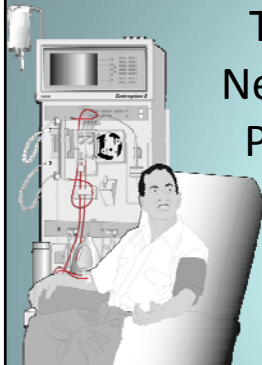


Race and Gender and Hemodialysis Treatment Outcomes: Do We Need to Individualize Treatment Prescriptions and Guidelines?



ASN 2010

Keith C. Norris, MD, FASN

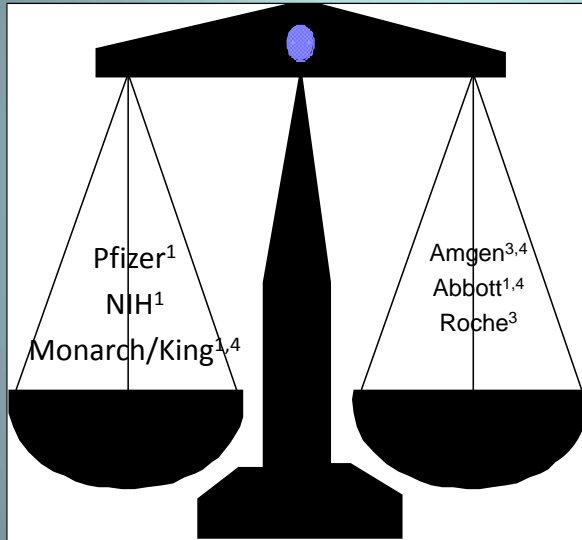
Executive VP for Research - Charles Drew University

Assistant Dean for Translational Science - UCLA

Objectives

- Controversies Clinical ESRD Outcomes by Race & Gender
 - Understand the key modifiers of Clinical ESRD Outcomes by Gender
 - Understand the key modifiers of Clinical ESRD Outcomes by Race
- Review Data for Relation of Mortality to Treatment Prescriptions for Dialysis Dose by Race and Gender
- Future Considerations

Potential Conflicts of Interest*

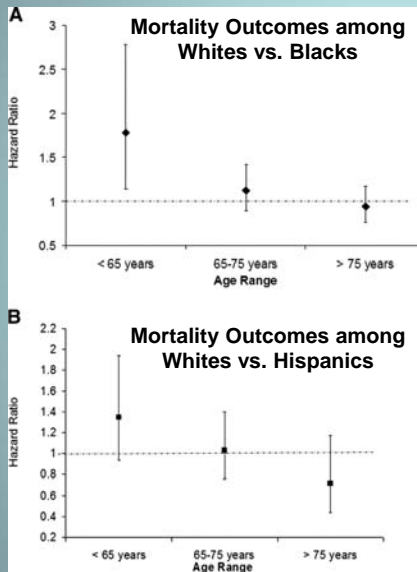


*Activities within the last year

Grants: 1
Honoraria: 2
Consulting: 3
Advisory Boards: 4
Speaker Bureau: 5
Financial Ownership: 6

CKD/ESRD Mortality Outcomes by Race & Gender

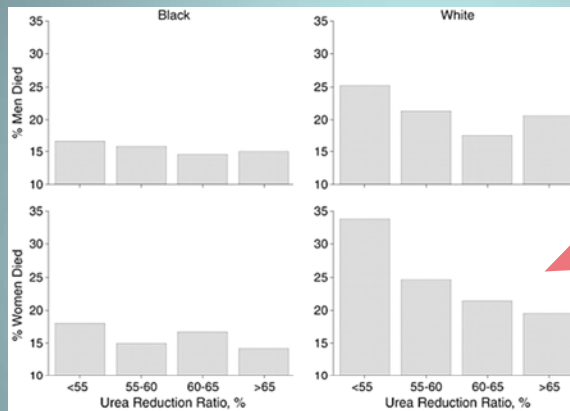
Mortality Outcomes among Individuals With CKD Enrolled In the NHANES III



No significant CKD/pre-ESRD mortality differences by race ethnicity overall but differs or trend in younger groups

Mehrotra, R. et al. J Am Soc Nephrol 2008;19:1403-1410

ESRD Death Rates For Each Race By Sex Cluster Stratified By Urea Reduction Ratio



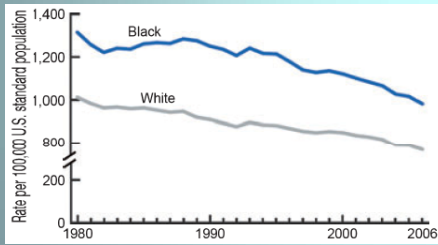
Lower mortality rates for Blacks. No influence of URR on mortality for Black Men.

