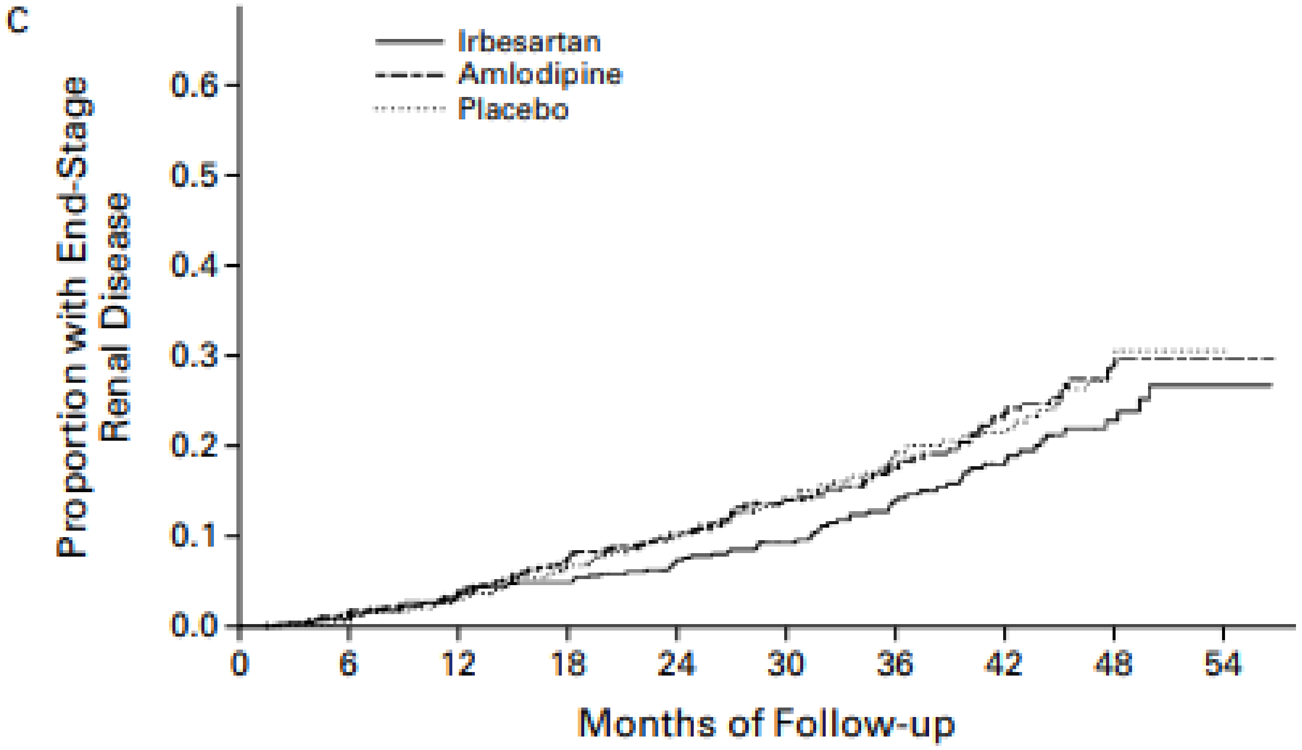
New biomarkers in CKD (Chronic Kidney Disease)

Ioannis Petrakis, MD. Ph.D., Consultant nephrologist, Department of Nephrology, University General Hospital, Heraklion, Crete, Greece.

EFFECT OF IRBESARTAN ON NEPHROPATHY DUE TO TYPE 2 DIABETES



No. at Risk

Irbesartan	579	549	523	501	418	327	234	162	78	7
Amlodipine	565	538	510	482	408	310	221	152	58	7
Placebo	568	542	517	487	418	302	205	141	63	2

Even patients (;) in the treatment arm could progress in CKD st. 5 – HD/PD

Lewis et al NEJM 2017

Clinical case

- 65 year old lady with CKD st 3 A2 (DM t II, AH), CAD.
- Cholecystitis (cholecystostomy due to recent AMI) → AKI st III → renal replacement therapy Δt=4 months →
- CKD st 4 A2 → Cholecystectomy ?
- Relevant question : Peri/post-operative prognosis concerning her renal function?

In clinical practice:

- BP
- Serum Cr
- Urinary Protein
- **Renal biopsy**

Renal biopsy

Biopsy cylinder

Clinical decision

~0,2-0,05 % renal mass

?

Biomarkers

A biomarker is **any substance**, **structure** or **process** that can be **measured** in the **body** or its **products** and **influences** or **predicts** the incidence of **outcome or disease**.

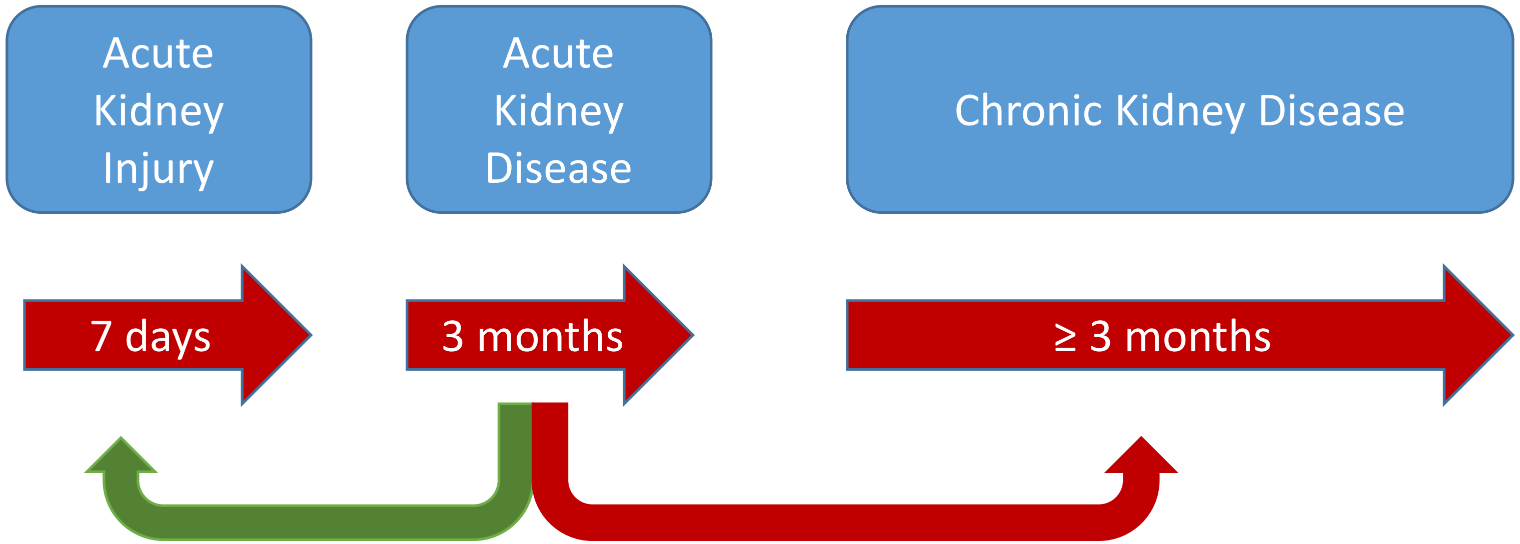
Chronic Kidney Disease (*CKD*)

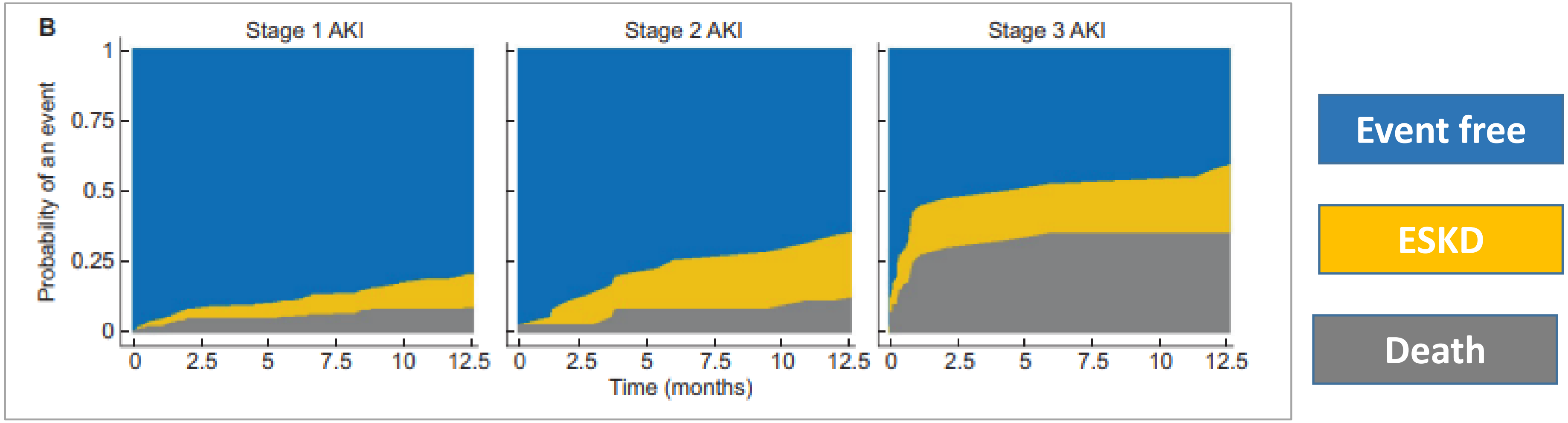
- Presence of **renal (structural) disease**
- **Renal function deterioration**
- **Independent of Aetiology**
- **Dt ≥ 3 months**

