Round table:
Special problems in CKD

Stroke and cognitive dysfunction in CKD patients

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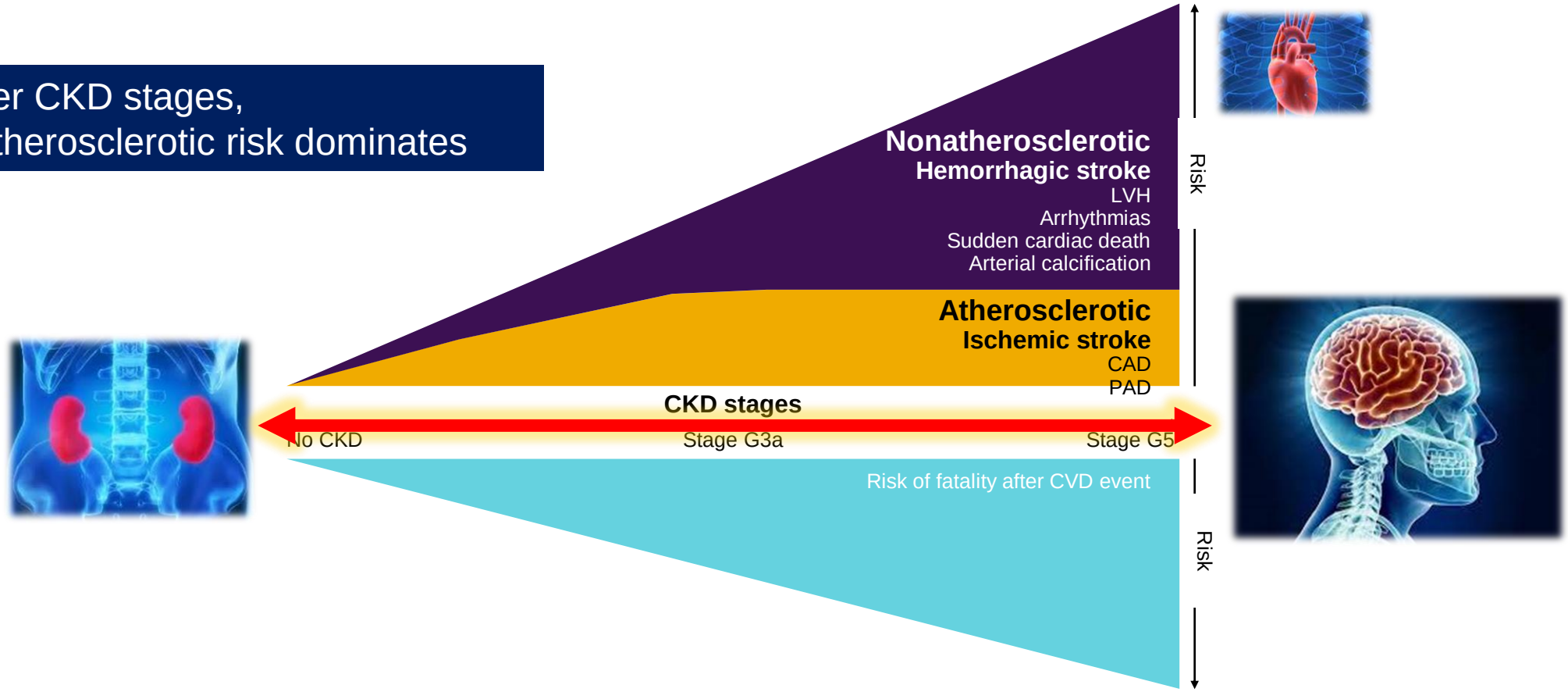
Disclosure of Interest

Honorarium and/or AB from AstraZeneca, Bayer, Chiesi, Faran, Genesis, Sanofi

Risk of cardiovascular morbidity and mortality increases with progression of CKD

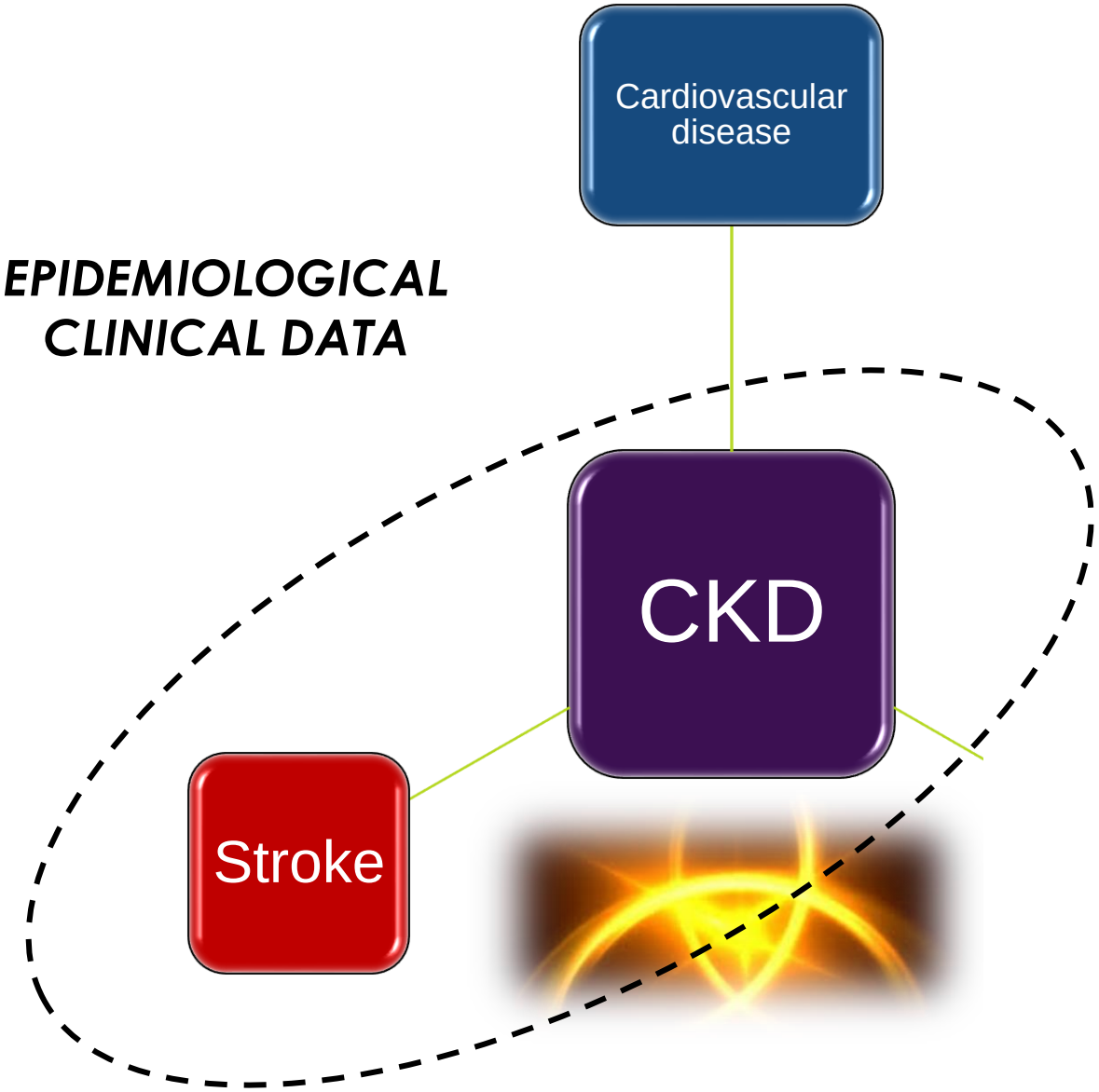
- In later CKD stages, nonatherosclerotic risk dominates



CAD = coronary artery disease; CV = cardiovascular; CVD = cardiovascular disease; LVH = left ventricular hypertrophy; PAD = peripheral artery disease.

Sarnak MJ et al. J Am Coll Cardiol. 2019;74:1823–1838.

EPIDEMIOLOGICAL CLINICAL DATA



RESEARCH ARTICLE

Representation and reporting of kidney disease in cerebrovascular disease: A systematic review of randomized controlled trials

Ioannis Konstantinidis[1☯]*, Shanti Patel[2], Marianne Camargo[2], Achint Patel[2], Priti Poojary[3], Steven G. Coca[2☯], Girish N. Nadkarni[2☯]

PLOS ONE | https://doi.org/10.1371/journal.pone.0176145 April 20, 2017

- 36,5% of Cerebrovascular disease trials have excluded CKD patients

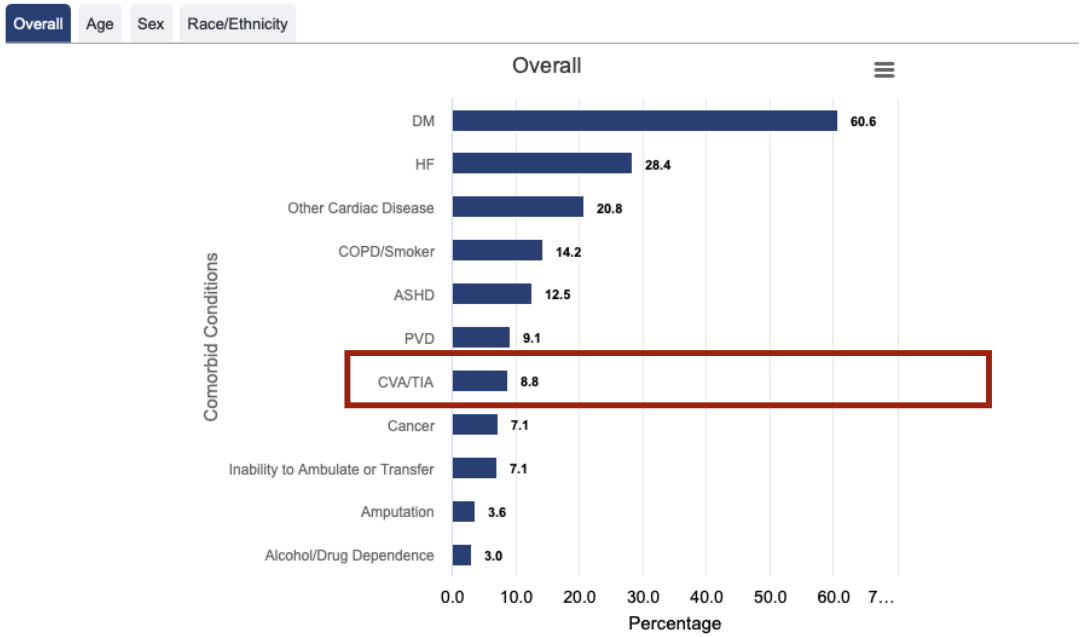
Strong associations between CKD and incidence of stroke

Stroke is the third cause of cardiovascular death in CKD pts

- **Stroke incidence in CKD:**
  - **nonD - CKD**: 13.4/1000 person- years
  - **Dialysis**: 25.3/1000 person-years (HD>PD)
  - **KTRs**: 6.0/1000 patient-years

  Vs General population: 1.04/1000 person-years

USRDS – annual report 2022



Data Source: USRDS ESRD Database. U.S. and U.S. territory ESRD patients with a Medical Evidence Report (form CMS 2728) in 2019; Abbreviations: DM, diabetes mellitus; HF, heart failure; COPD, chronic obstructive pulmonary disease; ASHD, atherosclerotic heart disease; PVD, peripheral vascular disease; CVA/TIA, cerebrovascular accident/transient ischemic attack.

- Incident ESRD patients: **Overall, 8.8% had CVA/TIA**, 28.4% HF, 20.8% other cardiac disease, 60.6% DM

Bansal et al. JAMA Cardiol 2017, Findlay et al. Kidney Int Rep 2018
Findlay et al. Clin Transplat 2018, Lee et al, BMJ 2010

Meta-analyses investigating stroke risk in CKD pts

BMJ 2010;341:c4249
doi:10.1136/bmj.c4249

RESEARCH

Low glomerular filtration rate and risk of stroke: meta-analysis

Meng Lee, visiting scholar and instructor,[1,3] Jeffrey L Saver, director and professor,[1] Kuo-Hsuan Chang, instructor,[4] Hung-Wei Liao, director,[5] Shen-Chih Chang, epidemiologist,[6] Bruce Ovbiagele, associate professor[1,2]

33 studies (1947-2009),
>280.000 people
8000 stroke events

eGFR <60 ml/min/1.73 m² was an independent risk of future stroke, **43%** greater vs normal eGFR

Association between Low Estimated Glomerular Filtration Rate and Risk of Cerebral Small-Vessel Diseases: A Meta-Analysis

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.11.016

Yuanyuan Liu, PhD,* Pu Lv, PhD,* Haiqiang Jin, PhD,* Wei Cui, PhD,* Chenguang Niu, PhD,† Mingming Zhao, PhD,† Chenghe Fan, PhD,* Yuming Teng, PhD,* Bing Pan, MD,† Qing Peng, MD,* Jingjing Luo, MD,* Lemin Zheng, PhD,† and Yining Huang, MD*

16 studies (1966-2014),
10.534 people

For every **10 mL/min/1.73m²** **decrease** in GFR the risk of having a stroke increases by **7%**
(RR: 1.07, 95% CI: 1.04–1.09)

Epidemiology, thrombolytic management and outcomes of acute stroke among patients with chronic kidney disease: a systematic review and meta-analysis

Ido Zamberg [1,2], Marie Assouline-Reinmann[3], Emmanuel Carrera[4], Manish M. Sood[5], Stephen M. Sozio[6,7], Pierre-Yves Martin [1,3,8] and Thomas A. Mavrakanas [2,9]

Nephrol Dial Transplant (2022) 37: 1289–1301 doi: 10.1093/ndt/gfab197

39 studies
(up to 3/2021),
>99.281 people

Ischaemic stroke remains the most common type of stroke among pts with nonD-CKD, and haemorrhagic stroke in dialysis ESKD pts

Proteinuria might be a better predictor of stroke risk in CKD than eGFR, possibly as an indicator of microvascular disease

Proteinuria and Stroke: A Meta-analysis of Cohort Studies

Toshiharu Ninomiya, MD, PhD,[1] Vlado Perkovic, MD, PhD,[1] Christine Verdon, MSc(A),[2] Federica Barzi, PhD,[1] Alan Cass, MD, PhD,[1] Martin Gallagher, MD, MPH,[1] Meg Jardine, MD,[1] Craig Anderson, MD, PhD,[1] John Chalmers, MD, PhD,[1] Jonathan C. Craig, MD, PhD,[2] and Rachel Huxley, DPhil[1]

American Journal of Kidney Diseases, Vol 53, No 3 (March), 2009: pp 417-425

10 studies
140.231 participants
3,266 strokes

Participants (general pop / DM) with proteinuria had a **71% greater risk of stroke** vs those without proteinuria (95%CI, 1.39- 2.10)
eGFR -NA

BMJ 2010;341:c4249 doi:10.1136/bmj.c4249

RESEARCH

Low glomerular filtration rate and risk of stroke: meta-analysis

Meng Lee, visiting scholar and instructor,[1,3] Jeffrey L Saver, director and professor,[1] Kuo-Hsuan Chang, instructor,[4] Hung-Wei Liao, director,[5] Shen-Chih Chang, epidemiologist,[6] Bruce Ovbiagele, associate professor[1,2]

