



Diabetic Kidney Disease: Update

GKA Master Class

Istanbul 2011





DKD: Challenging dogmas



Old Dogmas

- **Type 1 and Type 2 DN have the same natural history**
- **Microalbuminuria is an early stage of DN**
- **Tight Glycemia control delays ESRD**
- **ACEi/ARBs are the treatment of choice for all diabetics with kidney disease**



Case study 1

- 42 year old with history of type1 DM
- BP: 142/96mmHg
- Serum Creatinine 210umol/l
- eGFR = 32ml/min
- Proteinuria 2.9g/24h
- PCR = 290mg/mmol
- ACR = 200mg/mmol

- **What is the treatment of choice?**

Case study 2

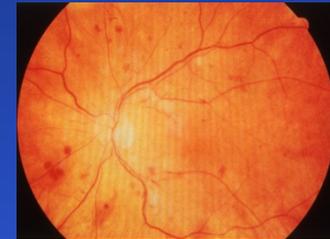
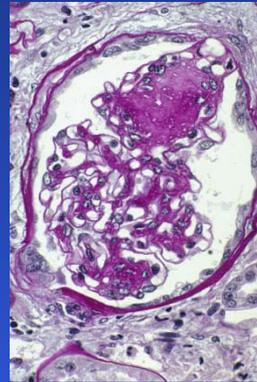
- 76 year old man
- Hypertension for 18 years
- Known IHD and intermittent claudication
- Type 2 DM since 2003
- BP: 178/86mmHg
- Serum Creatinine 210umol/l
- eGFR = 32ml/min
- Proteinuria: 0.8g/24h
- PCR: 80mg/mmol
- ACR: 60mg/mmol

- **What is the treatment of choice?**

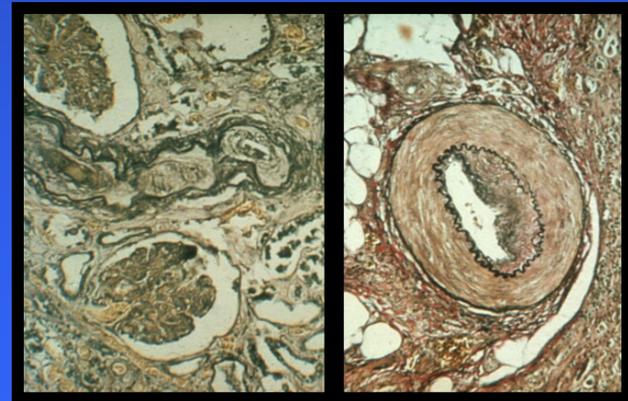


Diabetic Nephropathy

- Microvascular Disease



- Macrovascular disease



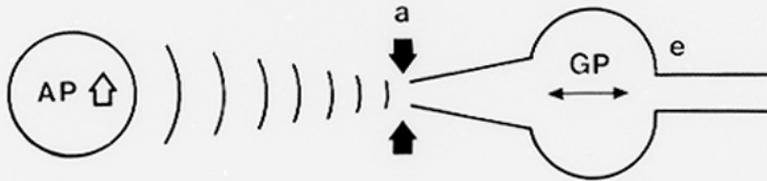
Diabetic Nephropathy Microvascular (Hyperperfusion/Hyperfiltration)

- Other microvascular manifestations
- Onset:
 - Microalbuminuria
 - Overt Proteinuria/Albuminuria
- Declining kidney function (CKD)
- ESRD



GLOMERULOSCLEROSIS

HYPERTENSION : HOW?



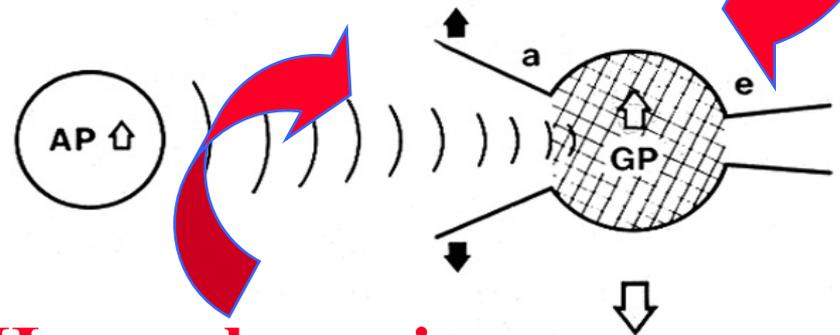
NO GLOMERULOSCLEROSIS

Afferent arteriolar vasoconstriction

Angiotensin II

GLOMERULOSCLEROSIS

HYPERTENSION

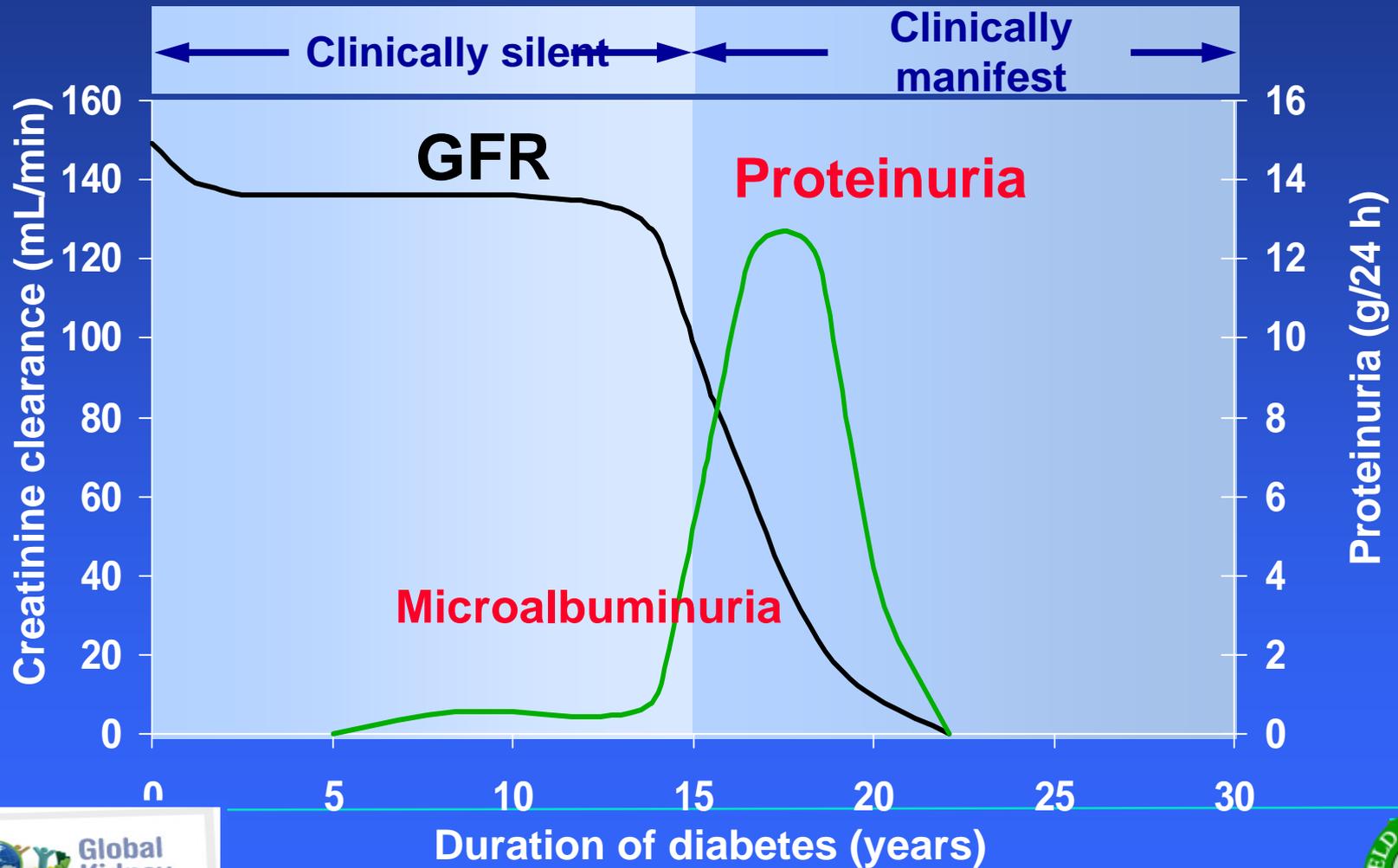


Hyperglycemia

GLOMERULOSCLEROSIS

Afferent arteriolar vasodilatation

Course of Diabetic Nephropathy Natural History

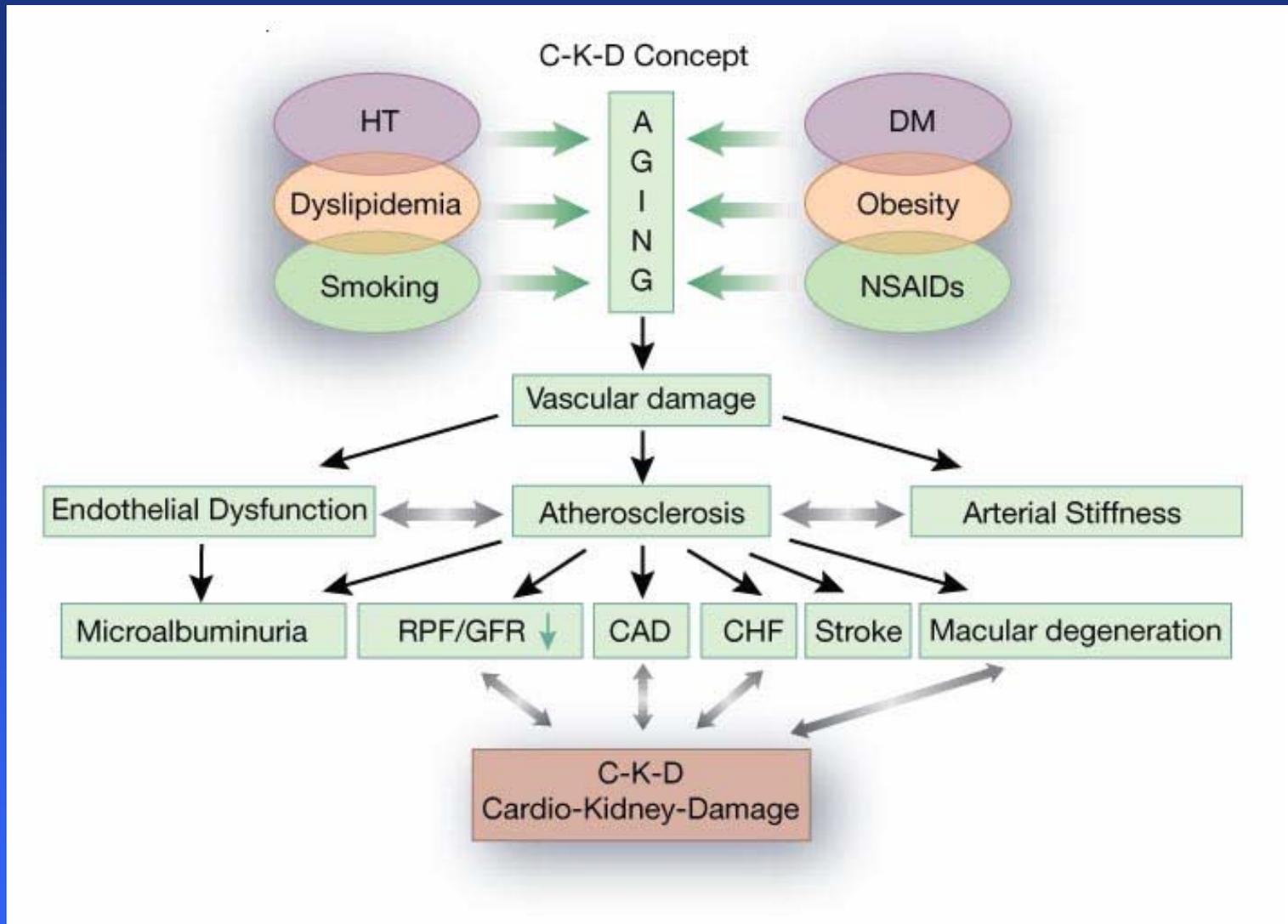


Diabetic Nephropathy

Macrovascular Ischemic Disease

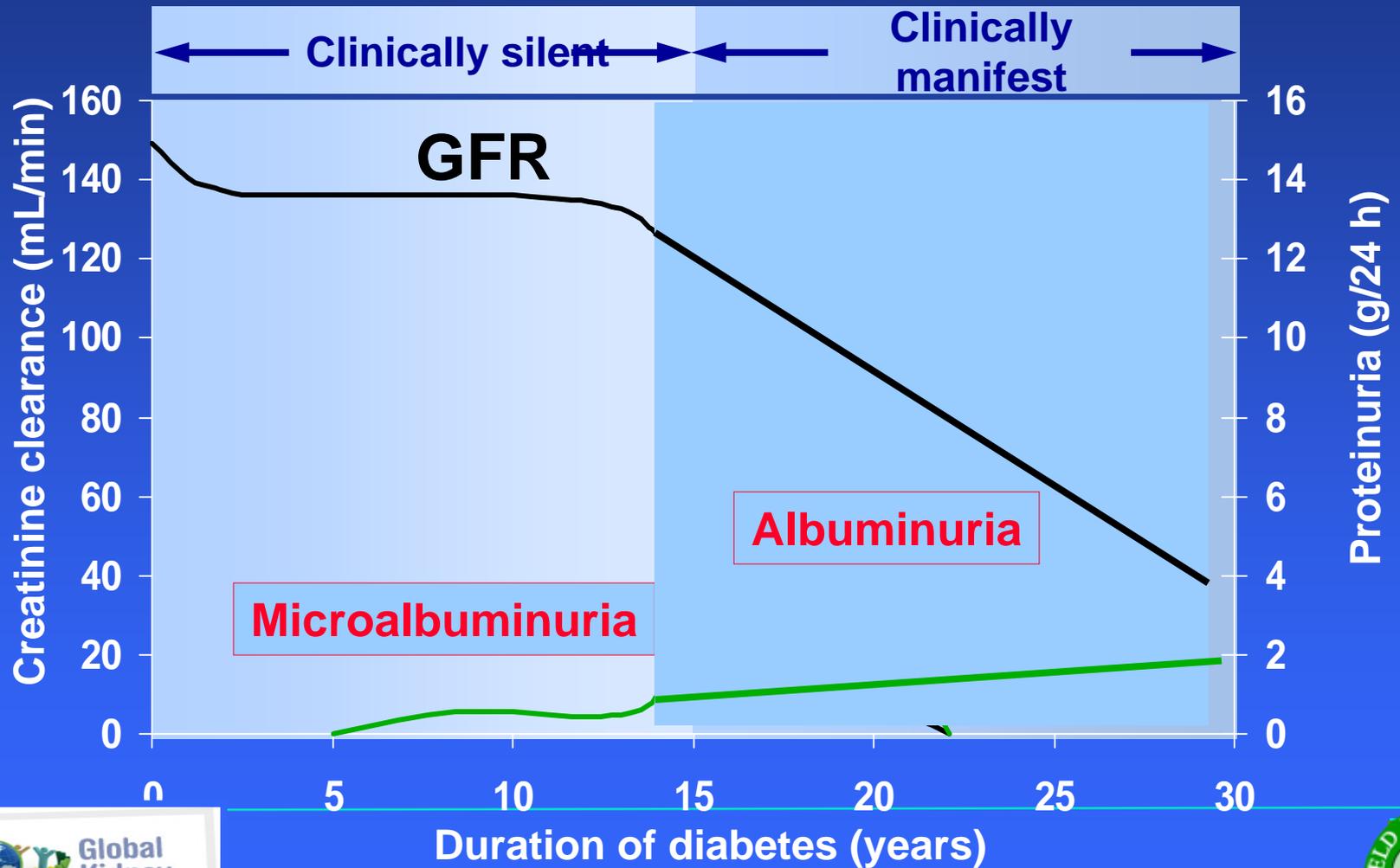
- Systemic Systolic Hypertension
- CAD
- PVD
- NO / LITTLE PROTEINURIA
- CKD
- Declining Kidney Function