CKD: 10th cause reducing life expectancy

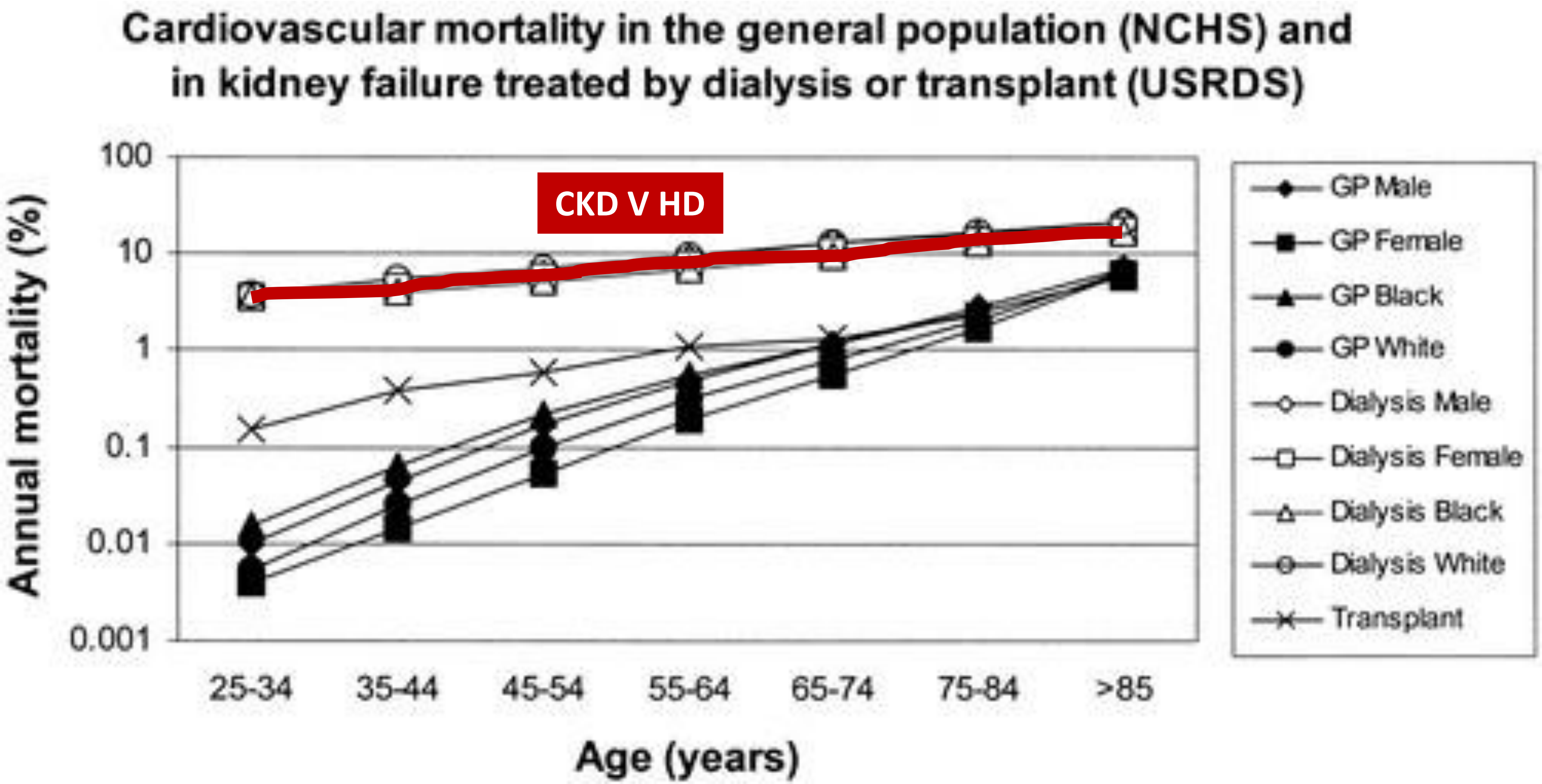
Kidney International Supplements (2022) 12, 7-11

Prognosis...

