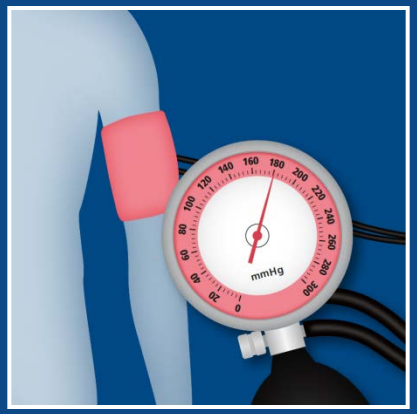
Nephro Update Europe 2017

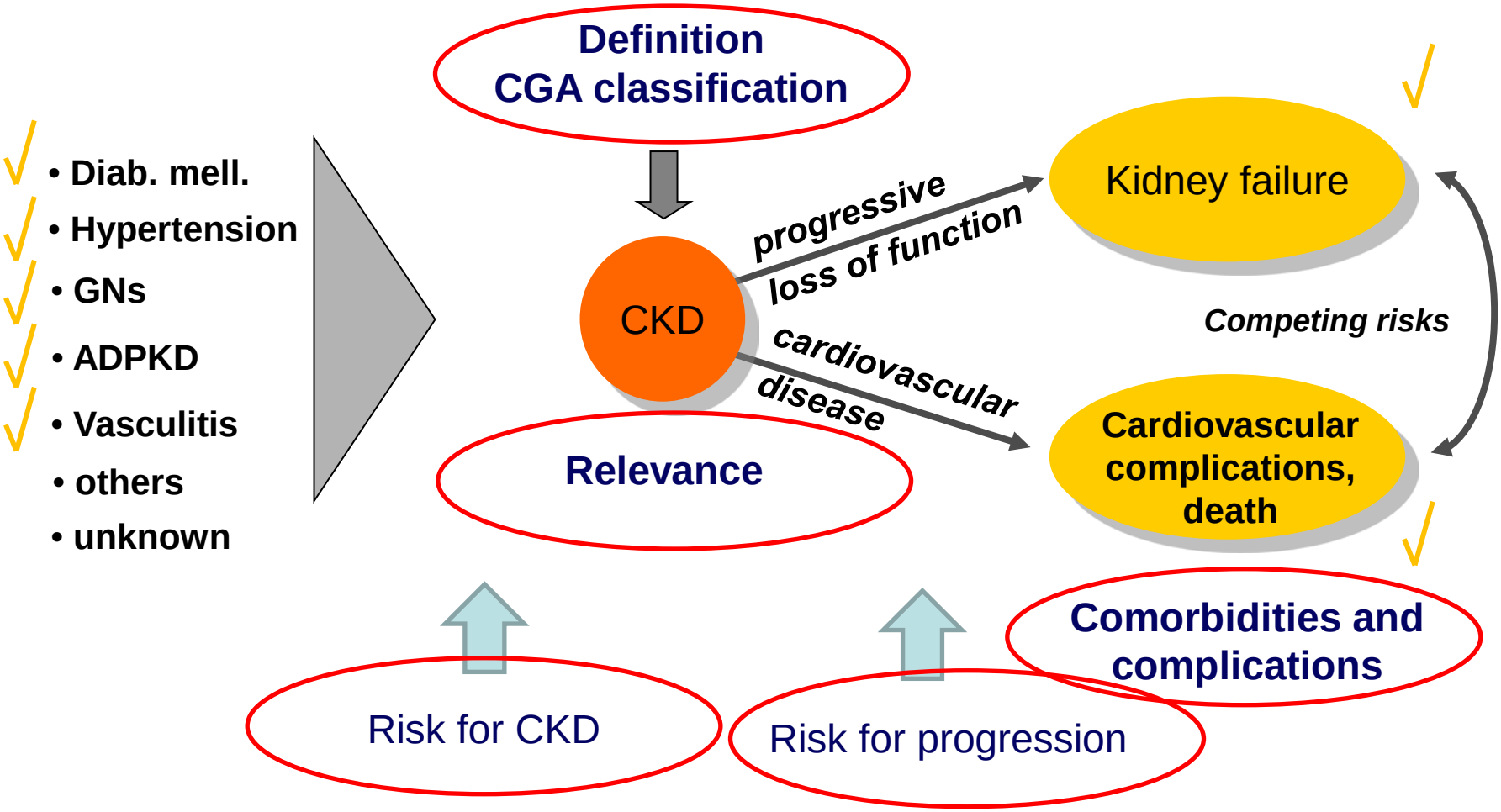
6-7 October, Vienna

Chronic Kidney Disease



Kai-Uwe Eckardt , Germany

State of the Art



Chronic Kidney Disease

- Definition and staging of CKD
- Relevance of CKD
- Risk factors for the development and progression of CKD
- CKD and Infection / Inflammation
- CKD and bleeding tendency
- Interventions to retard CKD progression

Chronic Kidney Disease

- **Definition and staging of CKD**
- Relevance of CKD
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CKD Classification

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

No news is good news !

Cause
GFR
Albuminuria

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

eGFR Equations
State of the Art

Cockroft - Gault

$$\frac{(140 - \text{Age}) \times \text{BW (kg)}}{[\text{Crea}]\ S \times 72} \times 0{,}85 \text{ for females}$$

MDRD IV

$$[\text{Crea}]\ S \times 186^{-1{,}154} \times \text{Age}^{-0{,}203} \times 0{,}74 \text{ for females}$$

CKD EPI crea

(„non-Black“)

$$144 \times ([\text{Crea}]\ S / 0{,}7)^{-0{,}329 \textit{ oder } 1{,}209} \times 0{,}993^{\text{Alter}} \text{ for females}$$

$$141 \times ([\text{Crea}]\ S / 0{,}9)^{-0{,}411 \textit{ oder } 1{,}209} \times 0{,}993^{\text{Alter}} \text{ for males}$$

CKD EPI cys C
CKD EPI crea-cys C

CKD-EPI cystatin C equation§			
Female or male		≤0.8	$133 \times (\text{Scys}/0.8)^{-0.499} \times 0.996^{\text{Age}}$ [× 0.932 if female]
Female or male		>0.8	$133 \times (\text{Scys}/0.8)^{-1.328} \times 0.996^{\text{Age}}$ [× 0.932 if female]
CKD-EPI creatinine–cystatin C equation¶			
Female	≤0.7	≤0.8	$130 \times (\text{Scr}/0.7)^{-0.248} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$130 \times (\text{Scr}/0.7)^{-0.248} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]
Female	>0.7	≤0.8	$130 \times (\text{Scr}/0.7)^{-0.601} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$130 \times (\text{Scr}/0.7)^{-0.601} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]
Male	≤0.9	≤0.8	$135 \times (\text{Scr}/0.9)^{-0.207} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$135 \times (\text{Scr}/0.9)^{-0.207} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]
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Inker et al., NEJM. 2012; 367: 20-29

eGFR Equations
State of the Art

Cockroft - Gault	$\frac{(140 - \text{Age}) \times \text{BW (kg)}}{[\text{Crea}]\ \text{S} \times 72}$	x 0,85 for females
MDRD IV	$[\text{Crea}]\ \text{S} \times 186^{-1,154} \times \text{Age}^{-0,203}$	x 0,74 for females
CKD EPI crea („non-Black“)	$144 \times ([\text{Crea}]\ \text{S} / 0,7)^{-0,329\ \textit{oder}\ 1,209} \times 0,993^{\text{Alter}}$	for females
	$141 \times ([\text{Crea}]\ \text{S} / 0,9)^{-0,411\ \textit{oder}\ 1,209} \times 0,993^{\text{Alter}}$	for males

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CKD EPI cys C

CKD EPI crea-cys C

Becomes more and more established;
better than MDRD IV if GFR > 60 ml/min x m^2

BIS Formula — for elderly
(*Schaeffner et al., Ann Int Med. 2012; 157: 471-481)*

Schwartz — for children

One Equation Fits all ?

Pottel et al., Nephrol Dial Transpl 2017; 32: 497-507

- Full Age Spectrum = FAS Formula
- Based on S-Crea, Cys C or S-Crea + Cys C

$$\mathrm{FAS}_{\mathrm{cysC}} = \frac{107.3}{\frac{\mathrm{ScysC}}{\mathrm{Q}_{\mathrm{cysC}}}} \times \left[0.988^{(\mathrm{Age}-40)} \text{ when age} > 40 \text{ years}\right].$$

$$\mathrm{FAS}_{\mathrm{combi}} = \frac{107.3}{\alpha \times \frac{\mathrm{Scr}}{\mathrm{Q}_{\mathrm{crea}}} + (1-\alpha) \times \frac{\mathrm{ScysC}}{\mathrm{Q}_{\mathrm{cysC}}}} \times \left[0.988^{(\mathrm{Age}-40)} \text{ when age} > 40 \text{ years}\right].$$

→ As good or superior to CKD-EPI and equations for specific age groups

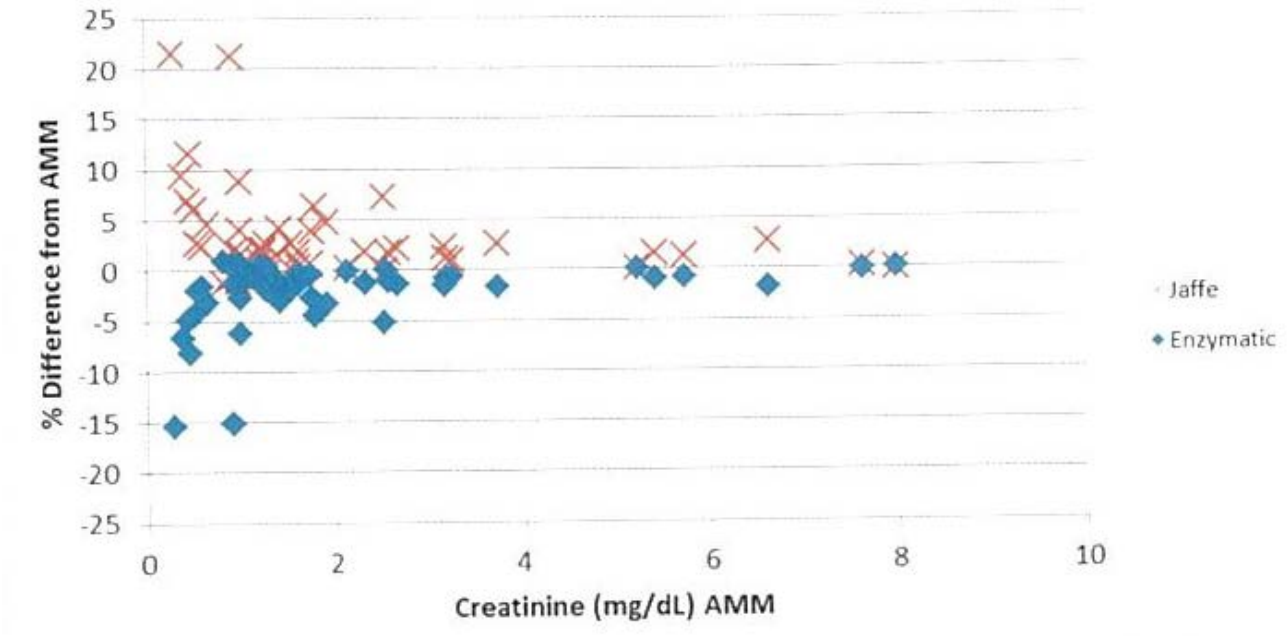
Variability of S-Crea Measurements
State of the Art