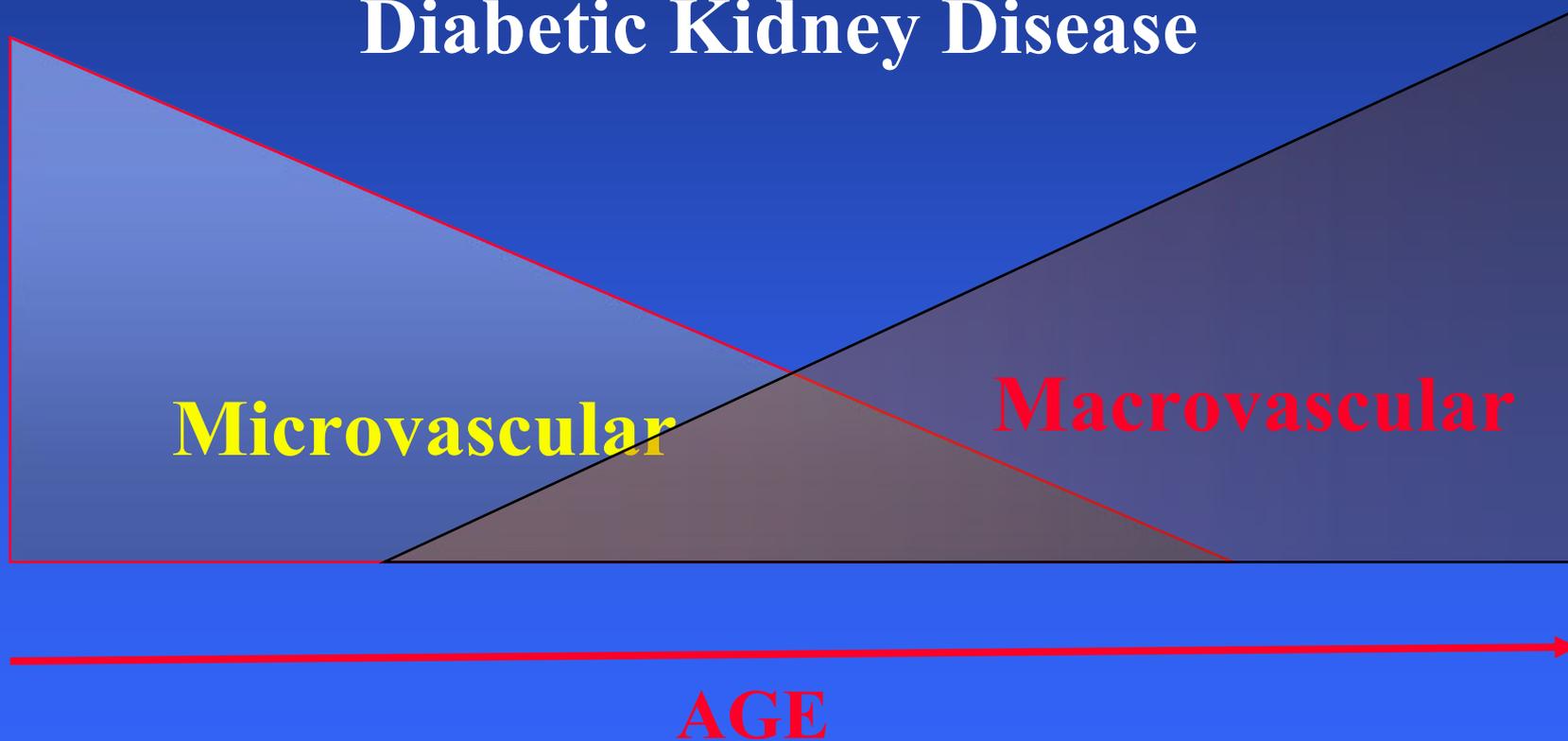


Course of Diabetic Nephropathy

Natural History



Diabetic Kidney Disease

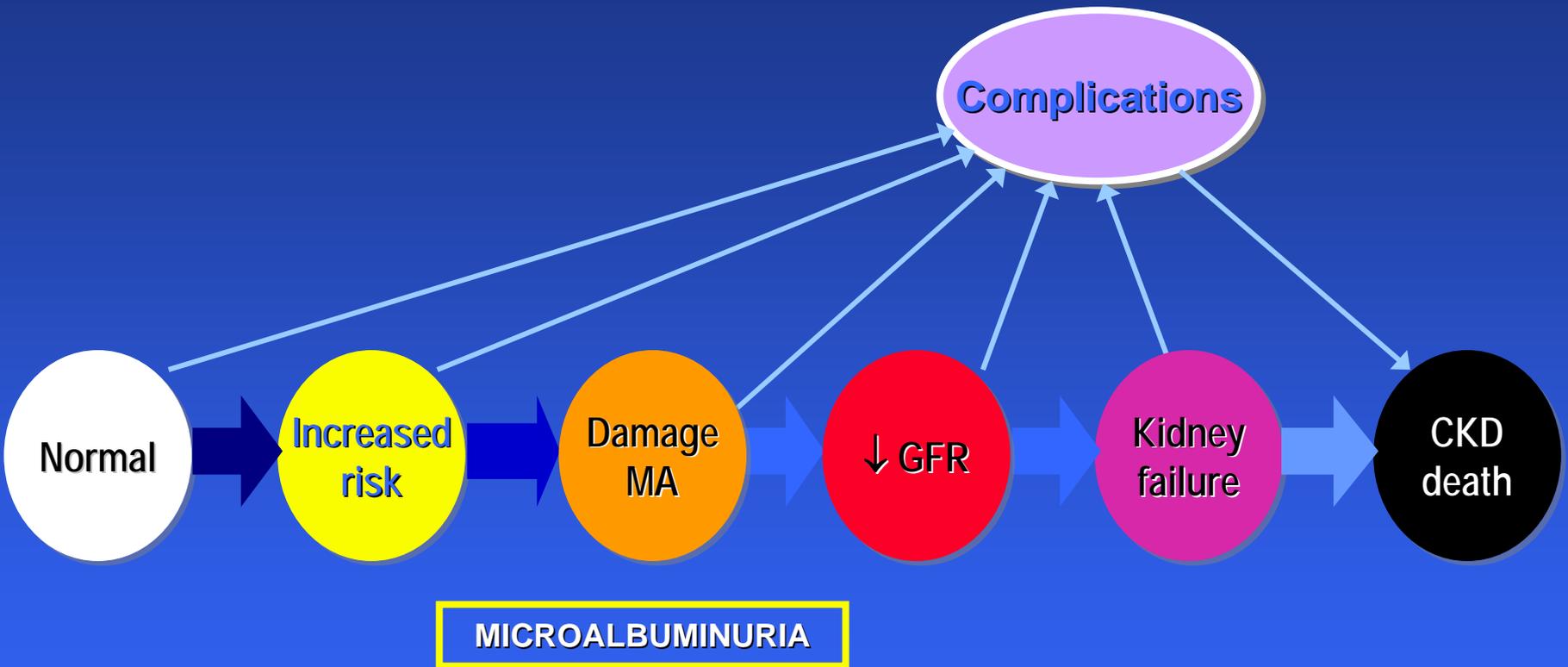


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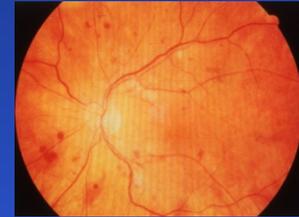
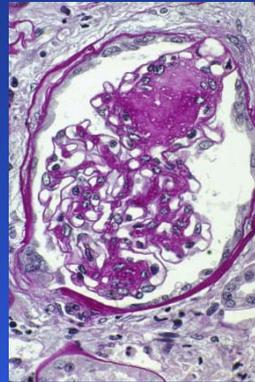