33 studies (1947-2009),
>280.000 people
8000 stroke events

In pts with **eGFR <60 ml/min/1.73m²**, the presence of albuminuria **increased the risk of stroke**
(RR **1.75**, 95%CI 1.10-2.87 p<0.2 vs **2.20**, 95%CI 1.45-3.33 p<0.001)

Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis

Philip Masson[1], Angela C. Webster[1,2], Martin Hong[3], Robin Turner[1], Richard I. Lindley[3,4] and Jonathan C. Craig[1]

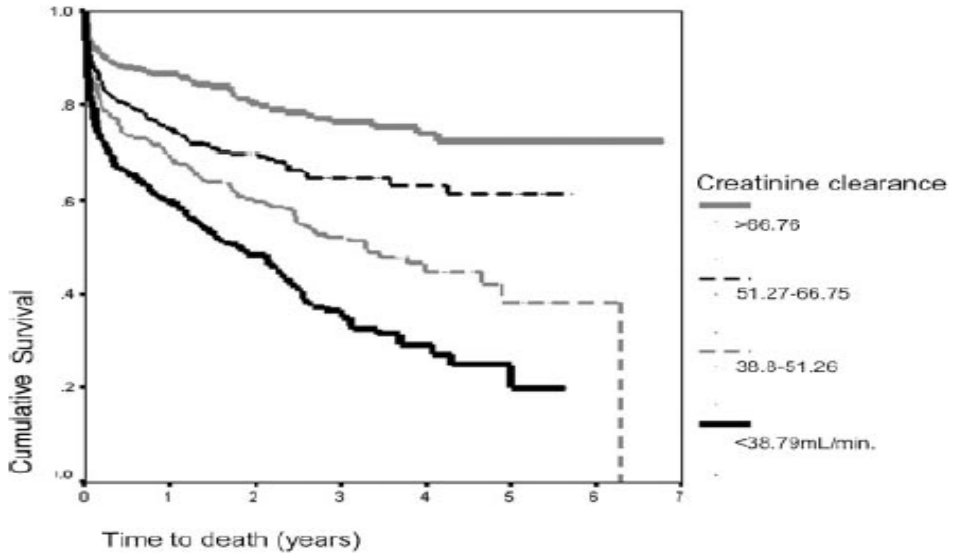
Nephrol Dial Transplant (2015) 30: 1162–1169 doi: 10.1093/ndt/gfv009

63 cohort studies
(2.085.225 participants)
and 20 RCTs
(168.516 participants)
30.392 strokes

A **25 mg/mmol increase in ACR** was associated with a **10% increased risk of stroke** (RR: 1.10, 95% CI: 1.01–1.20).
The effect of albuminuria was **independent of GFR**.

CKD is associated with worse stroke outcomes, greater likelihood of institutionalization, dialysis initiation and higher short- and long-term mortality

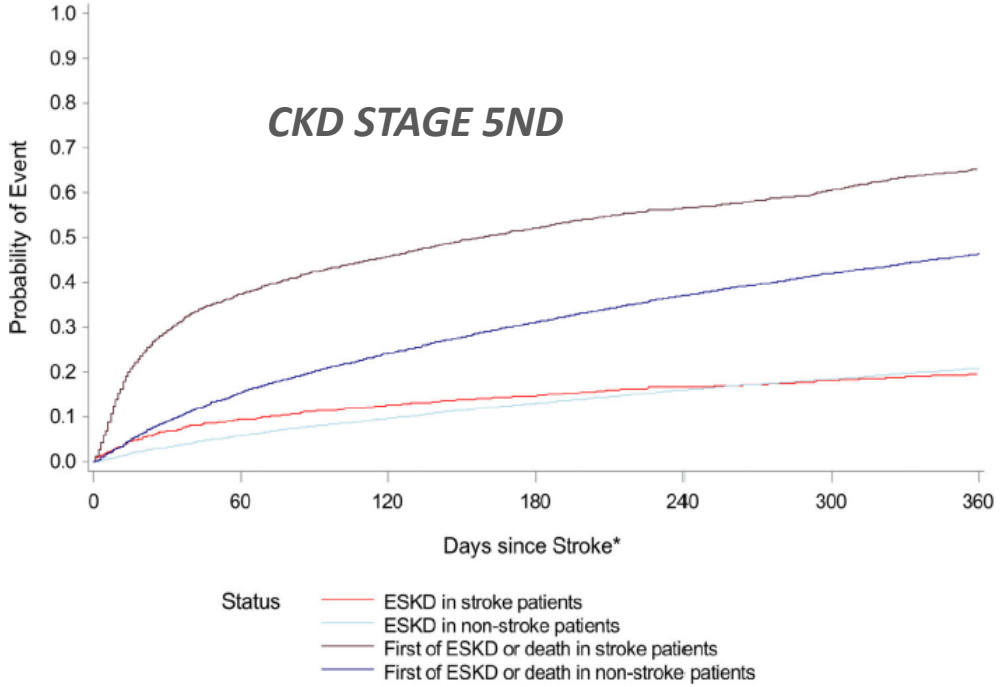
Increased adjusted relative risk for mortality of 1.5 to 2.1 in CKD patients compared to non-CKD patients with stroke



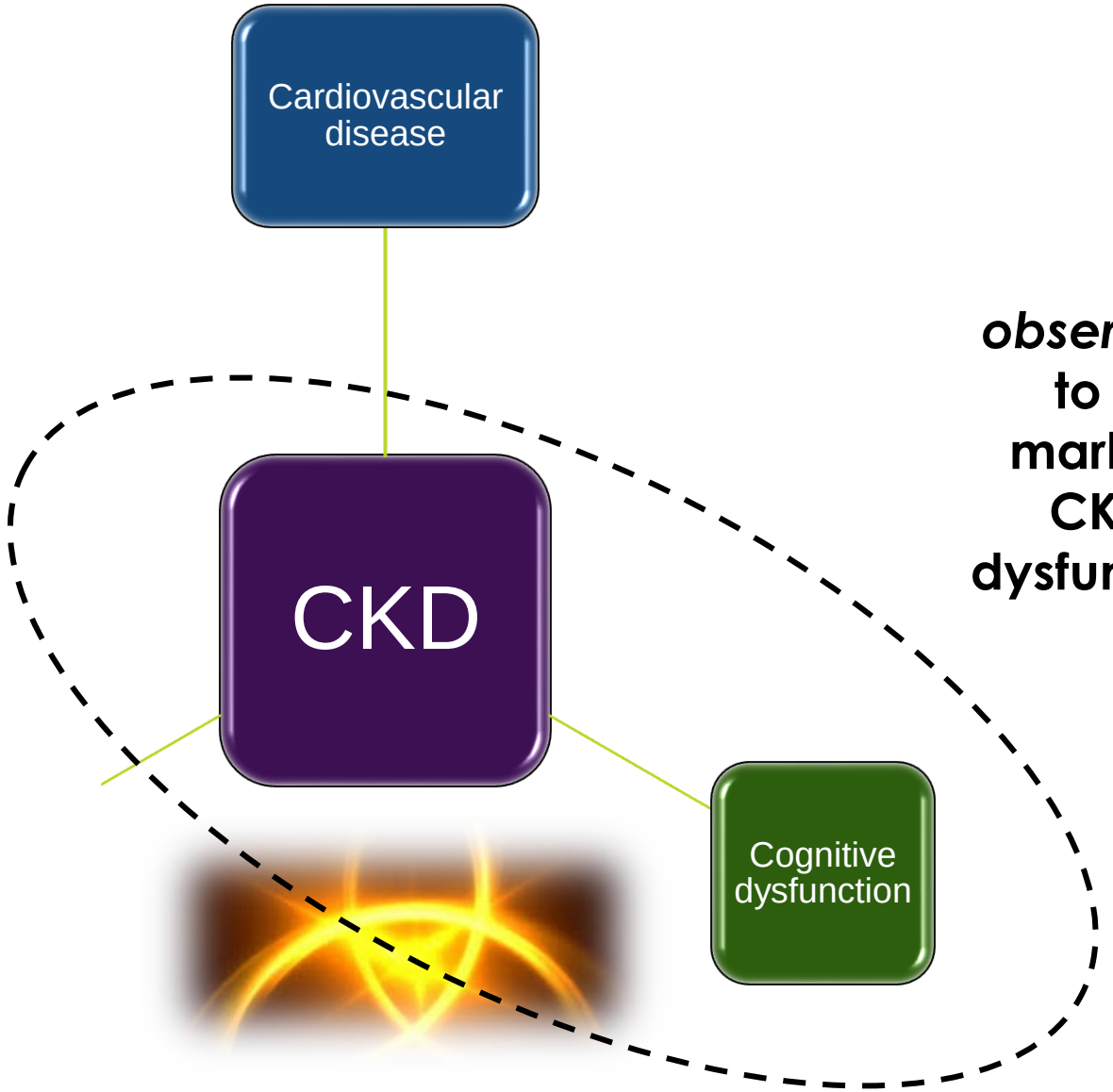
Kaplan-Meier survival analysis for calculated creatinine clearance on admission among stroke patients (log-rank test, $P<0.0001$).

MacWalter et al, Stroke 2002

Accelerated time to death or dialysis initiation in patients with advanced CKD after ischemic stroke

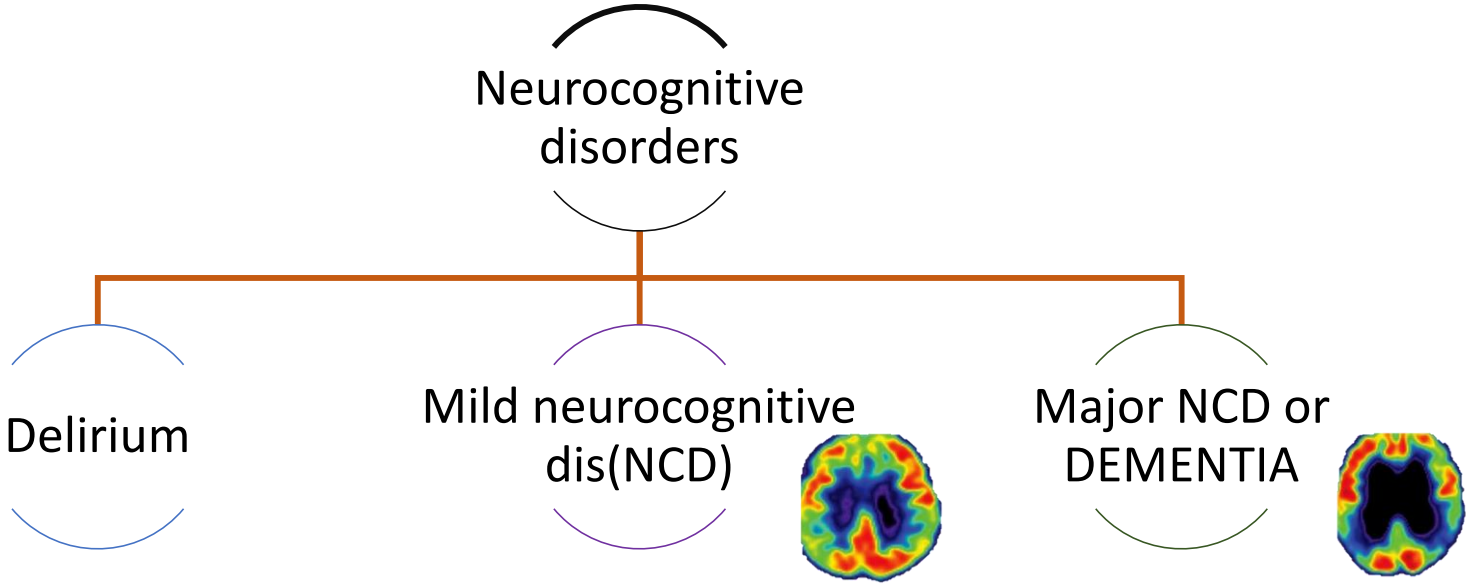


Wetmore et al, Am J Kidney Dis. 2020



Epidemiological and observational **clinical data trying to connect kidney function markers (eGFR/albuminuria) in CKD patients with cognitive dysfunction risk have been MIXED**

Neurocognitive Disorders – DSM-5



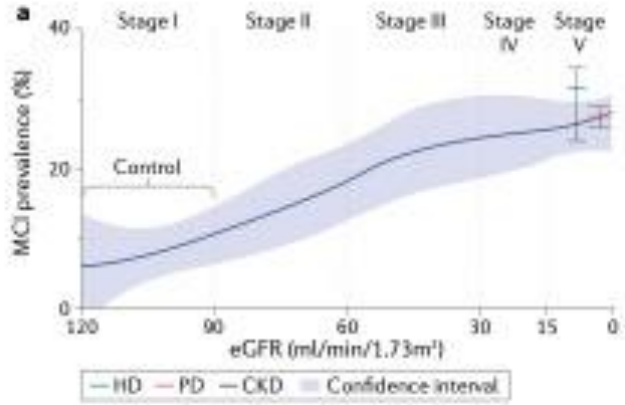
Etiological subtypes of major & mild NCD

- Alzheimer's disease
- Frontotemporal lobar degeneration
- Cortical Lewy body disease
- Vascular disease
- Traumatic brain injury
- Substance/medication use
- HIV infection
- Prion disease
- Parkinson's disease
- Huntington's disease
- Another medical condition
- Multiple etiologies
- Unspecified

Mild Cognitive Impairment (MCI)

- *memory impairment*
- *language difficulties*
- *attention deficit*
- *disorientation*
- *altered visuospatial skills*

- ***MCI is only a risk state for dementia***
- ***MCI prevalence increases with CKD stage and possibly also with the time spent at each stage***
- ***5–10% of patients with MCI will eventually progress to clinical dementia***



Perminder S. Sachdev et al. *Harv Rev Psychiatry*. 2015, Viggiano et al, Nat Rev Nephrol. 2020, Viggiano et al, Nephrol Dial Transplant 2020

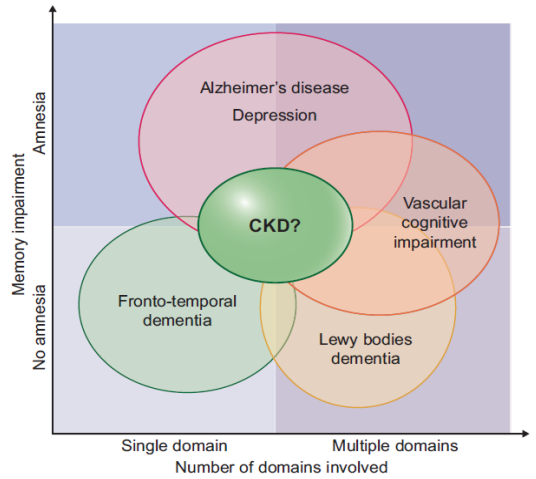
Epidemiology of dementia in ***ESKD*** patients and KTRs

Dementia incidence in ESKD:
- 10.7 cases/1,000 patient-years vs 1.4 cases/1,000 patient-years in non-CKD

Dementia prevalence:
- **HD**: 8-37%
- **PD**: 4–33%
- **KTRs**: 7-22%

High variation in prevalence

Risk increases linearly with age



vs 5% in general population

Dementia 10years risk:
- HD: 20% (at 65 years)
- KTRs: 5% (at 55 years)

?? In the early CKD stages a direct link and the time point of cognitive dysfunction initiation is not clear cut ??

