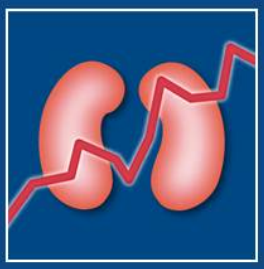
Nephro Update Europe 2019
20 – 21 September, Prague

Chronic Kidney Disease



Kai-Uwe Eckardt, Germany

Coplexity of Patients Seen by Different Specialists

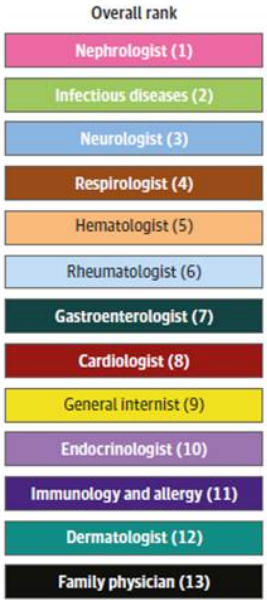
Complexity of patients ~ time consumption and costs

2,6 millionen residents of Alberta, Canada; studied over 1 year

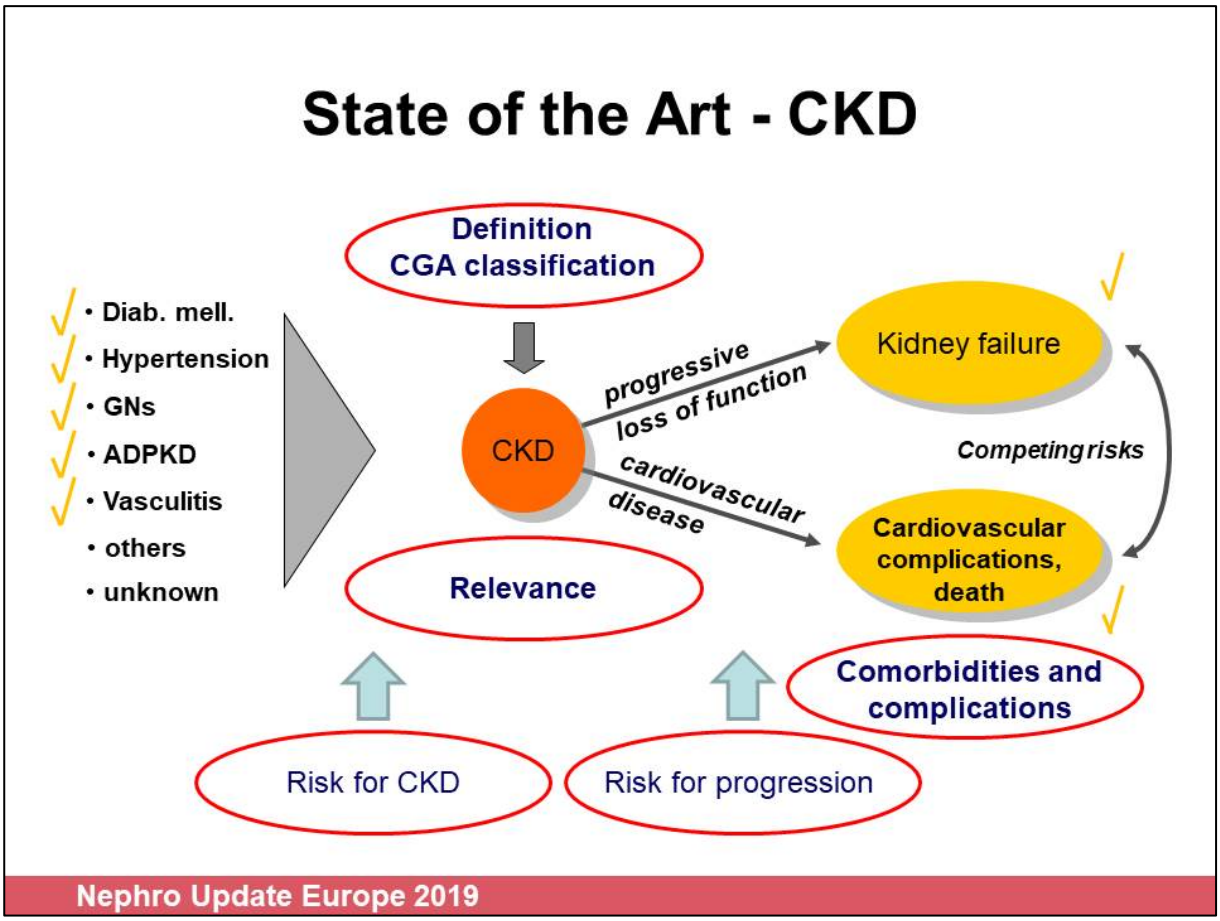
Possible parameters:

