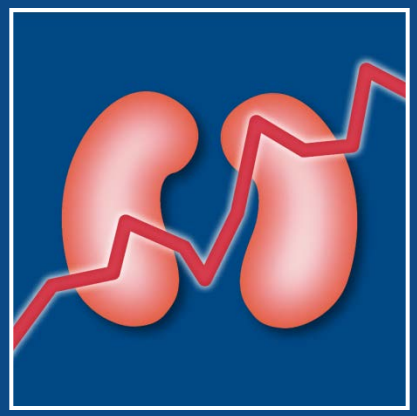
Nephro Update Europe 2018

5-6 October, Budapest

Chronic Kidney Disease



Kai-Uwe Eckardt, Germany

Conflicts of Interest

Research Support:

GCKD Study – Astra Zeneca, Bayer, FMC, Roche, Vifor

Other projects: Amgen

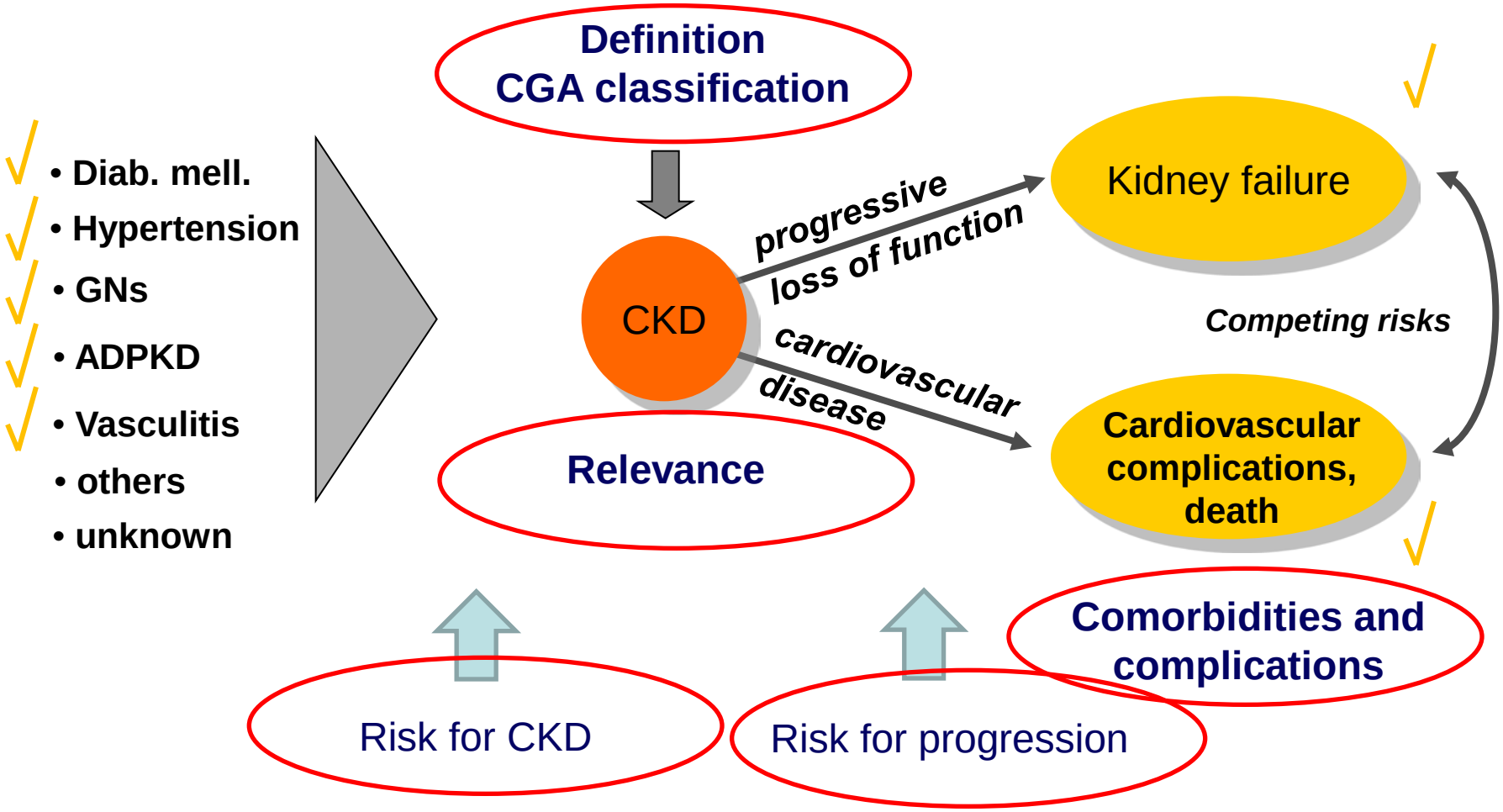
Lecturing:

Bayer, Sanofi-Aventis, Vifor

Consulting activities:

Akebia, Bayer, Johnson & Joshnson

State of the Art - CKD



Subtopics

- Definition and stages of CKD
- Risk factors for development and progression of CKD
- Complications and co-morbidities of CKD

Subtopics

- **Definition and stages of CKD**
- Risk factors for development and progression of CKD
- Complications and co-morbidities of CKD

CKD Classification

KDIGO CKD Guideline; Kidney Int Suppl 2013; 3: 1-150

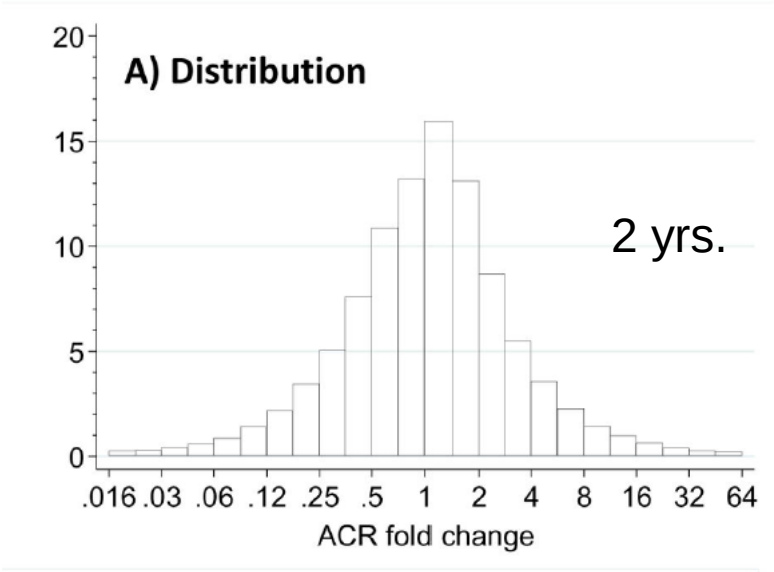
Cause
GFR
Albuminuria

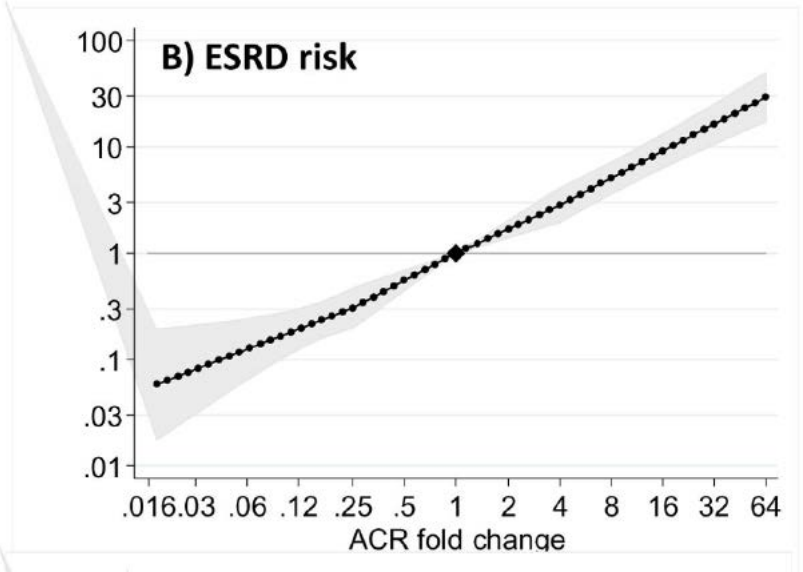
Prognose von CKD nach GFR- und Albuminurie-Kategorien: KDIGO 2012

GFR-Kategorien (ml/min/ 1,73 m²) Beschreibung und Bereich			Persistente Albuminurie-Kategorien Beschreibung und Bereich		
			A1	A2	A3
			Normal bis leicht erhöht	Moderat erhöht	Stark erhöht
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
G1	Normal oder hoch	≥90			
G2	Leicht verringert	60-89			
G3a	Leicht bis moderat verringert	45-59			
G3b	Moderat bis stark verringert	30-44			
G4	Stark verringert	15-29			
G5	Nierenversagen	<15			

Albuminuria Changes and Subsequent Risk of ESRD and Mortality

N = 31.732 (from SCREAM)
Association between change in albuminuria (ACR) within 1, 2 or 3 years and ESRD or death





→ Is a change in albuminuria a “valid“ surrogate marker for interventions ?