Viggiano et al, Nat Rev Nephrol. 2020, Pepin M et al. CONNECT project, NDT 2021

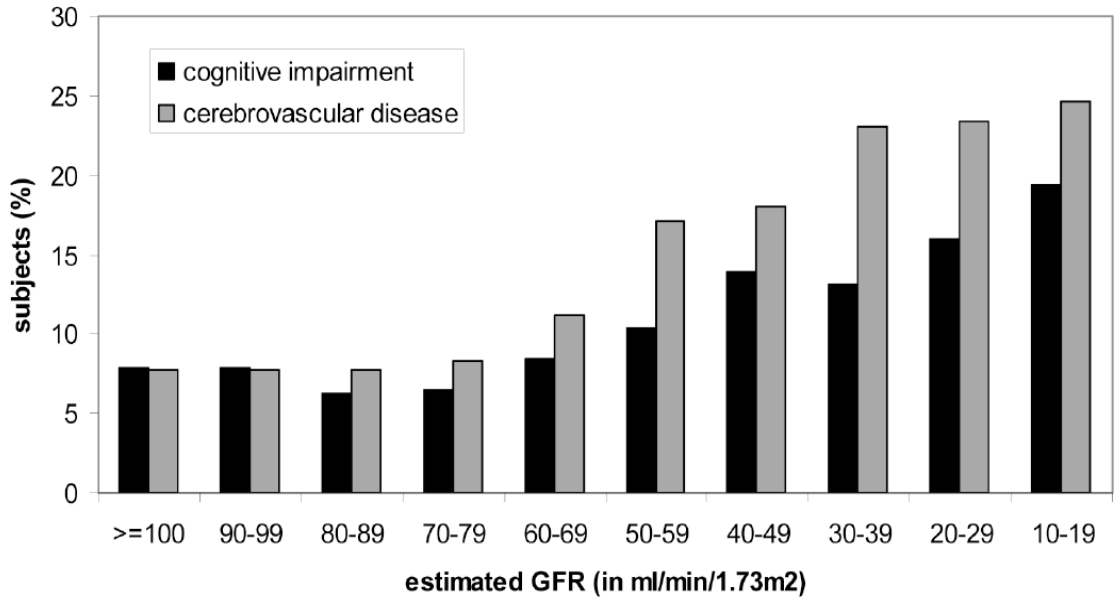
REGARDS Study
(REasons for Geographic And Racial Differences in Stroke)

23,405 participants, 6 item cognitive screening examination

Kidney function	Adjusted odds ratio (and 95% confidence interval) [1]
CKD vs. no CKD	1.23 (1.06, 1.43)
per 10 ml/min/1.73m^2 decrease in GFR *(reference = GFR ≥60 ml/min/1.73m^2)*	1.11 (1.04, 1.19)

[1] Model adjusted for age, sex, race, education, region, prevalent stroke/TIA, coronary heart disease diabetes, hypertension, elevated cholesterol, smoking, obesity, left ventricular hypertrophy, and atrial fibrillation.

CKD (eGFR<60 ml/min/1.73m^2) was associated with an increased prevalence of cognitive impairment, independent of confounding factors



In CKD patients, **each 10ml/min/1.73m^2 decrease in eGFR (**<60 ml/min/1.73m^2) was associated with an **11% increased prevalence of impairment** (OR 1.11, 95% CI 1.04, 1.19)

Kurella-Tamura et al, Am J Kidney Dis. 2008

Kidney Disease, Intensive Hypertension Treatment, and Risk for Dementia and Mild Cognitive Impairment: The Systolic Blood Pressure Intervention Trial

SPRINT Research Group*

8563 participants >50 y, median FU 5.1y

Incident dementia in 3.8% (325) and MCI in 7.6% (640)

- Baseline eGFR<60 ml/min/1.73m^2 and ACR>30mg/g **were not associated with risk of dementia or MCI**.
- Incident eGFR <60 ml/min/1.73 m^2 and eGFR decline >30% and **were associated** with a higher risk of dementia and MCI .
- Decline in eGFR occurred more frequently in the intensive treatment group, but did not modify the beneficial effect of intensive treatment on cognitive function.

Table 2. Association of baseline eGFR and UACR with the risk for cognitive impairment

Baseline Kidney Markers	Probable Dementia		MCI		Probable Dementia or MCI	
	Cases per 1000 PY	Adjusted HR (95% CI)[a]	Cases per 1000 PY	Adjusted HR (95% CI)[a]	Cases per 1000 PY	Adjusted HR (95% CI)[a]
eGFR, ml/min per 1.73 m^2						
eGFR<60						
Yes (*n*=2385)	13.0	1.04 (0.80 to 1.36)	21.9	0.98 (0.80 to 1.18)	31.1	1.02 (0.86 to 1.20)
No (*n*=6178)	12.1	Referent	14.5	Referent	18.9	Referent
UACR, mg/g						
UACR≥30						
Yes (*n*=1539)	12.4	1.24 (0.93 to 1.66)	22.3	1.11 (0.90 to 1.38)	31.4	1.05 (0.88 to 1.26)
No (*n*=6627)	7.1	Referent	15.3	Referent	20.3	Referent

Table 3. Association of postrandomization declines in eGFR and increases in UACR with the risk for subsequent cognitive impairment during follow-up

Kidney Marker	*N*	HR (95% CI)		
		Probable Dementia	MCI	Probable Dementia or MCI
eGFR, ml/min per 1.73 m^2				
Decline in eGFR ≥30%				
Yes	465	1.76 (1.03 to 2.77)	0.99 (0.61 to 1.60)	1.19 (0.83 to 1.70)
No	8896	Referent	Referent	Referent
Incident CKD				
Yes	212	1.70 (0.89 to 3.25)	2.10 (1.19 to 3.70)	2.14 (1.35 to 3.40)
No	6450	Referent	Referent	Referent
UACR, mg/g				
Incident UACR ≥30				
Yes	1837	0.90 (0.68 to 1.19)	0.91 (0.70 to 1.18)	0.93 (0.76 to 1.15)
No	5053	Referent	Referent	Referent

Kurella Tamura, JASN 2020

Lower kidney function & steeper kidney function decline are associated with higher risk of incident dementia

SCREAM - health care cohort (Stockholm Creatinine Measurements, 2006–2011)
205,622 residents , >65y old
18,983 incident cases of dementia (5.8%)-
median FU 5y

- Lower eGFR 30–59 mL/min associated with higher dementia risk (**HR 1.71**, 95% CI 1.54–1.91) vs eGFR >90mL/min.
- eGFR decline **>2 mL/min/1.73m²/y** associated with higher dementia risk.
- Risk magnitudes were stronger for **vascular dementia** vs Alzheimer dementia.
- **10% of dementia** cases could be attributed to **eGFR <60 mL/min/1.73m²**.

Figure 1 Risk of Dementia Associated With Baseline eGFR

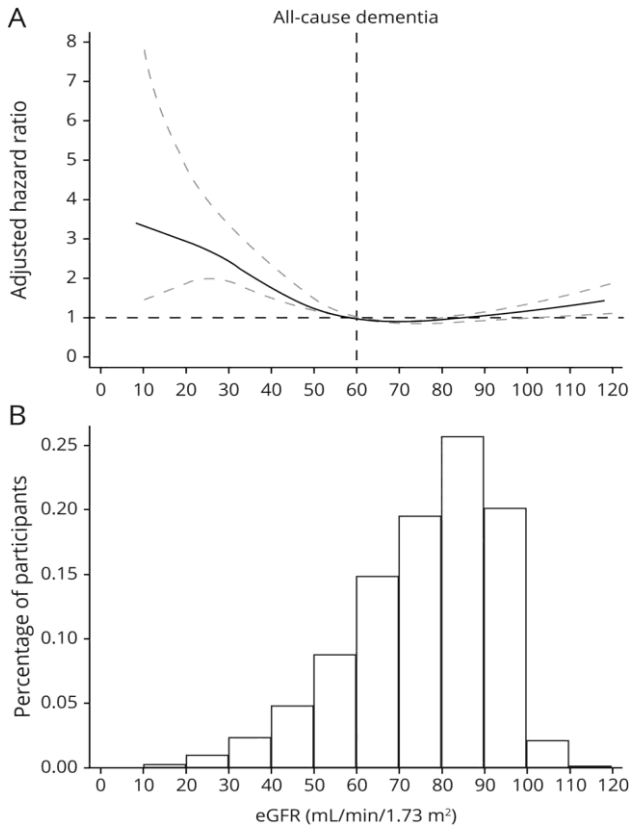
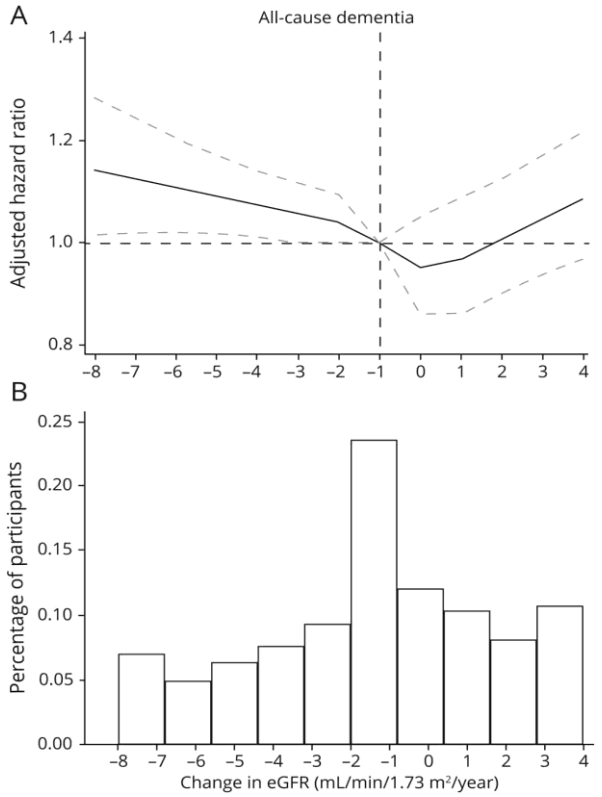


Figure 2 Risk of Dementia Associated With Rate of Kidney Function Decline



Xu et al, Neurology. 2021

Albuminuria and Estimated GFR as Risk Factors for Dementia in Midlife and Older Age: Findings From the ARIC Study

- ***Lower eGFR based on cystatin-C or B2M, not creatinine associated with dementia.***
- ***Albuminuria consistently associated with dementia incidence.***

Setting & Participants—
2 baselines ARIC Study:
Visit 4 (1996–1998) - 9967 participants, 54–74 years old
Visit 5 (2011–2013) 4626 participants, 70–90 years old
Participants were followed until 2017
Outcome: incident dementia

	UACR category		
	< 10 mg/g	10 – 30 mg/g	> 30 mg/g
Incident dementia after visit 4, age 54-74 years			
$eGFR_{cys}$ ≥ 60 mL/min/1.73 m^2	1.00 (reference) (n=7,459)	1.05 (0.89–1.23) (n=1,042)	**1.35 (1.11–1.64)*** (n=558)
$eGFR_{cys}$ < 60 mL/min/1.73 m^2	1.08 (0.89–1.31) (n=610)	**1.66 (1.15–2.38)*** (n=144)	**2.14 (1.50–3.05)*** (n=154)
Incident dementia after visit 5, age 70-90 years			
$eGFR_{cys}$ ≥ 60 mL/min/1.73 m^2	1.00 (reference) (n=1,286)	1.29 (0.87–1.90) (n=816)	**1.81 (1.11–2.96)*** (n=297)
$eGFR_{cys}$ < 60 mL/min/1.73 m^2	1.25 (0.86–1.83) (n=962)	**2.06 (1.42–2.98)*** (n=702)	**2.29 (1.56–3.36)*** (n=563)

Measure of CKD	Baseline visit 4, ages 54–74 years		Baseline visit 5, ages 70–90 years	
	Model 1	Model 2	Model 1	Model 2
eGFR CKD-EPI, Creatinine per V4-IQR (19.4ml/min) decrease	0.98 (0.92–1.04)	0.98 (0.91–1.04)	1.11 (0.99–1.24)	1.06 (0.94–1.19)
eGFR CKD-EPI, Cystatin-C per V4-IQR (24.3ml/min) decrease	**1.16 (1.07–1.25)***	**1.12 (1.04–1.21)***	**1.33 (1.16–1.53)***	**1.30 (1.12–1.52)***
eGFR CKD-EPI, Creatinine and Cystatin-C per V4-IQR (20.7ml/min) decrease	**1.08 (1.01–1.16)***	1.07 (0.99–1.14)	**1.23 (1.09–1.38)***	**1.19 (1.04–1.35)***
eGFR CKD-EPI, Beta-2-Microglobulin per V4-IQR (18.3ml/min) decrease	**1.18 (1.11–1.27)***	**1.15 (1.07–1.23)***	**1.36 (1.20–1.54)***	**1.34 (1.17–1.55)***
Log Urine albumin-to-creatinine ratio per V4-IQR (4.2) – fold increase	**1.19 (1.13–1.25)***	**1.15 (1.09–1.21)***	**1.32 (1.18–1.46)***	**1.27 (1.13–1.42)***

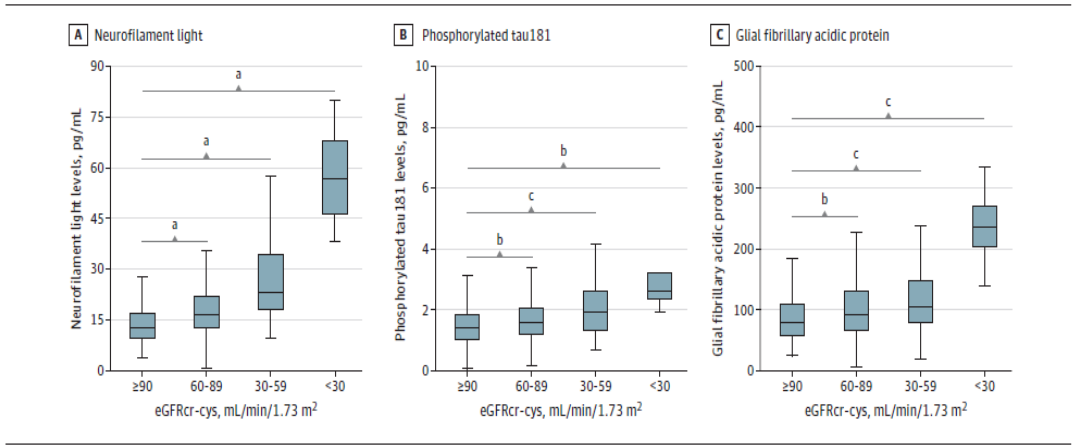
Scheppach et al, Am J Kidney Dis. 2020

Association of Kidney Function With Development of Alzheimer Disease and Other Dementias and Dementia-Related Blood Biomarkers

JAMA Network Open

- *6256 participants - prospective*
- Cumulative all-cause incidence of dementia was **8.2%** (510 participants) within 17 years FU (incidence rate, 5.5/1000 person-years)
- ***Reduced kidney function was associated with increased levels of dementia-related blood biomarkers (NfL, p-tau181, GFAP) but NOT increased dementia risk after adjustment for confounders***
- Kidney function might influence the accuracy of dementia-related blood biomarkers

