UKS
Universitätsklinikum
des Saarlandes

Univ.-Prof. Dr. Danilo Fliser

Innere Medizin IV
Nieren- und Hochdruckkrankheiten

Progressionsmarker bei (fortgeschrittener) CKD

DFG
SFB/TRR 219

DARLEGUNG POTENTIELLER INTERESSENSKONFLIKTE

Berliner DialyseSeminar

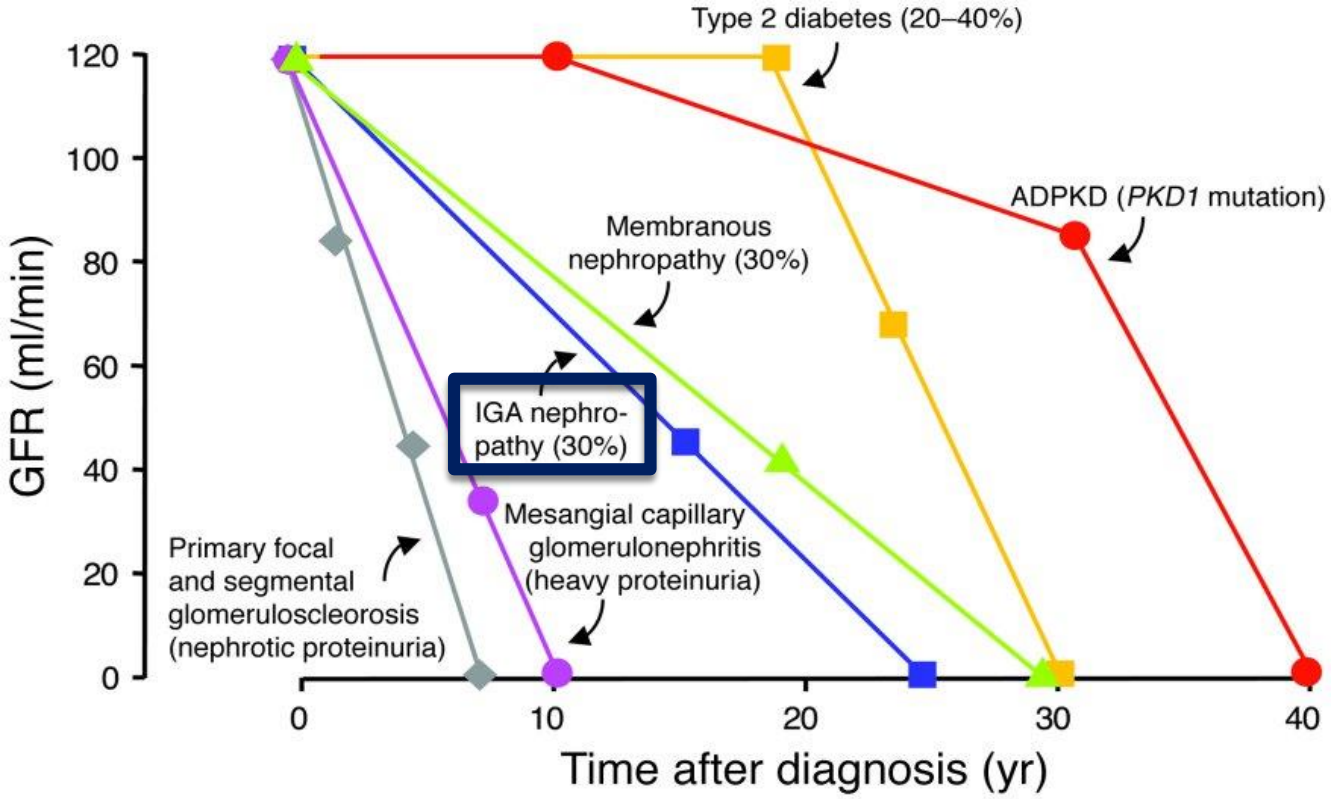
Der Inhalt des folgenden Vortrages ist Ergebnis des Bemühens um größtmögliche Objektivität und Unabhängigkeit.

Als Referent weise ich darauf hin, dass es **persönliche Verbindungen** zu Unternehmen gibt, deren Produkte im Kontext des folgenden Vortrages von Interesse sind. Dabei handelt es sich um die folgenden Unternehmen und Verbindungen:

Unternehmen	**Verbindungen** (Honorar für Vortrags-, Autoren-, Gutachter- oder Beratungstätigkeiten; Honorar für Vorbereitung von Fortbildungen; Erstattung von reise- oder Übernachtungskosten; Erstattung von Teilnahmegebühren an Fortbildungen; Patente; Geld aus Lizenzen/Tantiemen; Honorar für Durchführung von Auftragsstudien; Erhalt von Forschungsgeldern; andere)
DiaRen UG	Andere

Progression bei CKD

Remuzzi et al. ***J Clin Invest*** 2006



Progression bei CKD

Corresh et al. ***JAMA*** 2014

First eGFR in the 2-year baseline period	Follow-up time after the last eGFR	Percent decline in eGFR during the 2-year baseline period					
		57% decline	40% decline	30% decline	25% decline	20% decline	Stable
20	1 year	63%	31%	19%	15%	11%	3.9%
	3 year	97%	72%	52%	43%	34%	13%
	5 year	100%	94%	80%	71%	60%	26%
	10 year	100%	100%	99%	97%	92%	57%
35	1year	20%	8.1%	4.8%	3.7%	2.7%	0.95%
	3 year	54%	25%	16%	12%	9.2%	3.3%
	5 year	82%	47%	31%	25%	19%	7.0%
	10 year	99%	83%	64%	55%	44%	18%
50	1 year	5.0%	1.9%	1.1%	0.86%	0.63%	0.23%
	3 year	16%	6.4%	3.8%	3.0%	2.2%	0.80%
	5 year	32%	14%	8.1%	6.4%	4.7%	1.7%
	10 year	66%	33%	21%	17%	12%	4.8%
65	1 year	0.71%	0.20%	0.090%	0.061%	0.037%	0.014%
	3 year	3.9%	1.1%	0.49%	0.34%	0.21%	0.079%
	5 year	12%	3.5%	1.6%	1.1%	0.68%	0.26%
	10 year	37%	12%	5.5%	3.9%	2.4%	0.90%
80	1 year	0.45%	0.12%	0.054%	0.038%	0.023%	0.0090%
	3 year	2.5%	0.70%	0.31%	0.21%	0.13%	0.050%
	5 year	7.9%	2.2%	1.0%	0.69%	0.42%	0.16%
	10 year	25%	7.7%	3.4%	2.4%	1.5%	0.58%

Colors indicating absolute risk gradient (based on percentiles of the cells in the table):

100%	73%	43%	20%	12%	5.2%	3.1%	1.1%	0.62%	0.16%	0.01%

1,7 Mil. Probanden
12.344 CKD Stadium 5D
35 Kohorten
(CKD Prognosis Consortium)

