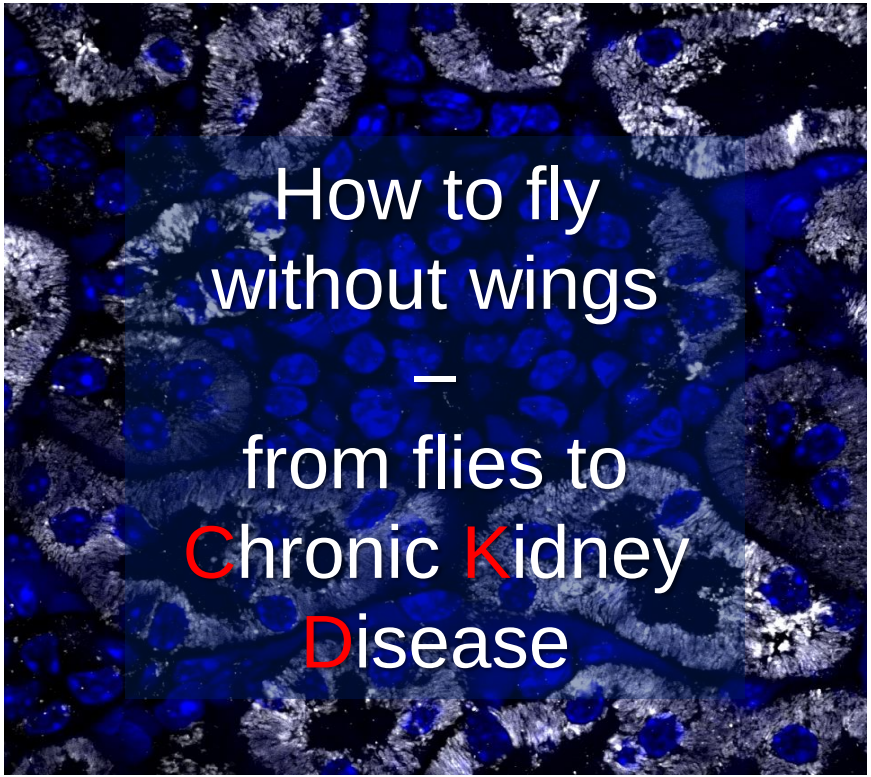
UKS
Universitätsklinikum
des Saarlandes

ERA
LEADING EUROPEAN NEPHROLOGY



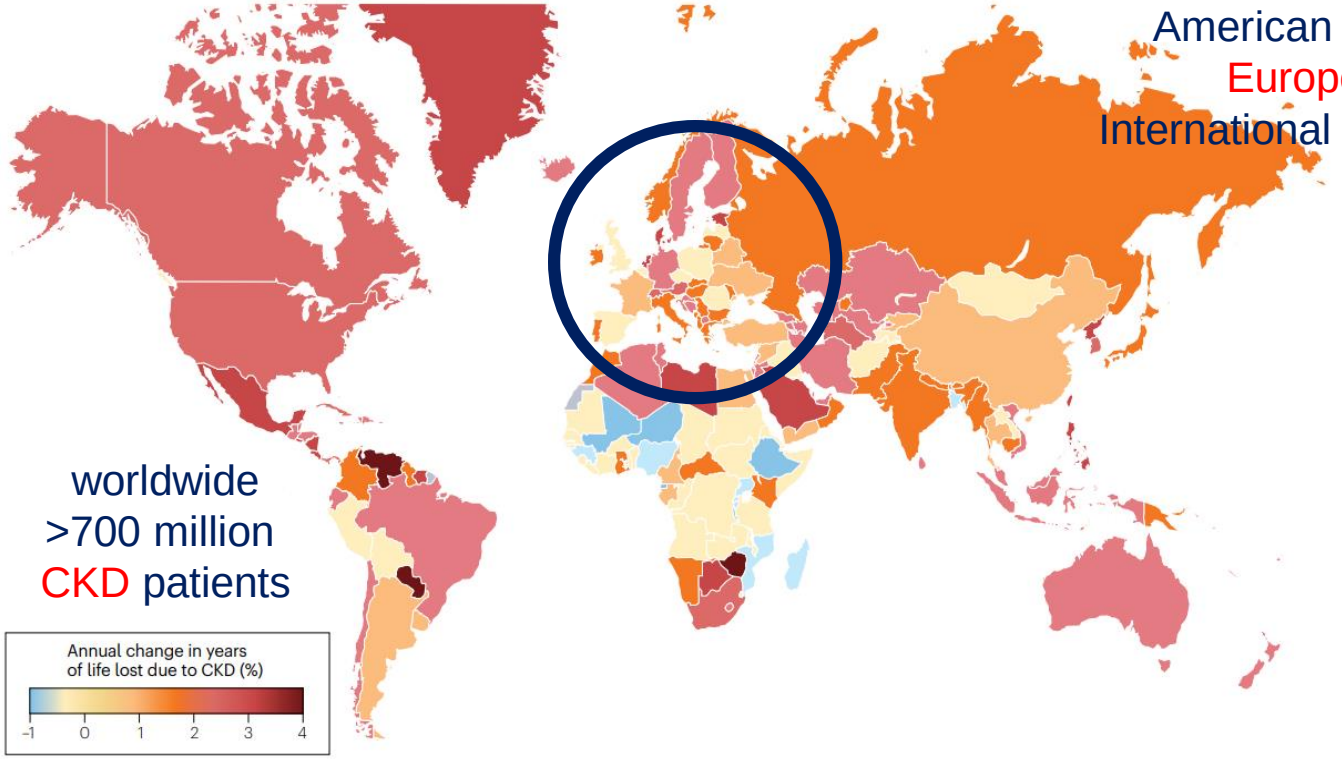
How to fly without wings – from flies to Chronic Kidney Disease

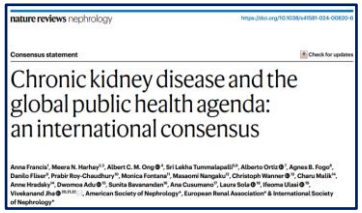
Danilo Fliser
Univ.–Prof. & Director
Saarland University Medical Centre
Internal Medicine IV
– Renal and Hypertensive Diseases –
& Kidney Transplant Centre

Renal Science Chair
European Renal Association

CKD – epidemiology

American Society of Nephrology
European Renal Association
International Society of Nephrology





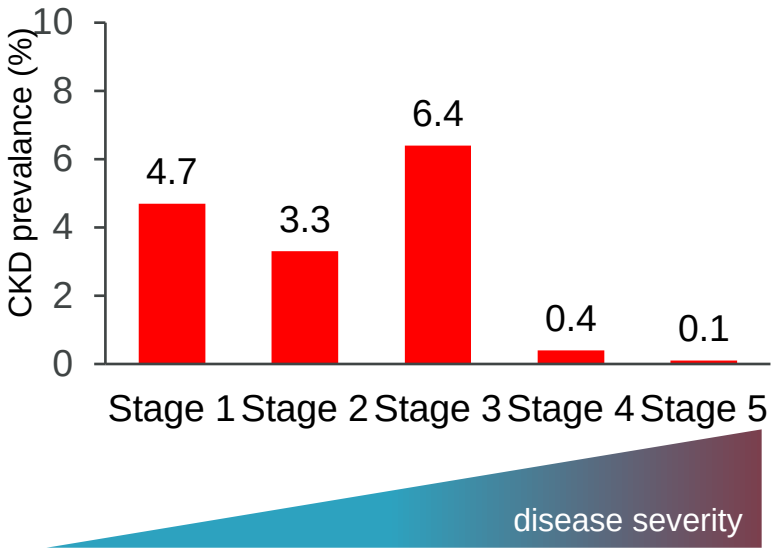
The burden of kidney disease

- Premature mortality
- Disability
- Reduced quality of life
- Psychosocial harm
- High costs to governments and health care systems
- High costs to individuals and families, in part because of lost productivity

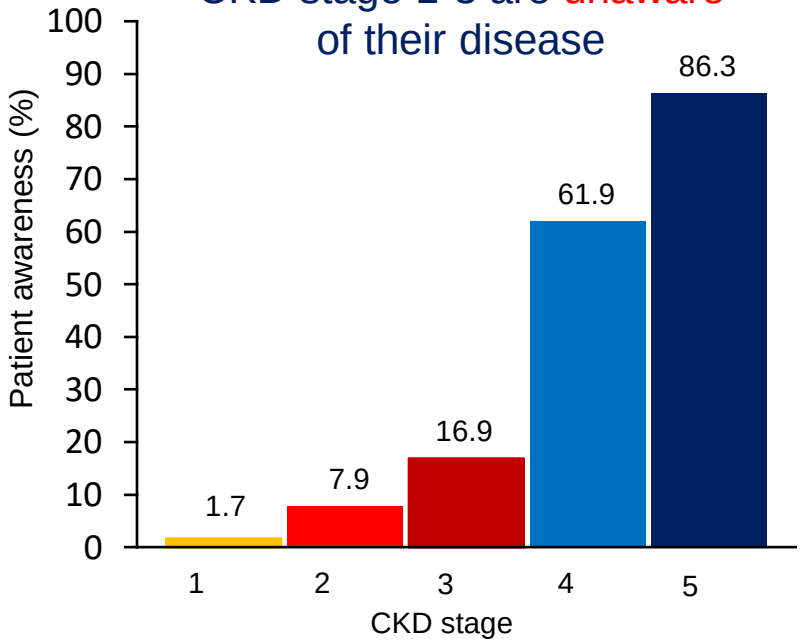
Francis et al. *Nat Rev Nephrol* 2024

CKD – epidemiology

CKD prevalence is highest at CKD stage 1-3



The majority of patients with CKD stage 1-3 are unaware of their disease



USRDS. 2020 Annual data report

CKD – diagnosis & prognosis

Cause

e**G**FR

Albuminuria

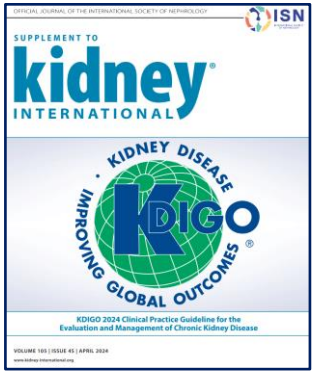
GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
G1	Normal or high	≥90		Screen 1	Treat 1	Treat 3
G2	Mildly decreased	60–89		Screen 1	Treat 1	Treat 3
G3a	Mildly to moderately decreased	45–59		Treat 1	Treat 2	Treat 3
G3b	Moderately to severely decreased	30–44		Treat 2	Treat 3	Treat 3
G4	Severely decreased	15–29		Treat* 3	Treat* 3	Treat 4+
G5	Kidney failure	<15		Treat 4+	Treat 4+	Treat 4+

Low risk (if no other markers of kidney disease, no CKD)