- **N: comorbidities**
- **Mental illness**
- **N: types of physicians involved**
- **N: physicians involved**
- **N: prescribed medications**
- **N: emergency department visits**
- **N: hospitalizations**
- **N: placement in longterm care faciity**
- **N: rate of death**

ranking of different disciplines according to patient complexity



Tonelli et al. JAMA Network Open 2018 (17)e184852


State of the Art - CKD
Definition
CGA classification
• Diab. mell.
• Hypertension
• GNs
• ADPKD
• Vasculitis
• others
• unknown
CKD
progressive loss of function
cardiovascular disease
Kidney failure
Competing risks
Cardiovascular complications, death
Relevance
Comorbidities and complications
Risk for CKD
Risk for progression
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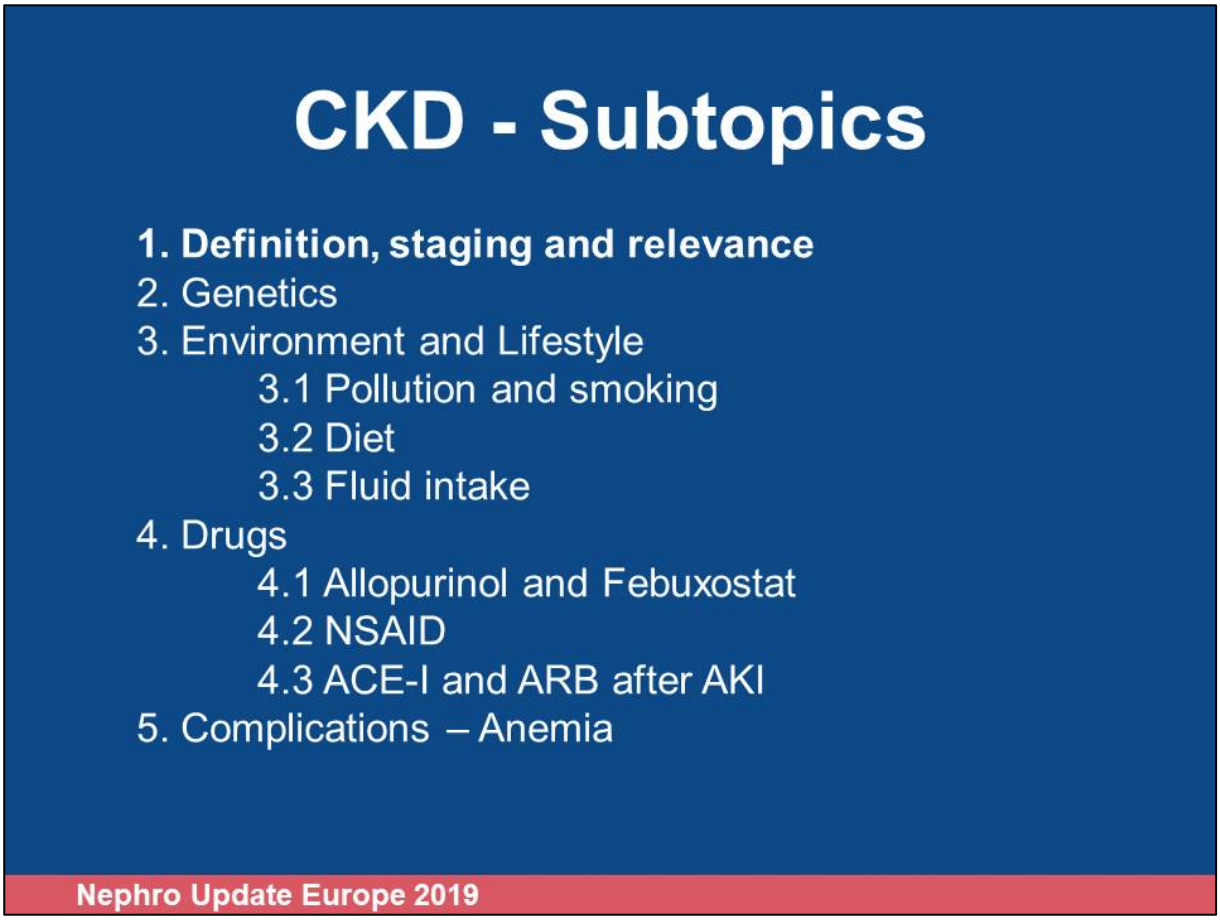
CKD - Subtopics
1. Definition, staging and relevance
2. Genetics
3. Environment and Lifestyle
3.1 Pollution and smoking
3.2 Diet
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CKD Classification

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			

KDIGO CKD Guideline, Kidney Int. Supplement; 3: 1-150, 2013

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State of the Art
Surrogates for Clinical Endpoints

- Necessary for testing and approval of novel medications, when it takes too long to reach clinical endpoints
- Can also be used to predict prognosis

	Before 2012	Since then
GFR	- Doubling of S-crea	- 30% and 40% decline - GFR slope
		- Decline in albuminuria

