micro (N=1283/98)	8.3	0.74	0.09	9.2	0.94	0.10	<0.001	<0.001	0.016
Micro->Macro (N=271/45)	8.8	0.77	0.09	9.6	1.08	0.11	0.001	<0.001	<0.001
Macro->ESRD (N=231/71)	9.0	0.84	0.09	8.8	1.07	0.12	0.261	0.005	0.001

N = number of non-progressors/progressors
SD: intra-personal standard deviations of HbA_{1c}
CV: intra-personal coefficient of variation

Wadén et al. Diabetes 58, 2649-2655, 2009

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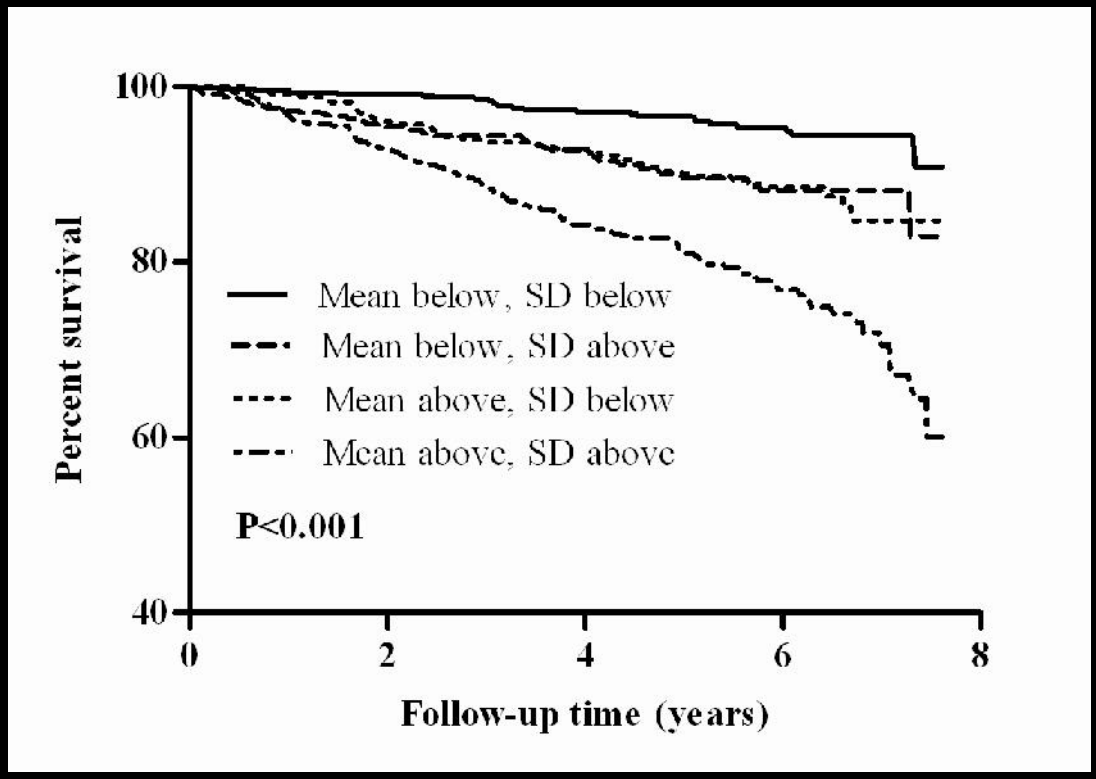
Wadén et al. Diabetes 58, 2649-2655, 2009

Impact of mean HbA_{1c} and SD of serial HbA_{1c} on progression of nephropathy



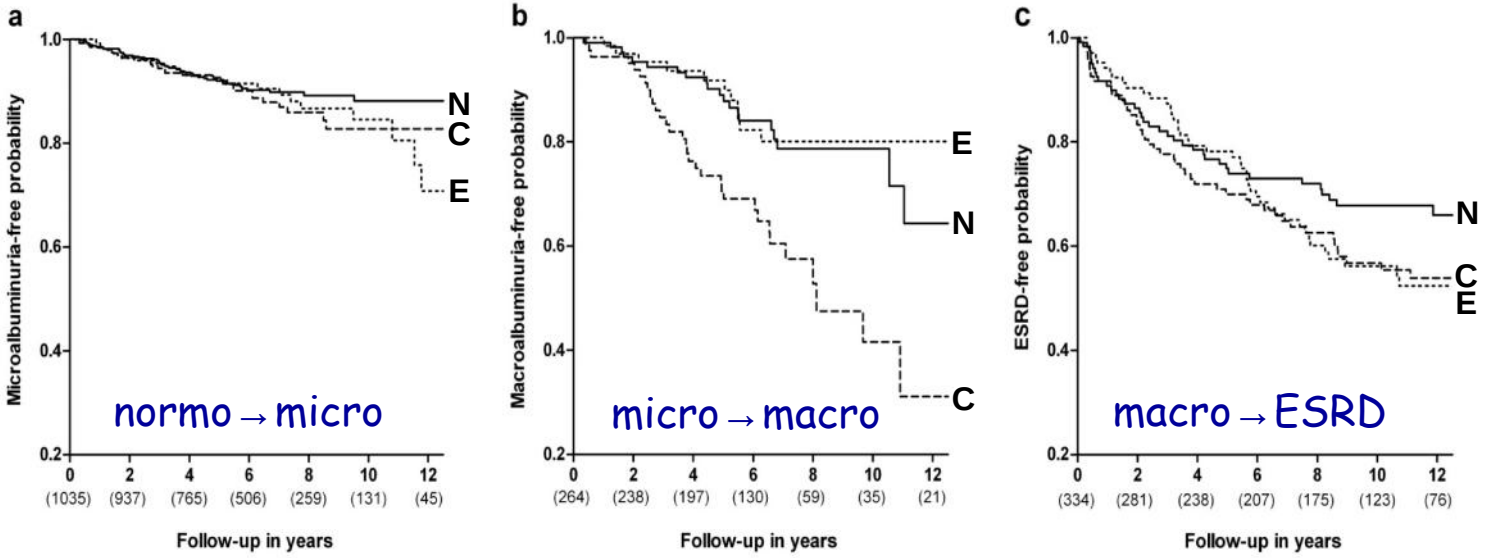
Population median of mean and SD of HbA_{1c} as reference

Wadén et al. Diabetes 58, 2649-2655, 2009

2. Smoking

Maija Feodoroff

Smoking and progression of diabetic nephropathy in type 1 diabetes/men



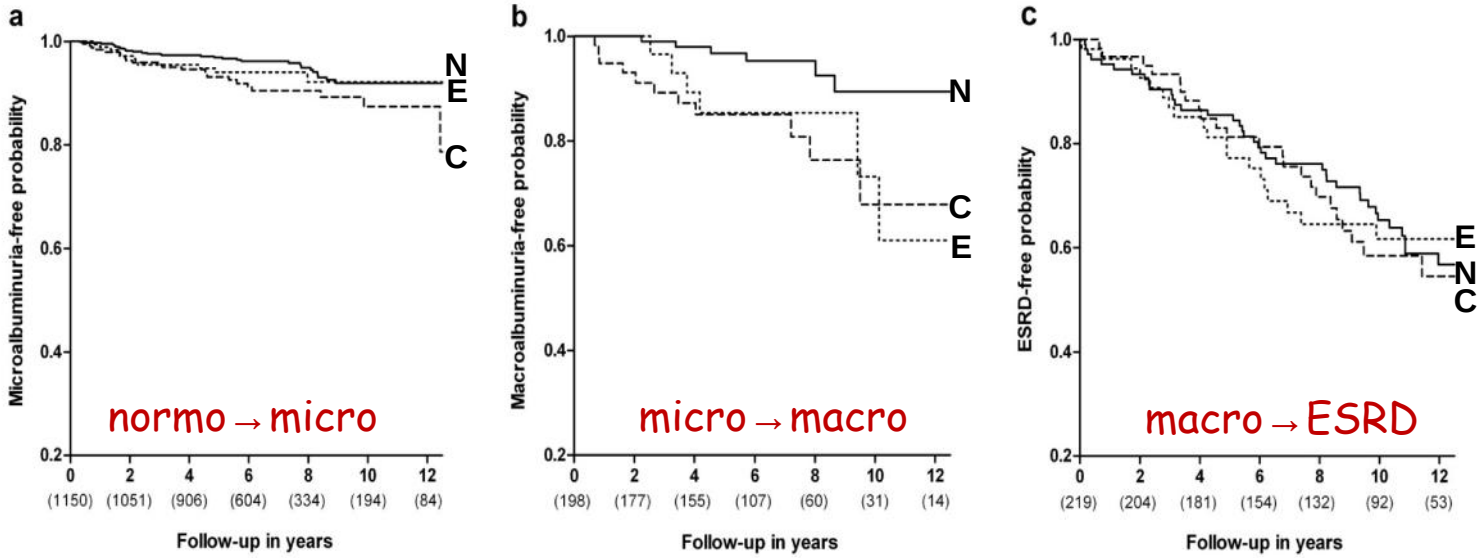
HR=ns* for current smokers HR=2.39* for current smokers HR=ns* for current smokers

*Adjusted for duration of diabetes, HbA_{1c} and hypertension

N=non-smokers, C= current smokers, E=Ex-smokers

Feodoroff et al Acta Diabetol 53, 525-533, 2016

Smoking and progression of diabetic nephropathy in type 1 diabetes/women



HR=1.76* for current smokers HR=3.02* for current smokers HR=ns* for current smokers

*Adjusted for duration of diabetes, HbA_{1c} and hypertension

N=non-smokers, C= current smokers, E=Ex-smokers

Feodoroff et al Acta Diabetol 53, 525-533, 2016

3. Lack of intensive physical exercise

Heidi Tikkanen

Lack of physical activity increases risk of diabetic nephropathy

Progression of diabetic nephropathy (normo -> micro, micro -> macro)
N=1288, 114 progressors, follow-up on average 6.1 years

Sedentary	9.4%
Moderately active	9.1%
Active	7.2%
P=NS	

Low intensity	14.3%
Moderate intensity	8.3%
High intensity	5.7%
P=0.001	

Incident microalbuminuria (normo -> micro)
N=974, 56 progressors, follow-up on average 6.0 years

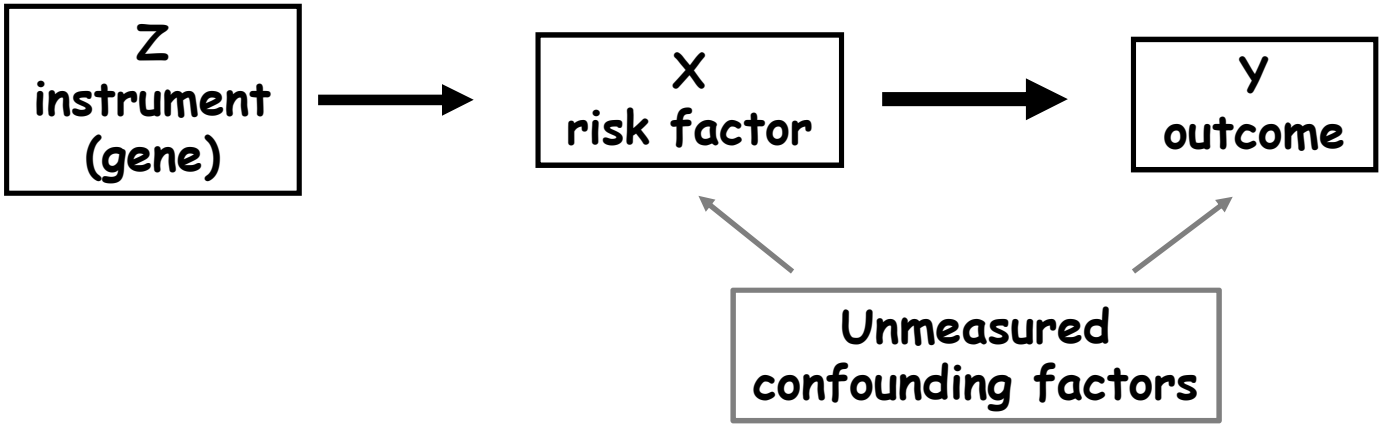
Sedentary	5.2%
Moderately active	6.3%
Active	4.8%
P=NS	

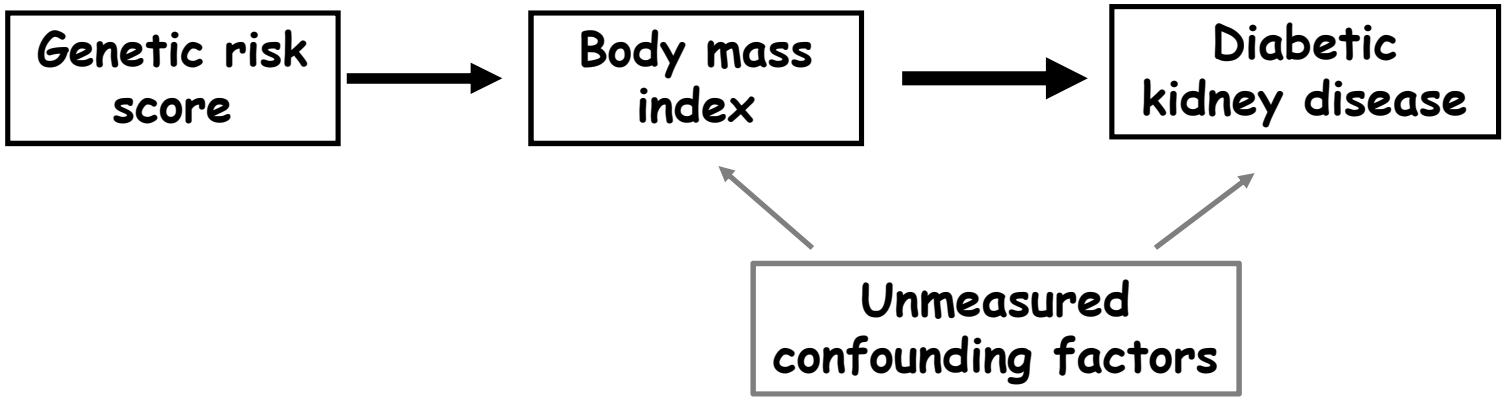
Low intensity	8.8%
Moderate intensity	5.5%
High intensity	3.9%
P=0.032	

Wadén, Tikkanen et al. Diabetologia 58, 929-936, 2015

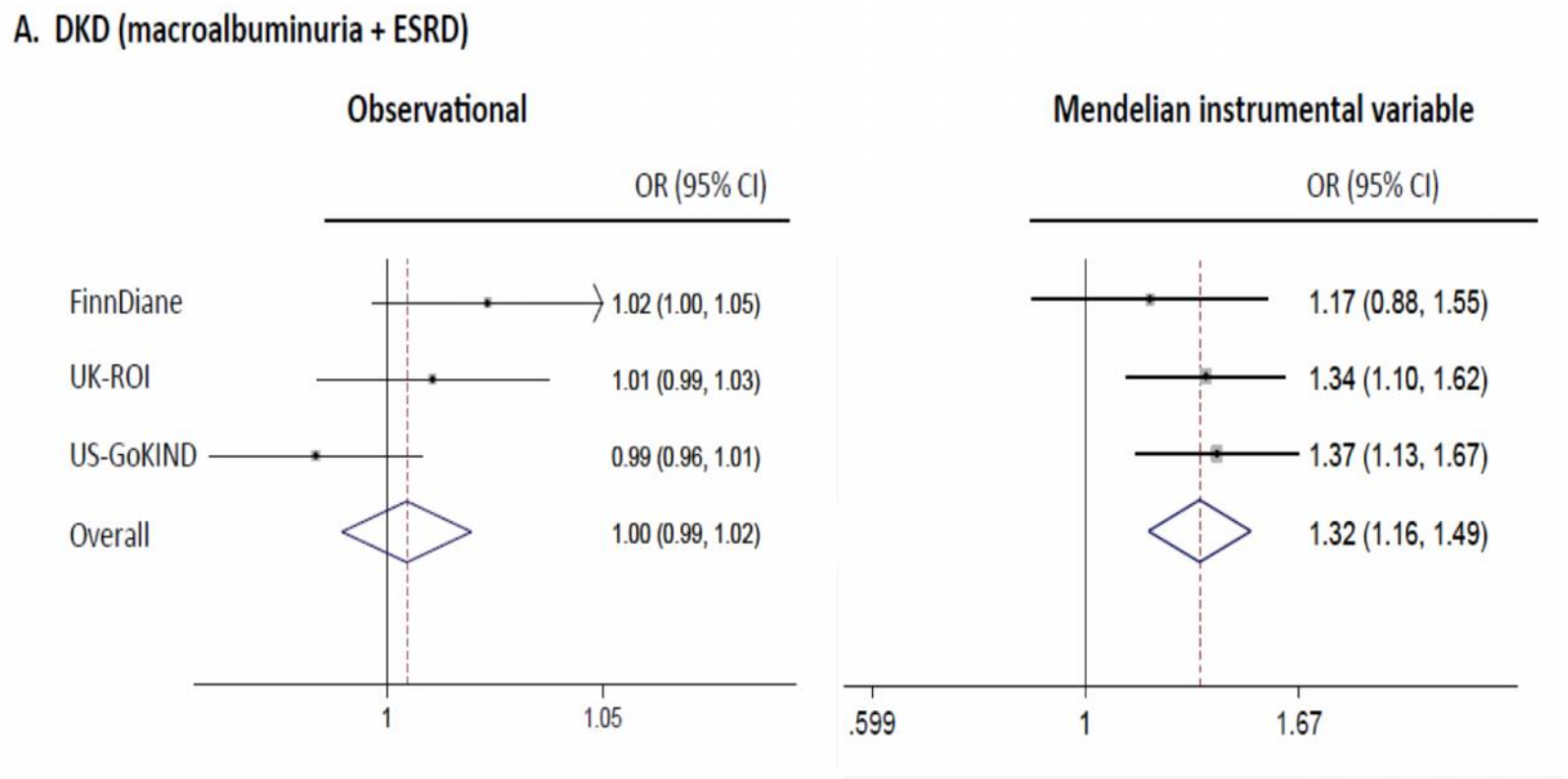
4. Causal relationship between obesity diabetic kidney disease