- Known variability of S-Crea measurements
- Causes of this variability:
  - Assay (Jaffe vs enzymatic)
  - Unspecificity
    endogenous: bilirubin, glucose, ketones, proteins, light chains
    exogenous: cephalosporine, dobutamin, lidocain
  - Different manufacturers
  - Differences in reference material **But: IDMS - Standard**
  - Assay platform
  - Assay performance
  - Pre-analytic factors

Variability of S-Crea Measurements

Lee et al., CJASN 2017; 12: 29-37

- Plasma from 53 patients (ICU) was sent to 12 different laboratories
- Mean values and eGFR (CKD-EPI) calculated



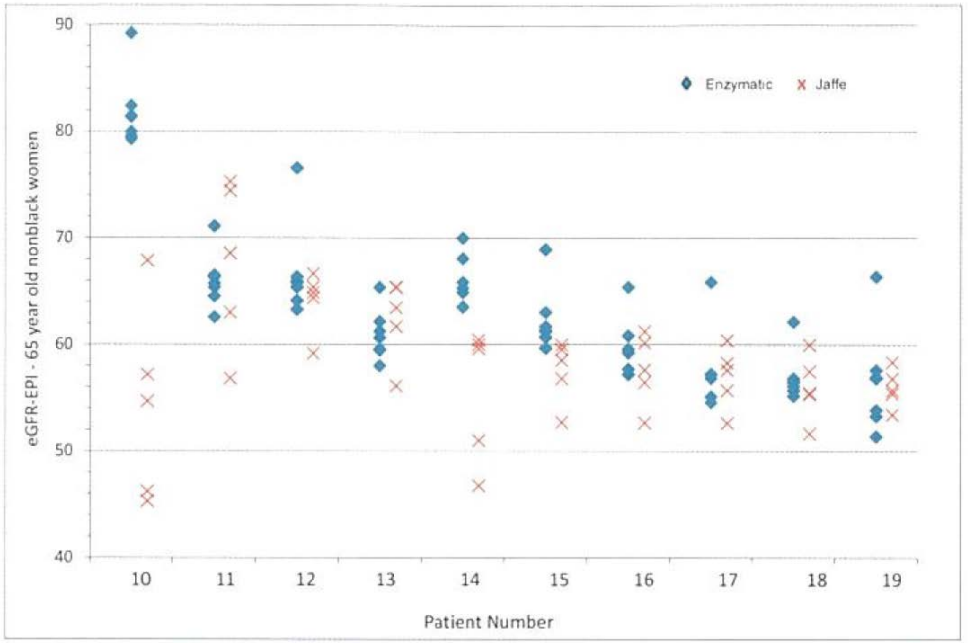
% difference from mean across all methods

Variability of S-Crea Measurements

Lee et al., CJASN 2017; 12: 29-37

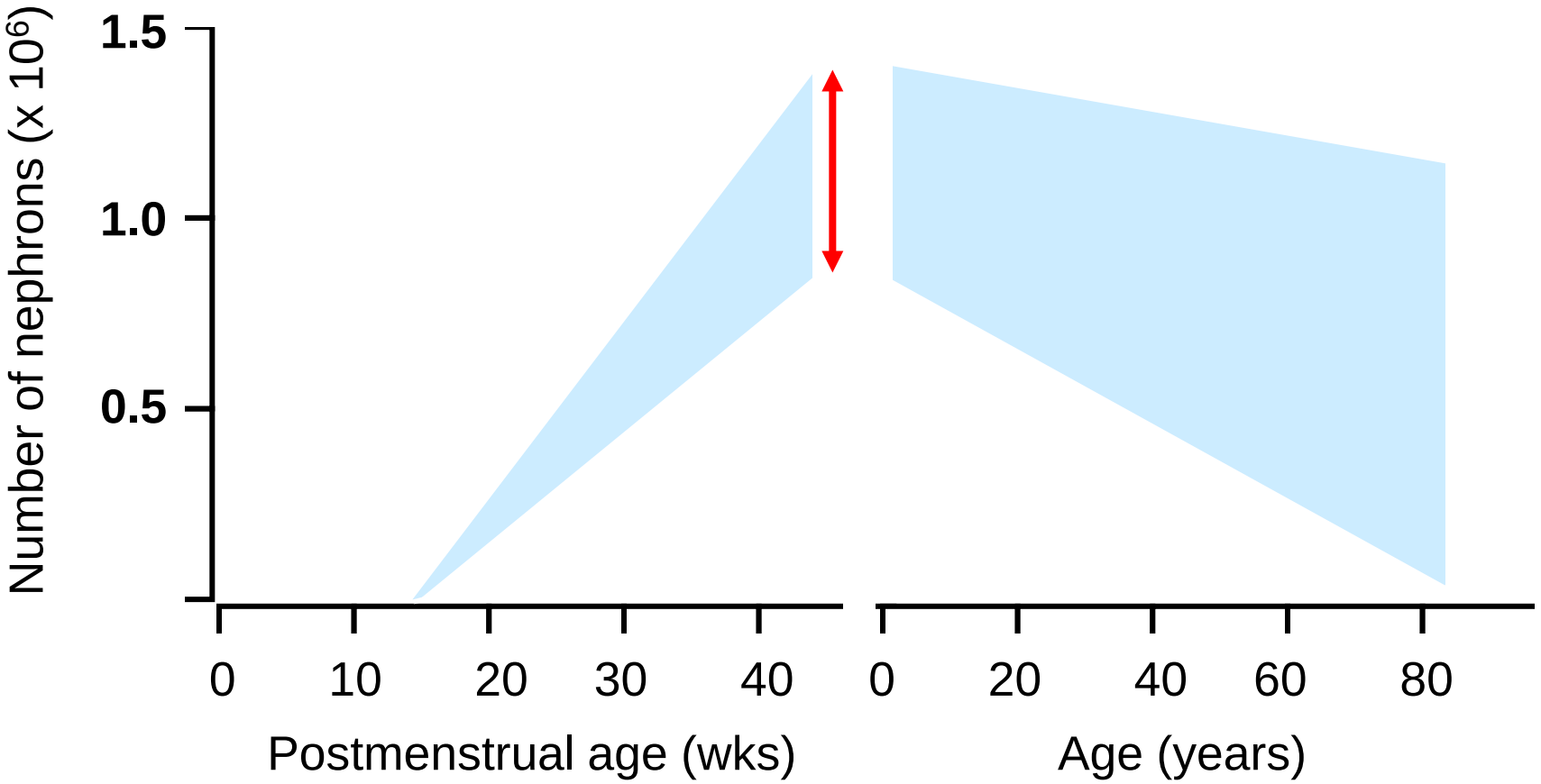
- Plasma from 53 patients (ICU) was sent to 12 different laboratories
- Mean values and eGFR (CKD-EPI) calculated

Individual variation



Change in Nephron Number with Age

State of the Art



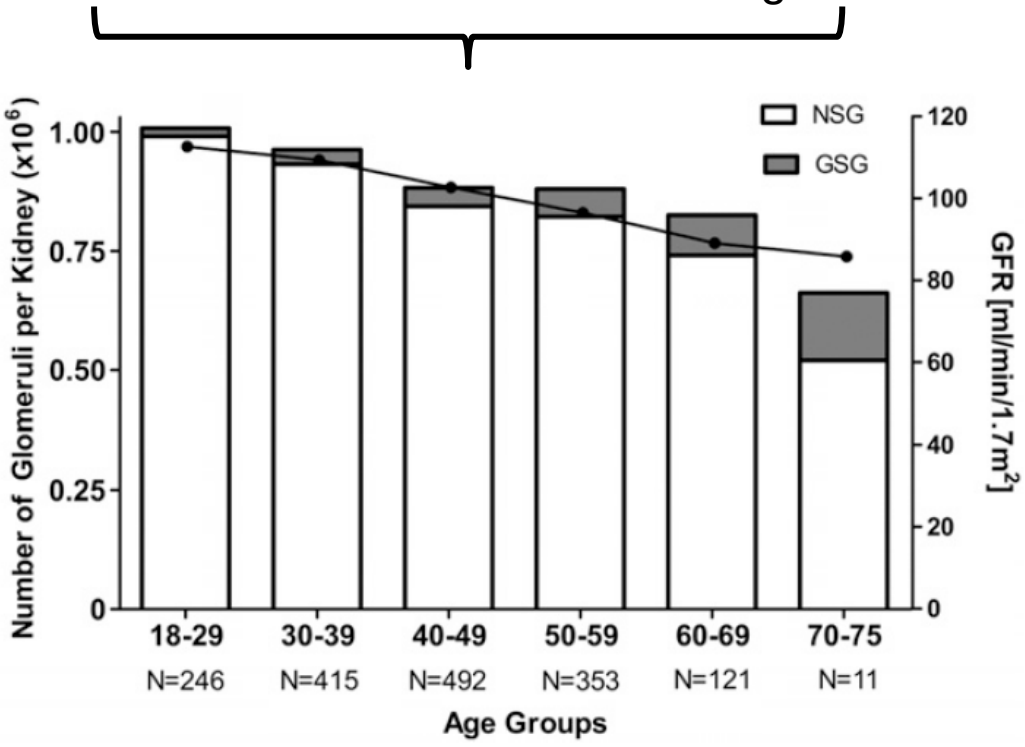
Nephron-Loss with Age

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

- **1638 Kidney donors**
  CT → cortical volume of both kidneys

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

Number of glomeruli
- non-sclerotic (normal; NSG) and
- globally sclerotic (GSG)



