Cognitive Function in Dialysis

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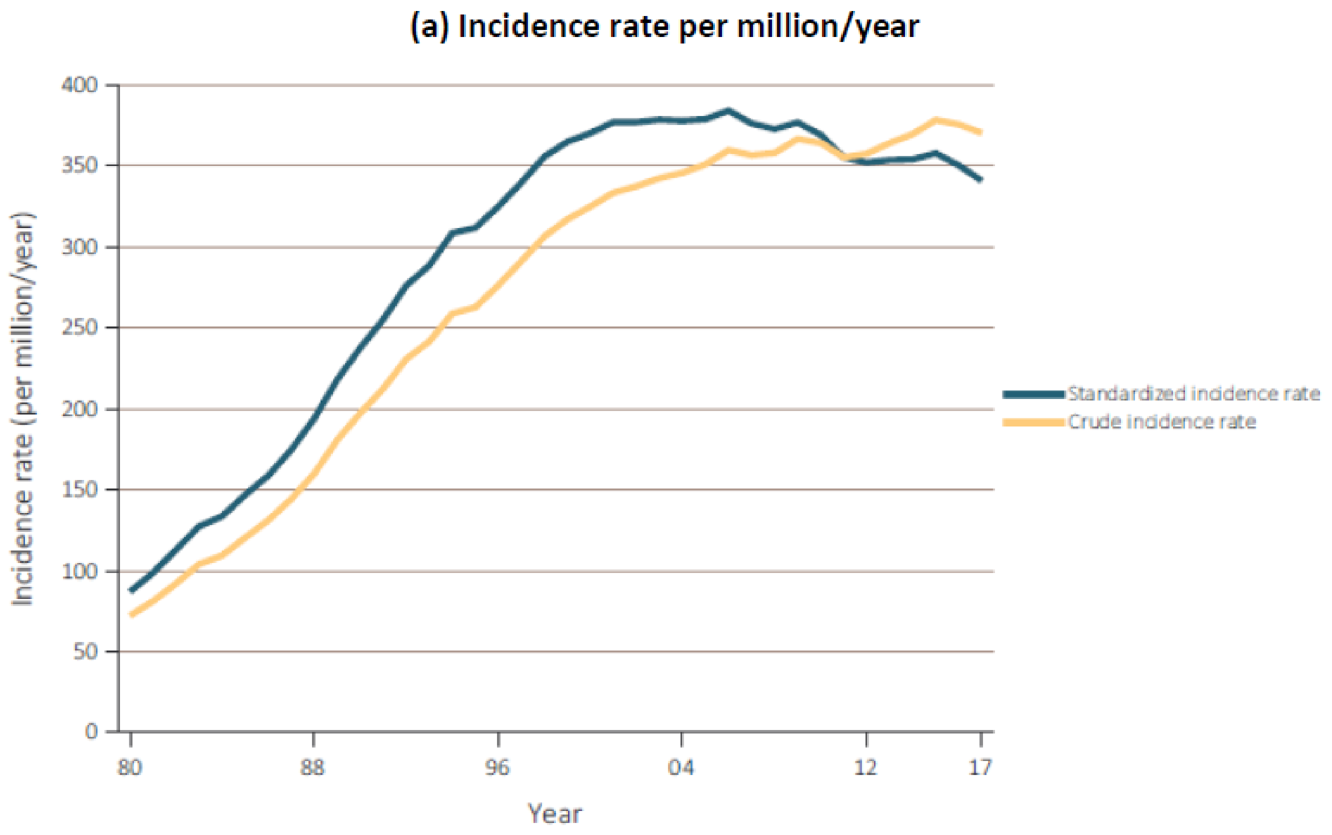
Outline

- Epidemiology of ESRD
- Cognitive burden in dialysis
- Mechanism for cognitive decline
- Comparison of HD with PD
- Summary

Growing dialysis population

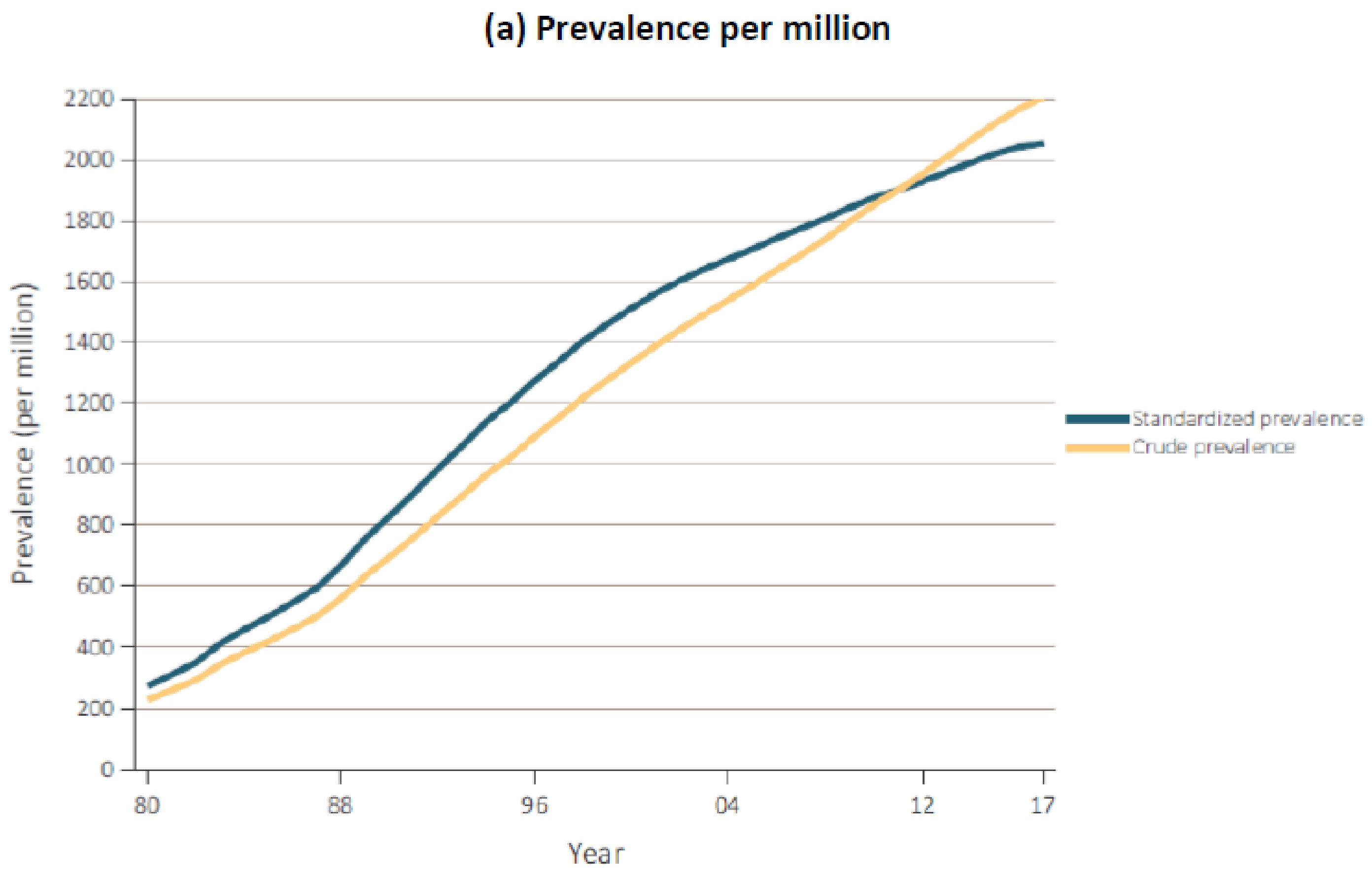
2019 USRDS ANNUAL DATA REPORT

Figure 9: Trends in the (a) crude and standardized incidence rates of ESRD, and (b) the annual percentage change in the standardized incidence rate of ESRD in the US population, 1980-2017