Moderately increased risk

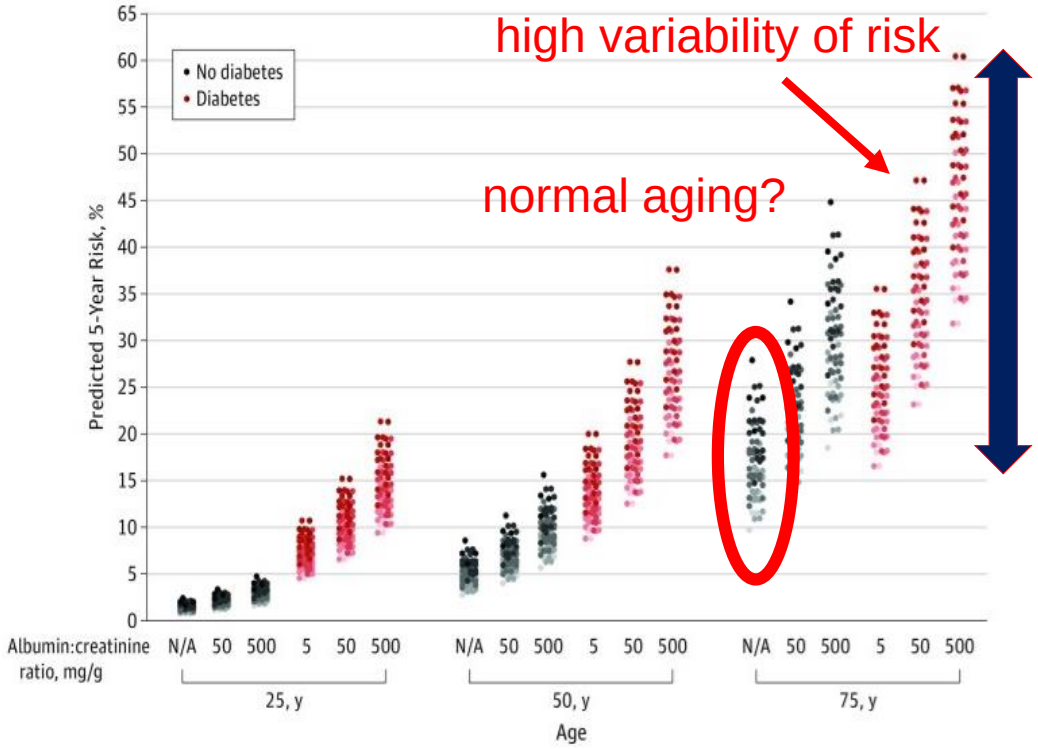
High risk

Very high risk



KDIGO. *Kidney Int Suppl* 2024

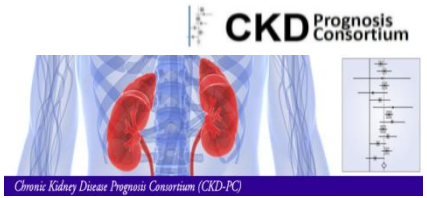
CKD progression risk



5.222.711 subjects (34 cohorts)

calculated risk of incident CKD, i.e. eGFR <60 ml/min/1,73m² (G2 → G3) in 5 years

data validated in 2.253.540 subjects (9 cohorts)



Nelson et al. *JAMA* 2019

CKD – diagnosis & prognosis

Cause

e**G**FR

Albuminuria

GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–299 mg/g 3–29 mg/mmol	A3 Severely increased ≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	Screen 1	Treat 1	Treat 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat 3	Treat 3
	G4	Severely decreased	15–29	Treat* 3	Treat* 3	Treat 4+
	G5	Kidney failure	<15	Treat 4+	Treat 4+	Treat 4+

Low risk (if no other markers of kidney disease, no CKD)

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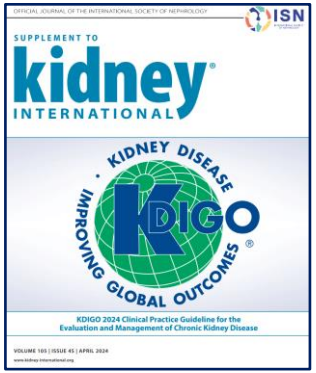
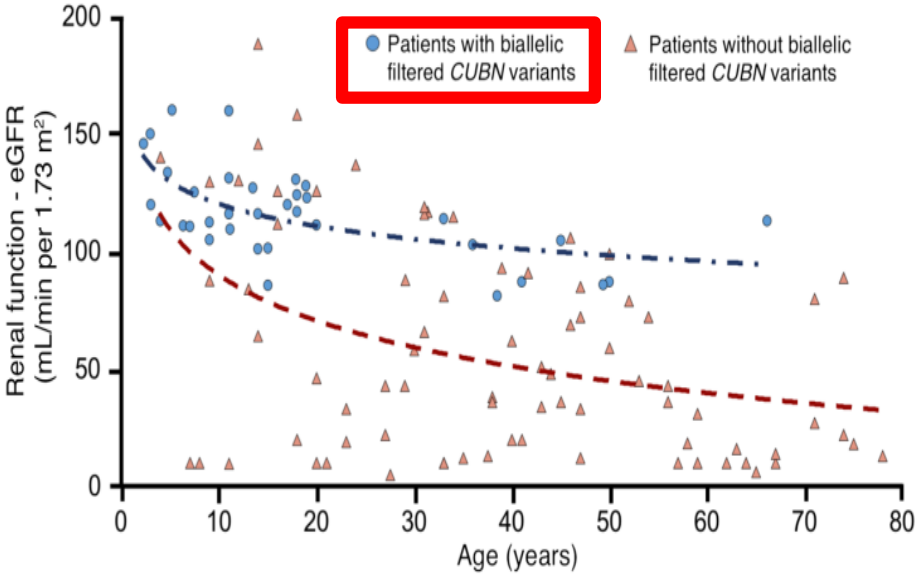


KDIGO. *Kidney Int Suppl* 2024

CKD progression – albuminuria

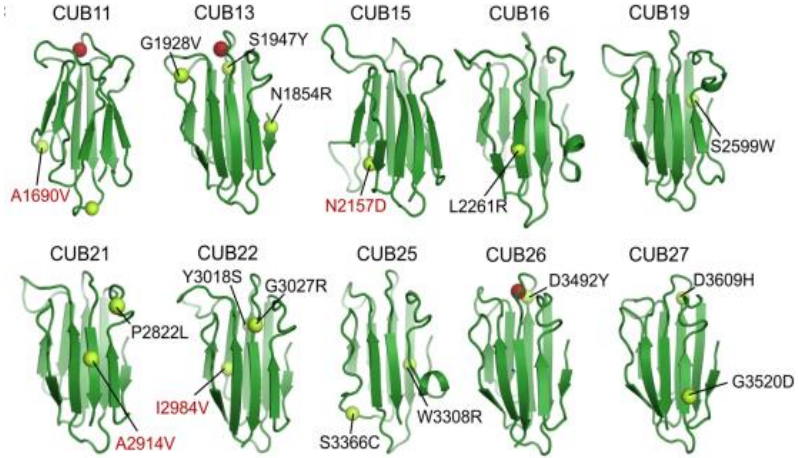


CONCLUSION. Collectively, our data suggest an important role for the C-terminal half of cubilin in renal albumin reabsorption. Albuminuria due to reduced cubilin function could be an unexpectedly common benign condition in humans that may not require any proteinuria-lowering treatment or renal biopsy.

The Journal of Clinical Investigation CLINICAL MEDICINE

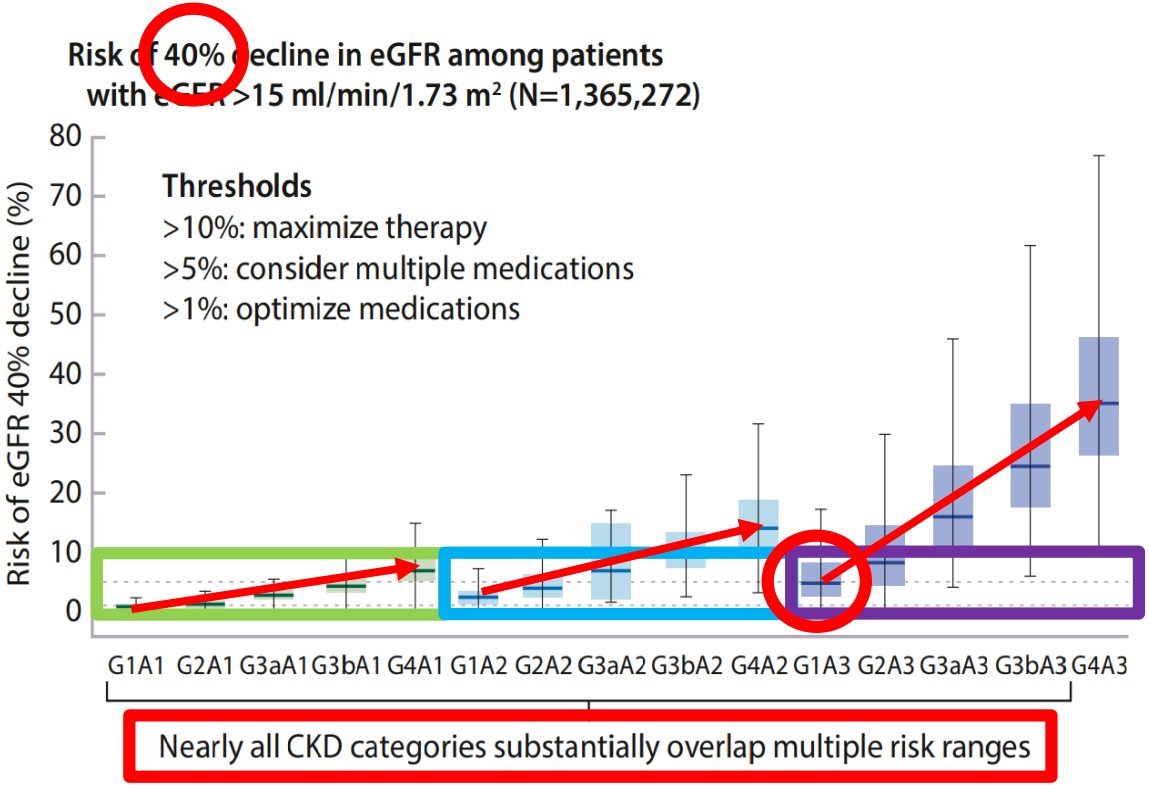
Human C-terminal *CUBN* variants associate with chronic proteinuria and normal renal function

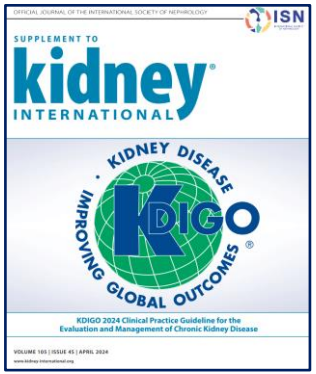
Mathilda Bedin,[1] Olivia Boyer,[2,3] Aude Servais,[2,4] Yong Li,[5] Laure Villoing-Gaudé,[1] Marie-Josephe Tête,[2] Alexandra Cambier,[4] Julien Hogan,[4] Veronique Baudouin,[4] Saoussen Krid,[4] Albert Bensman,[4] Florie Lammens,[1] Ferielle Louillet,[6] Bruno Ranchin,[6] Cecile Vigneau,[10] Iseline Bouteau,[11] Corinne Isnard-Bagnis,[12] Christoph J. Mache,[13] Tobias Schäfer,[14] Lars Pape,[15] Markus Gödel,[16] Tobias B. Huber,[16] Marcus Benz,[17] Günter Klaus,[18] Matthias Hansen,[19] Kay Latta,[19] Olivier Gribouval,[1] Vincent Morinière,[20] Carole Tournant,[21] Maik Grohmann,[21,22] Elisa Kuhn,[21] Timo Wagner,[21] Christine Bole-Feysot,[23,24] Fabienne Jabot-Hanin,[23,24] Patrick Nitschké,[23,24] Tarunveer S. Ahluwalia,[25] Anna Köttgen,[5] Christian Brix Folsted Andersen,[26] Carsten Bergmann,[21,22,27] Corinne Antignac,[1,20] and Matias Simons[1]