Emma Dahlström

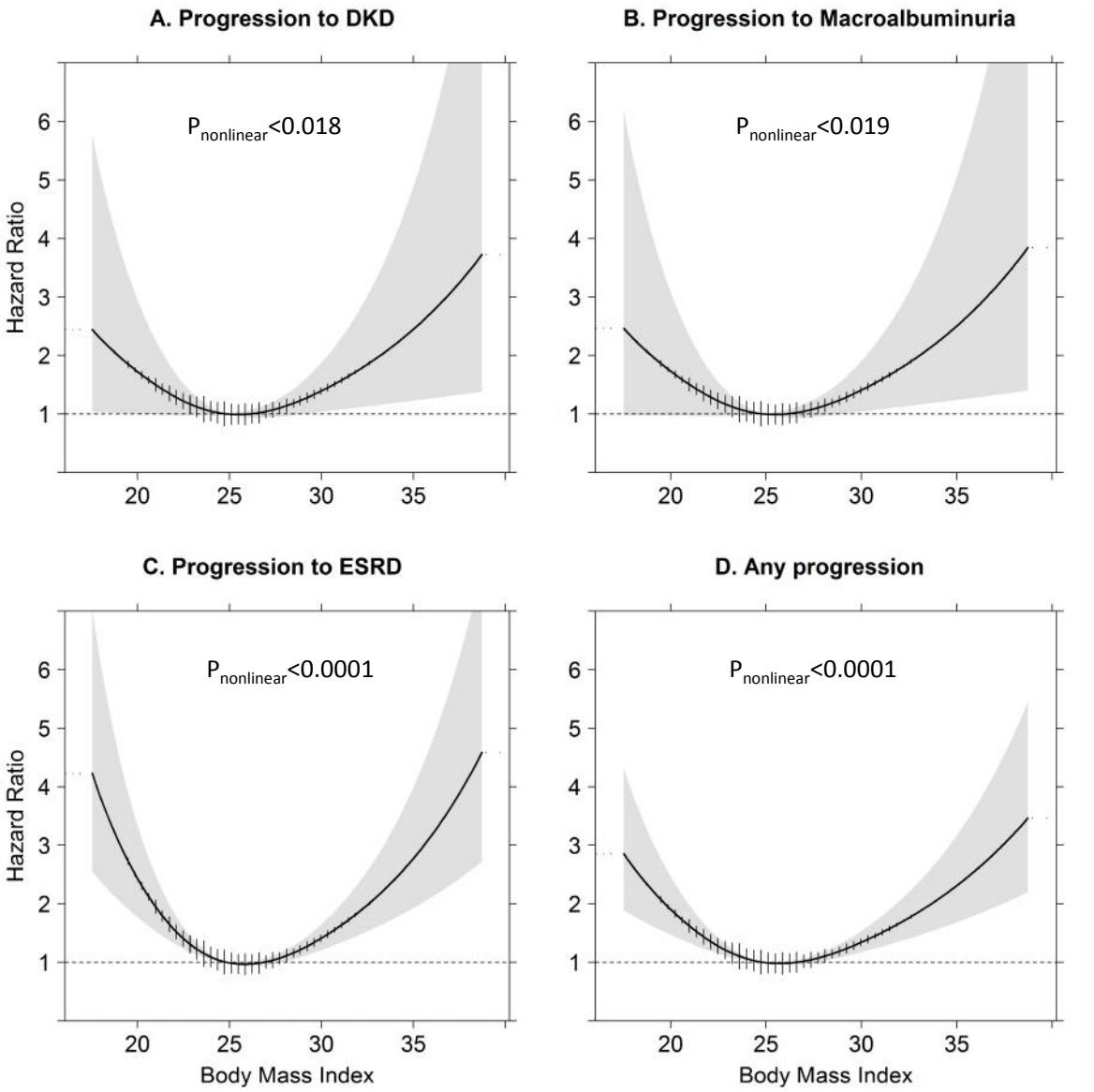

Z
instrument
(gene)
X
risk factor
Y
outcome
Unmeasured
confounding factors


Genetic risk
score
Body mass
index
Diabetic
kidney disease
Unmeasured
confounding factors

DKD (macroalbuminuria + ESRD)



Todd, Dahlström et al. 64, 4238-4246, 2015



Todd, Dahlström et al. 64, 4238-4246, 2015

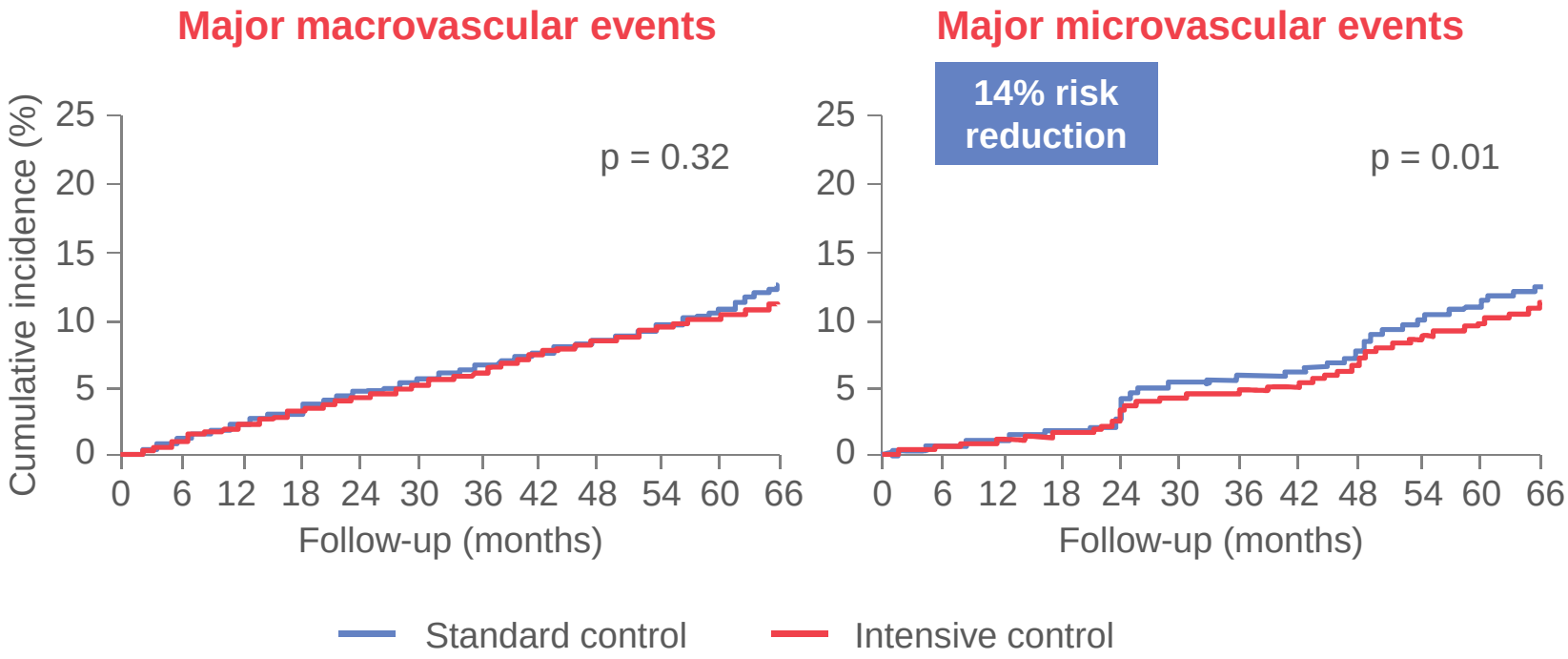
Prevention of diabetic kidney disease

- Optimal glucose control
- Optimal blood pressure control
- No smoking
- Intensive physical activity
- Avoid overweight and obesity

Glucose lowering and diabetic kidney disease

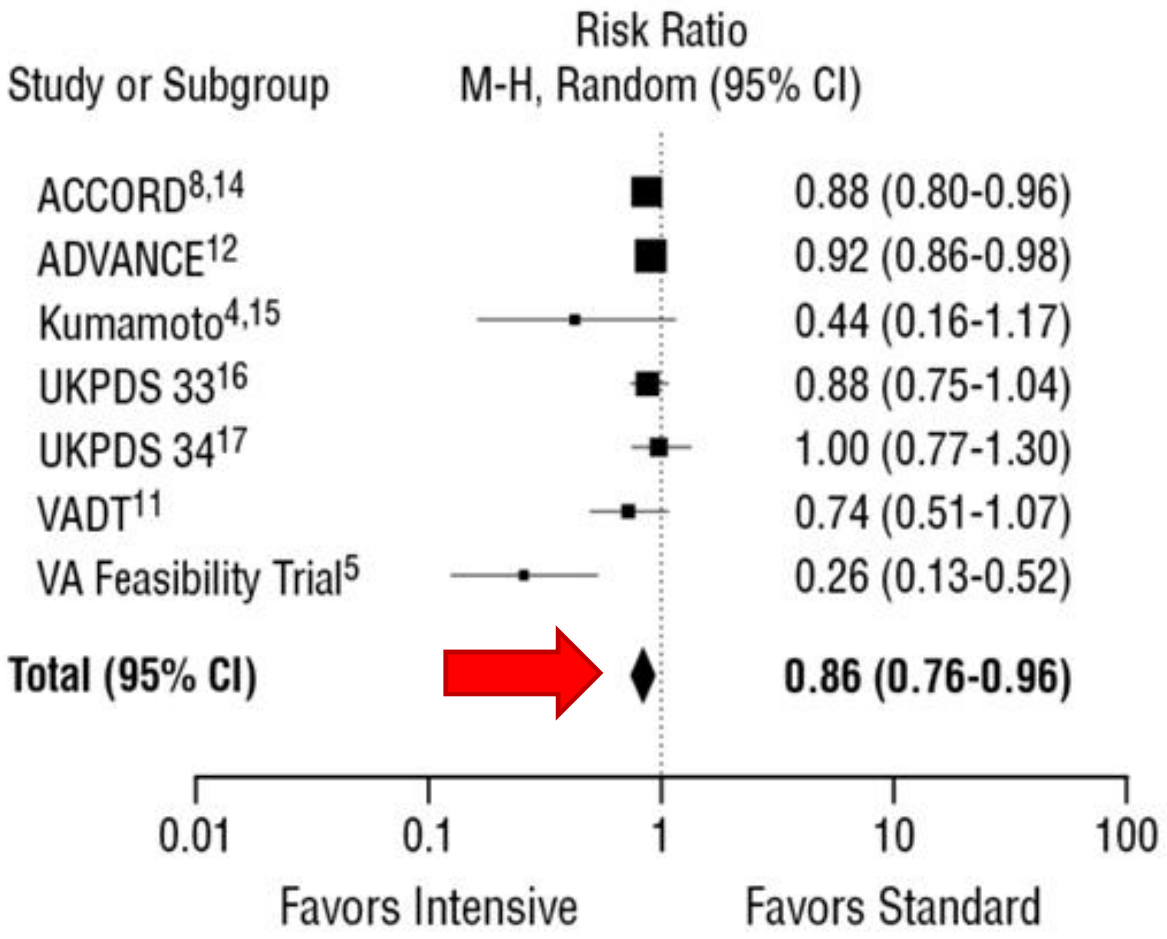
Glucose-lowering trials

ADVANCE: intensive glycaemic control reduced microvascular but not macrovascular events



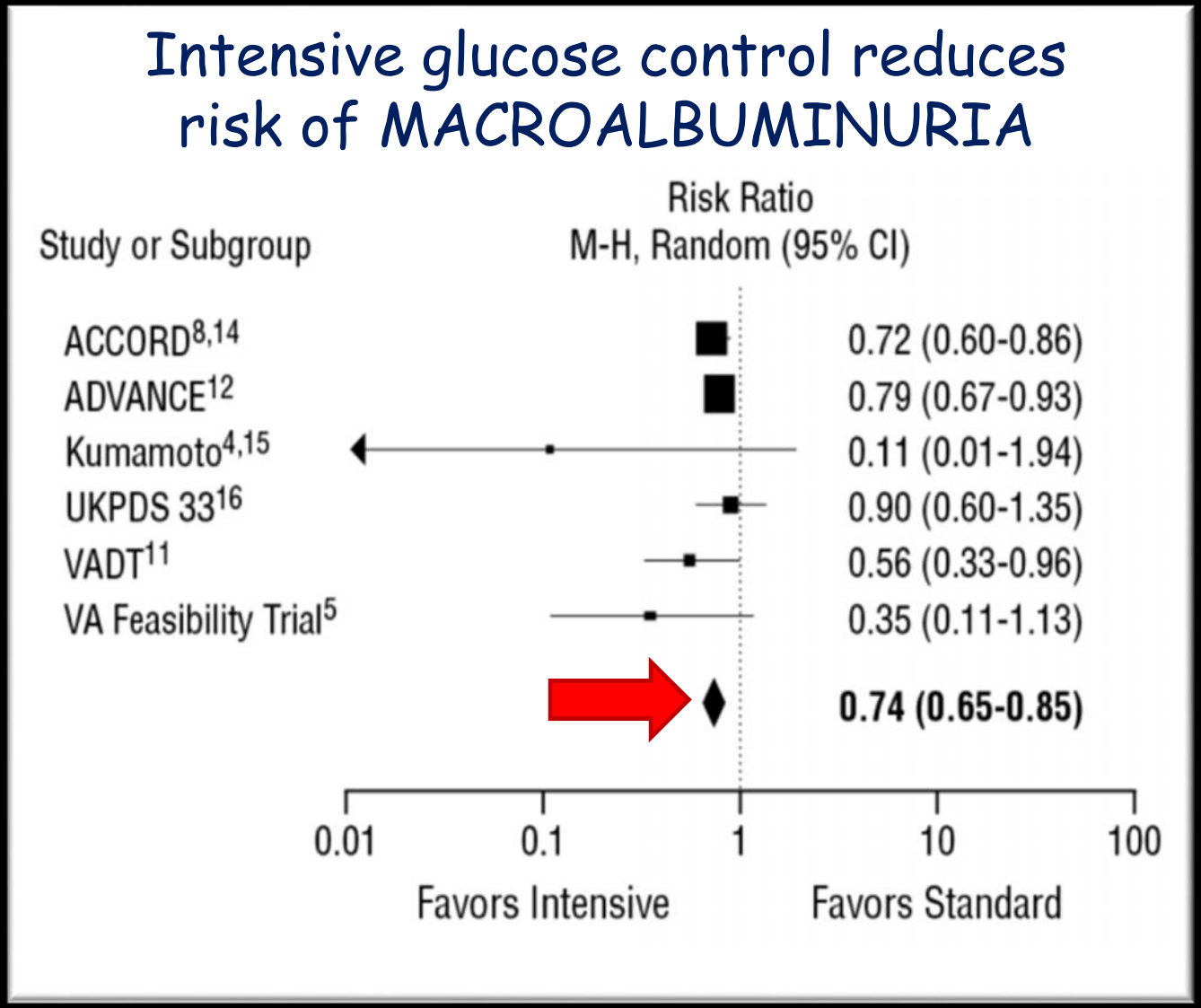
Patel et al. N Engl J Med 2008;358:2560–72.

Intensive glucose control reduces risk of MICROALBUMINURIA



Arch Intern Med. 2012;172(10):761-9

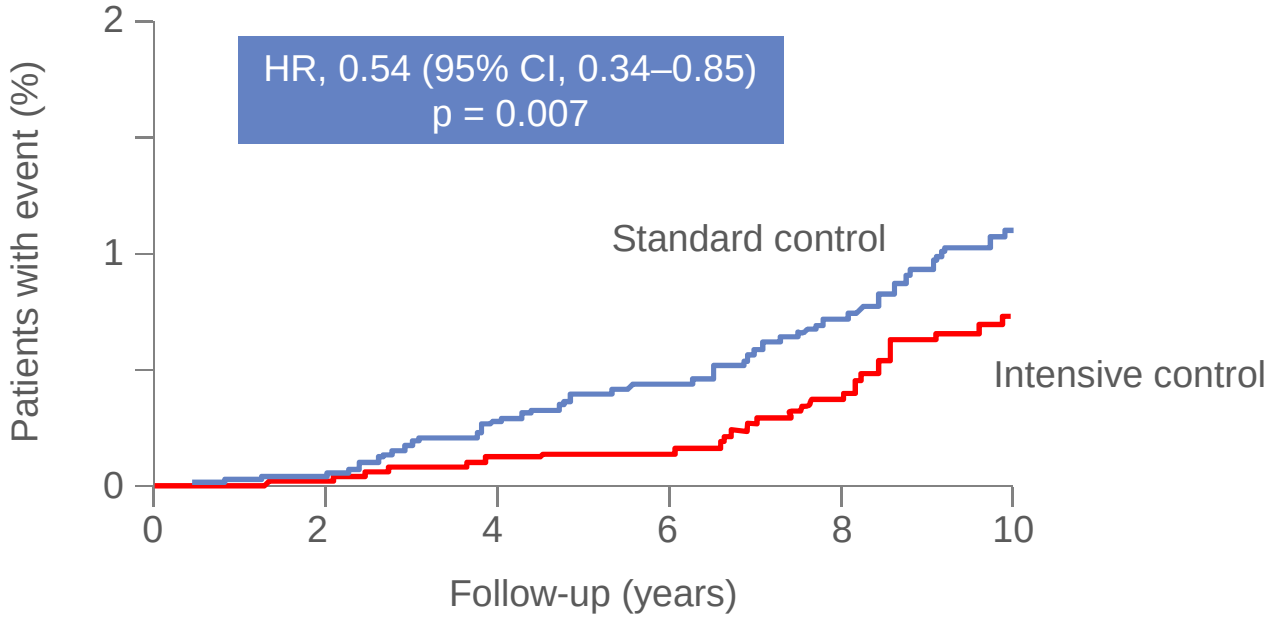
Intensive glucose control reduces risk of MACROALBUMINURIA



Arch Intern Med. 2012;172(10):761-9

ADVANCE-ON: intensive glycaemic control had significant benefit for end-stage renal disease

End-stage renal disease



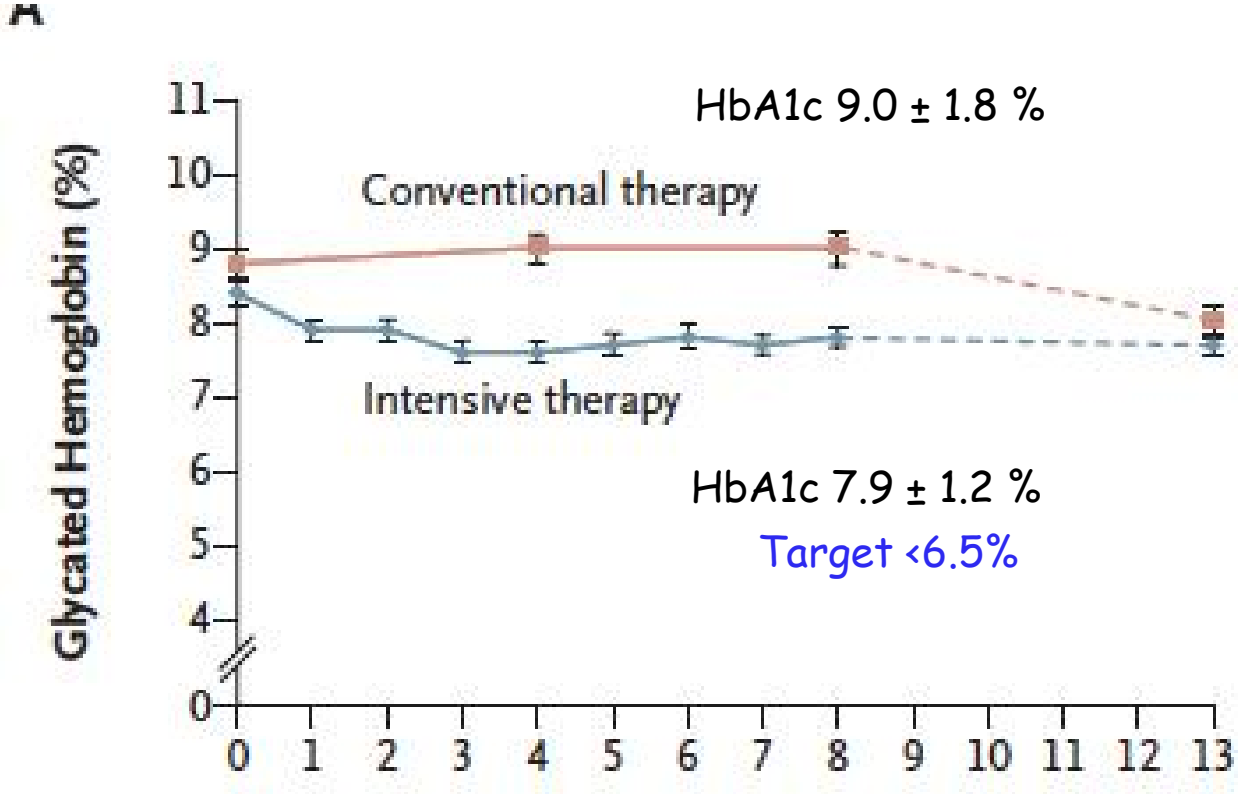
No. at risk						
Intensive	5571	5402	5186	4124	3764	2811
Standard	5569	5400	5173	4041	3681	2683

Zoungas et al. N Engl J Med 2014;371:1392-406.