Cluster	Linear χ^2	P Value	Residual χ^2	P Value
Black Men	0.99	.32	0.76	.68
Black Women	3.81	.05	3.12	.21
White Men	6.09	.01	12.34	.002
White Women	29.46	<.001	4.30	.12

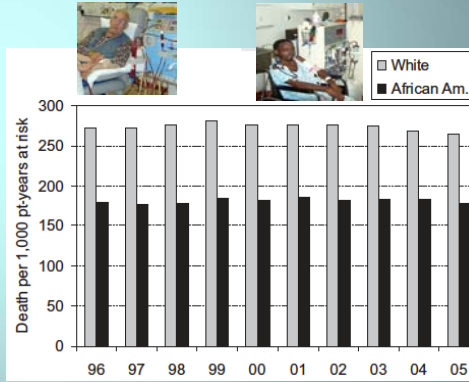
Owen, W. F. et al. JAMA 1998;280:1764-1768.

Black Dialysis Patients have Lower Mortality than Whites in Most Studies Despite Higher Mortality in General Population

Mortality Rate - African American & Whites (US Census Bureau Vital Statistics, 2010).

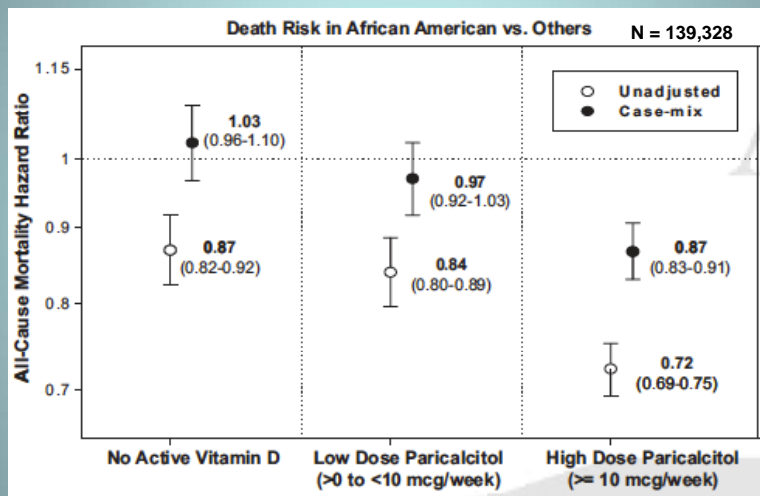


Crude Annual Mortality US Dialysis Patients: African Americans vs. Whites (USRDS 2009)



Kalantar-Zadeh K, Golan E, Shohat T; Streja F, Norris KC, and Kopple JD. Survival Disparities within American and Israeli Dialysis Populations: Learning from Similarities and Distinctions across Race and Ethnicity. *Sem Dial* (in press)

ESRD Death Risk in African American vs. Others

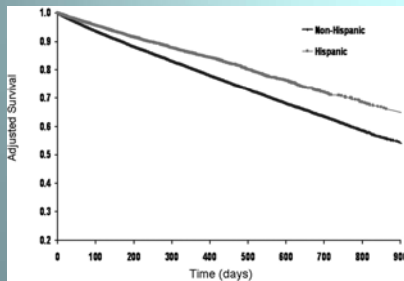


Kalantar-Zadeh K, Miller JE, Kovesdy CP, Mehrotra R, Lukowski LR, Streja E, Ricks J, Jing J, Nissenson AR, Greenland S, Norris KC. Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D and survival in hemodialysis patients. *J Bone Miner Res*. 2010 Jul 7 [Epub ahead of print].

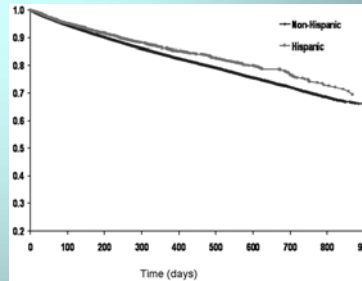
Mortality risks of Hispanic and non-Hispanic ESRD patients who were initiated on dialysis in the United States

Diabetes ^b	Ethnic Group	No. of Patients	% Deaths	Deaths per 100 Person-Years	Hazard Ratio ^c Unadjusted	95% CI	P ^c	Hazard Ratio ^c Adjusted ^d	95% CI	P ^c
No (n = 49,867)	Non-Hispanic	46,273	23.9	22.7	1.00	Reference		1.00	Reference	
	Hispanic	3,594	16.9	14.7	0.65	0.60-0.71	<0.0001	0.83	0.77-0.91	<0.0001
Yes (n = 50,751)	Non-Hispanic	43,952	27	26	1.00	Reference		1.00	Reference	
	Hispanic	6,799	21.3	19.2	0.74	0.70-0.78	<0.0001	0.70	0.66-0.74	<0.0001

Adjusted Cox survival curves for new diabetic ESRD patients by Hispanic Ethnicity