Carrero et al., Kidney Int 2017; 91: 244-251

National Kidney Foundation (NKF)

Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of Chronic Kidney Disease

A Scientific Workshop Collaboration by the National Kidney Foundation, the European Medicines Agency and the U.S. Food and Drug Administration

March 15-16, 2018

Goals: Evaluate **Surrogate Endpoints for Trials of Kidney Disease Progression** and **Improve Understanding of Change in Albuminuria** and GFR as Measures of Kidney Disease Progression in Early Stages of CKD ….

CKD Classification

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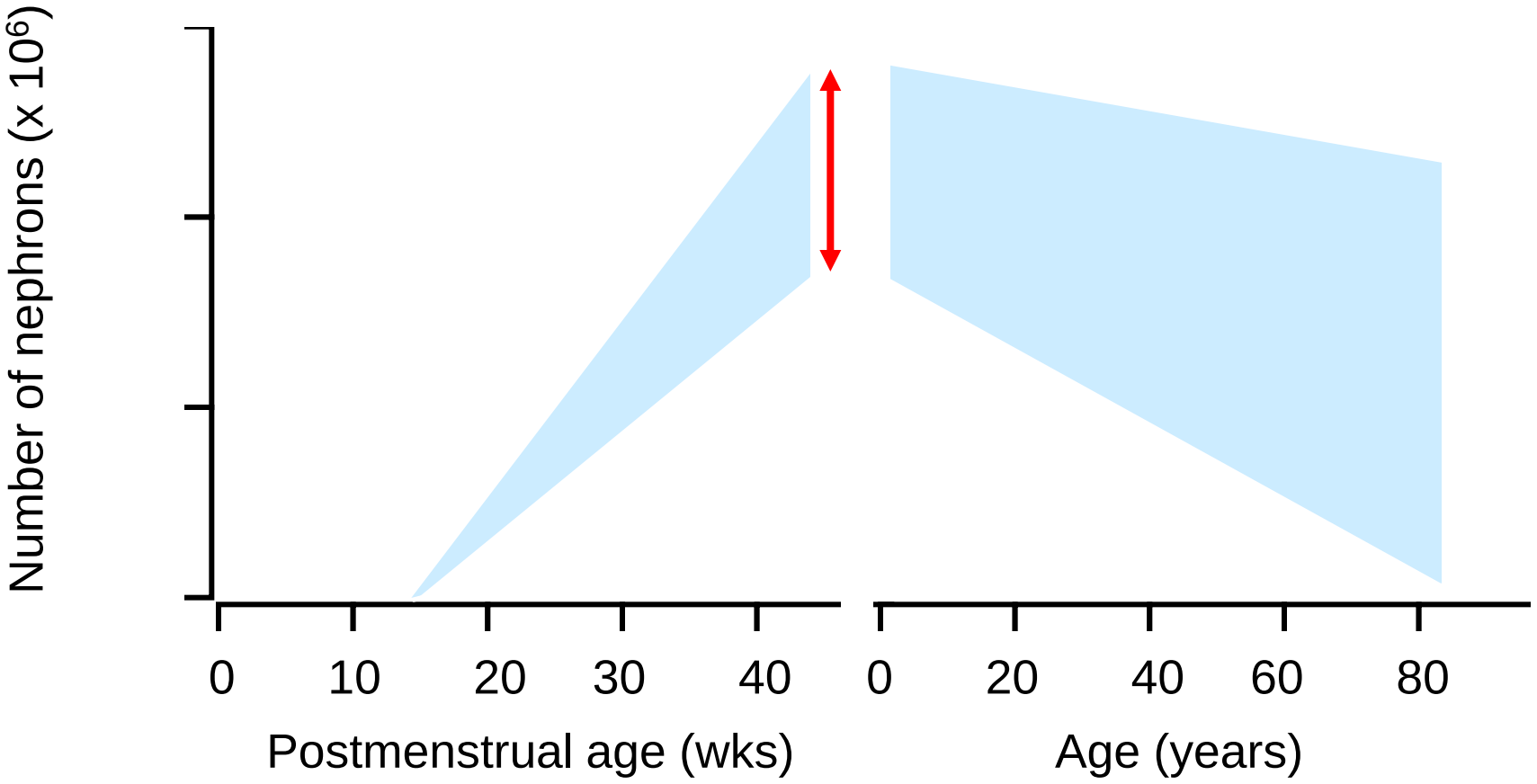
State of the Art - GFR

GFR = the key parameter of kidney function

GFR = nephrons x SNGFR;
both factors potentially important,
but usually not determined

GFR declines with age, but interpretation controversial (physiology or pathology ?)

State of the Art - GFR

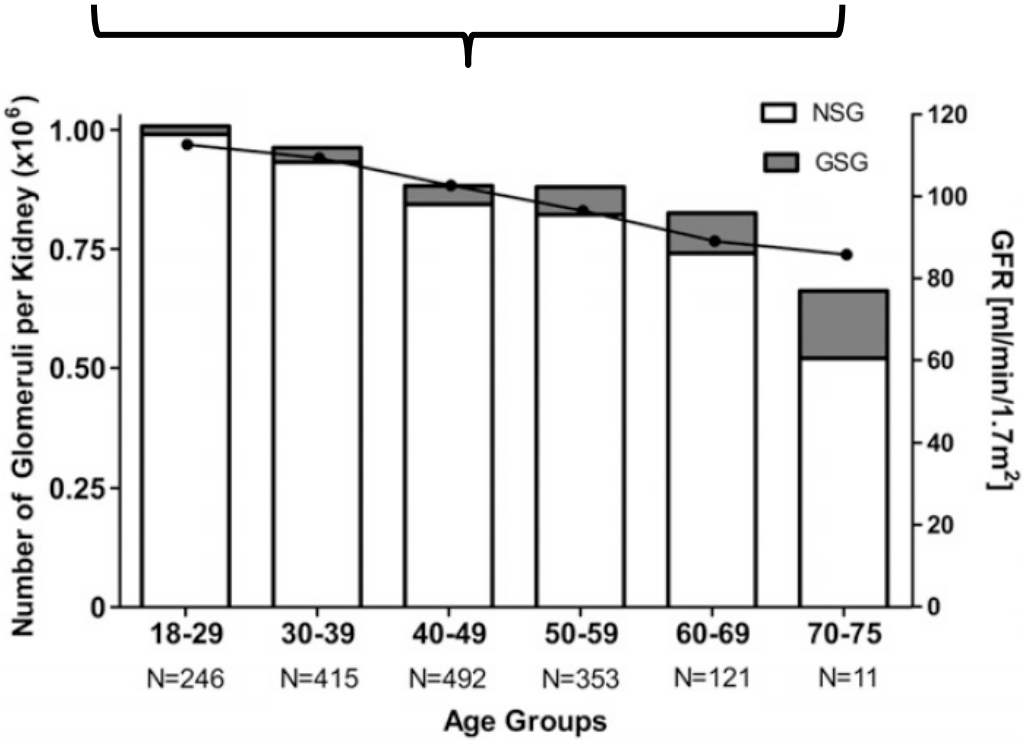


Loss of Nephrons with Ageing

- 1.638 living kidney donors
- CT → cortical volume of both kidneys

Biopsy after transplantation
→ density of non-sclerotic and sclerotic glomeruli

Total number of sclerotic (GSG) and intact glomeruli (NSG)



Denic et al., JASN 2017; 28: 313-320

Single Nephron GFR in Healthy Adults

- 1.388 living kidney donors
- CT → cortical volume of both kidneys

Biopsy after transplantation
→ density of non-sclerotic and sclerotic glomeruli

Age Group	No. of Donors	No. of Nephrons	Single-Nephron GFR	Total GFR
			nl/min	*ml/min*
18–29 yr	190	970,000±430,000	79±42	127±25
30–39 yr	339	930,000±350,000	77±36	124±24
40–49 yr	417	850,000±360,000	81±42	114±23
50–59 yr	300	810,000±360,000	80±40	106±20
60–64 yr	73	750,000±310,000	79±36	101±18
65–69 yr	56	720,000±260,000	76±33	95±17
70–75 yr	13	480,000±170,000	110±44	96±25

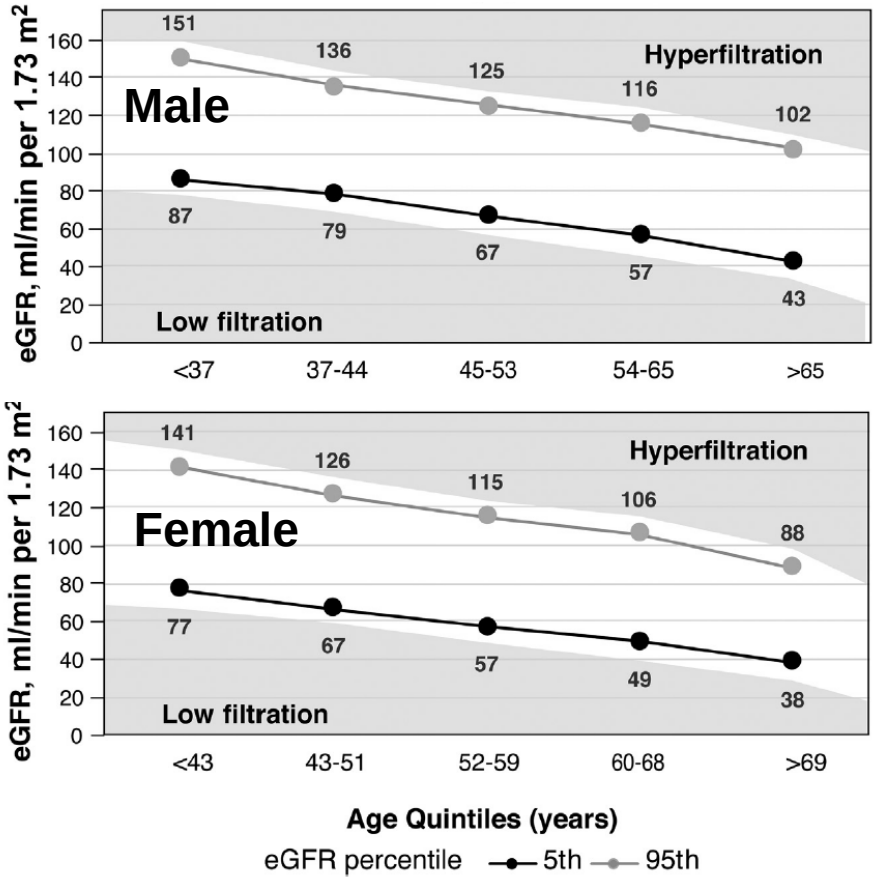
SNGFR: 80 ± 40 nl/min; very constant; not dependent on age (< 70), sex, height (< 190 cm)

