Brain&Kidney 2020

Resolved:
CKD is a Stroke Risk Factor: Con

THE UNIVERSITY OF ARIZONA

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Disclosures

- We have nothing to disclose

Brain&Kidney 2020

[Virtual Debate]
[Bruce M Coull, MD and Judy Dawod, MD]

Our Position

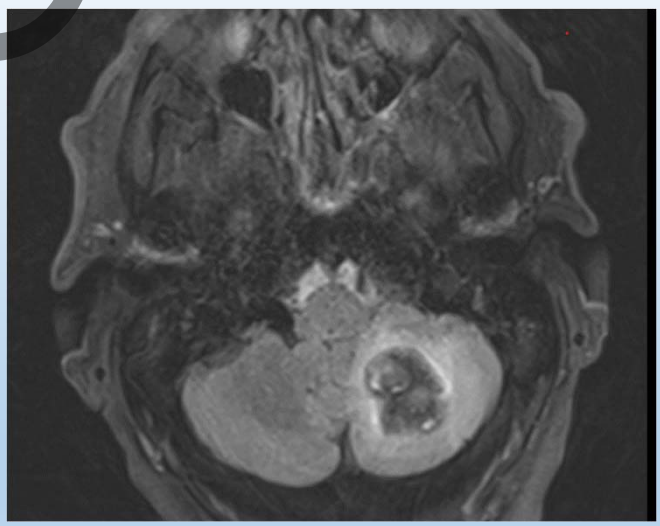
- CKD is more of a biomarker than a risk factor
  - Severity of factors causing CKD (HTN and DM)
  - Marker of biological aging
- Risk of CKD and Stroke are largely confounded
- In Typical Literature search for stroke RF's CKD is not prevalent
- CKD is not included in the CHA2DS2-VaSc (but is in HAS-BLED)
- Dose Response of degree of CKD and risk not totally defined
- Unique mechanism(s) of how CKD causes stroke not well defined
- Excepting Transplant Unique Stroke Prevention measures are lacking

56 YEAR OLD MAN

Chronic renal failure – dialysis X 5 years

Chronic Hypertension "shrank my kidneys"

U Tox – Positive for Cocaine



CKD: Is it a Biomarker or a Risk Factor for Stroke (or both)?

BMJ **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]

Results 21 articles derived from 33 prospective studies: 14 articles assessed eGFR <60 ml/min/1.73 m² and seven assessed eGRF at both <60 ml/min/1.73 m² and 60-90 ml/min/1.73 m² for a total of 284 672 participants (follow-up 3.2-15 years) with 7863 stroke events. Incident stroke risk increased among participants with an eGFR <60 ml/min/1.73 m² (relative risk 1.43, 95% confidence interval 1.31 to 1.57; P<0.001) but not among those with an eGFR of 60-90 ml/min/1.73 m² (1.07, 0.98 to 1.17; P=0.15). Significant heterogeneity existed between

Concluding Paragraph

At this juncture, a low baseline eGFR should be seen simply as a risk marker. Established evidence based strategies already proved to mitigate vascular risk, such as reduction of blood pressure, when promptly and appropriately applied are likely to avert future strokes in people with renal insufficiency. Specific patient subgroups with a low eGFR, such as people of Asian race, may particularly benefit.

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

Prevalence of eGFR < 60 mL/min in the general population and patients with stroke