Conceptual Model for DKD

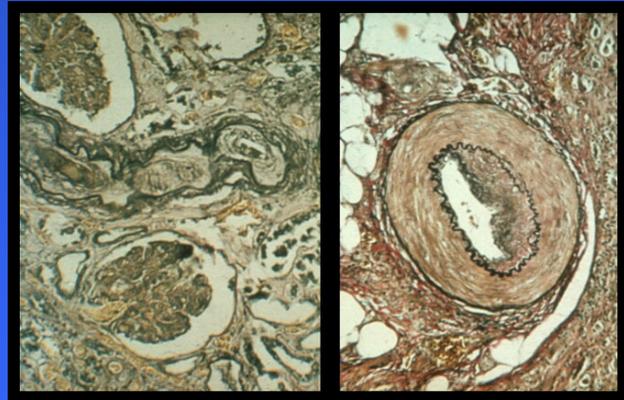


Diabetic Nephropathy

- Microvascular Disease

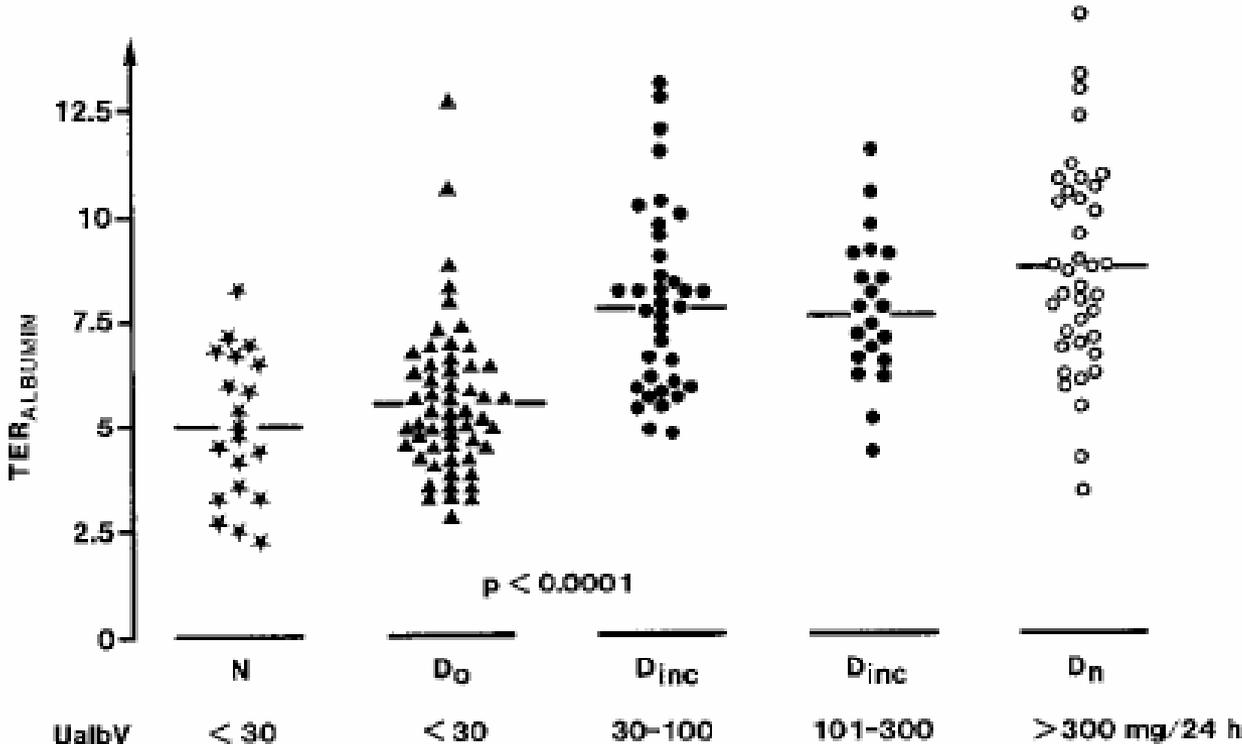


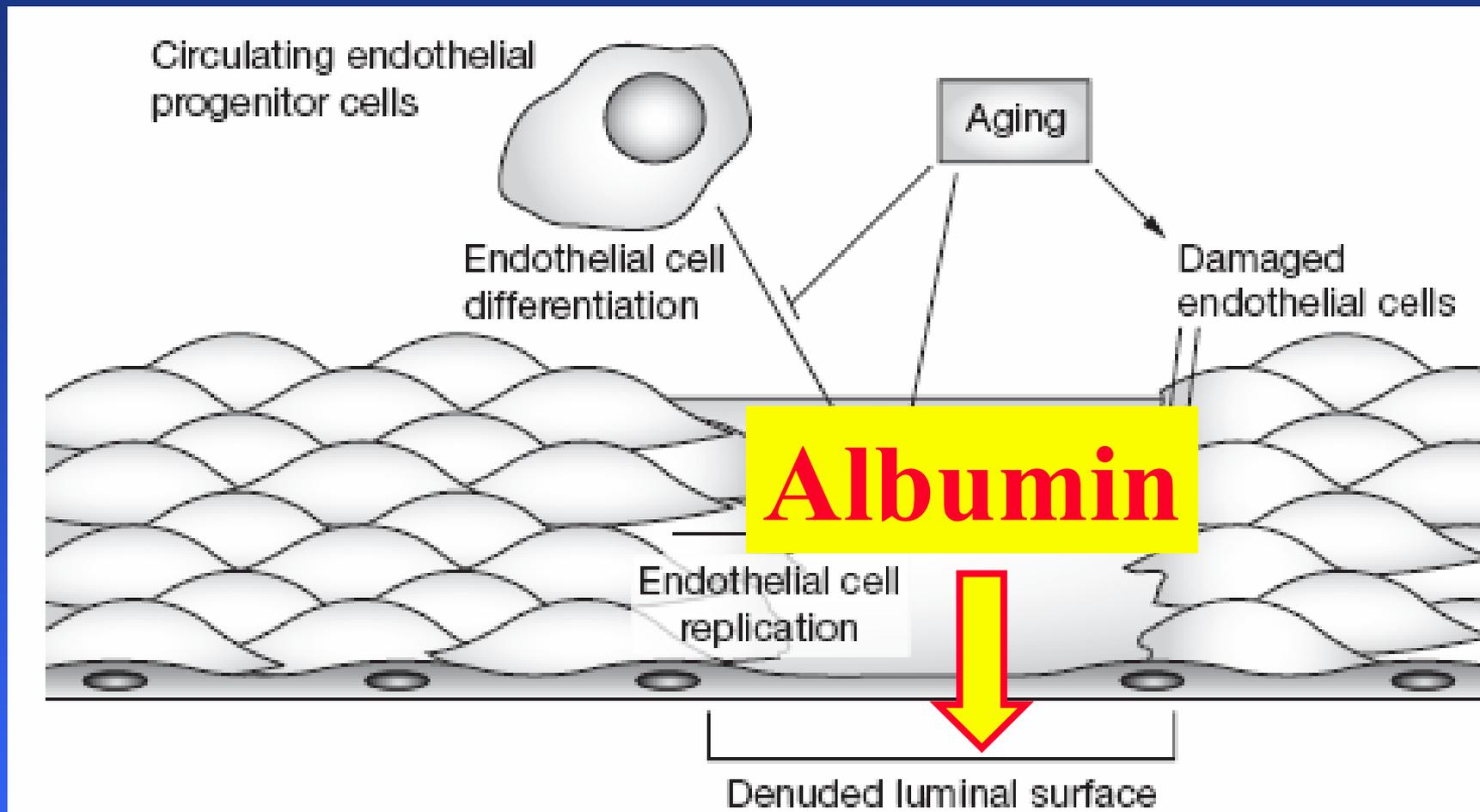
- Macrovascular disease



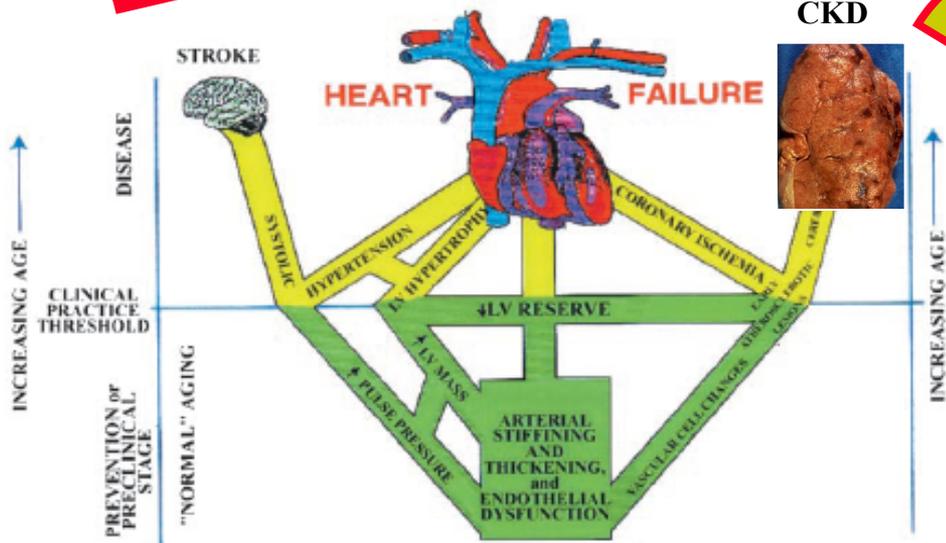
Steno Hypothesis

T. Deckert et al.: Albuminuria reflects widespread vascular damage



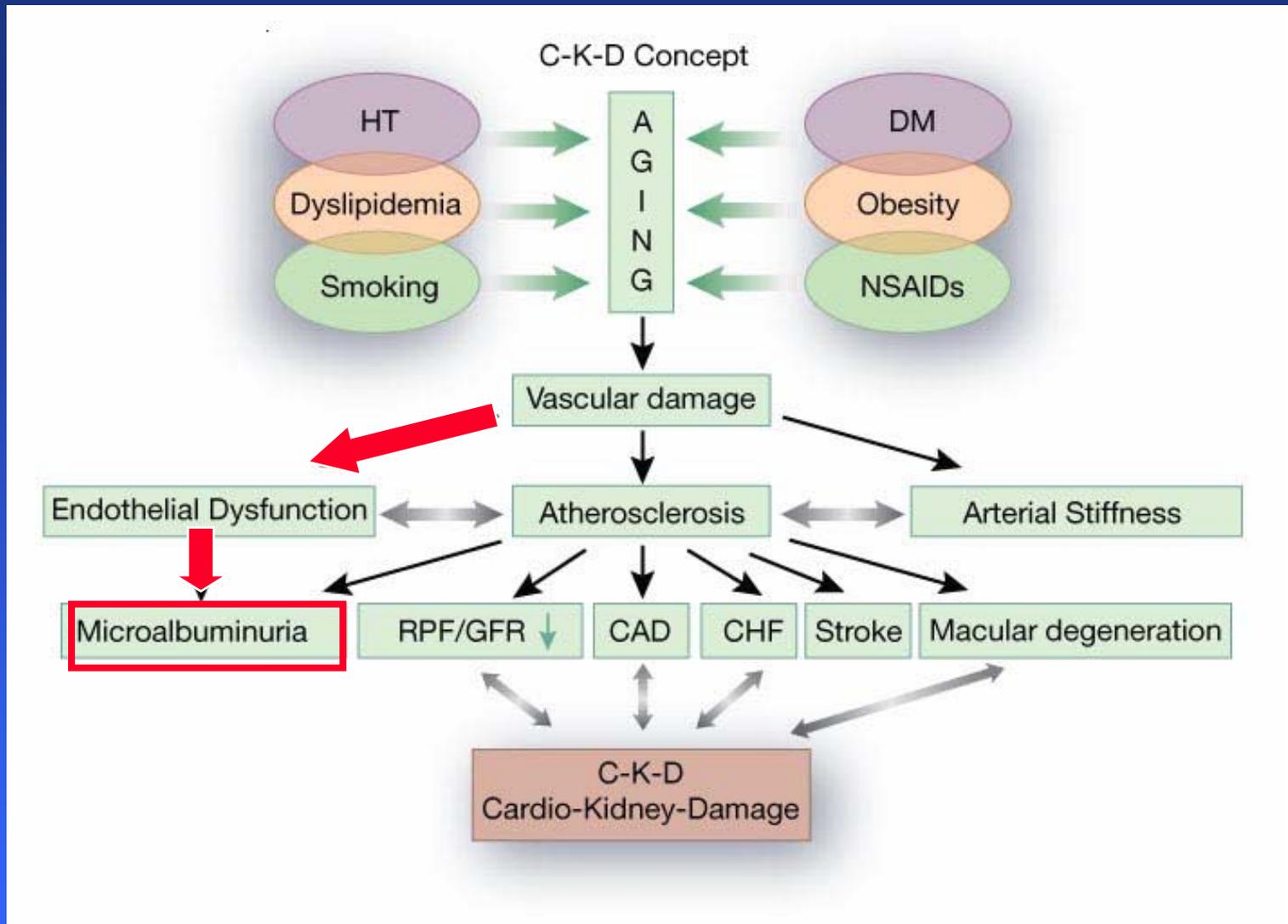


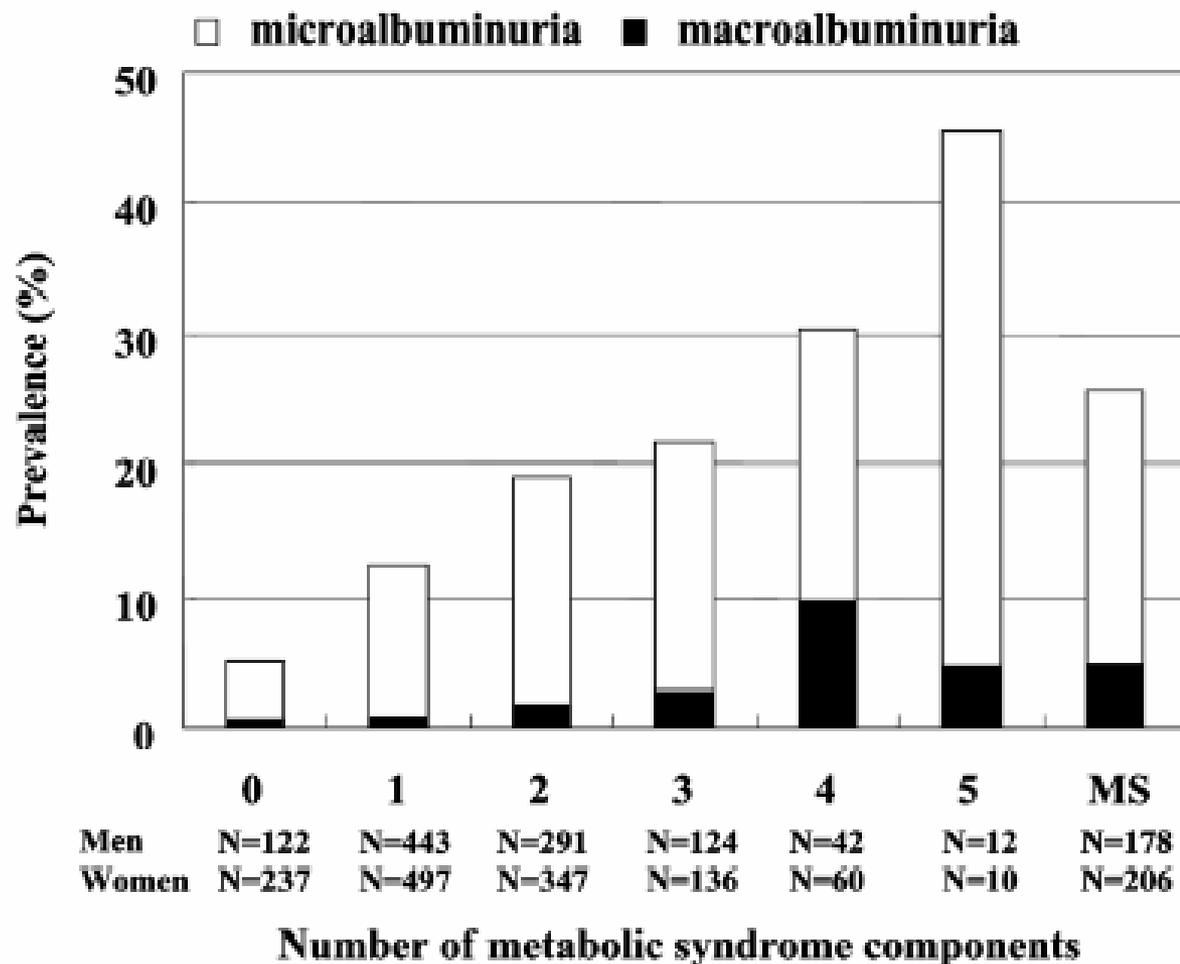
AGE: THE MAJOR RISK FACTOR FOR CARDIOVASCULAR MORBIDITY AND MORTALITY



Albuminuria







Impact of weight change on albuminuria in the general population

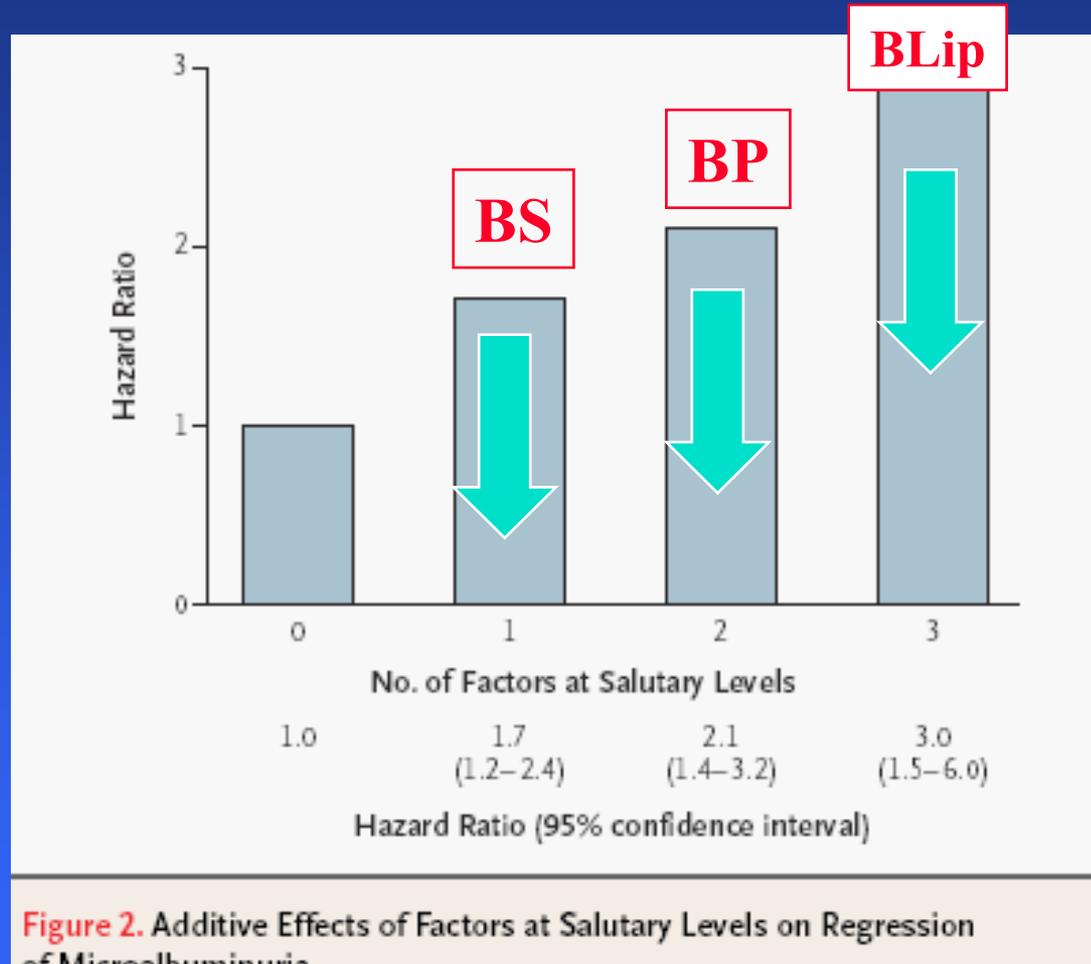
Aminu K. Bello¹, Dick de Zeeuw², Meguid El Nahas¹, Auke H. Brantsma³, Stephan J. L. Bakker³, Paul E. de Jong³ and Ronald T. Gansevoort³

¹Sheffield Kidney Institute, European Kidney Institute (EKI), The University of Sheffield, Sheffield S5 7AU, UK,

²Department of Clinical Pharmacology and ³Division of Nephrology, Department of Medicine, European Kidney Institute (EKI), University Medical Centre Groningen (UMCG), Groningen, The Netherlands



MA Regression

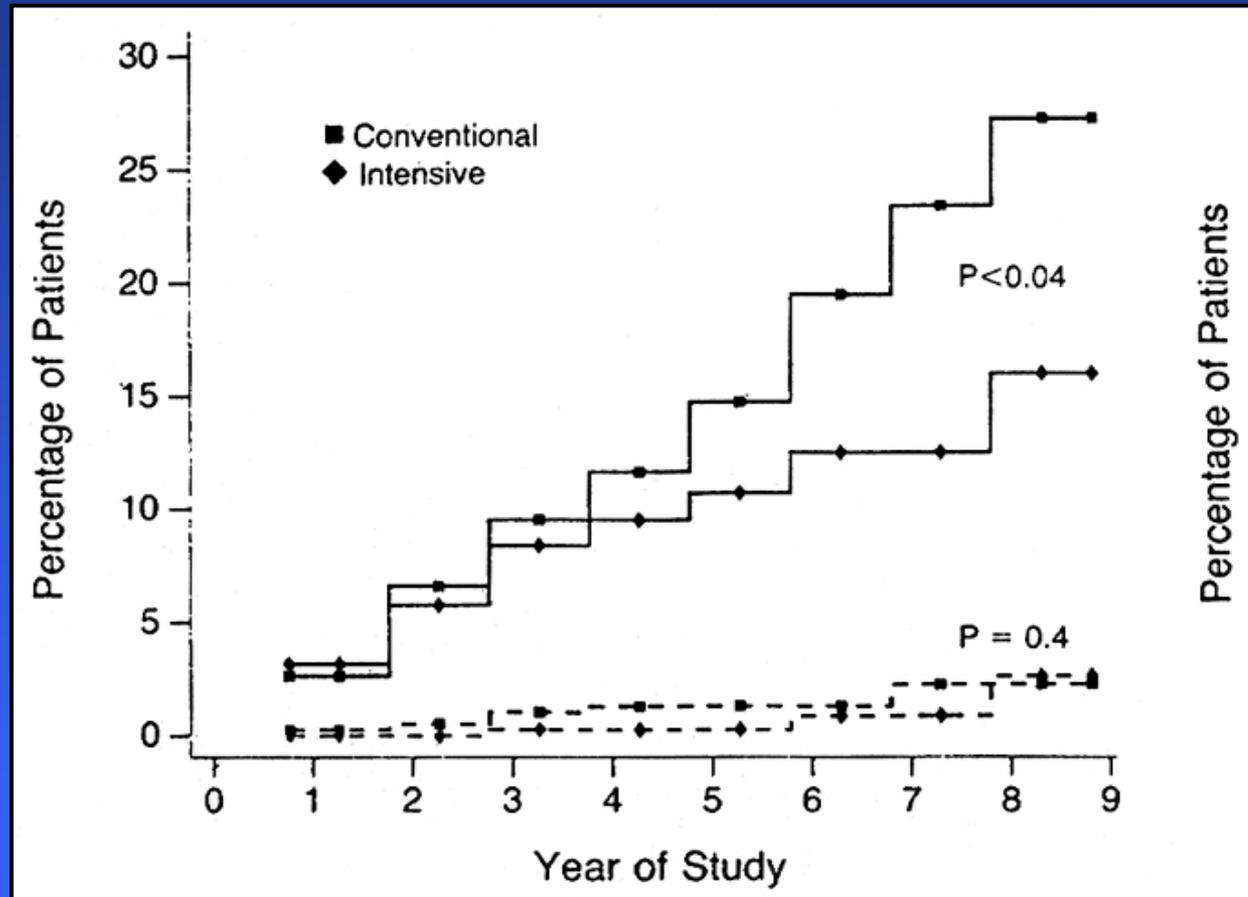


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DCCT



ACCORD

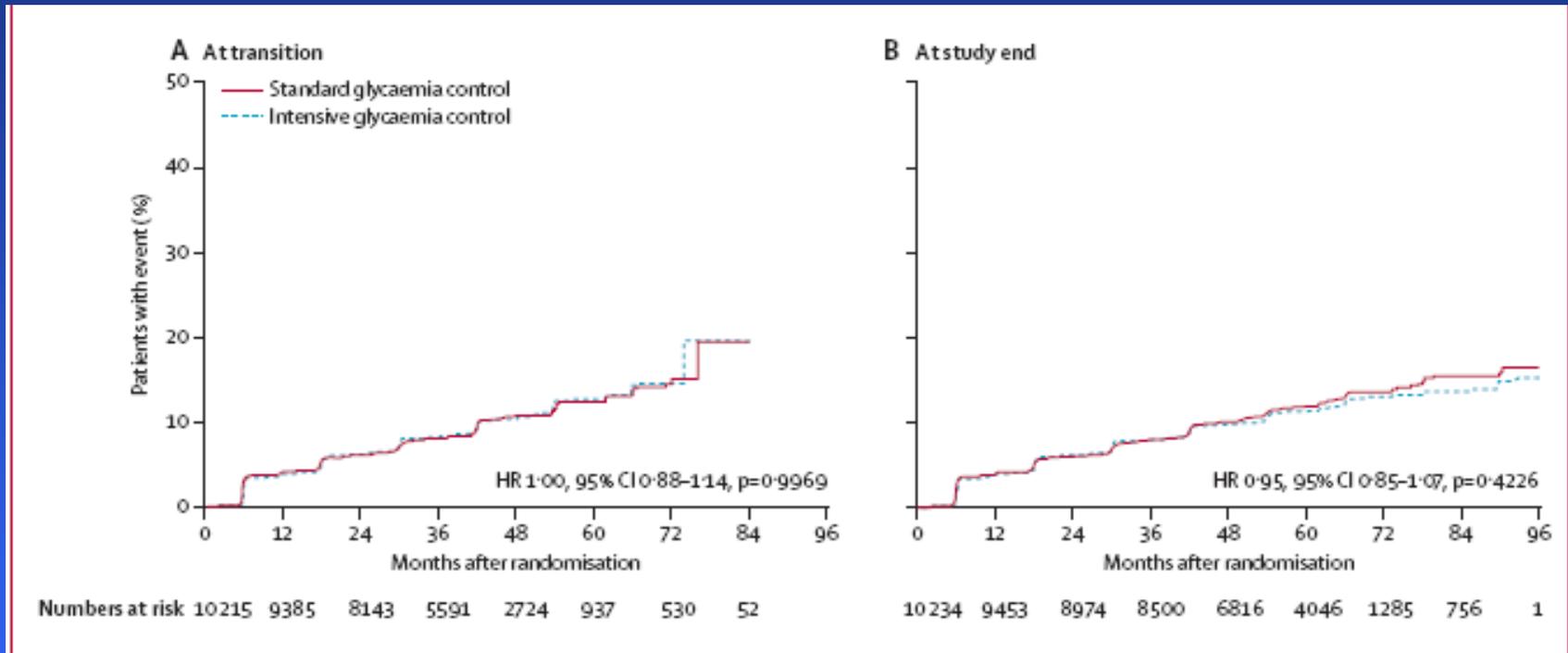


Figure 3: Kaplan-Meier plots of the microvascular primary composite outcome, by glycaemia group

The outcome was defined as development of renal failure, retinal photocoagulation, or vitrectomy to treat retinopathy. (A) Data until transition of intensive glycaemia group to standard therapy. (B) All data until end of study. Hazard ratios adjusted for baseline history of clinical cardiovascular disease and second trial treatment group assignment.