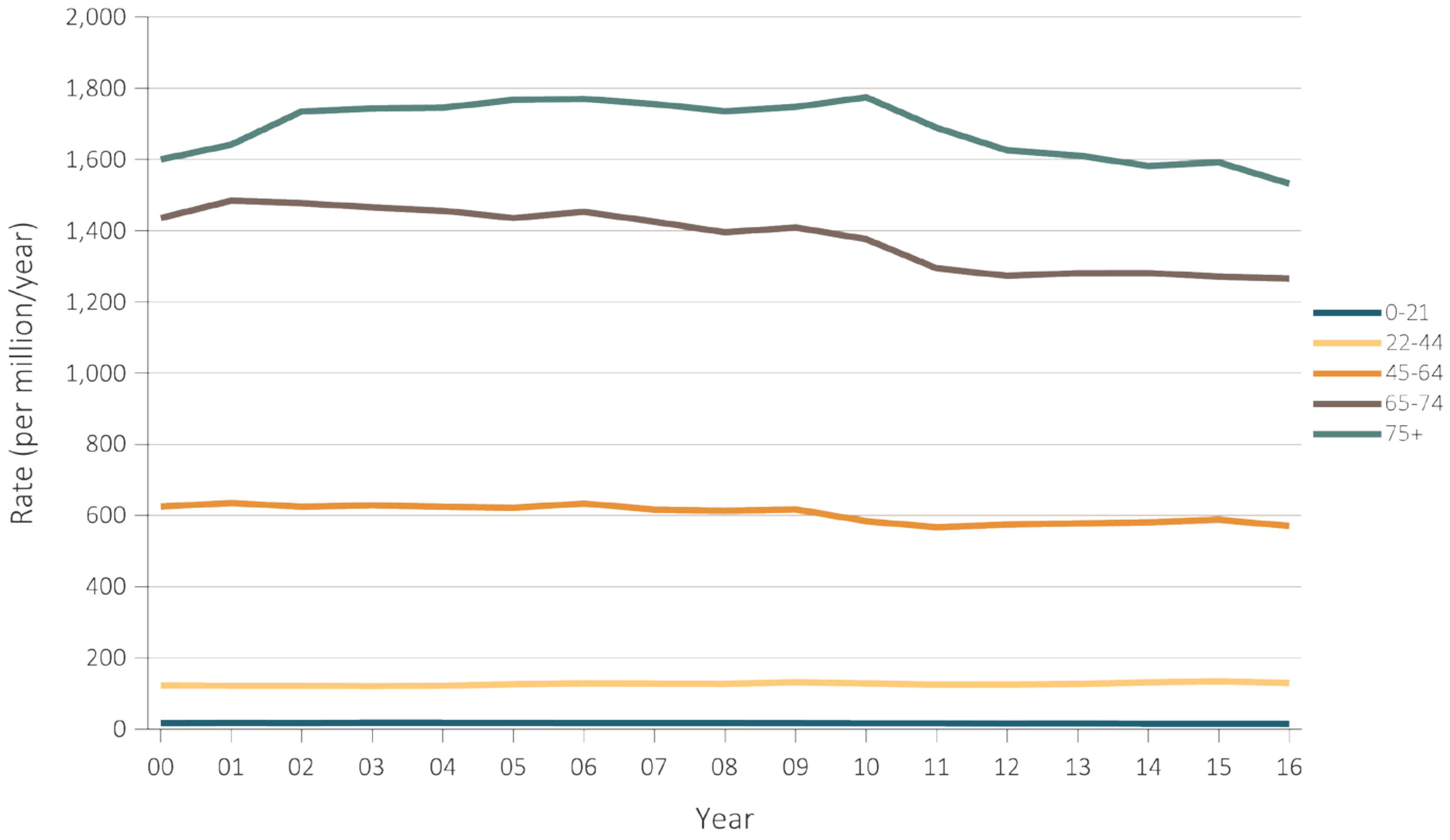


Growing dialysis population

Figure 11: Trends in the (a) crude and standardized prevalence of ESRD, and (b) annual percentage change in the standardized prevalence of ESRD, in the US population, 1980-2017



Aging dialysis population



Data Source: USRDS 2018 Annual data report. Special analyses, USRDS ESRD Database. Incidence standardized to the -sex-race distribution of the 2011 US population. Special analyses exclude unknown age, sex, and unknown/other race. Abbreviation: ESRD, end-stage renal disease.

Aging in dialysis and cognition

- The dialysis population is growing
- The highest growth is in older adults age 65+ years
- Older adults are already at risk for physical and mental decline
- Patients on dialysis can suffer from even greater cognitive impairment

High cognitive burden in hemodialysis

Table 4 Frequency of cognitive impairment in primary hemodialysis patient sample (n = 338)

Characteristic	n	None, n = 43	Mild, n = 47	Moderate, n = 122	Severe, n = 126
		Percent with cognitive impairment			
Age, y					
55–64	100	12.0	10.0	37.0	41.0
65–74	107	14.0	11.2	36.5	38.3
75–84	104	12.5	21.2	34.6	31.7
≥85	27	11.1	11.1	37.0	40.8

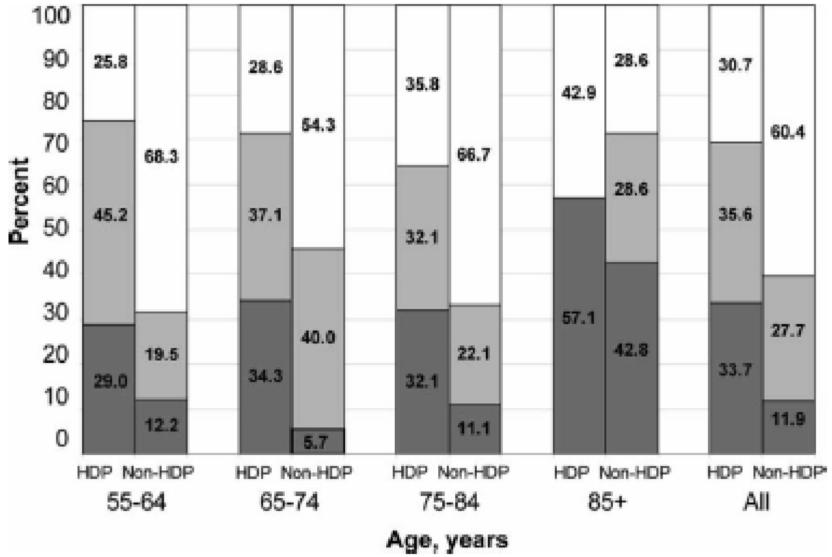


Figure 2. Frequency of cognitive impairment in hemodialysis patient (HDP) random sample (n = 101) and age-matched non-hemodialysis patient sample (n = 101). White = normal to mild, light gray = moderate, dark gray = severe cognitive impairment.

- Study evaluating cognitive function in over 300 HD patients in the Minneapolis area demonstrated over two-thirds had moderate to severe cognitive impairment
- Significantly more than the age-matched control group.