Multifactorial treatment and diabetic late complications

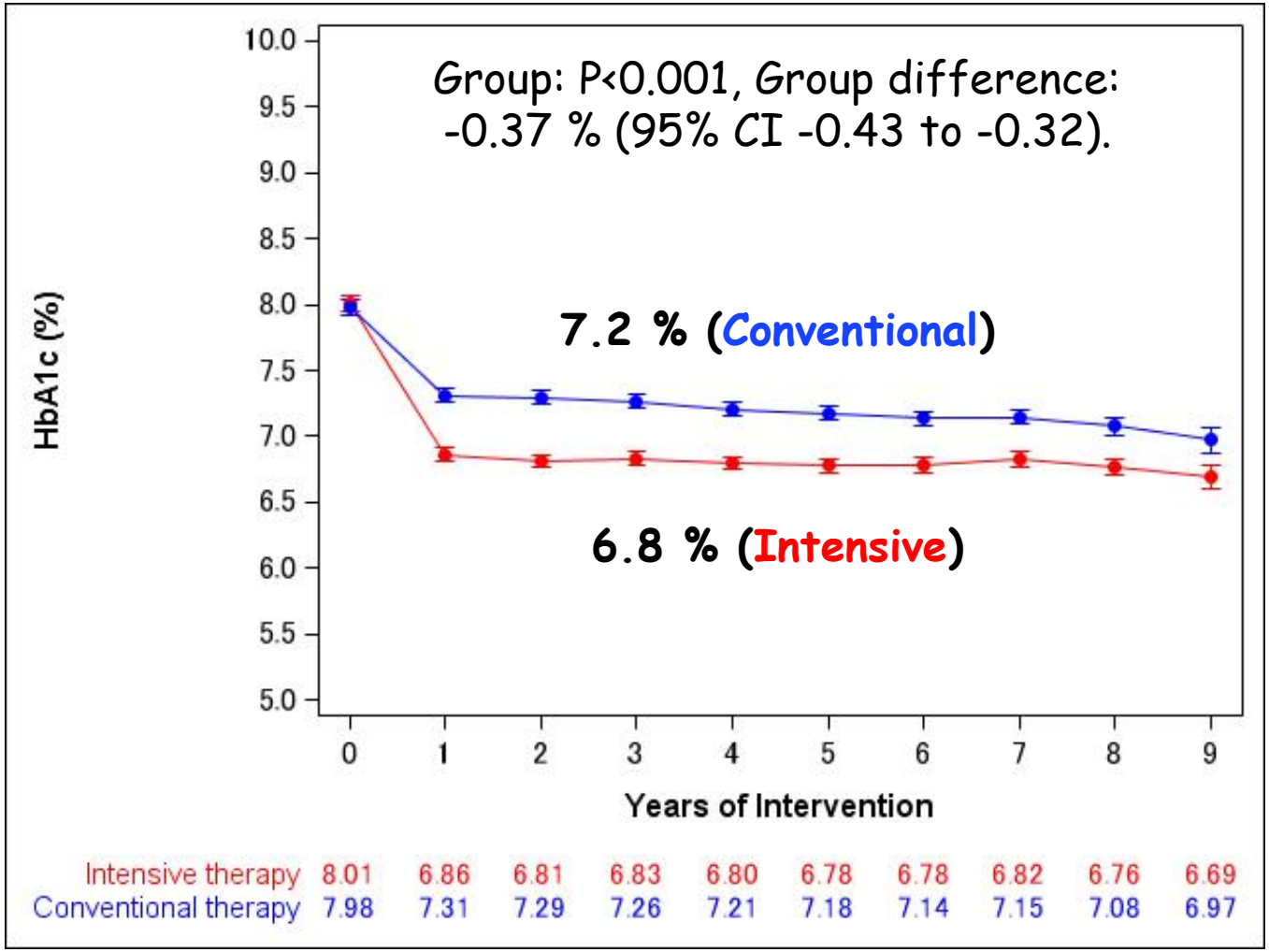
Steno-2 and J-DOIT3

Steno-2 study: HbA1c at end of trial



Gaede et al. NEJM 2008; 358 (6); 580-91

Mean HbA1c during intervention

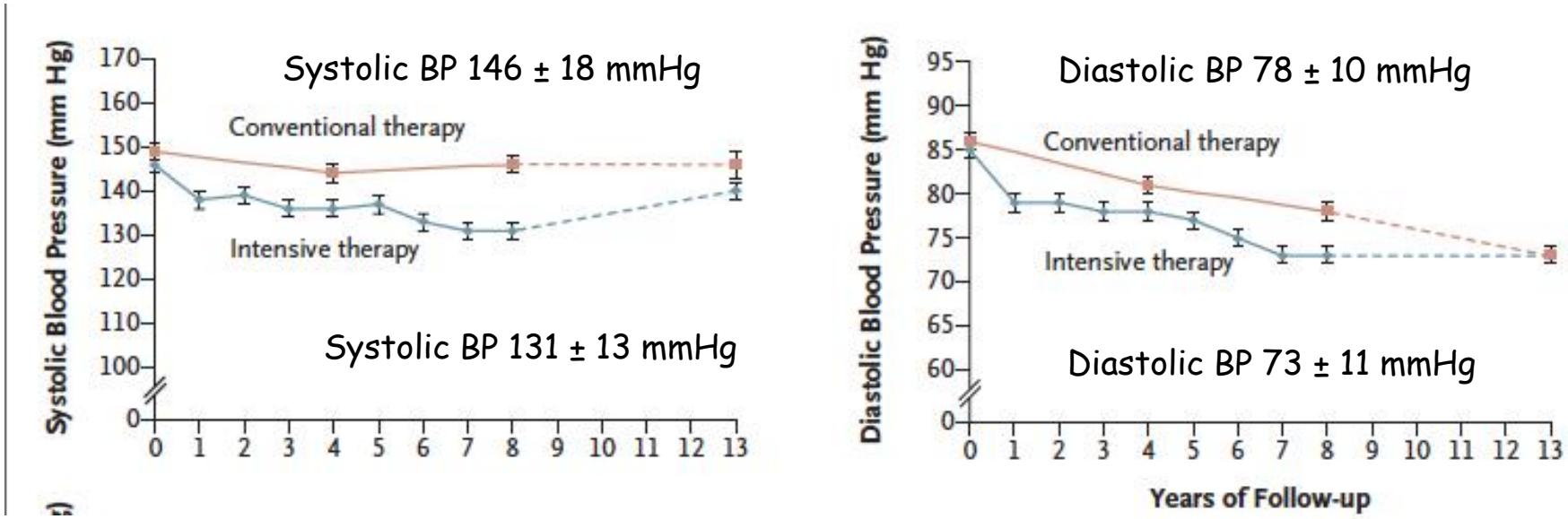


Target 6.9%

Target 6.2%

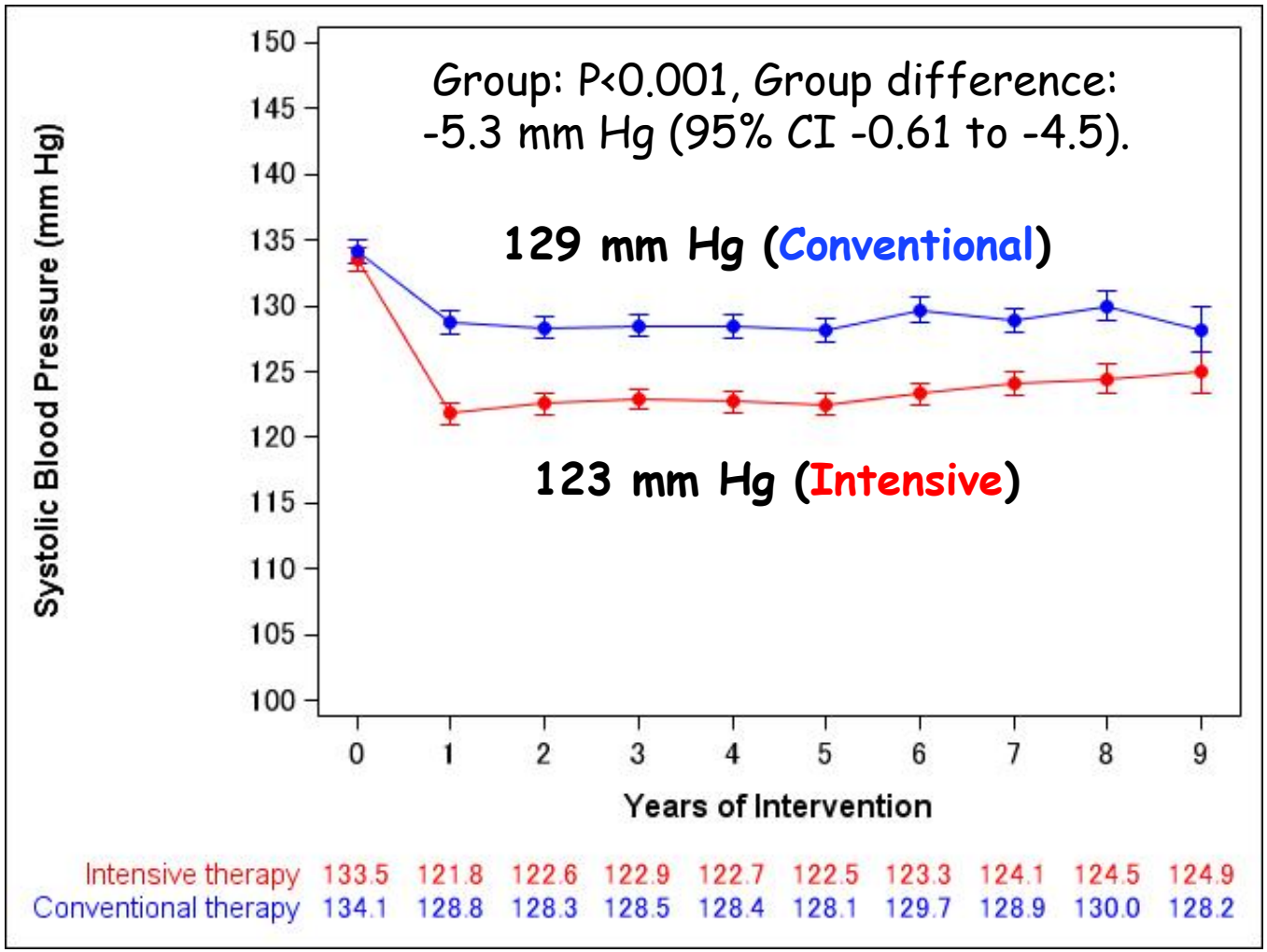
J-DOIT 3

Steno-2 study: Blood pressure at end of trial



Gaede et al. NEJM 2008; 358 (6); 580-91

Mean systolic blood pressure during intervention



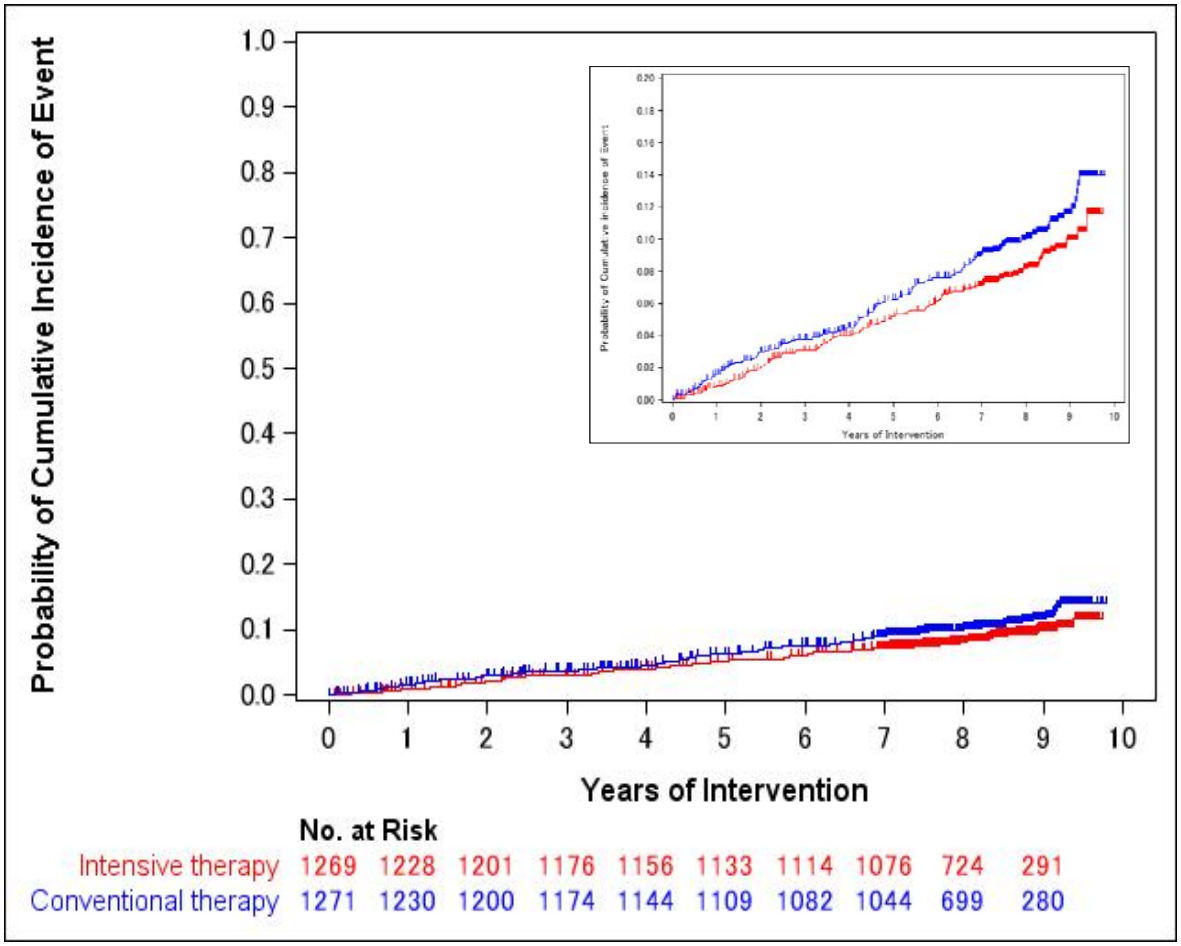
Target <130/80

Target <120/75

J-DOIT 3

Cumulative incidence of the modified primary outcome

Incidence of MI, stroke, all-cause mortality or revascularization



HR 0.81; 95%CI 0.63 to 1.04; P=0.094

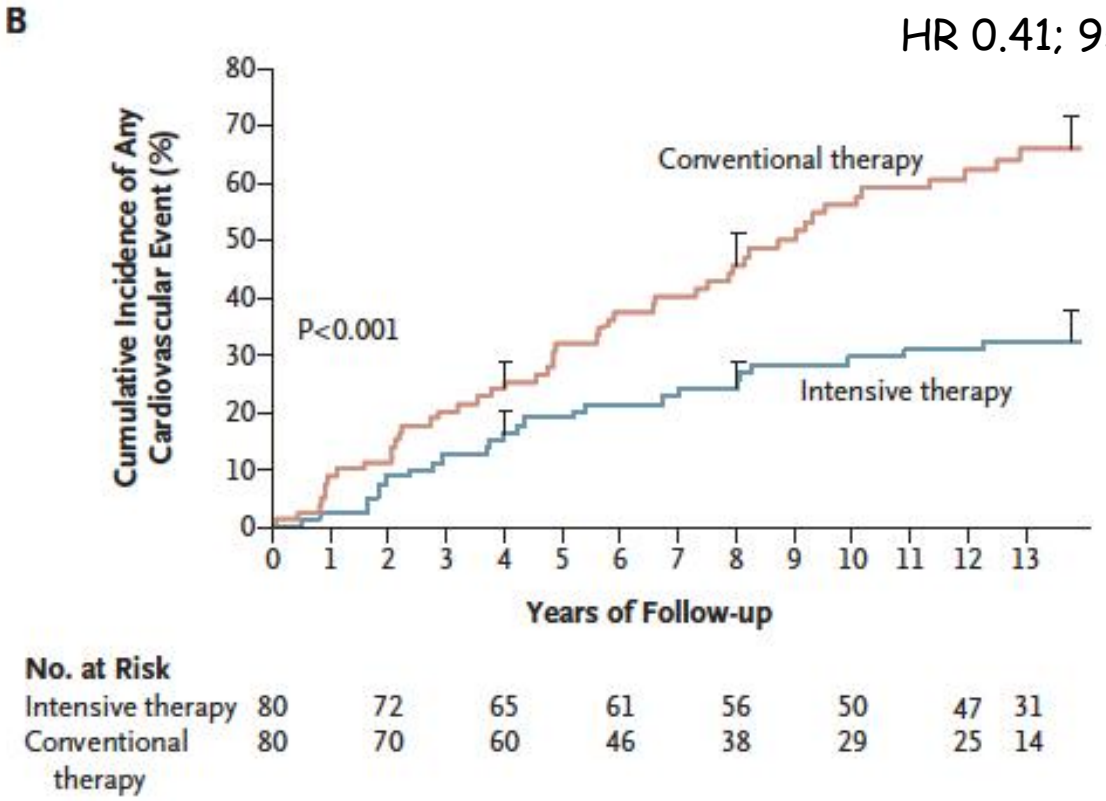
HR 0.76; 95%CI 0.59 to 0.99; P=0.042
after adjustment for baseline risk factors