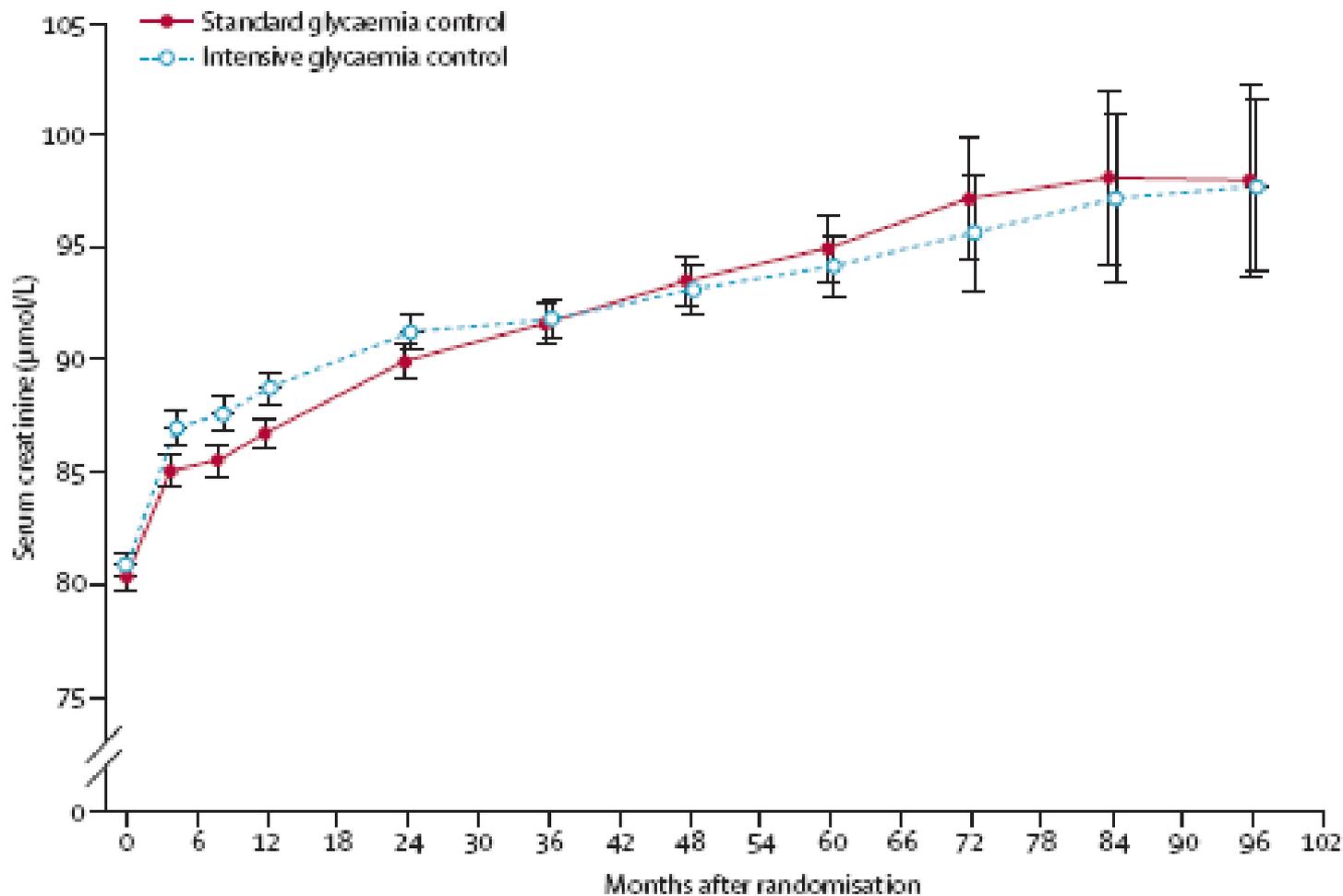
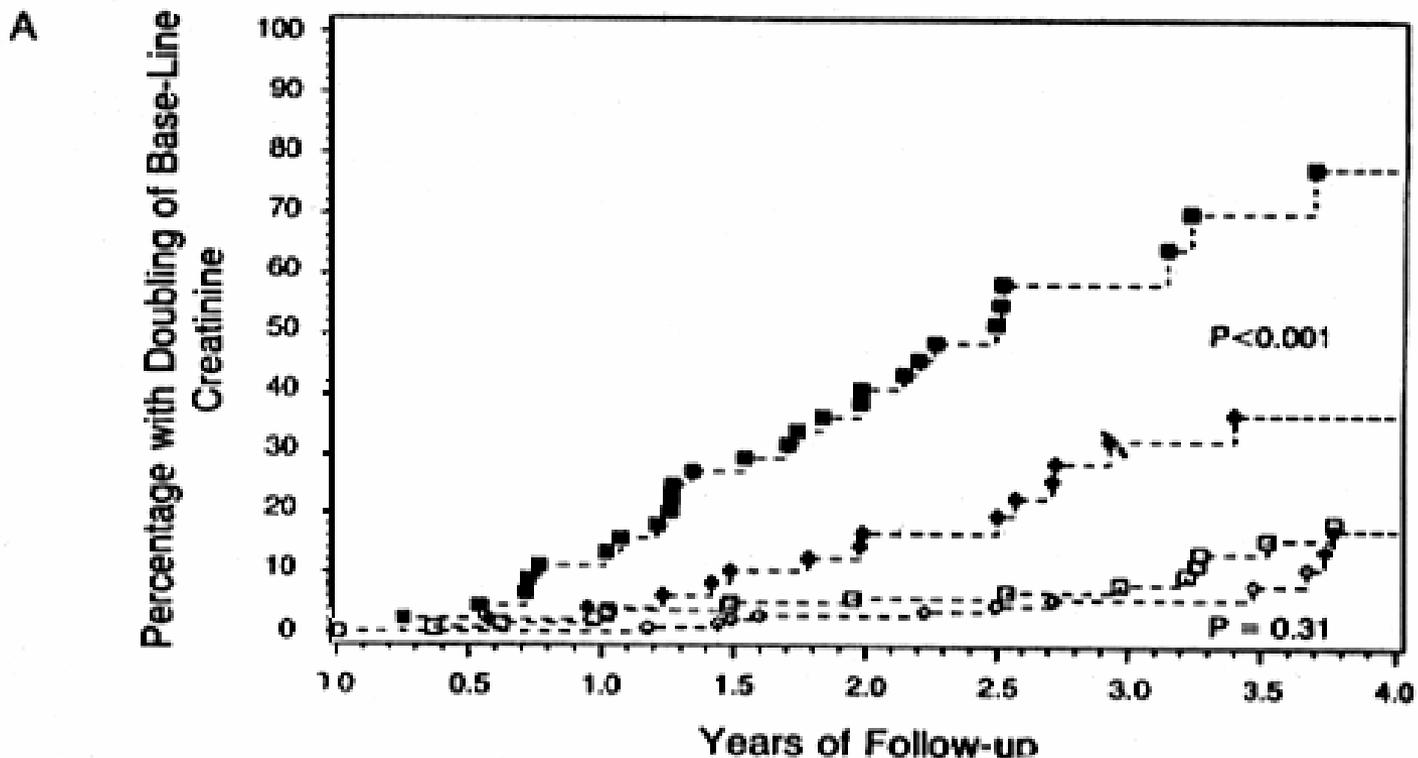


Figure 6: Mean serum creatinine levels at follow-up in intensive and standard glycaemic therapy groups. Vertical lines show \pm two standard errors of the mean.

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Creatinine ≥ 1.5 mg/dl

■ Placebo	49	44	39	32	25	15	8	4	1
◆ Captopril	53	50	46	42	37	28	17	13	3

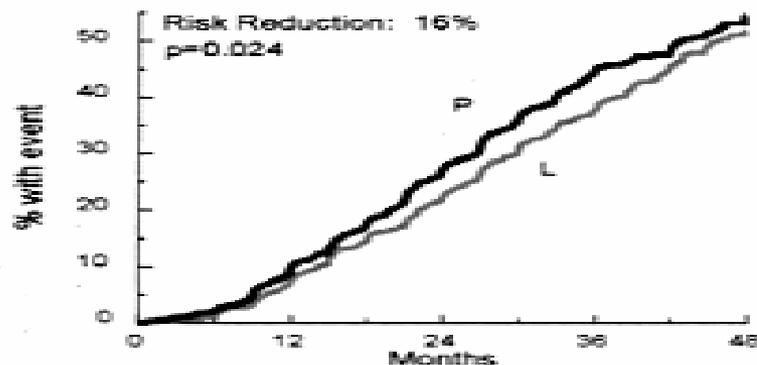
Creatinine < 1.5 mg/dl

□ Placebo	153	140	134	129	117	84	67	41	21
○ Captopril	154	149	144	138	130	92	65	37	21

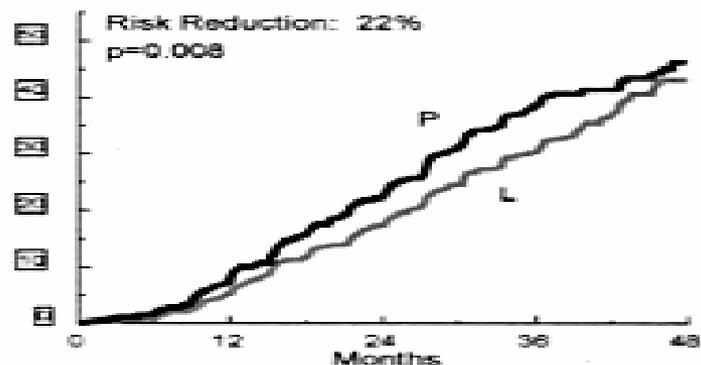
RENAAL

Primary Composite Endpoint Doubling of Serum Creatinine/ESRD/Death

Intention-to-treat analysis

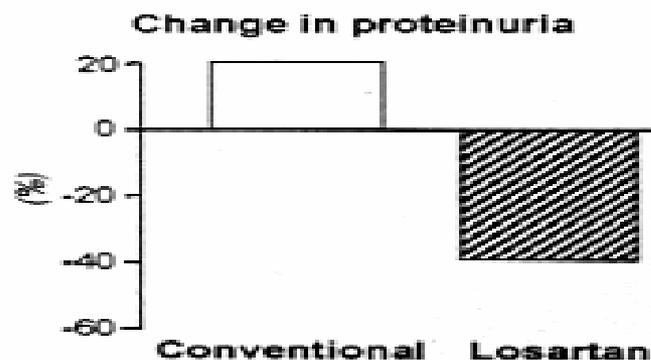
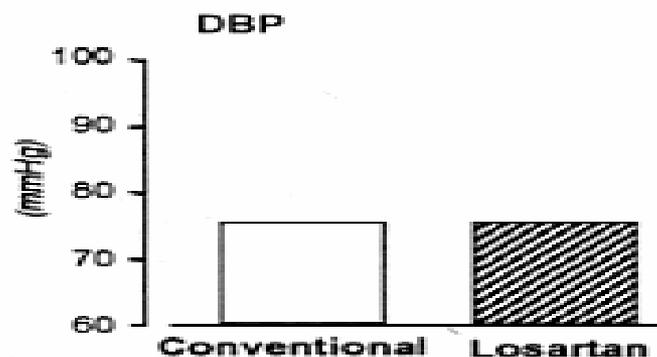


Per-protocol analysis



P (+ CT)	762	689	554	295	36
L (+ CT)	751	692	583	329	52

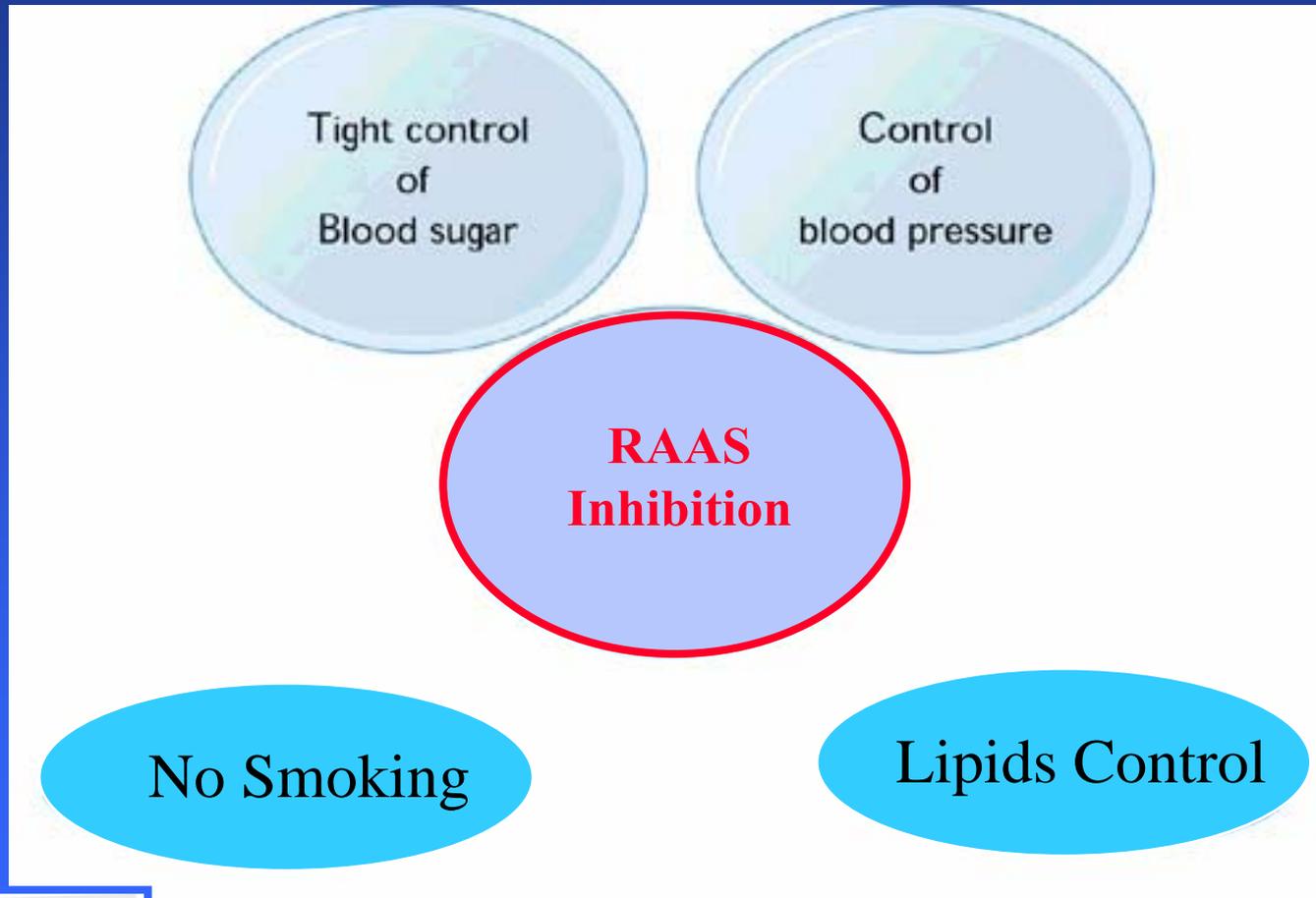
P	760	584	431	214	24
L	748	612	479	263	36



Brenner et al, 2001

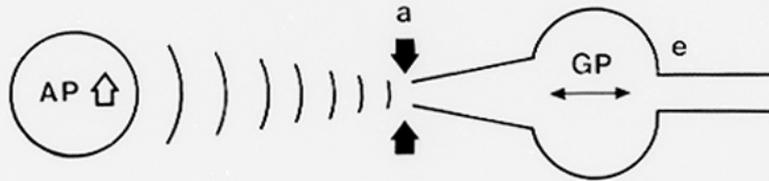
Management of Diabetic Microvascular Disease

Key Elements



GLOMERULOSCLEROSIS

HYPERTENSION : HOW?