Murray AM et al, Neurology. 2006 Jul 25;67(2) 216-23

Changes in cerebral structure in HD

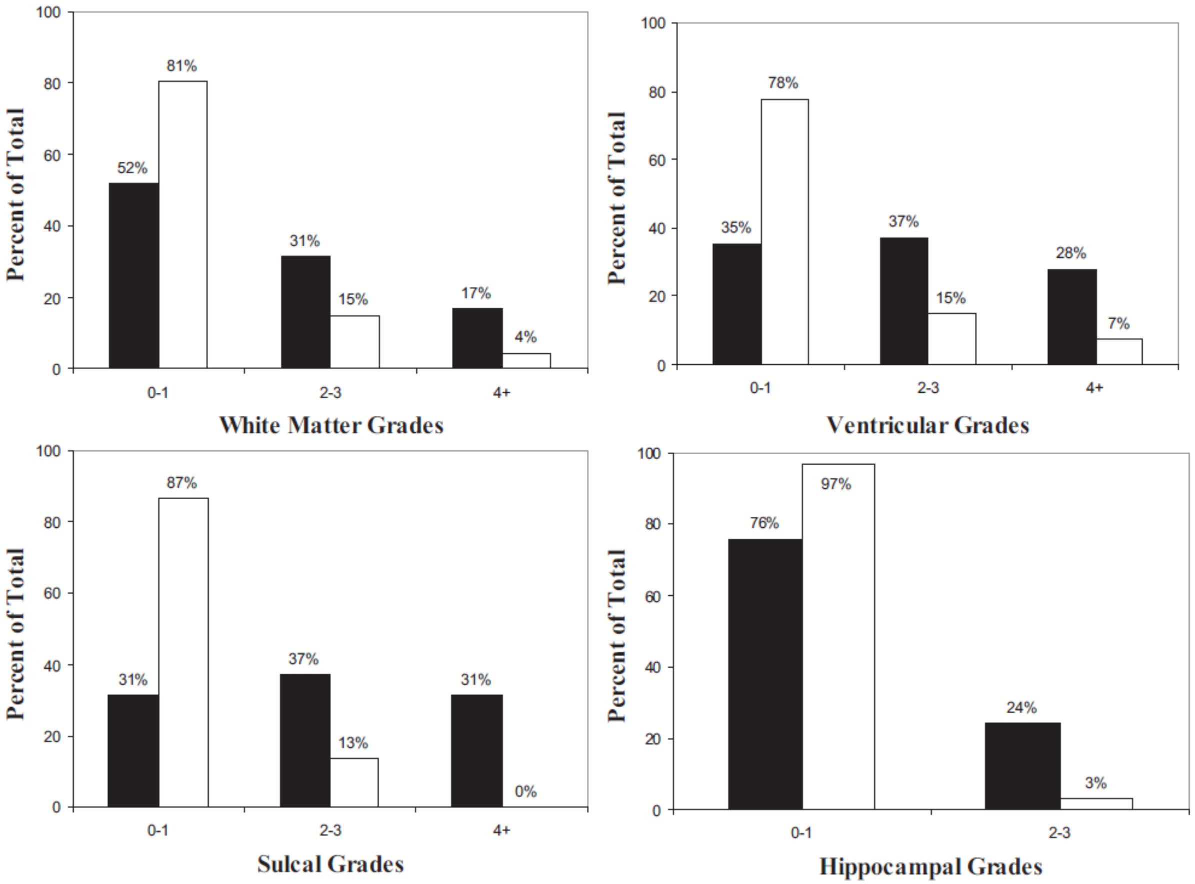


Figure 1. Distribution of white matter disease and atrophy grades. Black bars indicate hemodialysis group; white bars, control group without reported kidney disease.

- Increased infarcts
- Increased atrophy
- More white matter disease

Drew DA et al Am J Kidney Dis. 2013 Feb;61(2):271-8

Changes in cerebral structure in HD

Table 2
MRI findings in CHD patients and controls. WMH = white matter hyper-intensities.

	Patients (30)	Controls (30)	*p*
Cortical atrophy:			
none	15	20	
mild	13	6	
moderate-severe	2	4	n.s.
Ventricular atrophy:			
none	7	21	
mild	15	7	
moderate-severe	8	2	0.006
WMH:			
none	7	15	
punctate	13	12	
early confluent	10	3	0.01
Infarcts	5	0'	n.s
Lacunes	14	4	0.006

- 30 HD pts compared to 30 controls
  - matched with age, gender, HTN, cardiac disorder, DM
- MMSE score 22.9±4 vs 29.7±1.4
- 24 HD patients met criteria for dementia based on cognitive tests

Fazekas G et al, J Neurol Sci 1995 Dec; 134(1-2): 83-8

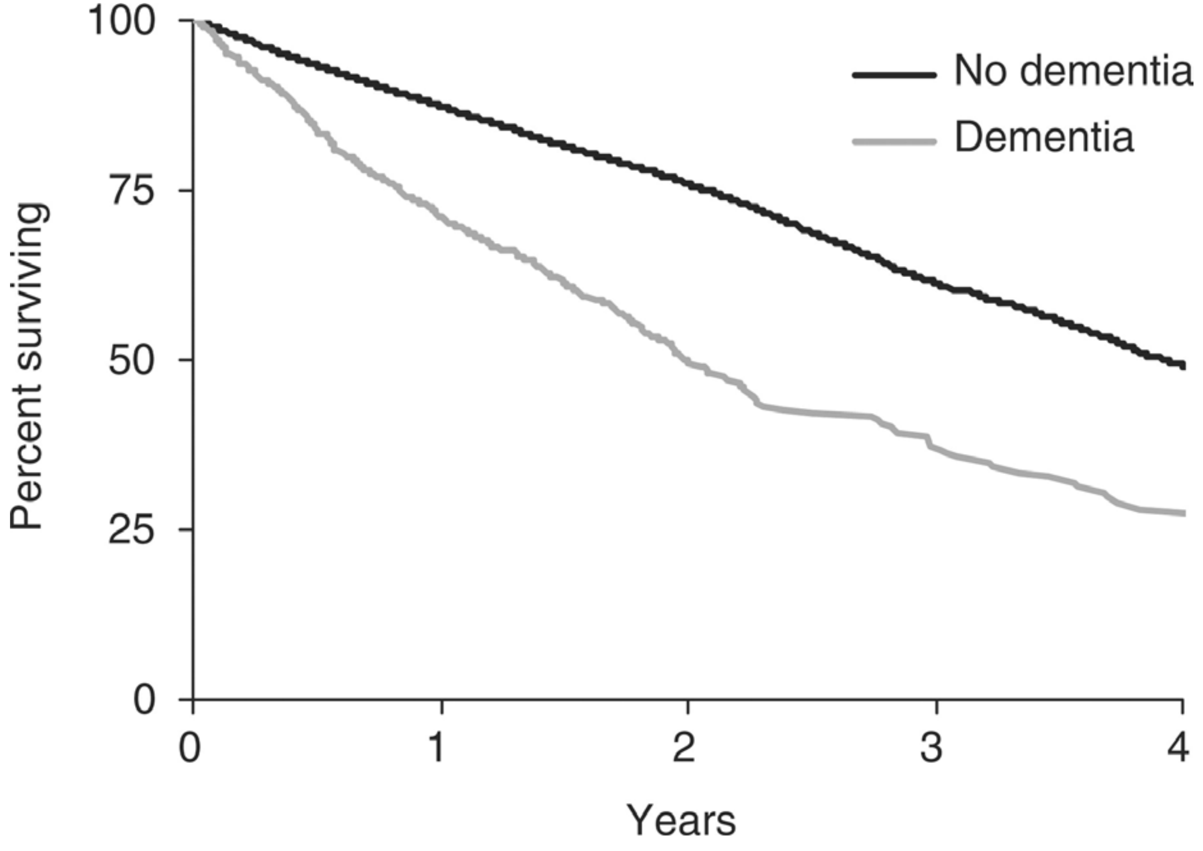
Importance of maintaining cognition

- Cognitive ability is important
  - for safety
  - for maintaining IADLs
  - for maintaining activity level
  - decreased risk of hospitalizations and institutionalization
  - decreased mortality
    - HD patient with dementia have half the two-year survival compared to non-demented counter parts
  - maintenance of quality of life