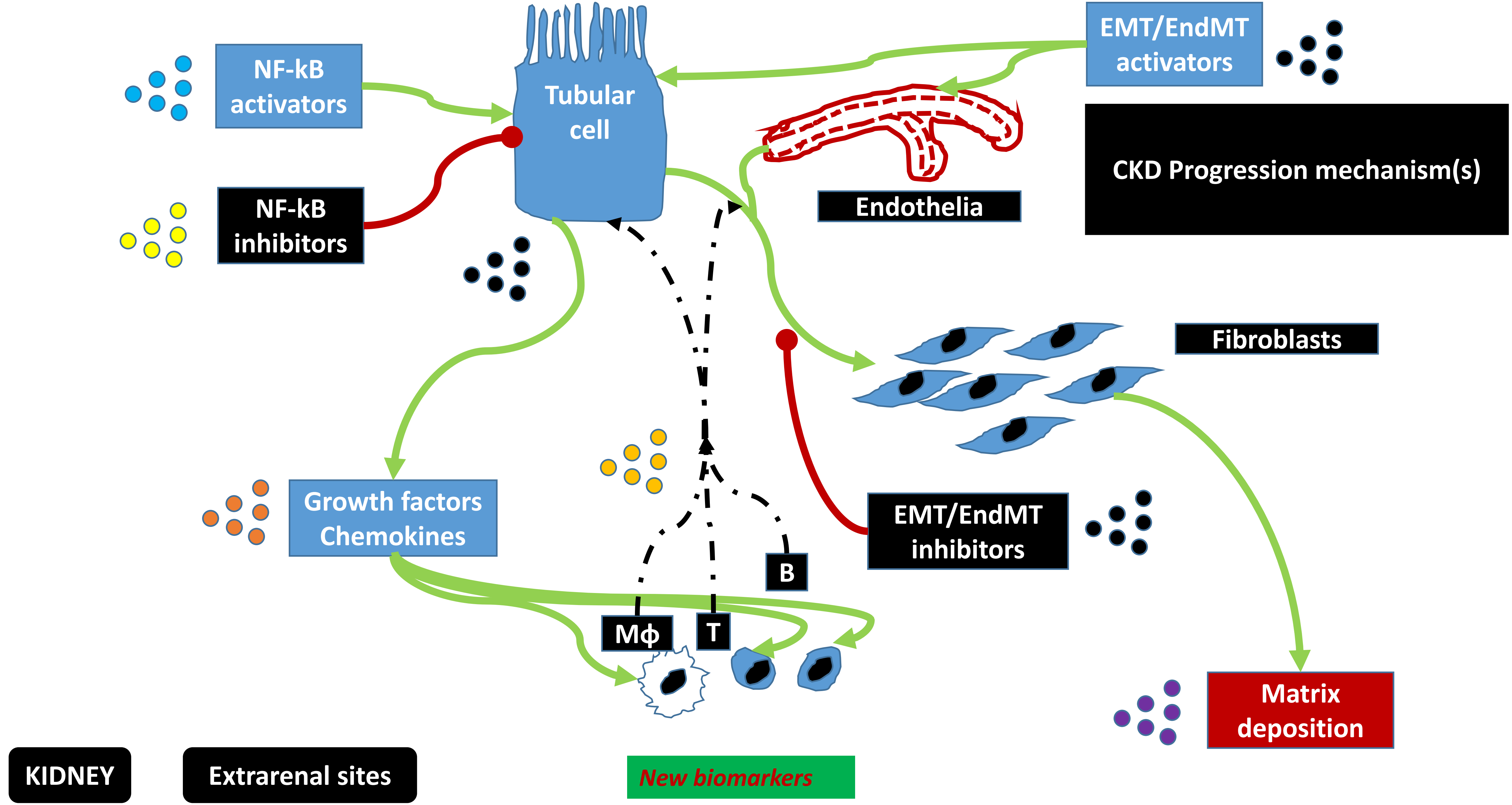




Hamroun et al NDT 2022



Hypertension (2003) 42, 1050–1065



Zeisberg et al JASN 2011

Biomarkers	Categories	Expression	Biological effects	Application	References
MMP-9	Endopeptidases	Increase	The inhibition of MMP-9 could reduce the infiltration of neutrophils and other inflammatory cells	Biomarker of renal fibrosis	Wang H et al. (2019b)
MMP-2	Endopeptidases	Increase	The increase of MMP-2 per unit of urine led to a decrease in eGFR (0.1 ml/min/m^2) during the 38-month follow-up	Biomarker of renal fibrosis	Nadkarni et al. (2016)
MMP-7	Endopeptidases	Increase	Activate the Wnt/β-catenin signaling pathway after renal injury	Biomarker of renal fibrosis	Li et al. (2021)
MCP-1	Chemokine	Increase	The upregulation of MCP-1 was accompanied by the activation of IκB/NF-κB signaling in CKD patients with macroalbuminuria	Biomarker of renal fibrosis	Feng et al. (2019)
DKK-3	Glycoprotein	Increase	Regulated the signal transduction of the Wnt/β-catenin signal pathway and induce renal tubulointerstitial fibrosis	Biomarker of renal fibrosis	Lipphardt et al. (2019)
5-MTP	Tryptophan metabolite	Decrease	Attenuated the expression of the pro-inflammatory factor NF-κB p65 and its target gene products MCP-1 and COX-2	Biomarker of renal fibrosis	Chen D. Q et al. (2019a)
1-AP	Polycyclic aromatic hydrocarbon metabolites	Increase	Activated of the aryl hydrocarbon receptor signaling pathway	Biomarker of renal fibrosis	Miao et al. (2020)
1-HP	Polycyclic aromatic hydrocarbon metabolites	Increase	Activated of the aryl hydrocarbon receptor signaling pathway	Biomarker of renal fibrosis	Miao et al. (2021b)
IS	Indole derivatives	Increase	Activated RAS system, induced cell senescence and apoptosis, promoted EMT, thus accelerated the progression of fibrosis, renal dysfunction, and CKD	Biomarker of gut–kidney axis disorder	Kim et al. (2012); Sun et al. (2012); Han et al. (2018)
PCS	Transformation of cresol	Increase	Induced renal injury and fibrosis by inhibiting Klotho gene expression, activating RAS/TGF-β pathway, inducing EMT, and causing NADPH oxidase-driven ROS	Biomarker of gut–kidney axis disorder	Sun et al. (2012) Watanabe et al. (2013)
TMAO	Byproducts of bacterial metabolism	Increase	Induced oxidative stress by inhibiting the expression of the oxidative stress inhibitor SIRT1, increasing H2O2, and reducing SOD activity	Biomarker of gut–kidney axis disorder	Ke et al. (2018)
Gal-3	Beta-galactoside binding protein	Increase	Modulated kidneys pro-inflammatory effects, regulated growth, differentiation, and proliferation of the cells, and mediated aldosterone-induced fibrosis of the heart and blood vessels	Biomarker of CVD based on CKD	Calvier et al. (2013); Madrigal-Matute et al. (2014); Vergaro et al. (2016)
sST-2	IL-1 receptor	Increase	Highly associated with adverse outcomes in patients with CVD, acute and chronic heart failure, or even death	Biomarker of CVD based on CKD	Dieplinger et al. (2014); Savic-Radojevic et al. (2017)
GDF-15	TGF-β cytokine	Increase	GDF-15 might take part in tissue inflammation, oxidative stress, and injured cardiomyocyte repair and show anti-apoptosis and anti-hypertrophy effects	Biomarker of CVD based on CKD	Kempf et al. (2006)
CypA	Cytoplasmic protein	Increase	Acted as inflammatory mediators under the stimulation of oxidative stress, inflammation, and hypoxia and participated in the process of inflammation and apoptosis by affecting multiple processes of transcriptional signal transduction	Biomarker of DN based on CKD	Sherry et al. (1992); Kim et al. (2004); Suzuki et al. (2006)
Periostin	Stromal cell protein	Increase	Increased the expression of TGF-β that could directly promote EMT and stimulate ECM synthesis and therefore induce extracellular matrix deposition	Biomarker of DN based on CKD	Gordon et al. (2012)
MicroRNAs	Composed of 19–24 nucleotides	Increase/ Decrease	Cleaved mRNA or suppressed the translation by interacting with the complementary sequence in the 3′-untranslated region of its mRNA target, followed by regulating gene expression	Biomarker of DN based on CKD	He and Hannon, (2004)
PTH	Single-chain hormone	Increase	Played an essential role in vitamin D and phosphate metabolism	Biomarker of CKD-MBD	Ardawi et al. (2012)
Activin A	Transforming TGF-β family protein	Increase	Stimulated skeletal growth and inhibited activin signal	Biomarker of CKD-MBD	Peng et al. (2018)
TRAP5b	Enzyme	Increase	Affected the function of phosphate by separating it from the protein	Biomarker of CKD-MBD	Lv et al. (2015)
FGF 23	Phosphaturic hormone	Increase	Acted on the calcineurin/activated T cell nuclear factor signaling pathway that led to pathological hypertrophy of cardiomyocytes	Prognostic biomarkers of CKD	Faul et al. (2011)
Klotho	Antiaging gene	Decrease	Inhibited the apoptosis of renal tubular epithelial cells and transdifferentiation and acted on the kidneys in an autocrine or paracrine manner to exert anti-inflammatory and antioxidant effect	Prognostic biomarkers of CKD	Liu et al. (2015); Liu et al. (2017)
UMOD	Glycoprotein	Increase	Combined with neutrophils to promote the synthesis of IL-8, induce mononuclear cells, secrete IL-1β and TNF-α, then affect the prognosis of CKD	Prognostic biomarkers of CKD	Kottgen et al. (2010); Satanovskij et al. (2017)

New biomarkers

Combination

Isolated

Differential approach (CKD aetiology, therapeutic approach)

Individualized interpretation

Yan et al Front. Pharmacol 2021

Examples of Approaches in Biomarker Diagnosis involving

Proteomic Analysis

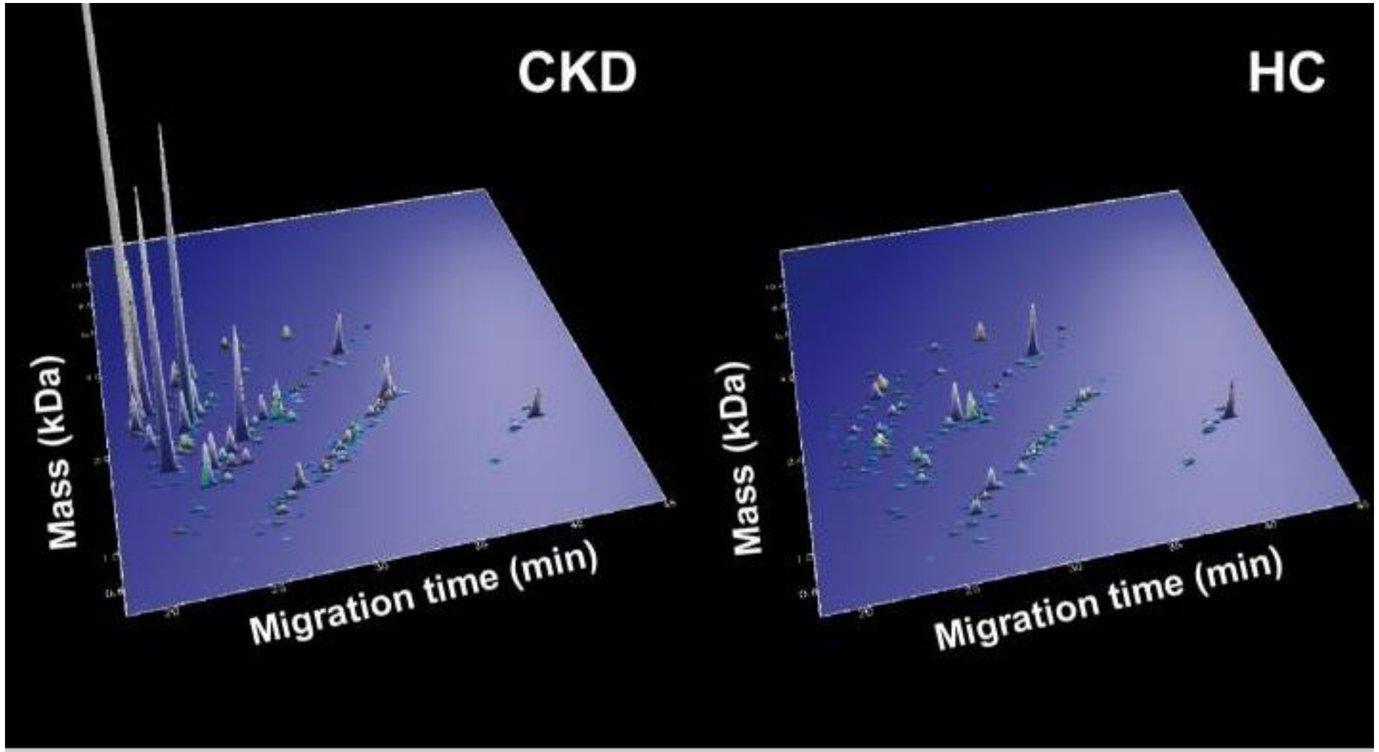
Protein Analysis

Radiological Analysis

Naturally Occurring Human Urinary Peptides for Use in Diagnosis of Chronic Kidney Disease

MCP MOLECULAR & CELLULAR PROTEOMICS

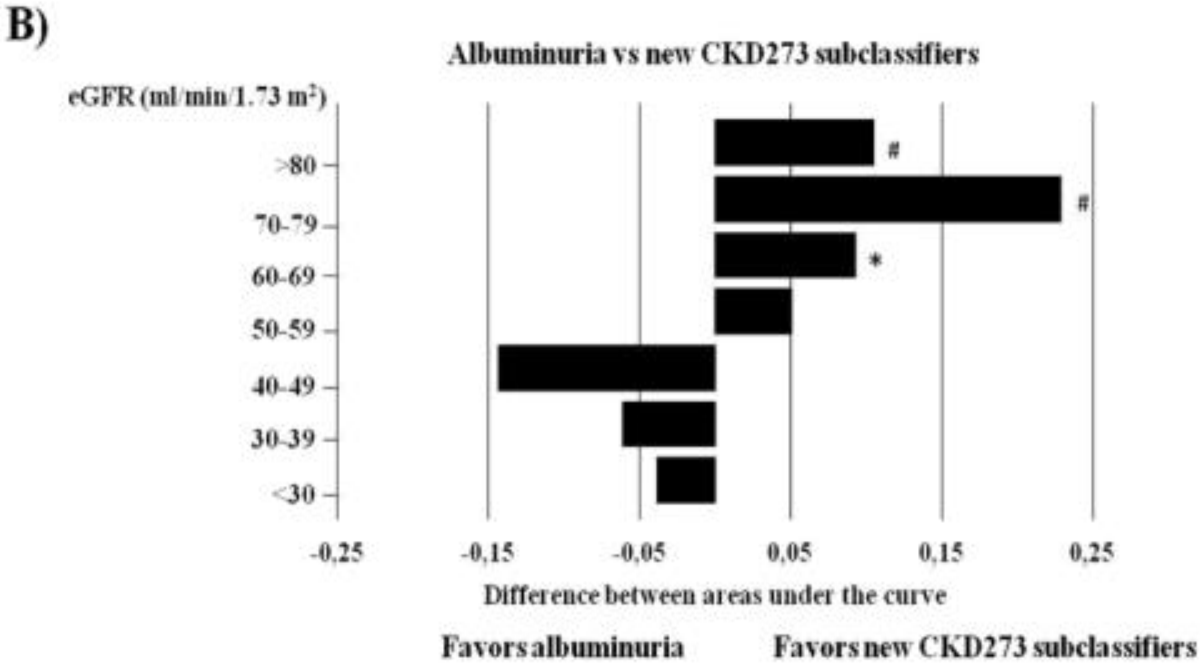
Published by the American Society for Biochemistry and Molecular Biology