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

Levey et al., Am J Kidney Dis. 2019 Aug 23. pii: S0272-6386(19)30883-2

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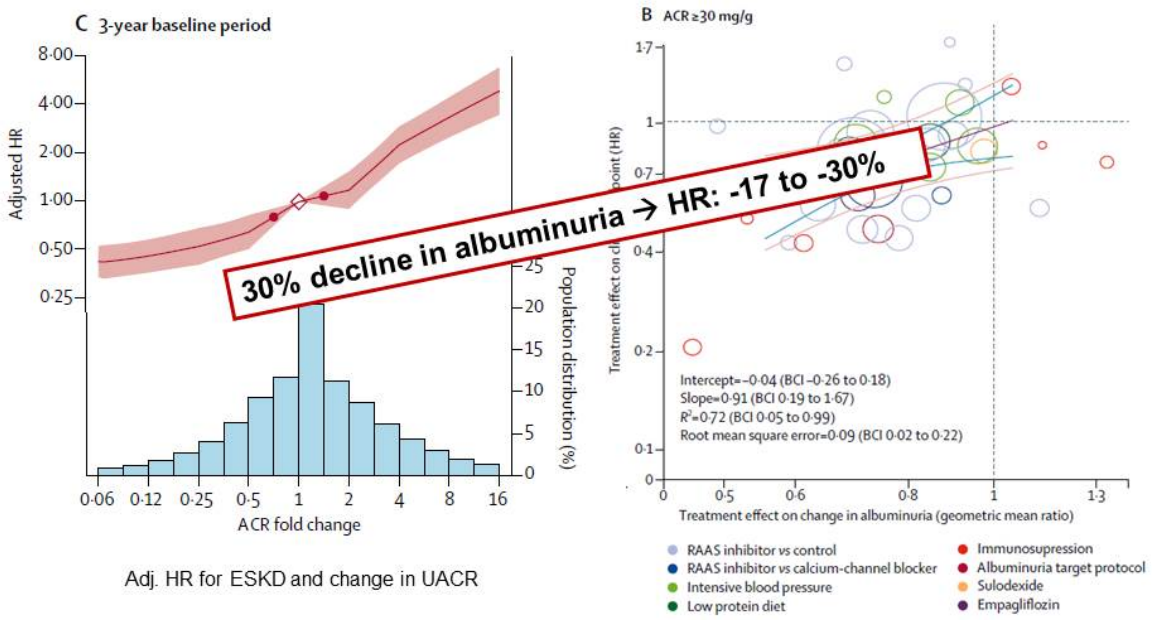
Change in Albuminuria Predict Clinical Endpoints



Heerspink et al. The Lancet. Diabetes & Endocrinology; 7(2): 128-139, 2019

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State of the Art – Genetics and CKD

- Emerging evidence for an important genetic component of development and progression of CKD.
- Focus so far on monogenic diseases in children with CKD.
- Almost 500 monogenic causes of CKD have been identified.
- > 20% of all adult dialysis patients have a positive family history for CKD.
- Monogenic causes only recognized in < 10%.
- In ~ 50% of adult patients with CKD the cause / etiology remains unknown.
- Are monogenic diseases in adults underrecognized ?

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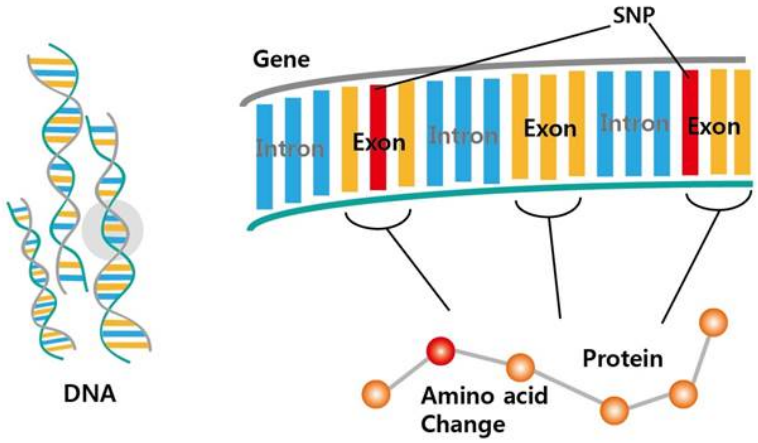
State of the Art – Whole Exome Sequencing (WES)

180.000 exons = 30 million base pairs, 1% of the genome



https://ngxbio.com/blog/post/Whole-Exome-Sequencing/

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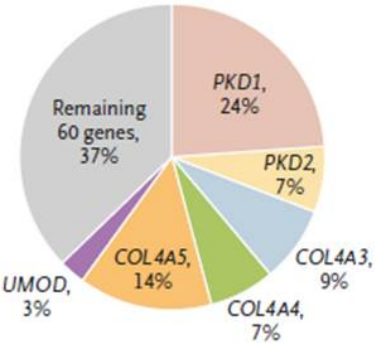
Diagnostic Value of Exome Seqencing in CKD

N=3315: AURORA study (N=2773), Columbia study cohort (N=2187)
35,6% „Non-European“

Table 2. Diagnostic Yield and Heterogeneity of Genetic Diagnoses across Clinical Diagnostic Categories.

Clinical Diagnosis	Sequencing Performed	Diagnostic Variants Present	Diagnostic Yield	Distinct Monogenic Disorders Detected	Singleton Genetic Diagnoses
	number of patients		*percent*	*number*	
Congenital or cystic renal disease	531	127	23.9	27	20
Glomerulopathy	1411	101	7.2	23	14
Diabetic nephropathy	370	6	1.6	3	2
Hypertensive nephropathy	319	8	2.5	6	4
Tubulointerstitial disease	244	11	4.5	10	9
Other	159	6	3.8	4	2
Nephropathy of unknown origin	281	48	17.1	28	17
Total	3315	307	9.3	66*	39*



- Diagnostic variants: in 307 patients(9,3%); 48/281 (17,1%) with „CKDu“
- 66 monogenic disorders, 6/66 accounting for 63% of diagnosis
- Reclassification in several patients

Groopman,…, Garavi NEJM; 380(2): 142-151, 2019

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State of the Art – Sex and CKD

- The prevalence of CKD in the general population is higher in women than in men.
- Among patients on dialysis the proportion of men is higher than that of women.
- Is the course of CKD different between males and females ?