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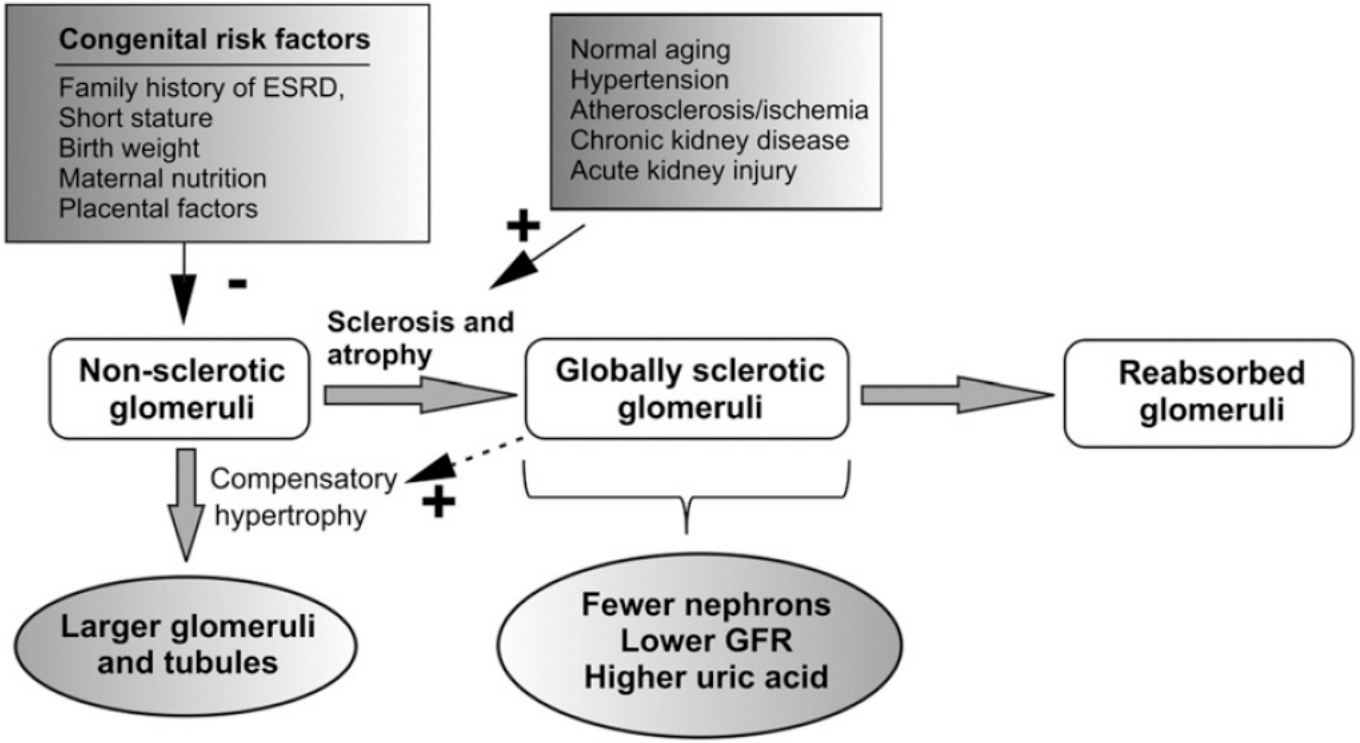


Take Home Messages
Definition and Staging of CKD

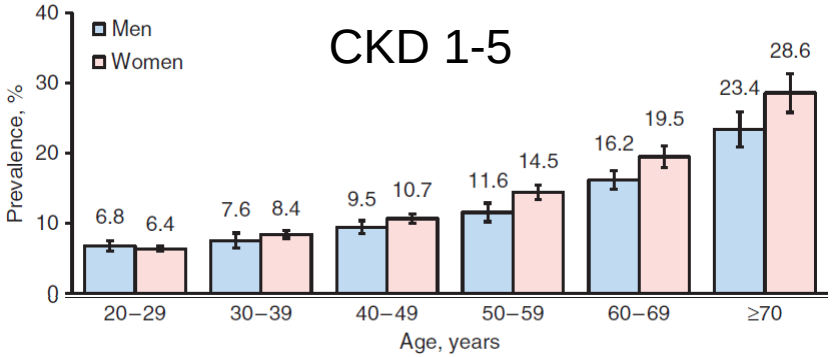
- No change since KDIGO GL; “CGA“ only partially implemented
- eGFR $_{crea}$ for initial assessment
- CKD-EPI eGFR$_{crea}$ increasingly implemented
- FAS (Full Age Spectrum) equation – “unknown relevance“
- Substantial reduction in nephron number with age
- Not all changes in S-crea indicate changes in GFR
- Stick to your lab !

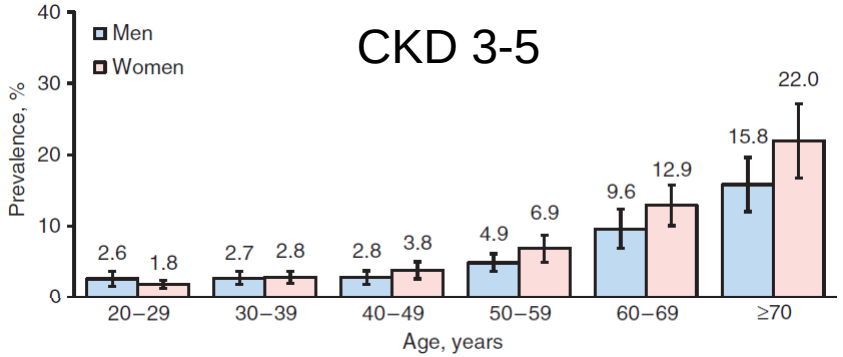
Chronic Kidney Disease

- Definition and staging of CKD
- **Relevance of CKD**
- Risk factors for the development and progression of CKD
- CKD and Infection / Inflammation
- CKD and bleeding tendency
- Interventions to retard CKD progression

Relevance of CKD
State of the Art

- 10-15% of the population
- Strong age-dependency
- Interesting regional variability
- Increasing prevalence since many years





Mills et al., Kidney Int 2015; 88: 950-57

Trends in CKD Prevalence

***Hallan et al., Kidney Int 2016**; 90, 665–673*

Nord-Trøndelag Health Study (HUNT) 2, N= 65.237
Nord-Trøndelag Health Study (HUNT) 3, N= 50.586

Albuminuria (mg/g)	A1 (ACR <30)			A2 (ACR 30-300)			A3 (>300)		
eGFR (ml/min/1.73 m^2)	HUNT-2	HUNT-3	*P* value	HUNT-2	HUNT-3	*P* value	HUNT-2	HUNT-3	*P* value
G1 (>90)	65.88%	65.43%	*0.15*	3.80%	3.64%	*0.32*	0.05%	0.04%%	*0.021*
G2a (75–89)	15.87%	16.63%	*0.001*	1.76%	1.69%	*0.50*	0.05%	0.02%	*0.009*
G2b (60–74)	6.94%	6.84%	*0.49*	1.08%	0.96%	*0.12*	0.08%	0.02%	*0.001*
G3a (45–59)	2.64%	2.71%	*0.49*	0.61%	0.62%	*0.78*	0.07%	0.02%	*0.001*
G3b (30–44)	0.64%	0.79%	*0.012*	0.25%	0.32%	*0.11*	0.05%	0.01%	*0.008*
G4 (15–29)	0.10%	0.16%	*0.044*	0.09%	0.11%	*0.29*	0.04%	0.02	*0.057*

→ **“Stable disease“**

Trends in CKD Prevalence

Hallan et al., Kidney Int 2016; 90, 665–673

Table 3 | Predicted changes in CKD prevalence from HUNT-2 (1995–1997) to HUNT-3 (2006–2008) if modifiable kidney risk factors remained at 1995–1997 level

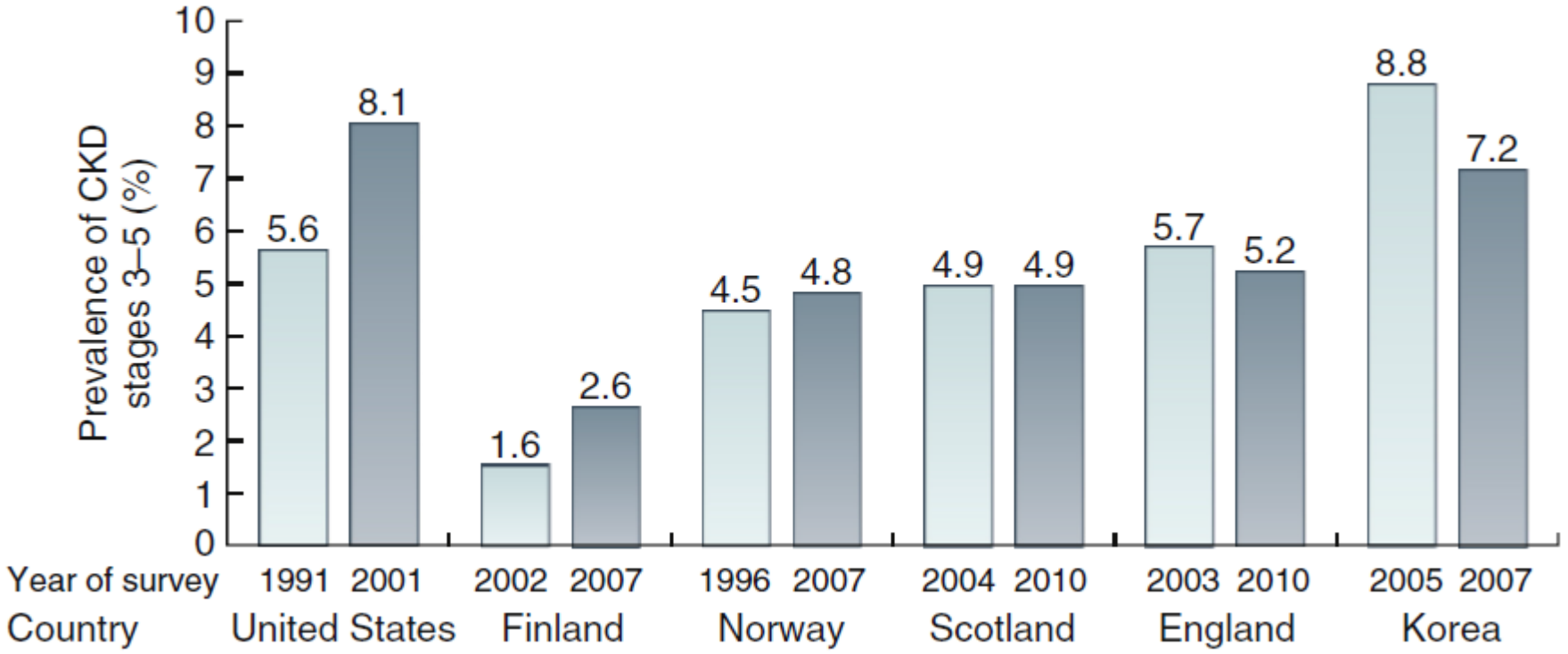
	eGFR <60 ml/min	ACR >30 mg/g	CKD total	CKD high/ very high risk
Observed prevalence 1995–1997 (%)	4.49	7.93	11.30	2.01
Improved variables				
Predicted CKD change if no change in	(Absolute prevalence change [percentage points], 2006–2008 vs. 1995–1997)			
Systolic BP	+2.06***	+1.11***	+2.77***	+0.91***
CVD	+0.49**	−0.43	−0.01	+0.18
Cholesterol	+1.01***	−0.23	+0.58*	+0.36**
Physical inactivity	+0.93***	−0.13	+0.69*	+0.37**
Smoking	+0.19	−0.34	−0.15	−0.06
None of these risk factors	+3.41***	+1.36***	+3.78***	+1.43***
Worsened variables				
Predicted CKD change if no change in				
Prediabetes/diabetes	+0.03	-0.83**	−0.73**	−0.06
BMI	+0.04	−0.74**	−0.65*	−0.02
None of these risk factors	−0.12	−0.95***	−1.00***	−0.13