Bedin et al. *J Clin Invest* 2020

CKD progression – proteinuria





KDIGO. *Kidney Int Suppl* 2024

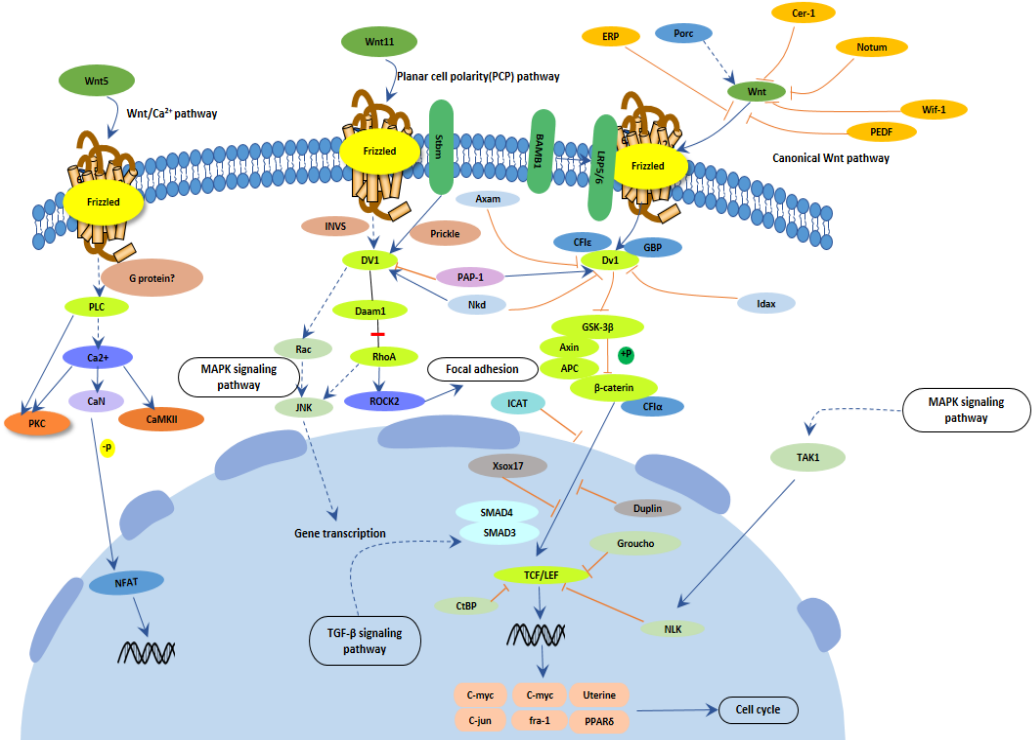
CKD progression – albuminuria

- male, 53 years, non-smoker, no diabetes (HbA_{1C} 5.3%)
- nephrotic syndrome since 2007!
- proteinuria 8,952 mg/24h; albuminuria 7,583 mg/24h
- s-creatinine: 0.86 mg/dl; eGFR: 99 ml/min/1,73m²
- s-cystatin C: 0.79 mg/l; eGFR creatinine-cystatin C: 108 ml/min/1,73m²
- hypertension: 150/88 mmHg despite antihypertensive combination therapy incl. losartan 100 mg/d

CKD progression – albuminuria

- kidney biopsy 2014 in USA without definite pathological finding:
  - 3/35 glomeruli sclerosed
  - moderate arteriosclerosis (hypertensive damage?)
- uDKK3: <200 pg/mg

Wnt/β-catenin pathway

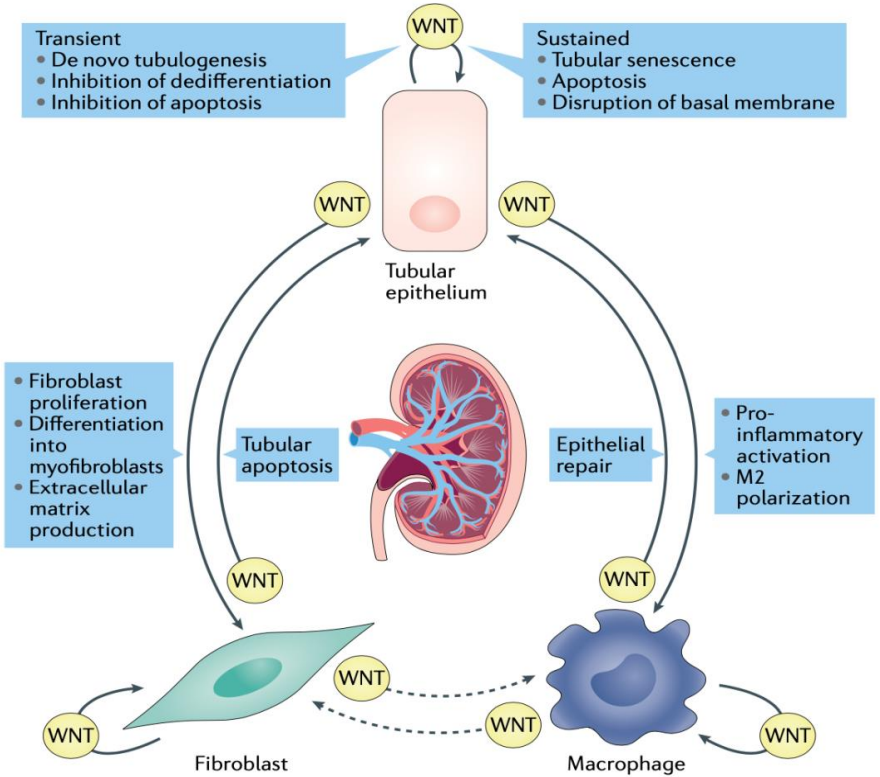


The name Wnt is created from the names Wingless and Int-1

The pathway is evolutionarily highly conserved – it is similar across animal species from fruit flies to humans

Speer et al. *Nat Rev Nephrol* 2020

Wnt/β-catenin pathway

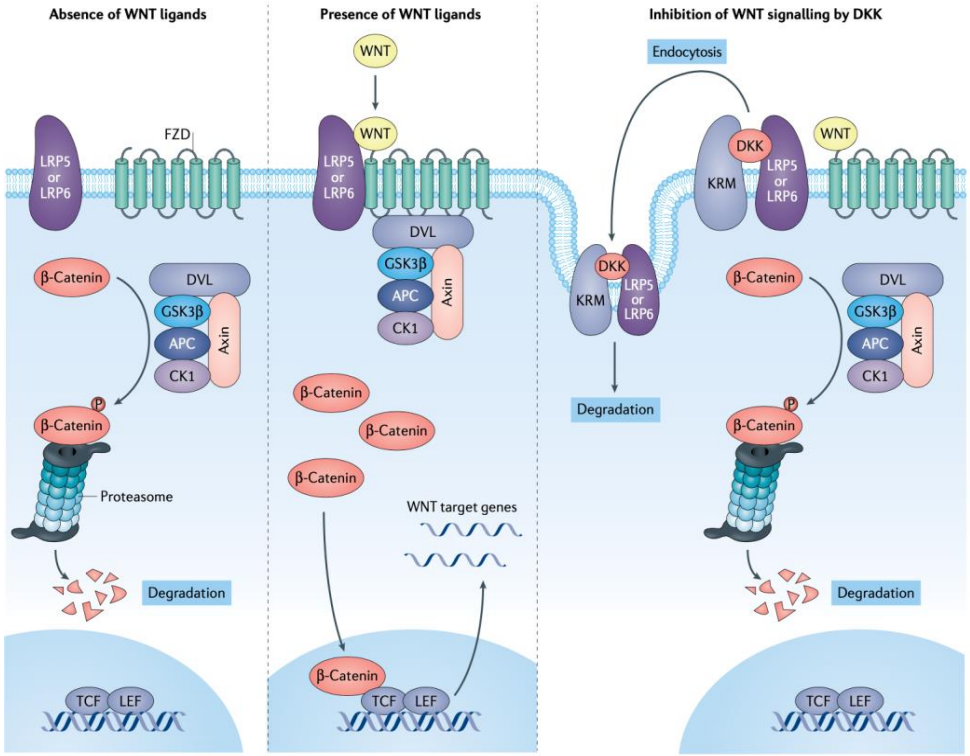


In renal tubular cells transient Wnt/β-catenin activation exerts repair and regeneration after injury

Prolonged uncontrolled Wnt/β-catenin signaling changes the phenotype of tubular cells into pro-inflammatory cells, which drive CKD progression, also through activation of the RAAS

Speer et al. *Nat Rev Nephrol* 2020

DKK and Wnt/β-catenin



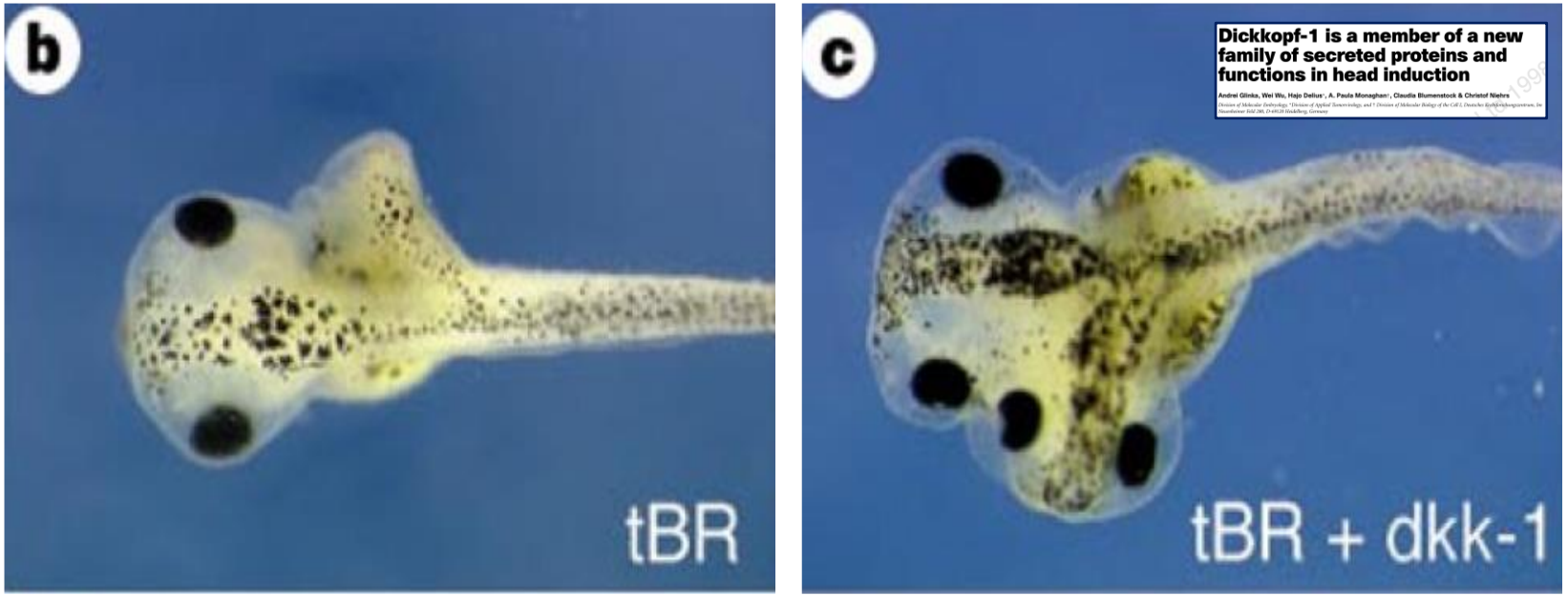
Dickkopf (DKK) proteins serve as modulators (ligands) of the Wnt/ß-catenin signaling pathway during embryogenesis and thereafter by re-expression after tissue injury

4 DKK proteins exist; mainly the role of DKK1 and DKK2 has been investigated in cancer biology

Speer et al. *Nat Rev Nephrol* 2020

DKK and Wnt/β-catenin

Dickkopf (German) = big head during enbriogenesis after knock-out of DKK1

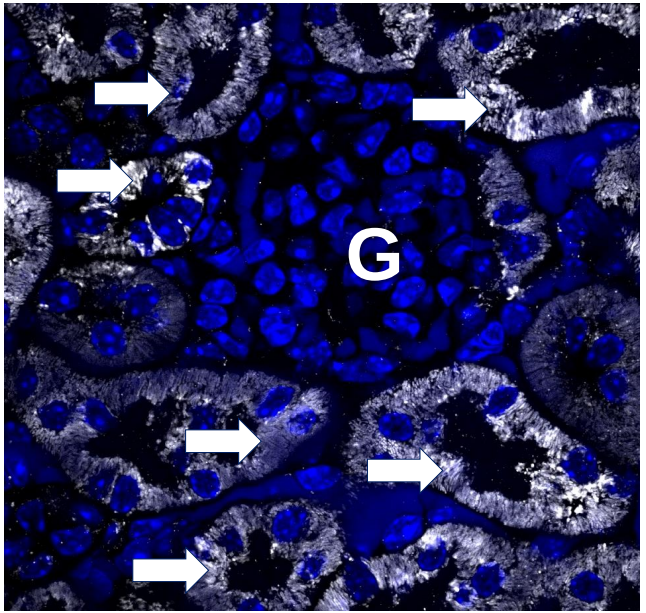


Glinka et al. *Nature* 1998

uDKK3 and CKD progression

DKK3 can be measured in urine using ELISA

Healthy subjects do not have detectable DKK3 in urine, whereas in CKD patients the urine DKK3 (uDKK3) concentration correlates with CKD progression irrespective of the type of kidney injury