Outcome of cognitive impairment in HD

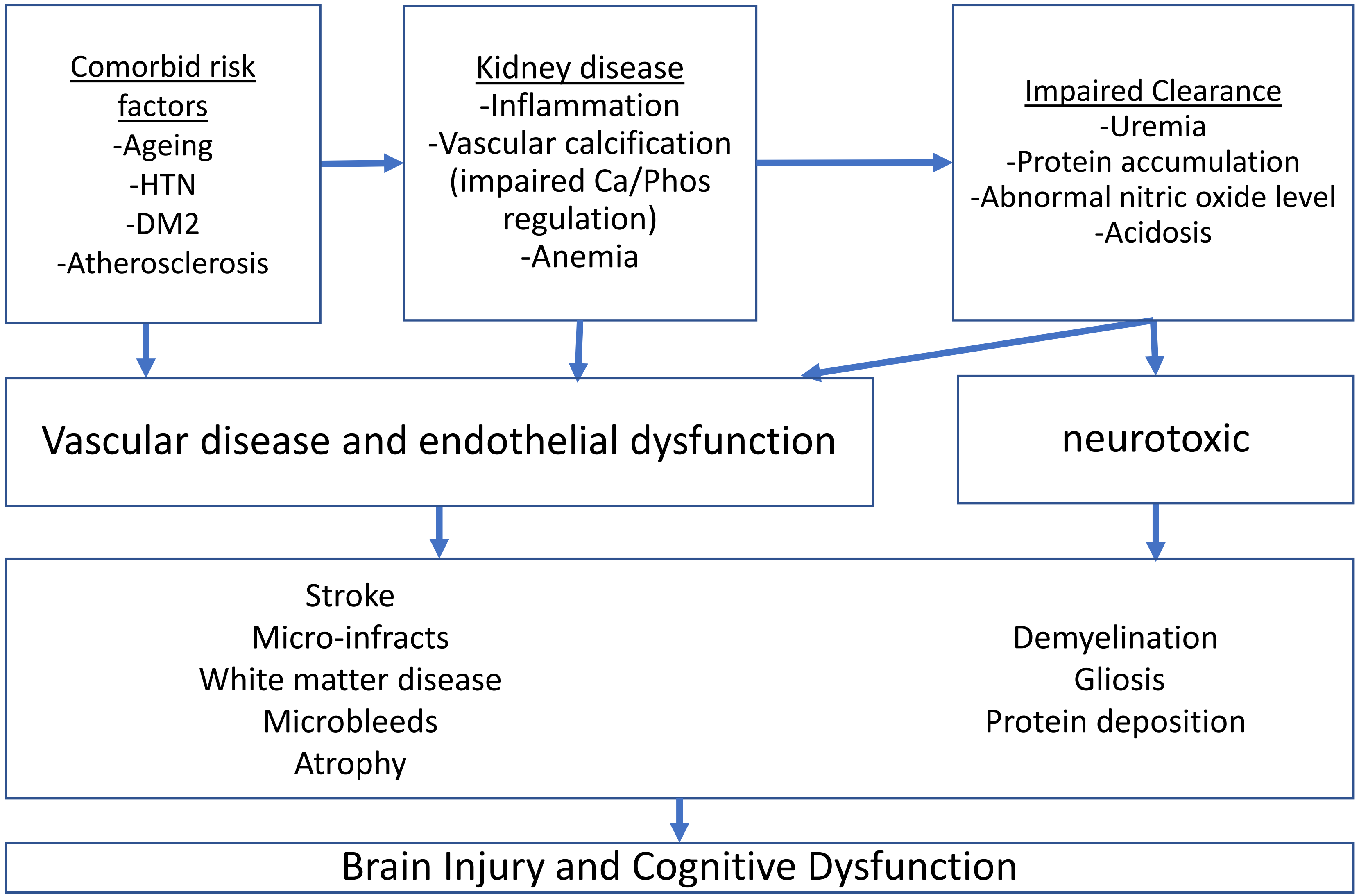
- Higher mortality
- Lower quality of life
- Increased hospitalizations and hospital days
- Worse nutritional state

Survival curve for all-cause mortality for patients with and without diagnosed dementia, adjusted to the mean 60 years

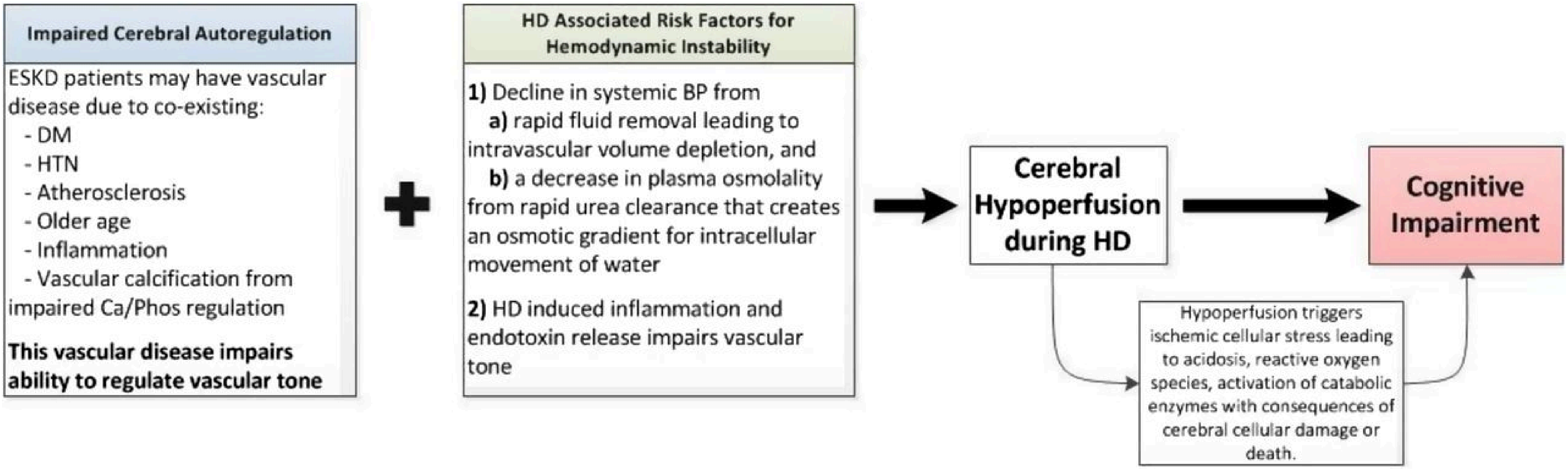


Kurella M, NDT, Volume 21, Issue 9, September 2006, Pages 2543–2548

Mechanism of cognitive decline



Addition of HD to risk factors



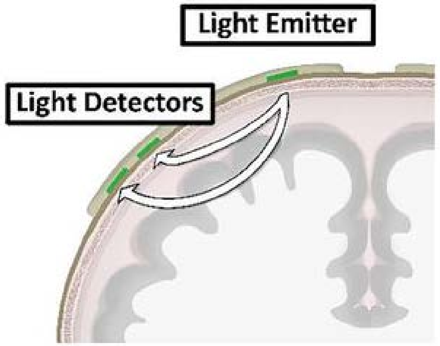
Wolfgram DF, J Am Soc Nephrol Nov 2019, 30 (11) 2052-2058

Intradialytic cerebral ischemic events

Table 3. Events temporally associated with a fall in MAP below absolute levels

MAP threshold, mmHg	Number of episodes (% of sessions with one or more episode)	Incidence new onset cerebral ischemia, % of episodes	Incidence of symptoms, % of episodes	Intervention rate, % of episodes
90	619 (69.7)	4.2	5.2	3.1
80	548 (57.6)	6.8	7.3	3.7
70	379 (40.6)	7.8	7.7	8.2
60	181 (24.0)	10.8	4.4	8.8
50	57 (11.1)	29.8	21.1	17.5
40	17 (3.5)	35.3	23.5	17.7

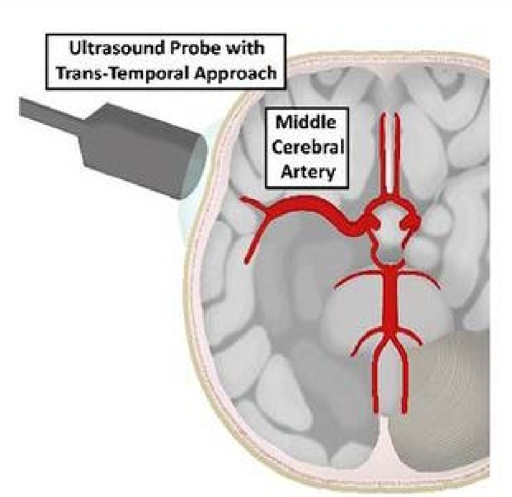
Each episode refers to a sustained drop (2 minutes minimum) below the specified MAP threshold. Note that one dialysis session could feature repeated episodes. Sessions where the starting MAP was below the specified threshold were excluded.