Progression bei CKD

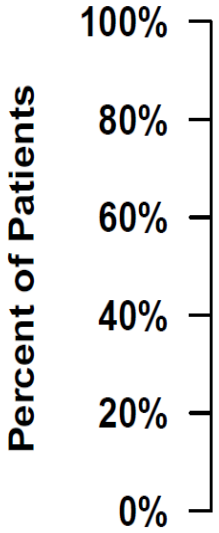
Reichel et al. ***ERA-EDTA*** 2018

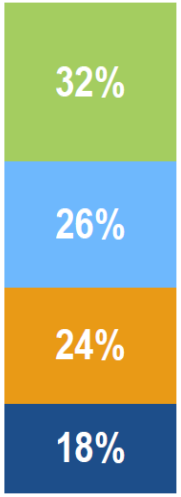
	Overall	Stage 3	Stage 4
N	1836	483	1353
Age, years	75 (67-81)	74 (65-78)	76 (68-82)
Male	58%	64%	56%
Primary Cause of CKD			
Diabetes	29%	24%	**31%**
Hypertension	33%	35%	**32%**
Polycystic Kidney Disease	4%	3%	4%
Tubulointerstitial Nephritis	6%	7%	6%
Other	26%	29%	25%
Comorbidities			
Diabetes	43%	40%	**43%**
Hypertension	86%	86%	**86%**
Heart Failure	11%	6%	12%
Coronary Artery Disease	29%	29%	28%
eGFR, mL/min/1.73m²	25 (21-31)	40 (35-48)	**23 (19-26)**
Systolic Blood Pressure, mmHg	139 (19)	137 (18)	139 (19)
Diastolic Blood Pressure, mmHg	77 (11)	77 (11)	76 (11)

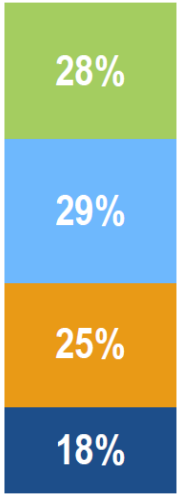
CKD PPS

Progression bei CKD

Reichel et al. ***ERA-EDTA*** 2018







	CKD Stage 3	CKD Stage 4
N:	432	1138
Months Follow-up, Mean (SD):	37 (16)	31 (16)