			Model 0[a]		Model 1[b]		Model 2[c]	
Characteristic	Overall, No.	Cases, No.	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause dementia								
eGFRcr-cys, mL/min/1.73 m^2								
≥90	2363	151	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
60-89	3418	298	1.46 (1.20-1.78)[d]	<.001	0.83 (0.68-1.02)	.07	0.78 (0.57-1.08)	.14
<60	475	61	2.57 (1.91-3.46)[d]	<.001	0.95 (0.69-1.29)	.73	0.77 (0.41-1.43)	.41
Alzheimer disease								
eGFRcr-cys, mL/min/1.73 m^2								
≥90	2363	49	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
60-89	3418	95	1.44 (1.02-2.04)[d]	.04	0.82 (0.58-1.17)	.82	0.88 (0.61-1.26)	.48
<60	475	20	2.64 (1.57-4.44)[d]	<.001	0.94 (0.55-1.63)	.94	0.98 (0.55-1.74)	.93
Vascular dementia								
eGFRcr-cys, mL/min/1.73 m^2								
≥90	2363	60	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
60-89	3418	110	1.37 (1.00-1.88)	.05	0.77 (0.56-1.07)	.11	0.78 (0.56-1.09)	.15
<60	475	27	2.93 (1.86-4.62)	<.001	1.06 (0.65-1.70)	.83	1.05 (0.63-1.75)	.84



Stocker et al, JAMA Network Open. 2023

Discrepancy between studies regarding MCI and dementia in CKD

- **differences in study design**

  screening vs health care extraction
  stage of CKD, screening test etc
- **differences in outcome ascertainment**

  neuropsychologist performance vs

  ICD diagnoses/drug dispensations
- **detection bias**
- **survival bias**
- **misclassification bias**

CONNECT PROJECT

COST ACTION CA19127

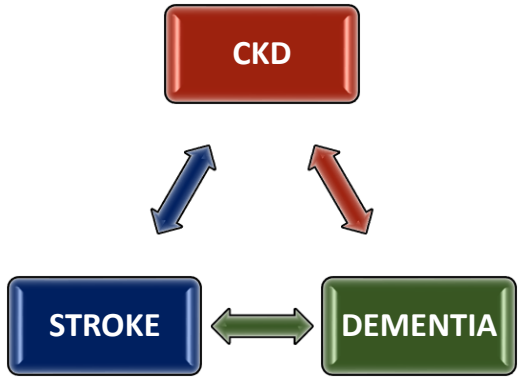
CONNECT

Cognitive decline in Nephro-Neurology: European Cooperative Target

CONNECT Action aims to coordinate research on cognitive impairment in chronic kidney disease (CKD). This requires exchanging clinical information between nephrologists and neurologists, and between neuroscientists and kidney physiologists, guided by big data analysts.

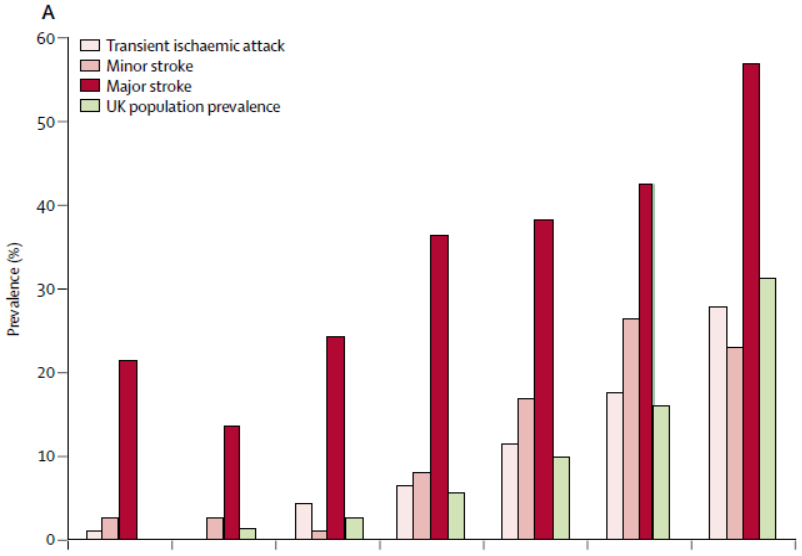
1. *nephrology clinicians*
2. *neurology clinicians*
3. *pre-clinical kidney science*
4. *pre-clinical neuroscience*
5. *bioinformatics experts*

Specific aim to consider all factors that may influence brain function and to shed light on those that impact the progression of MCI in CKD

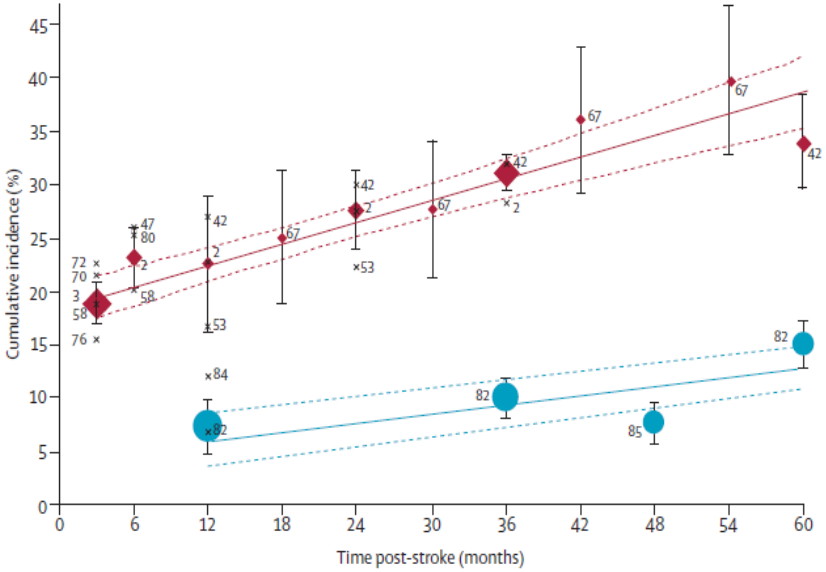


Stroke is associated with an increased risk of subsequent dementia

- **Dementia incidence is nearly 50 times higher in the year after a major stroke compared with that in the general population**
- 10% of patients had dementia before 1st stroke
- 10% of patients developed new dementia soon after 1st stroke
- More than 1/3 of patients had dementia after recurrent stroke



Prevalence of any dementia in patients 1 year after TIA or stroke and in the UK general population



Pooled cumulative incidence of post-stroke dementia excluding pre-stroke dementia in hospital-based cohorts

Pendlebury et al, Lancet Neurol 2009, Pendlebury et al, Lancet Neurol 2019 – Oxford Vascular Study

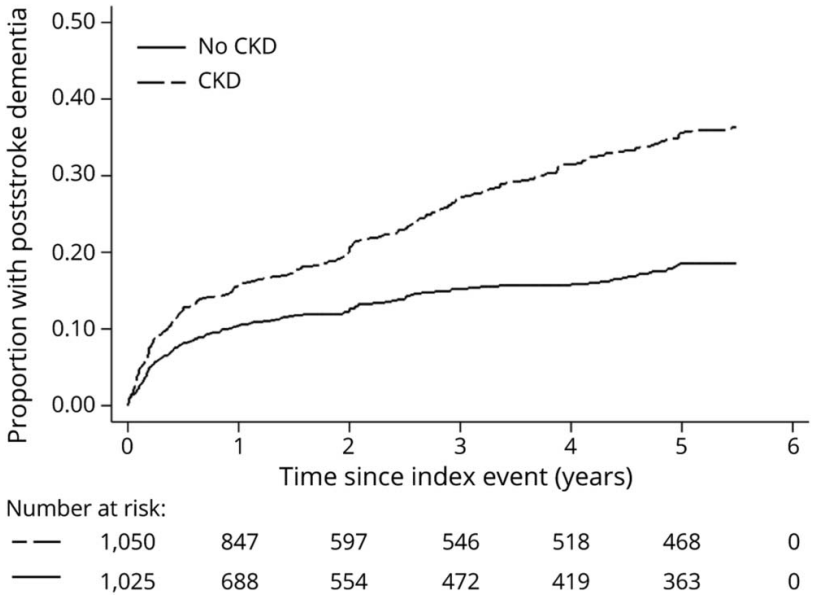
RESEARCH ARTICLE OPEN ACCESS

Associations of Chronic Kidney Disease With Dementia Before and After TIA and Stroke

Population-Based Cohort Study

- A prospective study in 2305 predialysis CKD patients with TIA or stroke

Figure 1 Kaplan-Meier (1 – Survival) Curve Showing the Cumulative Incidence of New Postevent Dementia (Excluding Pre-event Dementia) for All Patients (With and Without CKD) to 5-Year Follow-up



CKD = chronic kidney disease.

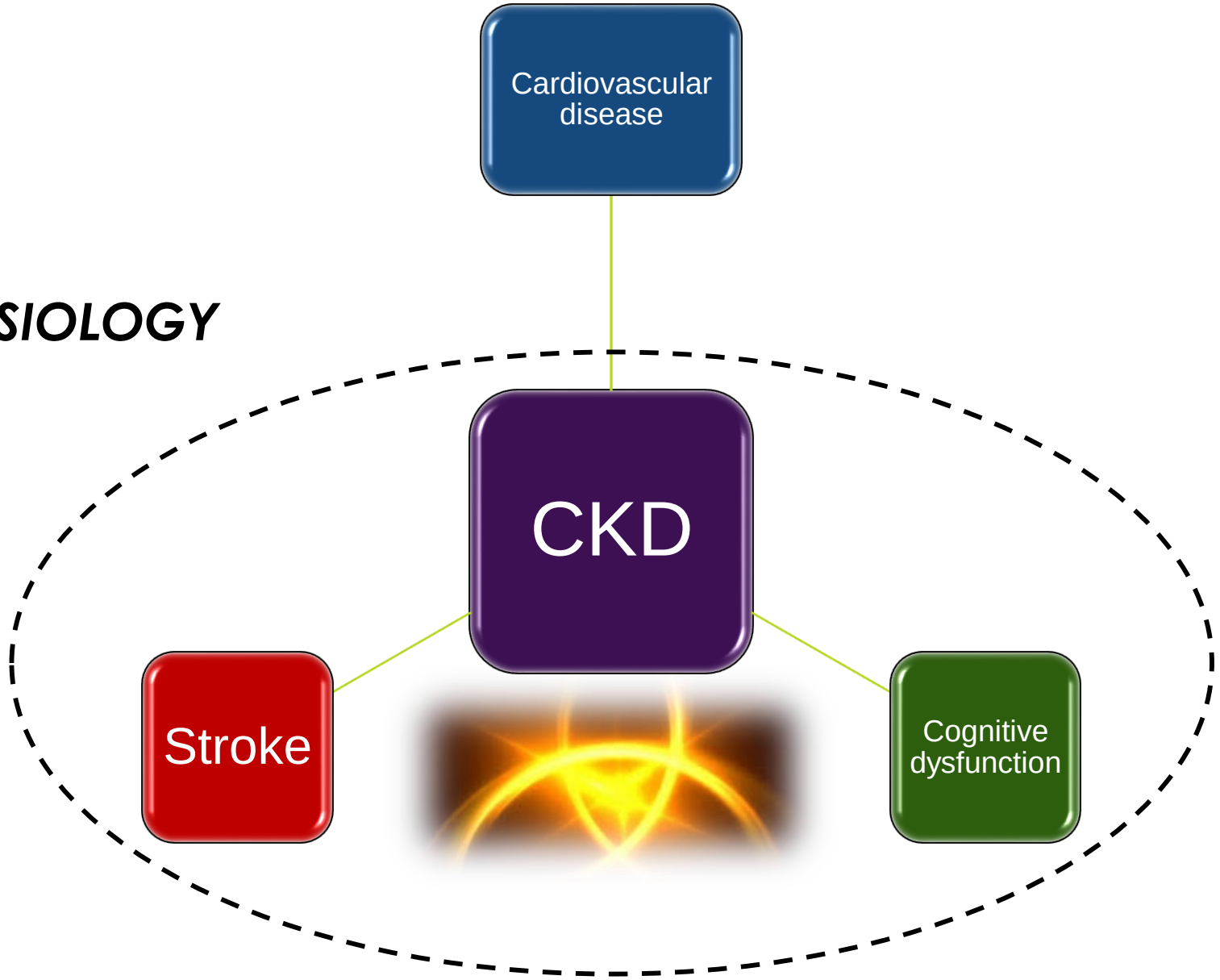
Table 3 Five-Year Incidence of Postevent Dementia Accounting for the Competing Risk of Death According to CKD Status and eGFR Category

	Unadjusted	*p* Value	Model 1	*p* Value	Model 2	*p* Value	Model 3	*p* Value
All patients (n = 2,080)								
No CKD (eGFR ≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR <60)	1.74 (1.43–2.12)	<0.001	0.97 (0.79–1.20)	0.77	0.94 (0.76–1.17)	0.60	1.01 (0.78–1.33)	0.92
eGFR ≥60	1.00		1.00		1.00		1.00	
eGFR 30–59	1.77 (1.45–2.16)	<0.001	0.99 (0.80–1.23)	0.96	0.97 (0.78–1.21)	0.80	1.03 (0.79–1.35)	0.82
eGFR <30	1.51 (0.98–2.30)	0.06	0.76 (0.48–1.20)	0.24	0.70 (0.43–1.13)	0.14	0.85 (0.48–1.51)	0.57

The prevalence of pre- or post-event dementia was twice as high in CKD patients, but CKD was not independently associated with dementia after adjustment for co-founders (age, gender, education, DM etc)

Kelly DM, et al. Associations of Chronic Kidney Disease With Dementia Before and After TIA and Stroke: Population-Based Cohort Study. Neurology. 2022 Feb 15;98(7):e711–20.