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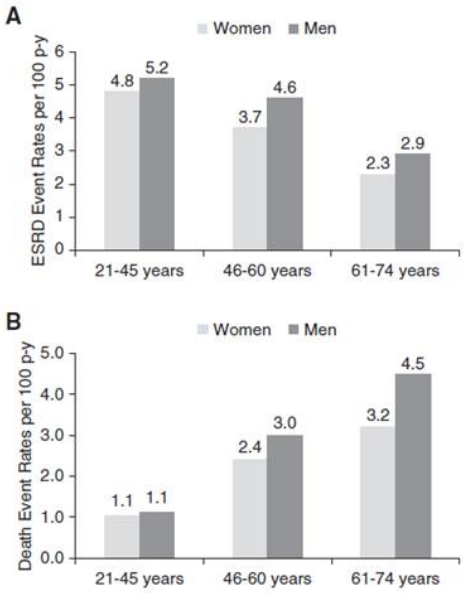
Women with CKD have lower risk for kidney failure

CRIC - Study (USA)
N=3939, mean age 58 yrs., 42% black, 13% Hispanics; mean FU 6,9 yrs.

Methods:
association between sex and
- ESKD (dialysis or Tx)
- 50% eGFR reduction
- eGFR < 15 ml/min/1,73 m^2
- death

Results:
following extensive adjustment females had a significantly lower risk for ESKD, 50% reduction in eGFR, CKD stage 5 and death



Ricardo et al. JASN; 30(1): 137-146, 2019

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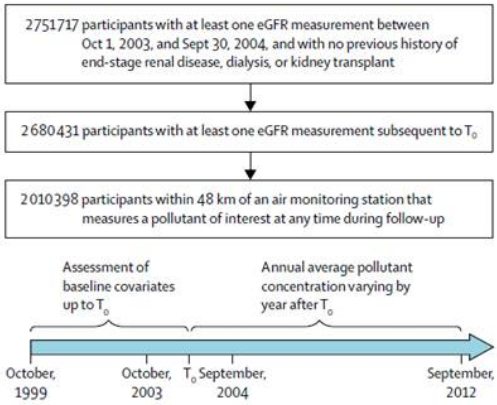
Air Pollution Enhances CKD Risk

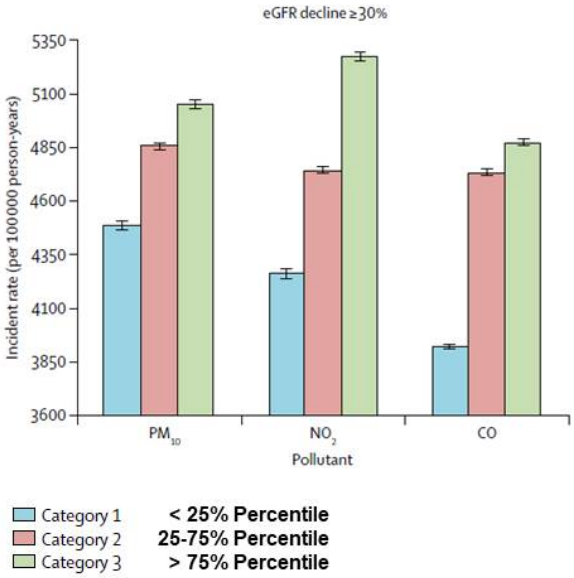
US Veterans

Exposure: PM_{10}, NO_2, CO

Renal endpoints:

incident CKD, incident eGFR < 60, eGFR ↓ ≥ 30%, ESKD; mean FU 8,5 yrs.





Bowe et al. The Lancet. Planetary Health; 1(7): e267-e276, 2017

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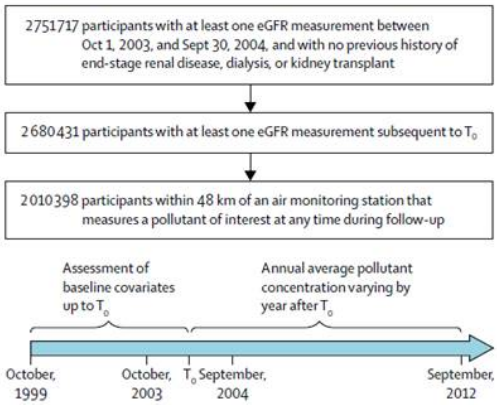

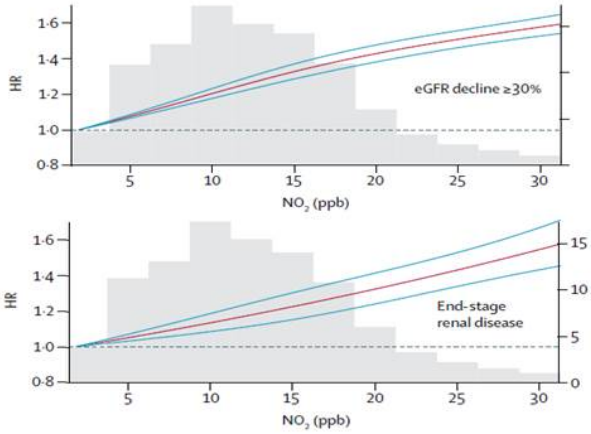

Renal risk and frequency of NO_2 concentrations

Bowe et al. The Lancet. Planetary Health; 1(7): e267-e276, 2017

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Passive Smoking Enhances CKD Risk