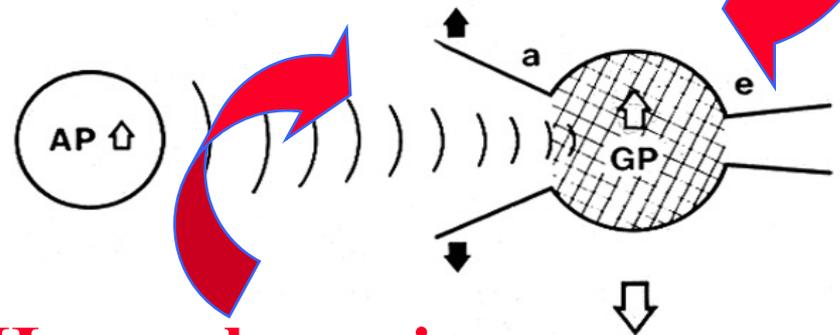
NO GLOMERULOSCLEROSIS

Afferent arteriolar vasoconstriction

Angiotensin II

GLOMERULOSCLEROSIS

HYPERTENSION



Hyperglycemia

GLOMERULOSCLEROSIS

Afferent arteriolar vasodilatation

CKD management guidelines

Parameter	Target	Agent used
BP	130/80 mmHg or 125/75 in DM and those with proteinuria.	Start with ACEI or ARBs <u>if</u> proteinuria or DM microalbuminuria – caution in the elderly and those with atherosclerosis. Monitor eGFR within 1-2 weeks of initiation, review if eGFR decreases by $\geq 15\%$, stop at $\geq 25\%$.
Proteinuria	Lowest achievable	ACEi/ ARBs
sCholesterol	Refer to national guidelines	
Lifestyle	Standard CV risk reduction measures, including salt restriction	
Avoid	NSAIDs, COX2s and radiocontrast agents	



Risk for ESRD in Type 1 Diabetes Remains High Despite Renoprotection

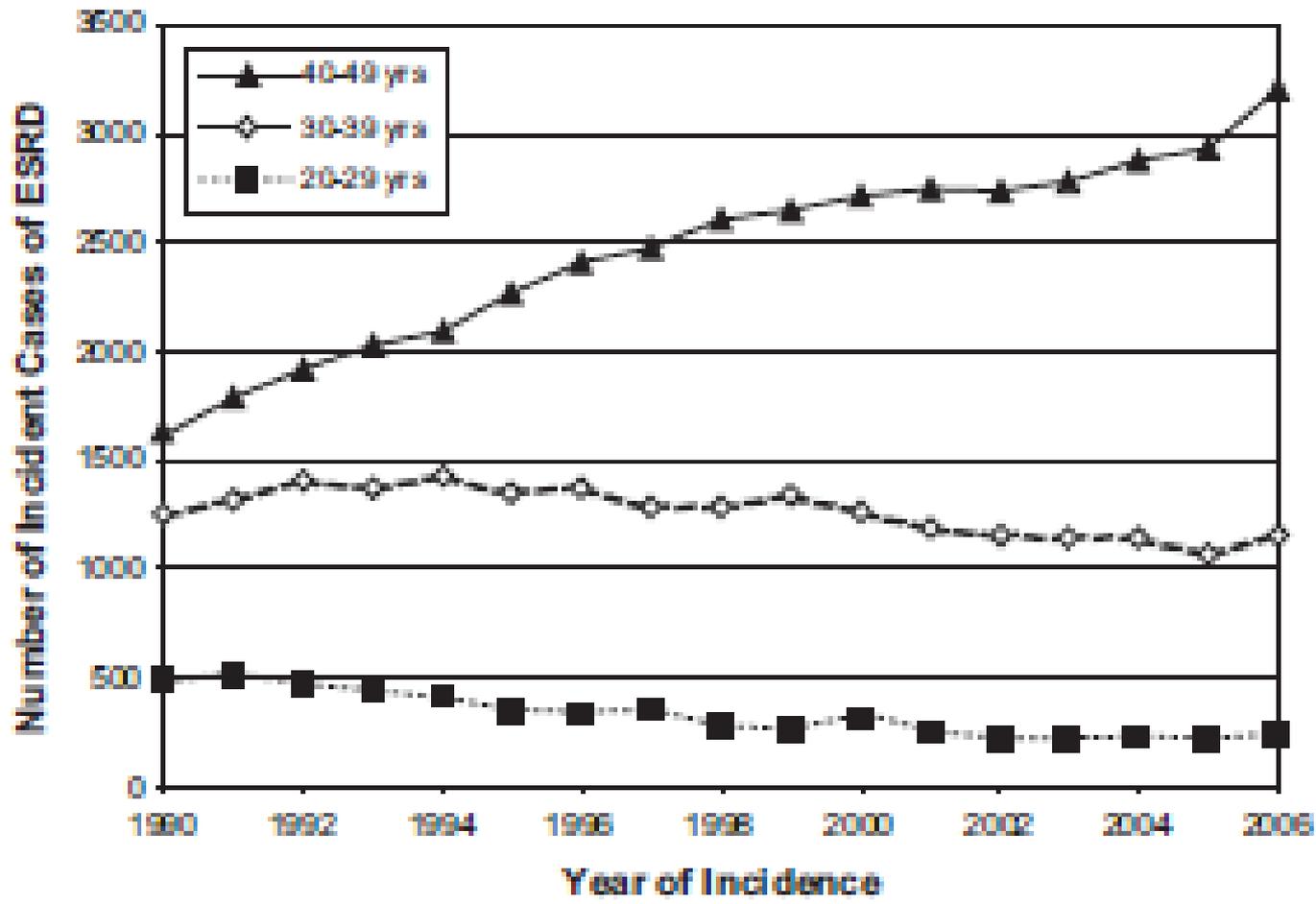
Elizabeth T. Rosolowsky,^{*†} Jan Skupien,^{*‡} Adam M. Smiles,^{*} Monika Niewczas,^{*‡} Bijan Roshan,^{*§} Robert Stanton,^{*§} John H. Eckfeldt,^{||} James H. Warram,^{*} and Andrzej S. Krolewski^{*‡}

^{*}Research and Clinic Divisions at Joslin Diabetes Center, Boston, Massachusetts; [†]Division of Endocrinology at Children's Hospital, Boston, Massachusetts; [‡]Department of Medicine at Brigham and Women Hospital and [§]Renal Division at Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; and ^{||}Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota



JASN, 2011

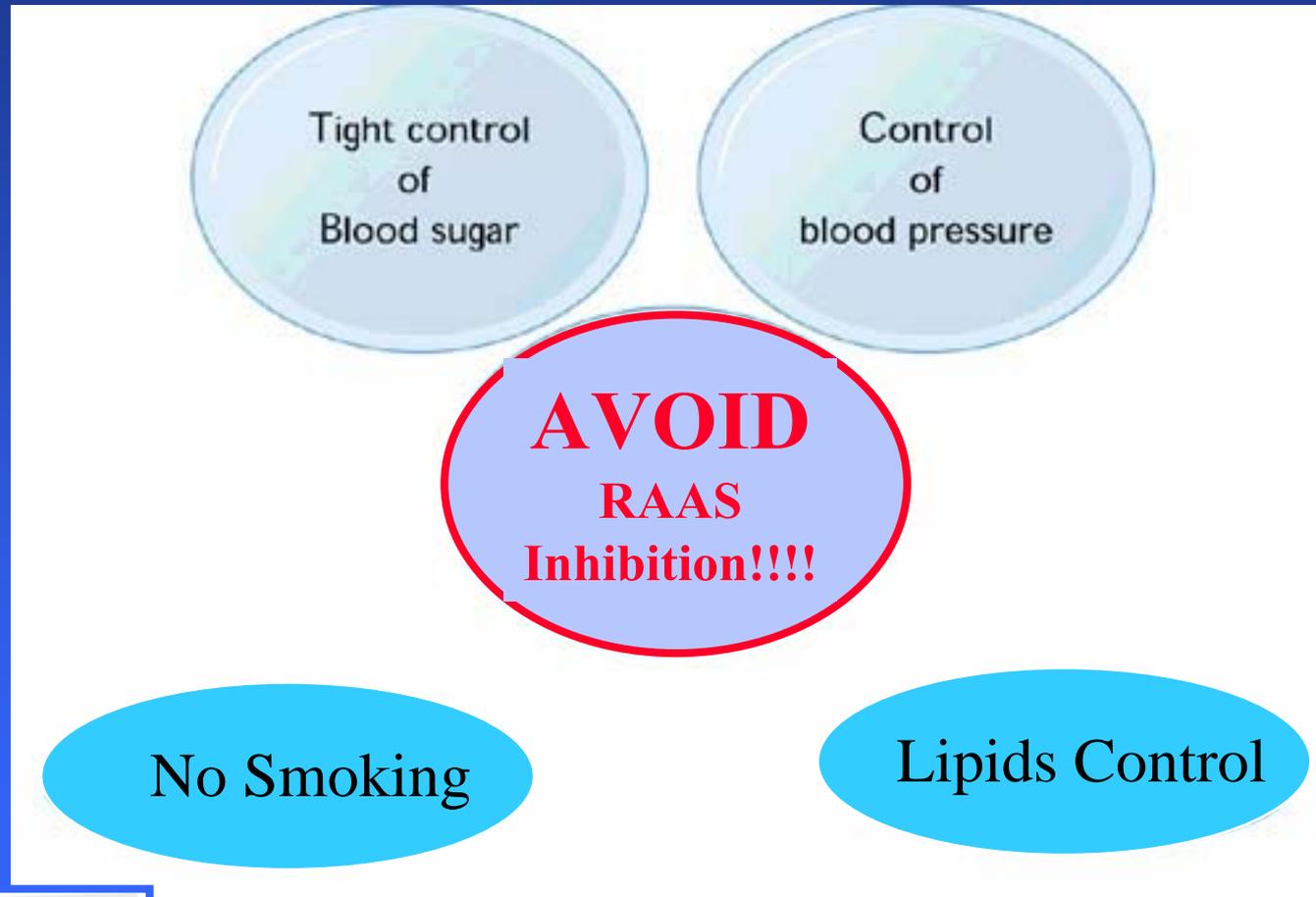






Management of Diabetic Macrovascular Disease

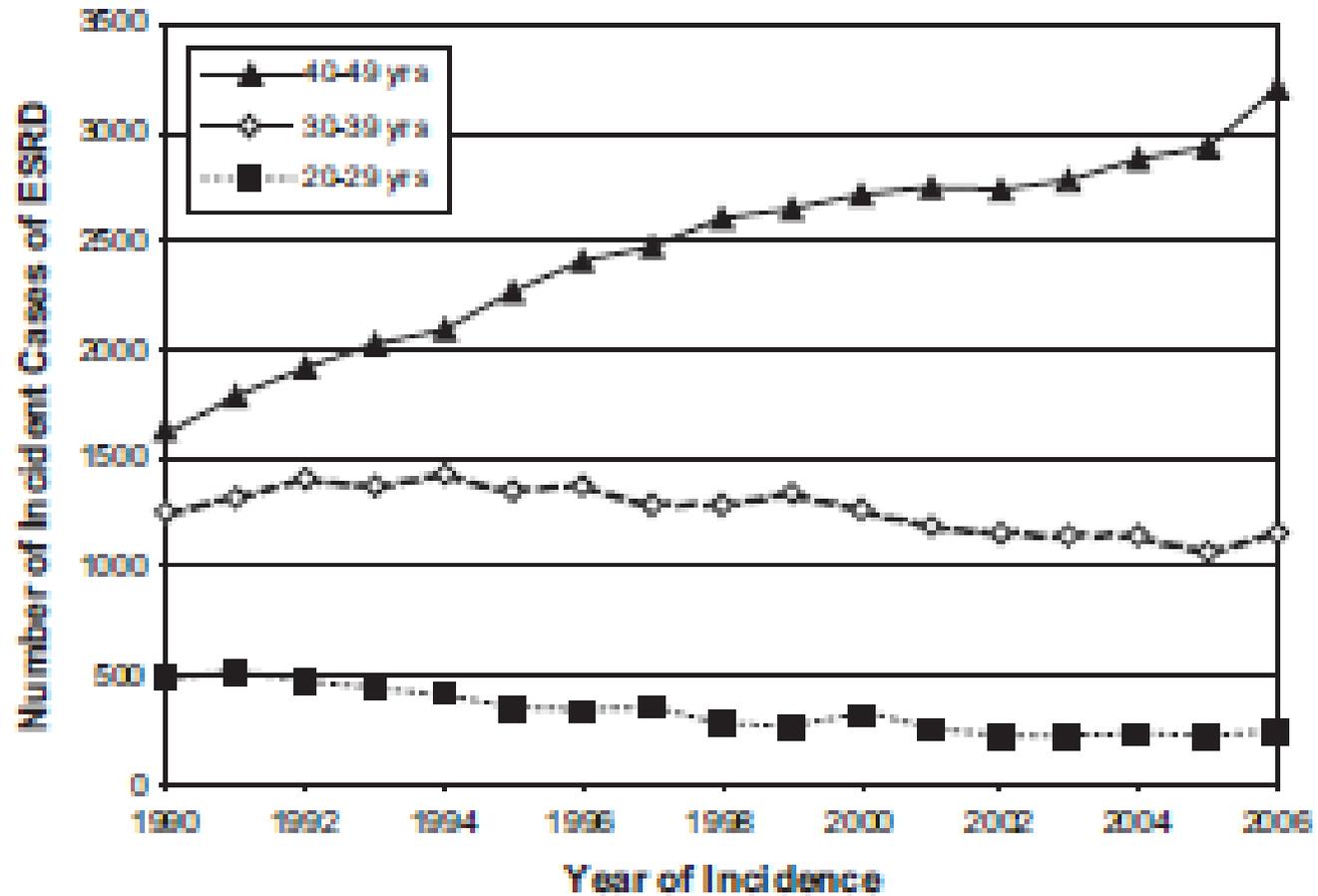
Key Elements



CKD management guidelines

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Proteinuria	Lowest achievable	ACEi/ ARBs
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ACE-inhibitor use and the long-term risk of renal failure in diabetes

S Suissa¹, T Hutchinson^{1,2}, JM Brophy^{1,3} and A Kezouh¹

¹The Departments of Epidemiology and Biostatistics and of Medicine, Division of Clinical Epidemiology, Royal Victoria Hospital, McGill University Health Centre, Montreal, Québec, Canada; ²Division of Nephrology, Royal Victoria Hospital, McGill University Health Centre, Montreal, Québec, Canada and ³Division of Cardiology, Royal Victoria Hospital, McGill University Health Centre, Montreal, Québec, Canada



ACEi in Long Term DN

Table 4 | Crude and adjusted rate ratio of renal failure for continuance of ACE inhibitor drug use during follow-up among subjects with over 3 years of follow-up

	Cases	Controls	Crude rate ratio	Adjusted ^a	
				Rate ratio	95% CI
Number of subjects	66	2618			
<i>ACE inhibitor use during follow-up among subjects with over 3 years of follow-up</i>					
First 3 years and after 3 years	19.7	4.1	8.0	7.5	2.8-20.1
First 3 years but not thereafter	3.0	2.0	2.6	2.3	0.3-17.5
Started use after 3 years only	48.5	21.1	5.1	4.9	2.4-9.8

ACE=angiotensin-converting enzyme; CI=confidence interval.

^aAdjusted, in addition to the matching factors, for concurrent use of other antihypertensive drugs and loop-diuretics, sex, continuous age, year of cohort entry, and cardiovascular disease and congestive heart failure, both before cohort entry and during follow-up.