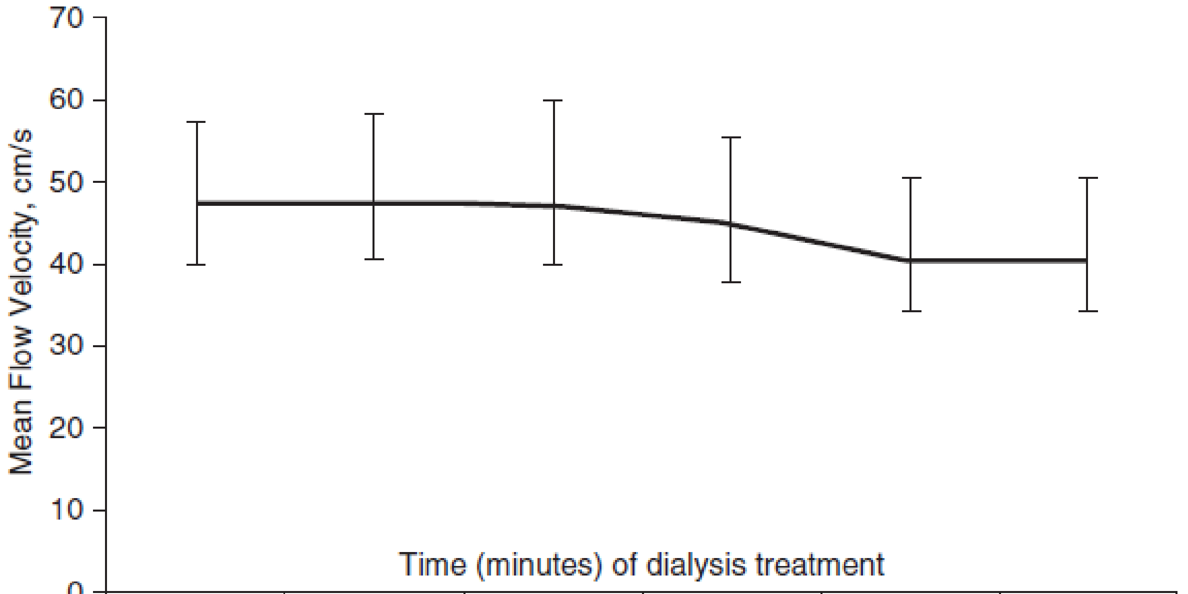


As the mean arterial BP decreased during dialysis the number of cerebral ischemic episodes increased, some asymptomatic

MacEwan et al, J Am Soc Nephrol August 2017, 28 (8) 2122-2132

Intradialytic reduction in cerebral blood flow



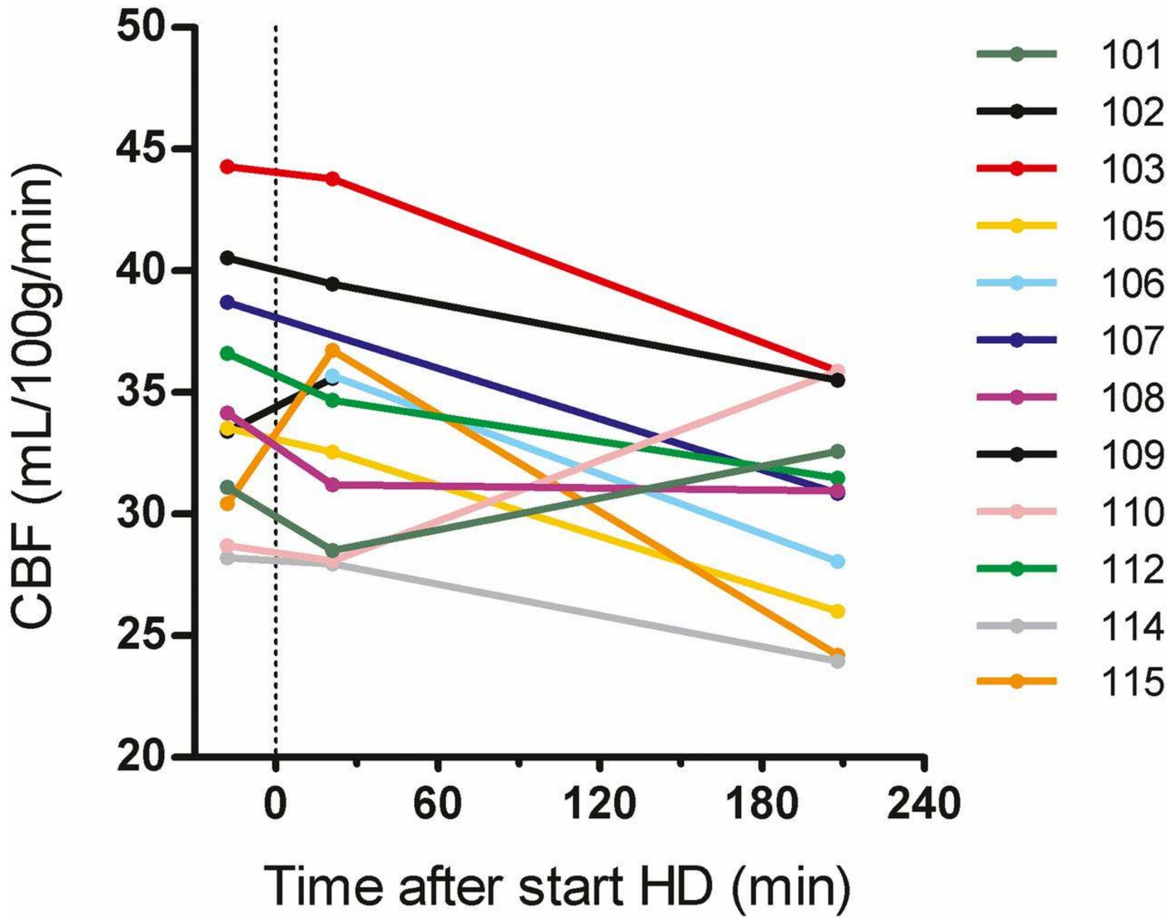


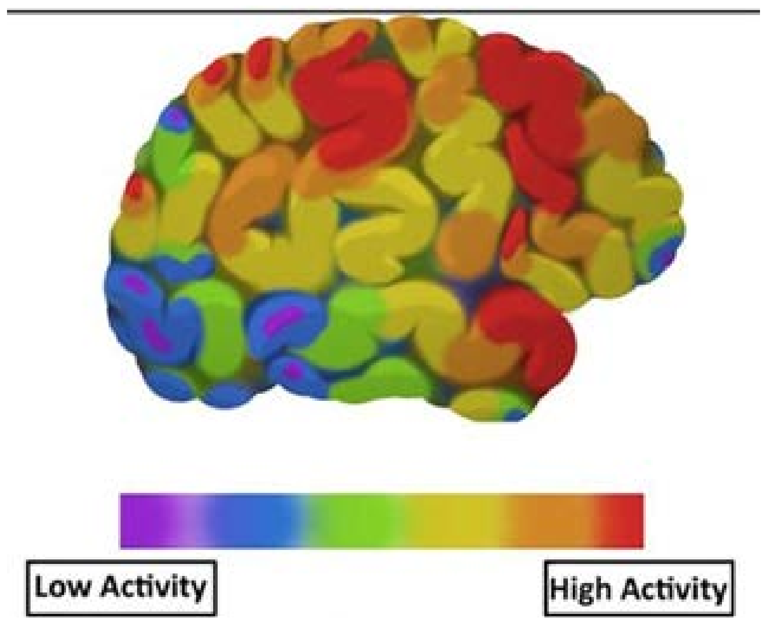
	–15	15	30	90	180	+30
Median MFV, cm/s	47.38	47.38	47.00	45.00	40.25	40.75

Figure 1. Haemodialysis related decline in cerebral mean flow velocity The change in MFV during dialysis session (*n*=82), is presented as a median value and IQR (error bars). TCD recordings were taken prior, during, and after completion of dialysis, demonstrating a significant decline in MFV after dialysis; weighted GEE *P*<0.001.

Findlay M et al, J Am Soc Nephrol, January 2019 30 (1) 147-158

Intradialytic reduction in cerebral blood flow





Polinder-Bos et al, J Am Soc Nephrol, April 2018, 29 (4) 1317-1325

Mechanisms of cognitive decline

- Renal associated causes
  - Anemia
  - Electrolyte disturbances
  - Uremia
- Comorbid associated causes
  - DM2
  - HTN
- Dialysis associated causes
  - Hemodynamic leading to changes in cerebral blood flow
    - Compare to peritoneal dialysis

Peritoneal Dialysis

- Daily dialysis that avoid rapid swings in blood pressure, electrolytes and osmolarity
- Demonstrated to preserve residual renal function compared to HD
  - Brain and kidney have similar high flow and autoregulation
- Improved quality of life
- Allows for more daytime activities, helping preserve function