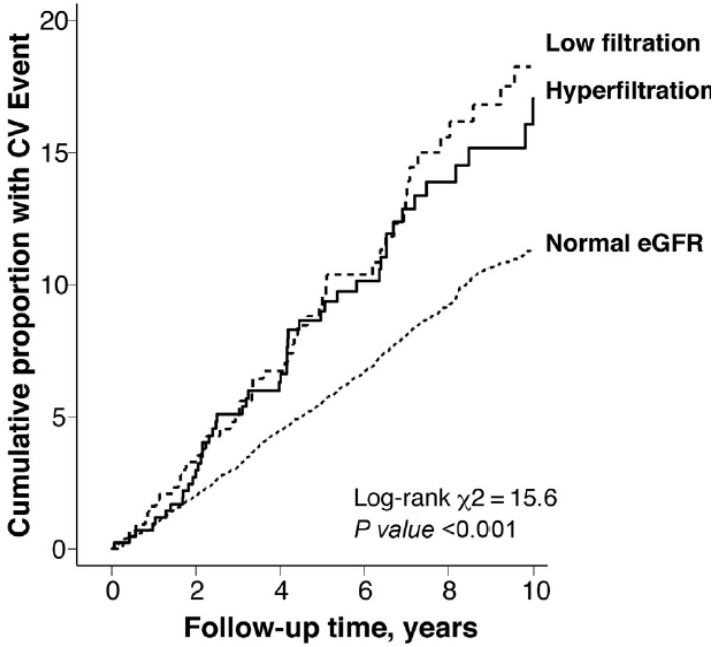
Higher SNGFR associated with enlarged glomeruli, glom. sclerosis, RF for CKD (family history, overweight)

Denic et al., NEJM 2017; 376: 2349-2357

Glom. Hyperfiltration is a Predictor of Adverse Cardiovascular Outcomes

N = 8.794; 52 studies, mostly patients with art. hypertension

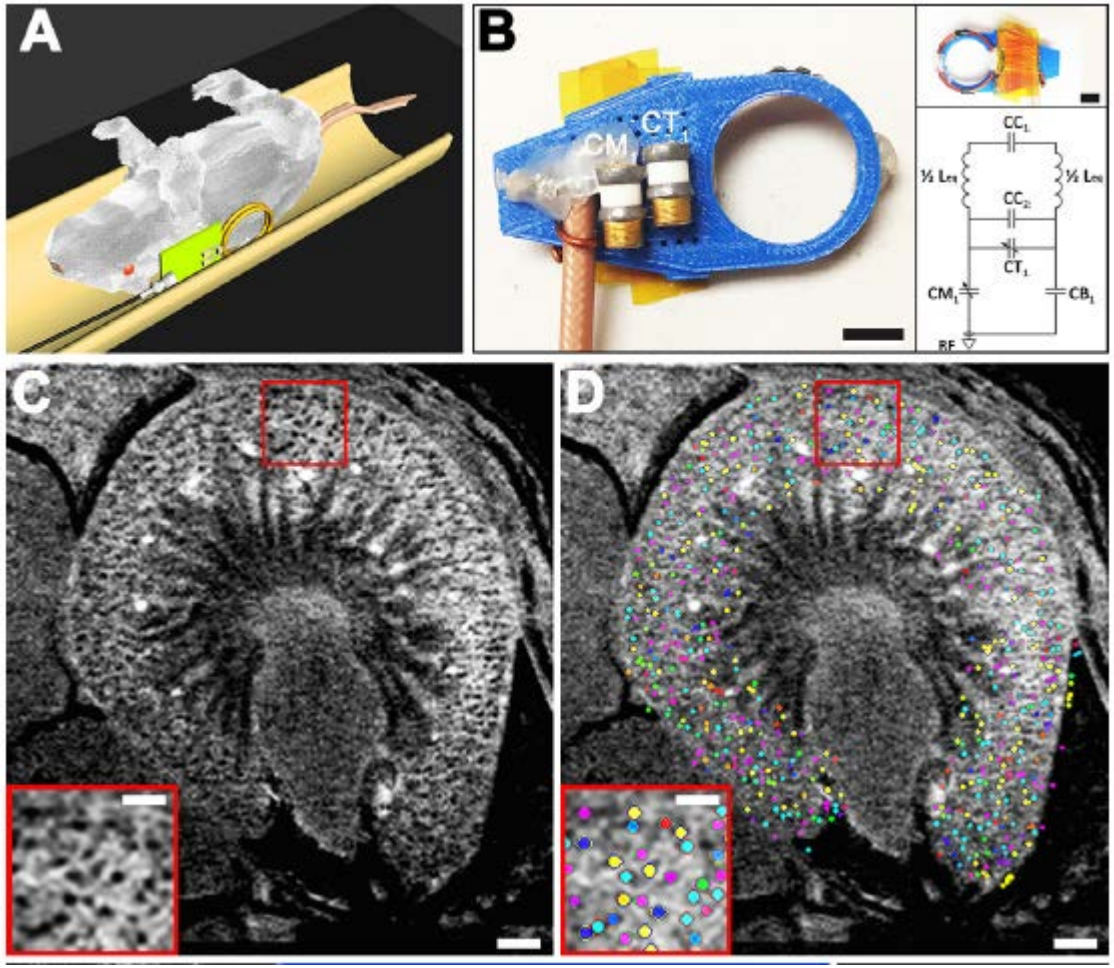




Reboldi et al., Kidney Int 2018; 93: 195-203

Measuring Rat Kidney Glomerular Number and Size *in vivo* with MRI

- **Rat experiments** small animal MRI
- IV-injection of cationized ferritin (CFE-MRI)
- → Determination of the number of glomeruli



Baldelomar et al., AJP Renal 2018; 314: F 399-406

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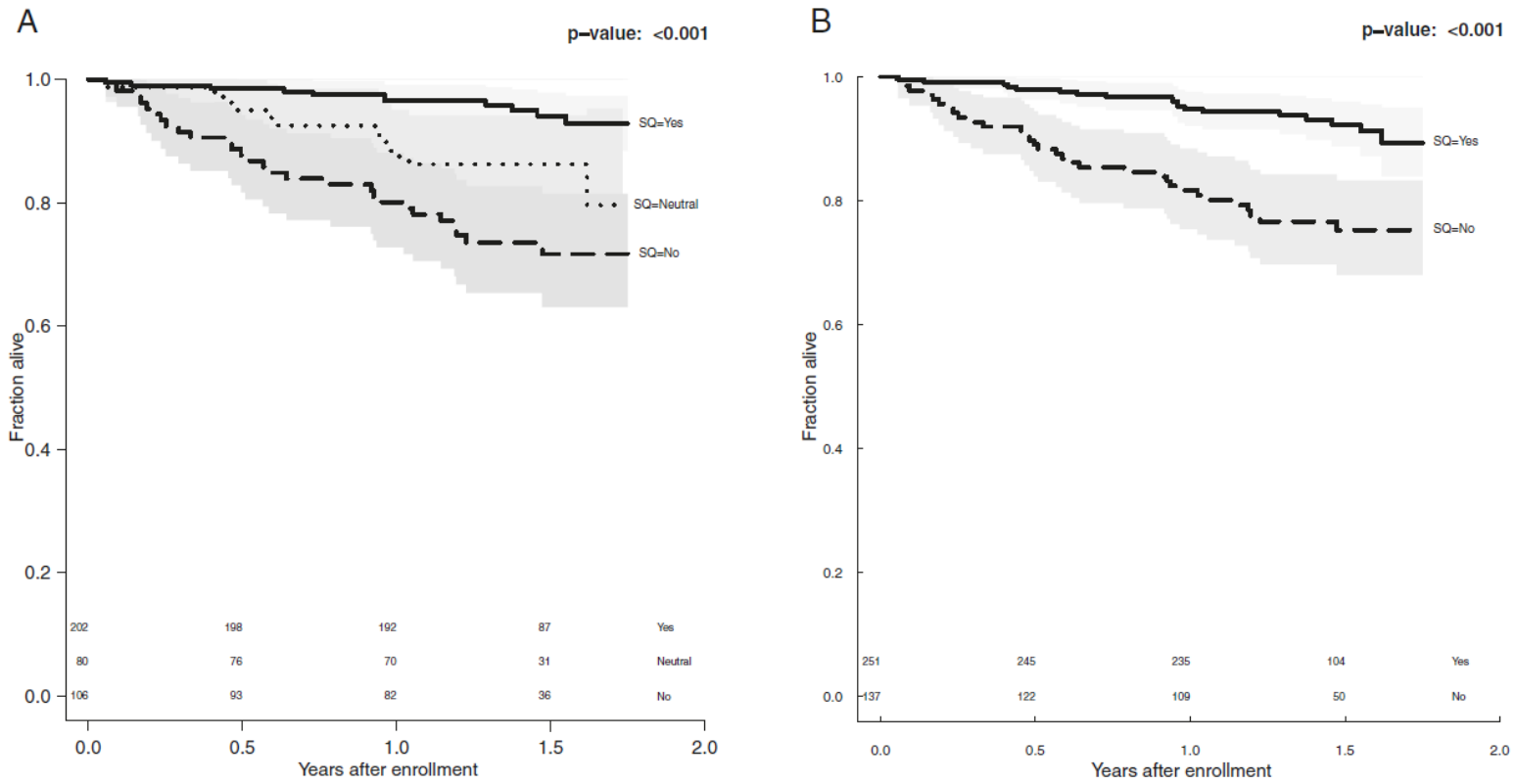
G5	Nierenversagen	<15			