Source proteins and peptide distribution of CKD biomarkers

Protein	Swiss-Prot name	Number of fragments
Collagen α-1 (I) chain	CO1A1_HUMAN	126
Collagen α-1 (III) chain	CO3A1_HUMAN	55
α_1-Antitrypsin	A1AT_HUMAN	18
Collagen α-2 (I) chain	CO1A2_HUMAN	15
Uromodulin	UROM_HUMAN	11
Serum albumin	ALBU_HUMAN	9
Fibrinogen α chain	FIBA_HUMAN	5
Polymeric immunoglobulin receptor	PIGR_HUMAN	4
α_2-HS-glycoprotein	FETUA_HUMAN	3
Clusterin	CLUS_HUMAN	2
Collagen α-1 (II) chain	CO2A1_HUMAN	2
Membrane-associated progesterone receptor component 1	PGRC1_HUMAN	2
Osteopontin	OSTP_HUMAN	2
Sodium/potassium-transporting ATPase γ chain	ATNG_HUMAN	2
Transthyretin	TTHY_HUMAN	2
α_{1B}-Glycoprotein	A1BG_HUMAN	1
Antithrombin-III	ANT3_HUMAN	1
Apolipoprotein A-I	APOA1_HUMAN	1
β_2-Microglobulin	B2MG_HUMAN	1
CD99 antigen	CD99_HUMAN	1
Collagen α-1 (V)	CO5A1_HUMAN	1
Cystatin-B	CYTB_HUMAN	1
Ig λ chain C regions	LAC_HUMAN	1
Neurosecretory protein VGF	VGF_HUMAN	1
Pro-SAAS	PCSK1_HUMAN	1
Prostaglandin-H_2D-isomerase	PTGDS_HUMAN	1
Psoriasis susceptibility 1 candidate gene 2 protein	PS1C2_HUMAN	1

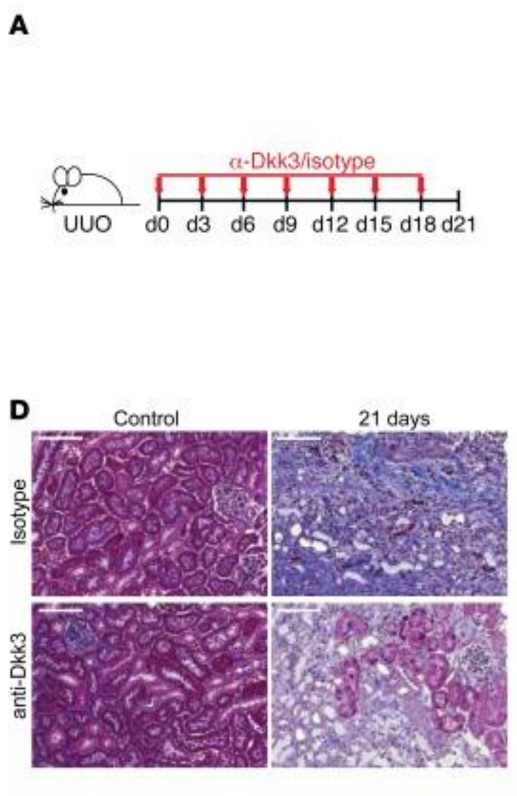
Novel Urinary Biomarkers For Improved Prediction Of Progressive eGFR Loss In Early Chronic Kidney Disease Stages And In High Risk Individuals Without Chronic Kidney Disease

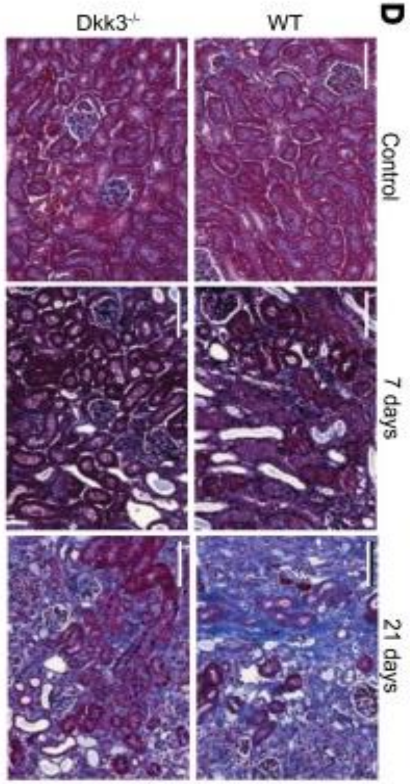


The CKD273 subclassifers **performed better** in predicting **rapid** CKD progression in the strata of patients with **eGFR>60ml/min/1.73m2** .

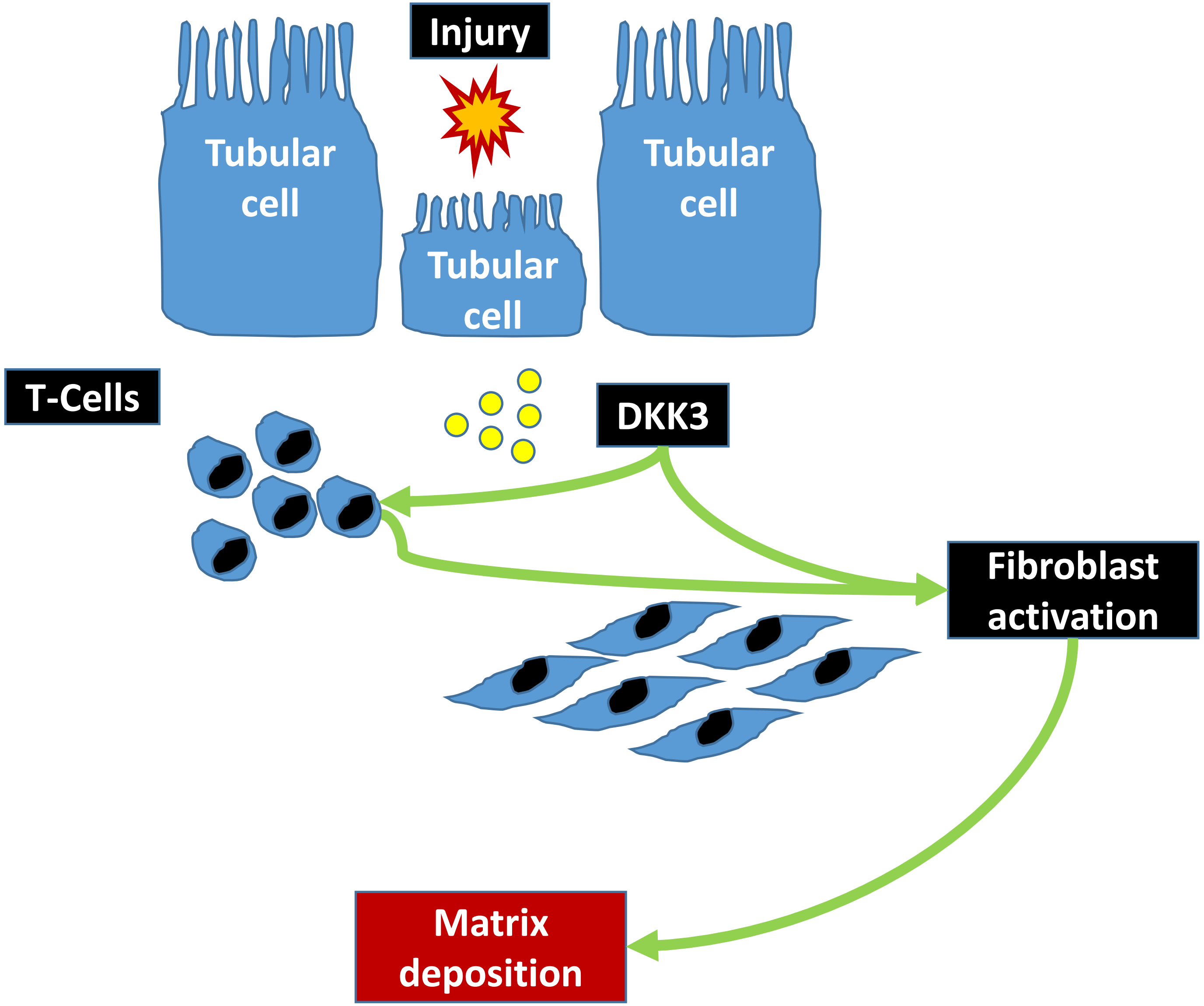
Rapid CKD progression: sustained decline in eGFR ≥ 5 ml/min/1.73 m2 /year