CKD PPS

Change in eGFR
mL/min/1.73m^2/year

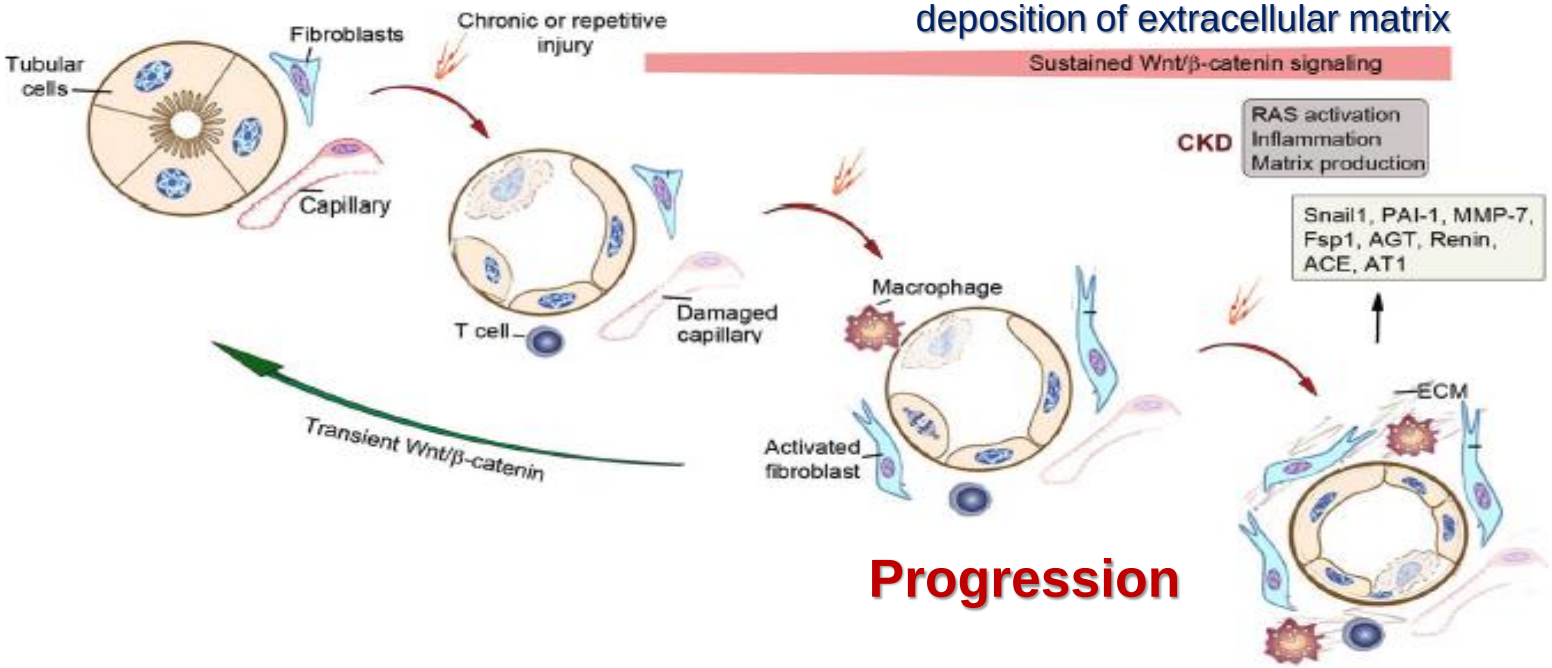
- > 0
- −2 to 0
- −5 to −2
- < −5

Wnt und Progression

Zhou et al. ***Lab Invest*** 2016

Regeneration/Reparatur

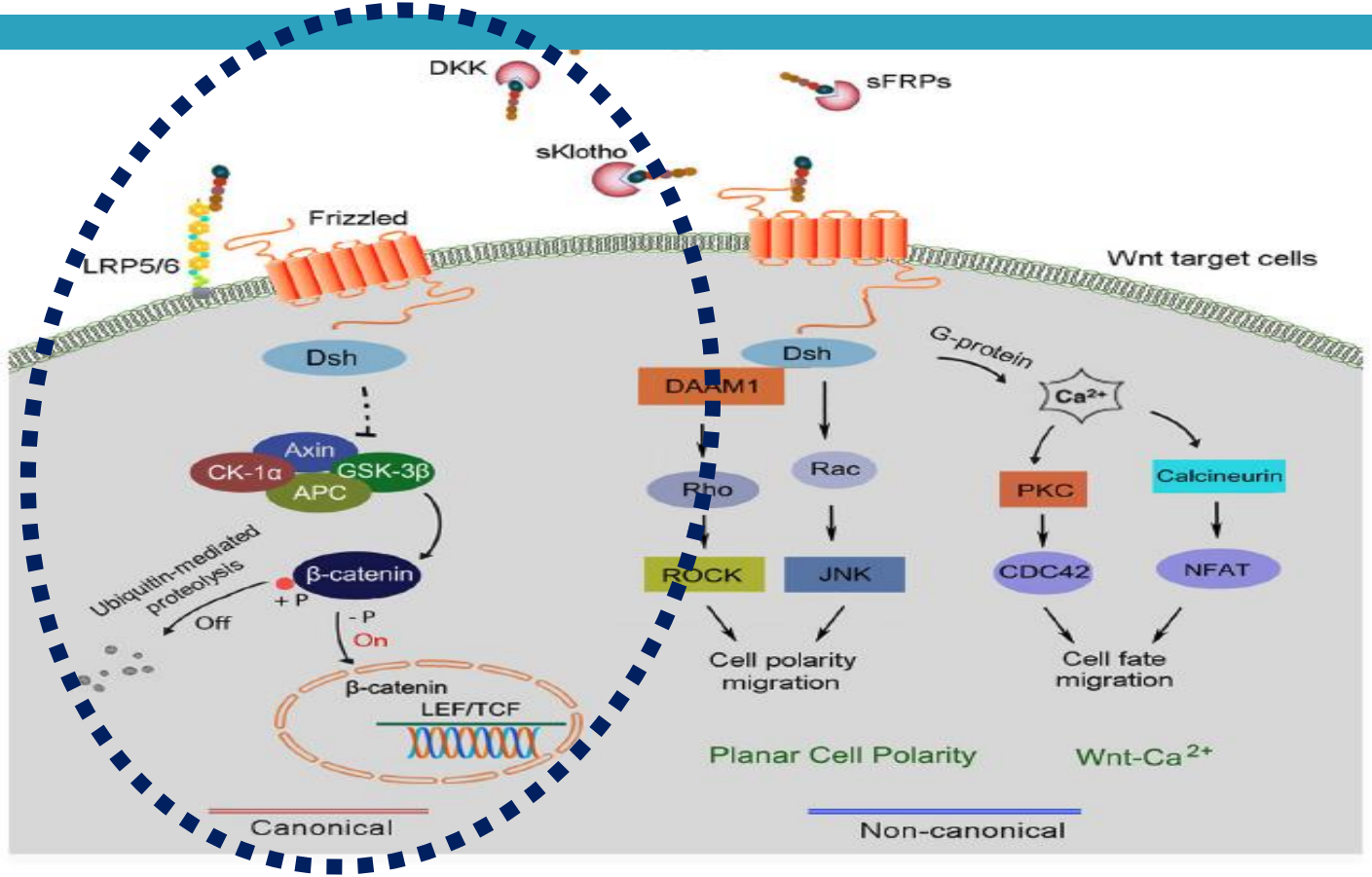
Sustained Wnt/ß-catenin signaling causes uncontrolled fibroblast activation, RAS activation, inflammation and excessive deposition of extracellular matrix



Progression

DKK und WnT

Zhou et al. ***Lab Invest*** 2016



DKK3 und Nierenfibrose

Federico et al. ***JCI Insight*** 2016

JCI insight

RESEARCH ARTICLE

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

Giuseppina Federico,[1] Michael Meister,[2] Daniel Mathow,[1] Gunnar H. Heine,[3] Gerhard Moldenhauer,[2] Zoran V. Popovic,[1] Viola Nordström,[1] Annette Kopp-Schneider,[4] Thomas Hielscher,[4] Peter J. Nelson,[5] Franz Schaefer,[6] Stefan Porubsky,[1] Danilo Fliser,[3] Bernd Arnold,[2] and Hermann-Josef Gröne[1]

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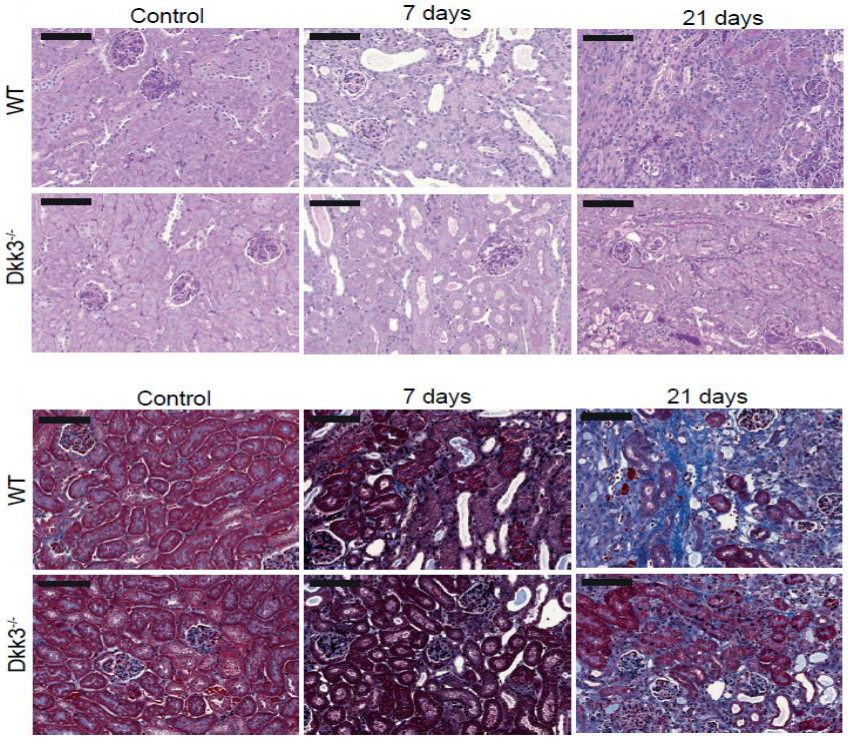
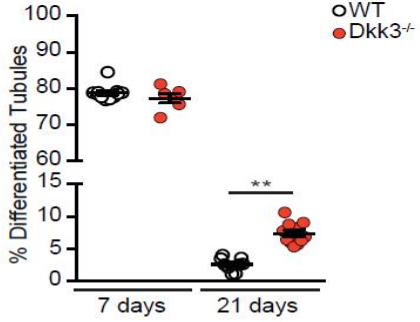
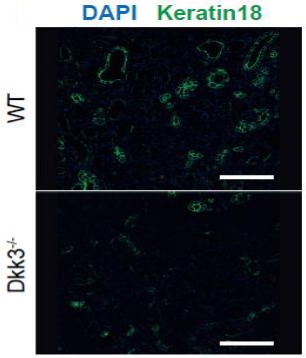
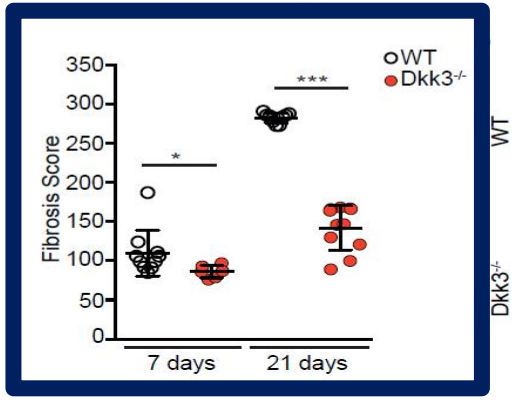
DKK3 und Nierenfibrose