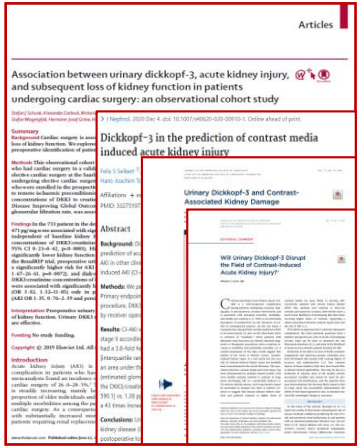
DKK3
(white staining within tubuli)

Speer et al. *Nat Rev Nephrol* 2020

uDKK3 and CKD progression

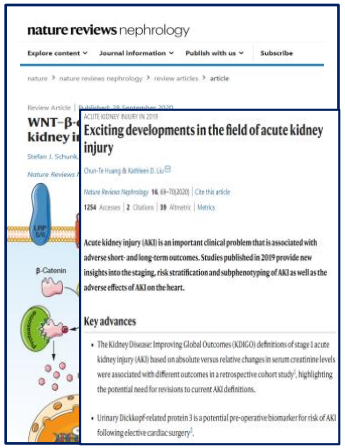
JCI insight 2016

JASN 2018
NDT 2019
Kidney Int 2021
NDT 2021
Front Med 2022
J Clin Med 2022
Lancet Child & Adolesc Health 2023
Clin Kidney J 2024



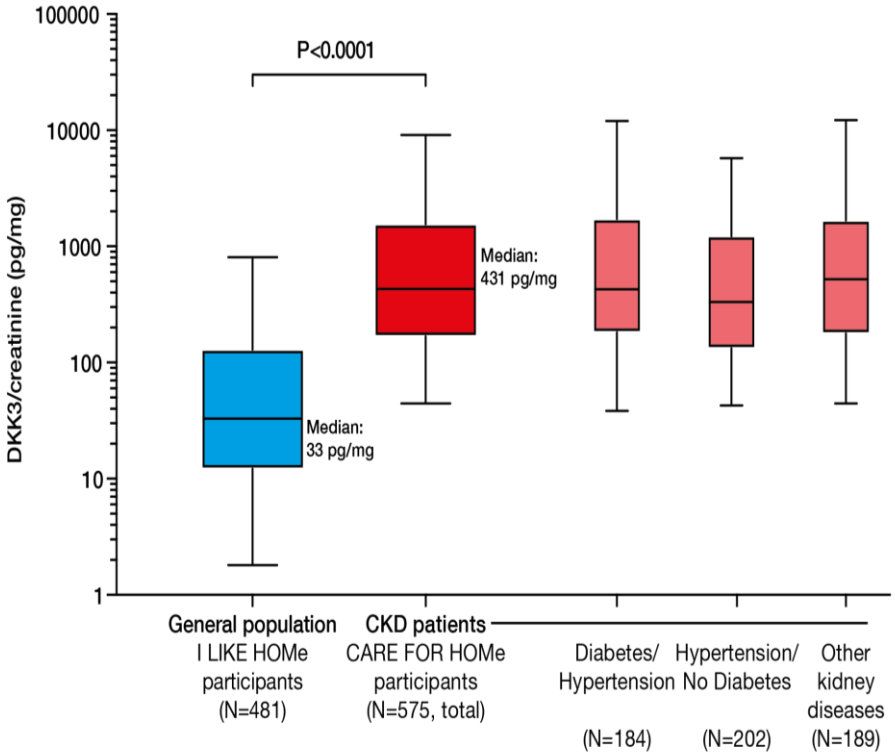
Lancet 2019
J Nephrol 2020
JACC 2021
JACC 2021
Ped Res 2022

NDT 2020
Front Physiol 2020
NDT 2021



Nat Rev Nephrol 2020
Nat Rev Nephrol 2020

uDKK3 and CKD progression



In healthy individuals only very small amounts of DKK3 are detectable in urine (blue box); in CKD patients the median urinary DKK3 level is ~13 times higher (red box) irrespective of the type of kidney injury

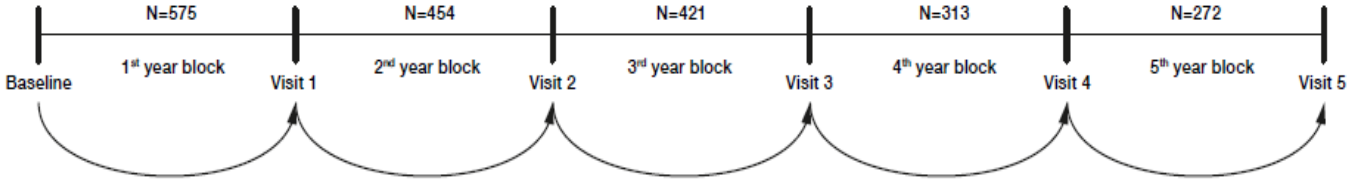
575 patients in CKD stage 2-4
481 controls

Zewinger et al. *J Am Soc Nephrol* 2018

uDKK3 and CKD progression

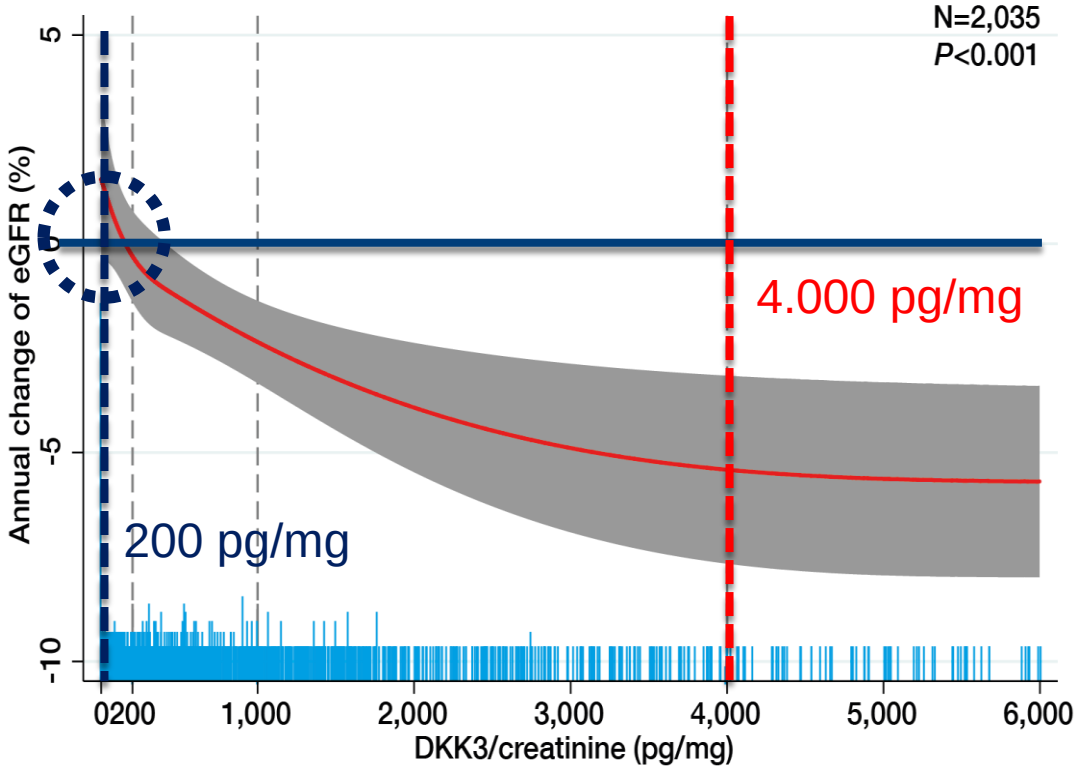
CARE FOR HOMe study

- 575 patients with CKD stage 2-4 (GFR >15 ml/min/1.73m²)
- mostly patients with diabetes mellitus and/or hypertension
- prospectively followed for up to 8 years (5.2 ± 2.1 years)
- annual visits with blood and urine samples
- a total of 2,035 person-years available for analysis



Zewinger et al. *J Am Soc Nephrol* 2018

uDKK3 and CKD progression



Association between uDKK3 and annual change of eGFR:

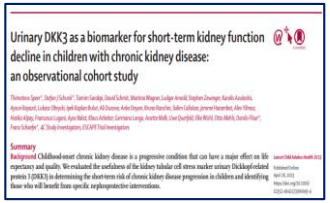
- red line: change of eGFR within the subsequent one year (the respective 95% confidence interval is the gray area)
- blue spikes: individual uDKK3 concentrations at the start of each 12-month observational period

Zewinger et al. *J Am Soc Nephrol* 2018

uDKK3 and CKD progression

4C Study

- observational study in 705 children between 6 and 17 years
- baseline eGFR 10-60 ml/min/1.73 m^2
- 6-monthly observations and biosampling for up to 8 years


Urinary DKK3 as a biomarker for short-term kidney function decline in children with chronic kidney disease: an observational cohort study

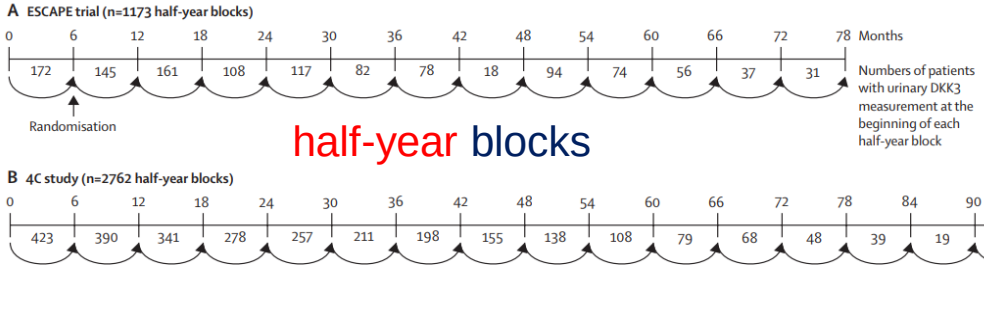
Summary

ESCAPE Trial

- randomized clinical trial in 385 children between 3 and 17 years
- all patients on fixed dose ACEI
- randomization for target 24h mean blood pressure 5^{th}-50^{th} v. 50^{th}-95^{th} pct
- baseline eGFR 15-80 ml/min/1.73 m^2
- 6-monthly observations and biosampling for up to 6 years