Tubular Dickkopf-3 promotes the development of renal atrophy and fibrosis





Adenine Diet

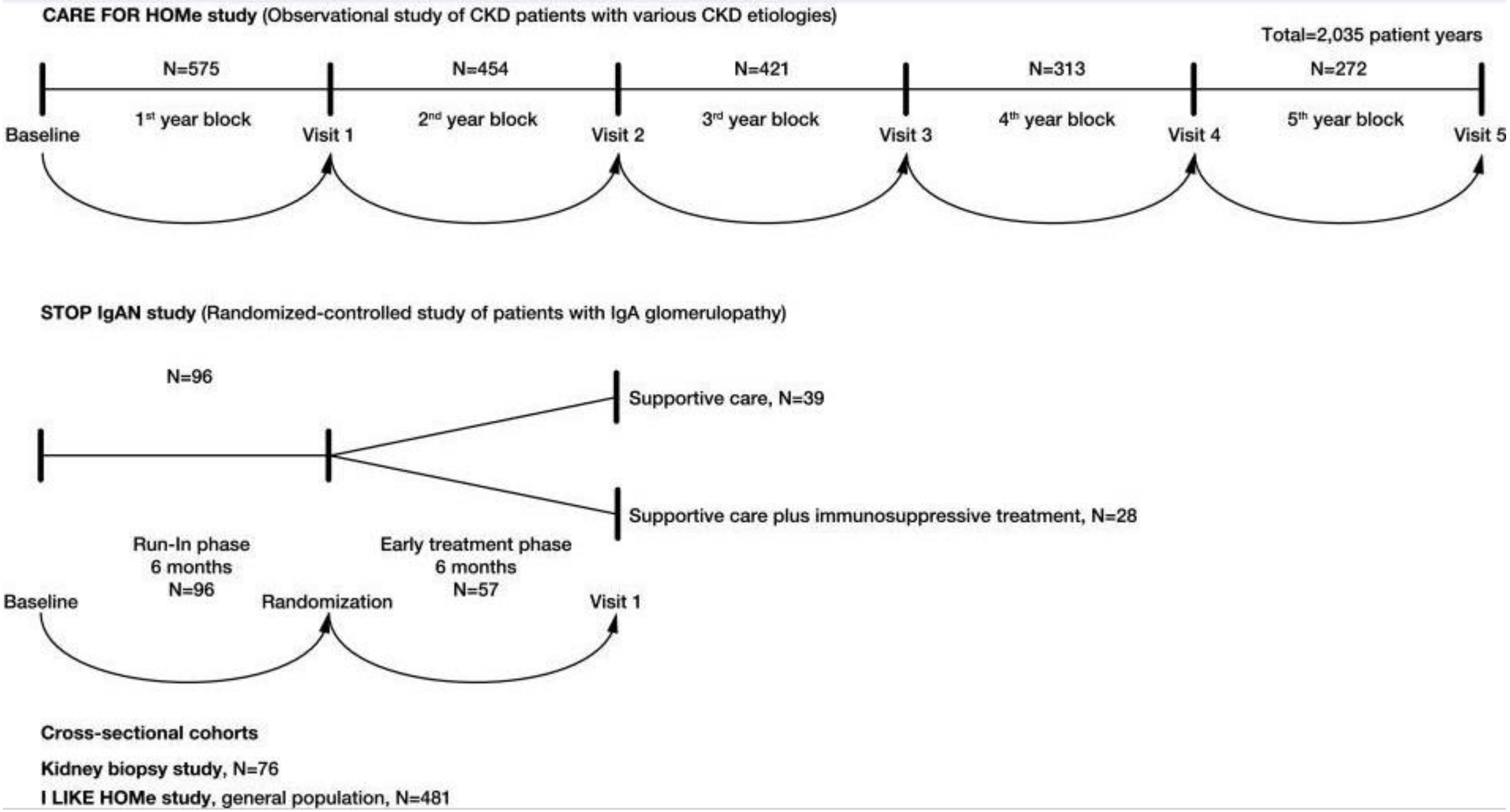


Giussepina et al JCI Insight 2016

Dickkopf-3 (DKK3) in Urine Identifies Patients with Short-Term Risk of eGFR Loss

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Zewinger, Stephen; Rauen, Thomas; Rudnicki, Michael; Federico, Giuseppina; Wagner, Martina; Triem, Sarah; Schunk, Stefan J.; Petrakis, Ioannis; Schmit, David; Wagenpfeil, Stefan; Heine, Gunnar H.; Mayer, Gert; Floege, Jürgen; Fliser, Danilo; Gröne, Hermann-Josef; Speer, Thimoteus

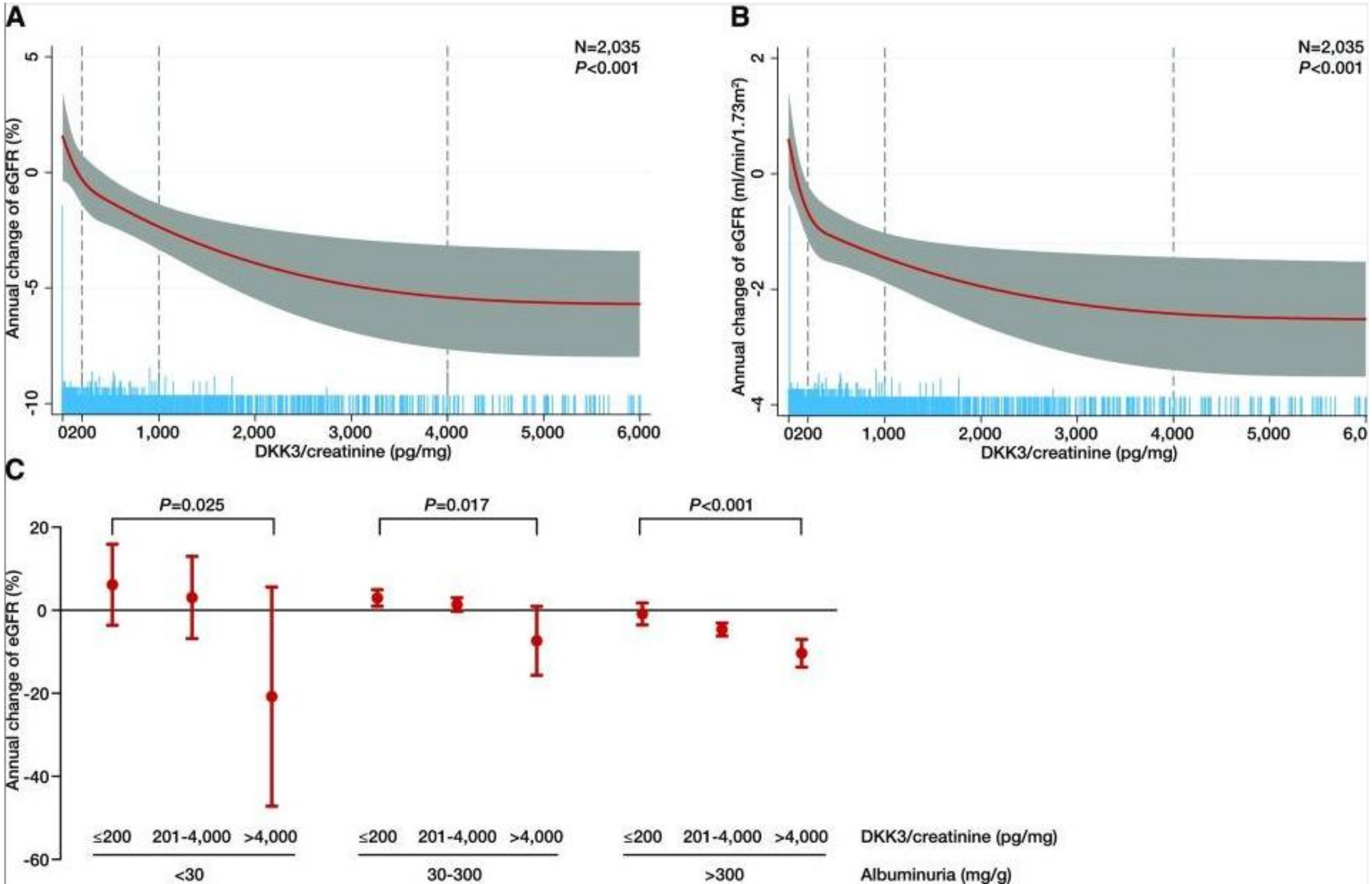


CLINICAL EPIDEMIOLOGY

Dickkopf-3 (DKK3) in Urine Identifies Patients with Short-Term Risk of eGFR Loss

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

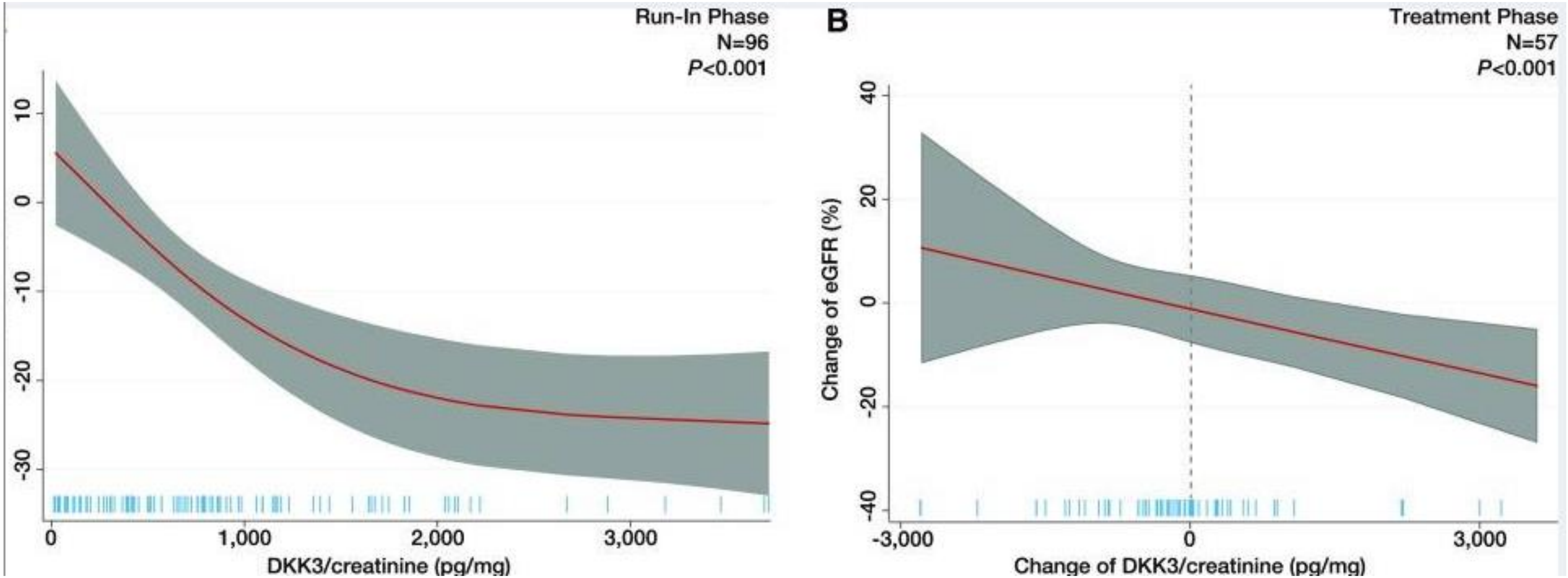
Zewinger, Stephen; Rauen, Thomas; Rudnicki, Michael; Federico, Giuseppina; Wagner, Martina; Triem, Sarah; Schunk, Stefan J.; Petrakis, Ioannis; Schmit, David; Wagenpfeil, Stefan; Heine, Gunnar H.; Mayer, Gert; Floege, Jürgen; Fliser, Danilo; Gröne, Hermann-Josef; Speer, Thimoteus