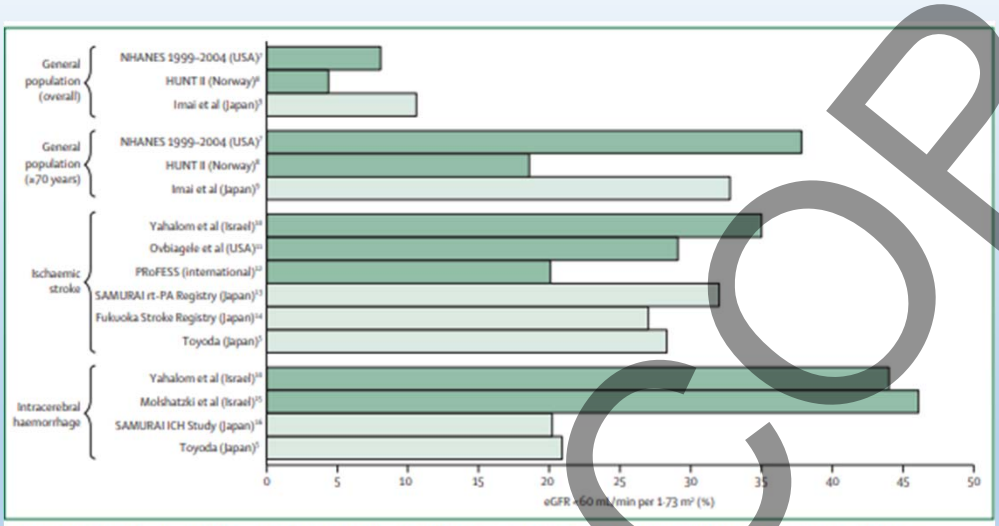


Figure 1: Prevalence of estimated glomerular filtration rate less than 60 mL/min per 1·73 m² in the general population and in patients with stroke

K Toyoda & T Ninomiya *Lancet Neurology* 2014;13:823-33

Dose Response and what parameters are important predictors of cardiovascular event or stroke

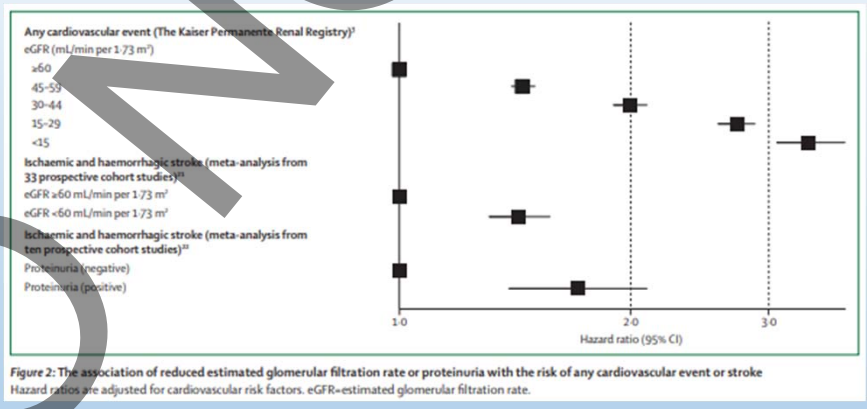


Figure 2: The association of reduced estimated glomerular filtration rate or proteinuria with the risk of any cardiovascular event or stroke
Hazard ratios are adjusted for cardiovascular risk factors. eGFR=estimated glomerular filtration rate.

K Toyoda & T Ninomiya *Lancet Neurology* 2014;13:823-33

Risk of stroke in ESRD depend in part on the cause of RF

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 887–898
doi:10.1093/eurheartj/ehy422

CLINICAL RESEARCH
Prevention and epidemiology

Cause of kidney disease and cardiovascular events in a national cohort of US patients with end-stage renal disease on dialysis: a retrospective analysis

Michelle M. O'Shaughnessy[1]*, Sai Liu[1], Maria E. Montez-Rath[1], Richard A. Lafayette[1], and Wolfgang C. Winkelmayer[2]

[1]Division of Nephrology, Department of Medicine, Stanford University School of Medicine, 777 Welch Road, Suite DE, Palo Alto, CA 94304, USA; and [2]Section of Nephrology, Department of Medicine, Selzman Institute for Kidney Health, Baylor College of Medicine, One Baylor Plaza, ABBR R705, Houston, TX 77025, USA

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See page 899 for the editorial comment on this article (doi: 10.1093/eurheartj/ehy544)

Table 2 Cardiovascular event rates from 91 days to 5 years and 90 days after dialysis initiation, among US patients with end-stage renal disease attributed to glomerular disease, diabetic nephropathy, or autosomal dominant polycystic kidney disease