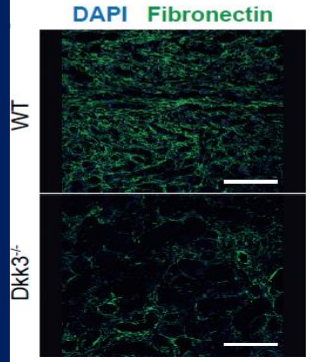
Federico et al. ***JCI Insight*** 2016





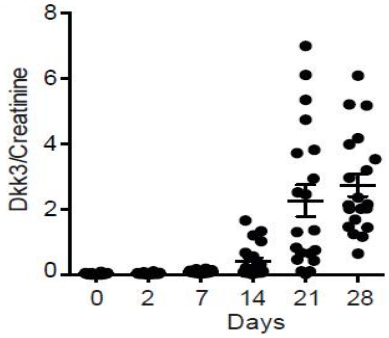


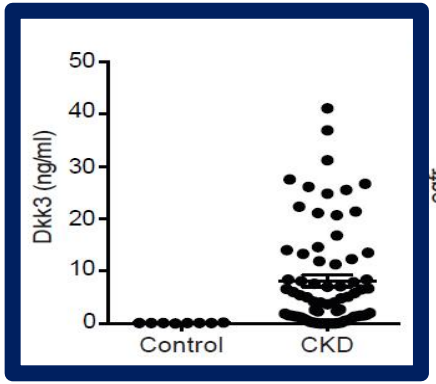


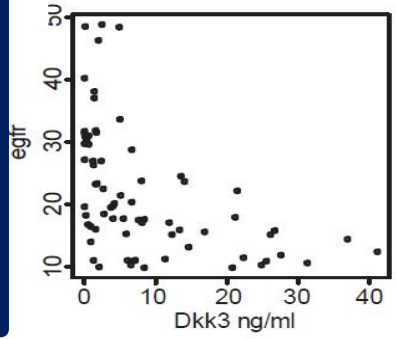


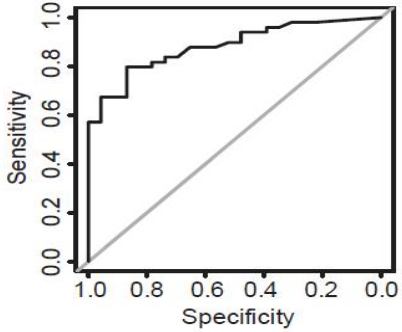
DKK3 und Nierenfibrose

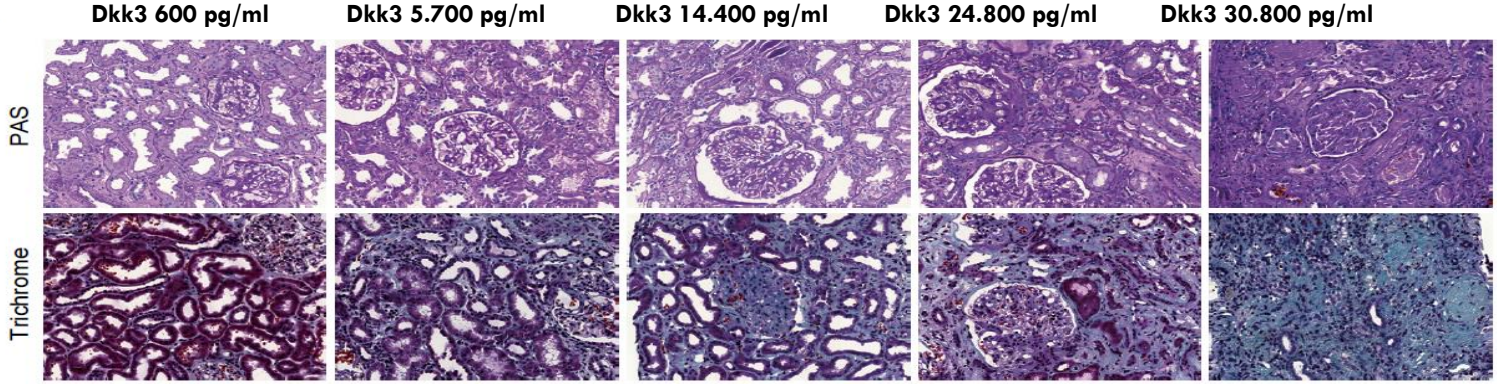
Federico et al. ***JCI Insight*** 2016





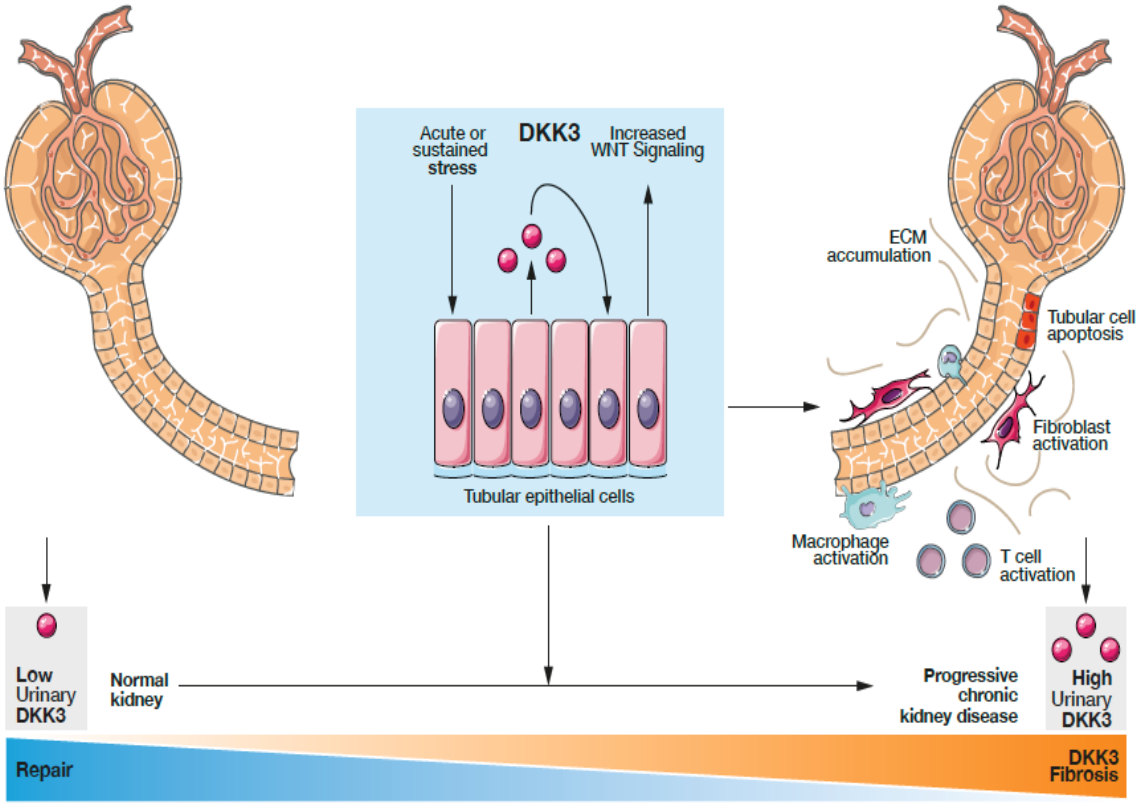






DKK3 im Urin

Zewinger et al. ***JASN*** 2018



1) Tubuluszellen sezernierern unter Stress Dkk3
2) Dkk3 kann mittels ELISA im Urin gemessen werden
3) Die im Urin gemessene Dkk3 Menge korreliert mit der CKD Progression und der tubulo-interstitiellen Fibrose in den Versuchtieren