J-DOIT 3

Steno-2: Cumulative incidence of CV events

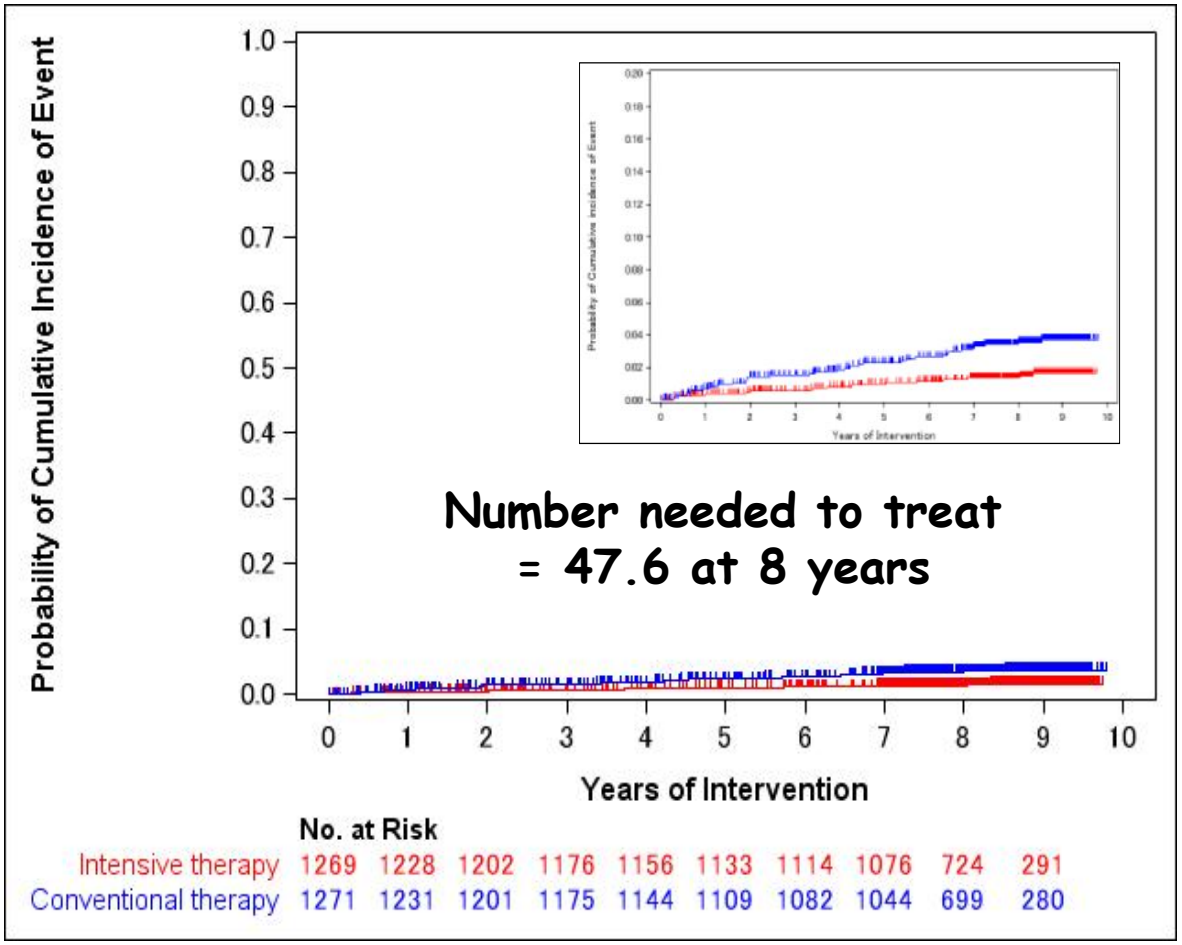
Death from CV causes, nonfatal stroke, nonfatal myocardial infarction, coronary-artery bypass grafting (CABG), percutaneous coronary intervention (PCI), revascularization for peripheral atherosclerotic artery disease, and amputation

HR 0.41; 95%CI, 0.25 to 0.67; P<0.001



Gaede et al. NEJM 2008; 358 (6); 580-91

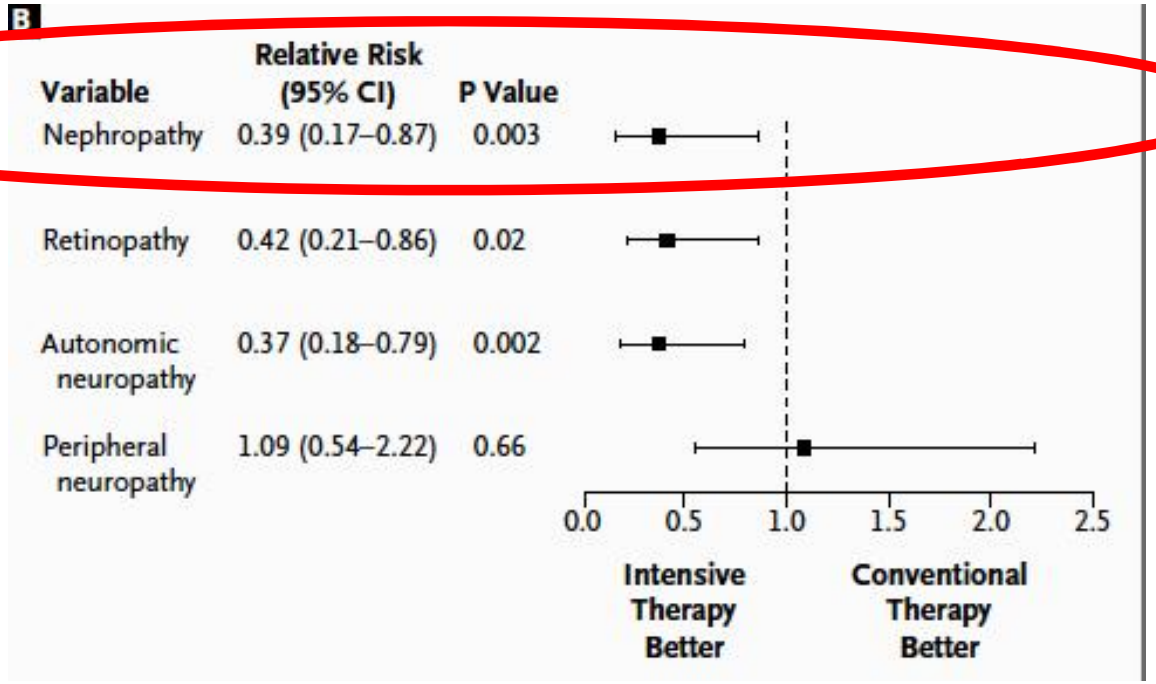
Cumulative incidence of cerebrovascular events (post-hoc analysis)



HR 0.42; 95% CI 0.24 to 0.74; p=0.002

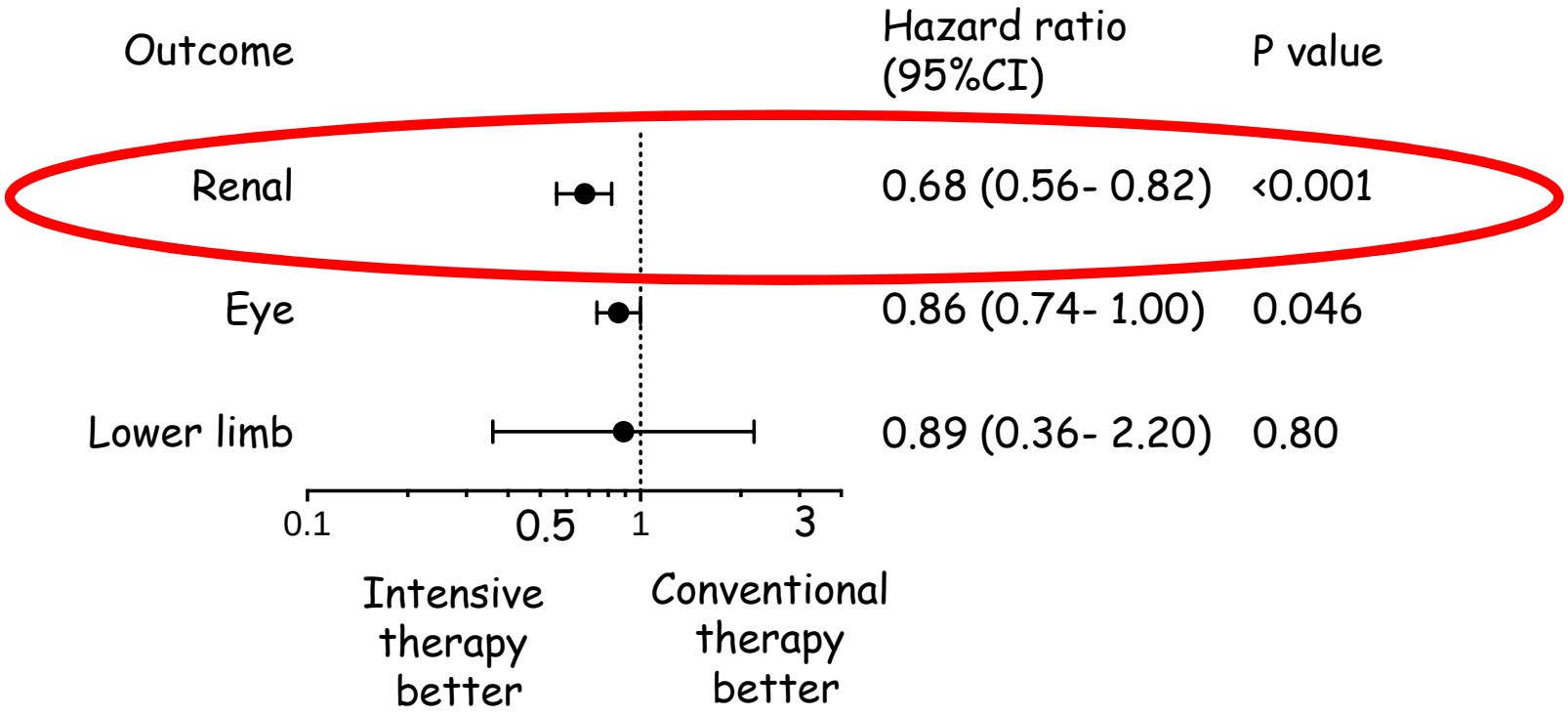
J-DOIT 3

Steno-2: Relative risk of developing microvascular complications



Gaede et al. NEJM 2003; 348 (5): 383-93

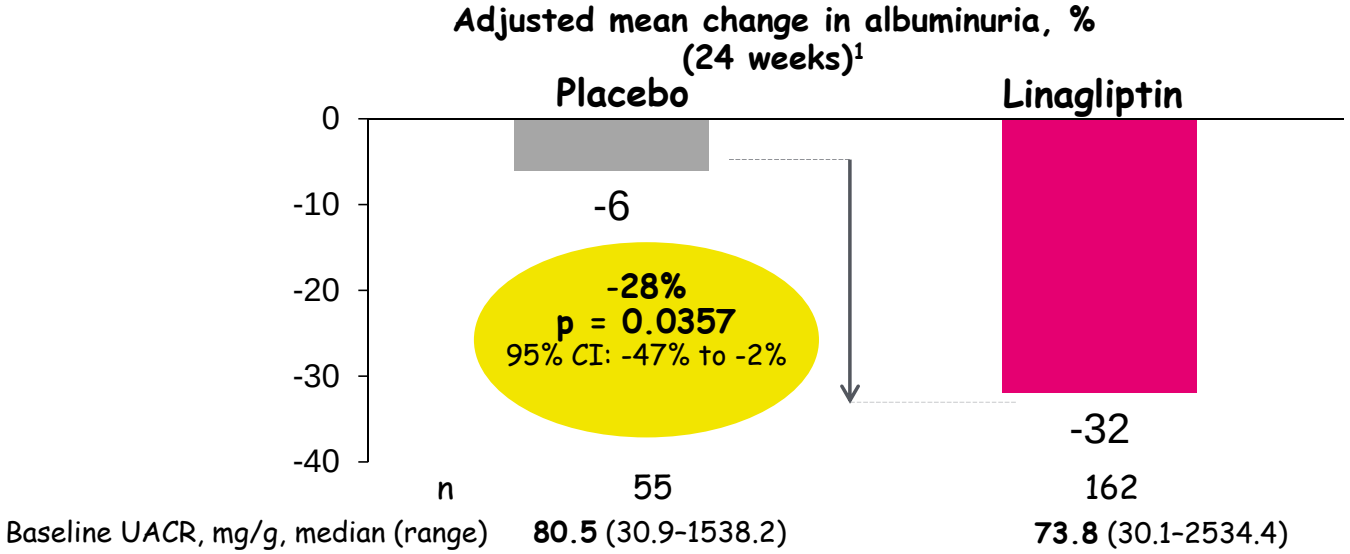
Hazard rations of other secondary outcomes



Effect of DPP-4 inhibitors on renal outcomes

Pooled analysis suggests that linagliptin reduces albuminuria

24 weeks' treatment
Meta-analysis: effect of linagliptin on albuminuria in humans*



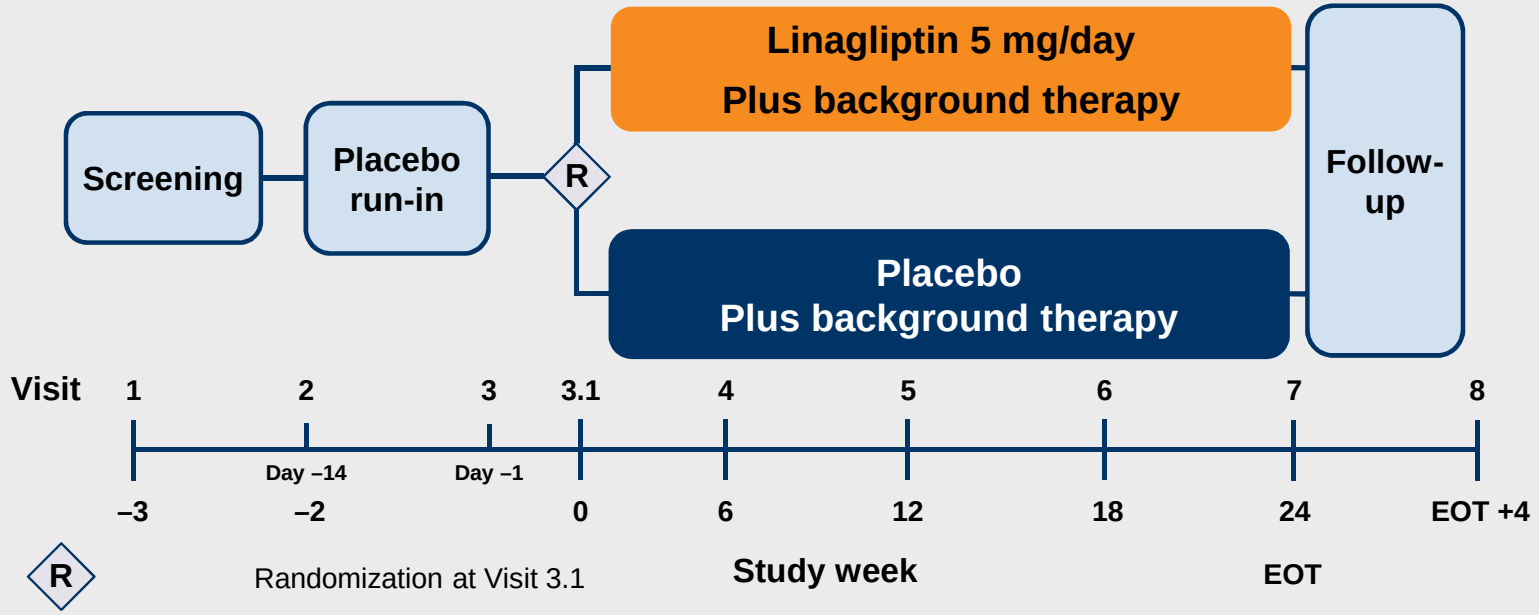
-28% in albuminuria versus placebo after 24 weeks' treatment on top of recommended standard treatment for diabetic nephropathy

1. Inclusion criteria: stable ACE/ARB background; albuminuria 30–3000 mg/g creatinine; GFR > 30.
*MARLINA-T2D™ (1218.89) will aim to demonstrate albuminuria-lowering evidence for linagliptin.