“Surprise Question” in CKD G4–G5

N = 388; > 60 years; CKD G4 or G5 (not on dialysis)

“Would you be surprised if this patient died in the next 12 months?”

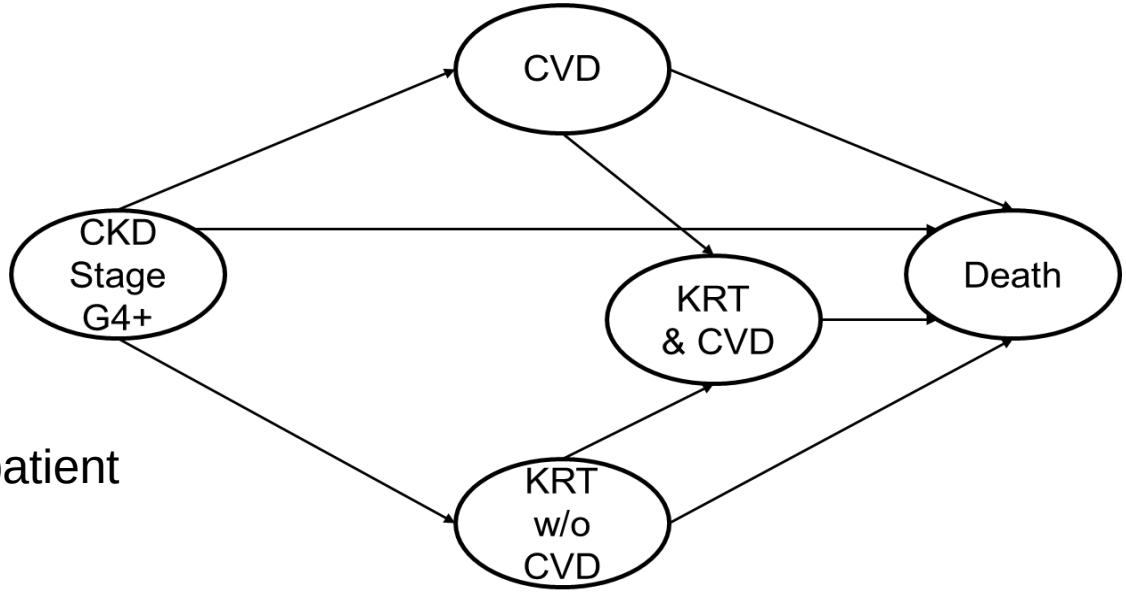


Javier et al., AJKD 2017; 70: 93-101

Prognosis of Patients with CKD G4–G5

KDIGO controversies conference
in collaboration with CKD Prognosis Consortium

Metaanalysis:
264,515 participants with eGFR < 30 ml/min/1.73 m^2
from 29 cohorts in 30 countries



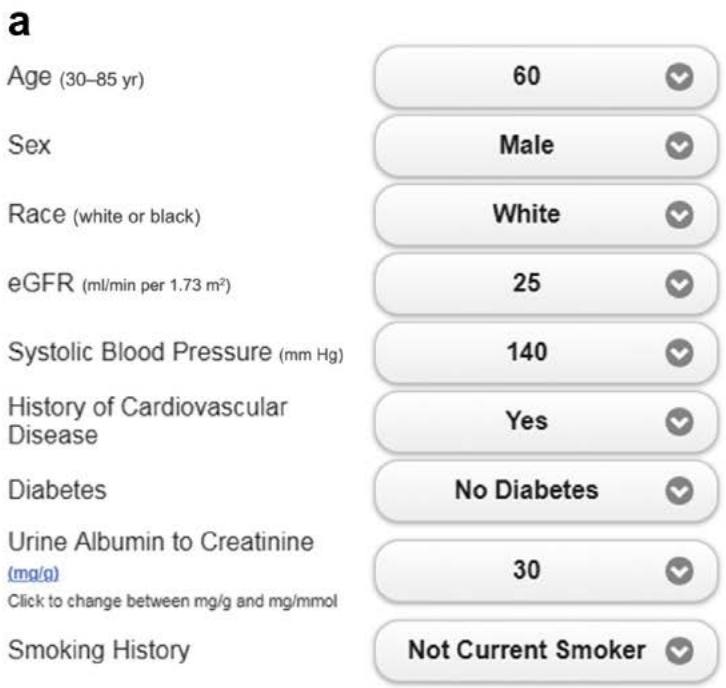
Possible scenarios for a patient
with CKD Stage G4+

Eckardt et al., Kidney Int 2018; 93: 1281-1292
Grams et al., Kidney Int 2018; 93: 1442-51

Prognosis of Patients with CKD G4–G5

http://ckdpcrisk.org/lowgfrevents/

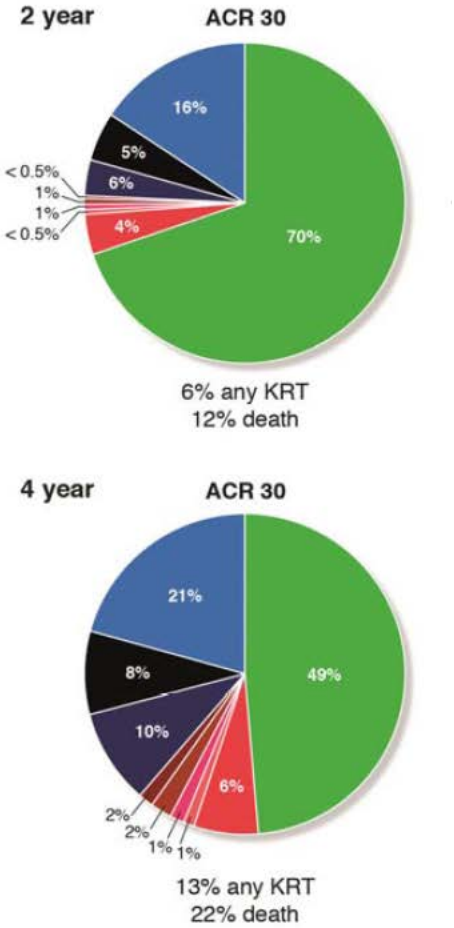
http://www.kdigo.org/equation/



Eckardt et al., Kidney Int 2018; 93: 1281-1292
Grams et al., Kidney Int 2018; 93: 1442-51

Prognosis of Patients with CKD G4–G5

- CKD G4+
- KRT
- KRT after CVD
- CVD after KRT
- Death after KRT
- Death after KRT & CVD
- Death after CVD
- Death only
- CVD only



Eckardt et al., Kidney Int 2018; 93: 1281-1292
Grams et al., Kidney Int 2018; 93: 1442-51

Take-Home Messages

- Changes in UAC: potentially a valid surrogate
- GFR declines with age, due to reduction in the number of glomeruli (SNGFR constant)
- SNGFR ↑ and GFR ↑ are risk markers (-factors ?)
- Prognosis of patients with CKD G4+ can be predicted; large proportion of patients with CKD G4 remain stable (no CVD event, no dialysis)

Subtopics

- Definition and stages of CKD
- **Risk factors for development and progression of CKD**
- Complications and co-morbidities of CKD

Childhood Kidney Disease and ESRD Risk

N = 1.521.501 Israeli adolescents; examined for compulsory military service; with normal renal function, no hypertension, but history of kidney disease