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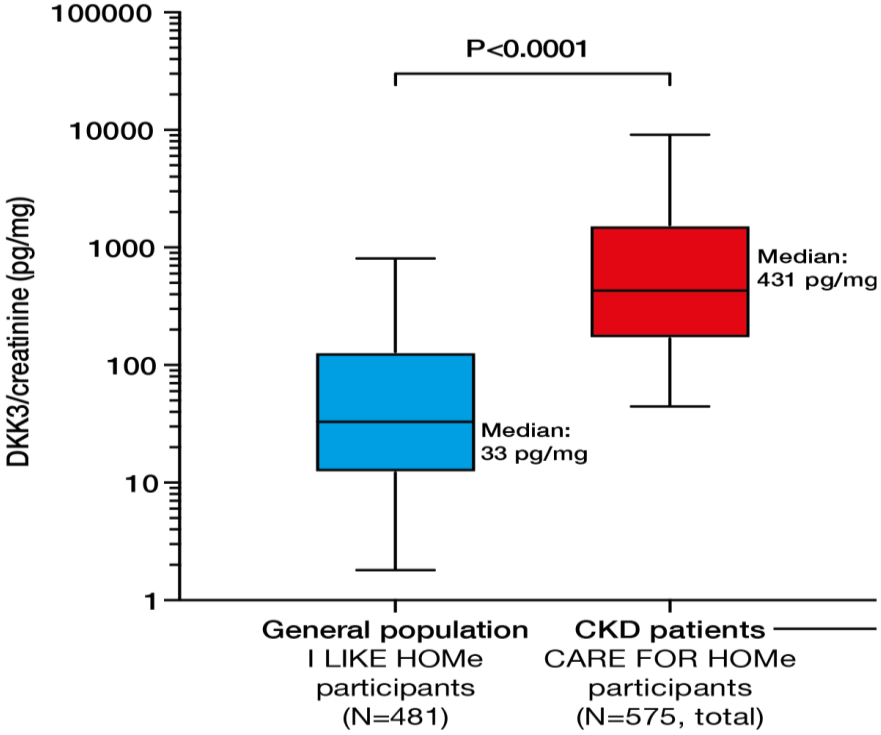
DKK3 im Urin