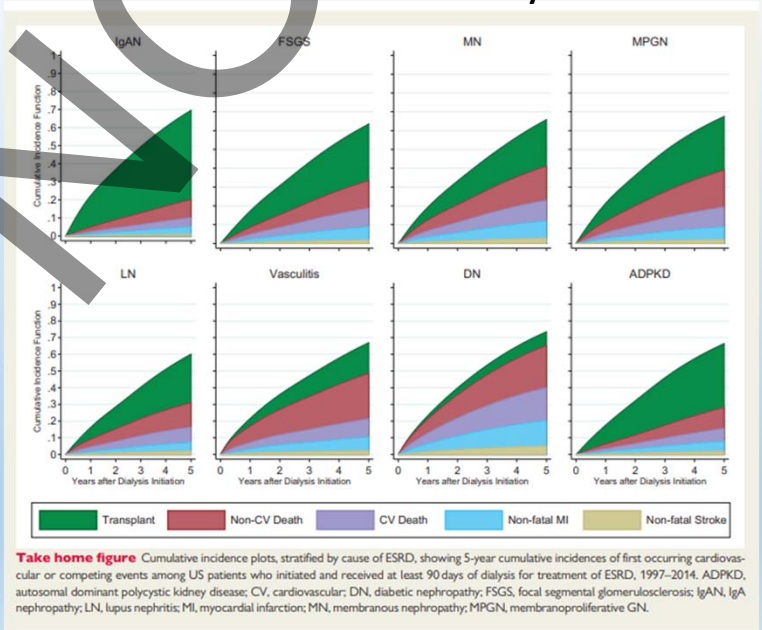
	Percent with event	Number of events	Years at risk	Event rate (per 100 person-years)
Stroke (fatal or non-fatal)				
IgAN	1.15	113	23 176	0.49
FSGS	2.29	619	73 002	0.85
MN	3.30	187	15 093	1.24
MPGN	2.61	97	9531	1.02
LN	2.45	304	33 771	0.90
Vasculitis	3.01	151	12 200	1.24
DN	5.99	33 994	1 383 828	2.46
ADPKD	2.47	660	70 747	0.93

ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; LN, lupus nephritis; MI, myocardial infarction; MN, membranous nephropathy; MPGN, membranoproliferative GN.

ESRD with dialysis started between 1997-2014
658168 patients
IgA nephropathy adjusted HR

Cumulative Incidence Plots Stratified by Cause of ESRD

European Heart Journal. 2019; 40:887-898.



Take home figure Cumulative incidence plots, stratified by cause of ESRD, showing 5-year cumulative incidences of first occurring cardiovascular or competing events among US patients who initiated and received at least 90 days of dialysis for treatment of ESRD, 1997–2014. ADPKD, autosomal dominant polycystic kidney disease; CV, cardiovascular; DN, diabetic nephropathy; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; LN, lupus nephritis; MI, myocardial infarction; MN, membranous nephropathy; MPGN, membranoproliferative GN.

Open access Research

BMJ Open

Absolute risk and risk factors for stroke mortality in patients with end-stage kidney disease (ESKD): population-based cohort study using data linkage

Nicole Louise De La Mata,[1] Maria Alfaro-Ramirez,[2] Patrick J Kelly,[1] Philip Masson,[3] Rustam Al-Shahi Salman,[4] Angela C Webster[5]

Stroke Mortality in ESRD linked to HTN and CVD

- In AU and NZ people with ESRD between 1980-2013 = 60,823
- Within 5 yrs of starting treatment incident stroke death = 0.9%; non-stroke death = 36.8%
- Stroke death greater
  - in old age SHR 1.92 (1.45-2.55)
  - In women 1.42 (1.21-1.64)
  - In people with cerebrovascular disease 2.39 (1.99-2.87)
  - With ESRD caused by hypertension 1.39 (1.09-1.78)

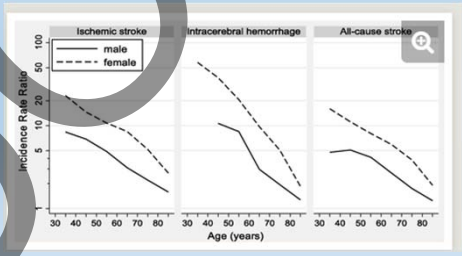
BMJ Open 2019;9:e026263. doi:10.1136/bmjopen-2018-026263

Risk of Stroke in ESRD: Role of Age and Cause of ESRD

Total n = 10,745

AGE at start of Study (yrs)	% With Stroke	% Without Stroke
< 30	1.6	9.3
30 – 50	17.3	27.3
50 - 70	50.7	45.1
70 - 85	30.2	18.1

Cause of Renal Failure	% With Stroke	% Without Stroke
Diabetes	26.5	22.7
HTN/ Renal Art	16.5	12.4
GN/IgA Neph	26.7	30.9
Polycystic KD	6.9	7.2



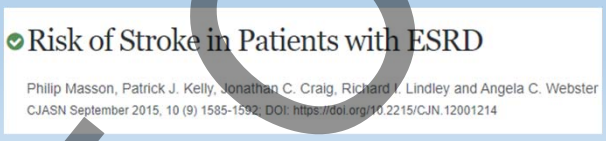
Risk of Stroke in Patients with ESRD

Philip Masson, Patrick J. Kelly, Jonathan C. Craig, Richard I. Lindley and Angela C. Webster
CJASN September 2015, 10 (9) 1585-1592; DOI: https://doi.org/10.2215/CJN.12001214

Risk of Stroke in ESRD: Role of Comorbidities

Comorbidities at ESRD	With Stroke %	Without Stroke %
Cerebrovascular Disease	29.5	14.5
Diabetes	35.3	30.8
Coronary Artery Disease	43.5	34.7
Peripheral Artery Disease	30.9	23.0
Prior Malignancy	6.7	7.7

Total n = 10,745



New Treatments for Prevention of Stroke in CKD?