PATHOPHYSIOLOGY

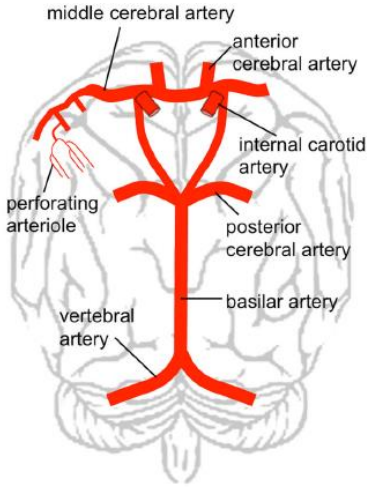


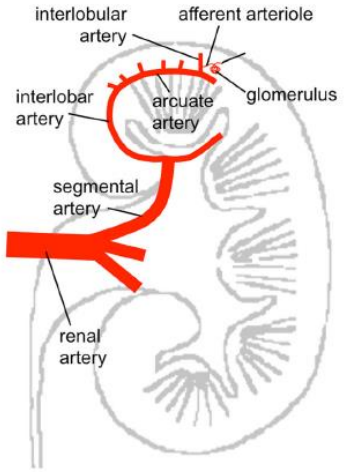
The kidney and brain share anatomical and functional characteristics making them vulnerable to similar vascular risk factors

- ✓ Require: continuous, stable high blood flow in a low vascular resistance system
- ✓ Depend on: short, small perforating arterioles which autoregulate perfusion pressure
- ✓ Are: susceptible to traditional arteriosclerotic risk factors

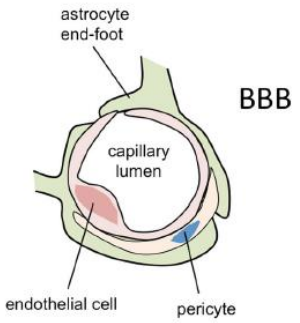
	Kidney	Brain
Arterioles/anatomy	High pressure load per unit length	High pressure load per unit length
Arterioles/regulation	Maintenance of vascular tone	Maintenance of vascular tone
Blood flow	Constant, 360 ml/min/100 gm	Constant, 50 ml/min/100 gm
Blood barrier	Fenestrated/permeable	Tight/limited passage
Small vessels damaged by risk factors	Yes	Yes
Hypertensive pathology	Hyalinosis	Lipohyalinosis

ARTERIAL VASCULATURE

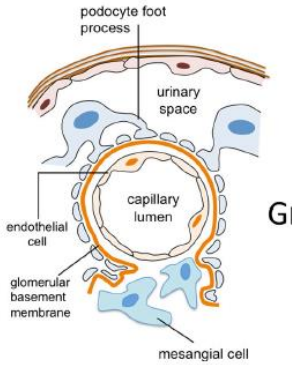




CAPILLARY LEVEL



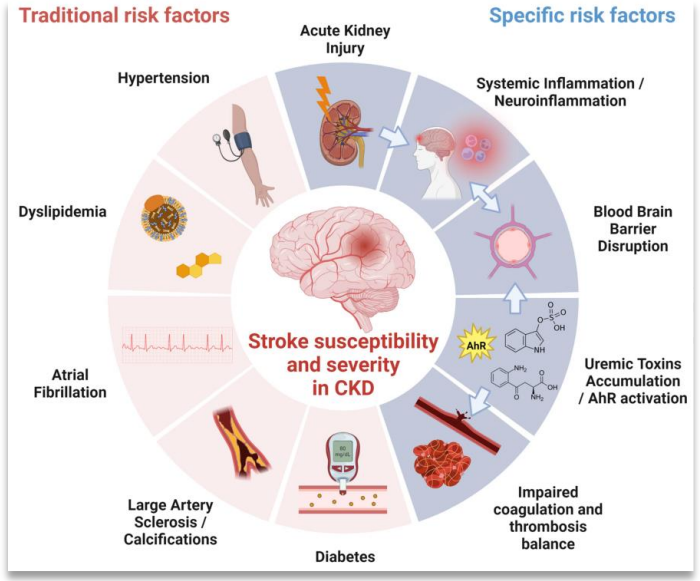
BBB

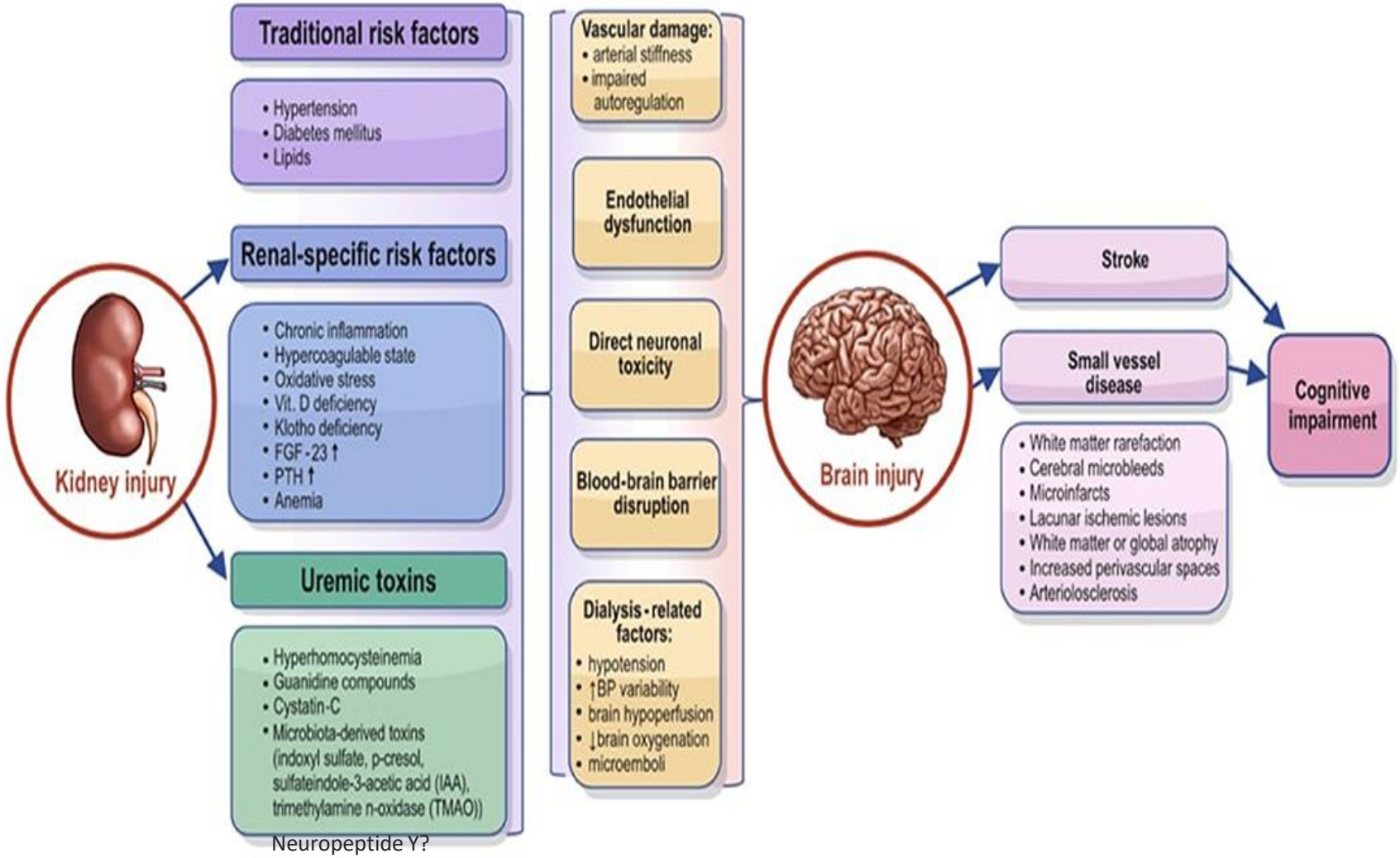


GLOMERULUS

Lau et al, Transl. Stroke Res 2017

Traditional and specific risk factors/markers of brain damage in CKD





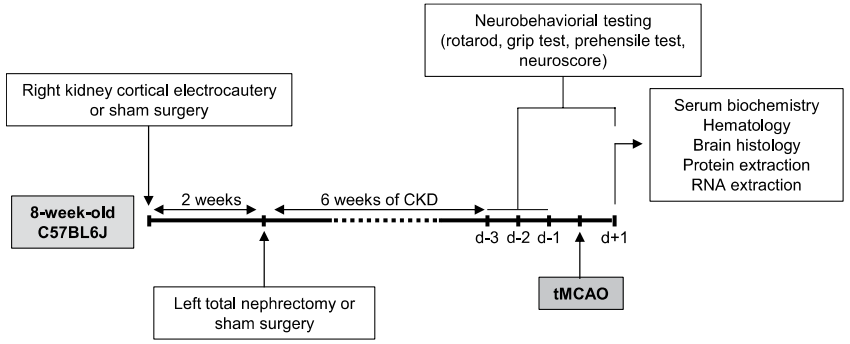
Neuropeptide Y?

Bobot M. et al. NDT 2023, Miglinas M et al. Front. Cardiovasc. 2020,

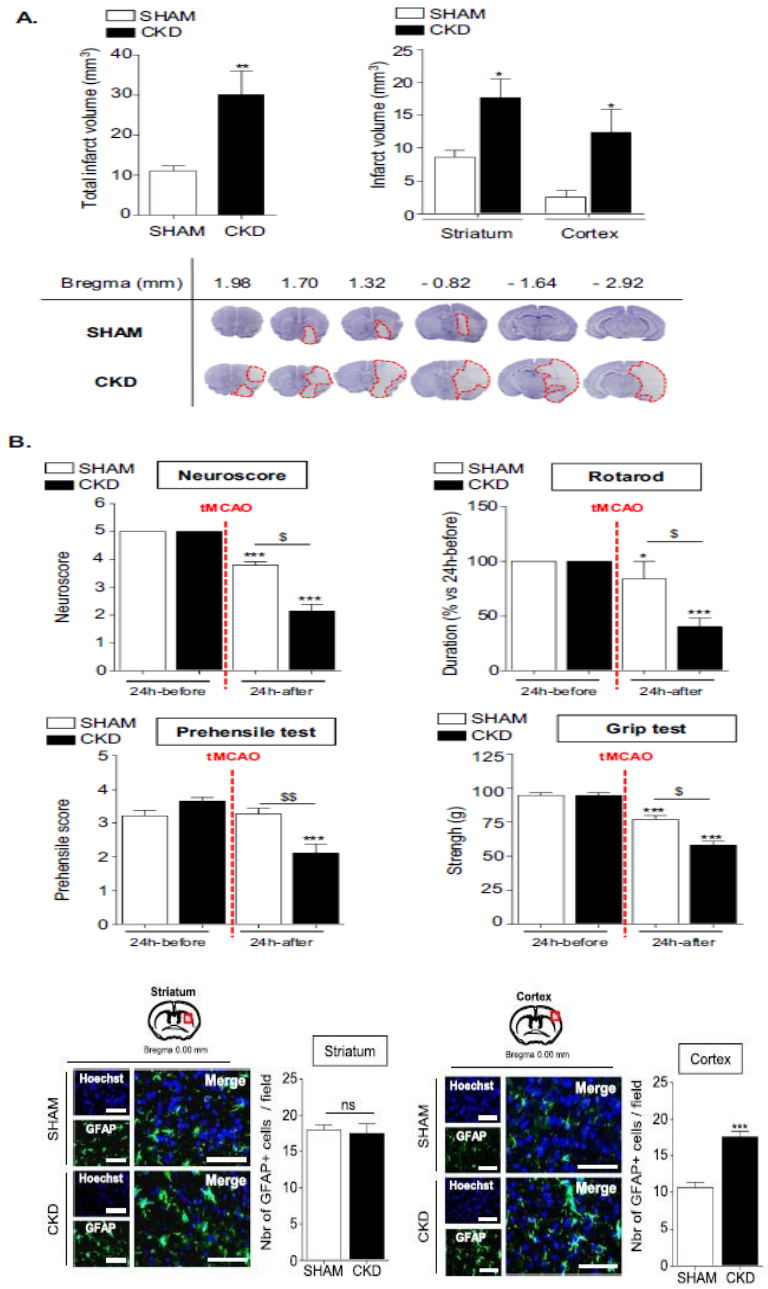
Cellular and molecular mechanisms associated with ischemic stroke severity in female mice with CKD

Transient middle cerebral artery occlusion in female CKD mice compared to control mice :

- ✓ worsened cerebral infarct volume size and functional recovery
- ✓ amplified stroke-induced apoptosis and neuronal loss
- ✓ impaired M2- and accentuated M1-polarization of the microglia/macrophages in the ischemic brain
- ✓ decrease of AMP kinase phosphorylation in ischemic brain
- ✓ amplified astrogliosis within the ischemic penumbra



Hénaut et al, Sci Rep 2019



Uremic toxins associated with brain dysfunction

CONNECT Action (Cognitive Decline in Nephro-Neurology European Cooperative Target)

Small water-soluble compounds	Protein-bound compounds	Middle molecules
ADMA SDMA TMAO Uric acid Urea Methylguanidine guanidine	Indoles • IS • Indoxyl glucuronide • IAA • Kynurenine Cresols • pCS • p-cresyl glucuronide Hippurates • HA • CMPF	B2M IL-6 PTH Neuropeptide Y?

Clinical data on the impact of uremic toxins on cognitive functions are scarce

- ✓ **Direct harmful effects**
- ✓ **Indirect harmful effects**
  - ✓ **endothelial dysfunction**
  - ✓ **inflammation**
  - ✓ **oxidative stress**
  - ✓ **vascular calcification**
  - ✓ **coagulation disorders**

Liabeuf et al, Nephrol Dial Transplant 2021

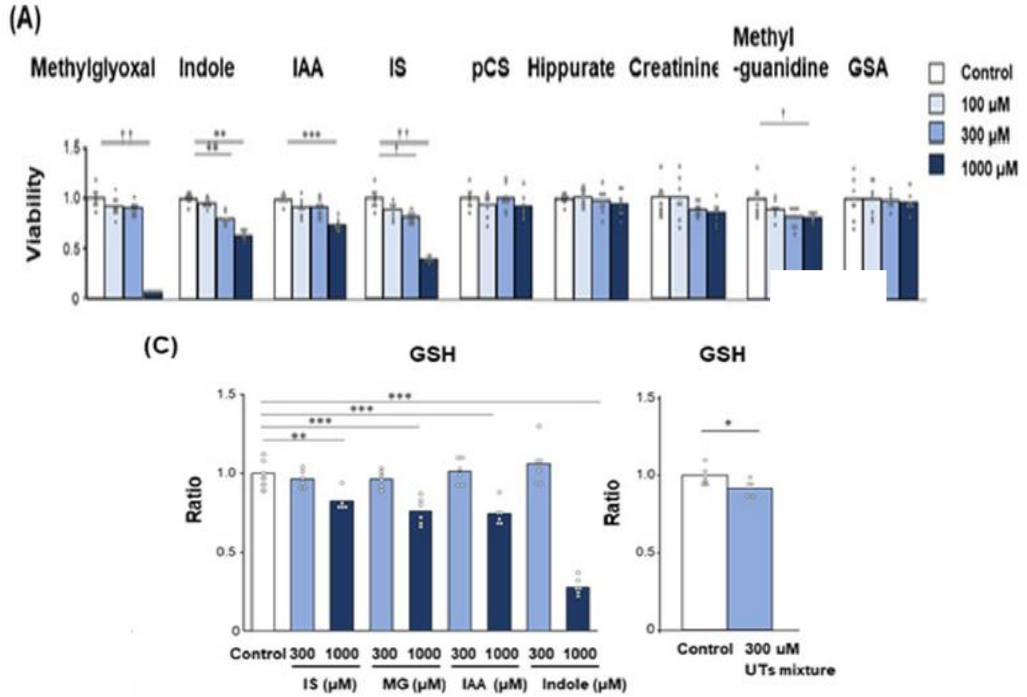
Uremic toxins can have direct toxic effects on neurons

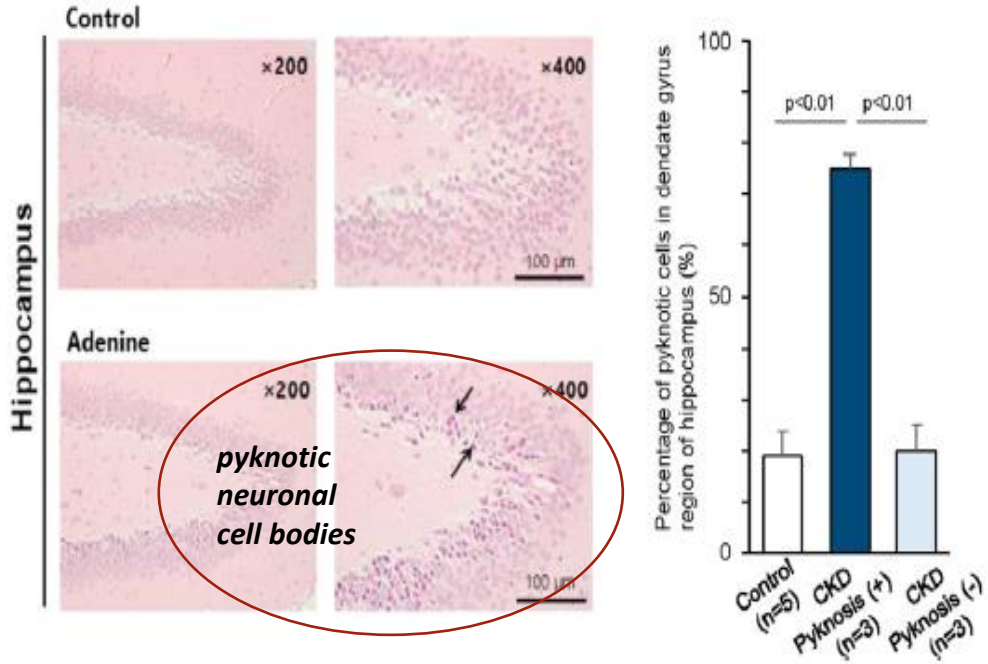
- ***Indol sulphate (IS) and indole acetic acid (IAA)*** ***in a rat model of adenine-induced CKD***