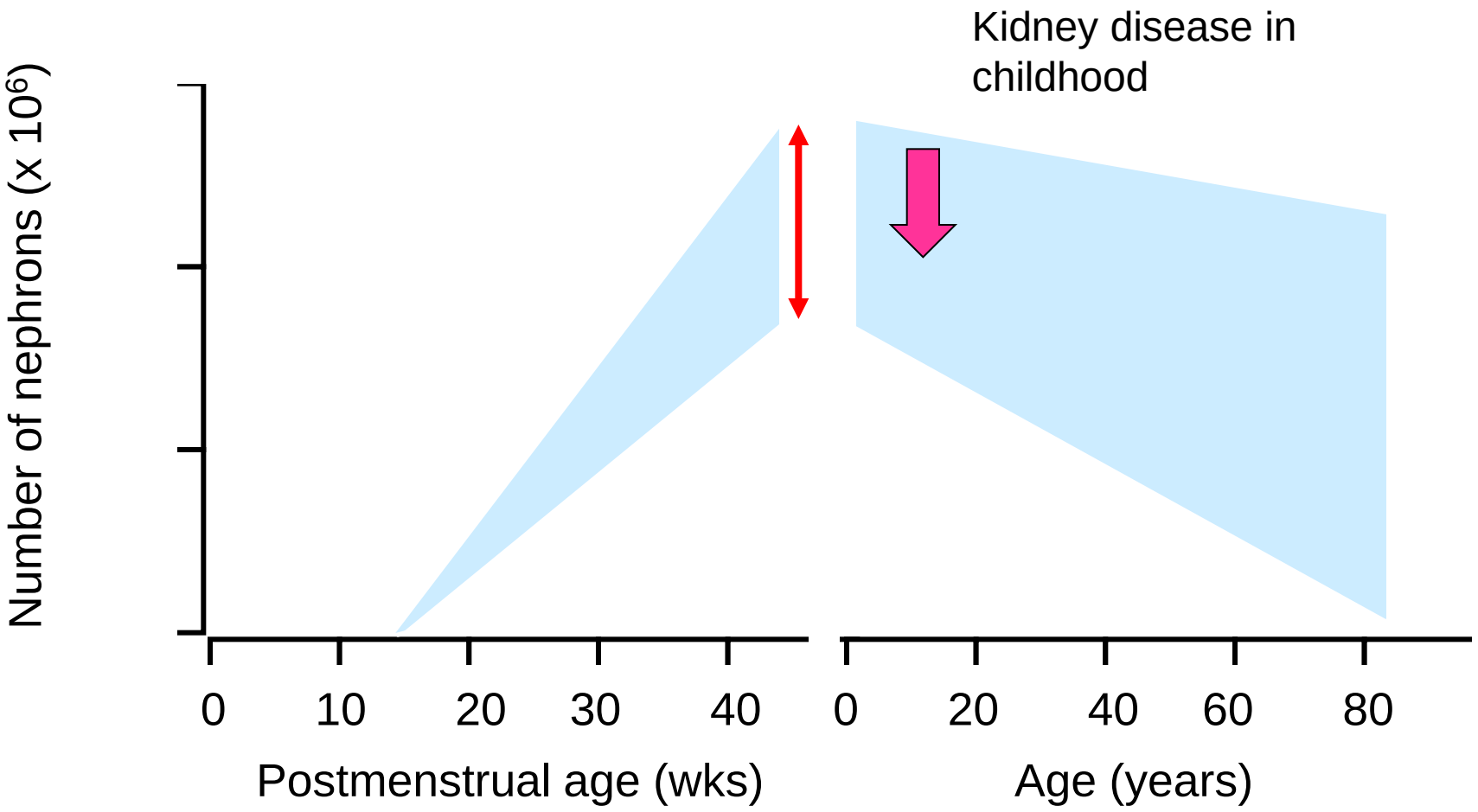
Table 3. Outcome Variables and Hazard Ratios for ESRD in Adulthood, According to Childhood Kidney Disease Category at Recruitment.*

Variable	History of Childhood Kidney Disease				No History of Childhood Kidney Disease (N = 1,502,909)
	CAKUT (N = 3198)	Pyelonephritis (N = 7231)	Glomerular Disease (N = 8611)	Any (N = 18,592)	
Incident cases of ESRD — no.†	26	73	42	140	2350
Age at ESRD diagnosis — yr	40.5±11.4	43.8±11.3	38.5±8.16	41.6±10.7	48.6±10.0
Total years of follow-up	94,211	257,673	257,940	596,773	45,592,197
Age at end of follow-up — yr	47.5±8.6	53.4±10.0	47.8±7.2	50.0±9.1	48.0±9.3
Incidence rate of ESRD — no. of cases per 100,000 person-years	27.6	28.3	16.3	23.5	5.15
Died — no. (%)	128 (4.0)	385 (5.3)	224 (2.6)	721 (3.9)	46,286 (3.1)
Hazard ratio (95% CI) for ESRD from any cause in adulthood					
Unadjusted	6.07 (4.04–9.12)	3.80 (2.94–4.76)	3.91 (2.83–5.41)	4.04 (3.49–4.93)	Reference
Model 1‡	5.47 (3.63–8.24)	3.74 (2.94–4.76)	3.84 (2.78–5.31)	4.04 (3.40–4.81)	Reference
Model 2§	5.19 (3.41–7.90)	4.03 (3.16–5.14)	3.85 (2.77–5.36)	4.19 (3.52–4.99)	Reference

History of kidney disease → 4fold increase in risk for ESRD

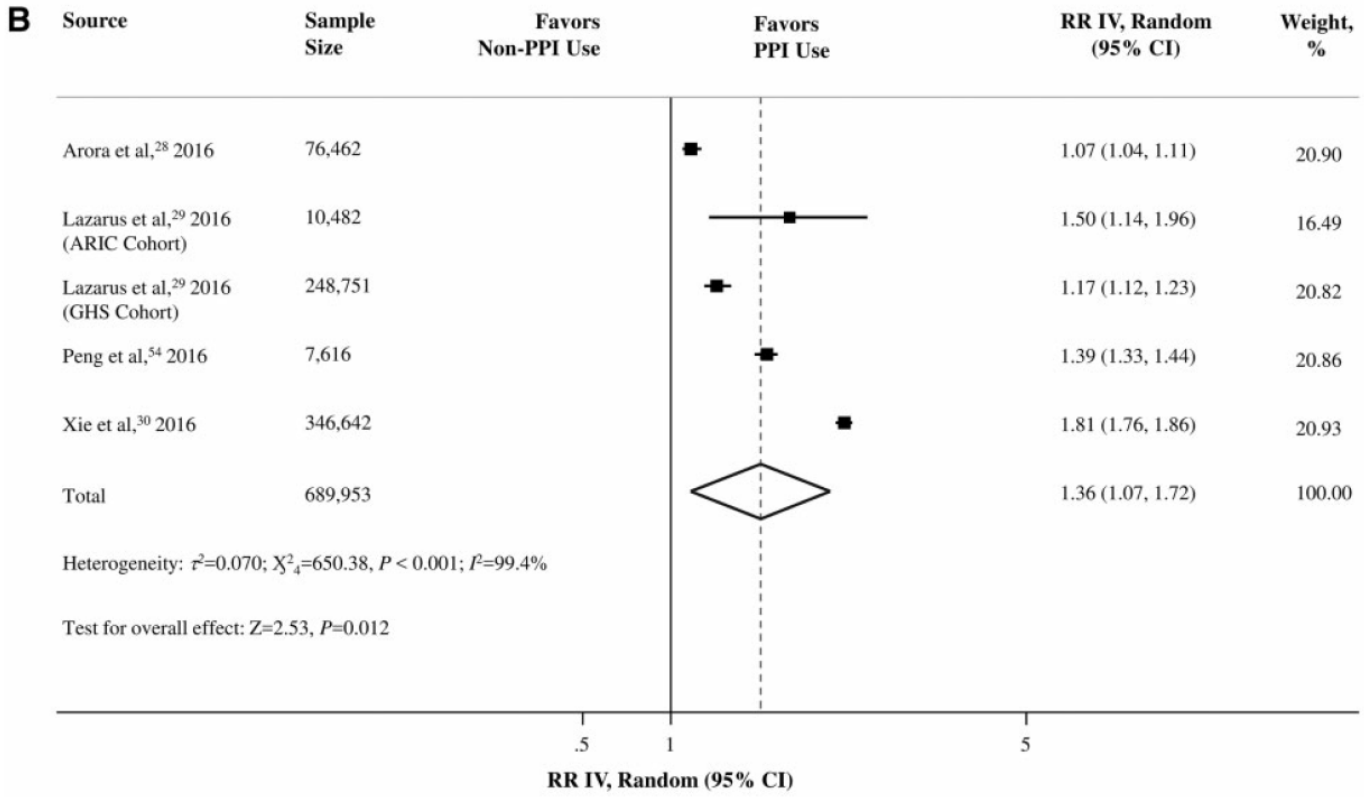
Calderon-Margalit et al., NEJM 2018; 378: 428-438