Note: Asterisks indicate that change from HUNT-2 to HUNT-3 is significantly different from 0 (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$). Data are based on generalized estimation equation analysis, an extension of logistic regression for clustered data. For example, with CKD total as a dependent variable and time period (HUNT-2 or HUNT-3) and systolic BP as independent variables, time period has an odds ratio of 1.245: CKD prevalence in HUNT3 would be 1.245 times higher if systolic blood pressure remained unchanged ($1.245 \times 11.3 - 11.3 = 2.77\%$ [percentage points] higher CKD prevalence could have been expected).

ACR, albumin to creatinine ratio; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

Trends in CKD Prevalence

De Nicola & Minutolo, Kidney Int 2016; 90, 482-4



More recently stabilization also in the US !

Murphy D et al. Ann Int Med 2016; 165: 473-81

Take Home Messages
Relevance of CKD

- CKD prevalence seems to have reached a plateau
- Prevention (risk factor control) and early detection (definition, staging, eGFR reporting), ….. may help !

Chronic Kidney Disease

- Definition and staging of CKD
- Relevance of CKD
- **Risk factors for the development and progression of CKD**
- CKD and Infection / Inflammation
- Interventions to retard CKD progression

Longterm Effects of PPI

Lazarus et al., JAMA 2016; 176: 238-46

- ARIC Study (N=10.482), bl eGFR > 60, median FU: 13.9 yrs
- validated in Geisinger (N=248.751); bl eGFR > 60, median FU: 6,2 yrs

CKD events

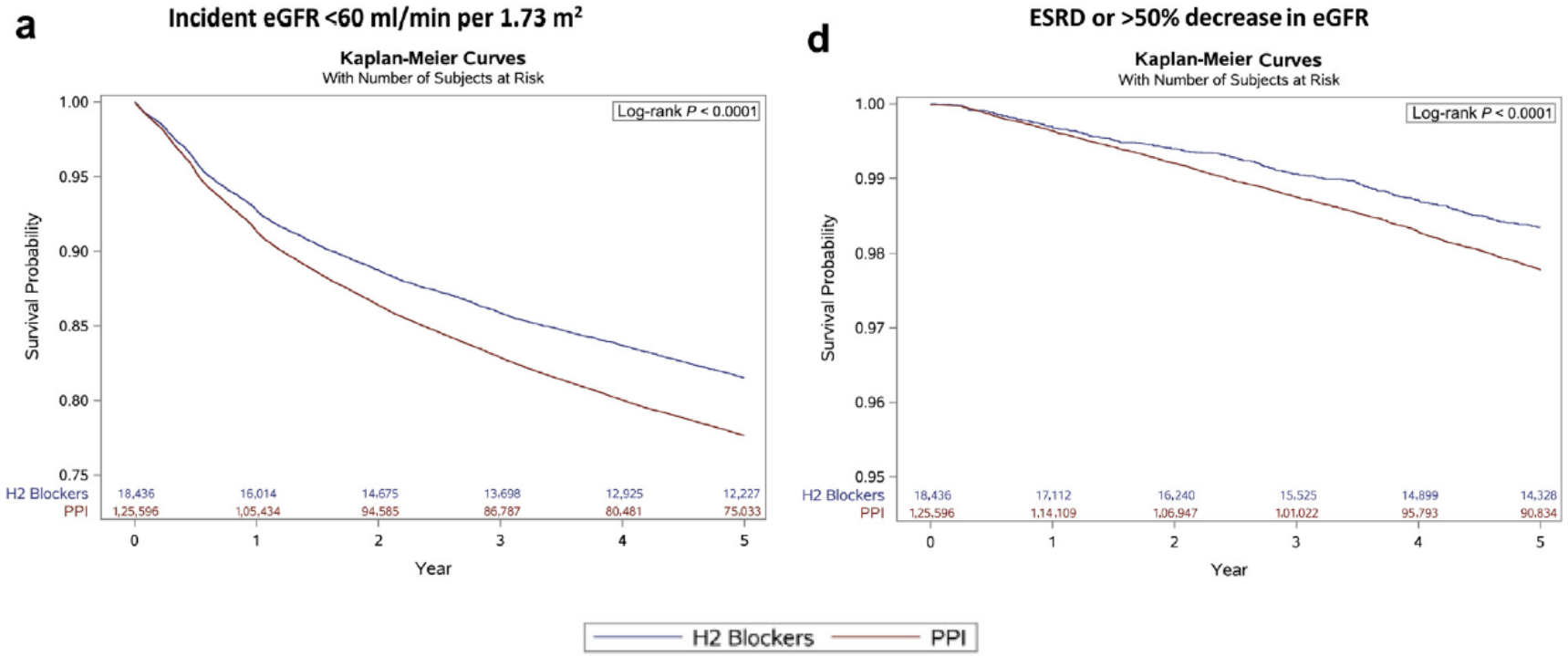
Variable	Atherosclerosis Risk in Communities Study (n = 10 4820 No. of Events	No. of Participants	Geisinger Health System Replication Cohort (n = 248 751) No. of Events	No. of Participants
PPI users	56	322	1921	16 900
H_2 receptor antagonist users	158	956	1022	6640
Nonusers	1224	9204	27 204	225 221
Association Between PPI Use and Incident CKD	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Unadjusted baseline PPI use vs no PPI use	1.45 (1.11-1.90)	.006	1.20 (1.15-1.26)	<.001
Baseline PPI use vs no PPI use	1.50 (1.14-1.96)	.003	1.17 (1.12-1.23)	<.001
Time-varying PPI ever use vs never PPI use	1.35 (1.17-1.55)	<.001	1.22 (1.19-1.25)	<.001
Baseline PPI use vs baseline H_2 receptor antagonist use	1.39 (1.01-1.91)	.05	1.29 (1.19-1.40)	<.001
Baseline PPI use vs propensity score-matched no PPI use	1.76 (1.13-2.74)	.01	1.16 (1.09-1.24)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.24 (1.20-1.28)	<.001
Negative Control				
Baseline H_2 receptor antagonist use vs no H_2 receptor antagonist use	1.15 (0.98-1.36)	.10	0.93 (0.88-0.99)	.03

in addition 1.3 to 2 fold increased risk for CKD

Longterm Effects of PPI

Xie et al., Kidney Int 2017; 91 (6): 1482-94

- Veterans Affairs database;
  (N=144.032) incident users of acid suppression therapy:
  (N=125.596 PPI; N=18436 H2 blocker); BL GFR > 60; FU 5 yrs
  censored at the time of AKI occurence