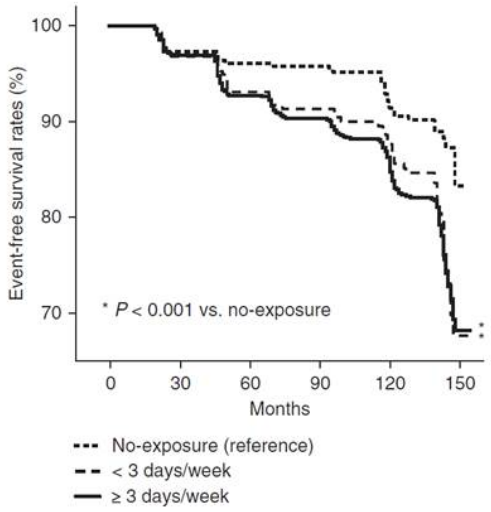
Cohort of non-smokers (Korea)

N=131.196
Cross-sectional study:
relationship between passive exposure to cigarette smoke and CKD

N=1948
Prospective observational study:
Mean. FU: 104 months

newly developed CKD:
319/1948 (16%)

Conclusion:
Passive smoking enhances CKD risk



Jhee et al. CJASN; 14(4): 515-522, 2019

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State of the Art – Oxalate and CKD

- Oxalate - "nephrotoxic" recognized as nephrotoxic agent in the conetxt of primary hyperoxaluria and disorders of intestinal reabsorption.
- Mechanism of damage: oxalate-containing kidney stones, tubulointerstitial kidney disease and inflammation.
- Oxalate is a component of many nutrients (citrus fruits, nuts, spinach,…) and is reabsorbed in variable amounts (depending on intestinal calcium).

- Can oxalate contribute to the progression of kidney disease in individuals without metabolic or intestinal disease ?

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Oxalate in urine is associated with CKD progression

CRIC - Study (USA)
N=3132, mean age 59 yrs., 46% white, 45% female; mean. FU ~ 7 yrs.

Methods:
association between Oxalate in 24h urine and
- ESKD (dialysis oder Tx)
- ESKD or 50% eGFR reduction

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* Value for Difference
Oxalate excretion, mg/24 h	1.4-11.4	11.5-16.1	16.2-21.0	21.1-27.7	27.8-102.1	NA
No. of participants	625	625	624	626	623	NA
CKD Progression						
No. of events	133	156	223	199	229	NA
Event rate per 1000 patient-years	3.80	4.56	6.89	6.21	7.16	NA
Hazard ratio (95% CI)						
Multivariable model 1[a]	1 [Reference]	1.21 (0.96-1.54)	1.86 (1.49-2.32)	1.89 (1.50-2.38)	2.32 (1.83-2.93)	<.001
Multivariable model 2[b]	1 [Reference]	1.06 (0.84-1.35)	1.66 (1.32-2.08)	1.55 (1.23-1.96)	1.83 (1.44-2.33)	<.001
Multivariable model 3[c]	1 [Reference]	0.94 (0.74-1.20)	1.35 (1.07-1.69)	1.14 (0.90-1.45)	1.33 (1.04-1.70)	.003
ESRD						
No. of events	99	128	171	168	186	NA
Event rate per 1000 patient-years	2.38	3.18	4.44	4.37	4.90	NA
Hazard ratio (95% CI)						
Multivariable model 1[a]	1 [Reference]	1.46 (1.11-1.91)	2.01 (1.56-2.60)	2.29 (1.75-2.98)	2.78 (2.12-3.65)	<.001
Multivariable model 2[b]	1 [Reference]	1.29 (0.98-1.69)	1.85 (1.42-2.40)	1.93 (1.48-2.52)	2.19 (1.66-2.88)	<.001
Multivariable model 3[c]	1 [Reference]	1.05 (0.79-1.39)	1.45 (1.11-1.89)	1.36 (1.04-1.78)	1.45 (1.09-1.93)	.008

Waikar et al. JAMA Internal Medicine; 179(4): 542-551, 2019

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Take-Home Message

- Oxalate is associated with progression of CKD
  → reduced oxalate reabsorption could potentially reduce the progression of CKD

- Possible strategies:
  - reduction of dietary intake
  - increased calcium intake
    oxalate-excretion is inversely correlated with calcium-excretion; CAVE: potential negative impact of increased calcium uptake
  - non-calcium containing oxalate binders
  - ….. additional strategies currently being tested in hyperoxaluria

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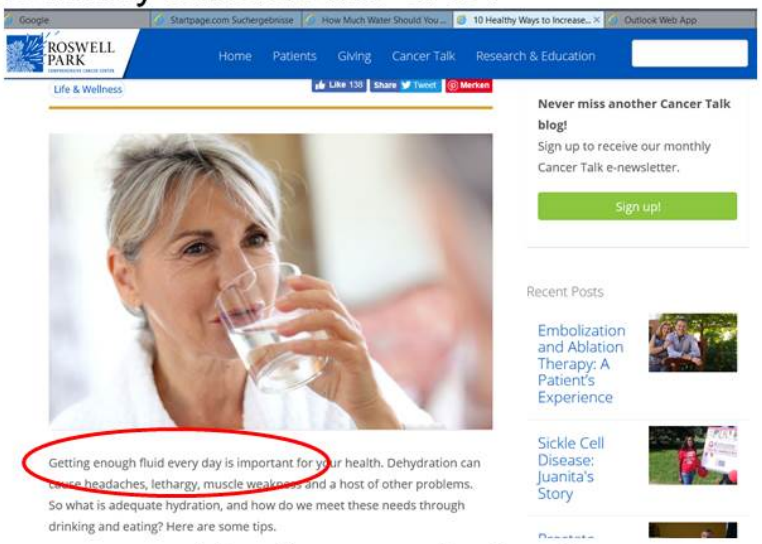
State of the Art – Fluid Intake and CKD