CLINICAL EPIDEMIOLOGY

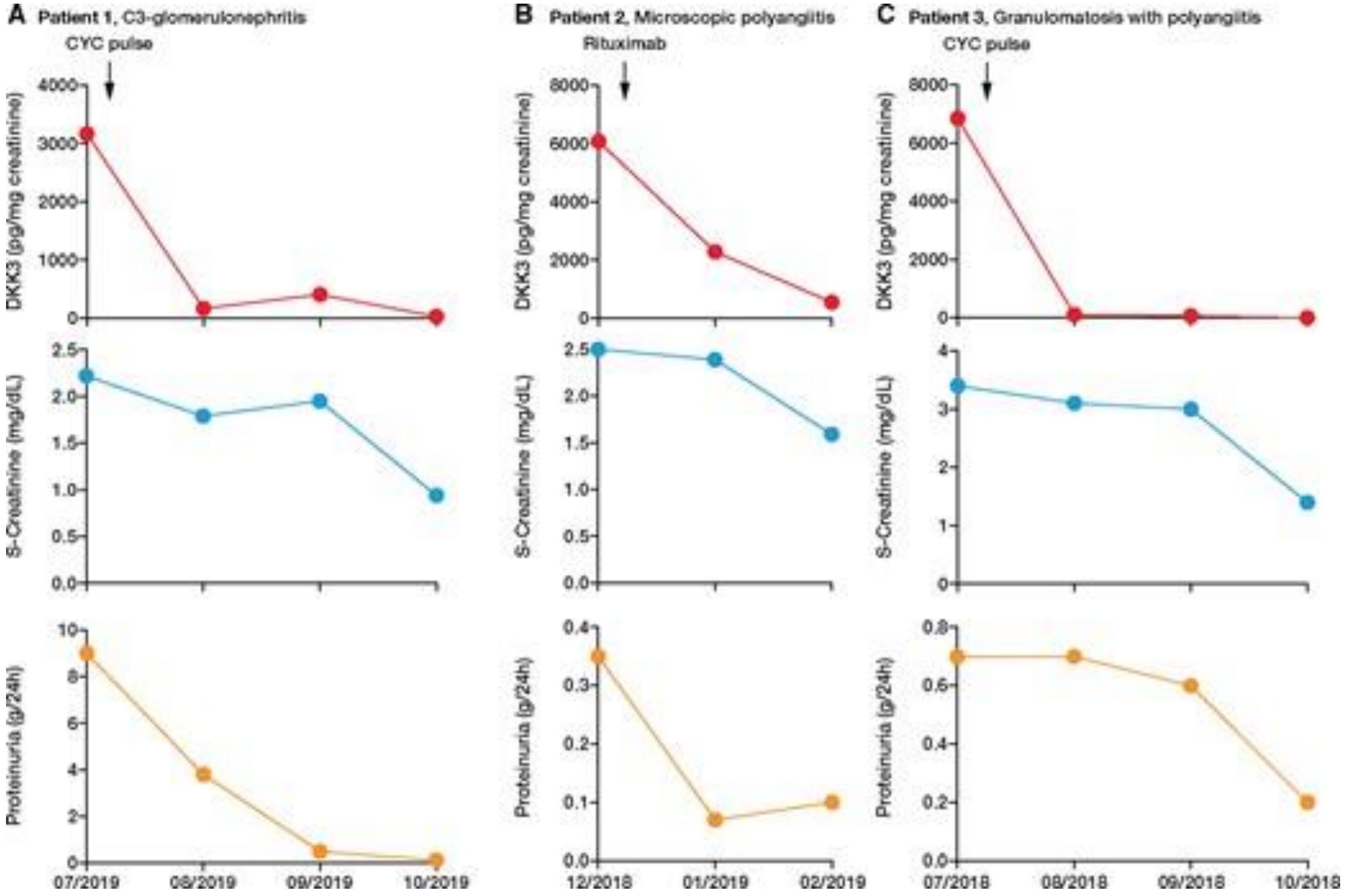
Dickkopf-3 (DKK3) in Urine Identifies Patients with Short-Term Risk of eGFR Loss

Zewinger, Stephen; Rauen, Thomas; Rudnicki, Michael; Federico, Giuseppina; Wagner, Martina; Triem, Sarah; Schunk, Stefan J.; Petrakis, Ioannis; Schmit, David; Wagenpfeil, Stefan; Heine, Gunnar H.; Mayer, Gert; Floege, Jürgen; Fliser, Danilo; Gröne, Hermann-Josef; Speer, Thimoteus



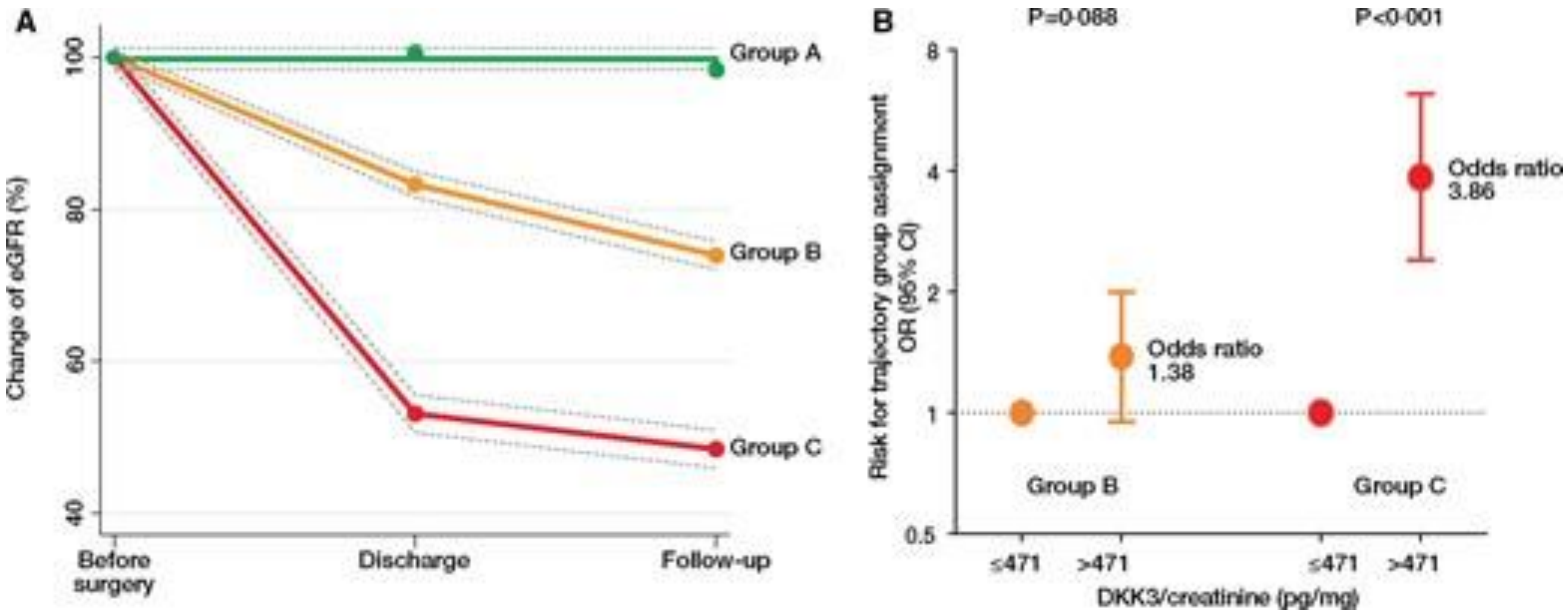
Dickkopf 3—a novel biomarker of the ‘kidney injury continuum’

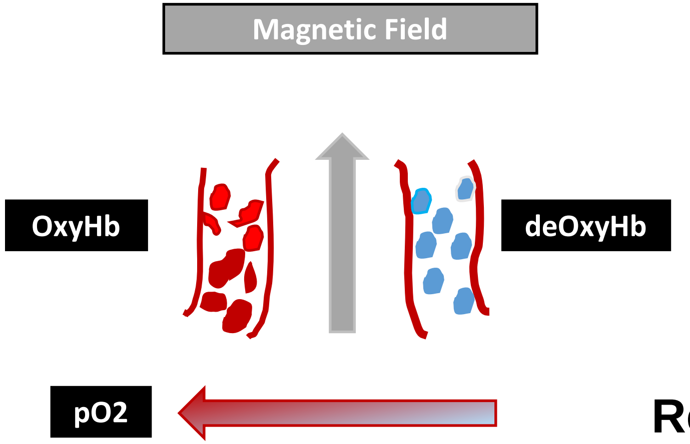
Stefan J. Schunk, Thimoteus Speer, Ioannis Petrakis and Danilo Fliser
Department of Internal Medicine IV – Nephrology and Hypertension, Saarland University Medical Center, Homburg/Saar, Germany