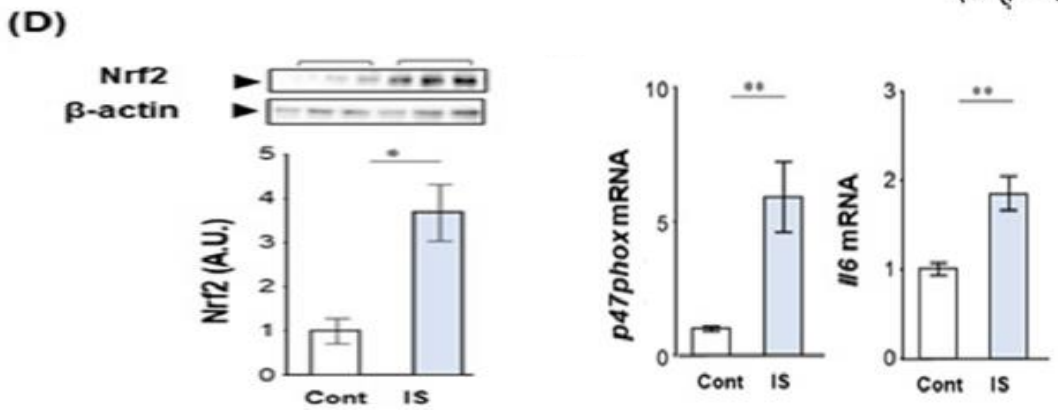
✓ diminished viability of hippocampal neuronal cells

✓ accentuated oxidative stress pathways (↓GSH, ↑Nrf2, ↑p47phox)

✓ promoted neuroinflammation (↑IL6)





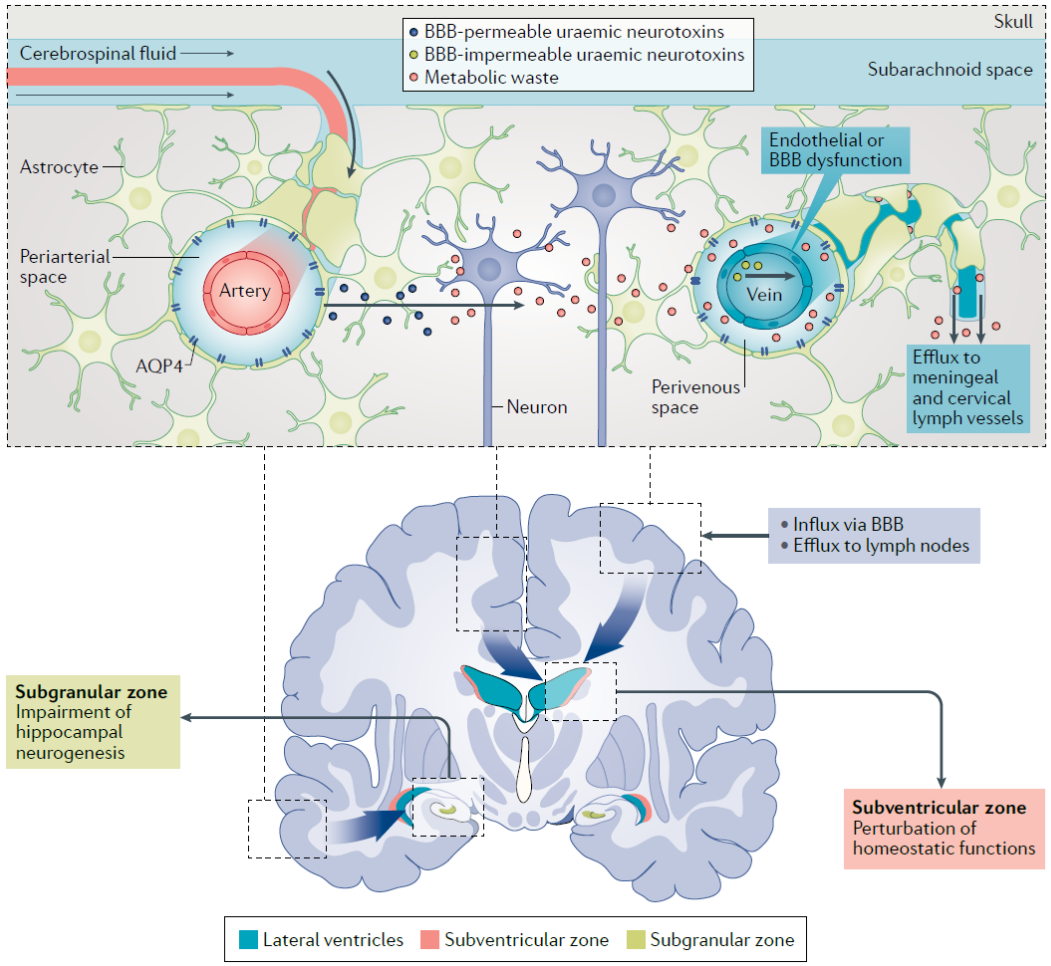


Watanabe et al, Heliyon 7 2021

Mechanisms of uremic toxin transport in the brain

- Uraemic toxins enter the brain via the BBB and blood–cerebrospinal fluid barrier and leave the brain via the glymphatic system

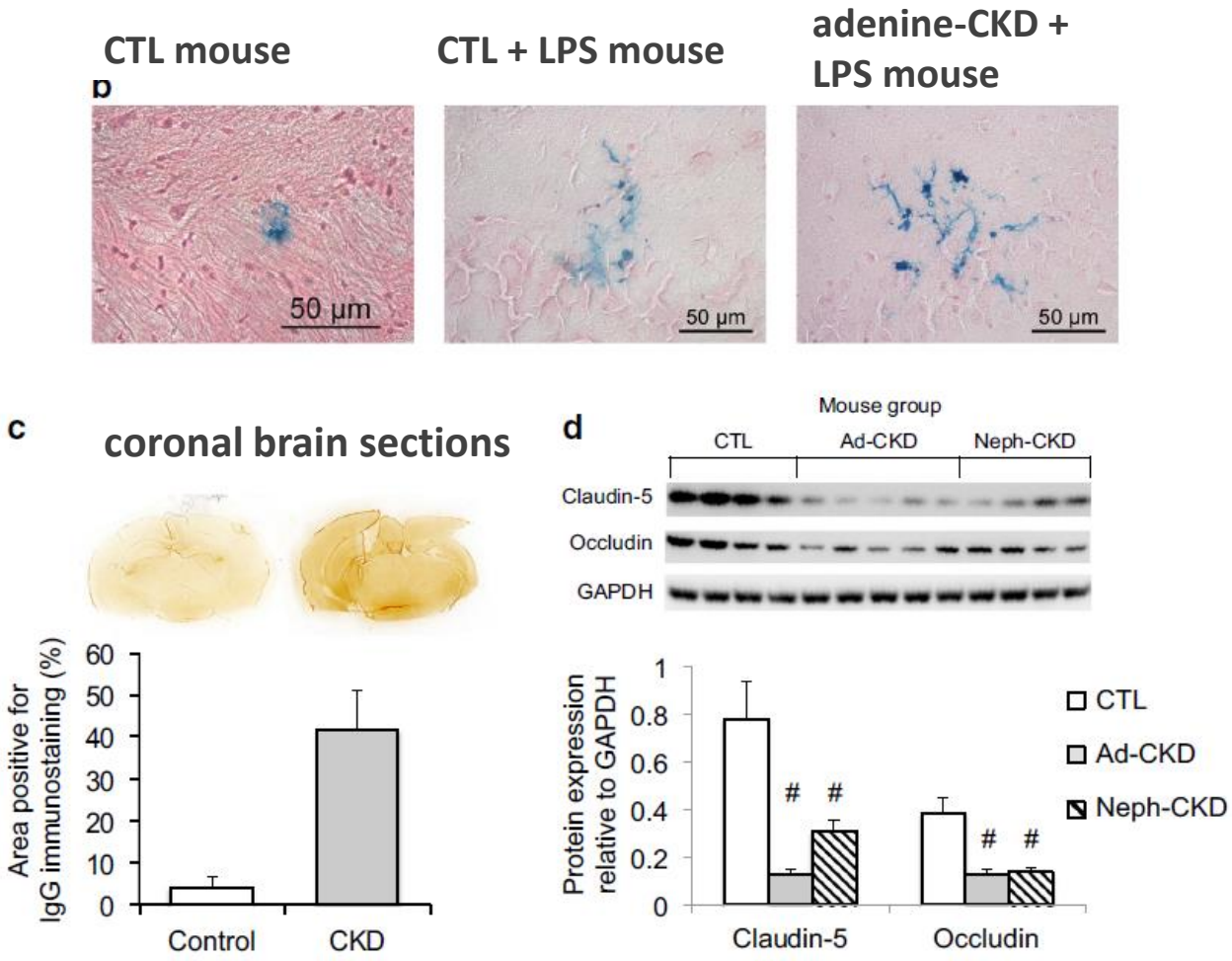
- **Uraemic neurotoxins** might interfere with various functions of **endogenous neural progenitor cells**, including neurogenesis and homeostasis, and thereby further contribute to perturbation of brain functions in CKD.



Viggiano et al, Nature reviews. Nephrology 2020

BBB dysfunction is associated with cognitive impairment in neurodegenerative diseases and chronic systemic diseases like hypertension, diabetes mellitus and CKD

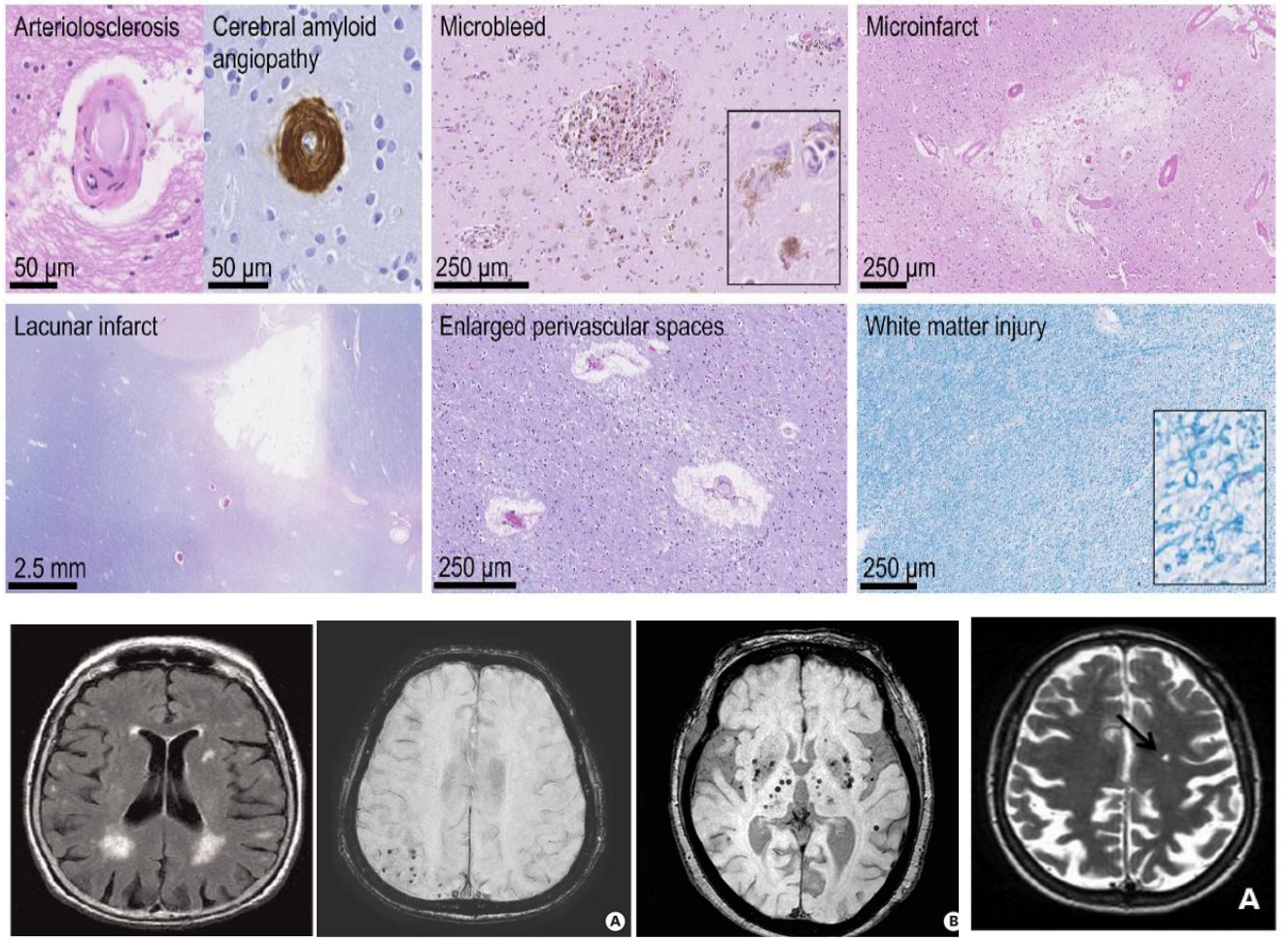
- **Potential mechanisms of endothelial barrier dysfunction in CKD**
  - ➢ disruption of the actin cytoskeleton
  - ➢ decreased tight junction proteins area



Lau et al, Translational Stroke Research2020, Katsi et al, J Hum Hypertens 2020, Nation et al, Nat Med. 2019, Mazumder et al, Life Sci. 2016

There is a strong association between cerebral small vessel disease and CKD

- ✓ white matter hyperintesities (leukoaraiosis)
- ✓ silent cerebral infarctions (SCI)
- ✓ perivascular spaces
- ✓ cerebral microbleeds



Rost et al, Circulation Research. 2023, Wardlaw et al, JAHA 2015
Makin et al, Cerebrovasc Dis. 2015, Xiao et al, Stroke. 2015

Brain imaging studies in CKD patients have identified associations between kidney biomarkers and the structural brain changes underlying cognitive impairment in uremia

Albuminuria may be better at capturing endothelial and microvascular damage

Association of Kidney Function Measures With Signs of Neurodegeneration and Small Vessel Disease on Brain MRI

Setting and Participants

Cross-sectional analysis from visit 5 of the ARIC Study
- 1,527 participants, community-based

Predictors:
- Estimated glomerular filtration rate (eGFR)
- Urine albumin-creatinine-ratio (UACR)