- The question most frequently raised in public discussions about kidney function and CKD.
- Little evidence (embarrassing)



https://www.roswellpark.org/

Water Intake and Loss of Renal Function

Chronic Kidney Disease Water Intake Trial (CKD WIT)

N=631 pat., CKD G3 + A2 or A3 (mean age 65 yrs., 63% male, mean GFR 43 ml/min/1,73 m^2)

Intervention:
„Coached" to drink more fluid vs. maintaining fluid intake constant

Endpoint:
delta eGFR after 12 months

Table 2. Change in 24-Hour Urine Volume and Self-reported Fluid Intake[a]

	Mean (SD)			
	Hydration Group (n = 291)	Control Group (n = 299)	Mean Difference (95% CI)[b]	P Value[b]
Urine volume, L/d				
Prerandomization	1.9 (0.6)	1.9 (0.6)		
6 Month	2.5 (0.9)	1.9 (0.6)		
12 Month	2.5 (0.8)	1.9 (0.7)		
12-Month change (95% CI)	0.6 (0.5 to 0.7)[c]	−0.04 (0.0 to 0.1)[c]	0.6 (0.5 to 0.7)	<.001
Self-reported fluid intake, L/d				
Prerandomization	2.1 (0.8)	2.0 (0.7)		
3 Month	2.8 (0.9)	2.0 (0.6)		
6 Month	2.8 (0.8)	2.1 (0.7)		
9 Month	2.8 (0.8)	2.0 (0.6)		
9-Month change (95% CI)	0.7 (0.6 to 0.8)[c]	0.0 (−0.1 to 0.1)[c]	0.7 (0.6 to 0.8)	<.001

Table 3. Primary Outcome: 1-Year Change in Estimated Glomerular Filtration Rate[a]

	Mean (95% CI)	
eGFR, mL/min per 1.73 m^2	Hydration Group (n = 311)	Control Group (n = 308)
Prerandomization	43.3 (42.1 to 44.4)	43.6 (42.6 to 44.7)
12 Months	41.0 (39.5 to 42.6)	41.7 (40.3 to 43.1)
Change	−2.2 (−3.3 to −1.1)[c]	−1.9 (−2.9 to −0.9)[c]

Clark et al. JAMA; 319(18): 1870-1879, 2018

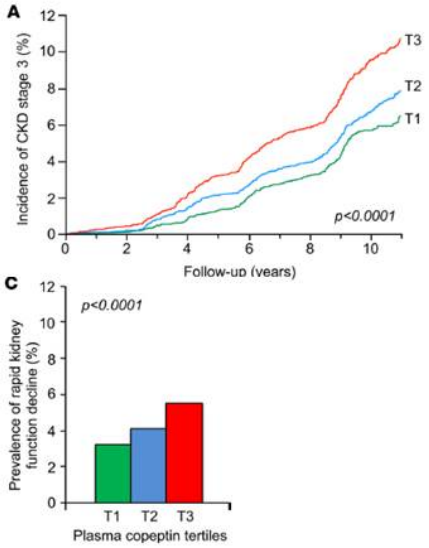
Plasma Copeptin is Associated with CKD Risk

Copeptin: C-term. part of pre-pro-vasopressin, secreted equimolar with vasopressin, more stable, easier to measure

3 Cohorts (general population):
DESIR, MDCS, PREVEND; N=17.000
Copeptin @ BL
FU 8,5; 16,5; 11.3 yrs.

Renal endpoints:
- incidence of CKD G3
- incidence of CKD A2
- eGFR decline > 3 ml/yr
- combinded endpoints

→ **Potential adverse effects mediated by V1 and V2 receptors**



El Boustany et al. JAC Insight; 3(13): 121479, 2018

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State of the Art – Urate (lowering) and CKD

- Hyperuricemia is associated with CKD development.
- Incidence of hyperuricemia and gout are increased in the presence of CKD.
- Preclinical evidence for kidney damage induced by uric acid.
- Therapeutic lowering of uric acid in patients with asymptomatic hyperurecemia?
- Febuxostat = non-purinergic xanthinoxidase-inhibitor (no metabolite-accumulation in the presence of red. GFR as with allopurinol)

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Allopurionol Treatment for Gout is Associated with Reduced Risk for CKD

Prospective cohort study:
Adults *with* newly diagnosed gout *without* CKD ≥ G3
UK general population

Propensity Matching:
4760 pat. with vs. 4760 pat. without initiation of allopurinol > 300 mg/d

Endpoint:
new CKD ≥ G3

Conclusion:
allopurionol-prescription is associated with reduced risk for CKD

Table 2. Risk of Developing Chronic Kidney Disease (Stage ≥3) Among Patients With Incident Gout and Incident Allopurinol Use (at Least 300 mg/d)

Main Results	Incident Allopurinol User	Non-Allopurinol User
Total, No.	4760	4760
Incident CKD stage ≥3, No. (%)	579 (12.2)	623 (13.1)
Death, No. (%)	254 (5.3)	240 (5.0)
Mean follow-up time, y	4.9	4.5
Crude incidence rate (CKD stage ≥3) per 1000 person-years	24.9	29.4
Propensity score-matched hazard ratio (95% CI)	0.87 (0.77-0.97)	
Adjusted hazard ratio (95% CI)[a]	0.88 (0.79-0.99)	