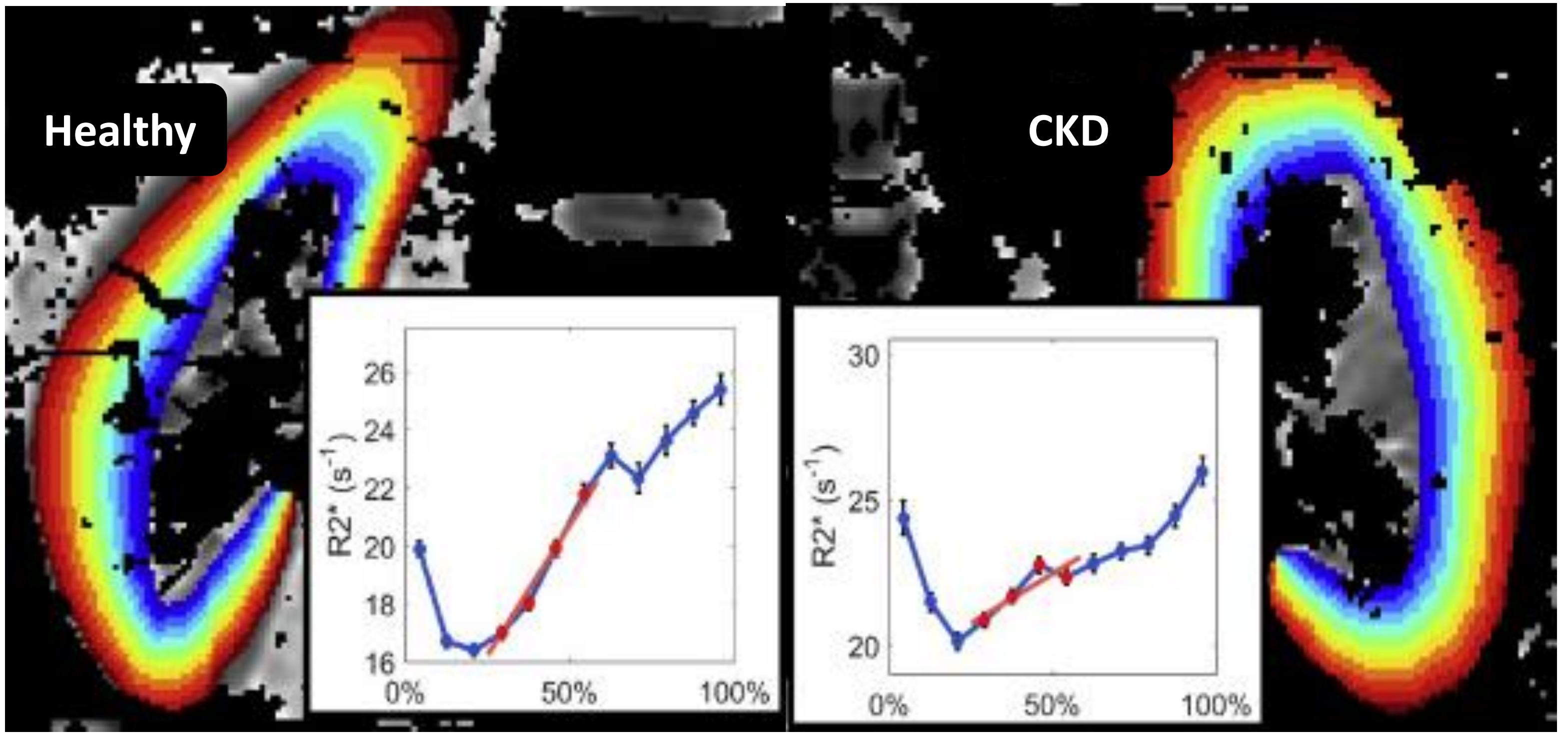
Dickkopf 3—a novel biomarker of the 'kidney injury continuum'

Stefan J. Schunk, Thimoteus Speer, Ioannis Petrakis and Danilo Fliser
Department of Internal Medicine IV – Nephrology and Hypertension, Saarland University Medical Center, Homburg/Saar, Germany



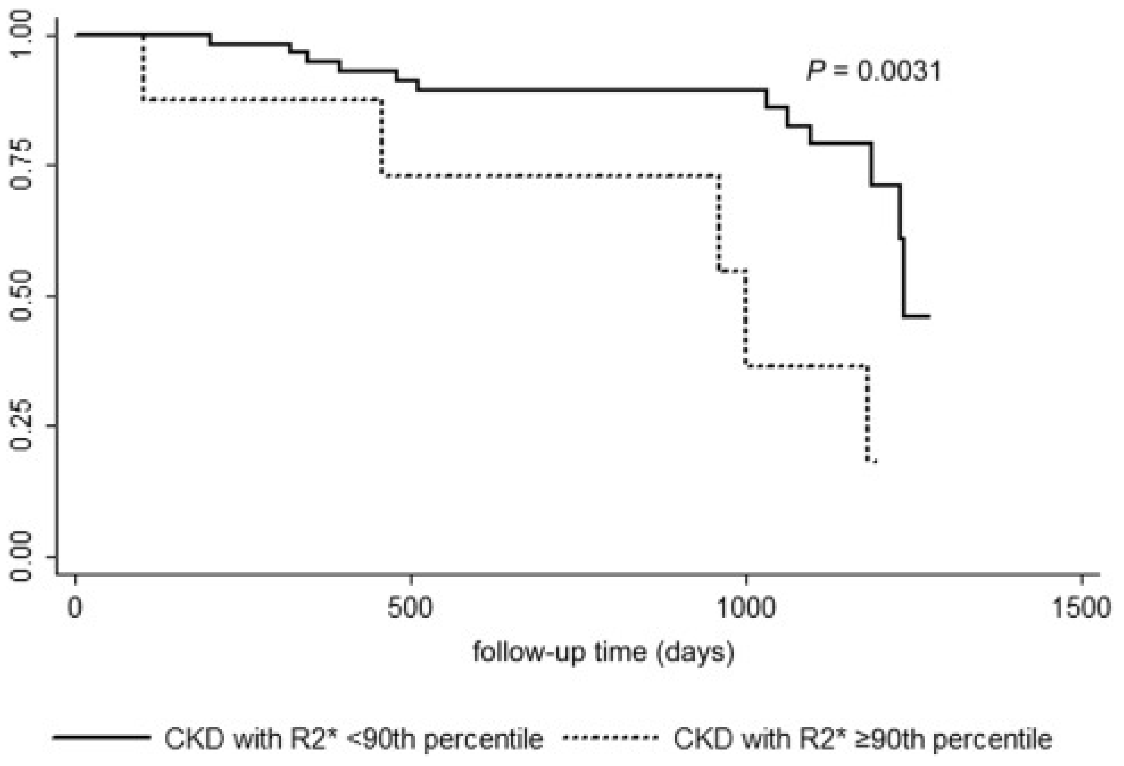


Reduced cortical oxygenation predicts a progressive decline of renal function in patients with chronic kidney disease



Pruijm et al KI 2018

Reduced cortical oxygenation predicts a progressive decline of renal function in patients with chronic kidney disease

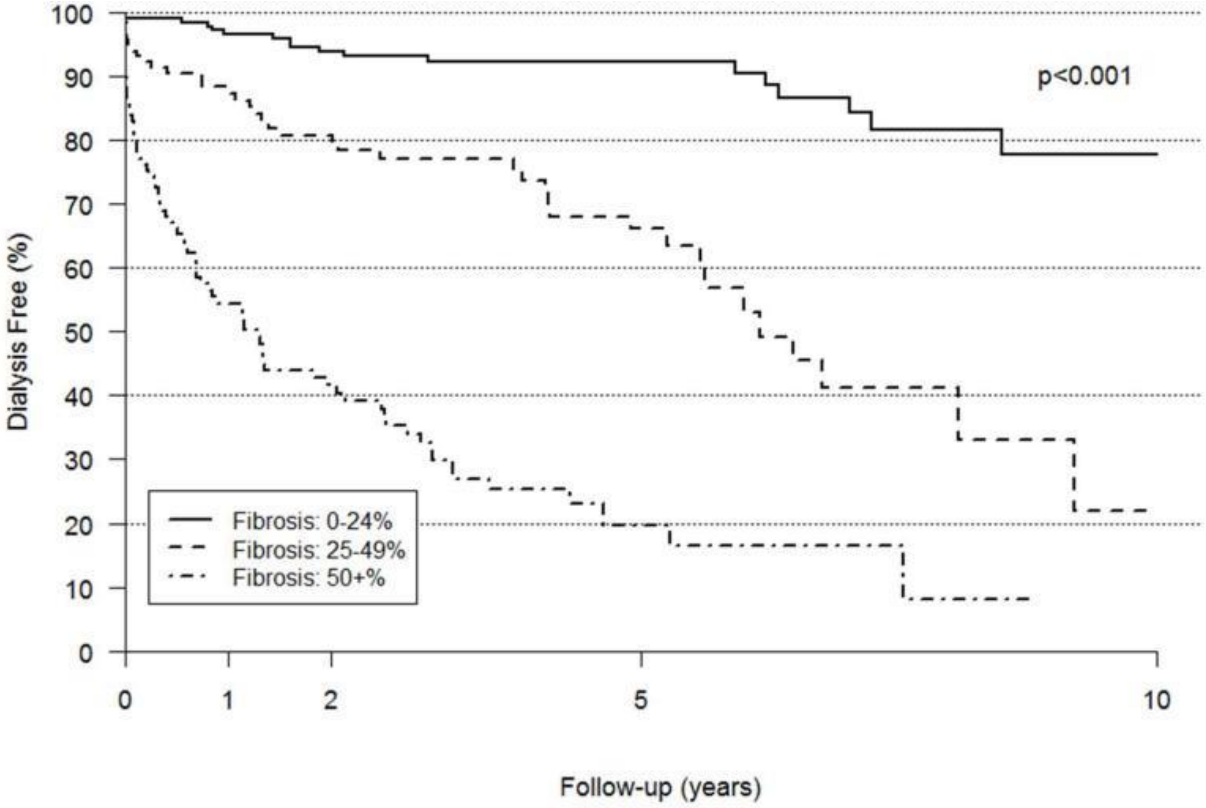


Characteristics of CKD patients according to their R2* value of the outer layers (above or below the 90th percentile)

Characteristics	R2* <90th percentile	R2* ≥90th percentile	*P*[a]
N	100	12	
Proteinuria (g/24 hr)	0.89 ± 1.52	0.81 ± 1.22	0.87
Diabetes (yes vs. no)	28.9	16.7	0.37
Baseline eGFR (ml/min per 1.73 m^2)	56.2 ± 29	49.4 ± 26	0.46
Yearly change in eGFR (ml/min per 1.73 m^2)	**−0.8 ± 5.8**	**−3.9 ± 6.6**	**0.008**
RAS blocker (yes vs. no)	47.4	58.3	0.48
Outer R2* (sec^{-1})	20.3 ± 1.6	26.6 ± 4.6	<0.001