Outcomes (Brain MRI):
- Brain volume reduction
- Infarcts
- Micro-hemorrhages
- White matter lesions

Findings

↓ eGFR associated with:
- ↓ Brain volume
- ↑ White matter lesions

No significant associations with infarcts & micro-hemorrhages

↑ log(UACR) associated with:
- ↓ Brain volume
- ↑ Brain infarcts
- ↑ Brain micro-hemorrhages
- ↑ White matter lesions

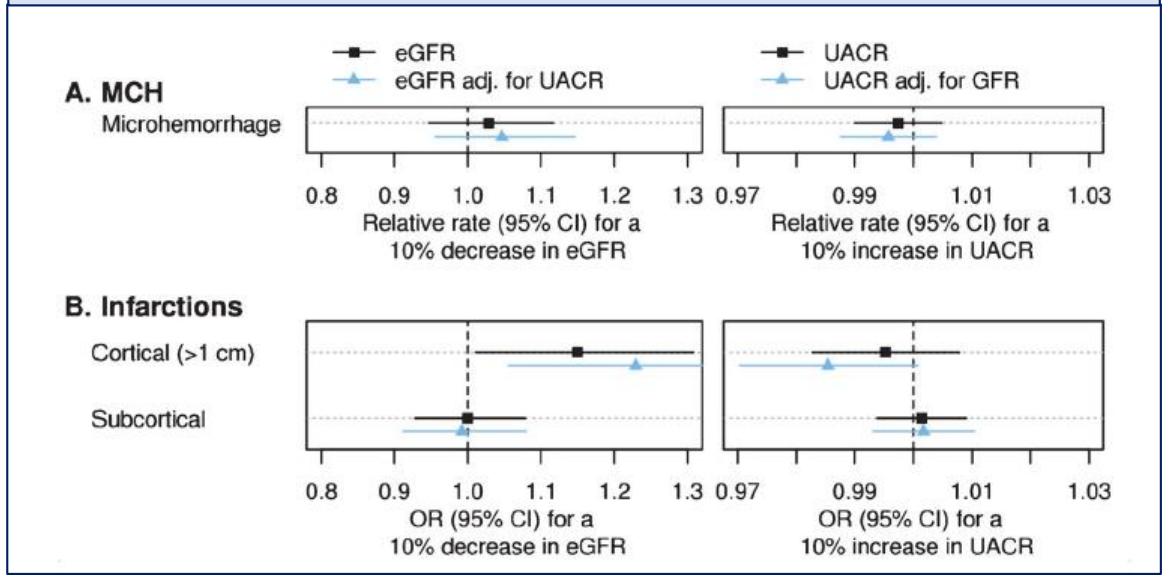
CONCLUSION: Kidney function measures are associated with structural brain damage visible on MRI across different domains of etiology.

Johannes B. Scheppach, Aozhou Wu, Rebecca F. Gottesman, et al
@AJKDonline | DOI: 10.1053/j.ajkd.2022.07.013
AJKD

Scheppach JB et al. Am J Kidney Dis. 2023

Association of Kidney Function Biomarkers with Brain MRI Findings: The BRINK Study

Only higher UACR associated with ↑ odds of cortical and lacunar brain infarcts and micro-hemorrhages.

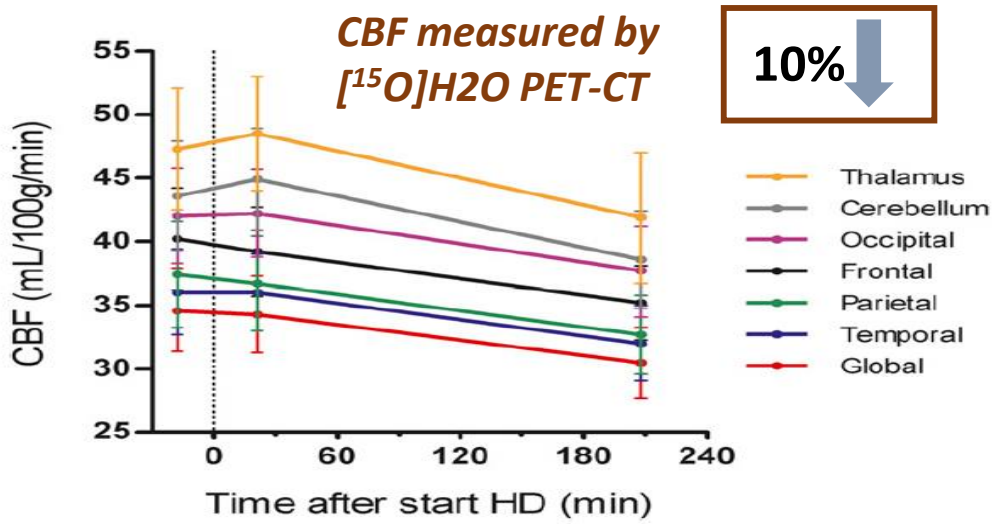


Vemuri et al, J Alzheimers Dis. 2017

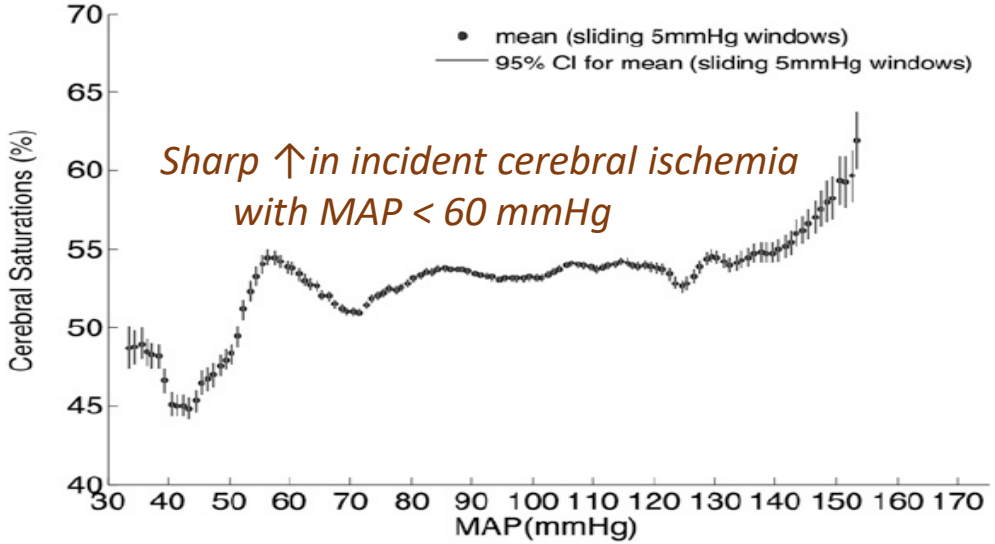
ESKD patients on hemodialysis are at risk for global and regional cerebral hypoperfusion and subsequent cognitive impairment

- **Impaired cerebral autoregulation in patients with ESKD on HD**
- **Increased susceptibility to cerebral ischemia during HD hemodynamic stress**

✓ *inflammation*
✓ *vascular calcification*
✓ *comorbidities (diabetes, hypertension, atherosclerosis and older age)*



Polinder-Boss et al, J Am Soc Nephrol 2018



Mac-Ewen et al, J Am Soc Nephrol 2018

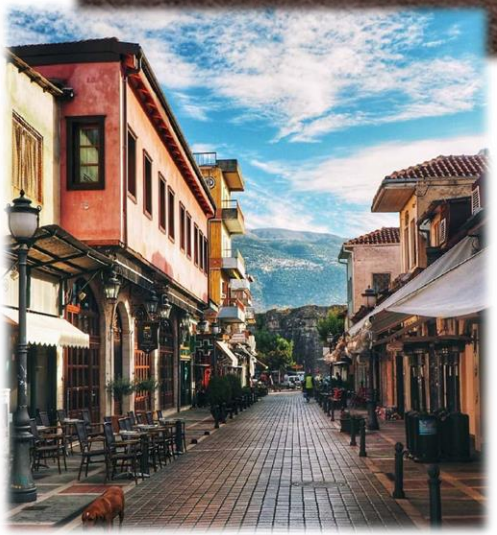
Summary - Future perspectives

- CKD is an important risk factor for cerebrovascular disease.
- CKD complicates routine stroke risk prediction, diagnosis, management, and prevention.
- CKD associates with worse stroke severity and outcomes
- The link between CKD and cognitive dysfunction remains challenging
- Elucidation of pathogenesis of cognitive impairment in CKD is necessary
- From an epidemiological point of view is crucial to discern independently causal associations from intermediate mediators, confounders, and epiphenomena

- Large epidemiological prospective studies with CKD and healthy participants, with appropriate screening tests, imaging studies and novel CKD and neurodegenerative disease biomarkers are required so as to to investigate the progression of brain changes and the relationship between kidney and brain function

Thank you for your attention

Ioannina the city of legends



Back up slides

Neuropeptide Y
neuroprotective peptide

- ✓ facilitates neurogenesis
- ✓ has trophic effects on the nervous system
- ✓ inhibits neuroinflammation

- ✓ NPY associates with proteinuria and faster CKD progression
- ✓ NPY predicts cardiovascular events in predialysis CKD patients

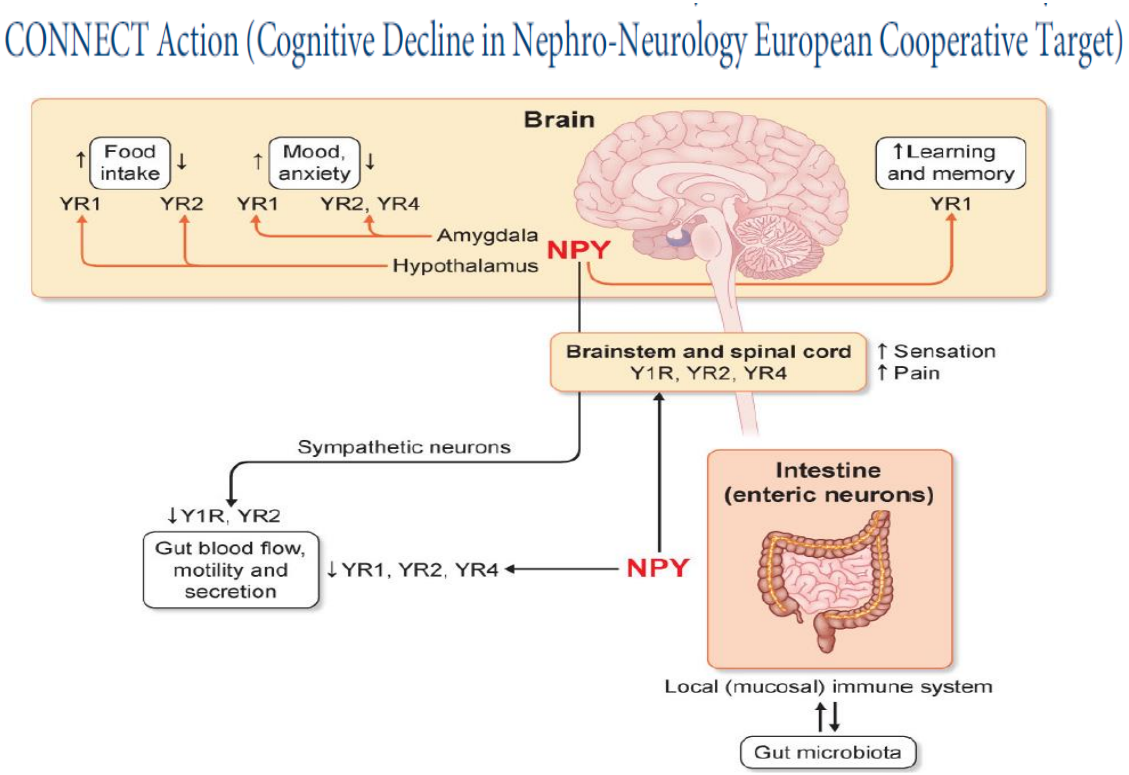
Zoccali et al, Nephrol Dial Transplant. 2018
Zoccali et al, J Hypertens. 2019

6 times higher in hemodialysis patients than in healthy individuals

NPY is an immunomodulatory factor

NPY protects kidney from AKI by inactivating M1 macrophages via the Y1R-NF-κB-Mincle-dependent mechanism

Tan et al, Int J Biol Sci. 2023



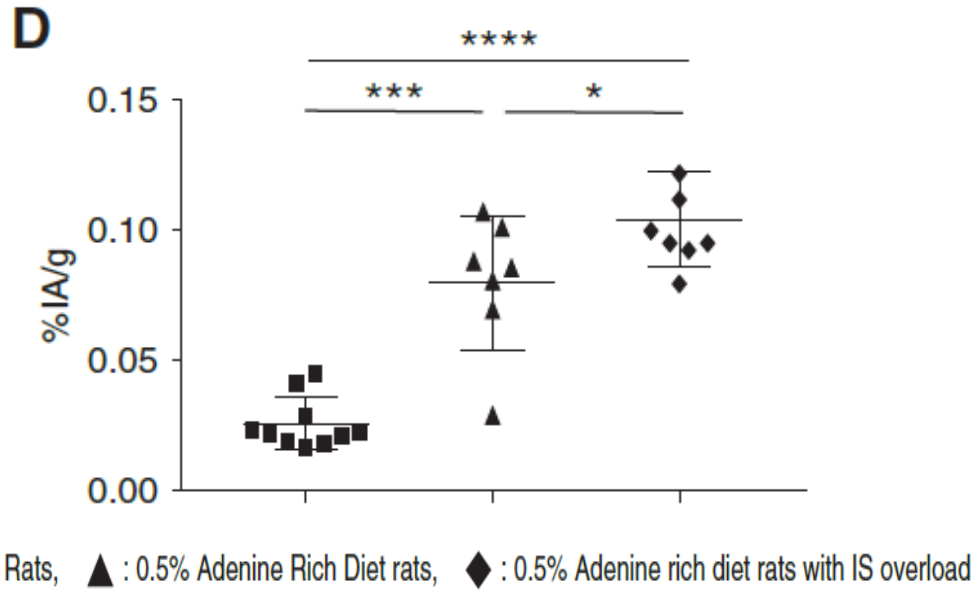
- **Role of increased NPY levels in CKD for cognitive dysfunction and dementia remains to be elucidated**

Zoccali et al, Nephrol Dial Transplant 2022

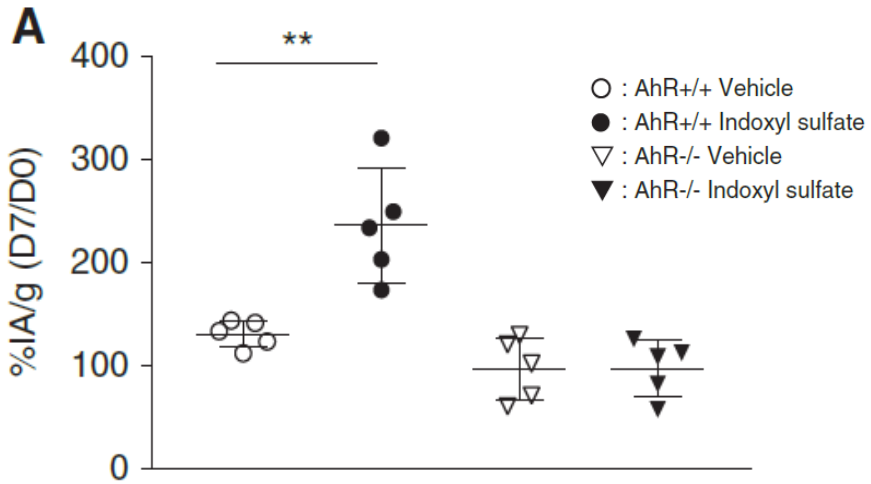
Uremic Toxic Blood-Brain Barrier Disruption Mediated by AhR Activation Leads to Cognitive Impairment during Experimental Renal Dysfunction