Speer et al. *Lancet Child Adolesc Health* 2023

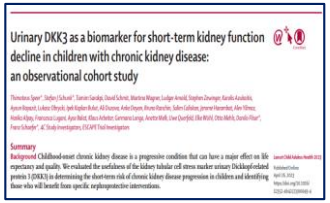
uDKK3 and CKD progression



ESCAPE trial

half-year blocks

4C study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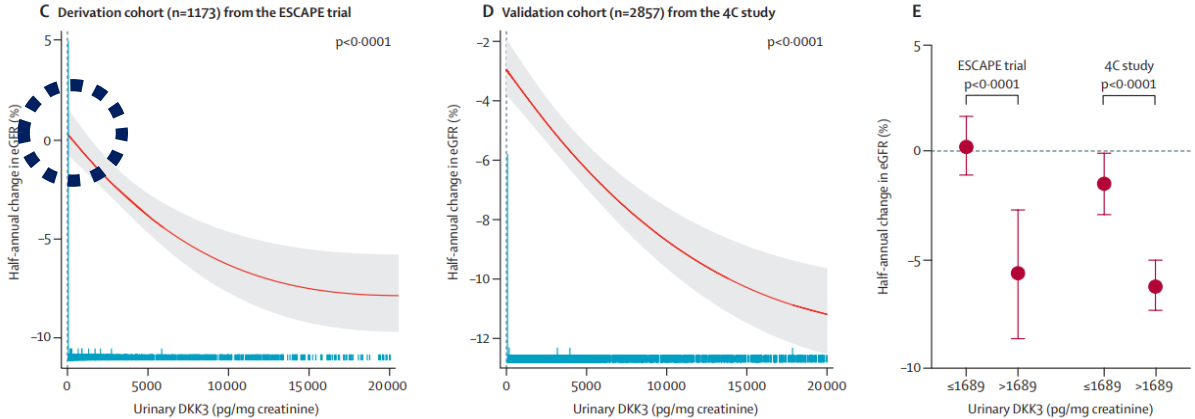


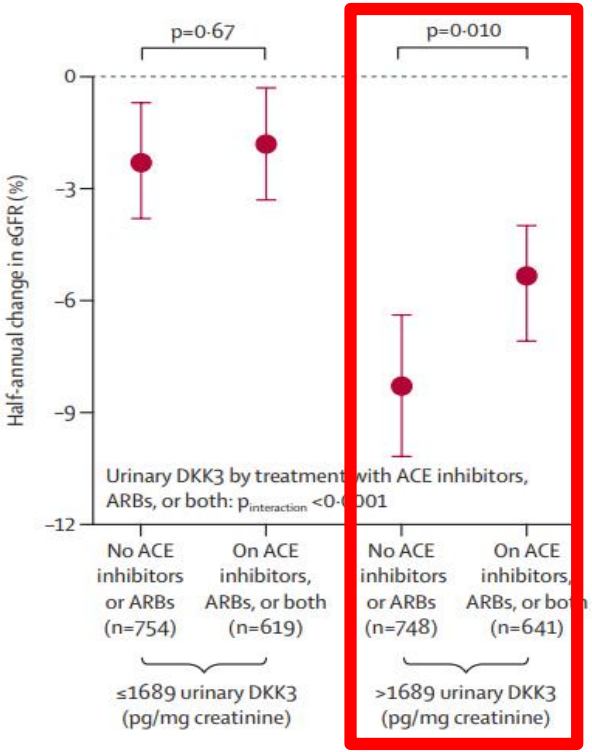
Speer et al. *Lancet Child Adolesc Health* 2023

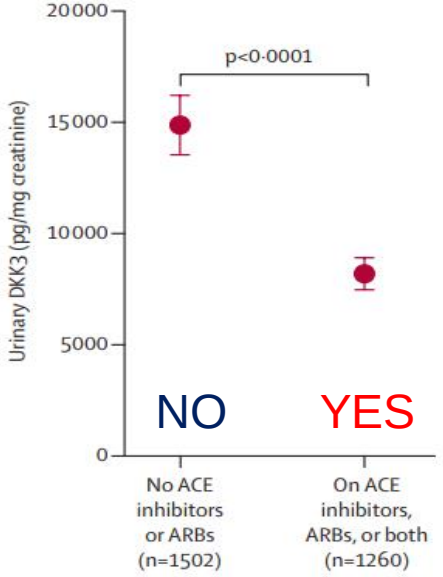
uDKK3 and CKD progression

uDKK3 is a supreme biomarker for progressive CKD:

- highly sensitive for detection of kidney tissue injury at any time
- non-specific, i.e. independent of the cause of kidney injury
- easy measurable in children and adults
- it might be relevant for treatment guidance or even a potential therapeutic target?

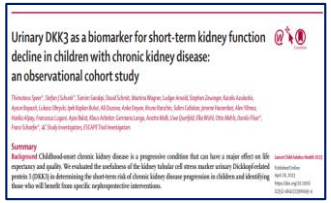
uDKK3 and treatment response





4CSTUDY

RAAS-inhibition


Urinary DKK3 as a biomarker for short-term kidney function decline in children with chronic kidney disease: an observational cohort study

Speer et al. *Lancet Child Adolesc Health* 2023

uDKK3 and treatment response

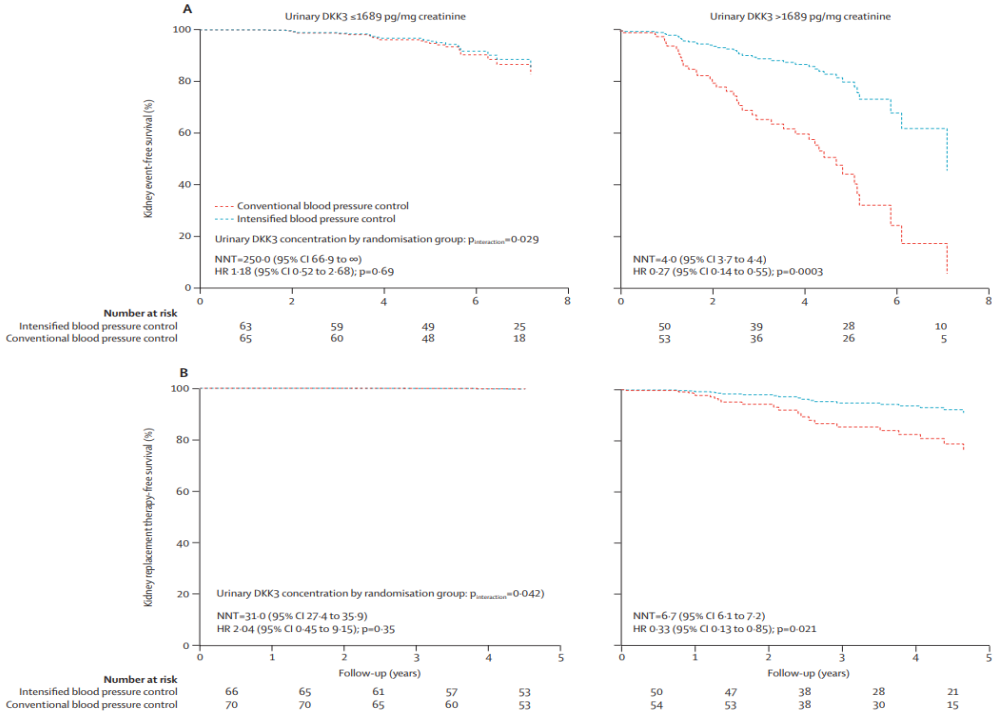
ESCAPE	all patients N=231	uDKK3 ≤1,689 pg/mg N=128	uDKK3 >1,689 pg/mg N=103	P
age (years)	12.0 ± 3.9	12.1 ± 3.8	11.7 ± 3.9	0.376
male (%)	58.9	59.9	57.7	0.792
glomerulonephritis (%)	12.9	14.6	10.6	0.159
CAKUT (%)	72.6	67.9	78.8	
others (%)	14.5	17.5	10.6	
diabetes (%)	0	0	0	0.999
hypertension (%)	3.5	3.8	3.1	0.999
systolic blood pressure	-0.01 ± 1.08	0.02 ± 1.01	-0.07 ± 1.15	0.529
eGFR (ml/min/1,73m^2)	44.9 ± 20.0	54.1 ± 19.3	36.1 ± 17.0	<0.001
albuminuria (g/g)	0.66 (1.83)	0.63 (1.49)	0.73 (3.97)	0.270
uDKK3 (pg/mg)	1,098 (7,168)	160 (716)	8,693 (20,259)	<0.001

Speer et al. *Lancet Child Adolesc Health* 2023

uDKK3 and treatment response

160 pg/mg

8,693 pg/mg



primary combined kidney endpoint

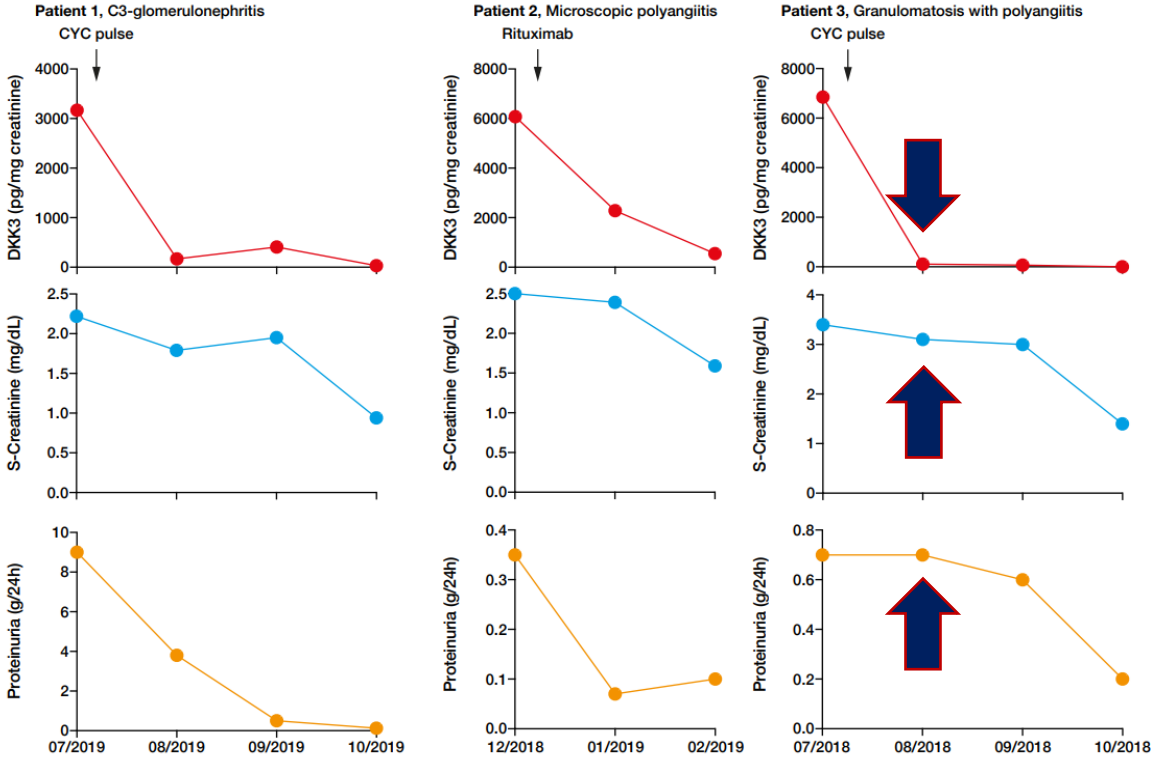
NNT 250.0 vs. 4.0

end-stage kidney disease (ESKD)