Longterm Effects of PPI

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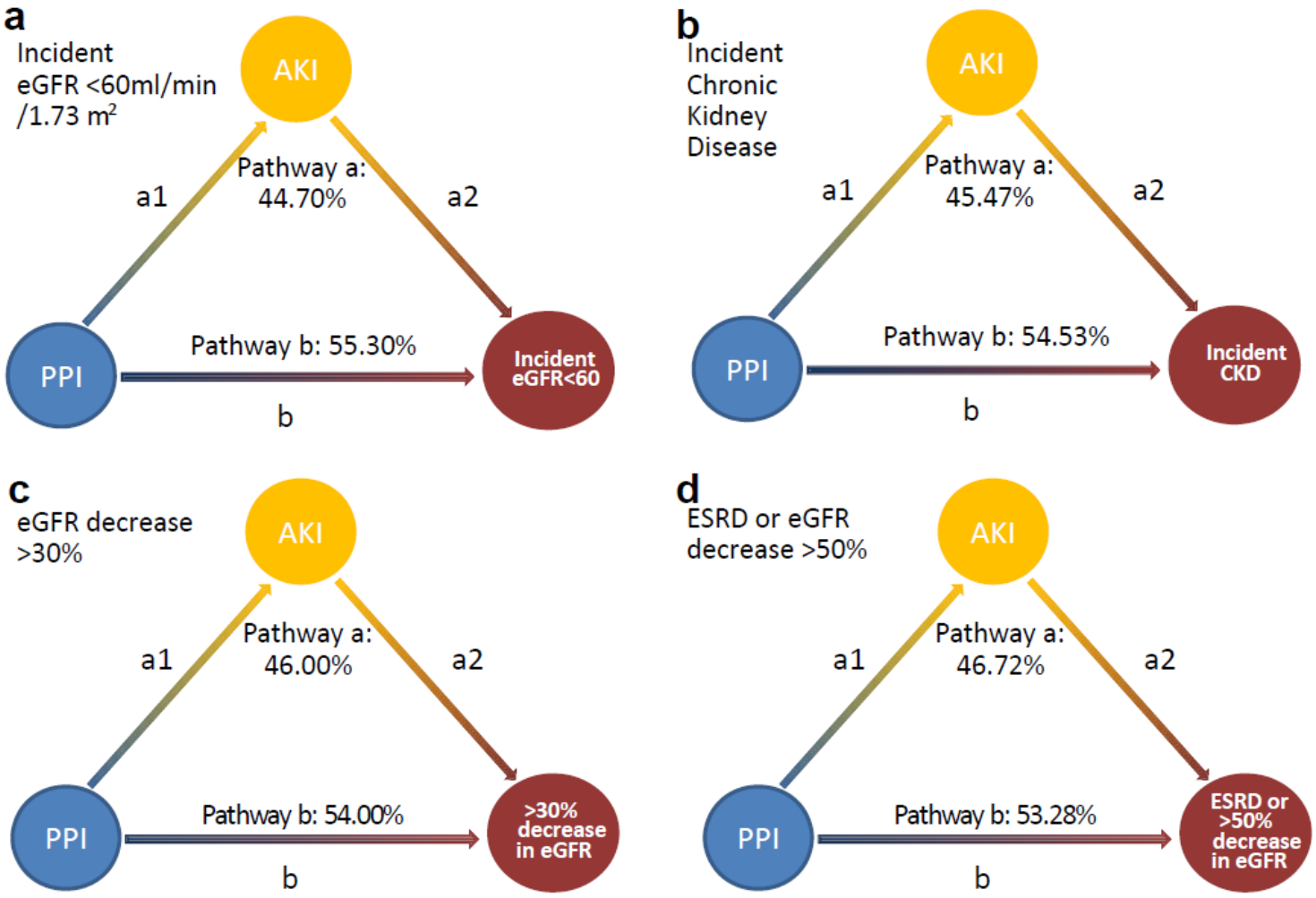


PPIs and Kidney Disease: from AIN to CKD

Toth-Manikowski & Grams, ***Kid Int Reports*** *2017; 29, 611–16*

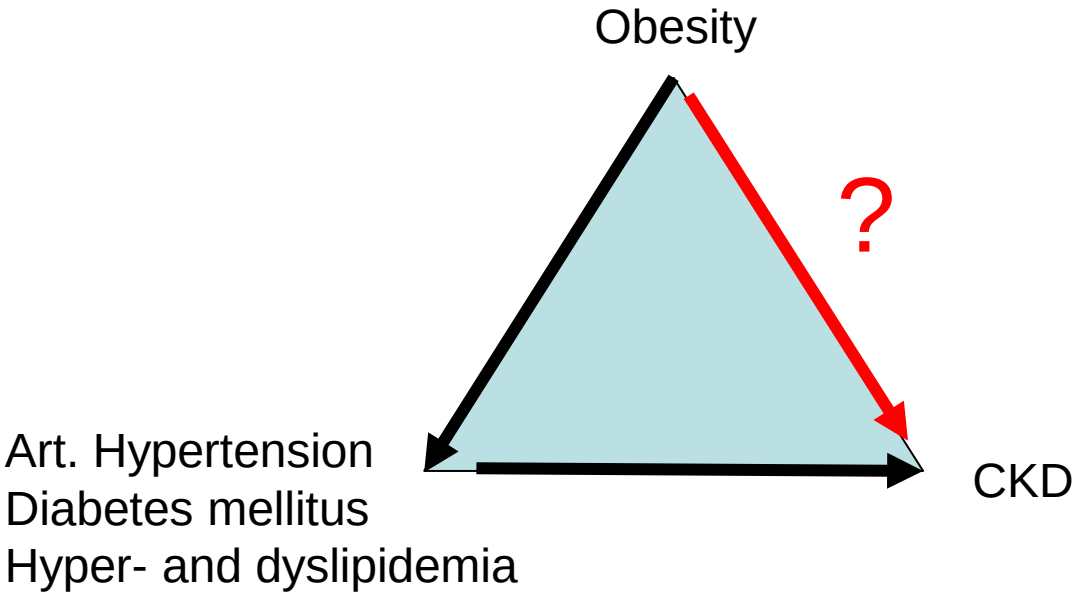
Table 1. Studies evaluating for an association between PPI exposure and kidney injury and corresponding findings

Author, year	Study design	Type of kidney injury evaluated	Reference group	Risk associations with PPI use
Geevasinga *et al.*, 2006[36]	Case series	AIN	NA	NA
Simpson *et al.*, 2006[37]	Case series	AIN	NA	NA
Leonard *et al.*, 2012[38]	Case-control	AIN	No PPI use	OR 3.20 (0.80–12.79)
Leonard *et al.*, 2012[38]	Case-control	AKI	No PPI use	OR 1.05 (0.97–1.14)
Klepser *et al.*, 2013[39]	Case-control	AKI	No PPI use	**OR 1.72 (1.27–232)**
Antoniou *et al.*, 2015[40]	Health system data	AKI	No PPI use	**HR 2.52 (2.27–2.79)**
Lazarus *et al.*, 2016[41]	Prospective cohort	AKI	No PPI use	**HR 1.64 (1.22–2.21)**
	Health system data		No PPI use	**HR 1.31 (1.22–1.42)**
	Prospective cohort	AKI	H_2RA use	**HR 1.58 (1.05–2.40)**
	Health system data		H_2RA use	**HR 1.31 (1.13–1.48)**
Lazarus *et al.*, 2016[41]	Prospective cohort	CKD	No PPI use	**HR 1.50 (1.14–1.96)**
	Health system data		No PPI use	**HR 1.17 (1.12–1.23)**
	Prospective cohort	CKD	H_2RA use	**HR 1.39 (1.01–1.91)**
	Health system data		H_2RA use	**HR 1.29 (1.19–1.40)**
Xie *et al.*, 2016[42]	Prospective cohort	CKD	H_2RA use	**HR 1.28 (1.23–1.34)**
Xie *et al.*, 2016[42]	Prospective cohort	ESRD	H_2RA use	**HR 1.96 (1.21–3.18)**
Peng *et al.*, 2016[43]	Case-control	ESRD	No PPI use	**OR 1.88 (1.71–2.06)**

AIN, acute interstitial nephritis; AKI, acute kidney injury; H_2RA, histamine$_2$ receptor antagonists; HR, hazard ratio; NA, not applicable; OR, odds ratio; PPI, proton pump inhibitor. Bold font indicates a positive and significant association. Odds and hazard ratios are followed by 95% confidence intervals.

Obesity and CKD
State of the Art

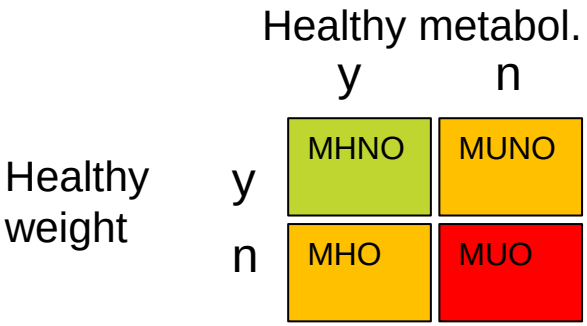
- Prevalence of obesity increases world-wide
- Factors associated with obesity are associated with CKD
- Is obesity an independent risk factor for CKD ?

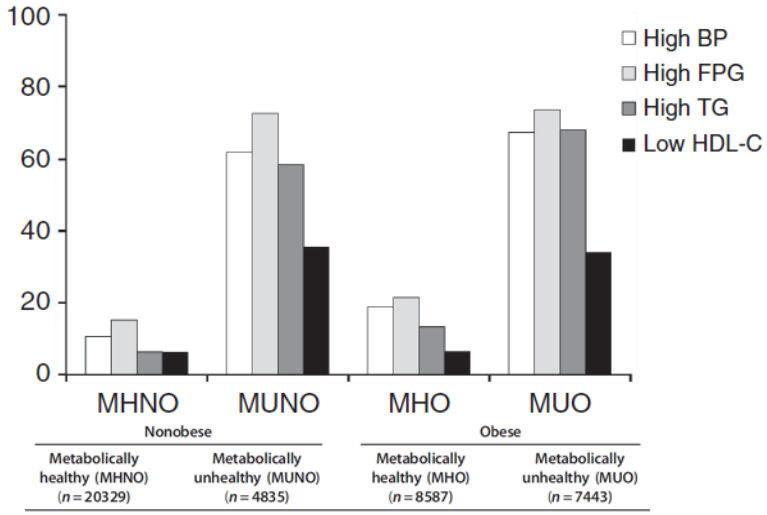


Obesity and Risk for CKD

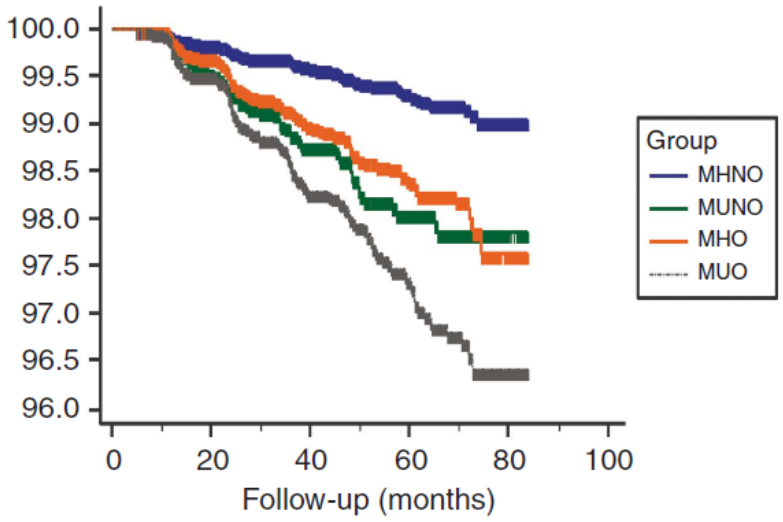
Jung et al., Kidney Int 2015; 88, 843-50

- Population from Korea (N = 41.194)