Zewinger et al. ***JASN*** 2018

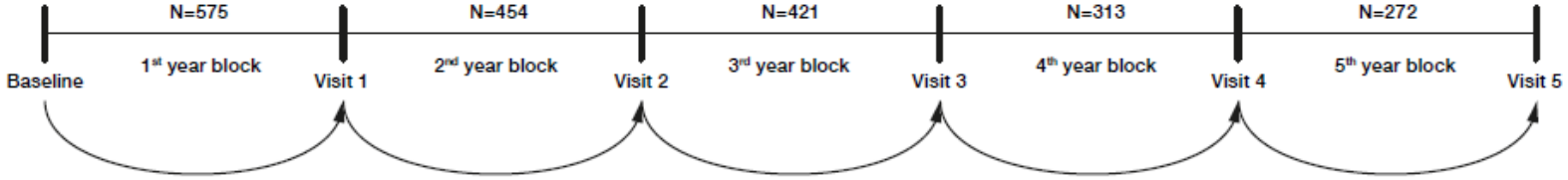


DKK3 und CKD **Progression**

Zewinger et al. ***JASN*** 2018

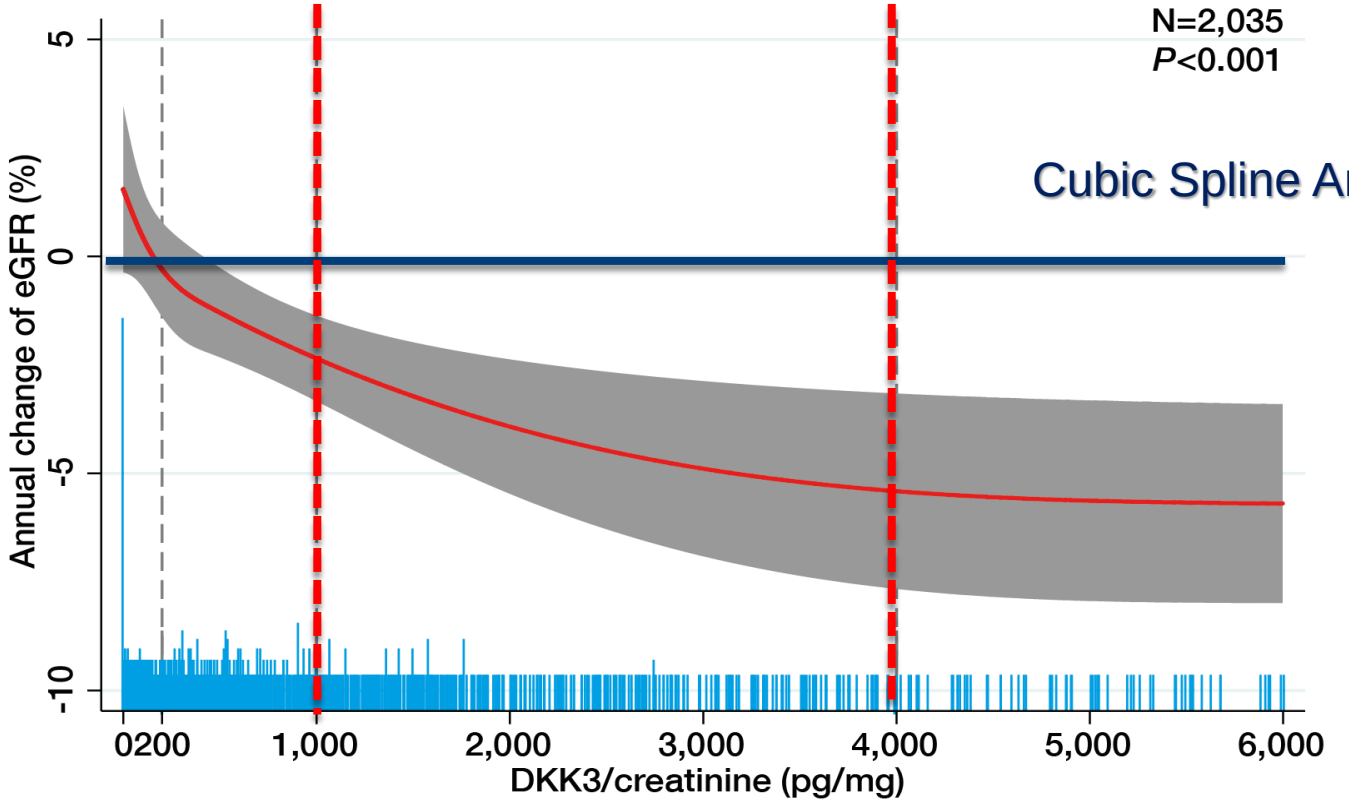
CARE FOR HOMe Studie

- 575 Patienten mit CKD Stadium 2-4 (GFR >15 ml/min/1,73m²)
- vor allem Patienten mit **Diabetes mellitus** und/oder **Hypertonie**
- prospektiver follow-up 8 Jahre (5.2 ± 2.1 Jahre)
- **jährliche Kontrollen** mit Blut- und Urinproben
- insgesamt **2,035 Personen-Jahre** zur Verfügung für Analysen