NNT: 31.0 vs. 6.7

Speer et al. *Lancet Child Adolesc Health* 2023

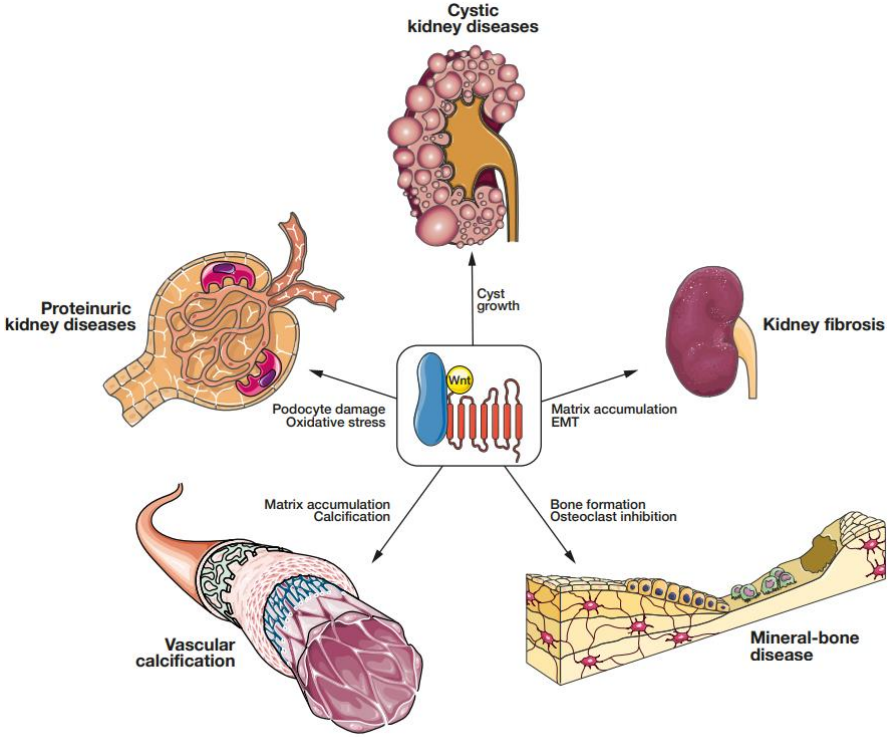
uDKK3 and treatment response



Schunk et al. *Nephrol Dial Transplant* 2020


Fin del Mundo

Wnt/β-catenin pathway

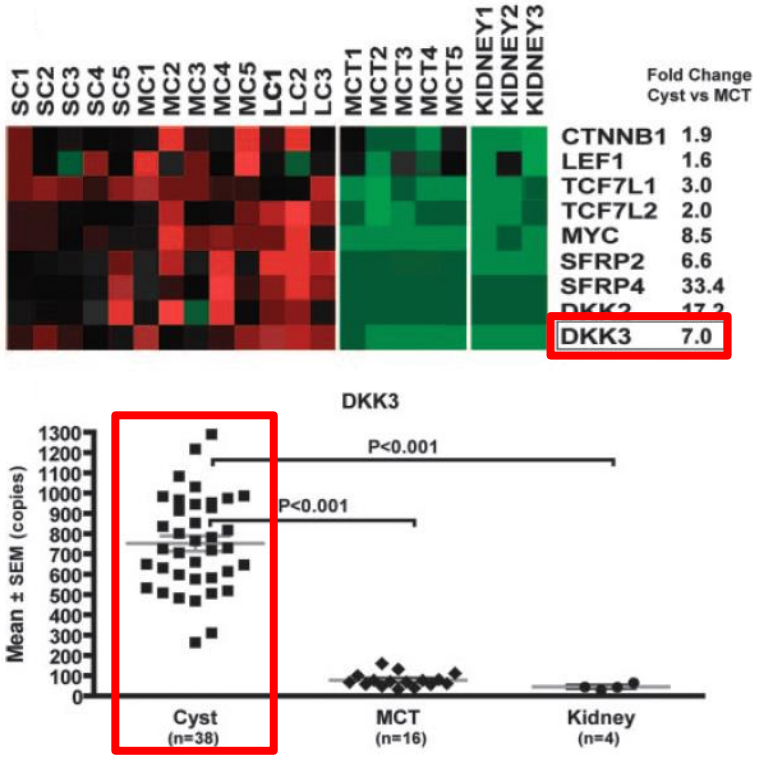


Wnt/b-catenin signaling promotes:

- cyst growth and kidney disease
- proteinuric kidney diseases
- vascular calcification
- mineral-bone disease
- kidney tissue fibrosis

Speer et al. *Nat Rev Nephrol* 2020

DKK3 and ADPKD



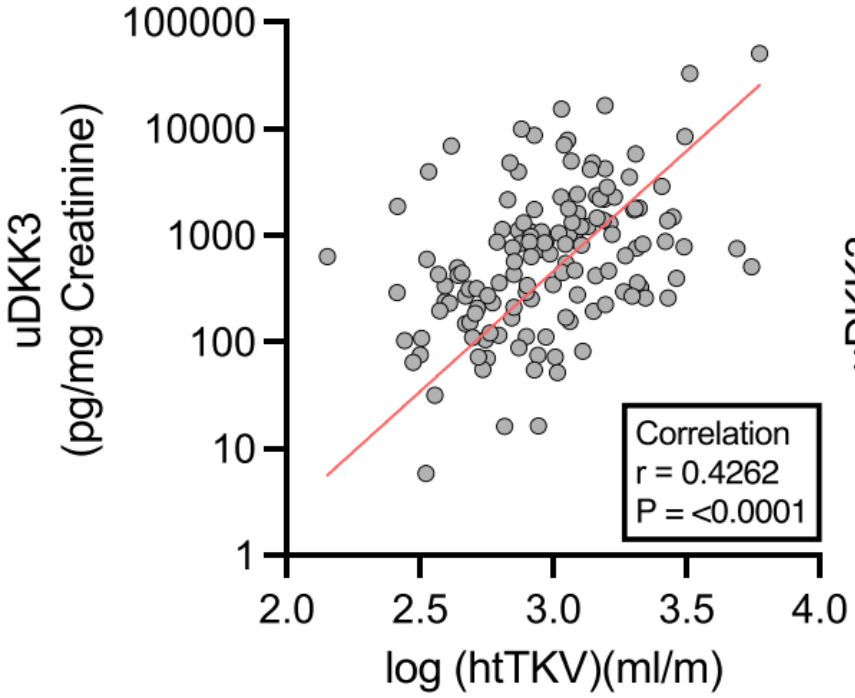
BASIC RESEARCH www.jasn.org

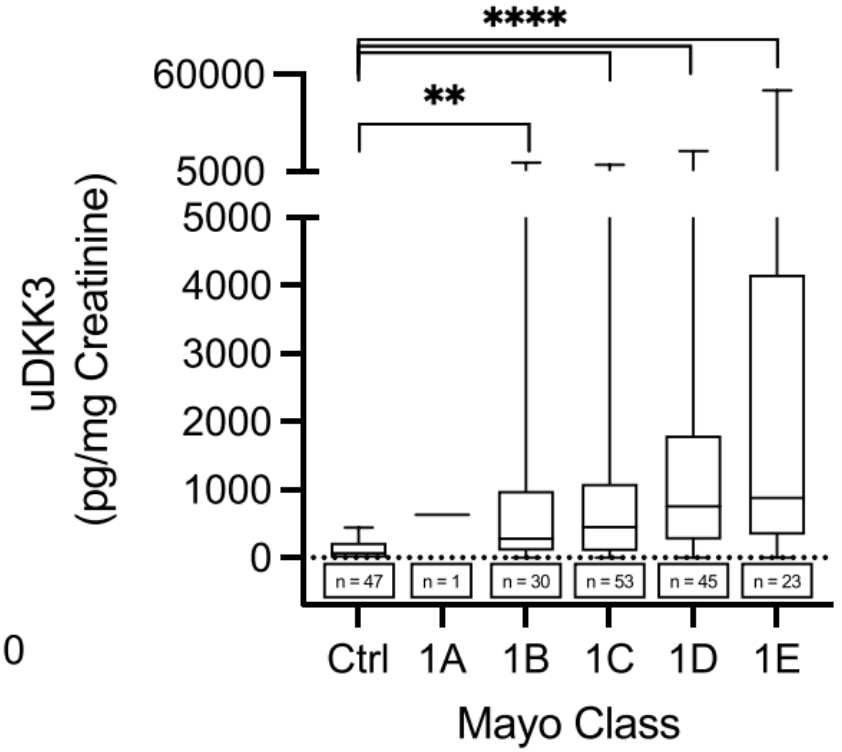
Genetic Variation of DKK3 May Modify Renal Disease Severity in ADPKD

- high-throughput single-nucleotide polymorphism (SNP) genotyping association study of 173 candidate genes in 794 white patients from 227 families with PKD1
- real-time RT-PCR analysis of DKK3 in renal cysts

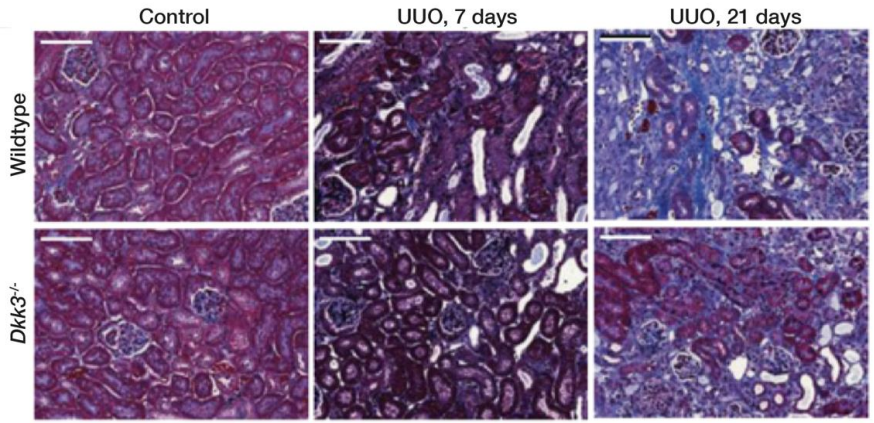
Liu et al. *J Am Soc Nephrol* 2010

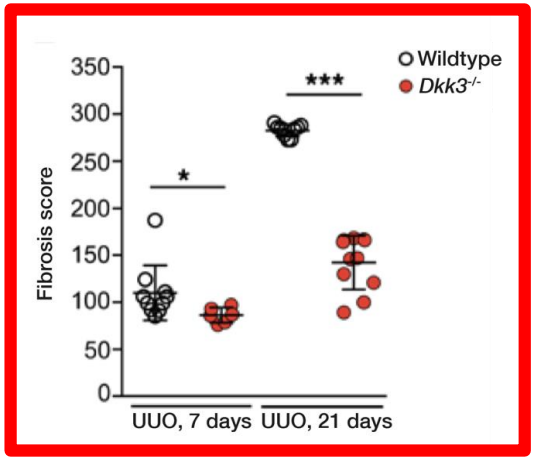
uDKK3 and ADPKD

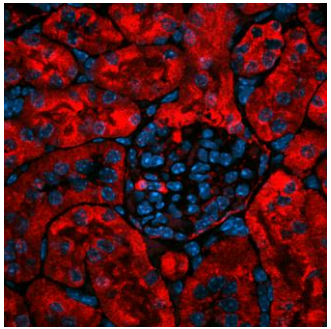


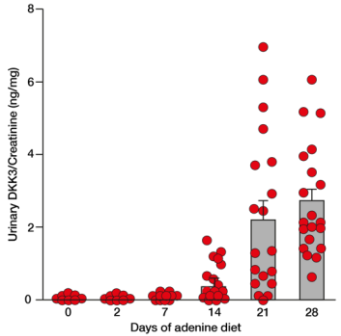


DKK3 and kidney fibrosis





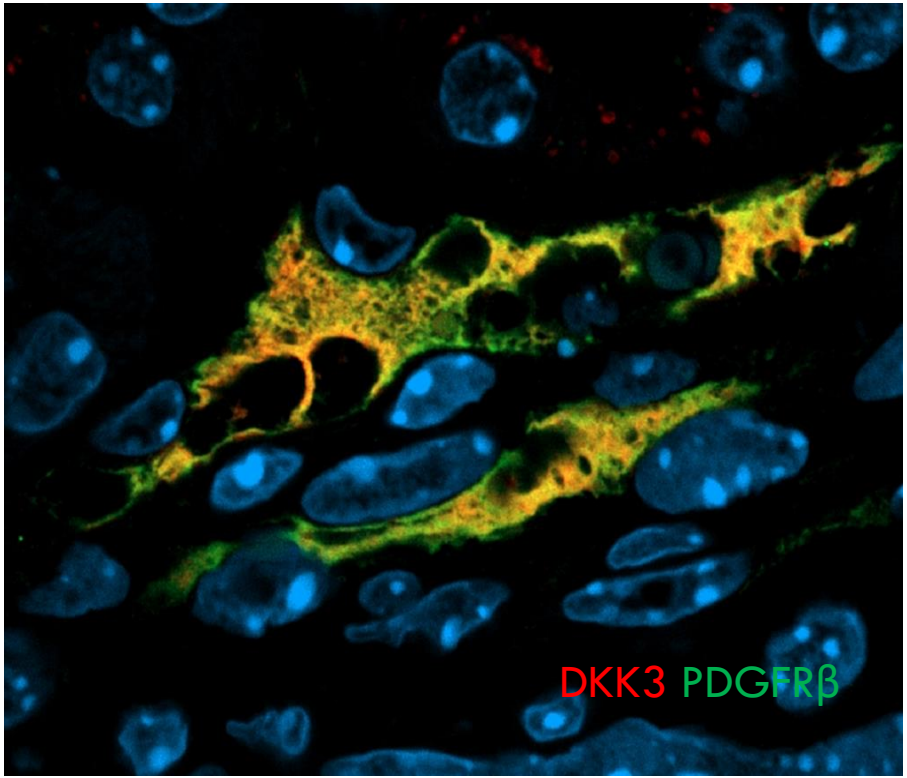




DKK3 is a stress-induced, mainly tubular cell derived pro-fibrotic glycoprotein that is secreted in the urine only upon kidney injury