Dementia onset in HD vs PD

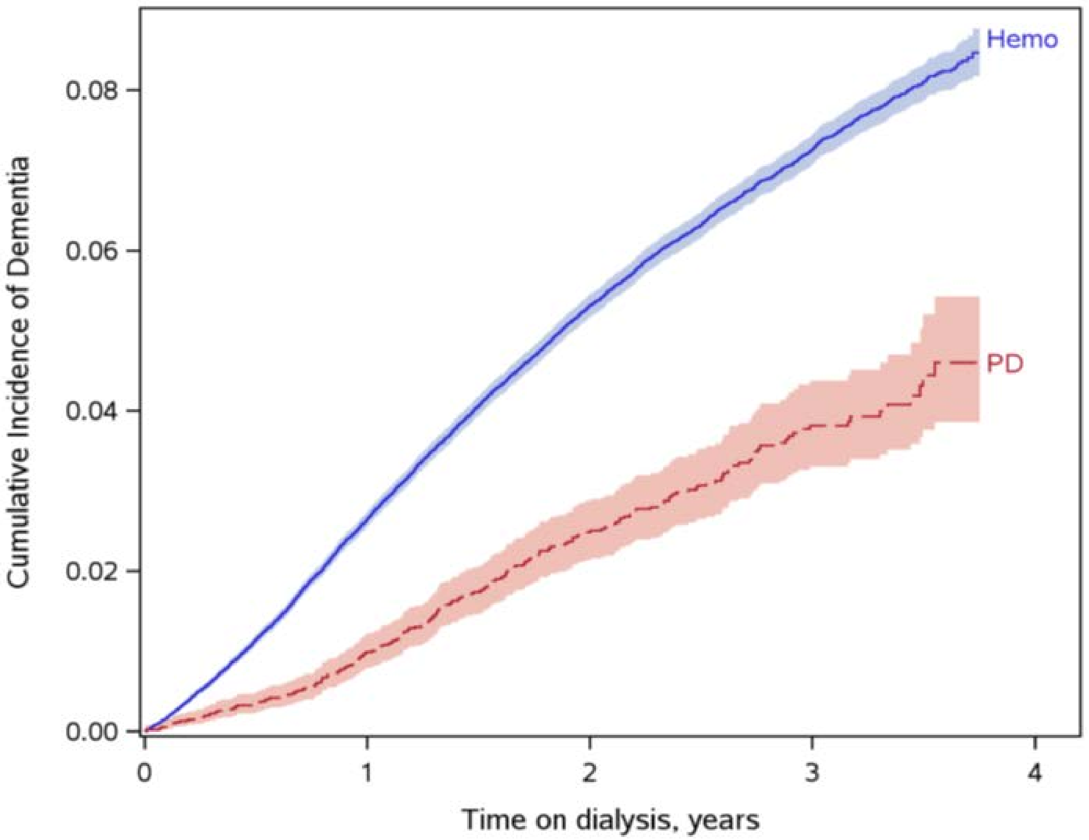


TABLE 5
Dementia Risk in Each Analytical Model

Groups	Analysis	HR	95% CI
Initial PD vs initial HD	Unadjusted (Model 1)	0.46	0.41–0.53
Initial PD vs initial HD	Adjusted for demographics (Model 2)	0.64	0.56–0.73
Initial PD vs initial HD	Adjusted for all baseline predictors (Model 3)	0.75	0.66–0.86
Initial PD vs initial HD	Stratified propensity score	0.76	0.66–0.86
Initial PD vs initial HD	Matched propensity score	0.74	0.64–0.86
Initial PD vs initial HD	Matched propensity score, >67 years	0.76	0.64–0.90

HR = hazard ratio; CI = confidence interval; PD = peritoneal dialysis; HD = hemodialysis.
The hazard ratio for risk of incident dementia is shown comparing patients who started on PD with those who started on HD. Model 1 is unadjusted. Model 2 is adjusted for baseline demographics: age, race, gender, and primary cause of renal disease. Model 3 is adjusted for the variables from Medical Evidence Form 2728 listed under methods. Propensity scores are based on variables from Medical Evidence Form 2728 and adjusted for baseline demographics.

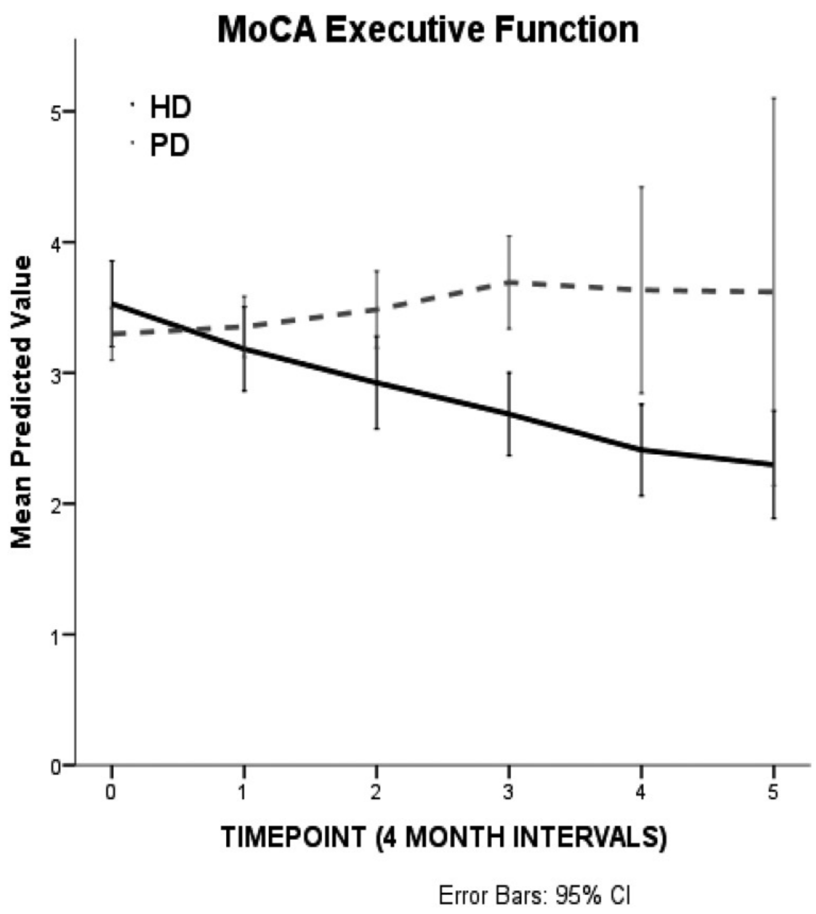
Wolfgram D, Perit Dial Int. 2015 Mar-Apr; 35 (2) 189-98

Cognitive changes in HD vs PD

Table 3. Comparison of cognitive test results at baseline and change over 1 year between those on HD and those on PD

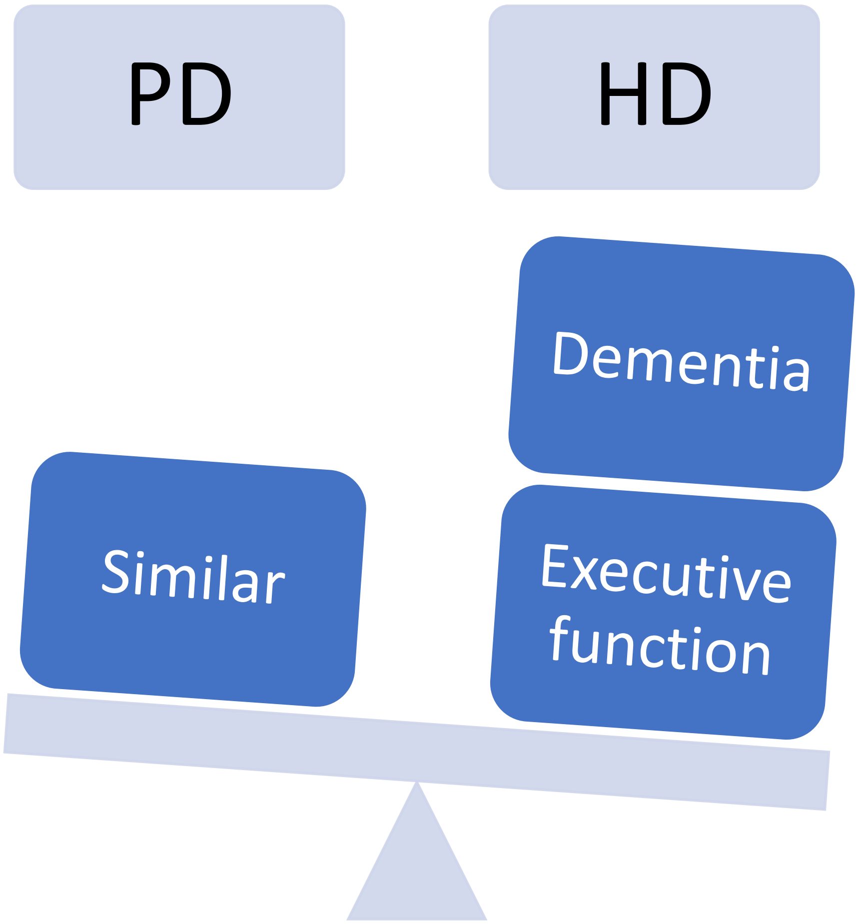
	HD patients (median, IQR)	PD patients (median, IQR)	p value Mann-Whitney U
Digit symbol			
Baseline	36.00 (15.0)	40.00 (18.0)	0.16
Change at 1 year	1.00 (8.5)	–0.50 (8.0)	0.34
Trails (B-A)			
Baseline	41.30 (45.15)	44.00 (39.4)	0.79
Change at 1 year	–5.00 (28.3)	2.80 (24.7)	0.30
Digit span backwards			
Baseline	4.00 (1.0)	4.00 (2.0)	0.40
Change at 1 year	0.00 (2.0)	0.00 (2.0)	0.91
FAS verbal fluency			
Baseline	36.00 (16.0)	32.00 (14.0)	0.65
Change at 1 year	1.00 (9.0)	–1.00 (7.0)	0.27