Groop et al. *Diabetes Care* 2013, 36, 1–9

Study design

- MARLINA-T2D was a randomized, double-blind, placebo-controlled trial that included patients with T2D and albuminuria on stable RAAS blockade



Major inclusion criteria:

- Patients with T2D; HbA1c 6.5–10.0%
- UACR 30−3000 mg/gCr or albuminuria >30 mg/L of urine or >30 µg/min
- Stable dose of single ACE inhibitor or ARB

Background therapy:

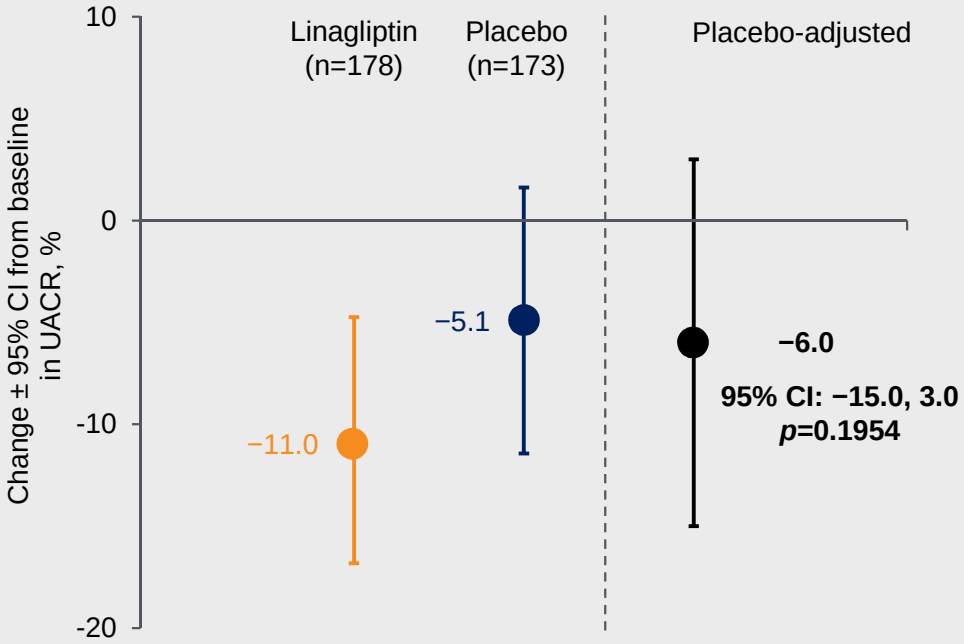
- Drug-naïve or receiving ≤2 OADs and/or basal insulin

ClinicalTrials.gov: NCT01792508

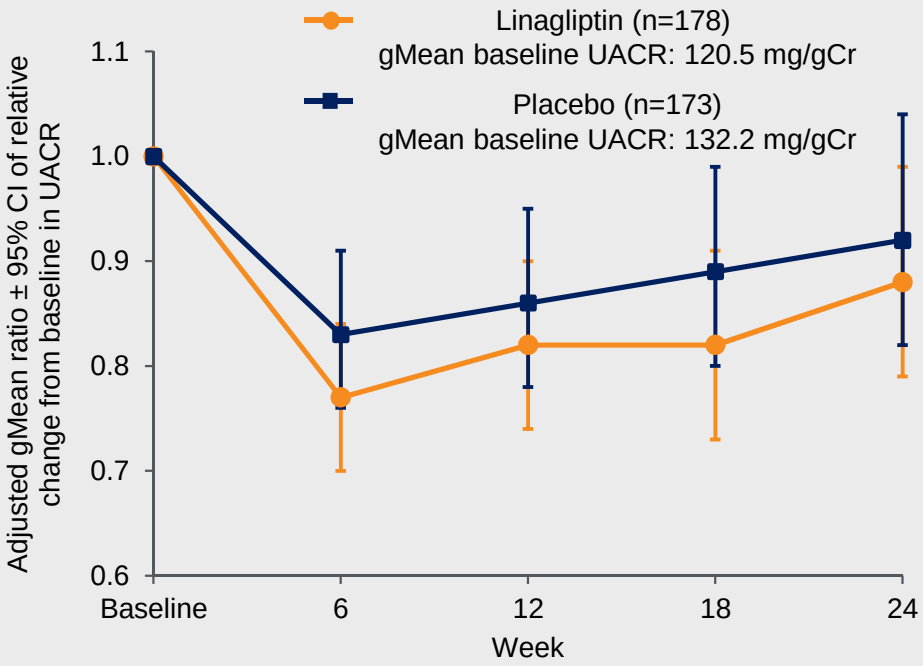
Groop et al. *Diabetes, Obesity and Metabolism* (in press) 2017

Adjusted change from baseline in UACR

Adjusted* geometric mean for time-weighted average of percentage change from baseline in UACR over 24 weeks†



Adjusted* geometric mean ratio of relative change from baseline in UACR over time

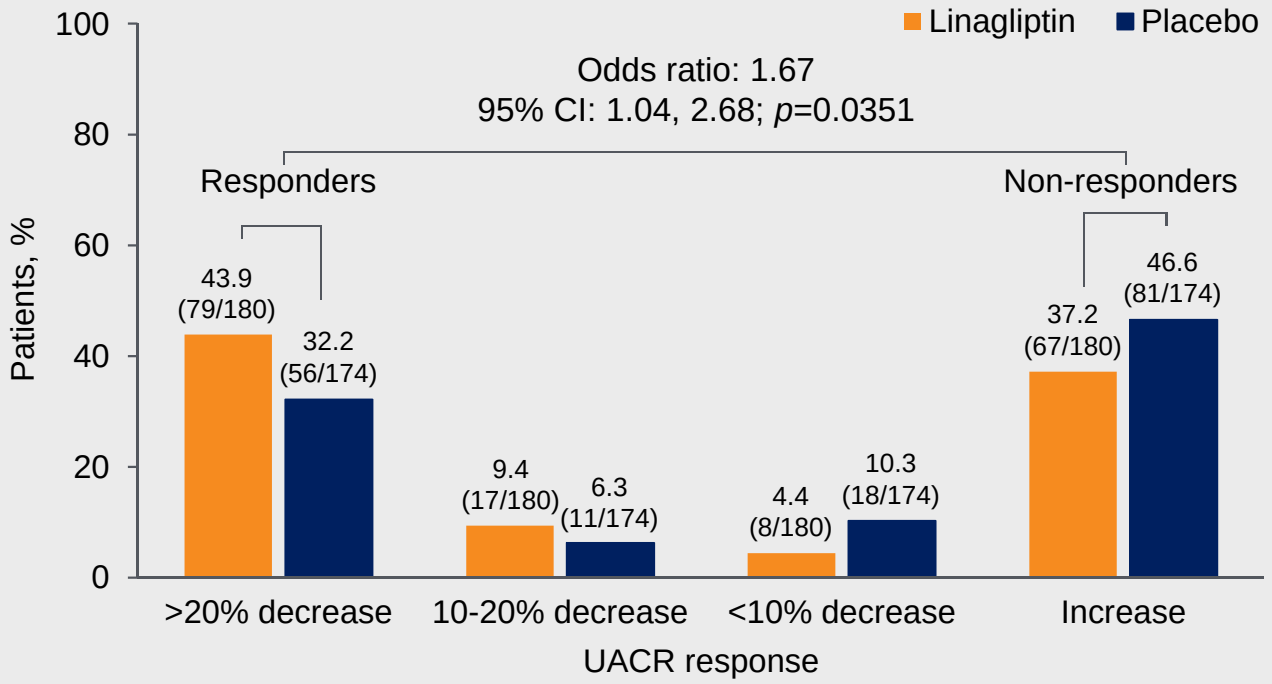


*ANCOVA model includes baseline HbA1c and baseline $\log_{10}$ (UACR) as linear covariates and treatment as fixed effect. Area under the curve (AUC) for UACR at a given week was divided by AUC for UACR at baseline; calculated per patient from UACR values at baseline and Weeks 6, 12, 18, and 24. The measures were summed over all days up to the scheduled visit date and divided by the number of days on treatment at scheduled visit date. AUC per patient was then normalized to 1 day

Groop et al. *Diabetes, Obesity and Metabolism* (in press) 2017

Distribution of UACR change from baseline at Week 24 by UACR response categories (FAS; OC-ROC*)

- 70% higher rate of achieving a meaningful response (>20% decrease in UACR from baseline) with linagliptin than with placebo



*Post hoc analysis. Logistic regression was performed on the proportion of UACR responders at Week 24. UACR responders were defined as patients from the FAS who had a UACR reduction of >20% at Week 24 relative to baseline; UACR non-responders were those who had a UACR increase or no change at Week 24 relative to baseline. Patients with UACR reduction ≤20% relative to baseline were excluded from the analysis, as well as those with missing UACR values at Week 24 (linagliptin, n=9 [5.0%]; placebo, n=8 [4.6%]). Patients with UACR value at Week 24 on rescue therapy (OC-ROC) were included in the analysis. The model includes treatment as factor and continuous baseline HbA1c and continuous baseline $\log_{10}$ (UACR) as covariates.

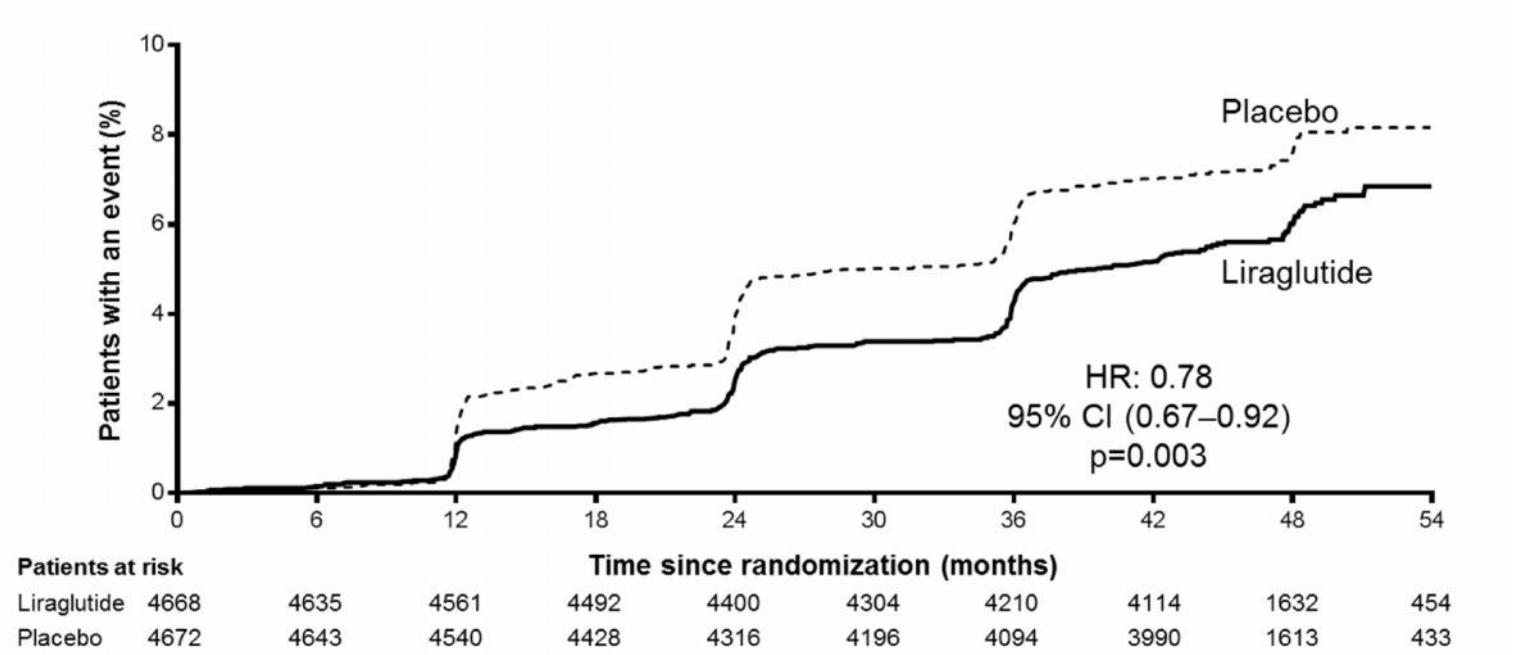
Groop et al. *Diabetes, Obesity and Metabolism* (in press) 2017 [14]

Effect of GLP-1 agonists on renal outcomes

Pre-specified renal endpoints

LEADER TRIAL: Time to first renal event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

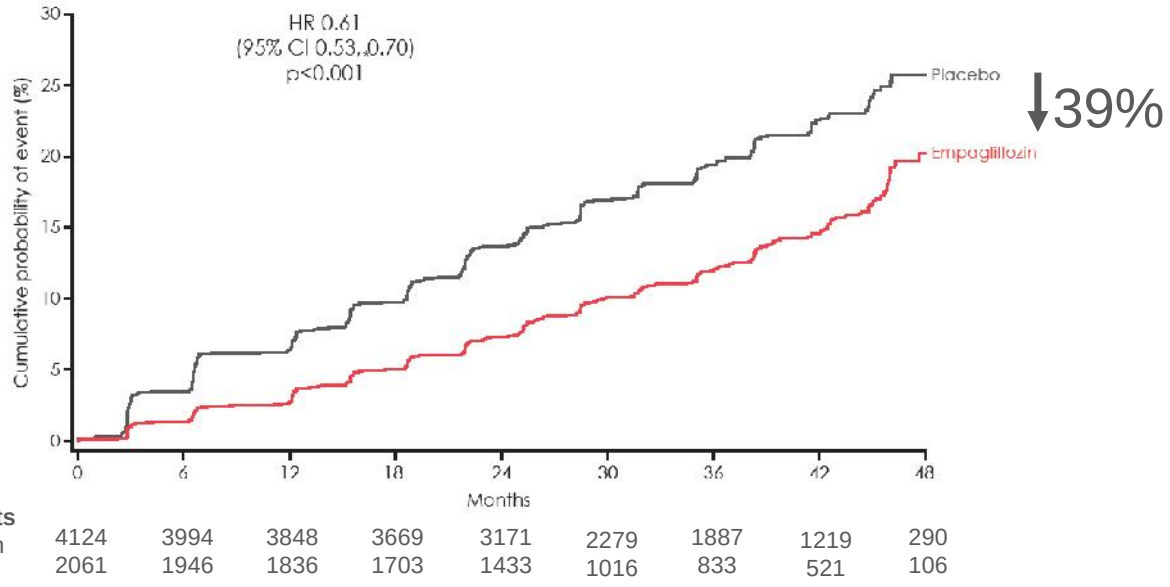
The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.

Marso et al. NEJM 2016

Effect of SGLT inhibition on renal outcomes

Pre-specified renal endpoints

New onset or worsening diabetic kidney disease

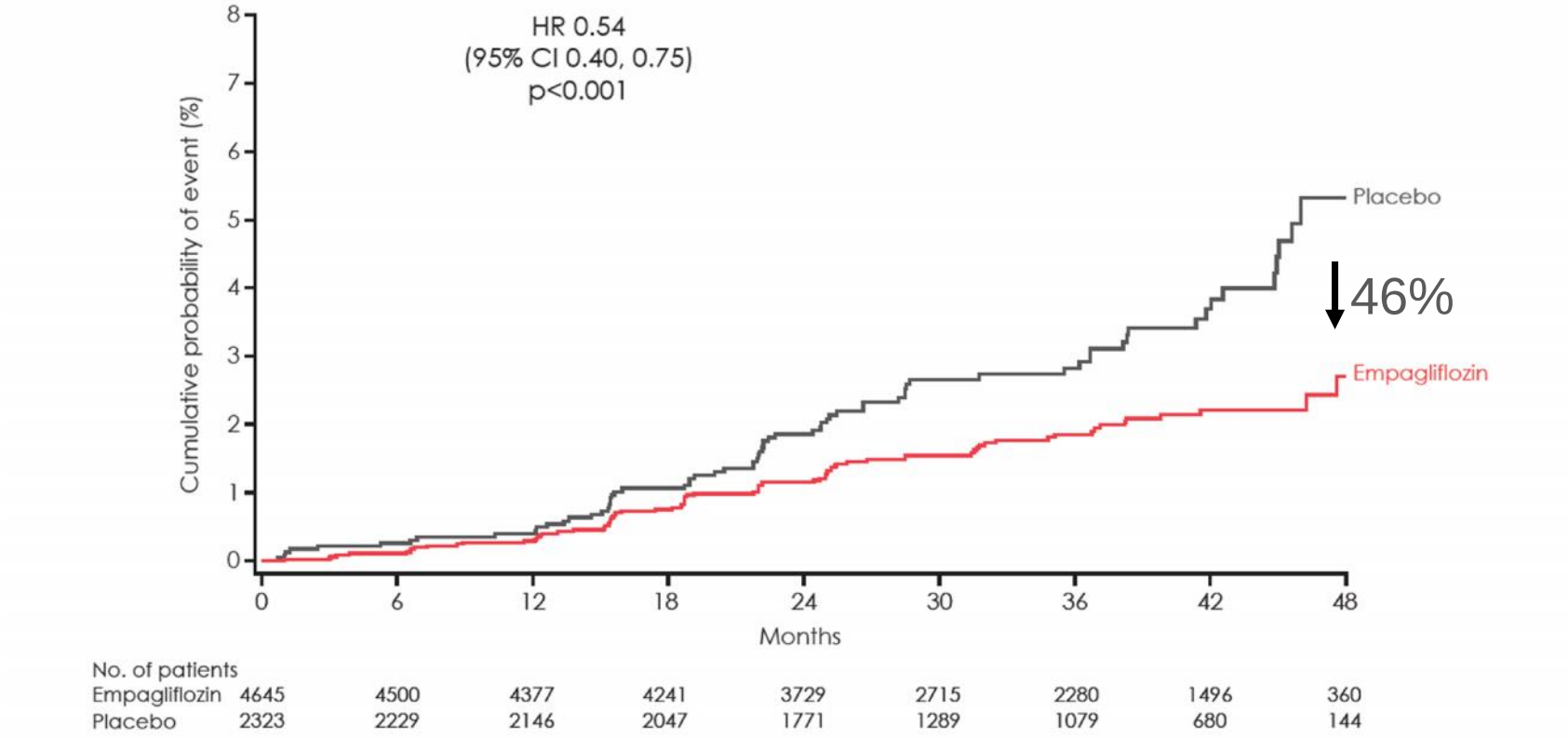


Empagliflozin is not indicated for CV risk reduction or kidney disease. Kaplan-Meier estimate. Treated set (≥1 dose of study drug)
*Nominal *p*-value. CI, confidence interval; CV, cardiovascular; HR, hazard ratio

Wanner *et al*. NEJM 2016

EMPA-REG OUTCOME®

Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease

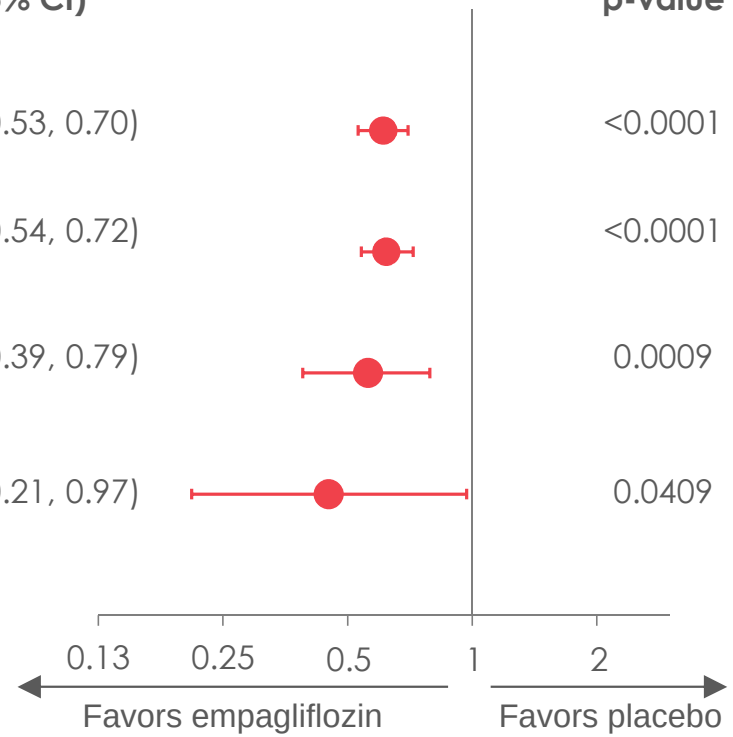


Kaplan-Meier estimate in patients treated with ≥1 dose of study drug.
Hazard ratios are based on Cox regression analyses.
*Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2.
HR, hazard ratio; CI, confidence interval. *Post-hoc* analyses.