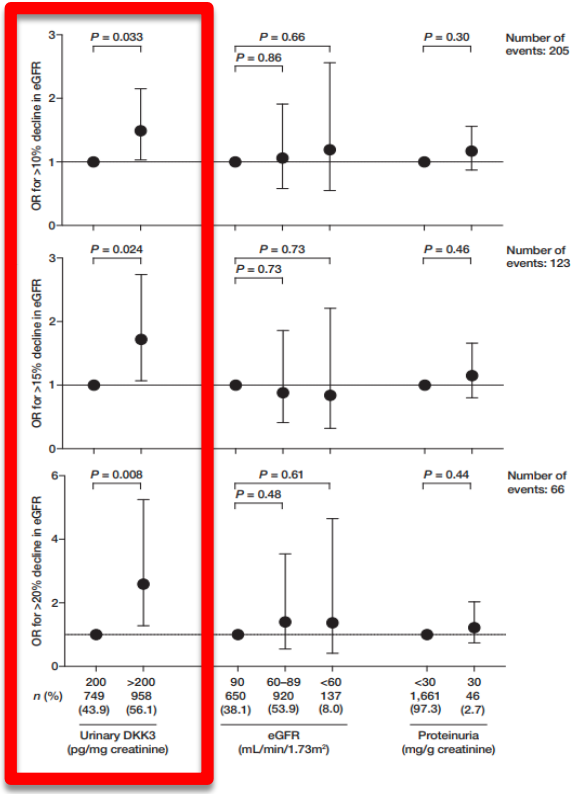
Federico et al. *J Clin Invest Insight* 2016

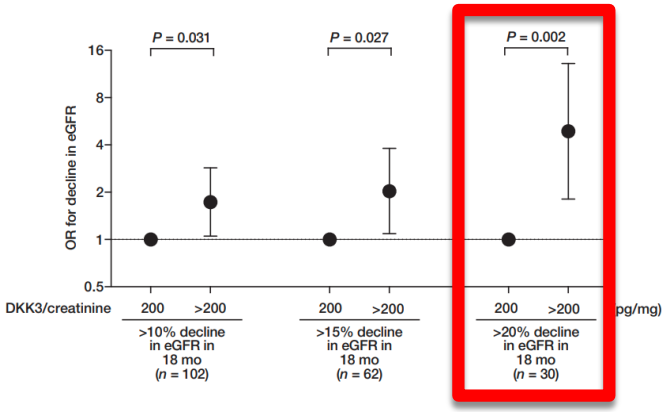
DKK3 and kidney fibrosis



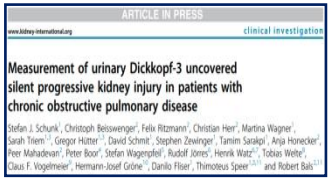
- Co-staining DKK3 and PDGFR-β
- fibroblasts seem to play a key role in (sustained) DKK3 expression
- they are probably „activated“ by co-localized tubular cells in a paracrine manner

uDKK3 and CKD progression





patients with
eGFR >90 ml/min/1,73m²
without albuminuria


ARTICLE IN PRESS
www.kidney-international.org
clinical investigation

Measurement of urinary Dickkopf-3 uncovered silent progressive kidney injury in patients with chronic obstructive pulmonary disease

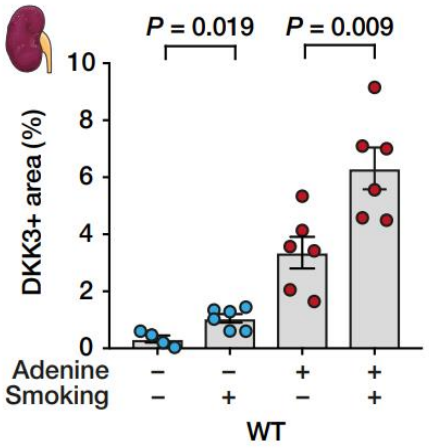
Stefan J. Schunk[1], Christoph Beiswenger[2], Felix Ritzmann[1], Christian Herr[2], Martina Wagner[1], Sarah Triem[1,3], Gregor Hütter[1,3], David Schmit[1], Stephen Zewinger[1], Tamim Sarakpi[1], Anja Honecker[1], Peer Mahadevan[1], Peter Boor[4], Stefan Wagenpfeil[5], Rudolf Jörres[6], Henrik Watz[7,8], Tobias Welte[9], Claus F. Vogelmeier[9], Hermann-Josef Gröne[10], Danilo Fliser[1], Thimoteus Speer[1,3,11] and Robert Bals[12]

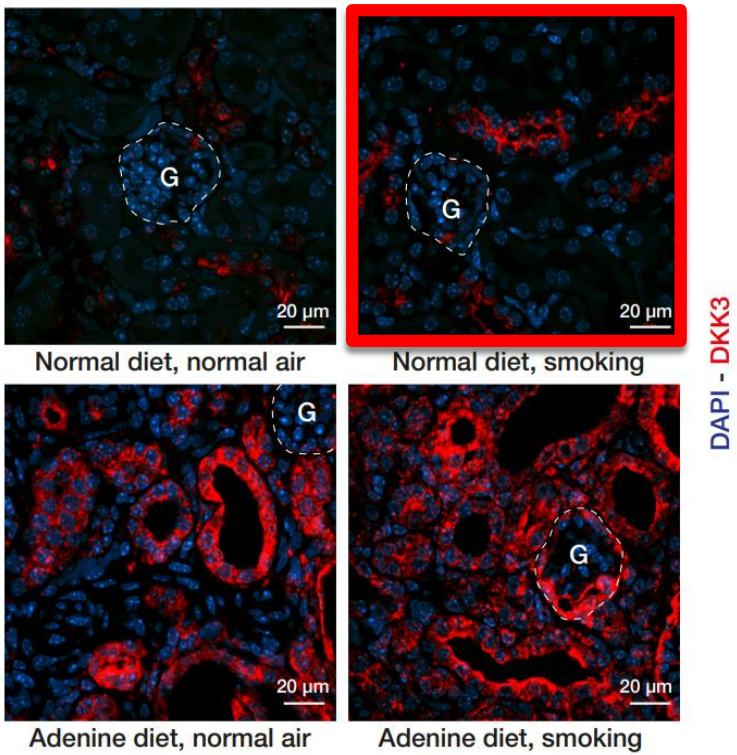
2.314 patients with
Chronic Obstructive
Pulmonary Disease