George et al, Nephron Clin Pract 2013; 123:1-6



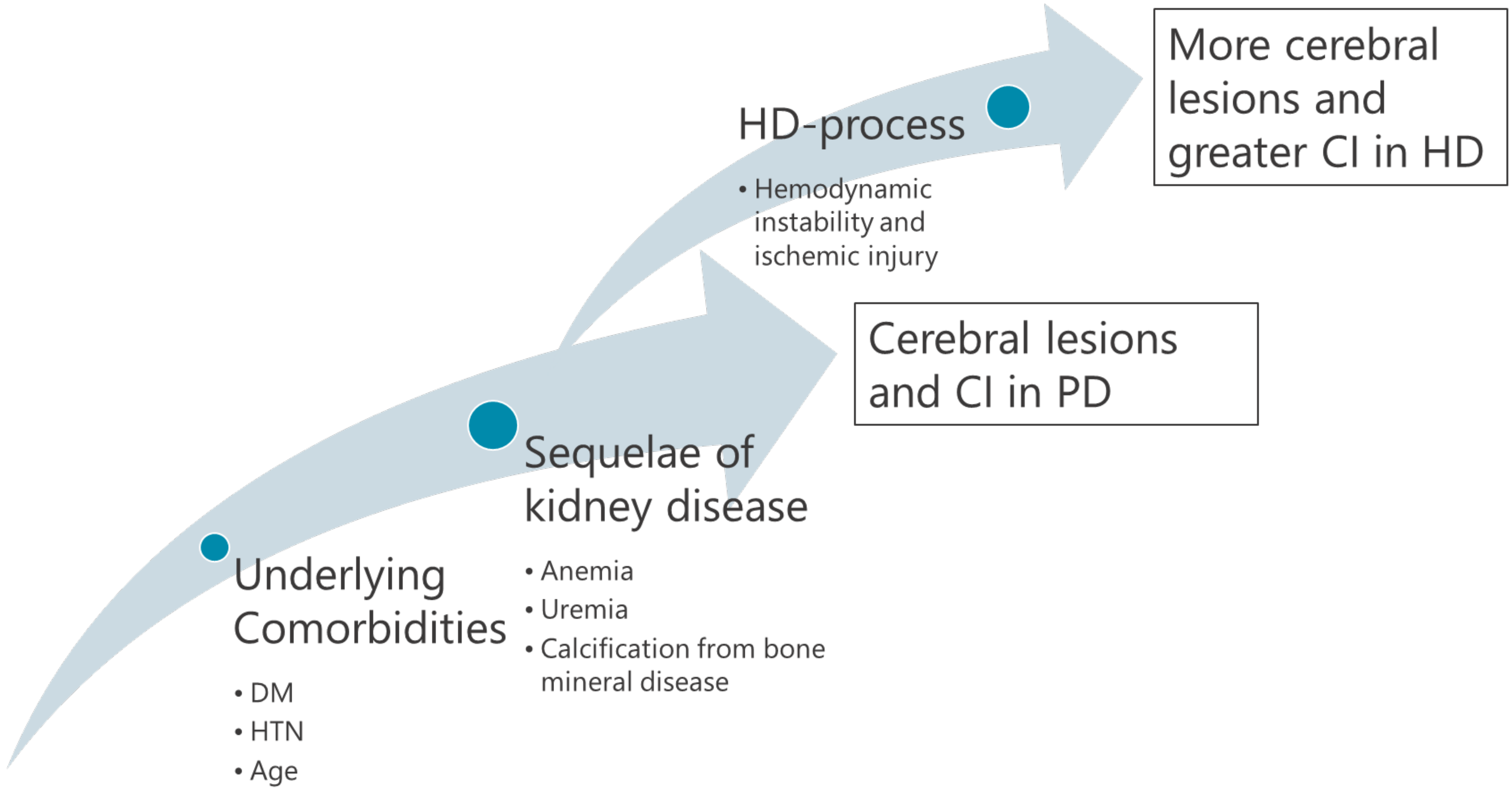
Isaysere et al, Clin Kidney J 2017; 10: 89-94

Summary of cognitive changes in HD vs PD



- Not clear cut, but overall more in favor of greater cognitive decline and dementia risk in HD
- Difficult to compare these two patient populations with varying degree of comorbidities