- Cognitive impairment in uremic rats correlated with serum levels of indoxyl sulfate and BBB disruption as detected by SPECT/CT imaging
- non-CKD AhR-/- knockout mice were protected against indoxyl sulfate–induced BBB disruption showing similar relative brain content of 99mTc-DTPA regardless of IS administration

BBB permeability assessed by brain content of 99mTc-DTPA cerebral scintigraphy



AhR activation involved in indoxyl sulfate-induced BBB disruption and cognitive impairment in mice

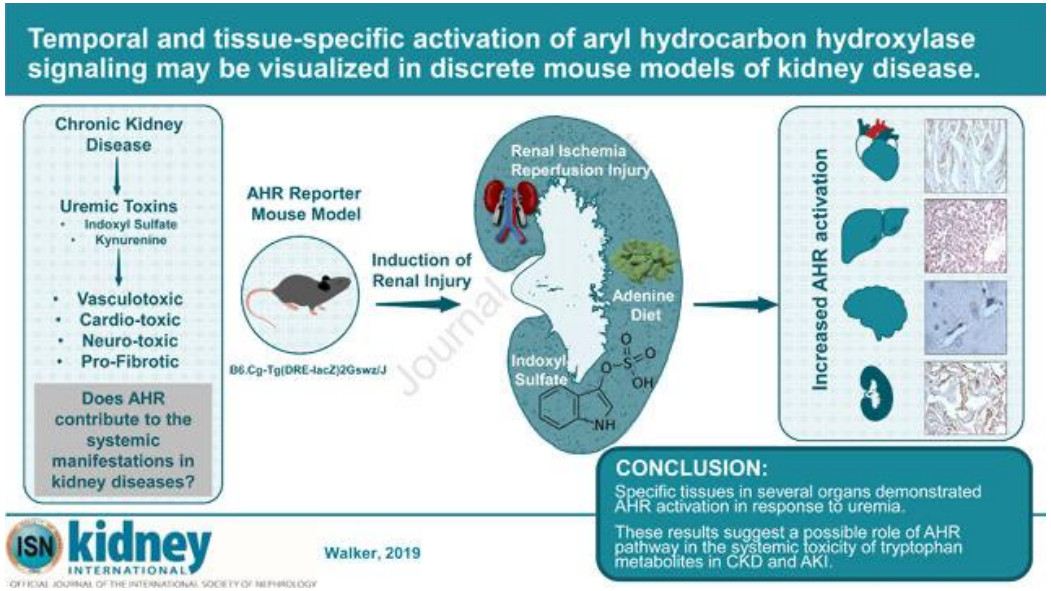


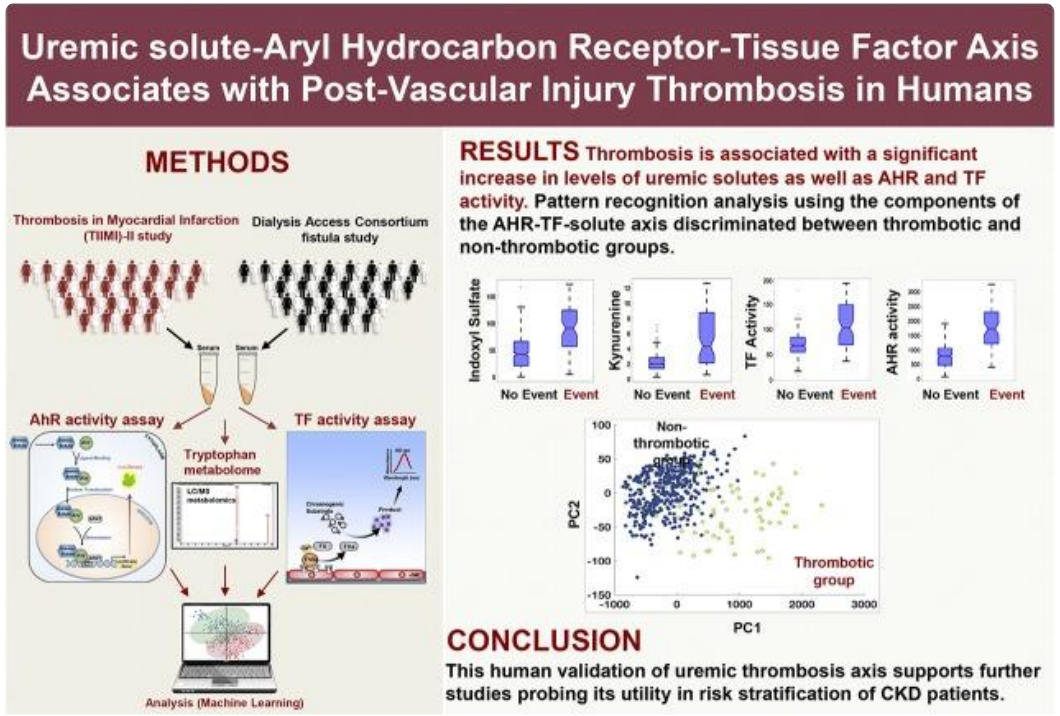
Bobot et al, JASN 2020

The Aryl Hydrocarbon Receptor (AHR) pathway activation in CNS: a mediator of toxicity of indolic-solutes in vascular-, cardio-, neuro-damage in **CKD**

- **AHR** is a cytosolic ligand-activated transcription factor with impact on neuronal proliferation, differentiation, and survival.
- **Indolic solutes** enhance **thrombogenicity** of the uremic milieu **through AHR** signaling which promotes tissue factor (TF) expression in the vessel wall and triggers thrombosis.
- Both clinical and experimental studies indicated a prominent role of indoxyl sulphate-AHR axis activation in the uremic brain, including the endothelial cells of cerebral microvasculature.

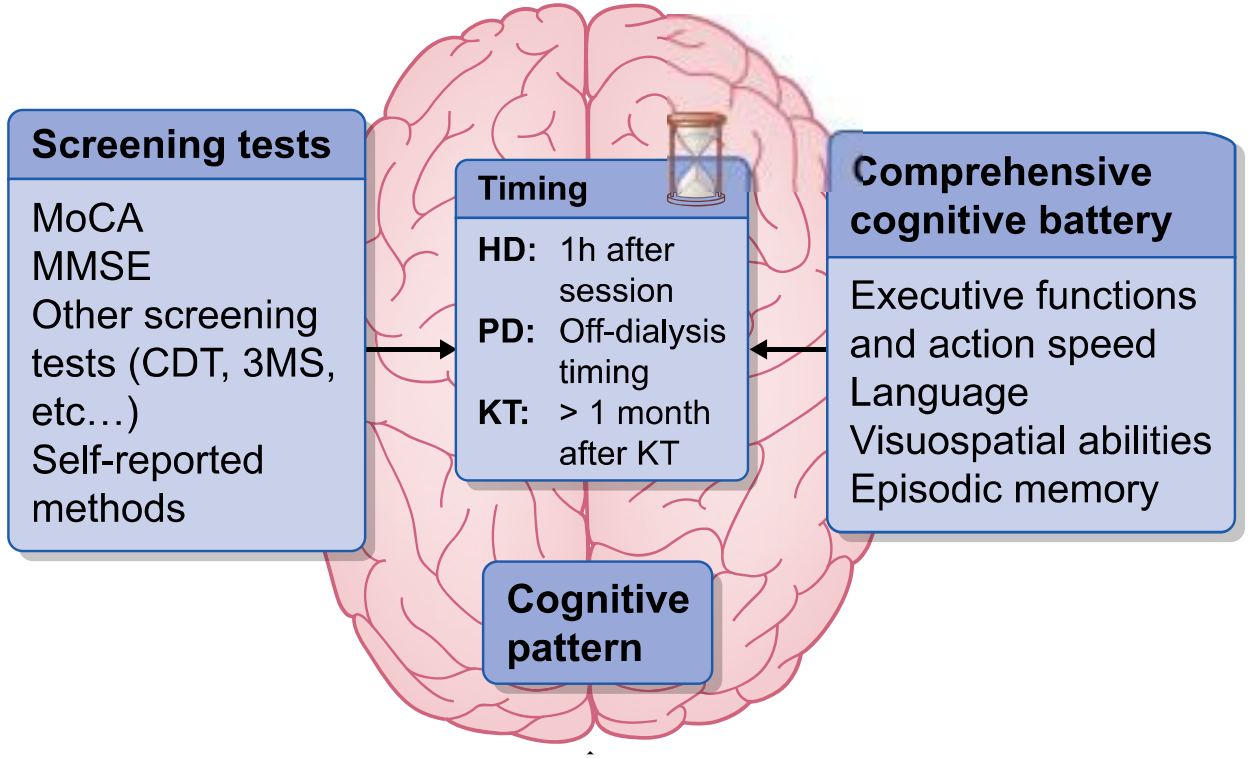
Juricek et al, Int J Mol Sci 2018
Kolachalama et al, J Am Soc Nephrol 2018, Walker et al, Kidney Int. 2020





Screening for MCI and dementia in CKD patients

Need of early screening in the course of CKD
Prospective , repeated assessment of cognitive function in ESKD
Variety of screening tools



Viggiano et al, Nat Rev Nephrol. 2020, Pepin M et al. CONNECT project, NDT 2021

Stroke. 2021;52:e328–e346. DOI: 10.1161/STROKEAHA.120.029680

Chronic Kidney Disease and Cerebrovascular Disease

Consensus and Guidance From a KDIGO Controversies Conference

Dearbhla M. Kelly, MBBChBAO, MSc, DPhil, MRCPI; Zanfina Ademi, MPH, PhD; Wolfram Doehner, MD, PhD; Gregory Y.H. Lip, MD; Patrick Mark, MB ChB, PhD; Kazunori Toyoda, MD, PhD; Christopher X. Wong, MBBS, MSc, MPH, PhD; Mark Sarnak, MD, MS; Michael Cheung, MD; Charles A. Herzog, MD; Kirsten L. Johansen, MD; Holger Reinecke, MD, PhD; Manish M. Sood, MD, MSc

A summary of the epidemiology, pathophysiology, diagnosis, and treatment of cerebrovascular disease in CKD from the KDIGO Controversies Conference on central and peripheral arterial disease with a focus on knowledge gaps, areas of controversy, and priorities for research.

Acute ischemic stroke	
Acute blood pressure targets	We would recommend following the AHA/ASA guidelines with regard to blood pressure targets depending on the eligibility for thrombolysis. The presence of CKD should not modify these targets.
High-dose aspirin therapy	This should be given if an ICH has been excluded, if the patient is not eligible for thrombolysis, and if there is no other contraindication present.
IV thrombolysis	A patient with CKD or who is dialysis-dependent should be treated with thrombolytic therapy provided that the aPTT is normal and that there is no other contraindication present. Dose modification for renal function is not recommended.
Mechanical thrombectomy	A patient with CKD or who is dialysis-dependent should undergo a mechanical thrombectomy for a large-vessel occlusive stroke if they are otherwise eligible for treatment.
Decompressive hemicraniectomy	Given the poor prognosis in the general population, the decision for surgical intervention for malignant hemispheric infarction should be individualized in this setting taking into account the patient's premorbid functional status.
Admission to an acute stroke unit	It is essential that a patient with an acute ischemic stroke who has CKD or who is dialysis-dependent be admitted to an acute stroke unit.

Spontaneous ICH	
Acute blood pressure targets	Early intensive blood pressure lowering (SBP <140 mm Hg in <1 h) appears to be equally safe and effective in CKD.[66]
Anticoagulation reversal	Patients with CKD or who are dialysis-dependent should receive reversal agents for vitamin K- and nonvitamin K anatagonists as per the general population. Idarucizumab is safe to use in impaired renal function.[67]
Surgical evacuation of hematoma	Patients with CKD or who are dialysis-dependent should be undergo surgical evacuation of ICH where indicated if they are otherwise eligible.
Admission to an acute stroke unit	It is essential that a patient with an acute ischemic stroke who has CKD or who is dialysis-dependent be admitted to an acute stroke unit.

Table 3. Recommendations for the Primary and Secondary Prevention of Stroke in CKD

	Primary Prevention	Secondary Prevention
Intervention:		
Lifestyle modifications	Smoking cessation, healthy diet, weight restriction, and regular exercise should all actively encouraged.	As per primary prevention.
Antiplatelet therapy	There is currently insufficient evidence to support the use of antiplatelet therapy for primary prevention.	Antiplatelet therapy for secondary prevention is uniformly recommended
Anticoagulation	In general, anticoagulation is recommended for the primary prevention of stroke with AF in this group. This is a high-risk group in which risk prediction tools such as CHA_2DS_2-VASc may have limited utility. For those with eGFR >30 mL/min per 1.73 m^2, first-line treatment should be with a NOAC. For those with eGFR 15–29 mL/min per 1.73 m^2, the choice of agent should depend on the trajectory of their renal function and should, therefore, be discussed with their nephrologist. For those with an eGFR <15 mL/min per 1.73 m^2, the decision to anticoagulate and the choice of agent should be discussed with their nephrologist.	As per primary prevention but we would advise having an even lower threshold to anticoagulate. The AHA/ACC[89] recommend using either a apixaban or warfarin in dialysis-dependent patients though long-term safety data on the former is lacking, and there is a risk of vascular calcification with the latter. Consider left atrial appendage occlusion devices in those with additional bleeding concerns as they have been shown to be safe and effective in advanced CKD after the initial periprocedural period.
Dual blockade (antiplatelet+low-dose DOAC)	There may be a role for dual pathway blockade in patients with CKD (eGFR 30-59 mL/min per 1.73 m^2) who have chronic coronary artery or peripheral artery disease and who are thought to be at low risk of bleeding.	There is no evidence to support the use of dual pathway blockade for secondary prevention at this time.
Blood pressure control	Tight blood pressure control to <120/80 mm Hg is essential. RAS blockers are the antihypertensive agents of choice.	As per primary prevention.
Lipid-lowering therapy	As per KDIGO,[90] if >50 y and CKD present, treat with statin or statin/ezetimibe. In dialysis-dependent CKD, do not start statins de novo but continue if already taking.	We would recommend statin therapy for all patients with CKD who have had a stroke event. As per KDIGO guidelines,[90] statins may be continued in dialysis patients who are already taking them but should not be started unless very high LDL-C levels (3.8 mmol/L).
SGLT-2 inhibitors	We recommend treating all diabetic CKD patients with an eGFR > 30 mL/min per 1.73 m^2 with an SGLT-2 inhibitor.	We recommend treating all diabetic CKD patients with an eGFR >30 mL/min per 1.73 m^2 with an SGLT-2 inhibitor.
Carotid interventions	We would not recommend carotid revascularization for patients with CKD with asymptomatic disease.	Consider carotid revascularization in nondialysis patients with CKD with symptomatic moderate-severe stenosis, and in very high-risk dialysis patients with symptomatic disease.
Dialysis-related interventions	Careful attention to blood pressure and volume control when a patient is first about to start dialysis. Maintain hemoglobin values between 100 and 120 g/L.	As per primary prevention.