Has the recognition of the role of CKD and ESRD led to the development of new or novel therapies for stroke?

Traditional and Non-Traditional Risk Factors for Stroke and Kidney Disease

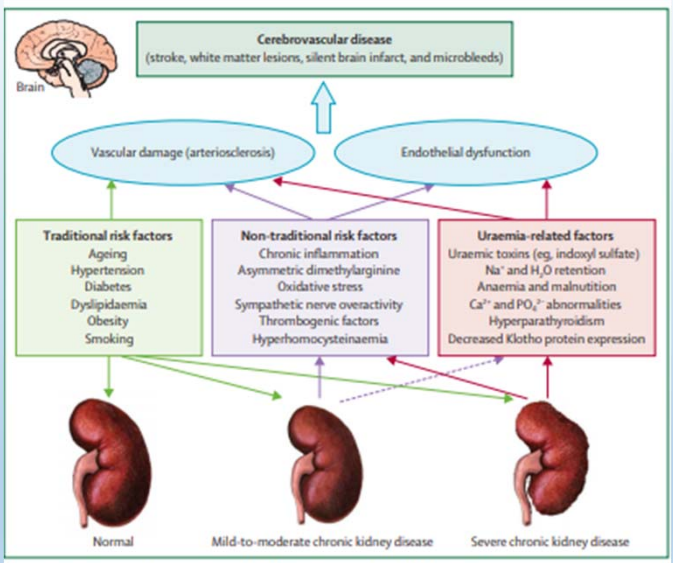


Figure 3: Traditional and non-traditional risk factors for stroke and kidney disease

Klotho Impairment in Kidney Disease

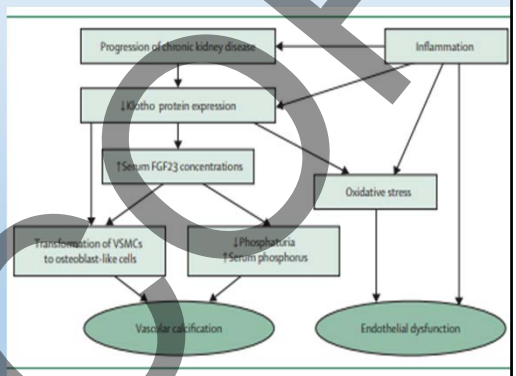


Figure 4: Effect of Klotho protein on vascular damage in patients with chronic kidney disease
FGF23=fibroblast growth factor 23. VSMC=vascular smooth muscle cell.

K Toyoda & T Ninomiya *Lancet Neurology* 2014;13:823-33

Some alterations in brain microanatomy and function in CKD are reversible – especially white matter health

American Journal of Nephrology

Original Report: Transplantation

Cognitive Function and White Matter Changes Associated with Renal Transplantation

Gupta A.[a-c] · Lepping R.J.[c, d] · Yu A.S.L.[a-c] · Perea R.D.[c] · Honea R.A.[c, e] · Johnson D.K.[c, g] · Brooks W.M.[c-f] · Burns J.M.[c, e]

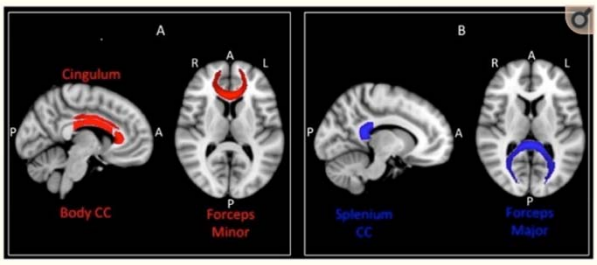


Figure 1

Tracts with increase in fractional anisotropy (FA) and decrease in mean diffusivity (MD) after renal transplantation.

A) FA increased in cingulum, body of corpus callosum and forceps minor after transplantation (shown in red).

B) MD decreased in splenium of corpus callosum and forceps major after transplantation (shown in blue). Body CC, body of corpus callosum; Splenium CC, splenium of corpus callosum; A, anterior; P, posterior; R, right; L, left.