Potential model

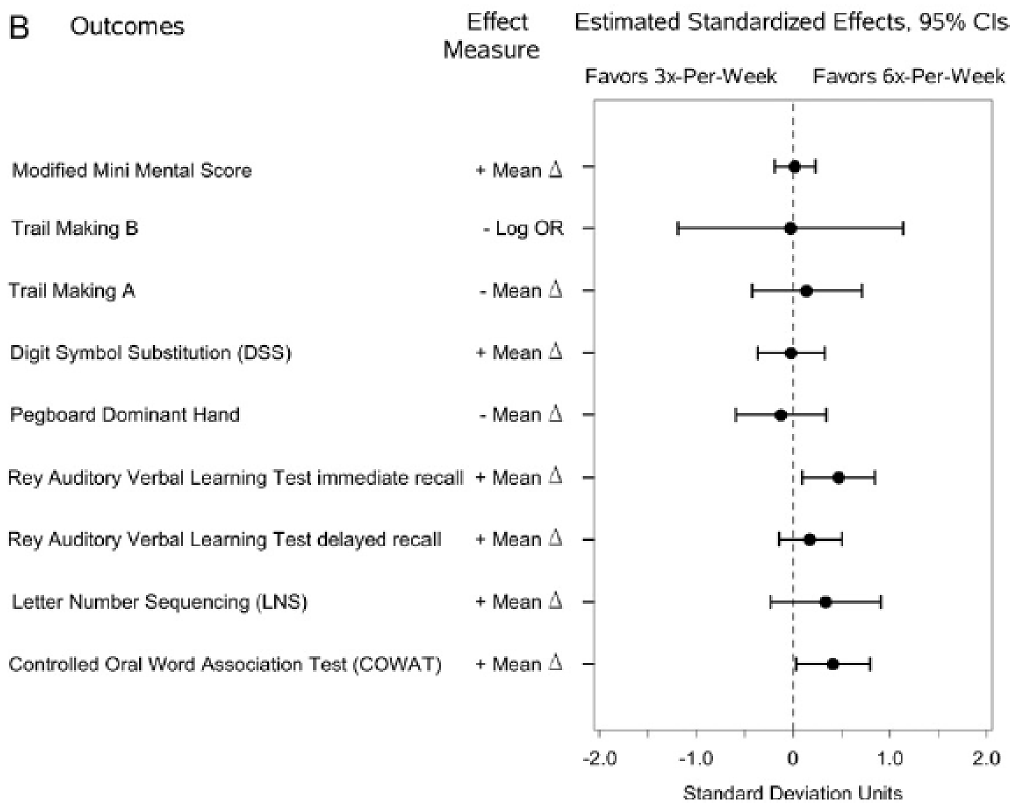


Prevention

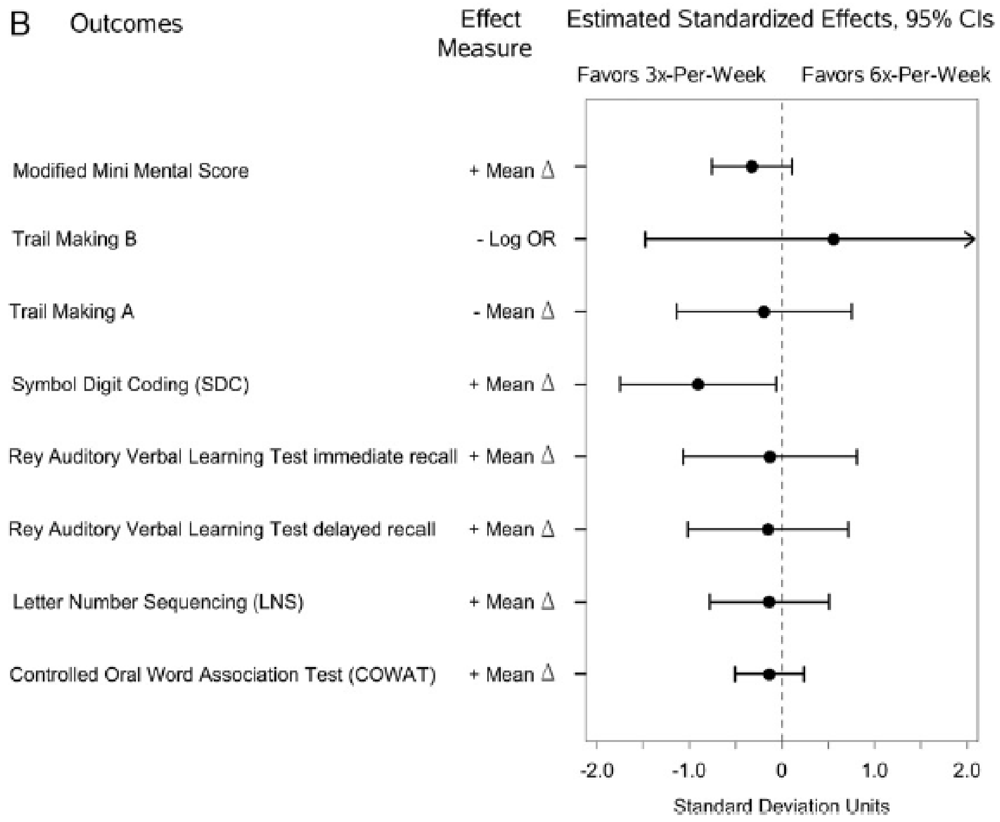
- Can HD-ischemic injury be mitigated
  - Dialysate cooling demonstrated to reduce BP fluctuations and reduce cerebral changes
  - Change to favoring other dialysis modalities
    - PD
    - Nocturnal (extended 8-hour HD session)
    - Home hemodialysis (more frequent session)
- Identify the patients who would be most at risk
  - Diabetics, vascular disease, older age
  - Pre-screen to measure cerebrovascular function
  - Use information in treatment recommendations

Frequent Daily and Nocturnal HD on Cognition

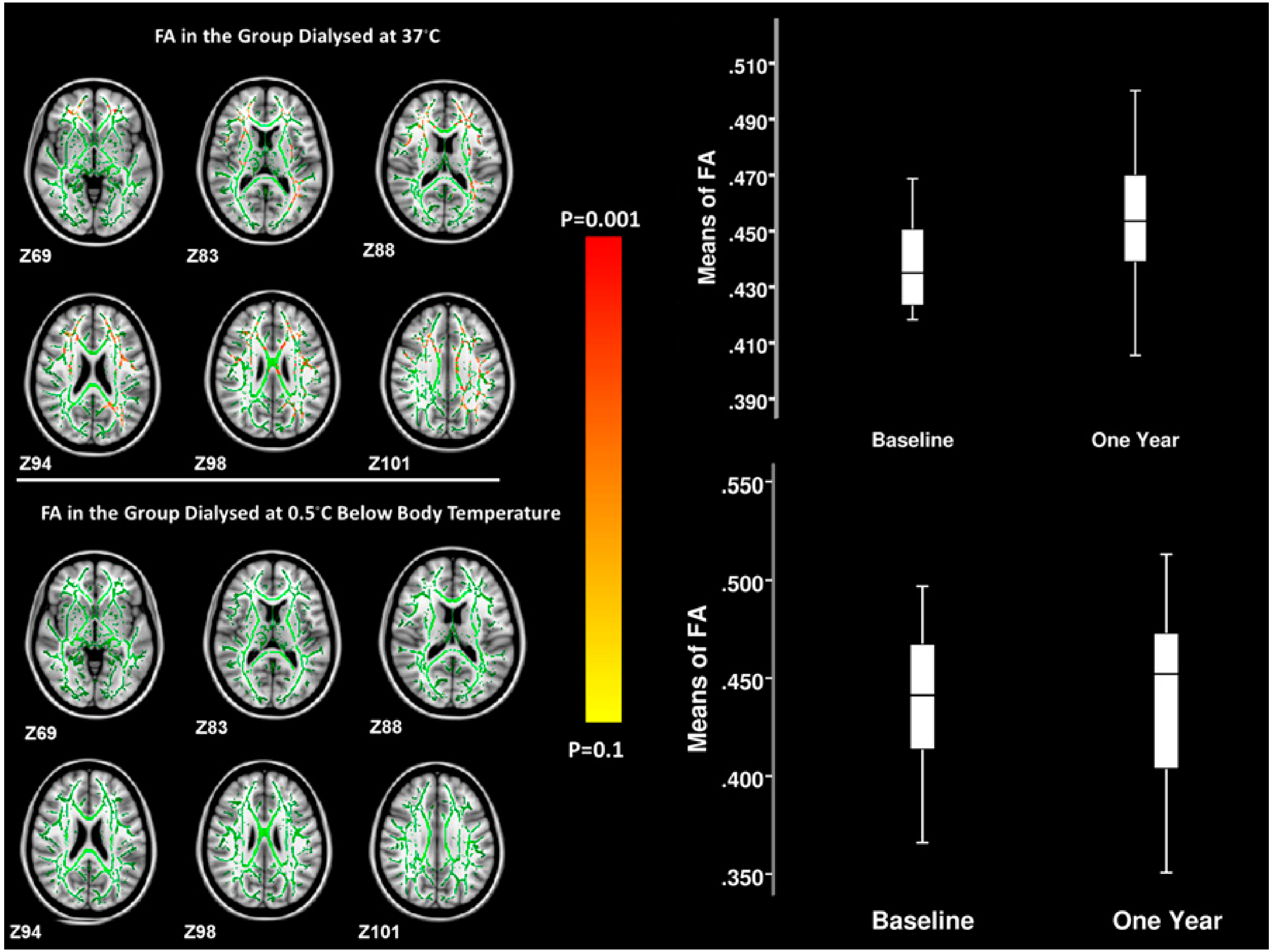
Conventional vs 6x per week daily HD



Conventional vs 6x per week nocturnal HD



Dialysate cooling



Prevention

- Need more info on nocturnal and frequent HD
- Need more info on dialysate cooling
- Need more info on PD
- Identify the patients who would be most at risk
  - Diabetics, vascular disease, older age
  - Pre-screen to measure cerebrovascular function
  - Use information in treatment recommendations

Caring for those with cognitive impairment

- Try to simplify medication regimens
  - Remove meds that can lead to more confusion (anti-histamines, anti-cholinergics)
  - Periodically check to see if meds help, stop if not helping
- Include caregivers in discussions on diet and importance of medications
  - Providing written instructions/handouts for patient to take home
- Consider dangers if medications not taken correctly
  - Risk of side effects by double dosing
- Treat the patient's symptoms over lab numbers
- Consider quality of life in changes to dialysis prescriptions

Summary

- Cognitive impairment is common and severe in dialysis patients
- Cerebral structural changes consistent with ischemic injury are common in HD patients
- Hemodialysis patients may have a higher risk of dementia and cognitive decline compared to peritoneal dialysis
- HD risk may be associated with reduction in cerebral perfusion during HD
- Pre-determining patients at highest risk for cerebral hypo-perfusion may be useful in dialysis decision making and counseling
- Increasing options with other dialysis modalities may help reduce cognitive decline

Questions?