EMPA-REG OUTCOME®

Incident or worsening diabetic kidney disease and its components

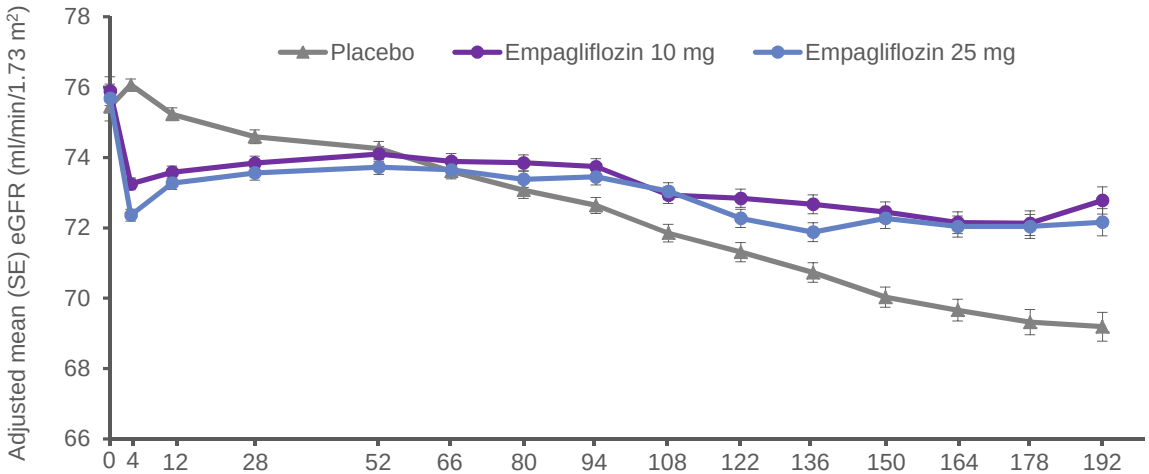
	Empagliflozin n with event/ N analyzed	Placebo n with event/ N analyzed	Hazard ratio (95% CI)	p-value
Incident or worsening nephropathy	525/4124	388/2061	0.61 (0.53, 0.70)	<0.0001
New onset macroalbuminuria	459/4091	330/2033	0.62 (0.54, 0.72)	<0.0001
Doubling of serum-creatinine*	70/4645	60/2323	0.56 (0.39, 0.79)	0.0009
Initiation of renal replacement therapy	13/4687	14/2333	0.45 (0.21, 0.97)	0.0409



*Accompanied by eGFR (MDRD) ≤45 mL/min/1.73m^2.
Cox regression analyses.

EMPA-REG OUTCOME®

eGFR (*CKD-EPI formula*) over 192 weeks



No. analysed															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in follow-up for adverse/outcome events															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Empagliflozin is not indicated for CV risk reduction or kidney disease. Pre-specified mixed model repeated measures analysis in all patients treated with ≥1 dose of study drug (OC-AD). All participants in the study were able to reach the study visit at week 94 and patient numbers declined thereafter based on study design.

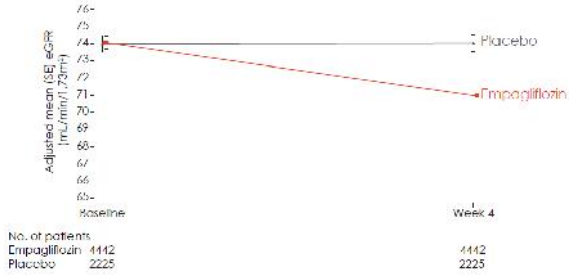
Wanner *et al*. NEJM 2016

EMPA-REG OUTCOME®

Adjusted mean eGFR values over prespecified time periods

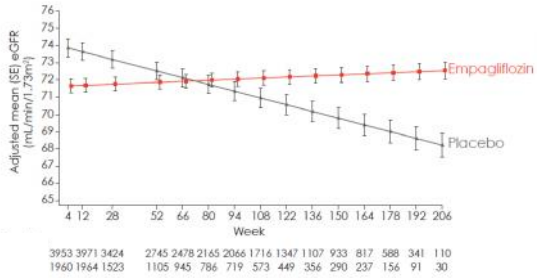
INITIATION (acute)

Baseline to week 4



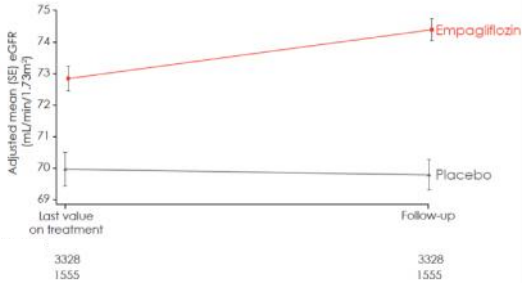
LONG-TERM (chronic)

Week 4 to last value on treatment



CESSATION (follow-up)

Last value on treatment to follow-up



Data on file

Median time from last value on treatment to follow-up: 34 days.

Low Renal Risk Population

High Percentage of "Normal" eGFR and Albuminuria

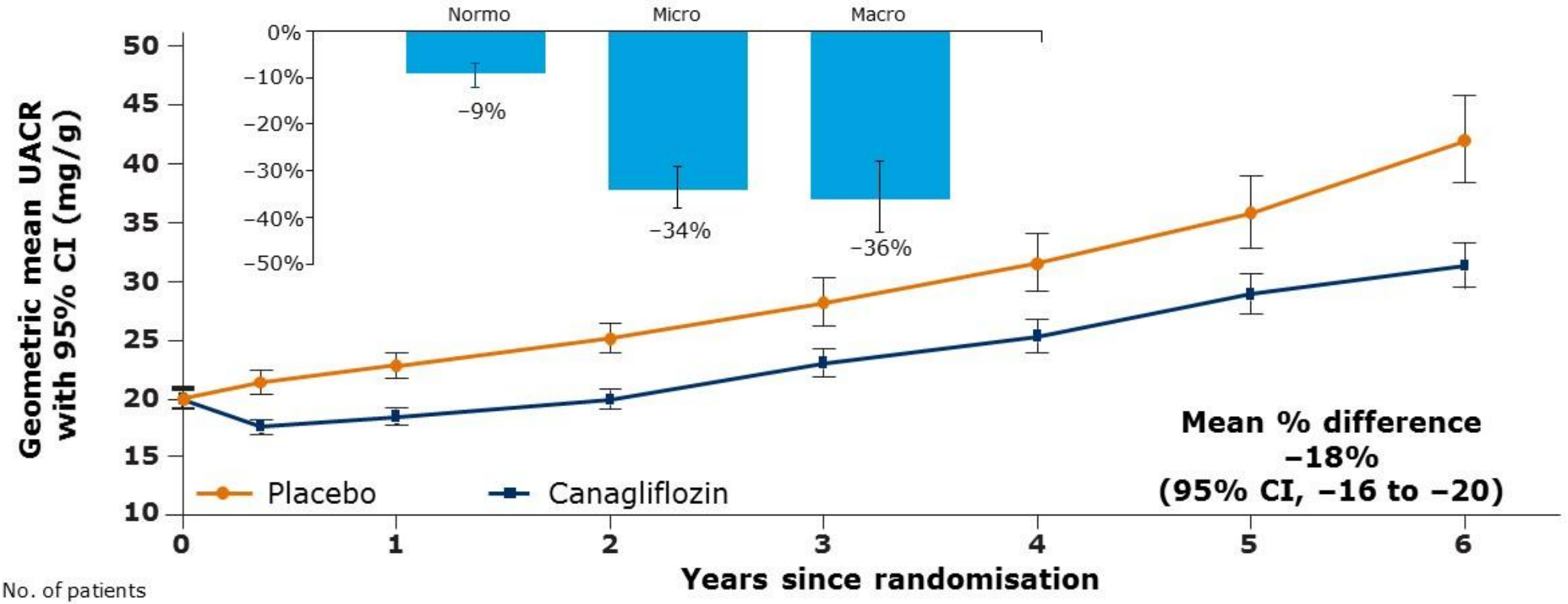
	Canagliflozin (n = 5795)	Placebo (n = 4347)
Mean eGFR, mL/min/1.73 m²	**77**	**76**
≥90 mL/min/1.73 m², %	*25*	*24*
60 to <90 mL/min/1.73 m², %	*56*	*54*
45 to <60 mL/min/1.73 m², %	*14*	*16*
<45 mL/min/1.73 m², %	*5*	*6*
Median albumin:creatinine ratio, mg/g	**12.4**	**12.1**
Normoalbuminuria (<30 mg/g), %	*70*	*70*
Microalbuminuria (30 to 300 mg/g), %	*23*	*22*
Macroalbuminuria (>300 mg/g), %	*7*	*8*

Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes; 15 September 2017; Lisbon, Portugal.

CANVAS Program

Change in Albumin:Creatinine Ratio (UACR)

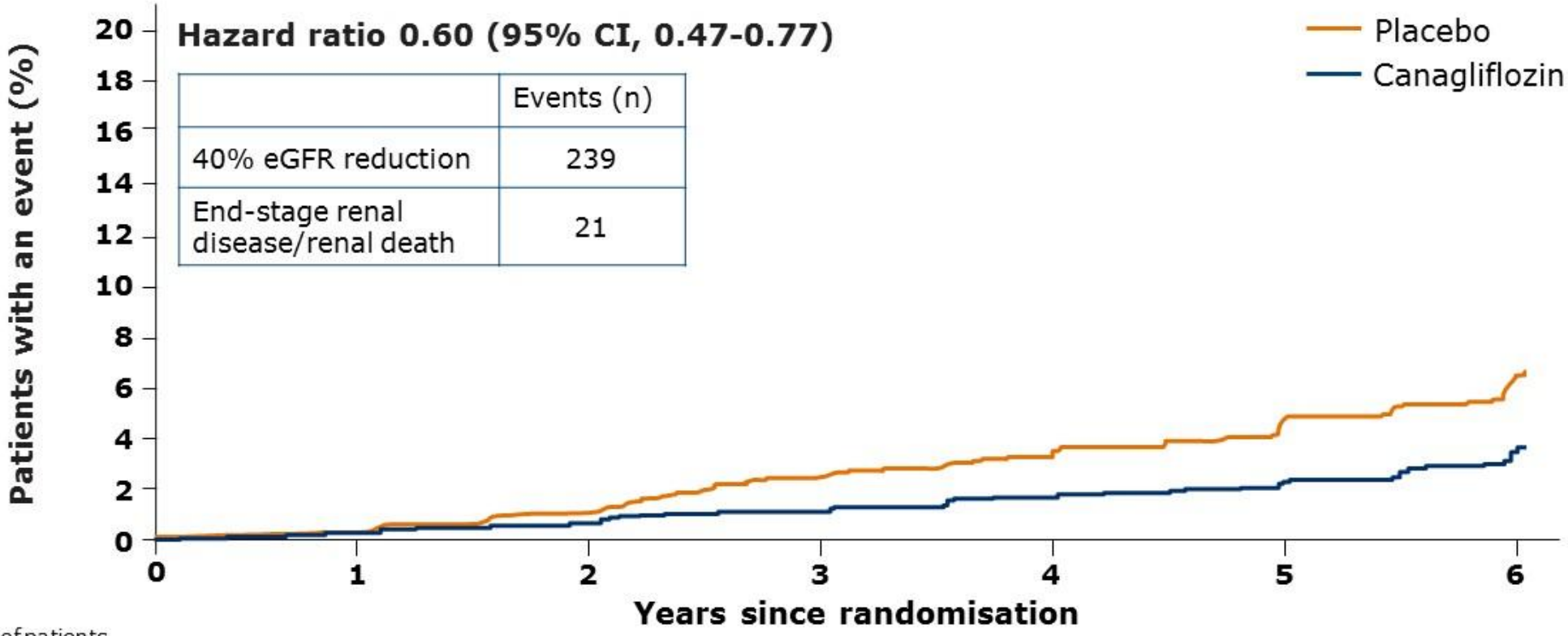
Percent Change in UACR per Albuminuria Class (inset)



No. of patients							
Placebo	4084	3775	2556	753	652	594	618
Canagliflozin	5500	5103	3565	1689	1541	1408	1534

Mixed model for repeated measures (MMRM) analysis
Excluding those below detection level

Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death



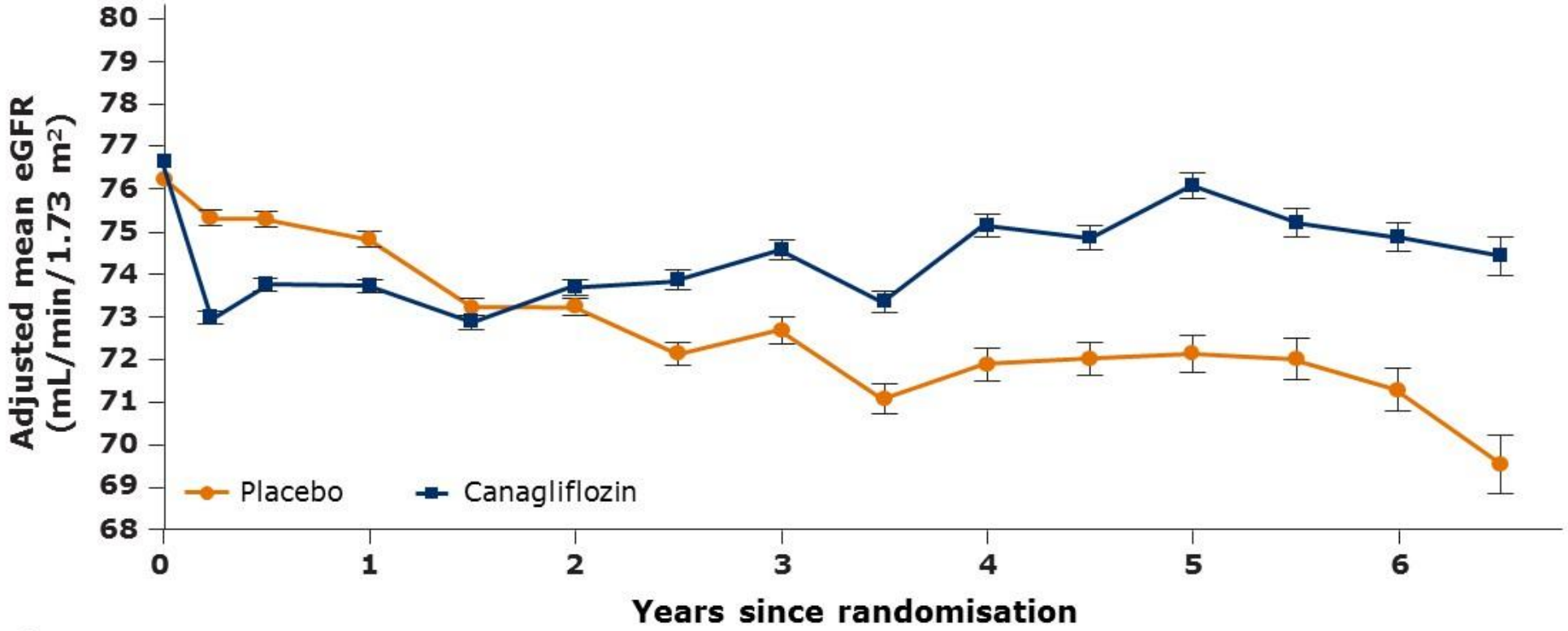
	Events (n)
40% eGFR reduction	239
End-stage renal disease/renal death	21

No. of patients

Placebo	4347	4227	3029	1274	1229	1173	819
Canagliflozin	5795	5664	4454	2654	2576	2495	1781

Intent-to-treat analysis

Effects on eGFR



No. of patients							
Placebo	4276	3867	3212	1030	899	809	694
Canagliflozin	5711	5212	4570	2230	2039	1895	1653

Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes; 15 September 2017; Lisbon, Portugal.

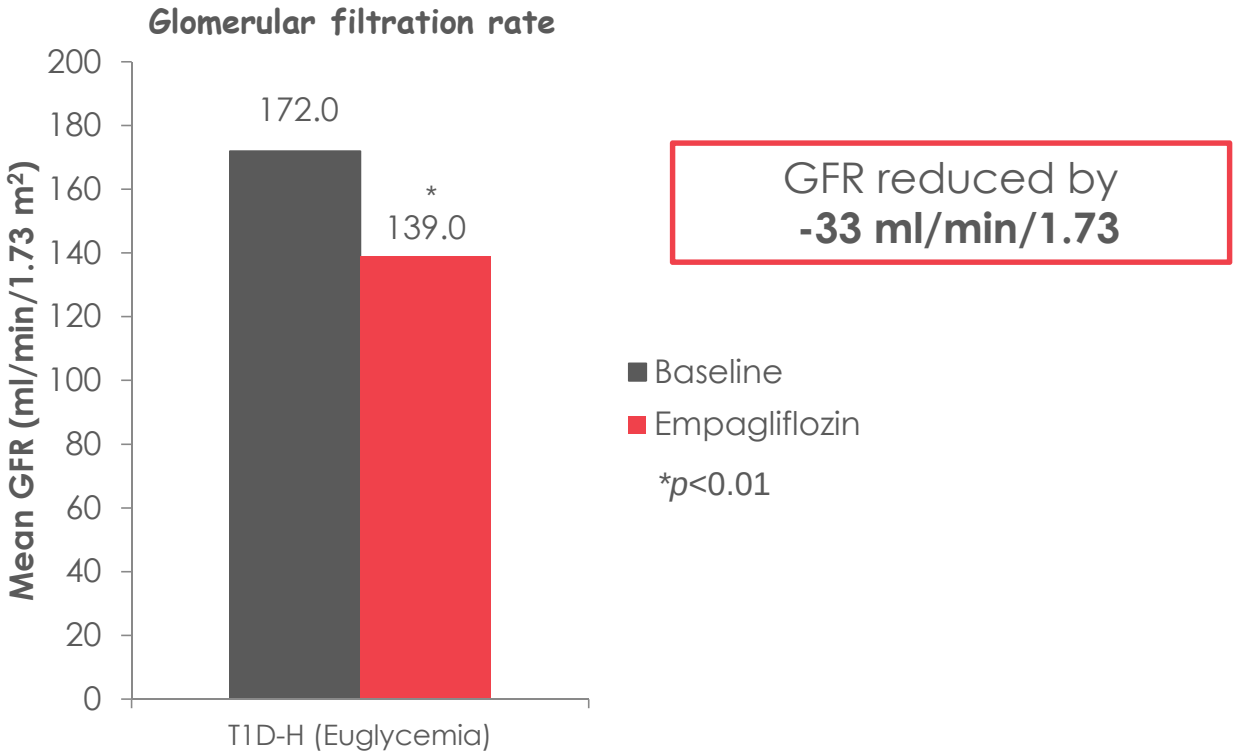
Unpublished data

CANVAS Program

Why does SGLT2 inhibition work so well?