18 months follow-up

Schunk et al. *Kidney Int* 2021

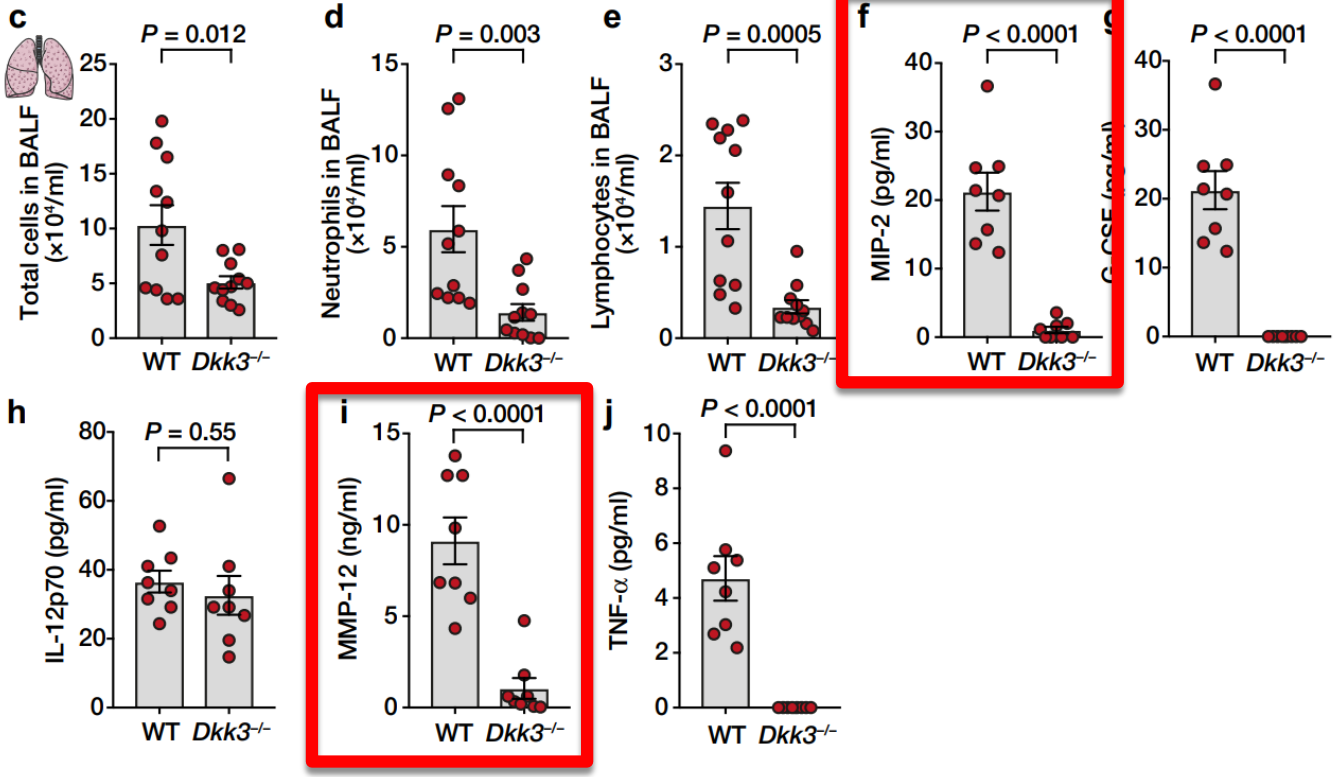
DKK3 and the lung



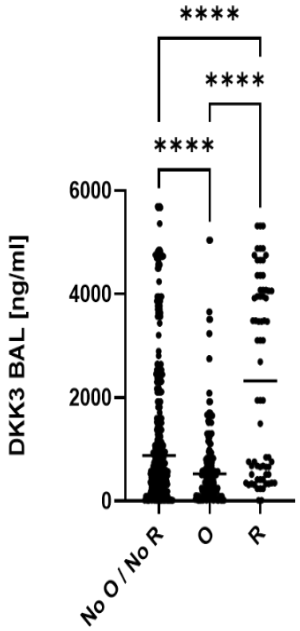


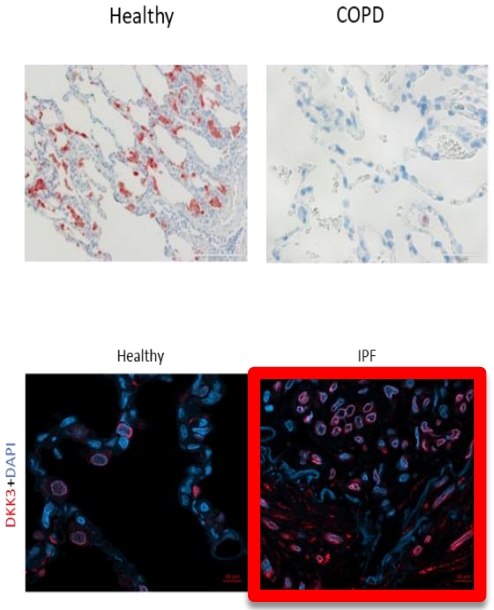
Schunk et al. *Kidney Int* 2021

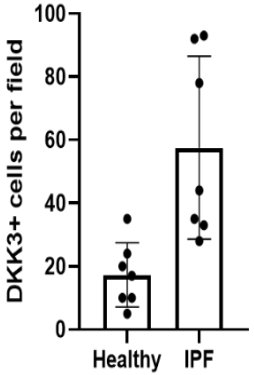
DKK3 and the lung



DKK3 and the lung

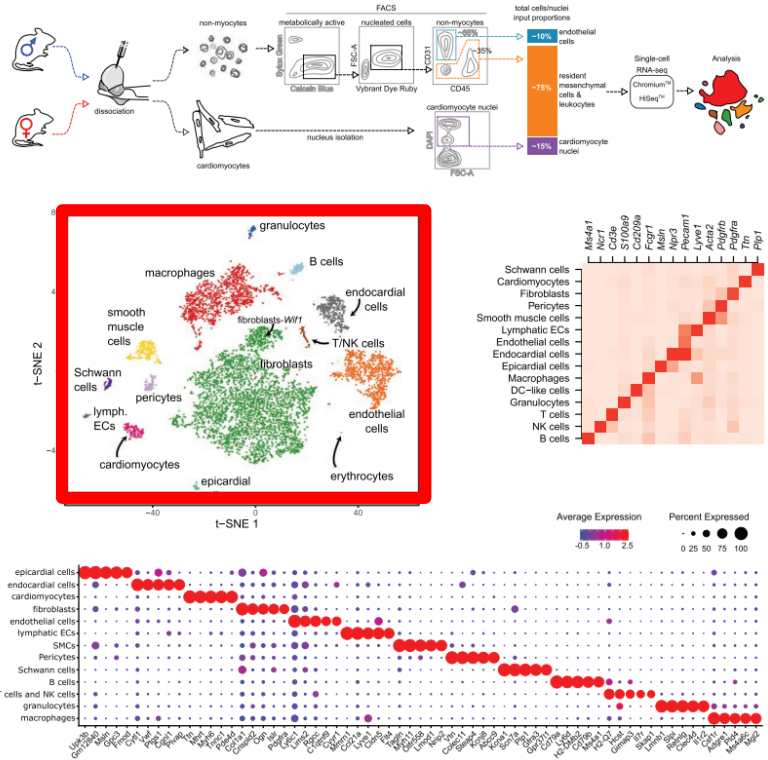






DKK3 is significantly increased in the BAL fluid in patients with COPD

DKK3 and the heart

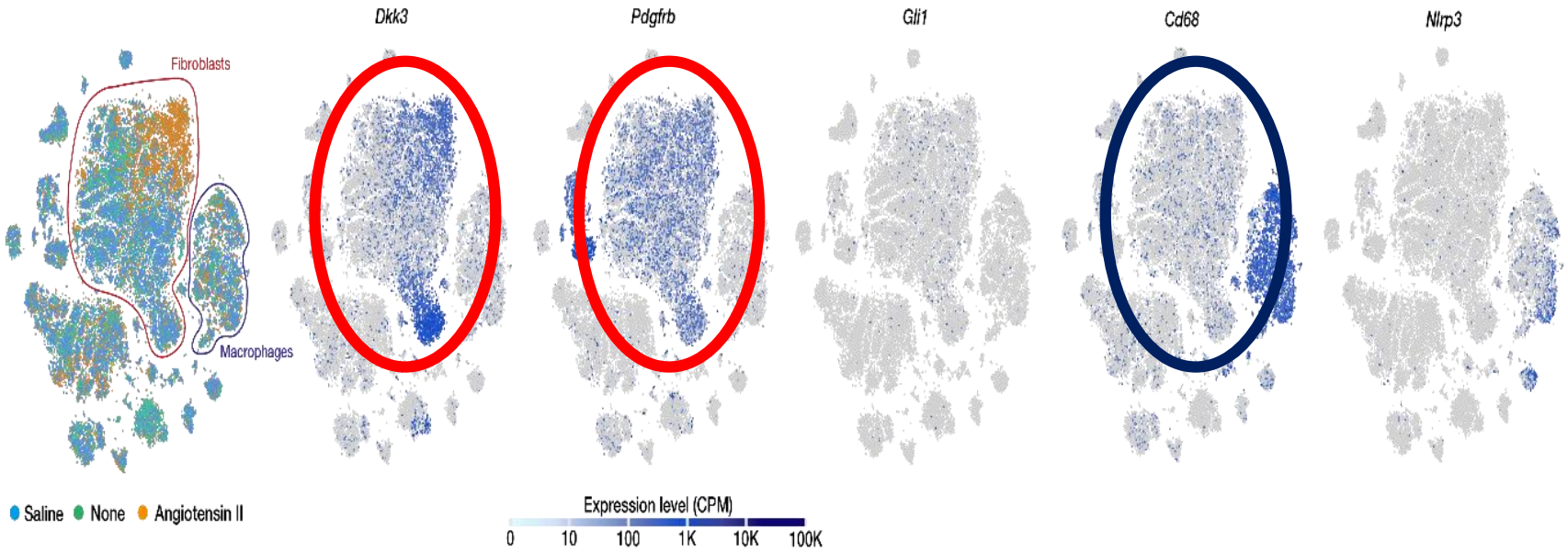


Cardiac single-cell transcriptomic strategy to characterize the cardiac cellulome – i.e. the network of cells that forms the heart – after 2 weeks of continuous administration of angiotensin II, a strong pro-fibrotic stimulus of pathological cardiac remodeling

McLellan et al. *Circulation* 2021

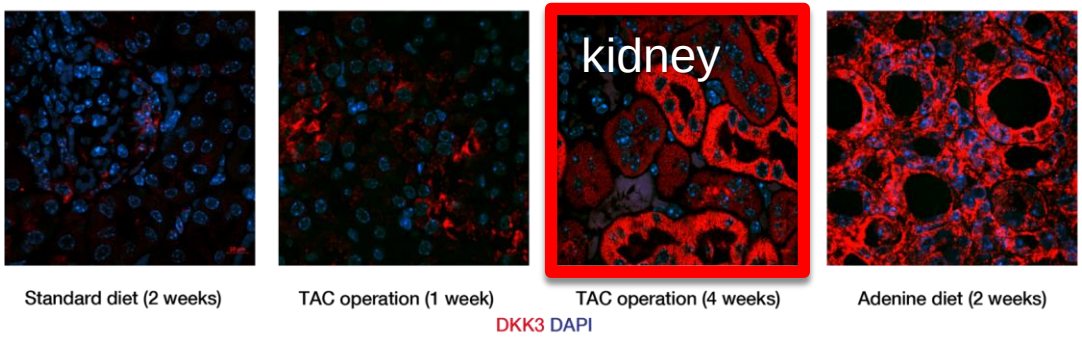
DKK3 and the heart

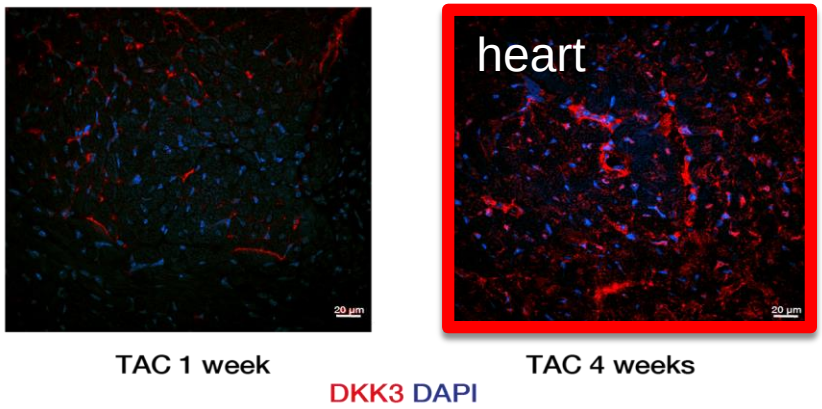
Significant expression of DKK3 in cardiac fibroblasts (PDGFR-ß+) and macrophages (CD68+)/NLRP3 in the left ventricle



McLellan et al. *Circulation* 2021

The kidney-heart interaction





doi:10.1093/eurheartj/ehy083

The new SFB/TRR219 Research Centre

A new Transregional Collaborative Research Center of the German Research Foundation (DFG) has been created to address reno-cardiovascular interactions underlying the increased cardiovascular risk in patients with chronic kidney disease to develop novel treatment strategies to reduce cardiovascular morbidity and mortality in these high-risk patients

uDKK3 and CKD progression

uDKK3 is a supreme biomarker for progressive CKD:

- highly sensitive for detection of kidney tissue injury at any time
- non-specific, i.e. independent of the cause of kidney injury
- easy measurable in children and adults
- it may be relevant for treatment guidance as well as a potential therapeutic target to prevent tissue fibrosis

UKS
Universitätsklinikum
des Saarlandes

Thank you!

ERA
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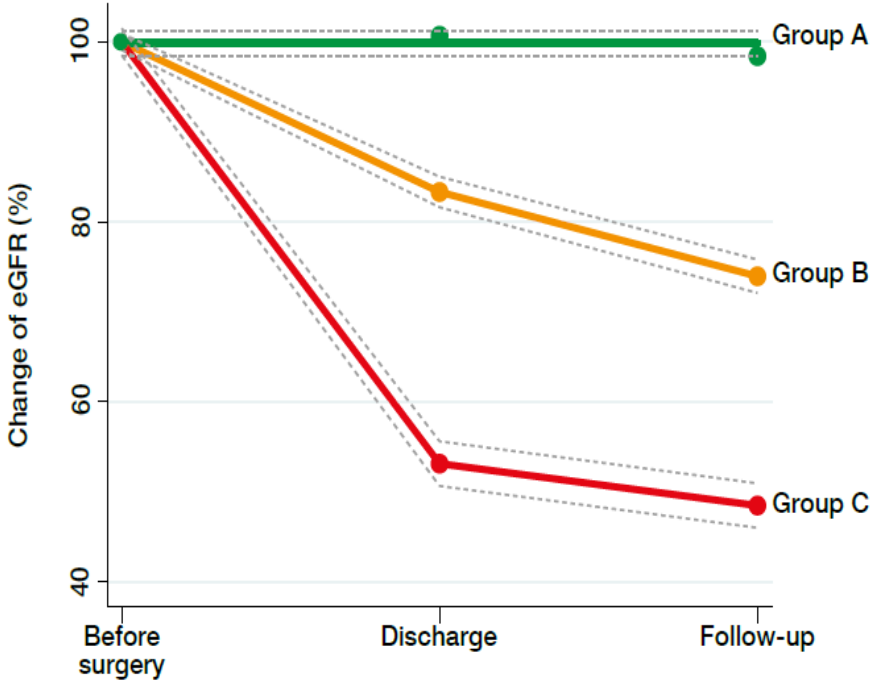
uDKK3 and AKI-CKD transition

HTC study

- prospective observational study with 733 consecutive patients undergoing elective cardiac surgery (mean eGFR 89 ml/min/1.73m²)
- assessment of kidney function (eGFR) before surgery, after hospital discharge and up to 3 years thereafter (median follow-up 820 days)
- measurement of uDKK3 before surgery

Schunk et al. *Lancet* 2019

uDKK3 and AKI-CKD transition



3 distinct eGFR trajectories corresponding to patients with:

- group A (low uDKK3): no AKI and no loss of kidney function
- group B (high uDKK3): moderate loss of GFR after AKI and CKD progression
- group C (very high uDKK3): severe loss of GFR after AKI and CKD progression

Schunk et al. *Lancet* 2019