ONTARGET

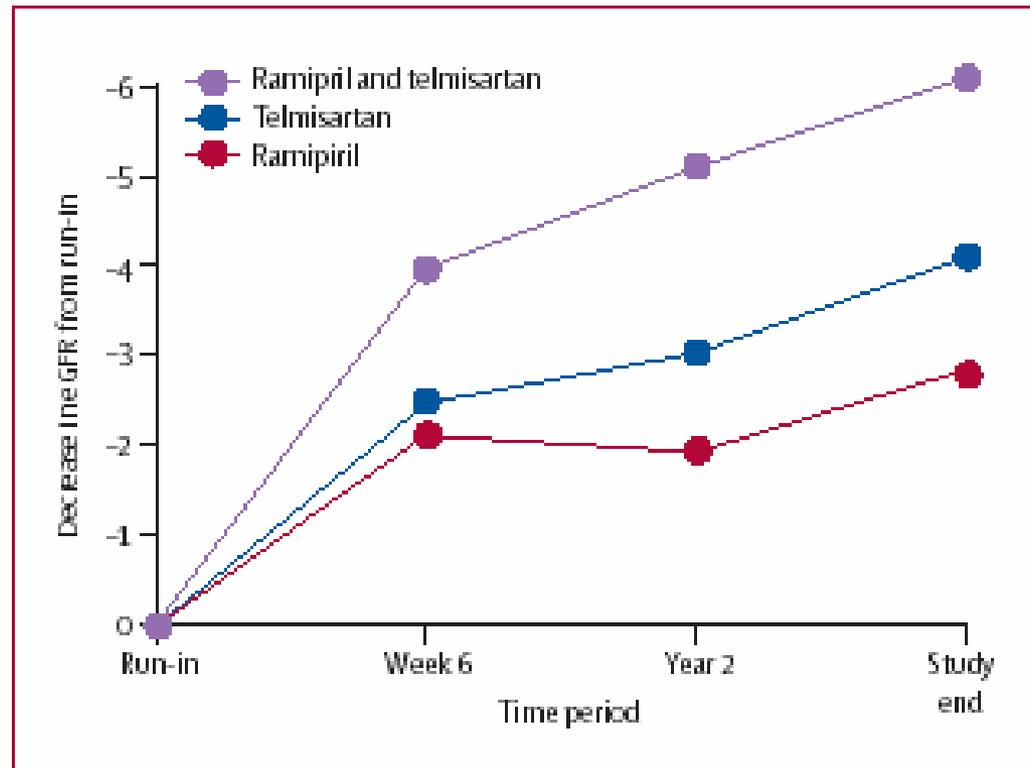
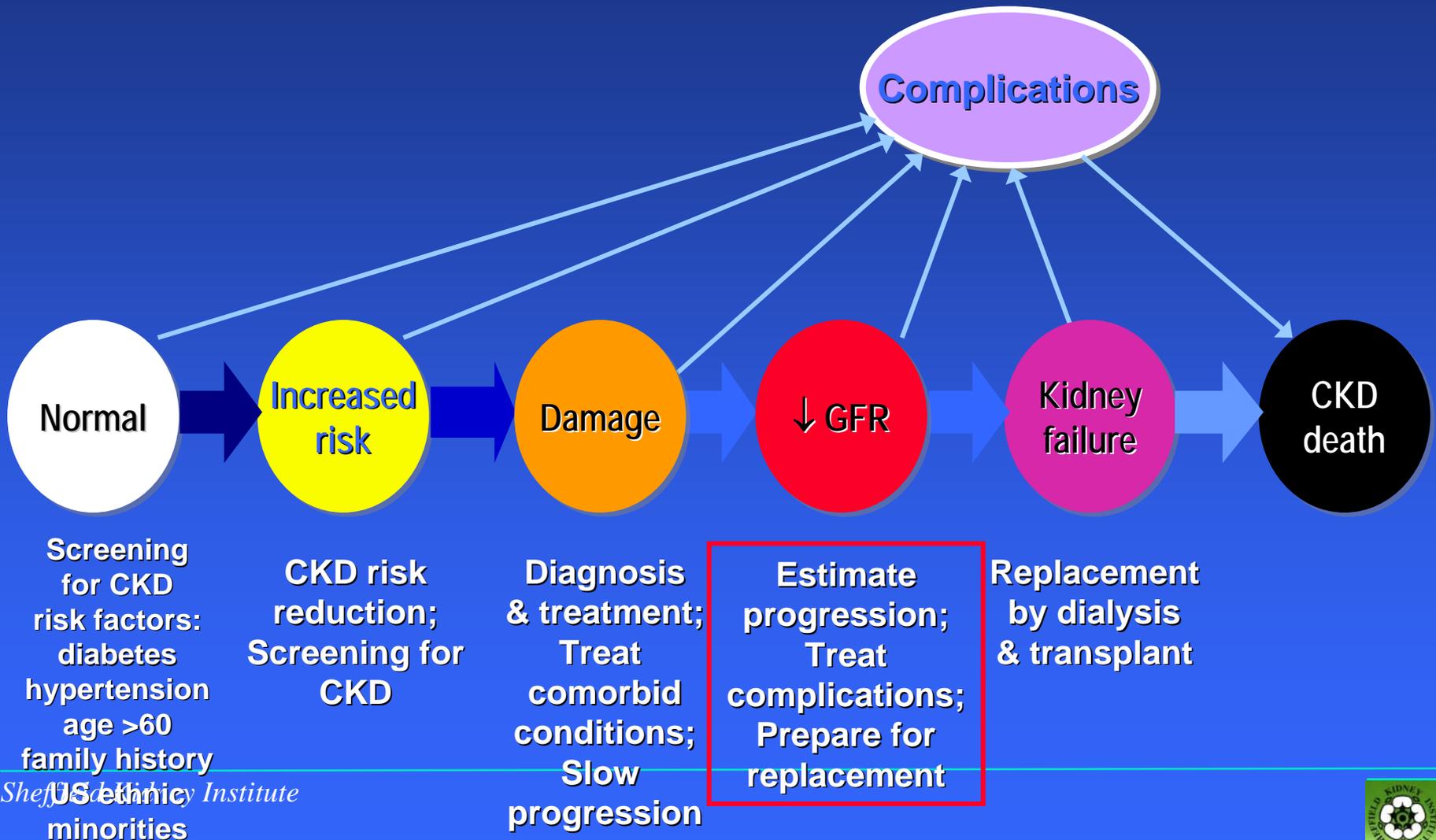
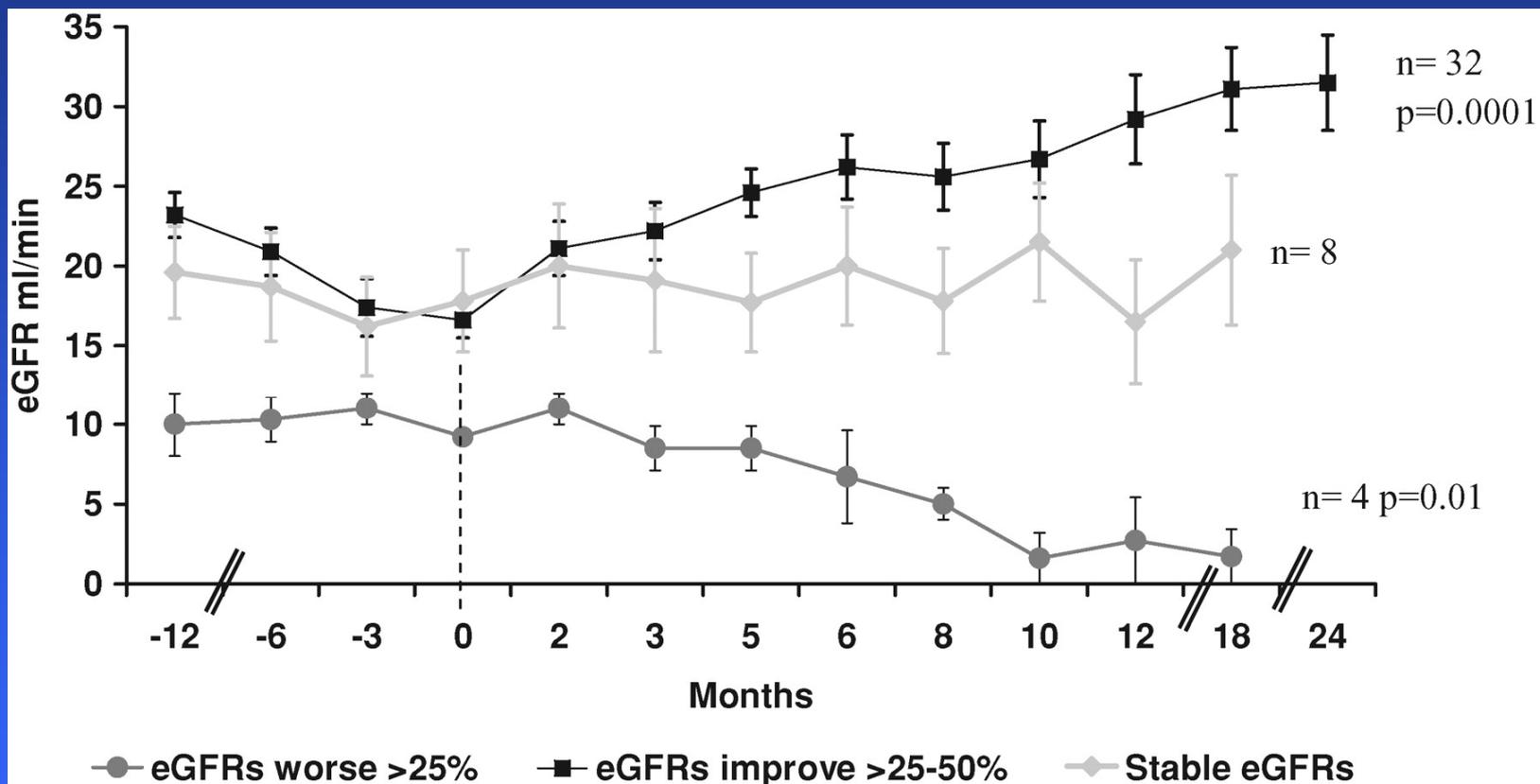


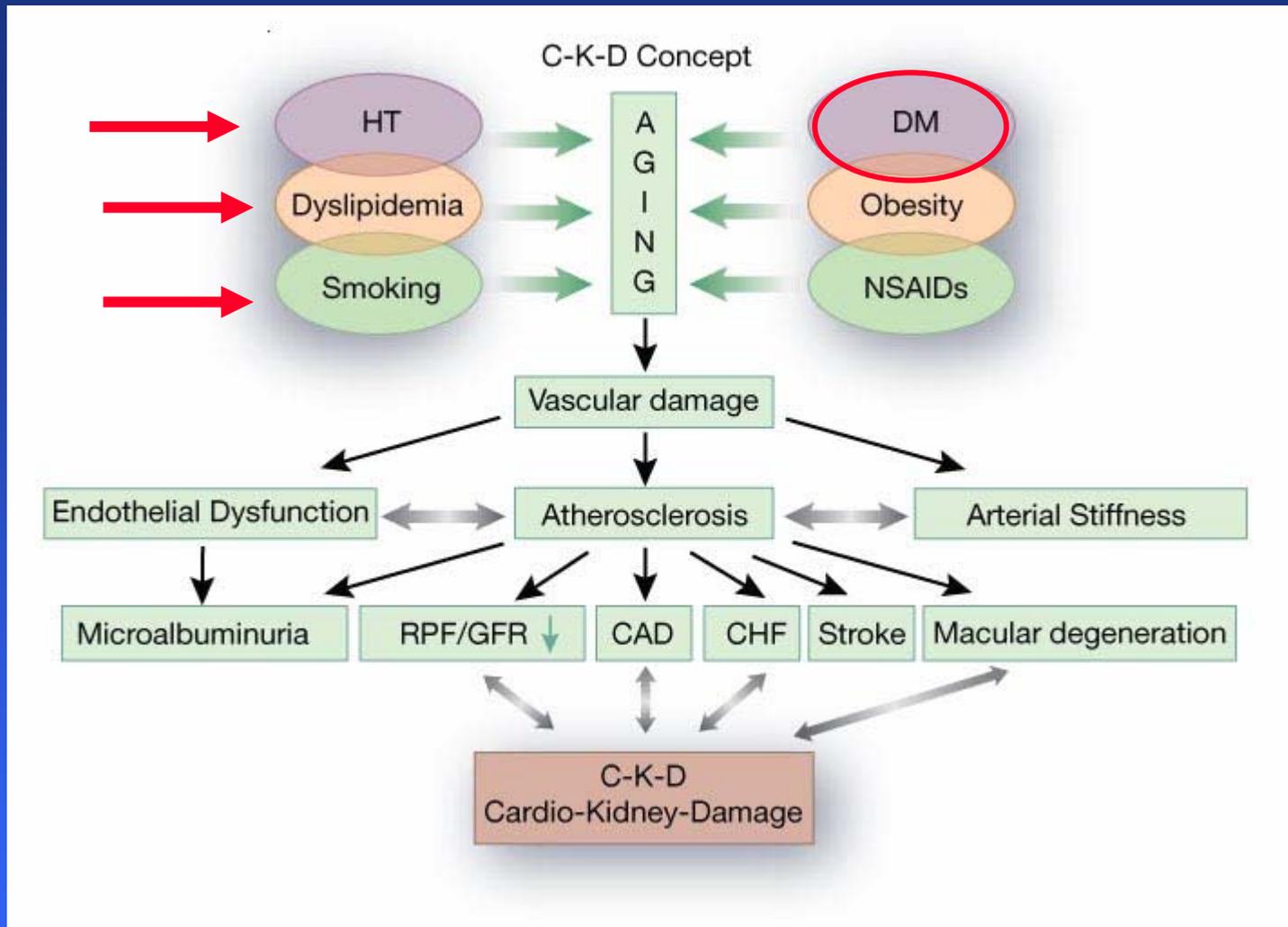
Figure 2: Decrease in estimated glomerular filtration rate (eGFR) during the trial, from baseline to study end

Conceptual Model for CKD



Changes in eGFR after stopping ACEi/ARB in patients with advanced CKD





Competing-Risk Analysis of ESRD and Death among Patients with Type 1 Diabetes and Macroalbuminuria

Carol Forsblom,^{*†} Valma Harjutsalo,^{*} Lena M. Thorn,^{*†} Johan Wadén,^{*†} Nina Tolonen,^{*†} Markku Saraheimo,^{*†} Daniel Gordin,^{*†} John L. Moran,[‡] Merlin C. Thomas,[§] and Per-Henrik Groop,^{*†§} on behalf of the FinnDiane Study Group

^{*}Folkhälsan Institute of Genetics, Folkhälsan Research Center, University of Helsinki, Helsinki, Finland; [†]Department of Medicine, Division of Nephrology, Helsinki University Central Hospital, Helsinki, Finland; [‡]The Queen Elizabeth Hospital, Adelaide, South Australia, Australia; and [§]Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia

Table 2. Competing-risk model of variables associated with the cumulative incidence of ESRD in patients with type 1 diabetes and macroalbuminuria from the FinnDiane cohort

Predictor Variables	Subhazard Ratio	[95% CI]	P
Men	1.96	1.39 to 2.76	0.001
Estimated GFR (FP) ^a	0.05	0.04 to 0.07	0.001
LDL cholesterol (FP) ^a	1.01	1.00 to 1.01	0.001
Duration of diabetes (years)	0.97	0.95 to 0.99	0.028
HbA _{1c} (%)	1.31	1.15 to 1.48	0.001
Body mass Index (FP) ^a	281	5.13 to 1548	0.006
Insulin dose (FP) ^a	0.87	0.79 to 0.97	0.010
Insulin dose (FP) ^a	0.30	0.13 to 0.69	0.005

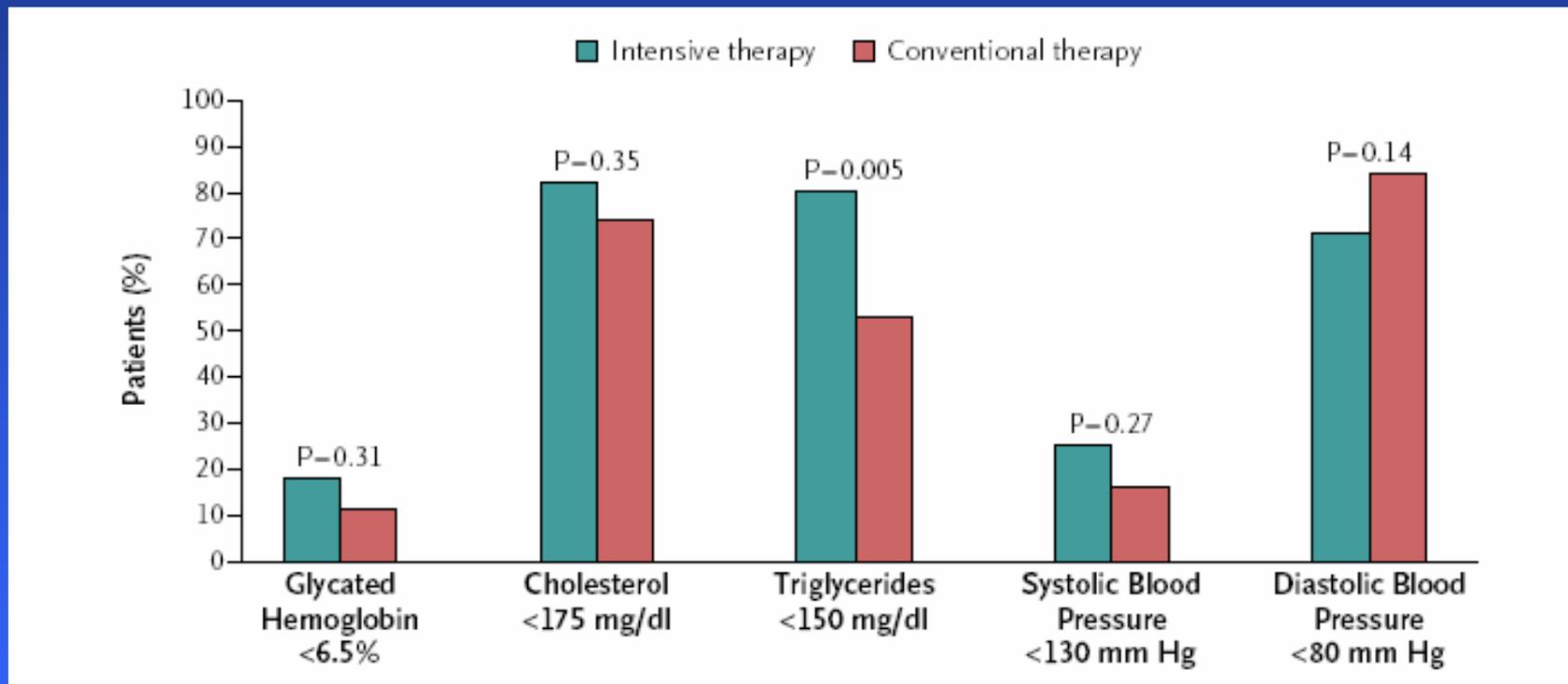
Table 3. Competing-risk model of variables associated with the cumulative incidence of death prior to ESRD in patients with type 1 diabetes and macroalbuminuria from the FinnDiane cohort. For graphical interpretation, see Figure 3