Empagliflozin attenuates glomerular hyperfiltration

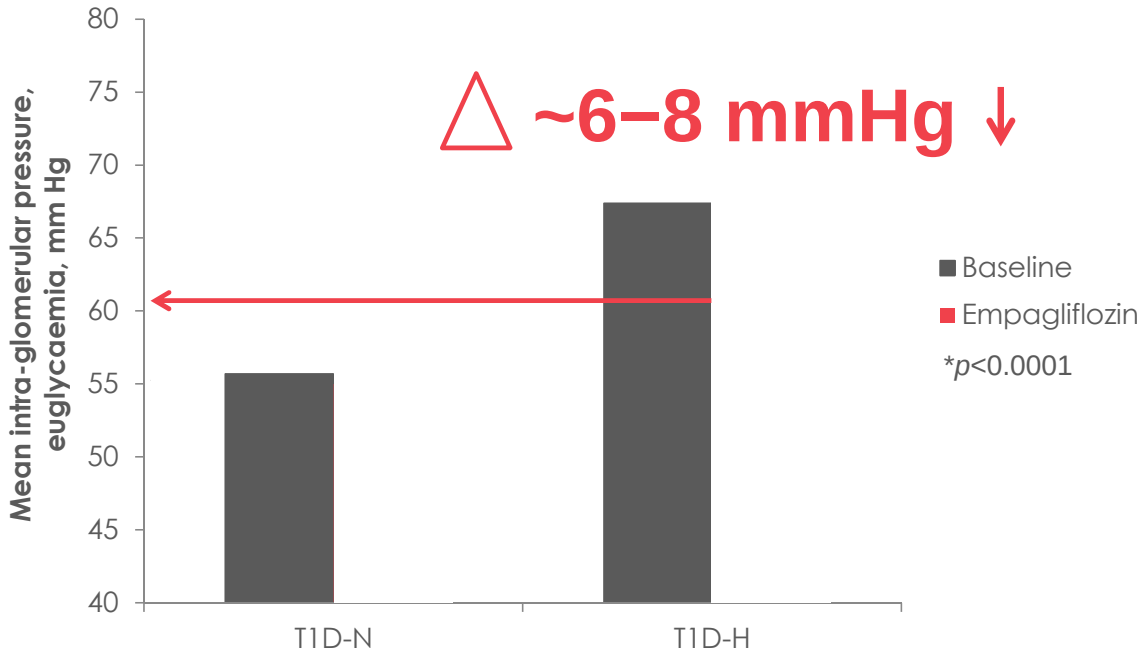
Type 1 Diabetes:



Type 1 diabetes patients with hyperfiltration. Mean GFR recorded at baseline and after 8 weeks treatment with empagliflozin 25 mg QD

Cherney D *et al. Circulation* 2014;129:587

Empagliflozin reduces intra-glomerular pressure



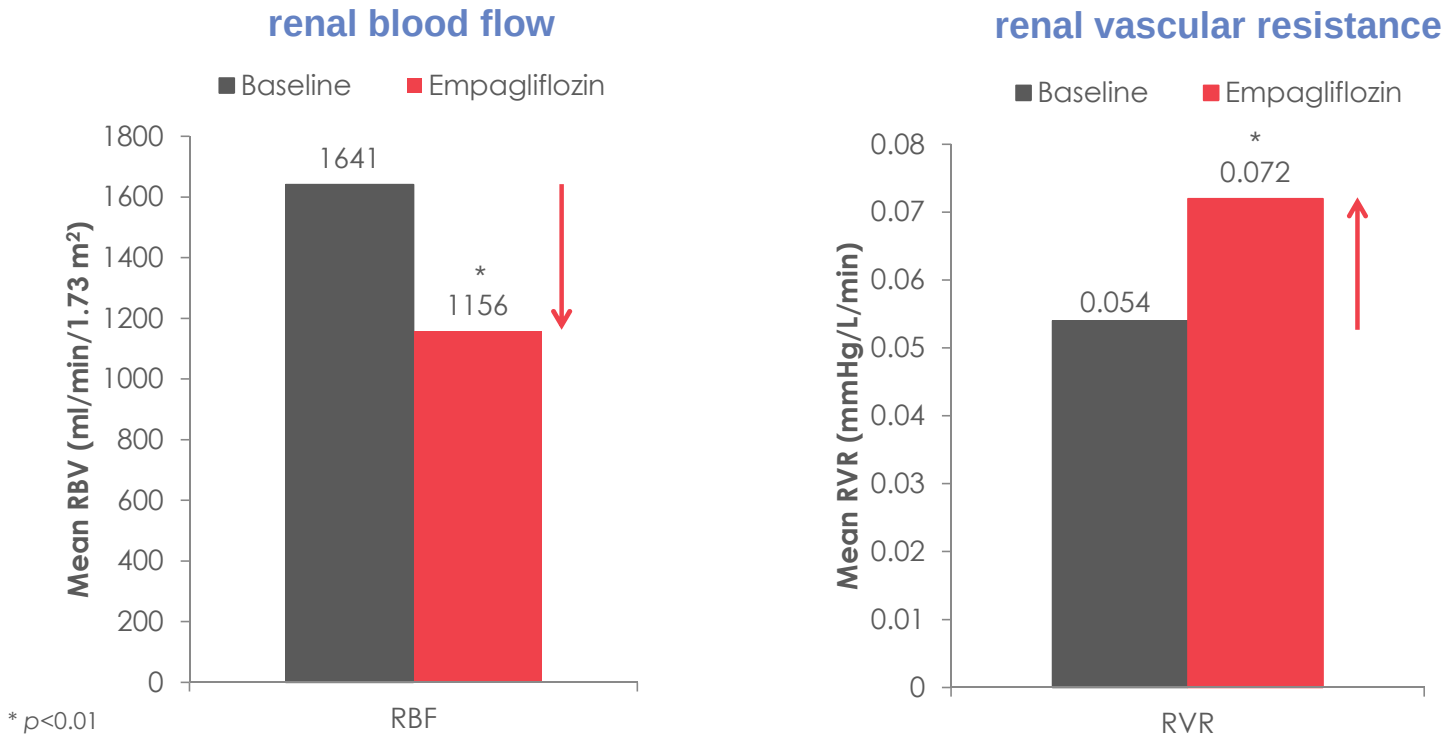
Intra-glomerular pressure recorded at baseline and after 8 weeks treatment with empagliflozin

Glomerular pressure T1D-H (mmHg)	Baseline	EMPA	p value	Change from baseline
Euglycaemia (mmHg)	67.4 ± 5.4	61.0 ± 5.2	<0.0001	9.5%
Hyperglycaemia (mmHg)	69.3 ± 6.5	61.6 ± 6.3	<0.0001	11.1%

Skrtic M *et al. Diabetologia* 2014;57:2599

Reduced hyperfiltration was mediated by effects on renal blood flow and vascular resistance

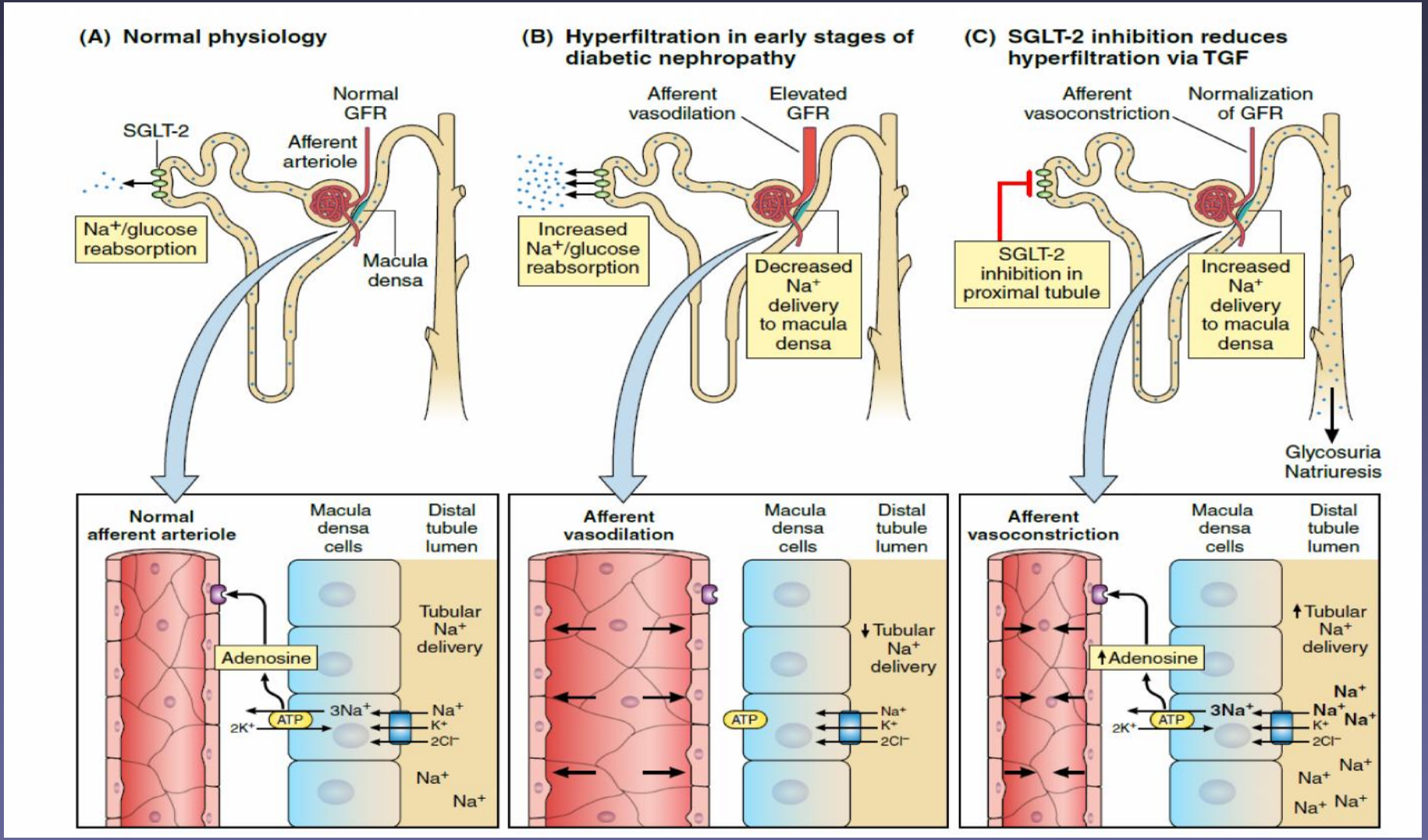
- Reduced **renal blood flow** (RBF) & increased **renal vascular resistance** (RVR) after empagliflozin treatment are consistent with **afferent arteriole vasoconstriction**



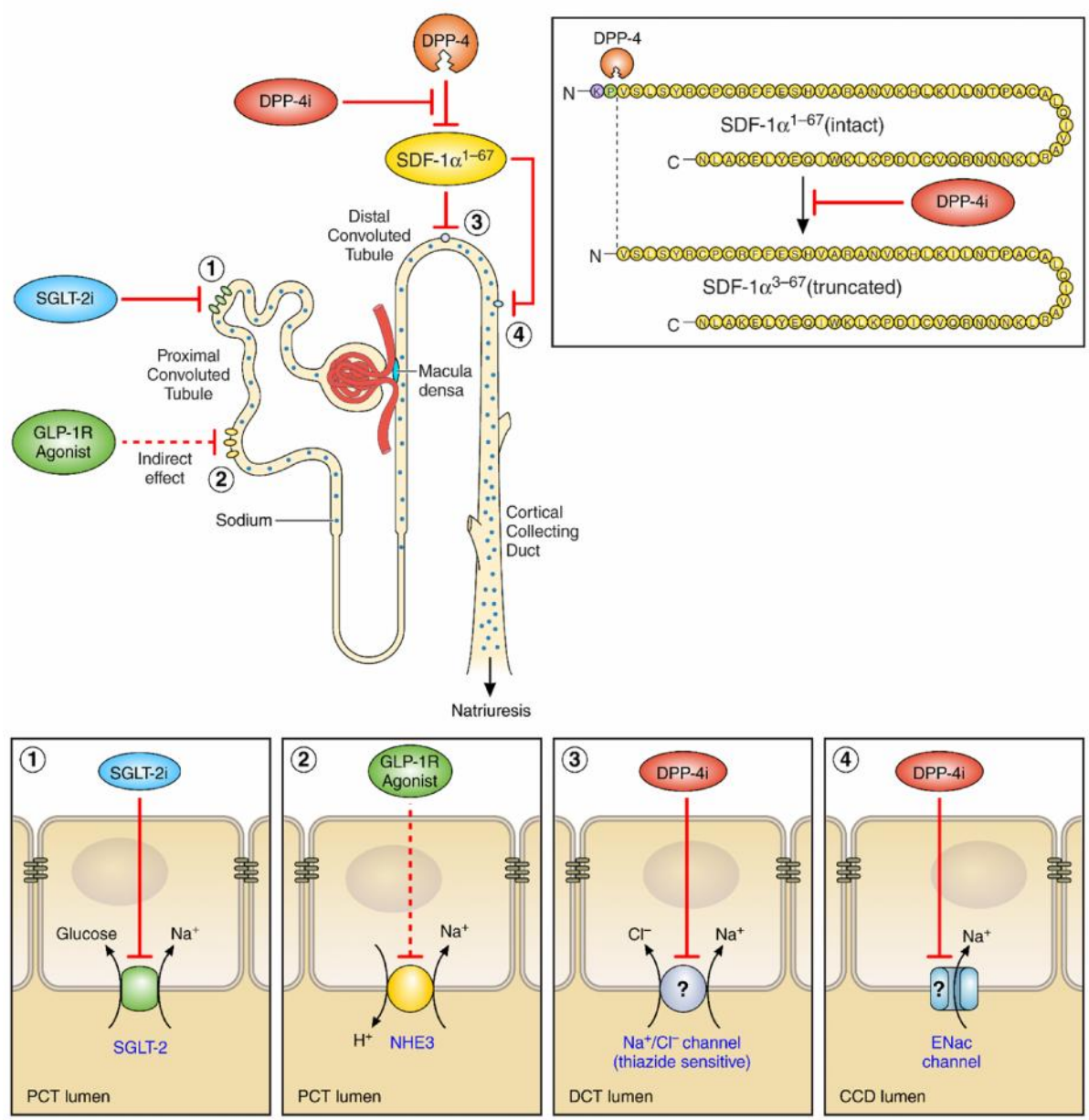
* $p<0.01$

Patients with type 1 diabetes and hyperfiltration at baseline. RBV and RVR recorded in euglycaemic state.
RBF, renal blood flow; RVR, renal vascular resistance
Cherney D *et al. Circulation* 2014;129:587

The "Tubular Hypothesis"

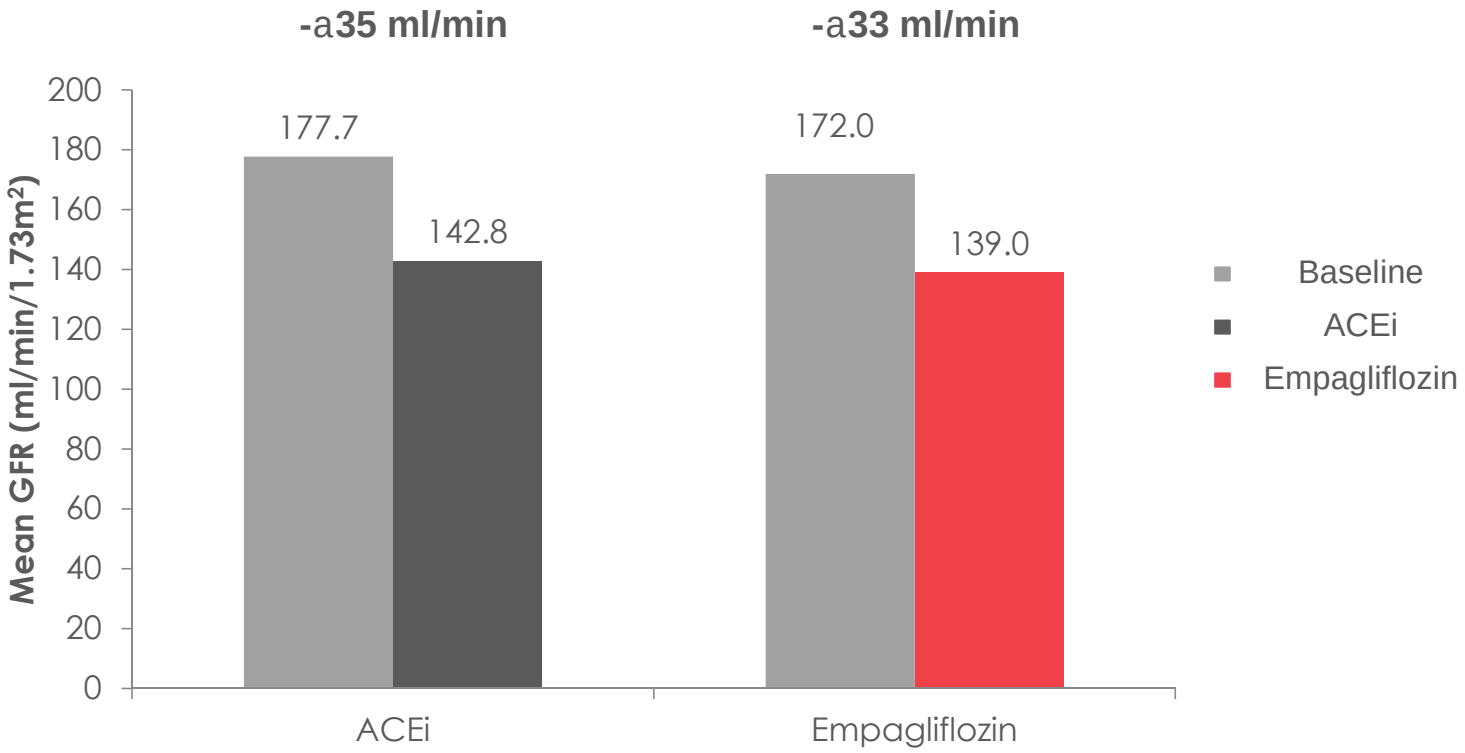


Heerspink and Cherney et al. Circulation (in press) 2016

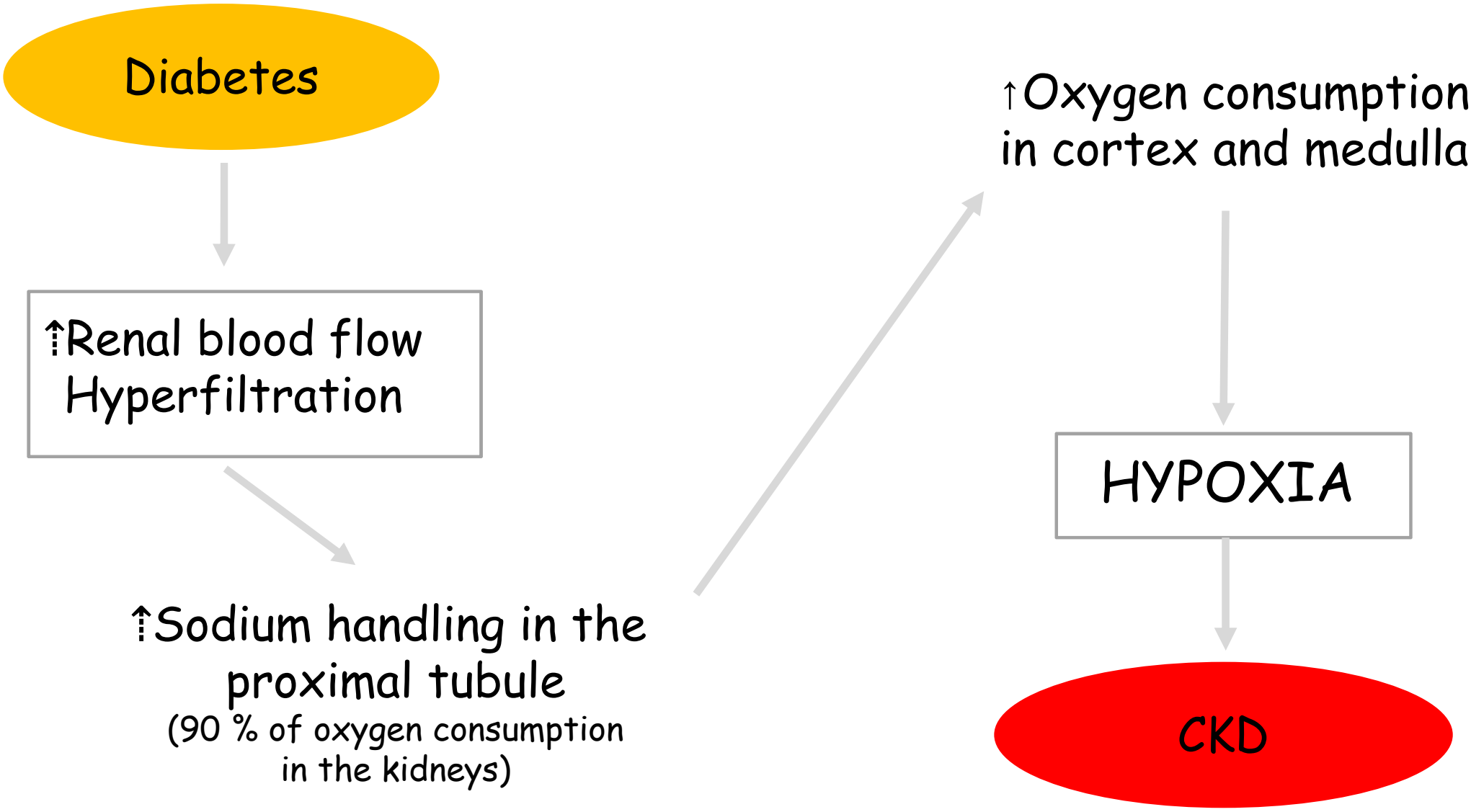


Lovshin, Cherney et al. Diabetes Care 2017

Empagliflozin effect on glomerular hyperfiltration shows similar magnitude as ACE inhibitor