CKD-free Survival



MHNO	20,329	15,473	9919	5517	111
MUNO	4835	3611	2345	1283	24
MHO	8587	6608	4340	2504	55
MUO	7443	5628	3558	1983	54

DASH Diet and Risk for CKD

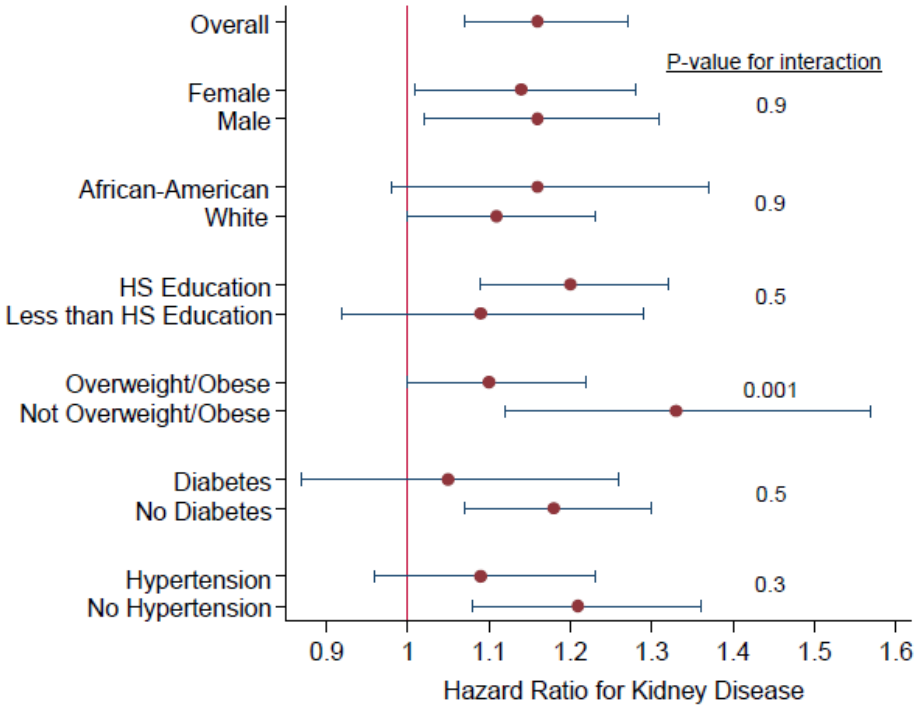
***Rebholz et al., Am J Kid Dis 2016**; 68: 853-61*

DASH = Dietary Approaches to Stop Hypertension

ARIC Studie, baseline
eGFR > 60ml/min x 1,73 m^2
(N=14.882)

3.720 developed CKD
during observation period

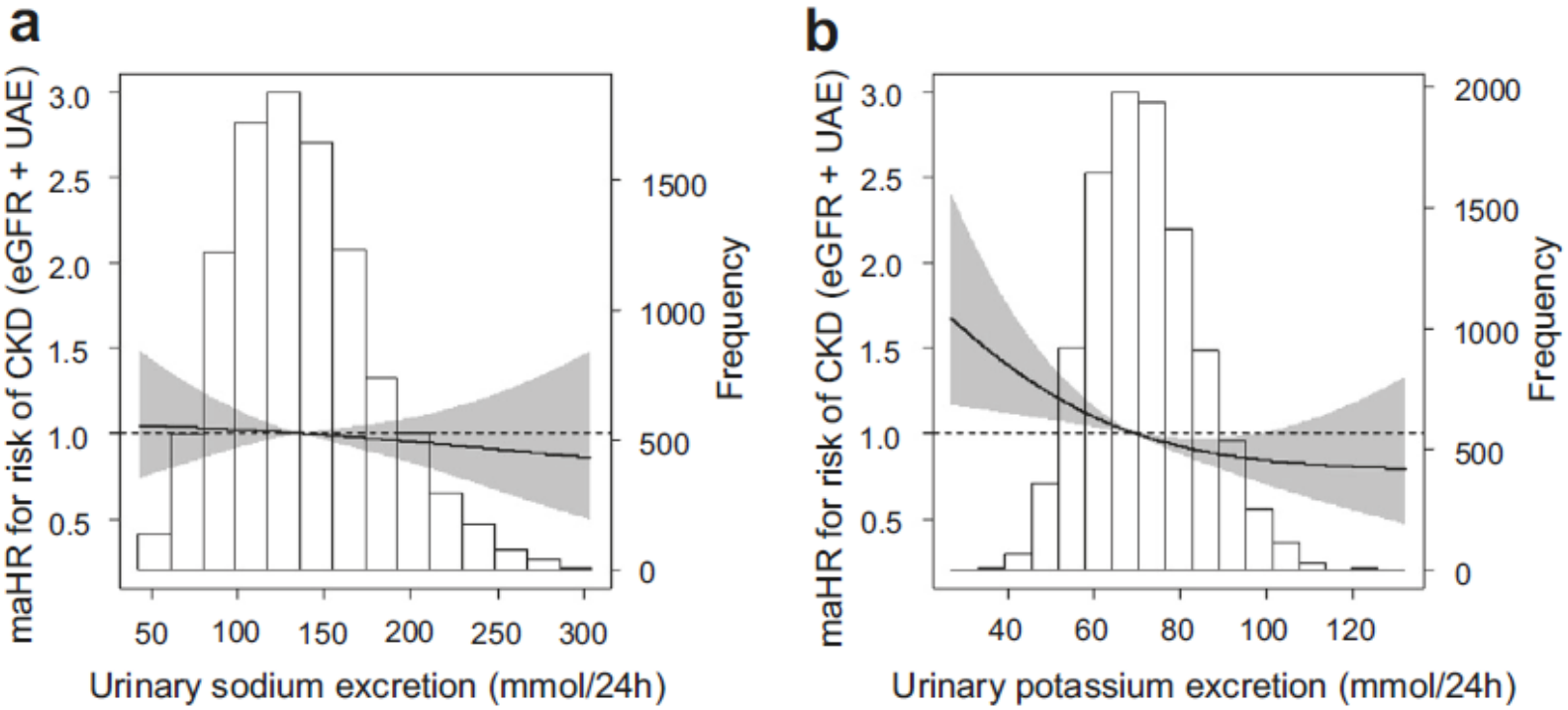
Risk for development of CKD, comparing lowest vs highest tertile of DASH score



Sodium- and Potassium – Excretion and Risk for CKD

***Kieneker et al., Kidney International* 2016; 90: 888-96**

PREVEND Study, (N= 5315), 2 x 24 hrs Urine-Collection, median FU 10.3 yrs



„Diet Coke“ et al.
State of the Art

“Soft-Drinks“ are a major source of calories; primary source of sugar intake
(33% of all added sugar)

→ Risk for DM, CVD

→ Advice to avoid “Soft-Drinks“ and other sweetened beverages

→ “Diet Soda“ – increasingly-used substitute in the US

Is this always good ?

“Diet Soda“ and Risk for ESRD

***Rebholz et al., CJASN 2017**; 12: 79-86*

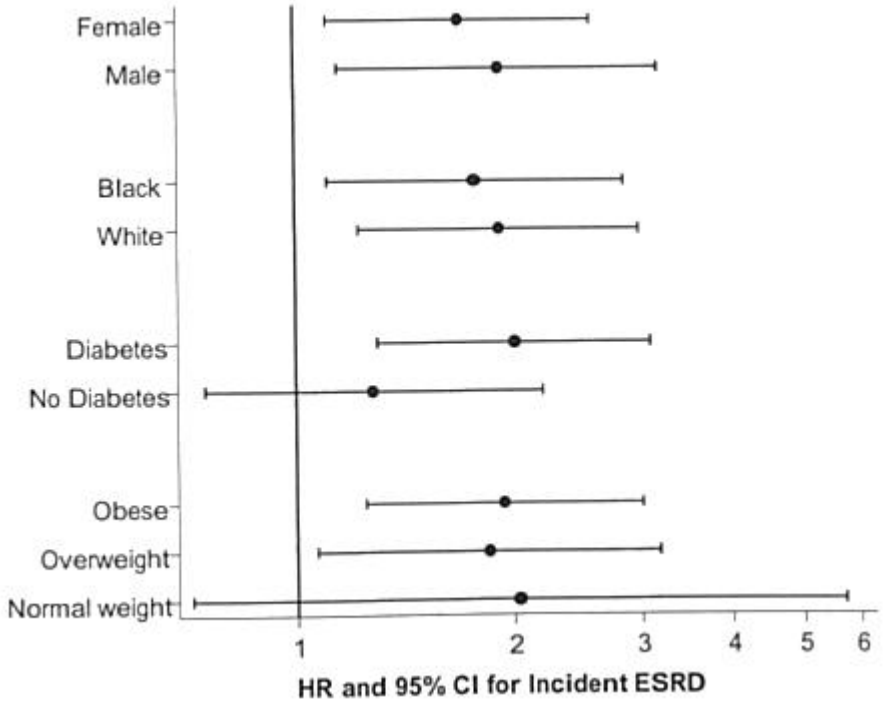
ARIC Study (N=15.368)

Food Frequency Questionnaire:

Diet Soda consumption:

< 1 glass / week	43.5 %
1-4 glasses / week	17.8 %
5-7 glasses / week	25.3 %
> 7 glasses / week	13.5 %

Increased risk for development of ESRD in study participants who consumed at least 1 glass of diet soda per week (compared to less than 1 glass)