Baseline Parameter	Subhazard Ratio	[95% CI]	P > t
Age (years)	1.05	1.02 to 1.07	0.001
Total cholesterol (mmol/L)	1.75	1.17 to 2.61	0.007
Macrovascular disease (yes/no) × age	1.01	1.00 to 1.03	0.03
eGFR (standardized) ^a	2.12	1.25 to 3.58	0.005
eGFR (orthogonalized basis) ^a	1.59	0.92 to 2.76	0.09
eGFR (orthogonalized basis) ^a	0.56	0.36 to 0.88	0.01

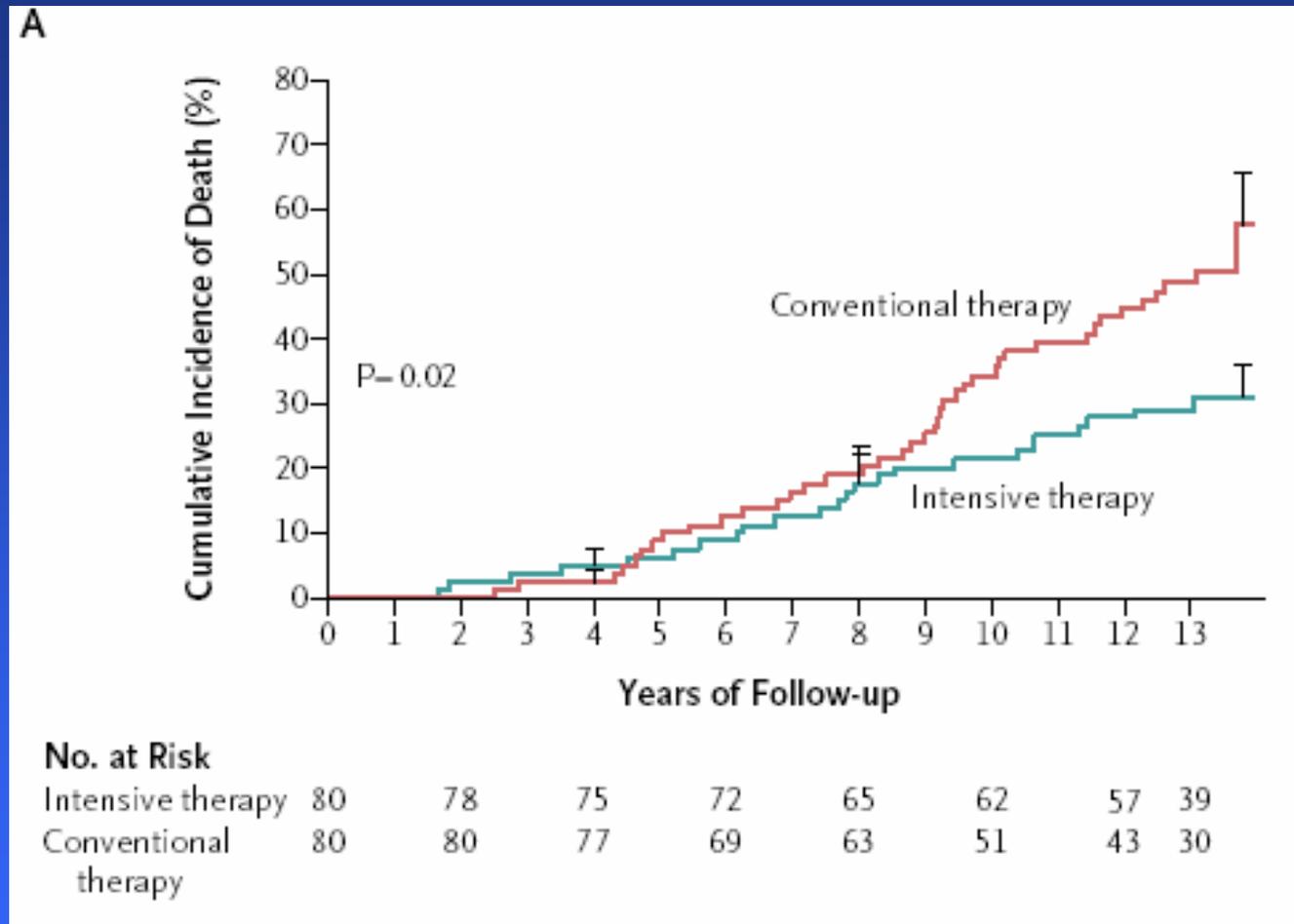
^aeGFR was parameterized as a 3rd-degree (cubic) regression spline with knots at 32.1 and 52.9. The parameterization of the spline is thus: a spline with m knots has $m + 1$ so-called basis functions (and similar degrees of freedom) and these basis functions are orthogonalized to have mean 0 and SD 1 and to be uncorrelated.²⁸

STENO 2

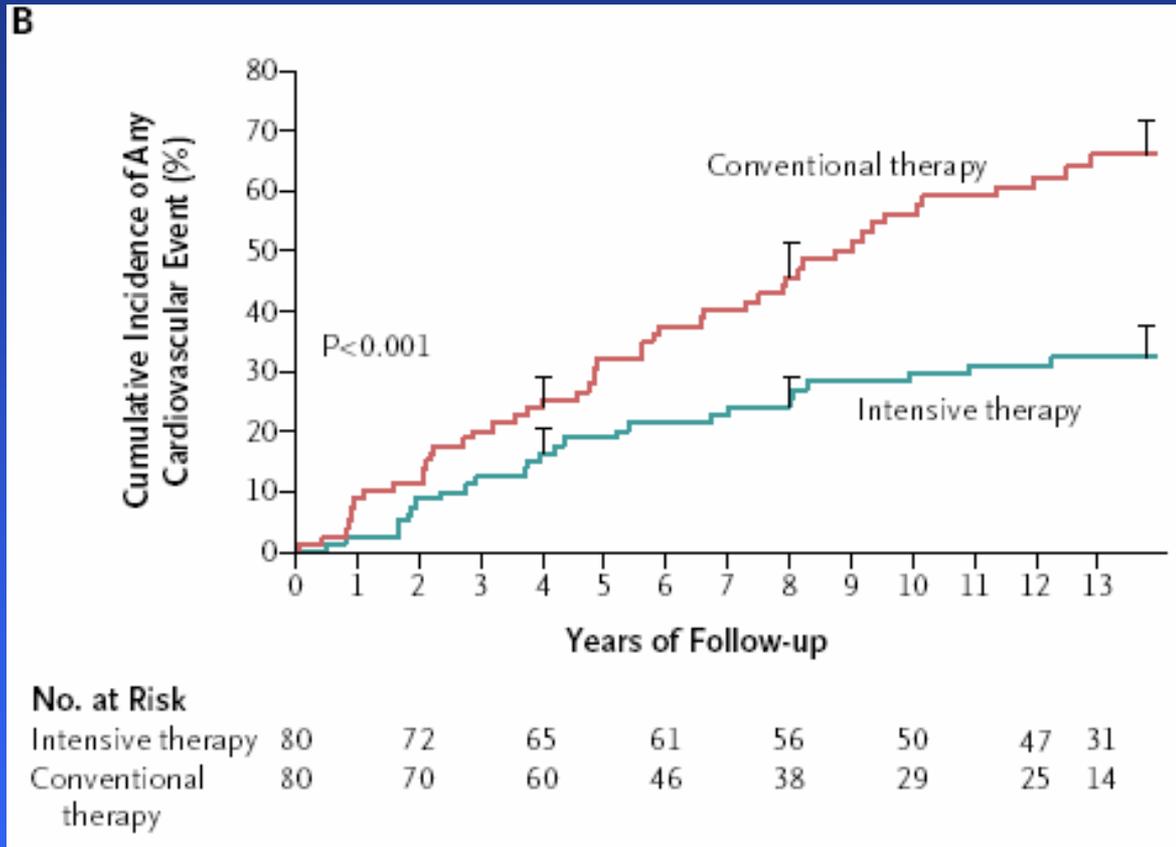
Intensive Multi-Factorial Intervention



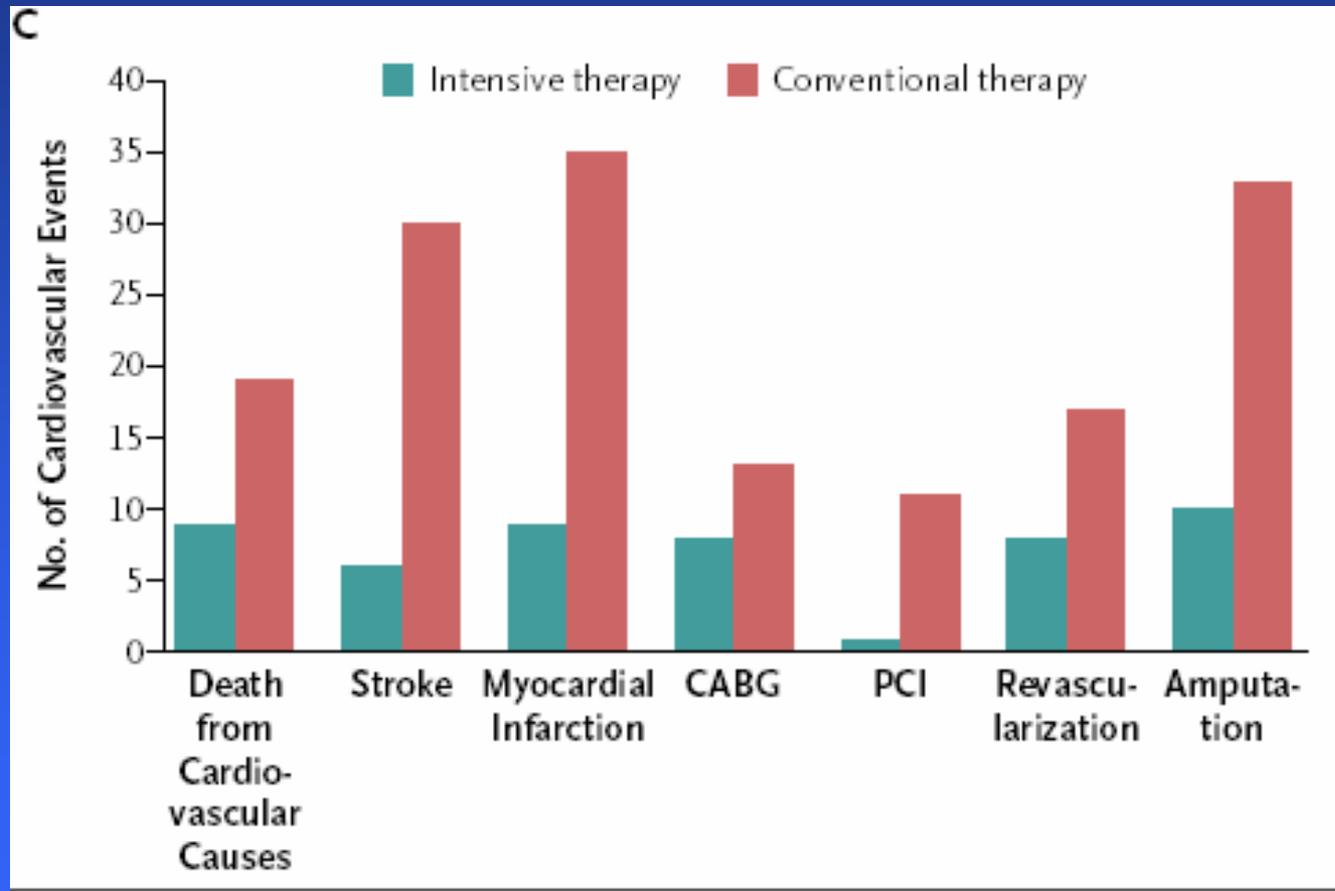
Intensive Multi-Factorial Intervention



Intensive Multi-Factorial Intervention



Intensive Multi-Factorial Intervention



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DKD

New Therapies



- **Vasoactive substances**
 - Renin antagonists DN
 - Endothelin antagonists DN
- **Growth Factors/Hormones antagonists:**
 - TGF- β 1: Neutralising antibodies, DN
 - GH: Antagonist/Somatostatin DN
- **Signal Transduction manipulations:**
 - PKC: Ruboxistaurin DN
 - PPAR γ agonists Glitazones DN
- **ECM Modulators:**
 - Heparinoids:Sulodexide DN
 - LMW heparin DN
 - MMP inhibitors XL784 DN
- **Anti-Fibrotics (miscellaneous):**
 - Pirfenidone DN

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

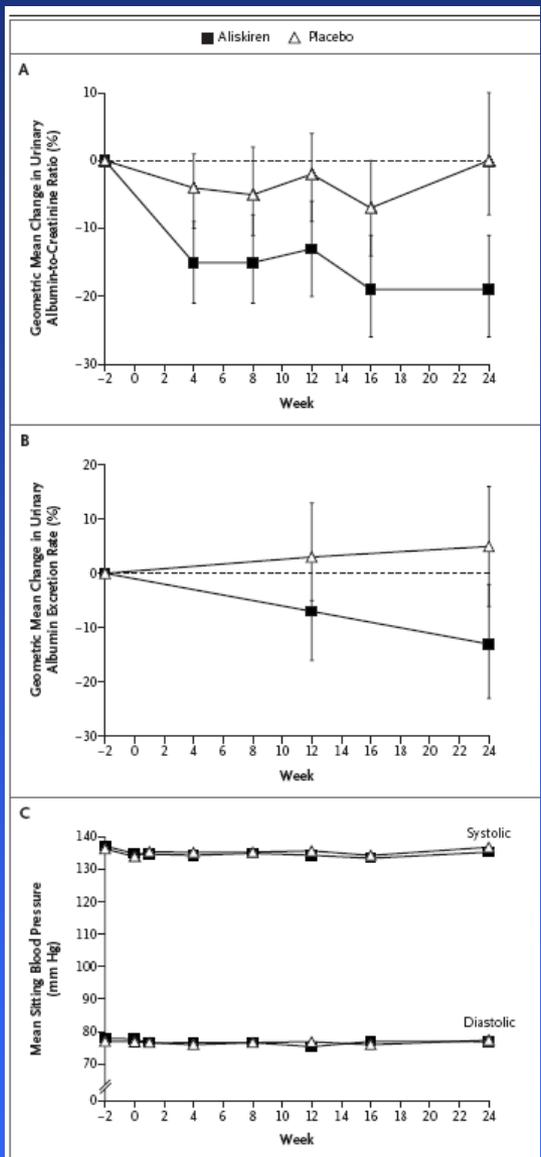
JUNE 5, 2008

VOL. 358 NO. 23

Aliskiren Combined with Losartan in Type 2 Diabetes
and Nephropathy

Hans-Henrik Parving, M.D., D.M.Sc., Frederik Persson, M.D., Julia B. Lewis, M.D., Edmund J. Lewis, M.D.,
and Norman K. Hollenberg, M.D., Ph.D., for the AVOID Study Investigators*





Avosentan for Overt Diabetic Nephropathy

Johannes F.E. Mann,^{*} Damian Green,[†] Kenneth Jamerson,[‡] Luis M. Ruilope,[§]
Susan J. Kuranoff,^{||} Thomas Littke,^{||} and Giancarlo Viberti,[¶] for the ASCEND Study Group

^{*}Schwabing General Hospital, and Department of Medicine IV, University of Erlangen and KfH Kidney Centre, Munich, Germany; [†]Quintiles Ltd., Strasbourg, France; [‡]University of Michigan, Ann Arbor, Michigan; [§]Hospital 12 de Octubre, Madrid, Spain; ^{||}Speedel Pharma Ltd., Basel, Switzerland; and [¶]King's College London School of Medicine, Guy's Hospital, London, United Kingdom

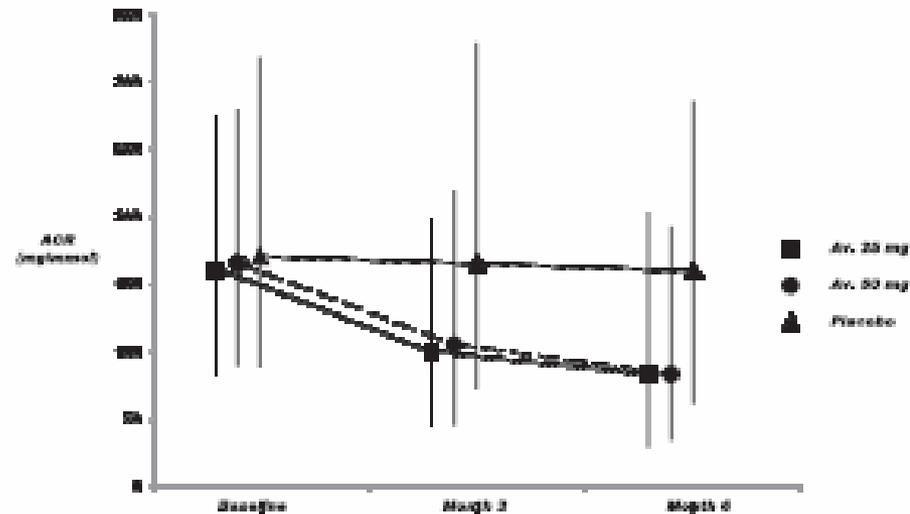


Figure 3. Urine ACR changed significantly ($P < 0.0001$; see Table 3) in the avosentan (av)-treated groups during the first 6 months of the trial. Medians and interquartile ranges are given. Similar differences were found for fractional excretion of urine albumin (see Supplemental Appendix 2).