Sochett, Cherney, Miller et al. JASN, 2006
Cherney, Perkins et al. Circulation 2014;129:587


Diabetes
↑Renal blood flow
Hyperfiltration
↑Sodium handling in the proximal tubule
(90 % of oxygen consumption in the kidneys)
↑Oxygen consumption in cortex and medulla
HYPOXIA
CKD

Pronounced and persistent intrarenal hypoxia as early as 3 days after induction of diabetes in mice

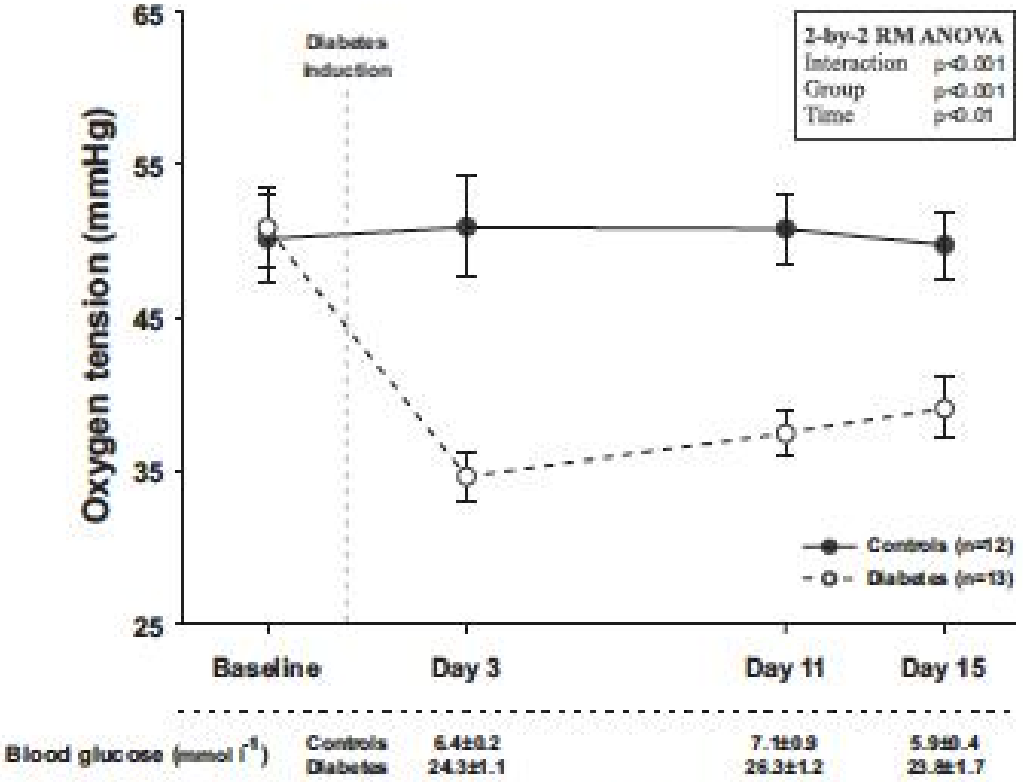


Fig. 1. Cortical oxygen tensions before and after induction of diabetes as well as blood glucose status during the study period.

Franzén et al. Am J Physiol Renal Physiol 310, F807-9, 2016

Induction of diabetes was associated with glomerular hyperfiltration but not significant albuminuria

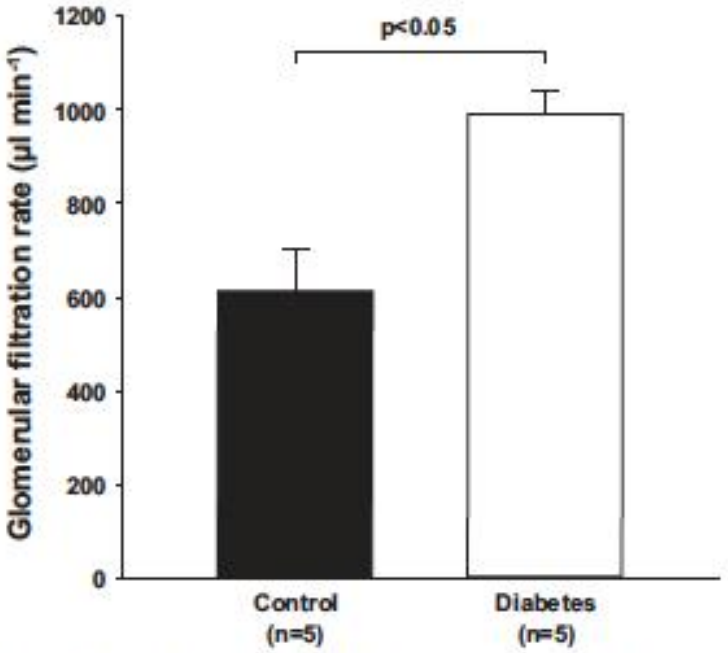


Fig. 3. Glomerular filtration rates at the end of the study period.

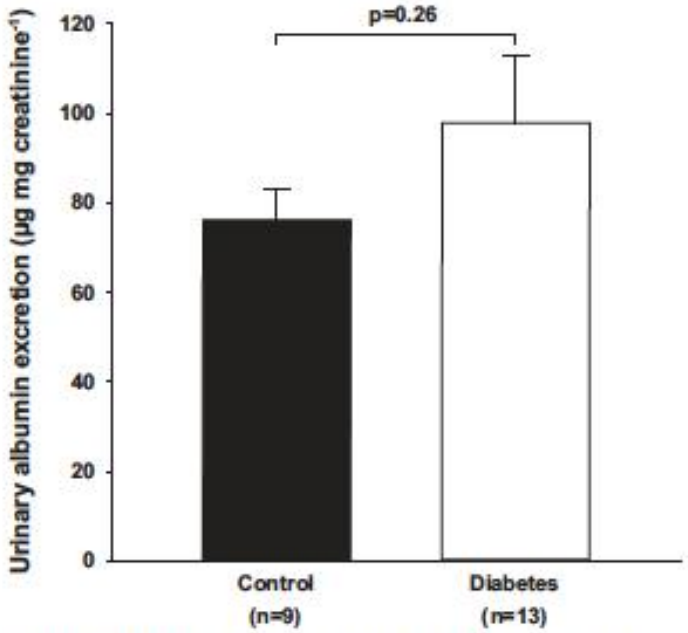


Fig. 2. Urinary albumin excretions at the end of the study period.

Franzén et al. Am J Physiol Renal Physiol 310, F807-9, 2016

Kidney hypoxia due to increased oxygen consumption induces kidney disease independently of hyperglycemia and oxidative stress

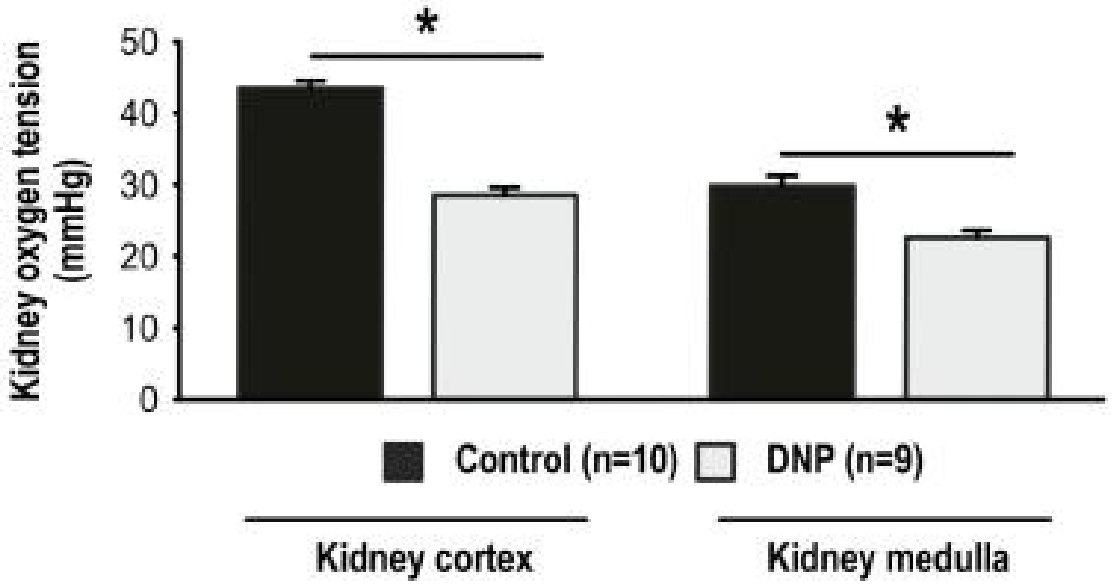


Figure 3.
Oxygen tensions in kidney cortex and medulla in rats with and without administration of dinitrophenol (DNP) for 30 days. * denotes $p<0.05$ compared to untreated controls.

Friederich-Persson et al. Hypertension 62 (5), 2013

Dinitrophenol increased urinary protein excretion, kidney vimentin expression and infiltration of inflammatory cells

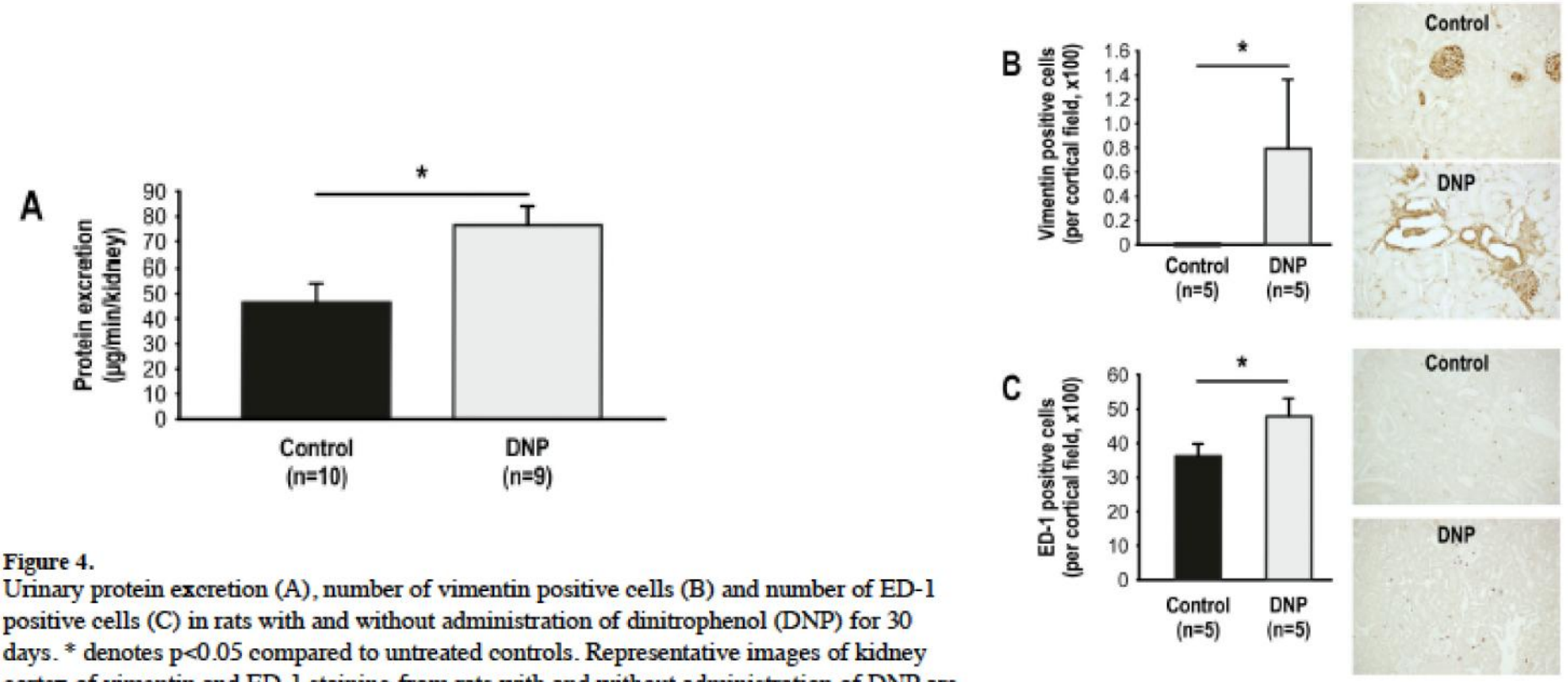
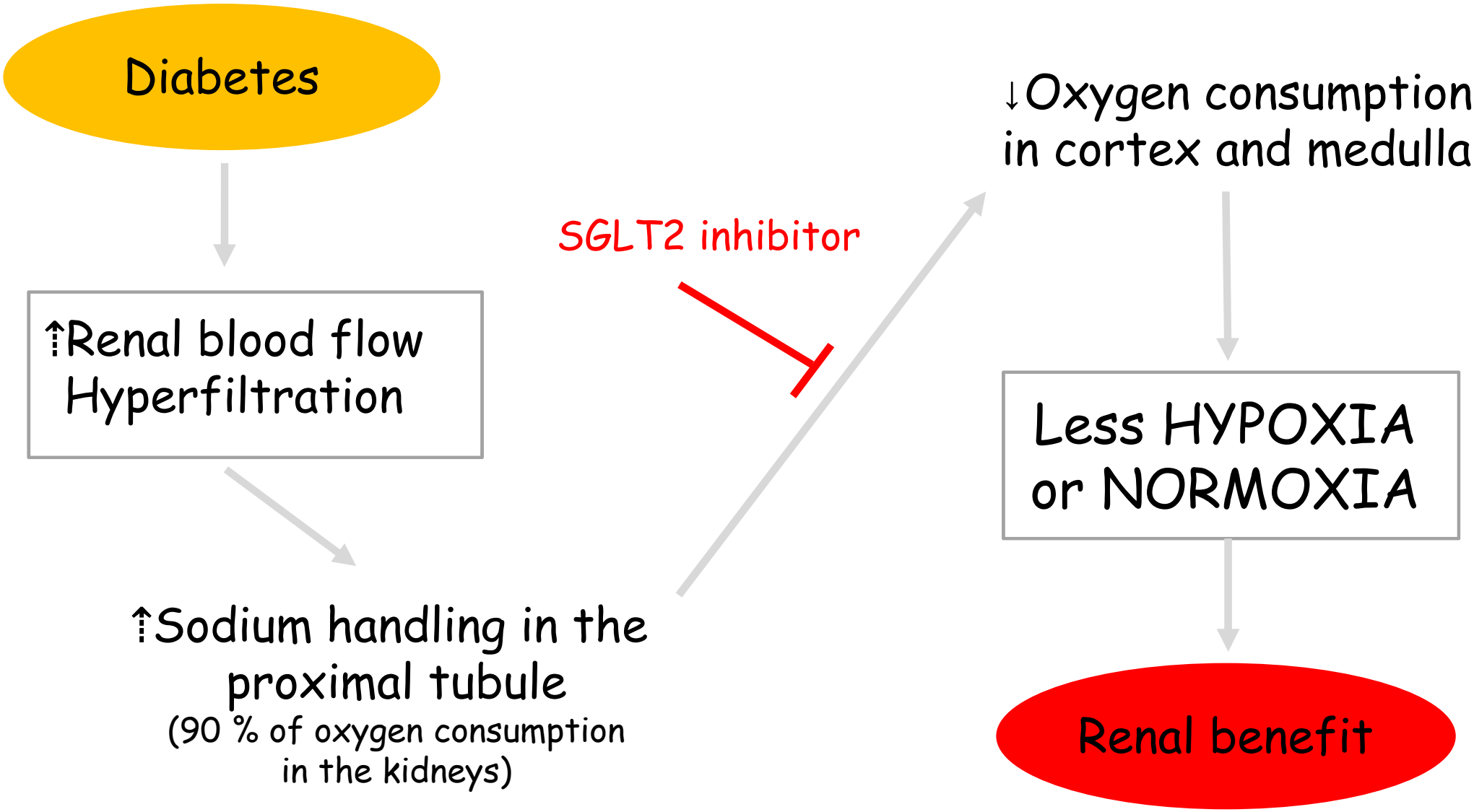


Figure 4.
Urinary protein excretion (A), number of vimentin positive cells (B) and number of ED-1 positive cells (C) in rats with and without administration of dinitrophenol (DNP) for 30 days. * denotes $p<0.05$ compared to untreated controls. Representative images of kidney cortex of vimentin and ED-1 staining from rats with and without administration of DNP are displayed to the right. Vimentin staining of the glomeruli in control animals is normal and does not indicate damaged tubules.

Friederich-Persson et al. Hypertension 62 (5), 1-16, 2013


Diabetes
↑Renal blood flow
Hyperfiltration
↑Sodium handling in the proximal tubule
(90 % of oxygen consumption in the kidneys)
SGLT2 inhibitor
↓Oxygen consumption in cortex and medulla
Less HYPOXIA or NORMOXIA
Renal benefit

Take home messages

- Diabetes is associated with increased risk of cardiovascular disease and remarkably shortened life expectancy

- Diabetic kidney disease is a common complication with grim consequences

- Traditional approaches such as optimal glucose control and multifactorial treatment decrease the risk of diabetic kidney disease

- Novel medications such as GLP-1 agonists and SGLT2-inhibitors show cardio- and renoprotective effects beyond their effects on glucose control


Thank you for your attention
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