Vargas-Santos et al. JAMA Internal Medicine; 178(11): 1526-1533, 2018

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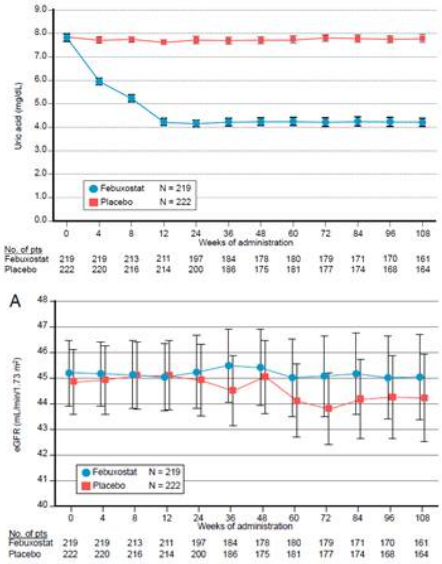
Febuxostat in CKD Patients with Asymptomatic Hyperuricemia

Prospective RCT
(FEATHER Trial):
467 pat. CKD ≥ G3 and asymptomatic hyperuricemia in Japan

Intervention:
Febuxostat 10-40 mg
vs. „standard of care“

→ No improvement of a non-existing progression (but reduction in arthritis episodes)



Kimura et al. AJKD; 72 (6): 798-810, 2018

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Febuxostat: Cardiovascular and Renal Events

Prospective RCT (FREED Study):
1070 elderly patients with hyperuricemia (> 7,0 - ≤ 9,0 mg/dl) and ↑ CVD risk

Combined primary endpoint:
cerebral, cardiovascular, renal events and all deaths

	Febuxostat group (*n* = 537)	Non-febuxostat group (*n* = 533)	Hazard ratio (95% confidence interval)	*P*-value
Primary endpoint				
Composite of death due to any cause, cerebrovascular disease, non-fatal coronary artery disease, heart failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal impairment, and atrial fibrillation	125 (23.3)	153 (28.7)	0.750 (0.592–0.950)	0.017
Secondary endpoints				
Death due to cerebral, cardiovascular, or renal disease	6 (1.1)	6 (1.1)	0.958 (0.314–2.926)	0.940
Cerebrovascular disease	9 (1.7)	7 (1.3)	1.271 (0.479–3.371)	0.630
Non-fatal coronary artery disease	4 (0.7)	7 (1.3)	0.559 (0.167–1.869)	0.345
Heart failure requiring hospitalization	9 (1.7)	12 (2.3)	0.699 (0.290–1.689)	0.427
Arteriosclerotic disease requiring treatment	2 (0.4)	3 (0.6)	0.644 (0.107–3.873)	0.631
Renal impairment	87 (16.2)	109 (20.5)	0.745 (0.562–0.987)	0.041
Atrial fibrillation	4 (0.7)	3 (0.6)	1.320 (0.292–5.968)	0.719
Death due to other causes	4 (0.7)	6 (1.1)	0.635 (0.179–2.253)	0.482
Hard endpoint: composite of death due to any cause, cerebrovascular disease, or non-fatal coronary artery disease	23 (4.3)	26 (4.9)	0.861 (0.492–1.506)	0.600

Kojima et al. *Eur Heart J; 40(22):1778-1786, 2019*

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Febuxostat is Associated with Increased Mortality

Prospective RCT (CARES Trial)
6190 patients with gout and CVD

Intervention
Febuxostat vs. Allopurinol

"Non-inferiority" comb. prim. endpoint:
cardiovascular death, non-fatal MI, stroke, unstable angina

Table 2. Major Safety End Points (Modified Intention-to-Treat Analysis).*

End Point	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina	335 (10.8)	321 (10.4)	1.03 (0.87–1.23)‡	0.66 (0.002)
Secondary end points				
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03–1.73)	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72–1.21)	0.61
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73–1.41)	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59–1.26)	0.44
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92–1.28)	0.33
Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01–1.47)	0.04

→ Febuxostat "non-inferior", but associated with increased cardiovascular and total mortality

White et al. New Engl J Med; 378(13): 1200-1210, 2018

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Take-Home Message

?

3.1.20: There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. (*Not Graded*)

KDIGO 2012 CKD Guideline

- Increasing evidence for the treatment of symptomatic gout
- No evidence for the treatment of asymptomatic hyperuricemia
- Allopurinol safer than febuxostat

KDIGO CKD Guideline, Kidney Int. Supplement; 3: 1-150, 2013

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CKD - Subtopics

1. Definition, staging and relevance
2. Genetics
3. **Environment and Lifestyle**
   - 3.1 Pollution and smoking
   - 3.2 Diet
   - 3.3 Fluid intake
4. **Drugs**
   - 4.1 Allopurinol and Febuxostat
   - **4.2 NSAID**
   - 4.3 ACE-I and ARB after AKI
5. Complications – Anemia

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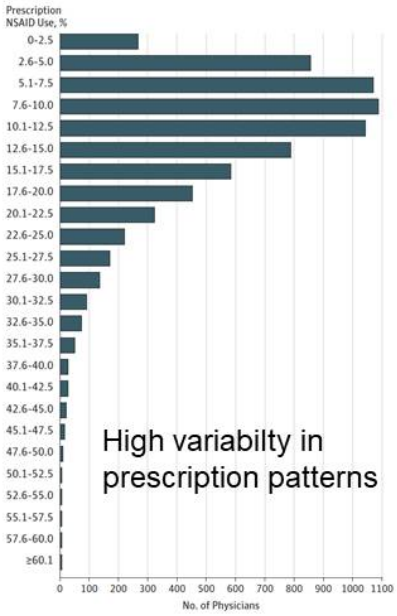
NSAID without Short-term Risks