J Am Soc Nephrol 21: 527–535, 2010

Mann et al, 2010

Addition of Atrasentan to Renin-Angiotensin System Blockade Reduces Albuminuria in Diabetic Nephropathy

Donald E. Kohan,^{*} Yili Pritchett,[†] Mark Molitch,[‡] Shihua Wen,[†] Tushar Garimella,[†] Paul Audhya,[†] and Dennis L. Andress[†]

^{*}Division of Nephrology, Department of Medicine, University of Utah Health Sciences Center, Salt Lake City, UT; [†]Abbott Laboratories, Abbott Park, IL; and [‡]Division of Endocrinology, Metabolism and Molecular Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL



JASN, 2011



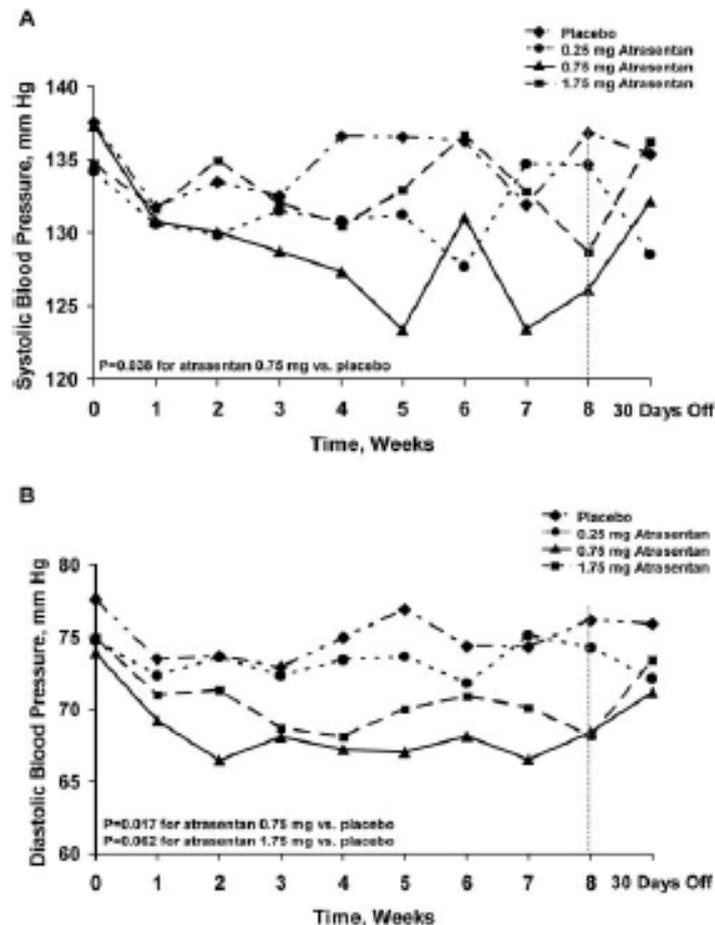


Figure 4. Atrasentan affects longitudinal measures of BP by repeated-measures analysis. Systolic BP was reduced in the 0.75-mg dose ($P = 0.038$ versus placebo by repeated-measures analysis). Diastolic BP was reduced in the 0.75-mg dose ($P = 0.017$ versus placebo by repeated-measures analysis). BP values returned toward baseline after 30 days from drug discontinuation.

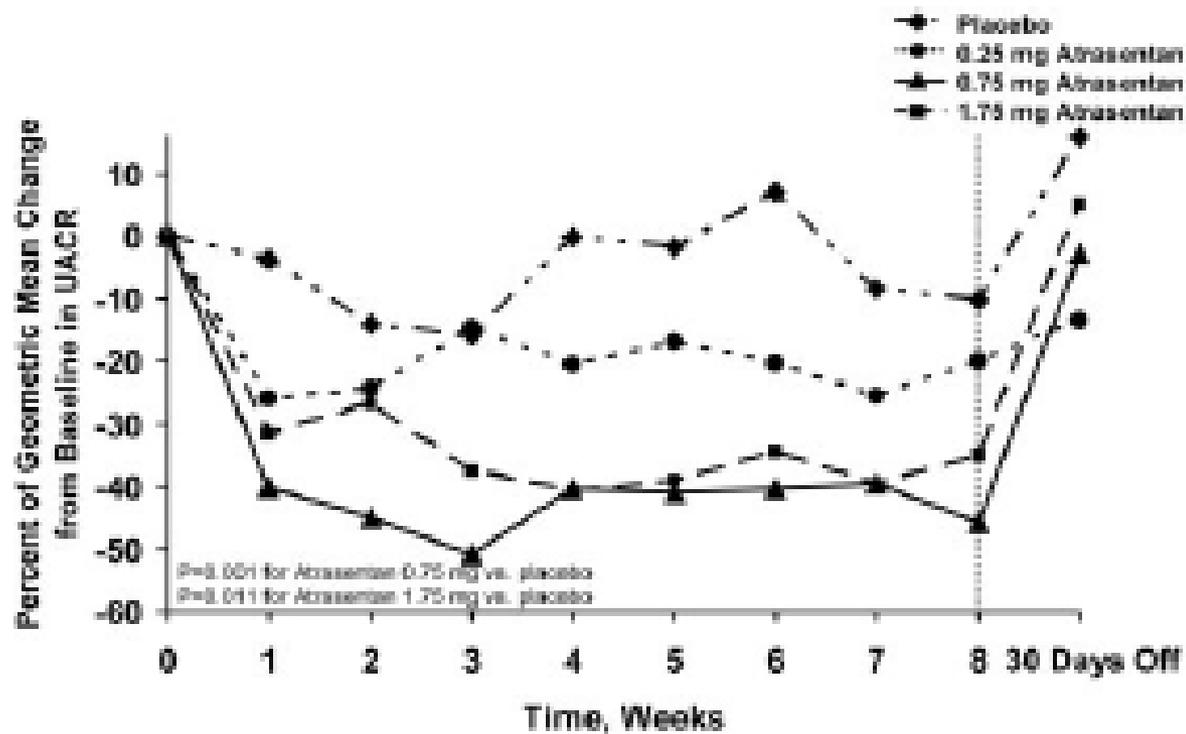


Figure 2. Atrasentan treatment significantly reduces albuminuria. Effect of atrasentan on change in UACR from baseline. Significant reductions in UACR were seen with the 0.75-mg dose ($P = 0.001$ versus placebo by repeated measures analysis) and 1.75-mg dose ($P = 0.011$ versus placebo by repeated-measures analysis). UACR returned toward baseline values after 30 days from drug discontinuation.

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Original Article

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Effects of sulodexide in patients with type 2 diabetes and persistent albuminuria

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VITAL

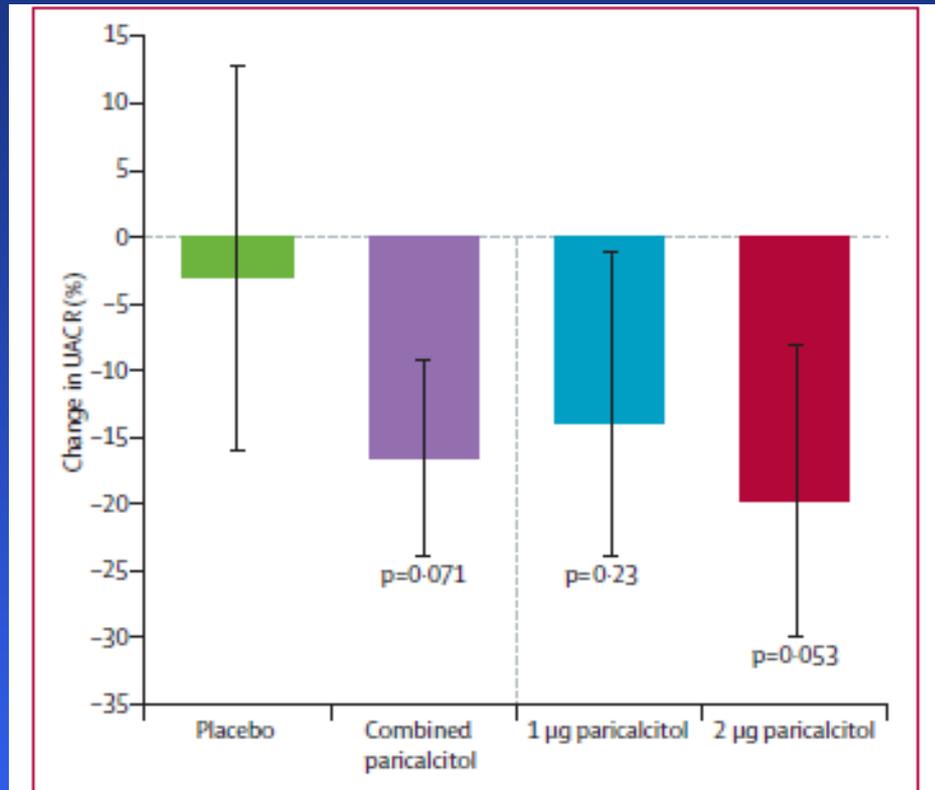


Figure 2: Change in urinary albumin-to-creatinine ratio from baseline to the last measurement during treatment

Error bars represent 95% CIs. p values are for the comparison of paricalcitol versus placebo. UACR=urinary albumin-to-creatinine ratio.

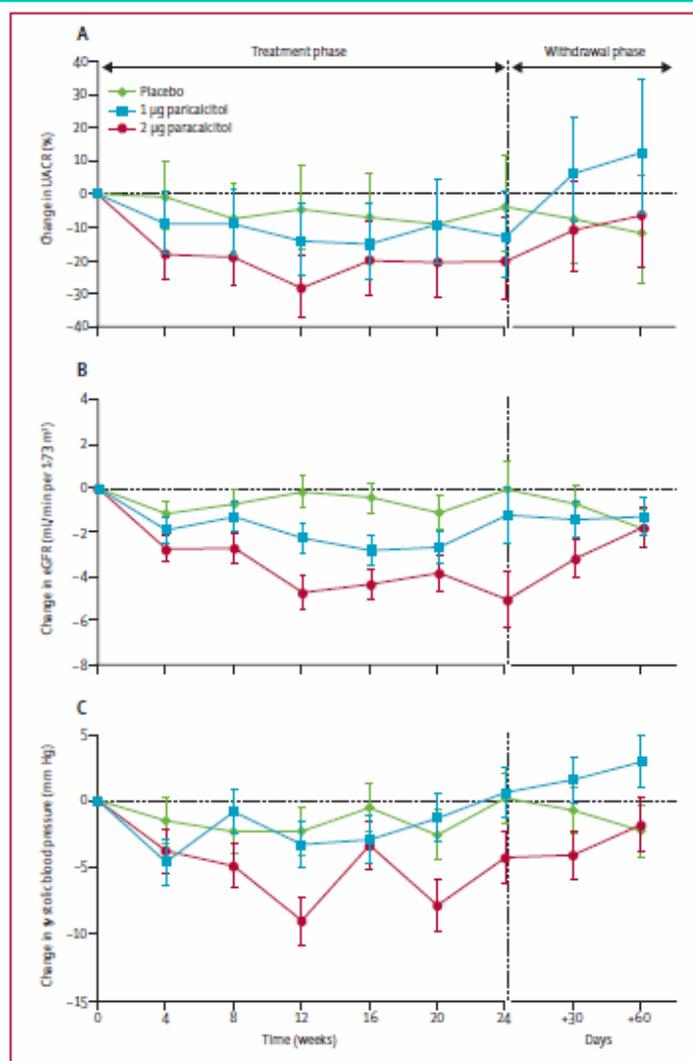


Figure 3: Change in urinary albumin-to-creatinine ratio, estimated glomerular filtration rate, and systolic blood pressure during treatment and withdrawal. Error bars represent 95% CIs in part A, and SEs in parts B and C. UACR-urinary albumin-to-creatinine ratio. eGFR-estimated glomerular filtration rate.

Pirfenidone for Diabetic Nephropathy

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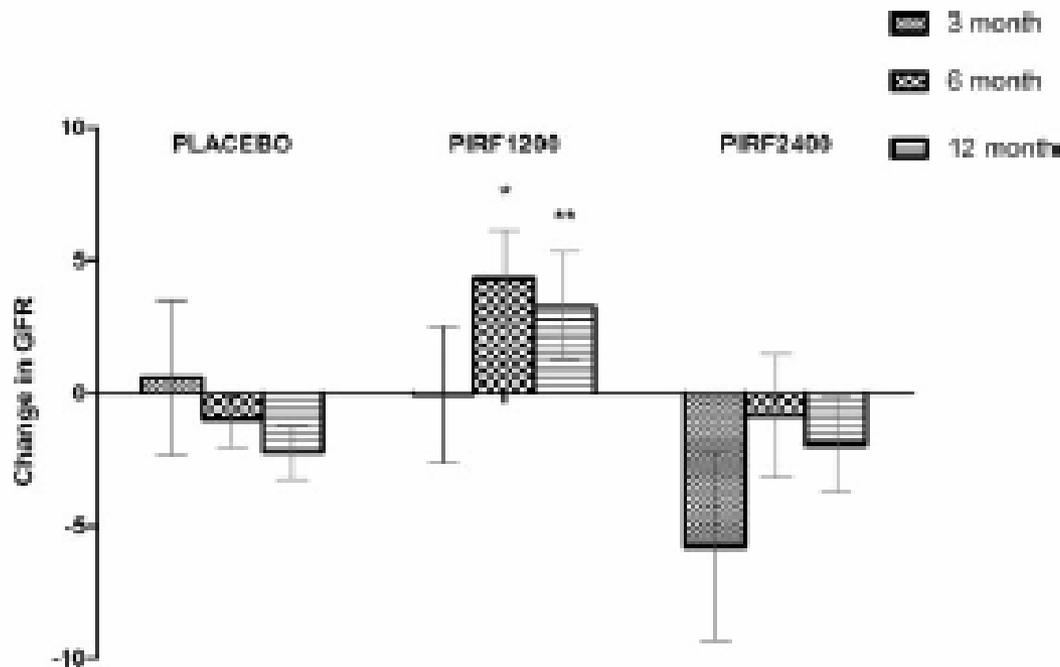


Figure 1. Pirfenidone at 1200 mg/d, but not 2400 mg/d, improves eGFR from baseline. The change in eGFR from baseline of the completers in the three groups: PLACEBO (placebo group; $n = 21$), PIRF1200 (pirfenidone 1200-mg group; $n = 17$), and PIRF2400 (pirfenidone 2400-mg group; $n = 14$) at 3, 6, and 12 months. Data are expressed as mean \pm SEM, * $P = 0.02$ when compared with placebo at 6 months, and ** $P = 0.026$ when compared with placebo at 12 months.

- **Vasoactive substances**
 - Renin antagonists DN
 - Endothelin antagonists DN
- **Growth Factors/Hormones antagonists:**
 - TGF- β 1: Neutralising antibodies, DN
 - GH: Antagonist/Somatostatin DN
- **Signal Transduction manipulations:**
 - PKC: Ruboxistaurin DN
 - PPAR γ agonists Glitazones DN
- **ECM Modulators:**
 - Heparinoids:Sulodexide DN
 - LMW heparin DN
 - MMP inhibitors XL784 DN
- **Anti-Fibrotics (miscellaneous):**
 - Pirfenidone DN



DKD: Challenging dogmas