Nephron Development with Age



PPI Use and Risk for Adverse Kidney Outcomes

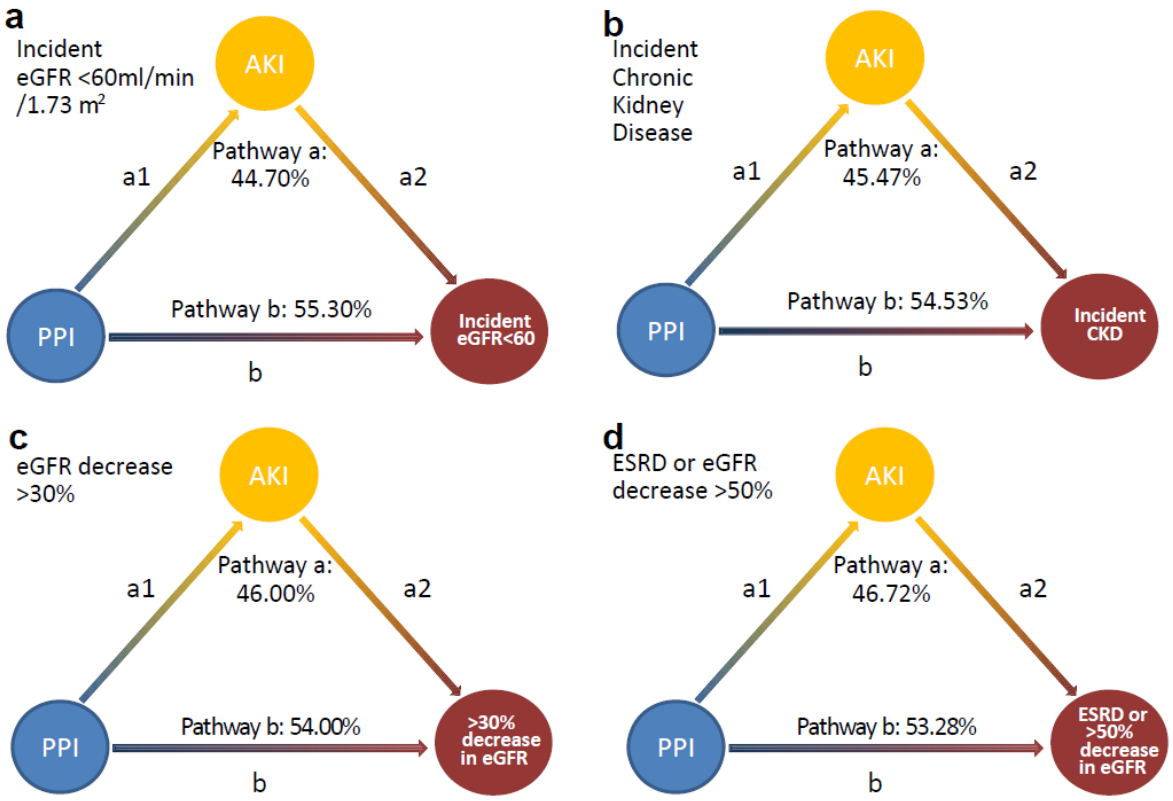
Sytematic review and metaanalysis: 9 studies, N ~ 2.6 million



Nochaiwong et al., NDT 2018; 33: 331-342

PPI Use and Risk for Adverse Kidney Outcomes

N= 144.032 PPI users in Veterans administration database



AKI → no sufficient risk indicator for adverse longterm effects on kidney function

Xi et al., Kidney Int 2017; 91: 1482-1494

Take-Home Messages

- Diagnose and treat kidney disease in children aggressively
- Ask for kidney disease episodes when assessing the history of adults with kidney disease
- Consider kidney disease episodes in childhood when evaluating the risk for living kidney donation

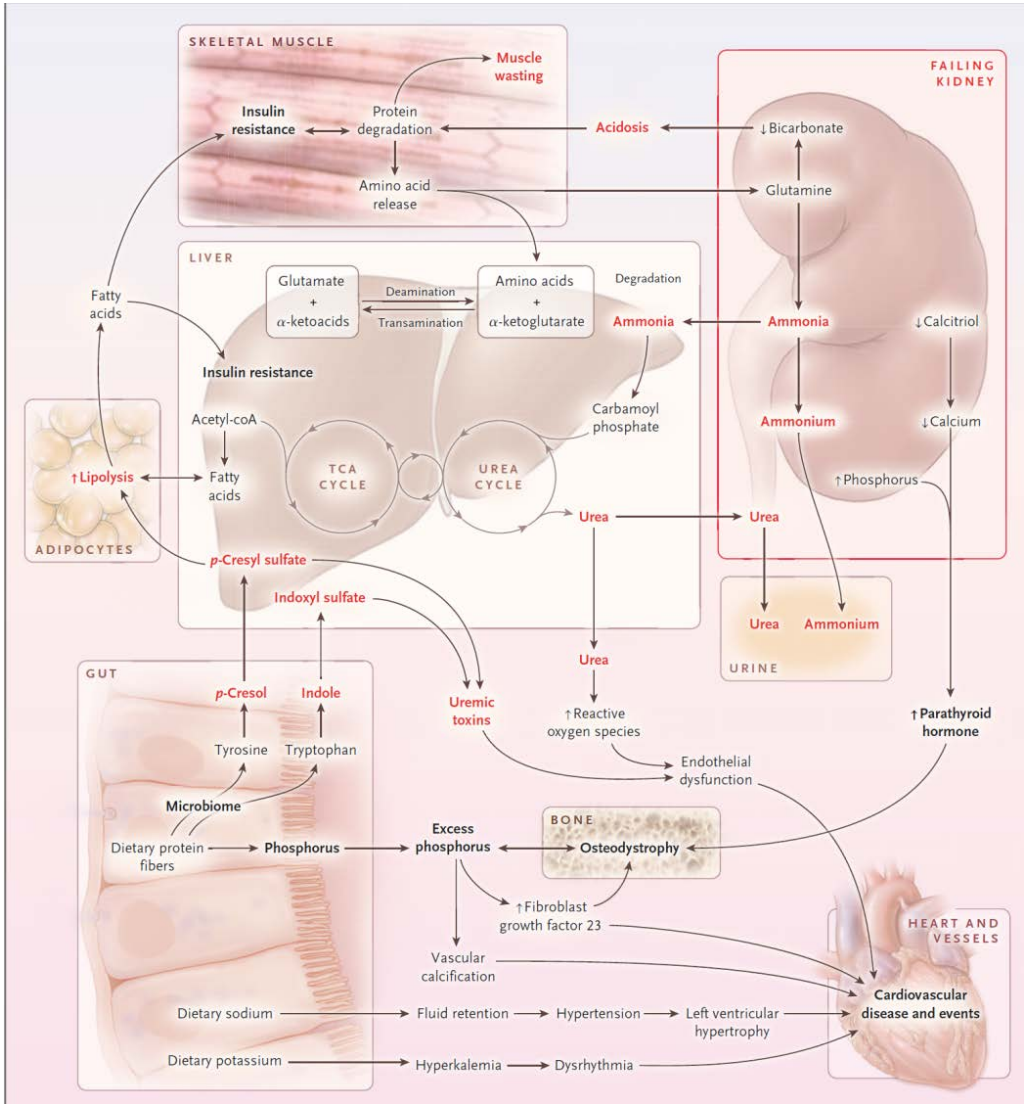
- Caution with longterm use of PPI in the absence of a clear indication; particularly in patients with CKD or increased risk for CKD

Subtopics

- Definition and stages of CKD
- Risk factors for development and progression of CKD
- **Complications and co-morbidities of CKD**

State of the Art – Muscle Wasting

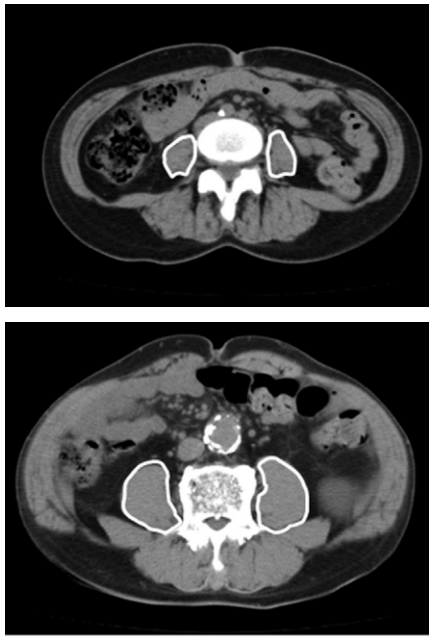
- Frequent in patients with CKD
- Associated with „malnutrition“, uremia, acidosis, metabol. and endocrine abnormalities, reduced QOL, frailty and reduced life expectancy
- Mechanisms largely unclear