How much do "standard" risk factors other than CKD contribute to stroke?

Population Attributable Fraction (Risk)

- PAF: population attributable fraction, is the incidence risk in the overall population that can be attributed to the exposure
- Two of the largest epidemiological studies for stroke risk factors (Interstroke and Siren) failed to ascertain that CKD is a major contributing risk factor for stroke
- Formula: (Observed Cases* – Expected Cases)/Observed Cases
- * Cases in exposed population

See Graeme Hankey, MBBS,MD, FRACP *Stroke.* 2020;51:719-728.

The Interstroke Study

Study Design

- Case control study, 32 countries between 2007 and 2015
- 13447 cases if first ever stroke compared to 13472 age-and sex-matched controls with no history of stroke
- 10 potentially modifiable risk factors were associated independently and significantly with all strokes, and associated with 90% PAF of stroke

Risk factors

- BP > 140/90
- lack of physical activity
- high apolipoprotein B
- unhealthy diet
- increased waist to hip ratio
- psychosocial factors
- current smoking
- cardiac disease
- high alcohol consumption
- DM
- CKD is not mentioned

***Lancet* 2016; 388:761-75**

Interstroke PAF for all risk factors by region (all stroke, ischemic stroke and ICH)

	All stroke, PAR (99% CI)	Ischaemic stroke, PAR (99% CI)	Intracerebral haemorrhage, PAR (99% CI)
Western Europe, North America, Australia	88·6% (82·5–92·8)	89·5% (83·4–93·5)	82·0% (43·6–96·4)
Eastern and central Europe, Middle East	90·5% (83·5–94·7)	90·4% (82·9–94·8)	90·7% (59·5–98·5)
South America	93·2% (86·1–96·8)	91·8% (82·0–96·5)	94·4% (80·2–98·6)
China	94·3% (91·0–96·4)	95·2% (91·8–97·3)	90·7% (83·7–94·9)
Southeast Asia	97·4% (90·2–99·3)	97·8% (89·0–99·6)	97·6% (85·1–99·7)
South Asia*	90·8% (83·6–95·1)	92·9% (85·1–96·7)	80·3% (62·8–90·7)
Africa†	82·7% (65·0–92·5)	83·2% (61·2–93·9)	86·5% (66·9–95·3)

Variables included in the model were age, self-reported hypertension or blood pressure ≥140/90 mm Hg, smoking, waist-to-hip ratio, diabetes or HbA_{1c} of ≥6·5%, physical activity, mAHEI, alcohol intake, psychosocial factors, apolipoproteins, and cardiac causes. PAR=population attributable risk. mAHEI=modified Alternative Healthy Eating Index. *Composite PAR including mAHEI as T3+T2 *vs* T1 for south Asia, consistent with direction of association. Composite PAR including mAHEI as T1+T2 *vs* T3 was 85·1% for all stroke, 88·1% for ischaemic stroke, and 78·2% for intracerebral haemorrhage. †Excluding psychosocial factors in Africa because of high prevalence in cases and controls resulting in implausible value for PAR.

Table 2: PAR for all risk factors by region (all stroke, ischaemic stroke, and intracerebral haemorrhage)

***Lancet* 2016; 388:761-75**

The Siren Study

Study design

- 15 sites in Sub-Saharan Africa
- Case-control study
- 2118 cases of stroke and 2118 age- and sex-matched stroke-free controls
- Composite PAF = 98.2 % (97.2-99.0)

***Lancet Global Health*. 2018;6:e436-e446.**

Risk factors

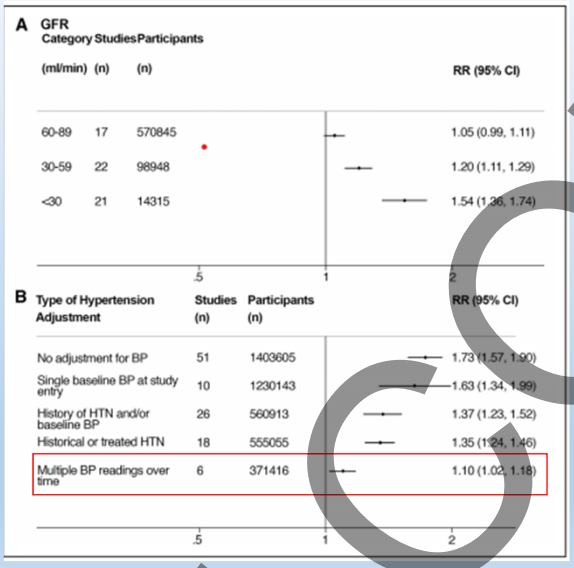
- Hypertension
- Dyslipidemia
- regular meat consumption
- elevated waist-to-hip ratio
- diabetes mellitus
- low green leafy vegetable
- Stress
- added salt at the table
- cardiac disease
- physical inactivity
- and current cigarette smoking

Does Chronic Kidney Disease Predict Stroke Risk Independent of Blood Pressure?