Pruijm et al KI 2018

Renal interstitial fibrosis: an imperfect predictor of kidney disease progression in some patient cohorts



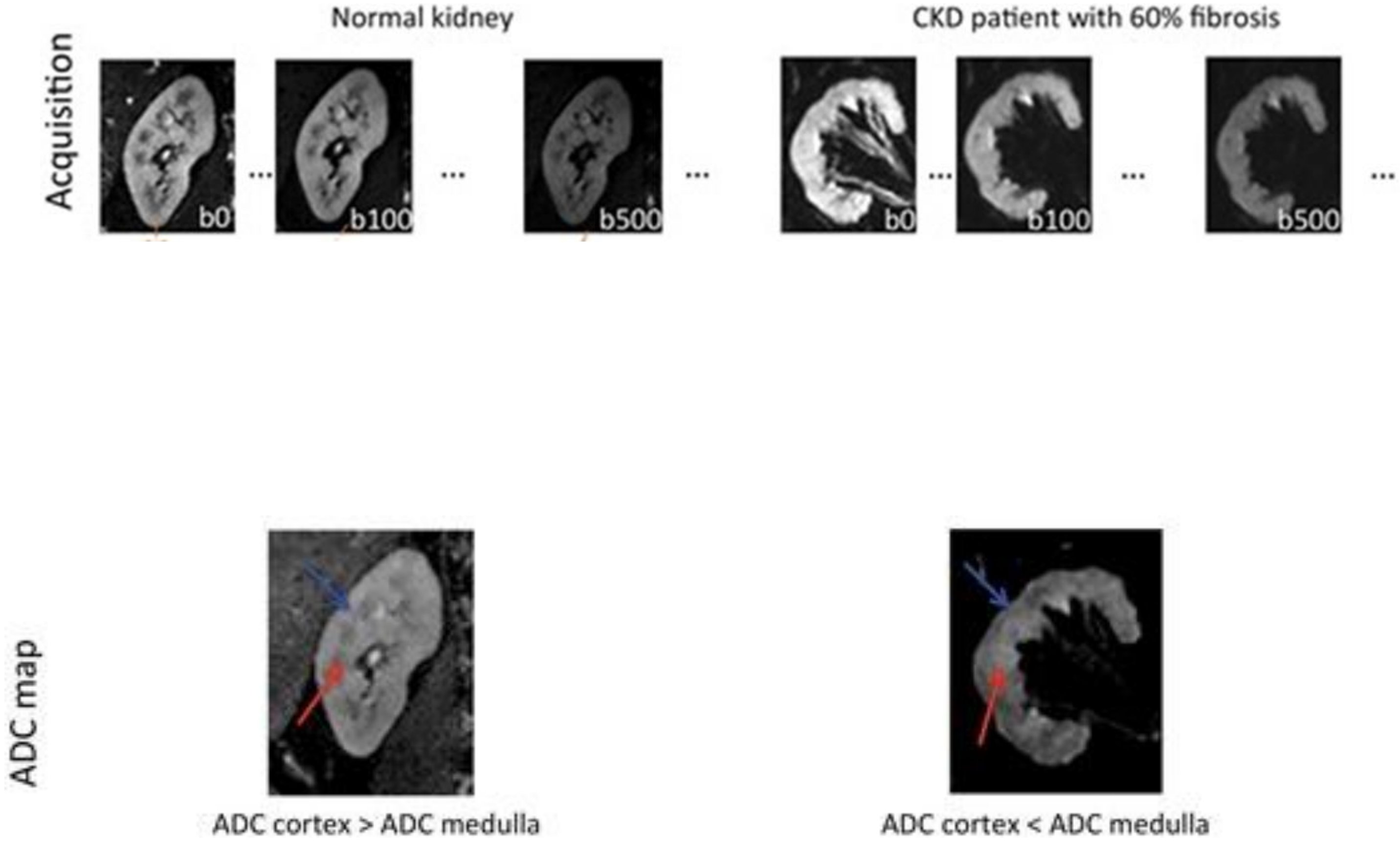
Sample					
0-24%	199	153	128	71	3
25-49%	117	85	67	31	1
50+%	118	54	36	6	0

…some of the patients who had >80% fibrosis on the biopsy did not progress to ESRD during a 10-year follow up period.

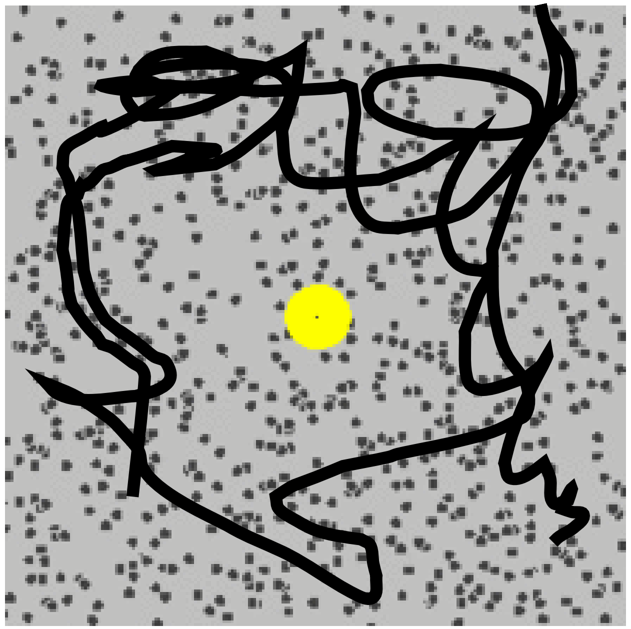
…Over-reliance on fibrosis on biopsy may therefore erroneously identify patients as having advanced CKD at a time when interventions may still be effective.

Hanni et al AJKD 2018

Renal Diffusion Imaging



- Degree of **tissue fibrosis**
- **Predict renal function evolution** follow **microstructure changes** occurring **under treatment.**
- **Reduce the number of renal biopsies** for diagnosis **and follow-up**.

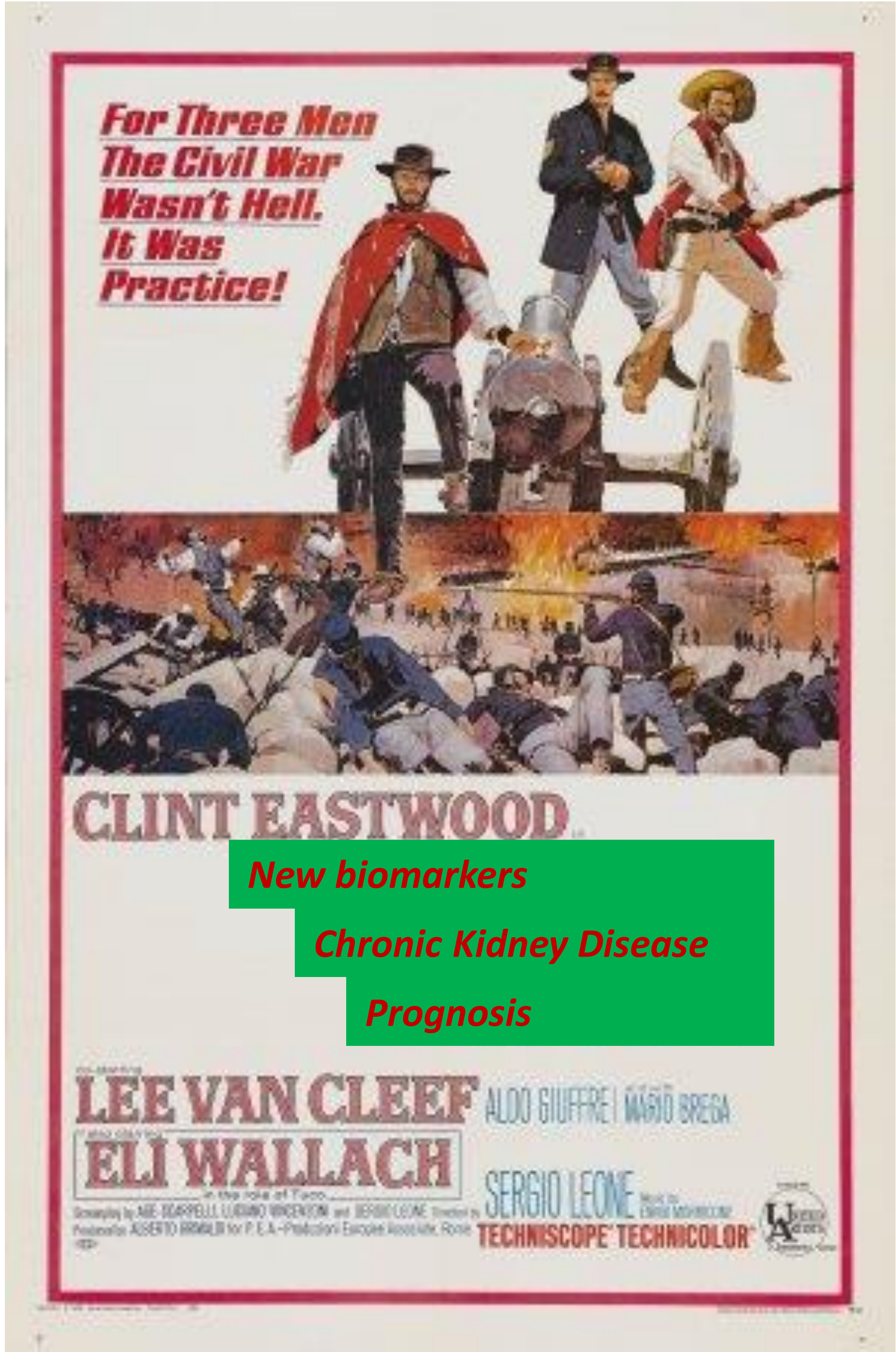


Brownian Motion

Caroli et al NDT 2018

Cost...

- Serum Cr~4€
- ELISA~30€
- Proteomics~100-300€
- MRI~200-250€



- Under development
- Individualized application
- Cost
- Equipment/Materials availability
- Clinical Examination & History.