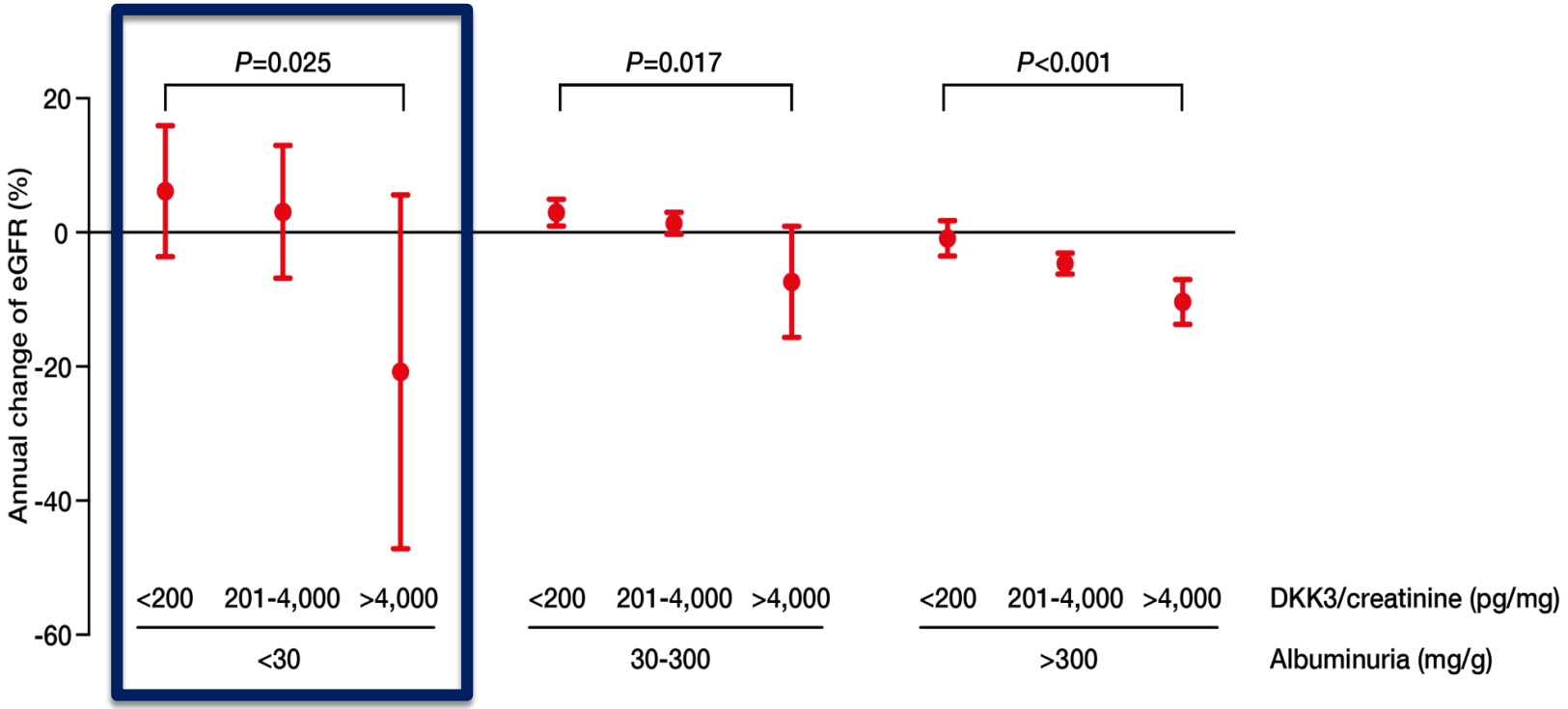
DKK3 und CKD **Progression**

Zewinger et al. ***JASN*** 2018

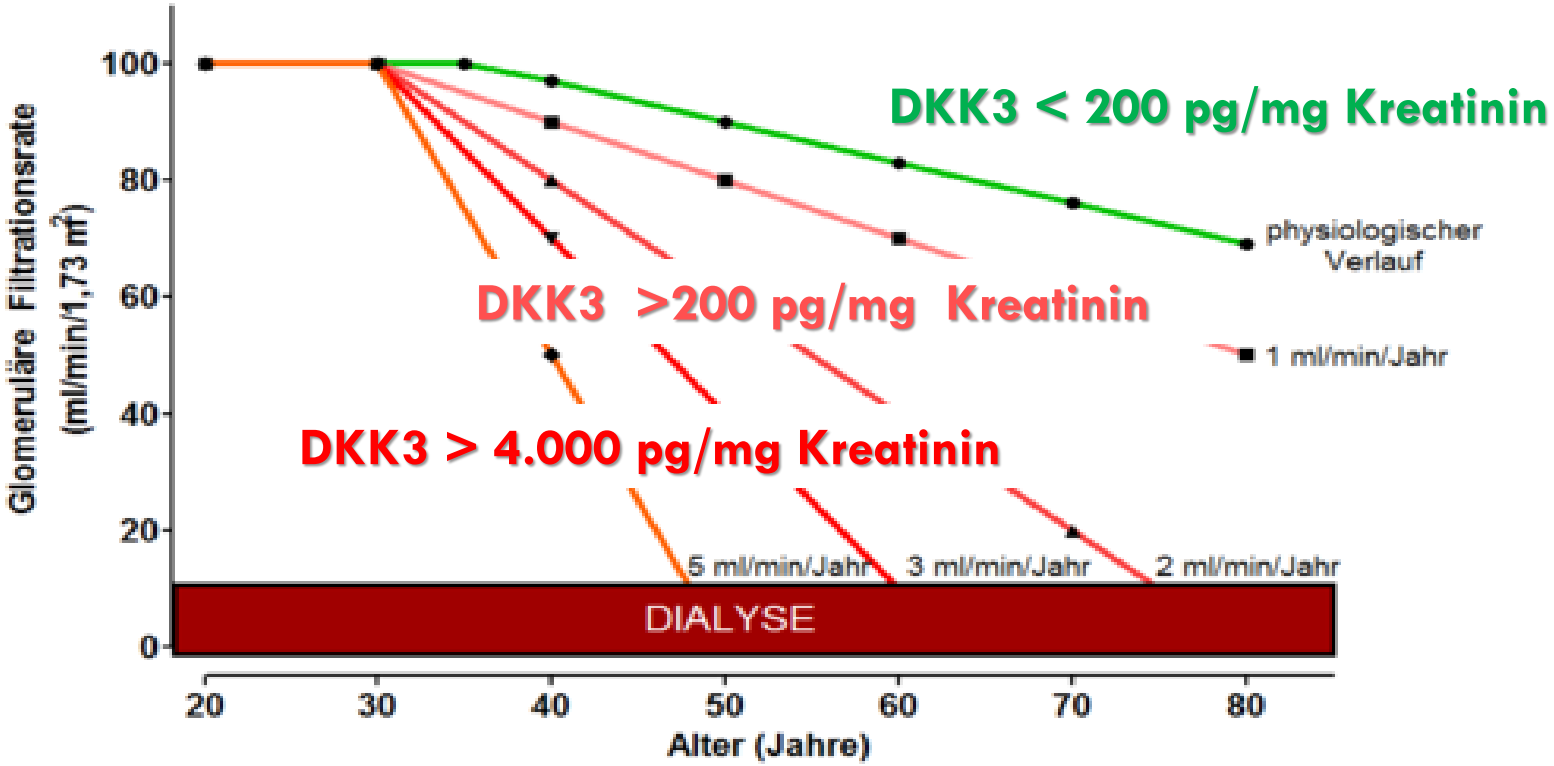


DKK3 und CKD **Progression**

Zewinger et al. ***JASN*** 2018



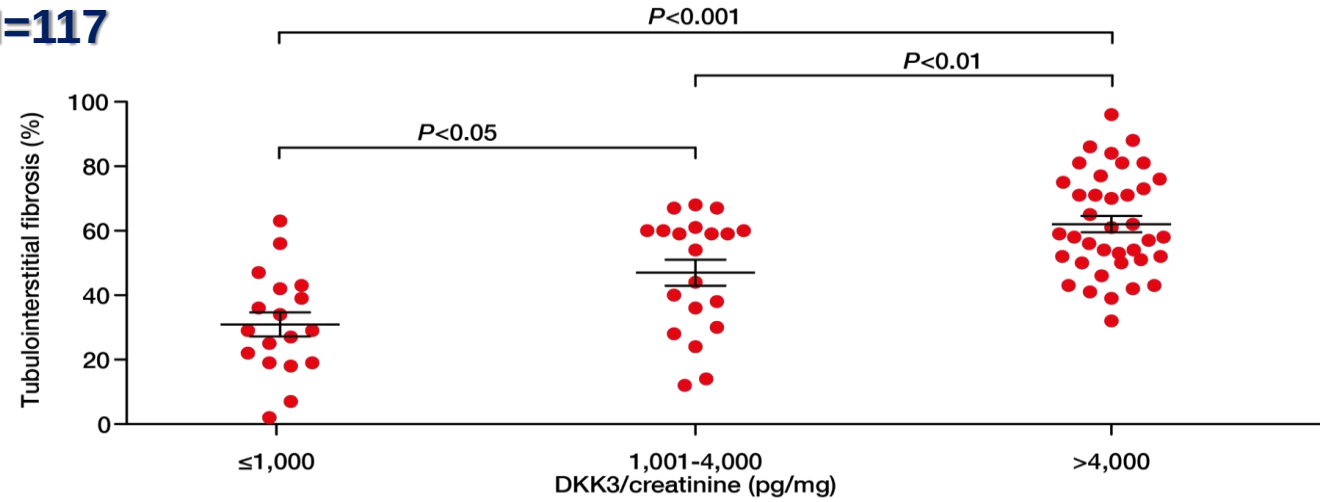
DKK3 und CKD **Progression**

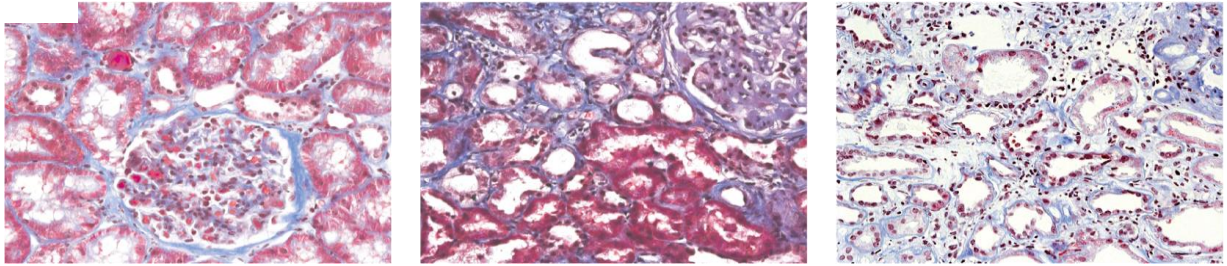


DKK3 und Nierenfibrose

Zewinger et al. ***JASN*** 2018

N=117





DKK3 und CKD **Progression**

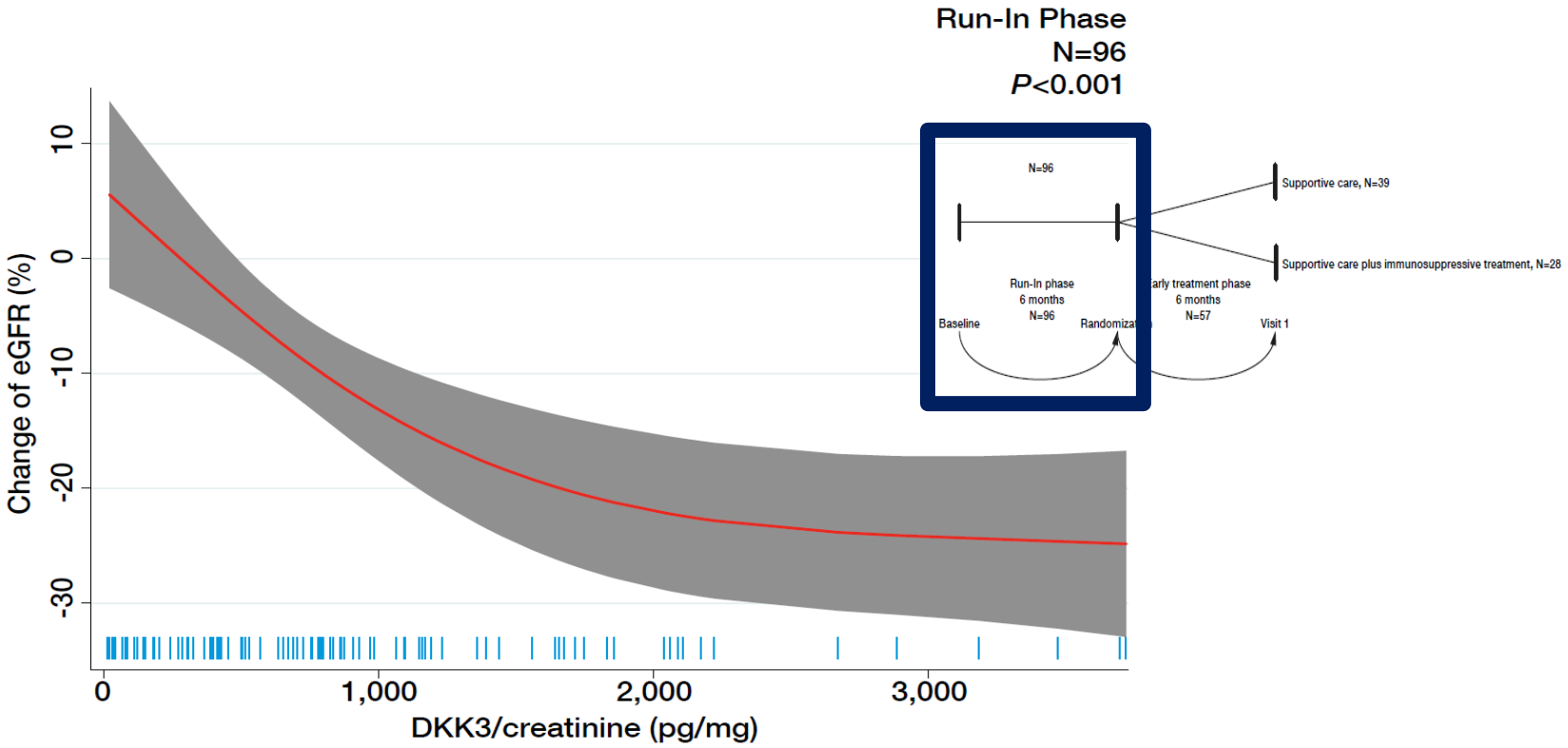
Zewinger et al. ***JASN*** 2018

STOP IgAN Studie

- Patienten mit **bioptisch-gesicherter IgA Nephropathie** (IgAN)
- 6 Monate **run-in Phase** mit supportiver Therapie (RAAS Blockade) adjustiert anhand der Proteinurie