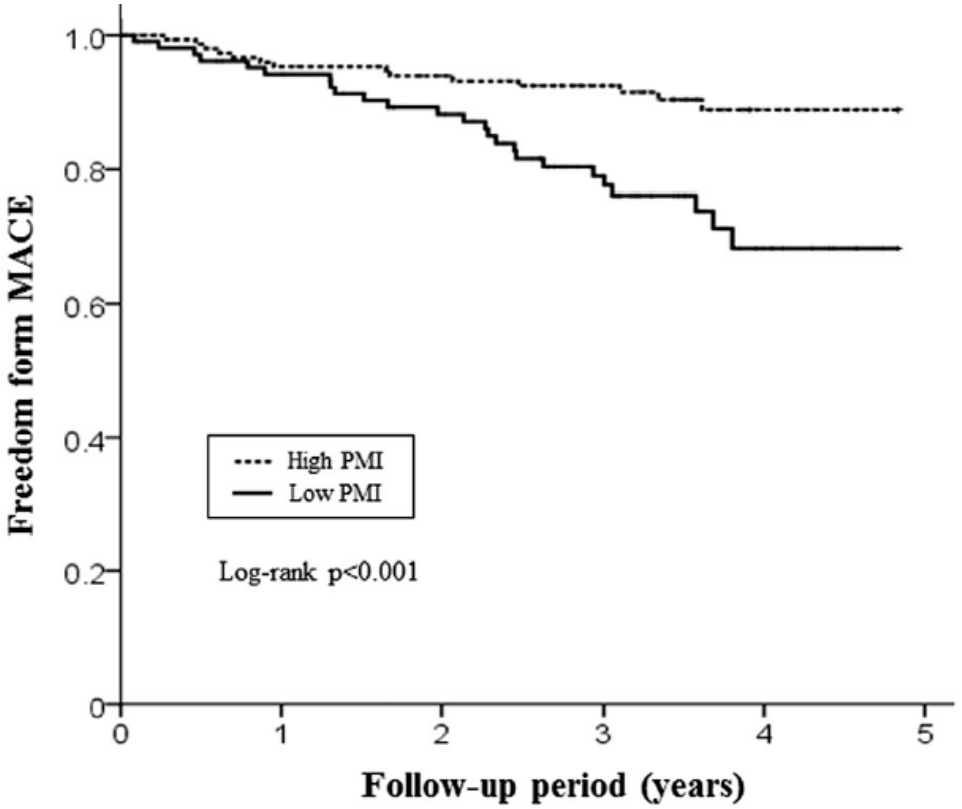
Kalatar-Zadeh & Fouque, NEJM 2017; 377: 1765-76

Skeletal Muscle Mass and Longterm adverse CVD Outcomes in CKD

N = 266 asymptomatic CKD patients
Median eGFR: 36.7 ml/min x m^2
Median follow-up: 3.2 years



Psoas Muscle Index (PMI)
Cross sections right + left (cm^2)/ BL^2 (m^2)

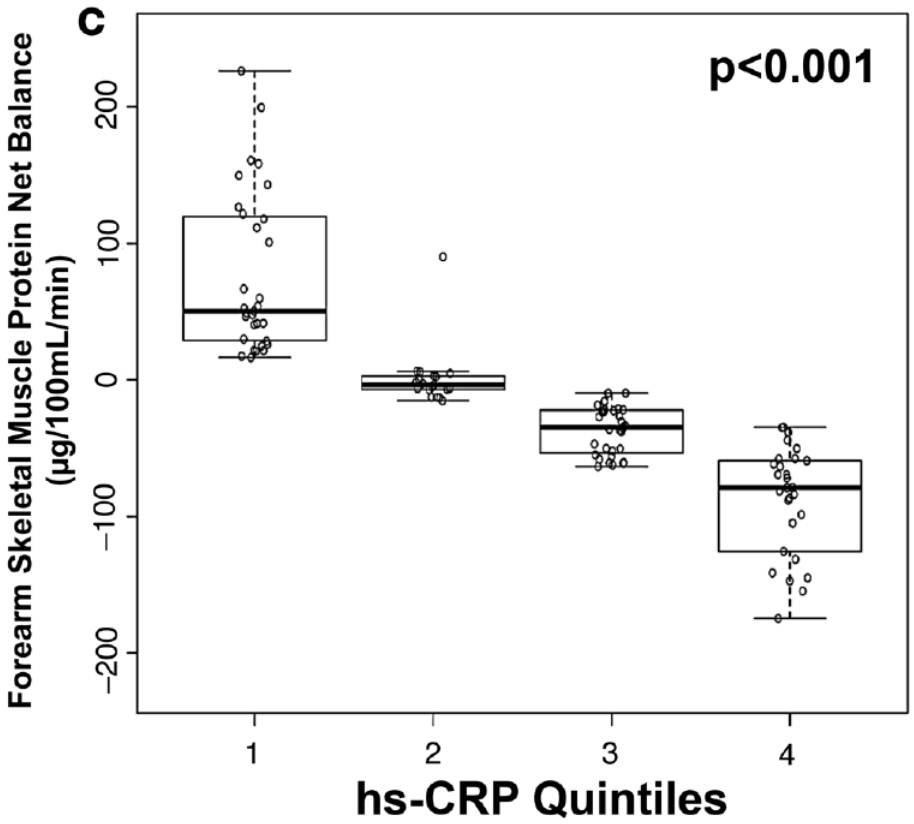


Harada et al., Am J Cardiol 2017; 119: 1275-1280

Exaggerated Skeletal Muscle Protein Metabolism in Maintenance HD Patients

N = 129 HD patients

Whole body and skeletal muscle protein turnover assessed by stable isotope kinetic studies

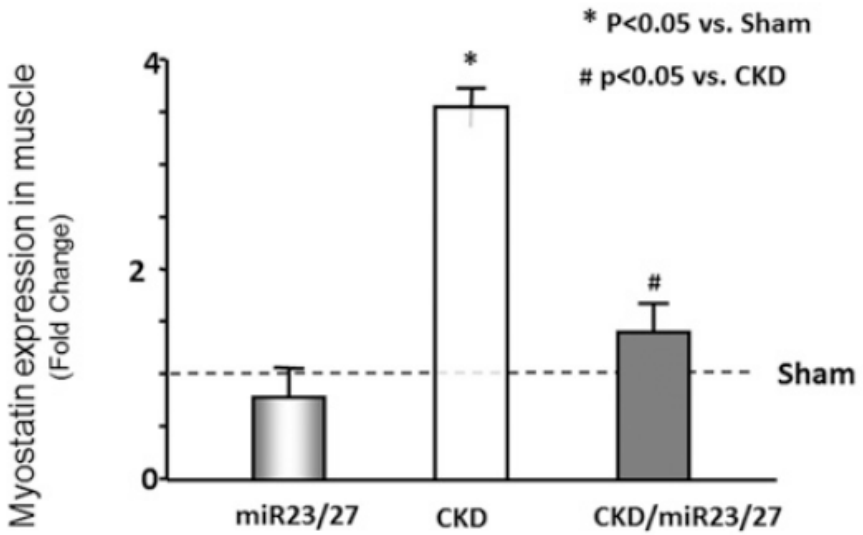


Significant associations with CRP, also after adaptation for clinical and demographic parameters

Deger et al., JCI Insight 2017; 2(22):e95185

MicroRNA-23a and MicroRNA-27a can Reduce CKD Associated Muscle Atrophy

- CKD-mice – Expression of miR-23a and miR-27a reduced, but can be enhanced through physical training
- AAV-overexpression of miR-23a/miR-27a in CKD-mice reduces muscle mass loss, improves muscle power, reduces myostatin expression and enhances the expression of muscle regeneration markers



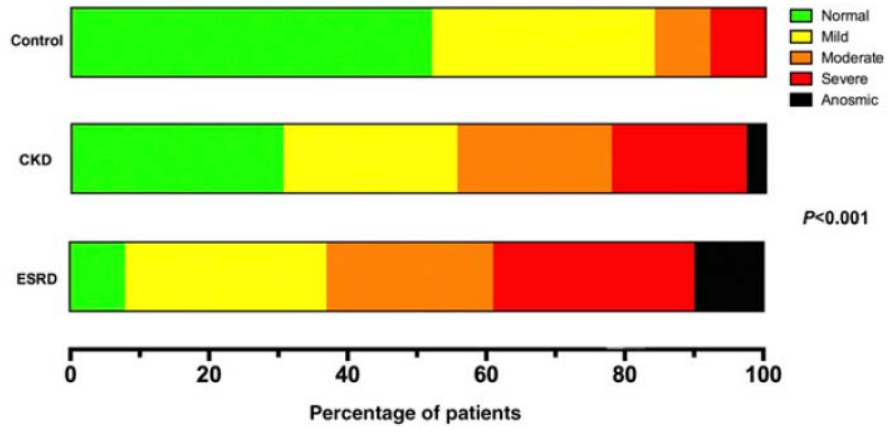
“MicroRNA as Novel Exercise Mimetic for Muscle Wasting in CKD“

Wang et al., JASN, 2017; 28: 2631-2640
Mak & Cheung, JASN 2107; 28: 2557-2559

Olfactory Function in CKD

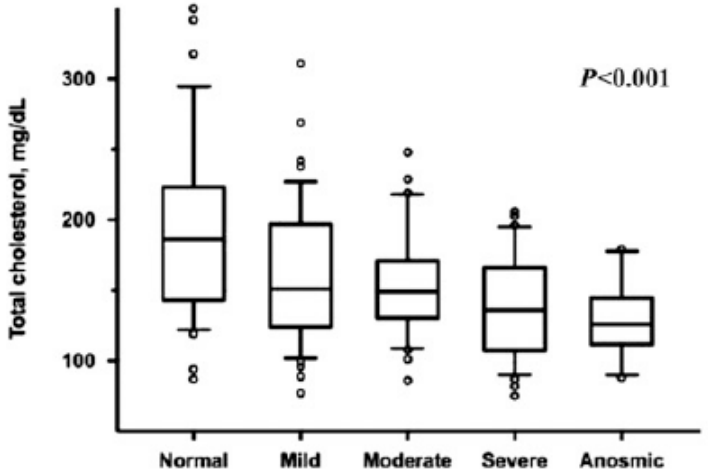
ESRD (n = 100)
CKD (n = 36)
Control (n = 25)