Take Home Messages
Risk factors for development and progression of CKD

- Medication: avoid *unnecessary* long-term use of PPI

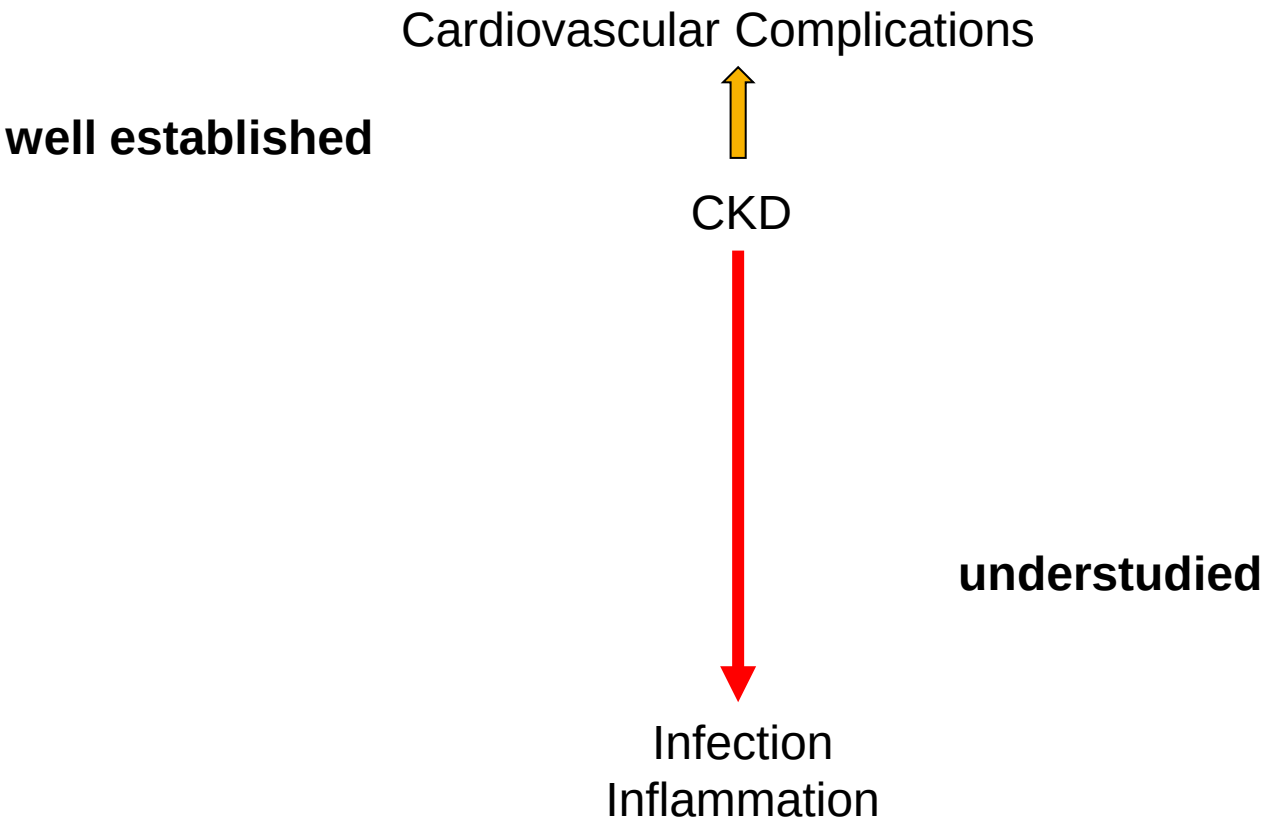
- Diet:
  - Too much is not good; a “healthy“ metabolic phenotype protects only partially in obesity
  - DASH seems to protect
  - Sodium not as important as frequently presumed
  - Diet–Soda perhaps not as healthy as presumed

Chronic Kidney Disease

- Definition and staging of CKD
- Relevance of CKD
- Risk factors for the development and progression of CKD
- **CKD and Infection / Inflammation**
- Interventions to retard CKD progression

Infection / Inflammation and CKD

State of the Art



Kidney Function and Infection Risk

Ishigami et al., AJKD 2016; 69: 752-761

ARIC Study (N=9.697)

Risk for hospitalization with infection

eGFR 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	30-299 mg/g	≥300 mg/g
	G1	Normal or high	≥90	1 [Reference] (n=897/3918)	1.38 (1.09-1.75) (n=76/213)	1.69 (0.99-2.88) (n=14/33)
	G2	Mildly decreased	60-89	1.05 (0.96-1.15) (n=1272/4576)	1.55 (1.28-1.88) (n=126/295)	2.48 (1.71-3.59) (n=30/51)
	G3a	Mildly to moderately decreased	45-59	1.46 (1.22-1.76) (n=147/353)	2.17 (1.55-3.05) (n=36/64)	2.24 (1.36-3.71) (n=16/24)
	G3b	Moderately to severely decreased	30-44	1.37 (1.00-1.89) (n=41/98)	2.92 (1.86-4.59) (n=20/34)	5.37 (3.15-9.15) (n=14/19)
	G4	Severely decreased	15-29	3.54 (1.99-6.29) (n=12/19)		

Kidney Function and Infection Risk

Ishigami et al., AJKD 2016; 69: 752-761

Table 4. Risk for Infection-Related Death According to eGFR and ACR Categories

Category	Person-y	No. of Events	Mortality Rate/1,000 person-y (95% CI)	Adjusted HR (95% CI)[a]
eGFR				
≥90 mL/min/1.73 m^2 (n = 4,164)	55,866	170	3.04 (2.62-3.54)	1.00 (reference)
60-89 mL/min/1.73 m^2 (n = 4,922)	64,053	274	4.28 (3.80-4.82)	0.99 (0.80-1.21)
30-59 mL/min/1.73 m^2 (n = 592)	6,659	74	11.11 (8.85-13.96)	1.62 (1.20-2.19)
15-29 mL/min/1.73 m^2 (n = 19)	167	5	29.93 (12.46-71.91)	3.76 (1.48-9.58)
ACR				
<10 mg/g (n = 7,821)	104,215	353	3.39 (3.05-3.76)	1.00 (reference)
10-29 mg/g (n = 1,131)	14,121	80	5.67 (4.55-7.05)	1.39 (1.09-1.78)
30-299 mg/g (n = 609)	7,106	60	8.44 (6.56-10.88)	1.57 (1.18-2.09)
≥300 mg/g (n = 136)	1,303	30	23.03 (16.10-32.94)	3.44 (2.28-5.19)

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

[a]The model was adjusted for age, race, sex, body mass index, smoking status, alcohol consumption, education level, use of antineoplastic agents and steroids, hypertension, diabetes, history of cancer, chronic obstructive pulmonary disease, prior heart failure, prior coronary disease, and prior stroke, and the ACR categories for the analysis of eGFR and the eGFR categories for the analysis of ACR.

Consequences of Infection in CKD

Hassan et al., Kidney International 2016; 90: 897-904

Can PREDDICT Study (N=15.368)
eGFR 15-45 ml/min x 1,73 m^2 at bl; under nephrological care
In 2370 patients 575 infection episodes (378 - one; 197 - two or more)

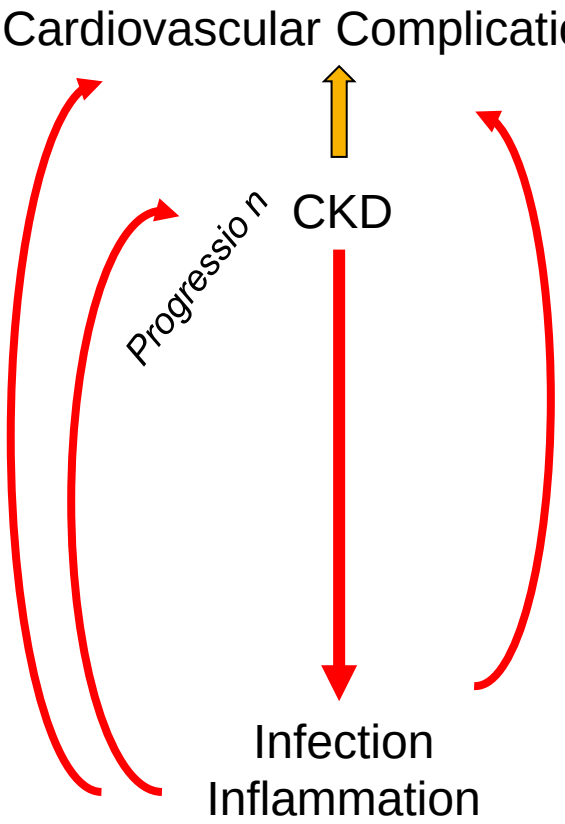
Table 3 | Hazard ratio for the association of infection with the outcomes of cardiac ischemia, congestive heart failure, end-stage kidney disease, and mortality

	Cardiovascular ischemia		CHF		ESKD		Mortality	
Model	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted	2.29	1.63–3.22	4.33	3.16–5.95	1.69	1.34–2.12	4.01	3.17–5.06
Adjusted	1.80	1.24–2.60	3.22	2.25–4.61	1.58	1.22–2.05	3.39	2.65–4.33

CHF, congestive heart failure; CI, confidence interval; ESKD, end-stage kidney failure; HR, hazard ratio.
All models adjusted for age, sex, cause of chronic kidney disease, comorbidities (diabetes, congestive heart failure, cardiac ischemia, cerebrovascular disease, peripheral vascular disease), baseline laboratory tests (estimated glomerular filtration rate, phosphate, albumin, C-reactive protein, bicarbonate, hemoglobin, urine albumin-to-creatinine ratio, and baseline systolic blood pressure.

→ Episodes of infection are associated with increased cardiovascular risk

Infection / Inflammation and CKD



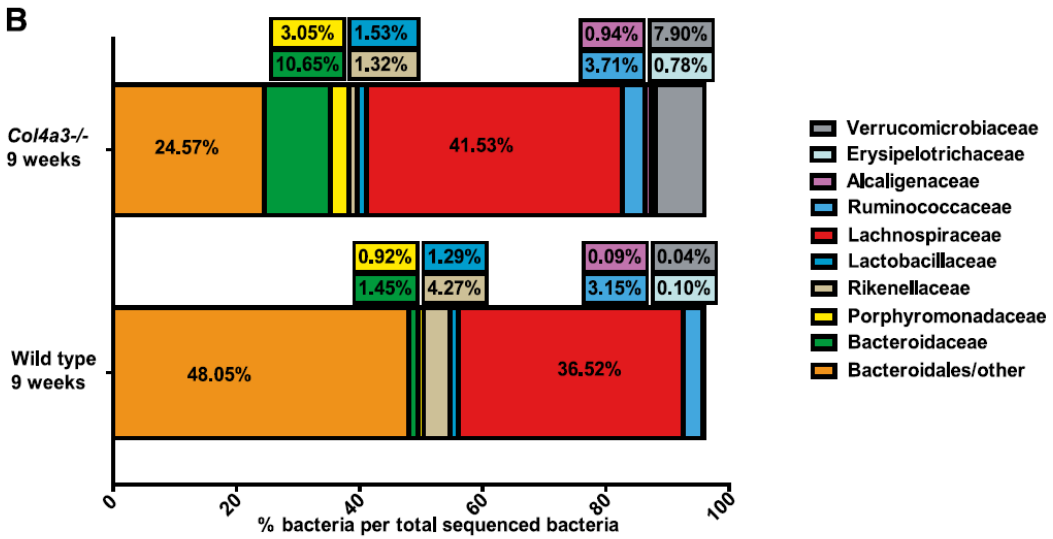
Amdur et al.
CJASN 2016;
11: 1546-56

Hassan et al.,
Kid Int 2016;
90: 897-904

Ishigami et al.,
AJKD 2016; (epub)

Dysbiosis as a Cause of Inflammation in CKD

Andersen et al. JASN 2017; 28: 76-83



!