Retrospective Study (Canada)
N=814.049 consultations for musculoskeletal diagnosis in patients with hypertension, CHF or CKD and ≥ 65 yrs.; FU 8-37 d

Methods:
- association between NSAID prescription, cardiac and renal complications and death
- "matched pairs"

Results:
- 2.415.291 physician visits with 224.825 NSAID prescriptions (9,3%)
- no difference in outcomes



Bouck et al. JAMA Internal Medicine; 178(11): 1516-1525, 2018

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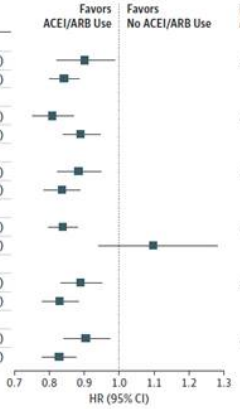
ACE-I and ARB after AKI are Associated with Improved Mortality

Retrospective Study (Canada)
N=46.253, AKI in hospital 2008-2015; FU at least 2 yrs.

Methods:
association between ACE-I/ARB within 6 month after AKI and
- mortality
- hosp. for renal indication, ESKD or S-Krea x 2
- „Matched pairs“

Condition	No. of Event/ No. of Patients	HR (95% CI)	Interaction, P Value
Proteinuria			
Yes	1945/4071	0.90 (0.82-0.99)	.19
No	6549/14841	0.84 (0.80-0.89)	
Baseline eGFR, mL/min/1.73m²			
≥60	3396/9789	0.81 (0.75-0.87)	.03
<60	5098/9123	0.89 (0.84-0.94)	
Diabetes			
Yes	3834/7932	0.88 (0.83-0.94)	.20
No	4660/10980	0.83 (0.79-0.89)	
Hypertension			
Yes	7823/16544	0.84 (0.80-0.88)	.001
No	671/2368	1.10 (0.94-1.28)	
Chronic heart failure			
Yes	3976/6296	0.89 (0.83-0.95)	.10
No	4518/12616	0.83 (0.78-0.88)	
Myocardial infarction or stroke			
Yes	3363/6025	0.90 (0.84-0.97)	.50
No	5131/12887	0.83 (0.78-0.88)	



Results:
- ACE-I / ARB in 39% never, in 13 / 58% not continued; in 7% newly prescribed
- HR for mortality 0.85 (95%CI 0.81-0.89);
- HR for hosp. for renal indication 1.28 (95%CI 1.12-1.46)

Brar et al. JAMA Internal Medicine; 178(12): 1681-1690, 2018

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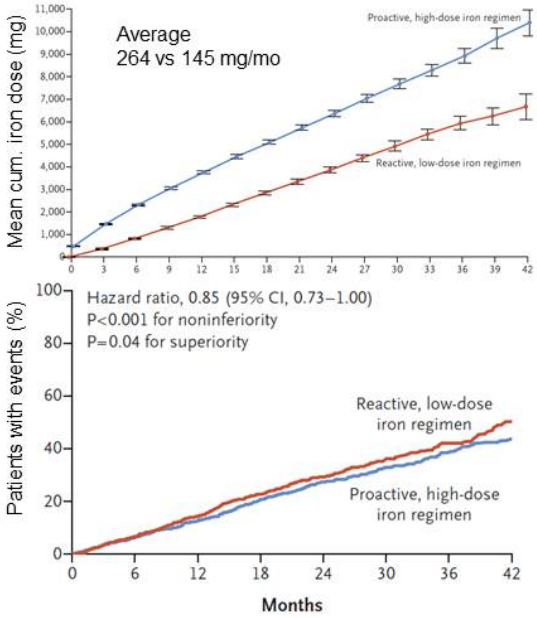
High Dose IV Iron is Associated with Improved Prognosis

PIVOTAL - RCT (UK):
N=2141 patients on HD

Methodology:
"Proactive" iron therapy (iron-sucrose):
400 mg /mo, if ferr ≤ 700, TSAT < 40%
vs.
"Restrictive" iron therapy
0-400 mg /mo, if ferr < 200, TSAT < 20%

Primary endpoint:
MACE (non-fatal MI or stroke, hospitalization for heart failure, death)

Result:
"Proactive" therapy was superior



Macdougall et al. New Engl J Med; 380(5): 447-58, 2019

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List of Abbreviations

ADPKD	autosomal-dominant polycystic kidney disease
AKI	acute kidney injury
CGA	Cause, GFR category and albuminuria category
CHF	congestive heart failure
CKD	chronic kidney disease
CKDu	chronic kidney disease of unknown etiology
Diab. mell.	Diabetes mellitus
eGFR	estimated glomerular filtration rate
ESKD	end stage kidney disease
FU	Follow Up
GCKD study	„German Chronic Kidney Disease" study
GFR	glomerular filtration rate
GN	glomerulonephritis
HR	hazard ratio
KDIGO	Kidney Disease: Improving Global Outcomes
MI	myocardial infarction
NSAID	non-steroidal anti-inflammatory drug
RAAS	Renin-Angiotensin-Aldosteron-System
RCT	randomized controlled trial
Tx	kidney tranplantation
UACR	urine albumin-to-creatinine ratio
WES	whole genome sequencing
WIT	water intake trial