Odor identification



Nutritional markers associated with olfactory function categories

SGA score, total cholesterol, LDL cholesterol, albumin, pre-albumin



Pilot trial

9 patients received intranasal theophylline for 6 wks; → 7/9 improved

Nigwekar et al., JASN 2017, 28: 3395-3403

Prevalence and Risk of Severe Cognitive Impairment in CKD

BRINK Study (Brain In Kidney disease)
Recruitment: 4 “Nephrology or Diabetes Community Clinics”
Inclusion criteria: age > 45 years, ability to conduct a 90 min test, English as first language
N = 574 adults; mean age 69 years

Almost 50 % of CKD patients were found to have “Cognitive impairment“
25 % of CKD G4 Patients had “Severe cognitive impairment“

Table 3. Prevalence of CI Severity by eGFR Group[a]

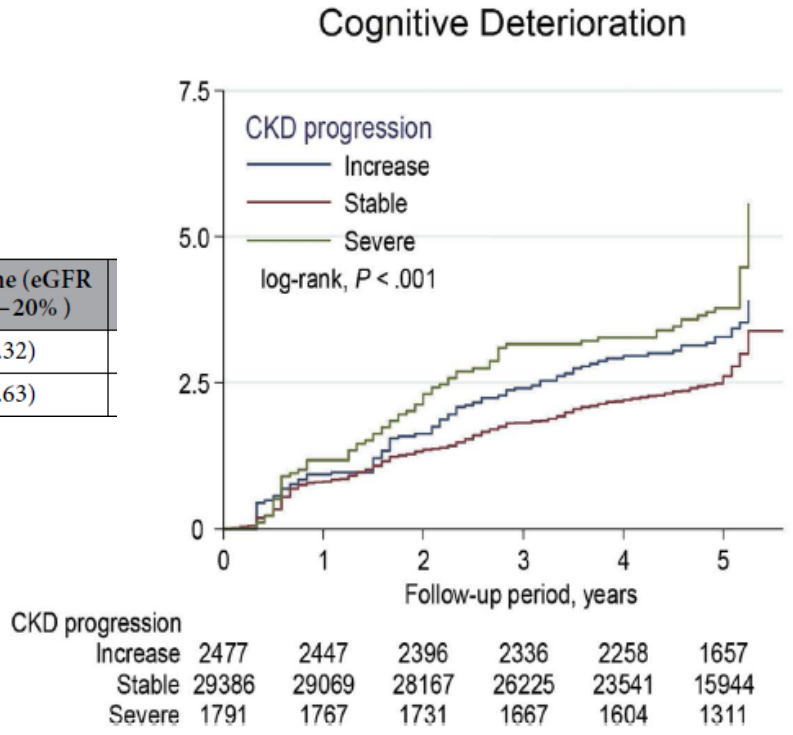
eGFR (mL/min/1.73 m²)	N	Normal *n* = 308	MCI *n* = 170	Severe CI *n* = 96
<30	148	64 (43.2%)	47 (31.8%)	37 (25.0%)
30 - <45	193	111 (57.5%)	56 (29.0%)	26 (13.5%)
45 - <60	92	50 (54.4%)	31 (33.7%)	11 (12.0%)
≥60	141	83 (58.9%)	36 (25.5%)	22 (15.6%)

Burns et al., The journals of gerontology Series A, Biological sciences and medical sciences 2018; 73: 393-399

Prevalence and Risk of Severe Cognitive Impairment in CKD

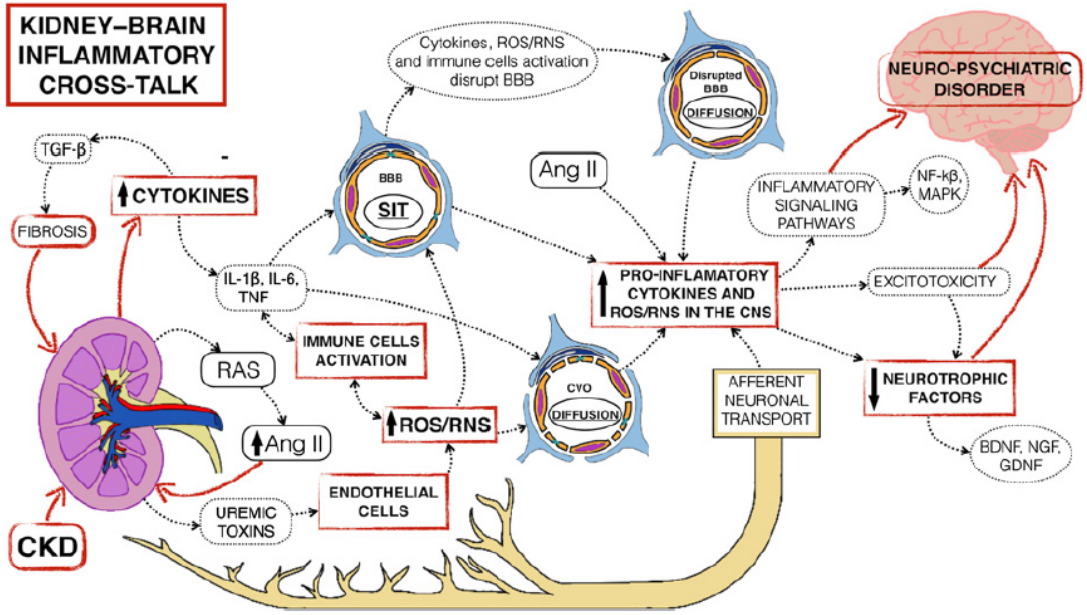
33,654 elderly (mean age approx. 75 yrs), data obtained during yearly assessment for Taipei City Elderly Health Examination Database with eGFR-data (94 % with eGFR > 60) and normal cognitive function test

	Increase (eGFR Change >20%)	Stable (eGFR Change −20 to 20%)	Severe Decline (eGFR Change >−20%)
N (%)	2,477 (7.36)	29,386 (87.32)	1,791 (5.32)
Age, mean (SD), y	74.87 (5.60)	75.41 (5.38)	75.86 (5.63)



Chen et al., Sci Reports 2017; 7: 42690

Mechanisms of Cognitive Impairment in CKD



N = 757 **CRIC participants** > 55 years

- hs CRP, fibrinogen and IL1 β associated with attention deficit
- TNF α associated with lower risk for reduced executive function

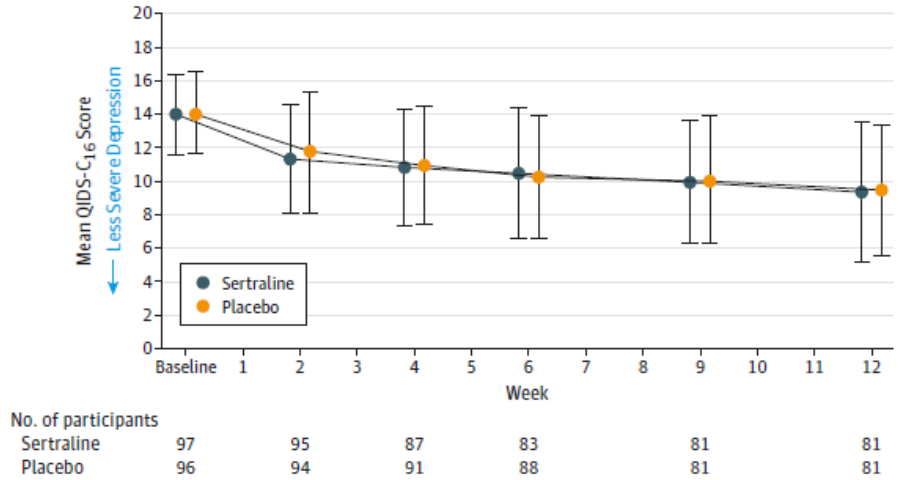
Miranda et al., Clinical Science 2017; 131:1093-1105
Kurella Tamura et al., Kidney Int Rep 2017; 2: 192-200

State of the Art – Depression and CKD

- Depression and CKD: large and increasing health problems
- Up to 25 % of patients with CKD suffer from depression
- Depression is associated with poor outcomes
- Selective serotonin-uptake inhibitors (SSRI) are a main form of therapy
- Data on their efficacy and safety in CKD are lacking

Effect of Sertraline on Depressive Symptoms in ND CKD Patients

CAST: Chronic Kidney Disease Antidepressant Sertraline Trial
N = 261; CKD 3, 4, 5 (no dialysis); oligocentric
Careful patient selection, psychiatric testing, pre-testing for adherence
Randomized, double-blind study:
N = 102: Sertraline (intial 50 mg/d, increased to 200 mg/d)
N = 99: Matching Placebo
Endpoints: Improvement of depressive symptoms after 12 weeks (16-item score); secondary endpoints QOL



This well-conceived, well-conducted, methodologically sound trial, the largest and best to this point addressing one of the most important challenges facing the CKD population, found that therapy with one of the most promising antidepressants for this population is largely no more effective than placebo and has adverse effects.

Editorial:
Walter, Shah, Winkelmayer
JAMA 2017; 318: 1873-4

Hedayati et al., JAMA 2017; 318: 1876-1890

Take-Home Messages

- Muscle wasting is associated with poor prognosis;
  it can be easily measured with CT (psoas muscle index);
  better understanding of pathomechansims may lead
  to novel therapies

- Cognitive disturbances are frequent in CKD patients;
  inflammation may contribute to the pathogenesis

- No evidence for the effectiveness of sertraline in CKD

- **We need more well performed trials in CKD patients**

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