- Patienten mit persistierender Proteinuria (>0,75 g/Tag) wurden randomisiert zur supportiven Therapie oder supportiven Therapie plus Immunosuppression

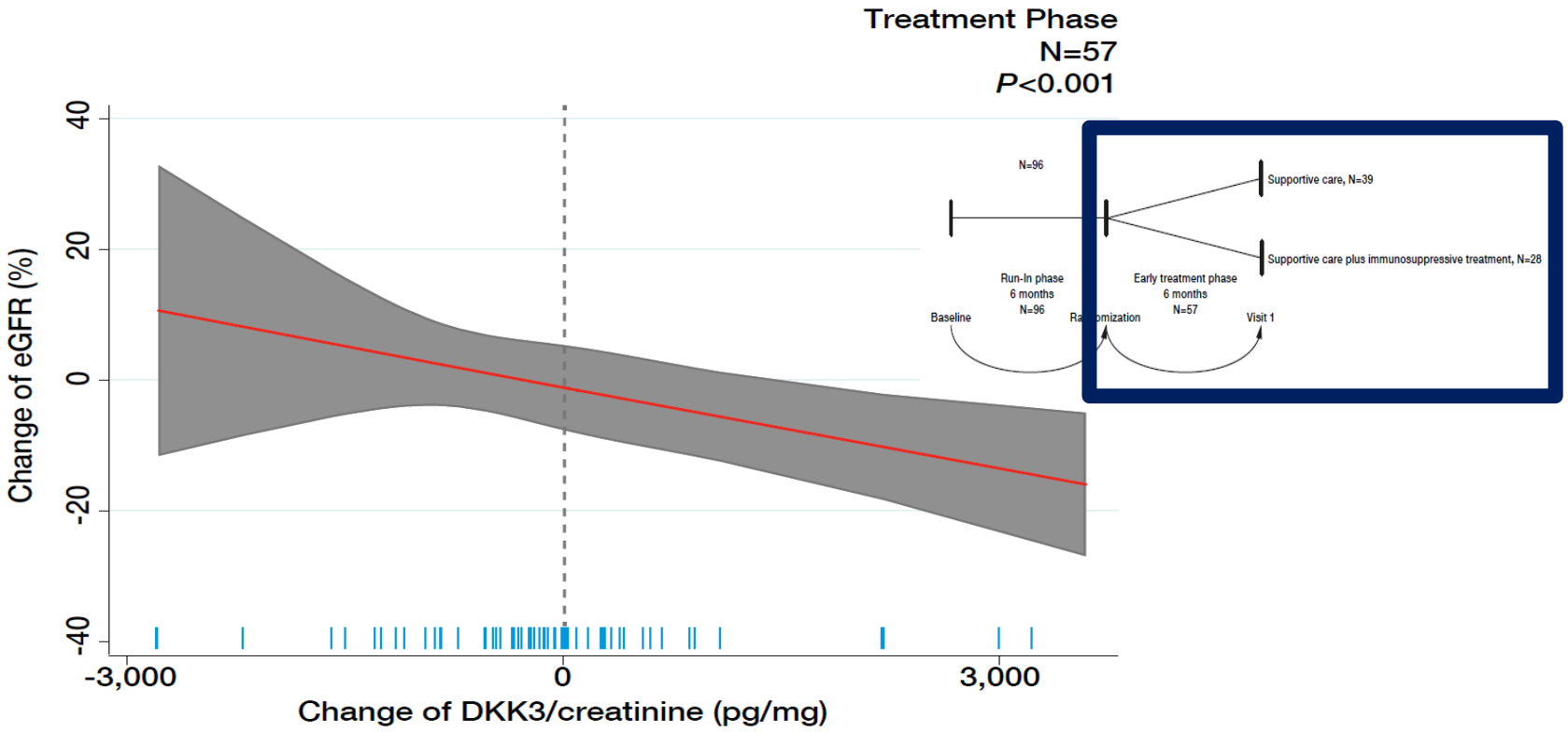
DKK3 und CKD **Progression**

Zewinger et al. ***JASN*** 2018



DKK3 und CKD **Progression**

Zewinger et al. ***JASN*** 2018



Zusammenfassung

- Der Verlust der Nierenfunktion (= **Progression**) ist bei Patienten mit chronischer Nierenschädigung individuell sehr variabel
- **DKK3** als profibrotisches Glykoprotein ist ein im Urin messbarer **Biomarker** des **tubulären Stresses** und der **individuellen CKD Progression**, auch unter Therapie

Vielen Dank!