CKD → Changes in the intestinal microbiom

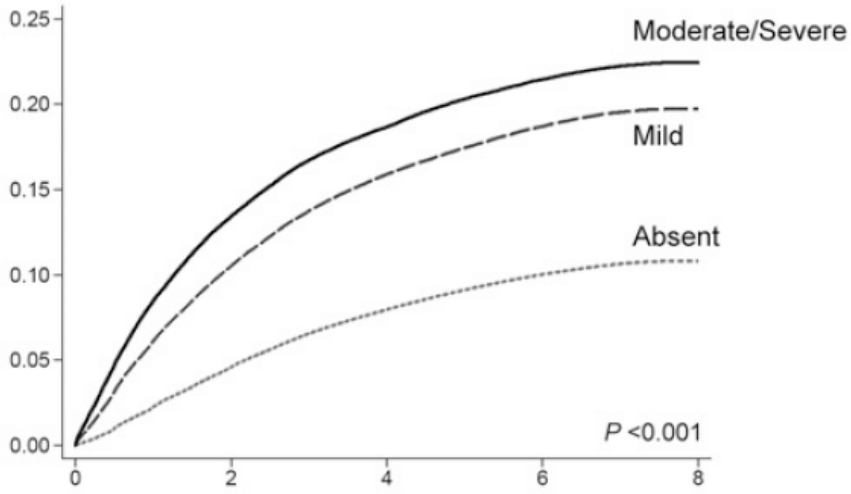
- bacterial translocation
- bacterial metabolites
- endotoxin

Constipation and CKD / ESRD Risk

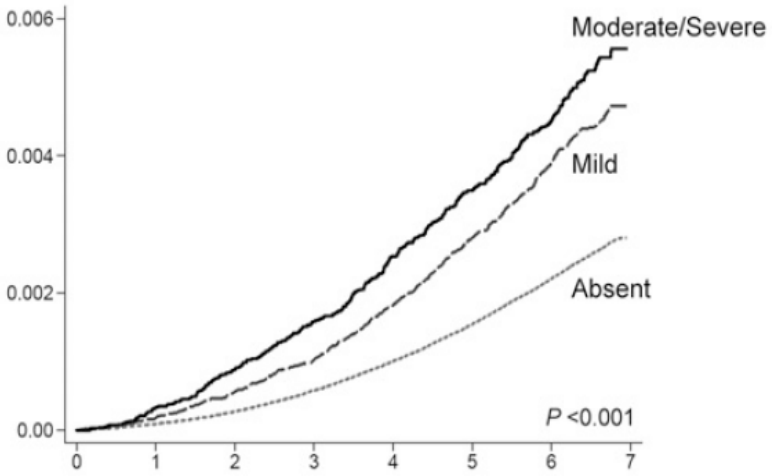
Samida et al. JASN 2017; 28: 76-83

3.504.732 US Veterans with an eGFR ≥ 60 ml/min x 1,73 m2

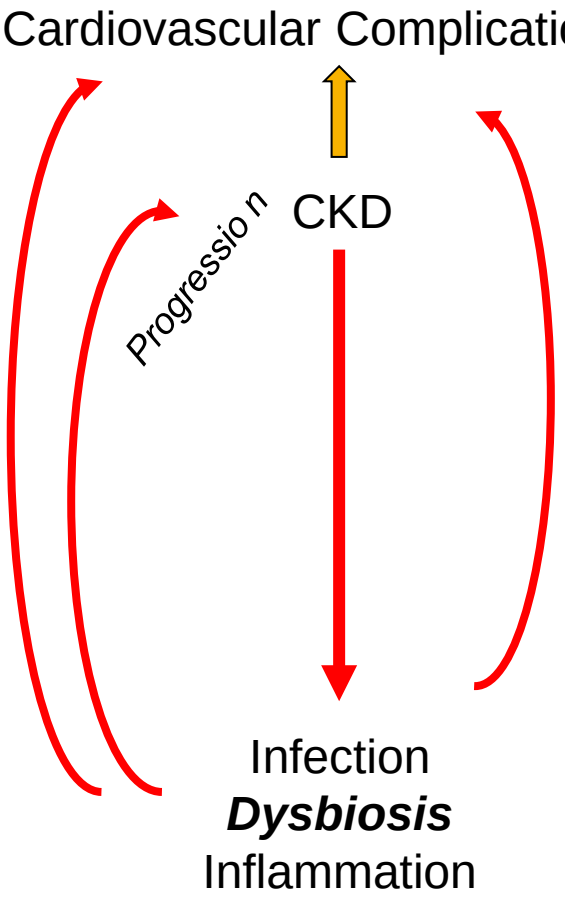
Cumulative Risk: CKD



Cumulative Risk: ESRD



Infection / Inflammation and CKD



Amdur et al.
CJASN 2016;
11: 1546-56

Hassan et al.,
Kid Int 2016;
90: 897-904

Ishigami et al.,
AJKD 2016; (epub)

Take Home Messages
Infection / Inflammation and CKD

- CKD is associated with / promotes infections
- Infections in patients with CKD are associated with / promote cardiovascular events
- Inflammation accelerates CKD progression
- One possible cause: Dysbiosis
- Constipation is a risk factor for CKD
  (perhaps via dysbiosis, inflammation…?)

Chronic Kidney Disease

- Definition and staging of CKD
- Relevance of CKD
- Risk factors for the development and progression of CKD
- CKD and Infection / Inflammation
- **Interventions to retard CKD progression**

Folic acid and CKD
State of the Art

- Hyperhomocysteinemia is a risk factor
- Substitution of folic acid and vitamin B12 so far without proven benefit
- Chinese Stroke and Primary Prevention Trial (CSPPT) (Hsu et al. JAMA 2015)
  - Enalapril vs Enalapril plus Folic acid

    in 20.000 hypertensive patients

Folic acid and CKD

Xu X et al., JAMA Int Medicine 2016; 176: 1443-50

Predefined substudy

RCT

Enalapril
N=7545

Enalapril + Folsre.
N=7545

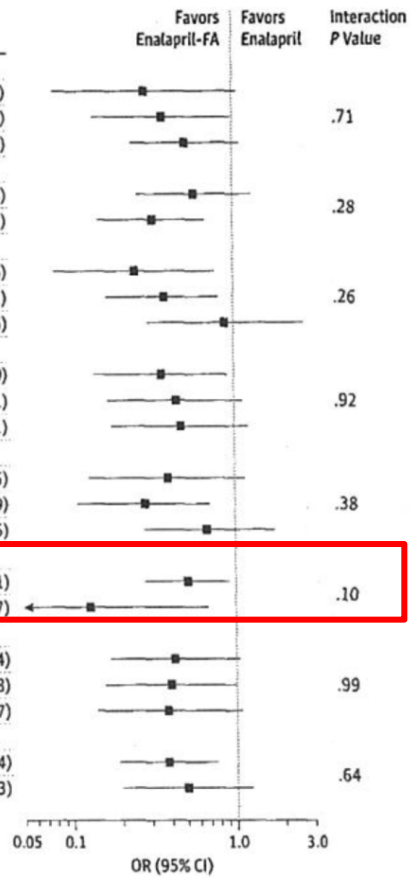
Primary endpoint:
progression of CKD, defined as decline in GFR < 60 or by 50% if GFR is already < 60

Median FU: 4.4 yrs.

Result: 164 vs 132

Figure. Primary Outcome in Subgroups of Patients With Chronic Kidney Disease

Source	Patients, No.	Enalapril Event No., %	Enalapril-FA Event No., %	OR (95% CI)	Interaction *P* Value
Age, y					
45-55	404	9 (4.7)	4 (1.9)	0.29 (0.08-1.06)	
55-65	554	15 (5.4)	7 (2.5)	0.37 (0.14-0.97)	.71
65-75	446	22 (10.4)	13 (5.5)	0.51 (0.24-1.10)	
Sex					
Male	585	18 (6.3)	12 (4.0)	0.58 (0.26-1.28)	.28
Female	819	28 (7.1)	12 (2.8)	0.32 (0.15-0.67)	
MTHFR C677T					
CC	320	16 (9.5)	5 (3.3)	0.25 (0.08-0.76)	
CT	697	22 (6.9)	12 (3.2)	0.38 (0.17-0.81)	.26
TT	387	8 (4.1)	7 (3.6)	0.89 (0.30-2.66)	
Folate, ng/mL					
≤5.54	465	16 (7.6)	8 (3.1)	0.36 (0.14-0.90)	
5.54-8.47	475	14 (6.0)	9 (3.7)	0.44 (0.17-1.11)	.92
≥8.48	464	16 (6.8)	7 (3.1)	0.47 (0.18-1.21)	
Total homocysteine, μmol/L					
≤12	479	11 (4.9)	6 (2.4)	0.39 (0.13-1.15)	
12-16.4	476	23 (9.5)	8 (3.4)	0.28 (0.11-0.69)	.38
≥16.5	449	12 (5.6)	10 (4.3)	0.70 (0.28-1.75)	
eGFR, mL/min/1.73 m^2					
≥60	1165	37 (6.5)	22 (3.7)	0.51 (0.28-0.91)	.10
30-60	239	9 (8.3)	2 (1.5)	0.13 (0.02-0.67)	
BMI					
≤24.2	461	17 (7.4)	8 (3.5)	0.42 (0.17-1.04)	
24.2-27.3	470	16 (7.4)	9 (3.5)	0.40 (0.16-0.98)	.99
≥27.4	473	13 (5.5)	7 (2.9)	0.38 (0.14-1.07)	
Diabetes					
Yes	1070	30 (5.8)	15 (2.7)	0.38 (0.19-0.74)	.64
No	334	16 (9.9)	9 (5.2)	0.50 (0.20-1.23)	



Take Home Messages
Folic Acid and CKD

- Results may not be generalizable because of higher baseline folic acid supply in other parts of the world
- Nevertheless: pharmacological prevention of CKD (progression) is possible ***Yes, we can !***

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