- A Systematic Review and Meta-Regression published in Stroke in 2019
- Eighty-five studies (3417098 participants; 72996 strokes) provided adequate data for meta-analysis of estimated glomerular filtration rate affecting risk of stroke.
- Conclusions: The association between chronic kidney disease and stroke appears to be highly dependent on the method of adjustment for hypertension. The apparently independent relationship between chronic kidney disease and stroke may be confounded by their shared association with long-term prior blood pressure

***Stroke*. 2019; 50:3085-3092**

Pooled Associations between CKD and Stroke Risk



***Stroke*. 2019; 50:3085-3092**

CLINICAL RESEARCH ARTICLE

Brain abnormalities in children and adolescents with chronic kidney disease

Mina Matsuda-Abedini[1], Kevin Fitzpatrick[2], Waverly R Harrell[3], Debbie S Gipson[4], Stephen R Hooper[5], Aysenil Belger[3], Ken Poskitt[6], Steven P Miller[7] and Bruce H Bjornson[2]

Pediatric Research 2018 Sep; 84:387-392

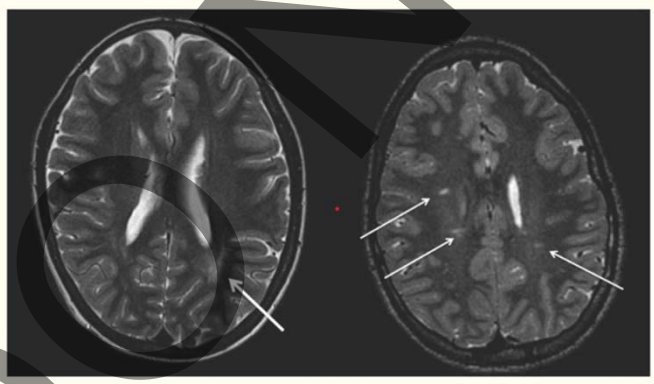


Figure 1

Focal and multifocal white matter injury was identified on conventional MRI in 6 children with CKD, including transplant (21%).

Table 2

Clinical characteristics of subjects with and without brain white matter injury

	White matter injury (N = 6)	No white matter injury (N = 23)
Age (Mean ±SD)	14.8 ± 2.8	14.3 ± 2.9
Male Sex (%)	4 (66%)	13 (57%)
CKD Stage (including transplant)		
Stage 2	1	7
Stage 3	2	8
Stage 4	1	3
Stage 5	2	5*
Duration of CKD (months), median (IQR)	62 (12, 120)	97 (57, 158)
Hypertension (%)	2 (33)	15 (65)
Hemoglobin, g/L (±SD)	124.7 ± 19.4	125.4 ± 14.0

Staging of CKD was based on the GFR categories outlined in the KDIGO 2012 clinical practice guideline for the evaluation and management of CKD, combining stage 3a and 3b [33].

*2/5 were on peritoneal dialysis

Conclusion

- CKD can increase the risk of having stroke but it is confounded by hypertension and diabetes
- GFR does not predict stroke incidence across the full range of renal function
- Controlling hypertension and diabetes in CKD patients decreases their risk for having strokes
- Composite sets of “standard risk factors” accounts for up to 90% of strokes.
- Hemorrhagic strokes seen in ESRD patients are more related to dialysis techniques rather than the ESRD itself

Rebuttal

Are we making the wrong argument?

- Does it matter if CKD is a Risk Factor or a Risk Marker for stroke?
- Of course CKD and EDRF is to be avoided at all cost
- We need to take Graeme Hankey's admonition to heart!
  - Prevention of a secondary stroke has relative low impact on overall stroke incidence
  - Identifying individuals at high risk for stroke has modest impact at most
  - The greatest number of strokes happen among individuals considered to be in lower risk pool because of the higher numbers of such individuals
  - eGFR declines as we age

Graeme Hankey, MBBS,MD, FRACP *Stroke.* 2020;51:719-728.

Some new thinking about the problem is needed!