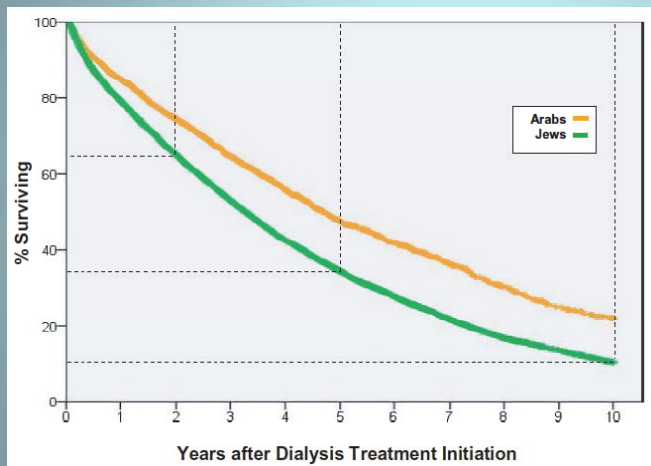


Adjusted Cox survival curves for new nondiabetic ESRD patients by Hispanic ethnicity



Murthy, B. V.R. et al. Survival Advantage of Hispanic Patients Initiating Dialysis in the United States Is Modified by Race. J Am Soc Nephrol 2005;16:782-790

Kaplan–Meier survival graphs in Israeli dialysis patients between Arabs and Jews (Israeli Renal Registry November 2009).

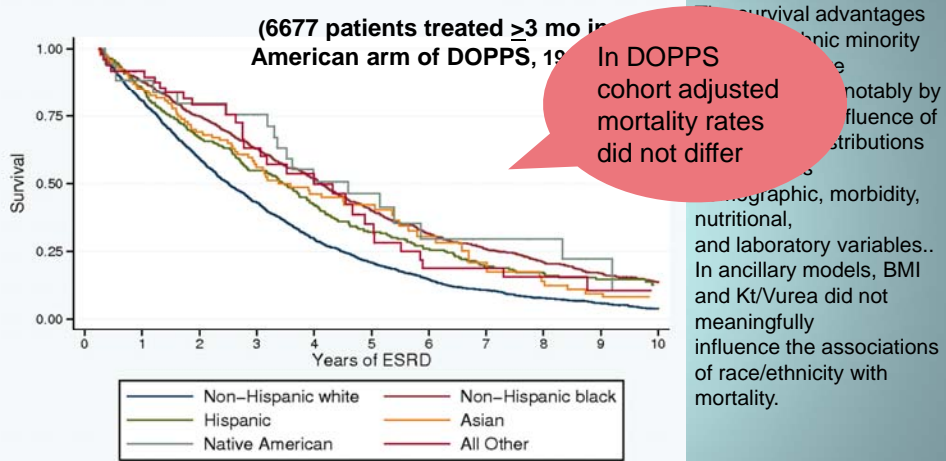


Survival disparity between Arab and Jewish dialysis patients in Israel; 85% of Arab and 79% of Jewish maintenance dialysis patients survived at least 1 year.

Life expectancy of Israeli Arabs without CKD, is 3–4 years lower than that of the Jewish population

Kalantar-Zadeh K, Golan E, Shohat T, Streja F, Norris KC, and Kopple JD. Survival Disparities within American and Israeli Dialysis Populations: Learning from Similarities and Distinctions across Race and Ethnicity. Sem Dial (in press)

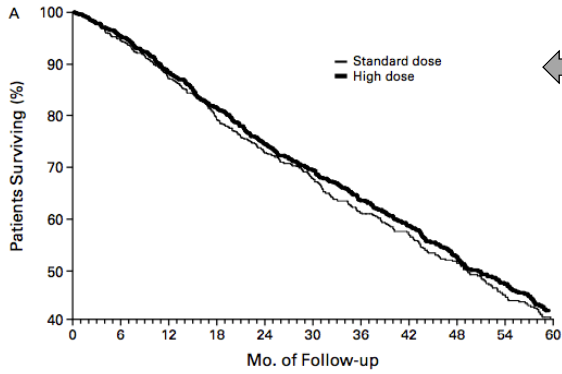
Kaplan-Meier Unadjusted Survivor Function for ESRD Patients by Race/Ethnicity



Robinson, B. M. et al. Revisiting Survival Differences by Race and Ethnicity among Hemodialysis Patients: The Dialysis Outcomes and Practice Patterns Study. *J Am Soc Nephrol* 2006;17:2910-2918

Dialysis Dose, Mortality, Race & Gender

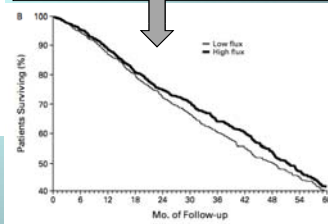
Survival Curves for Standard & High-Dose HD Treatment Groups (equilibrated Kt/V of 1.05 vs. 1.45)



No. AT Risk	0	6	12	18	24	30	36	42	48	54	60
Standard dose	854	759	630	524	451	382	315	253	197	149	
High dose	857	753	637	538	470	399	327	266	219	166	

After adjustment for the base-line factors, mortality in the high-dose group was 4 percent lower (95% CI, -10 to 16; P=0.53) than that in the standard-dose group (Panel A).

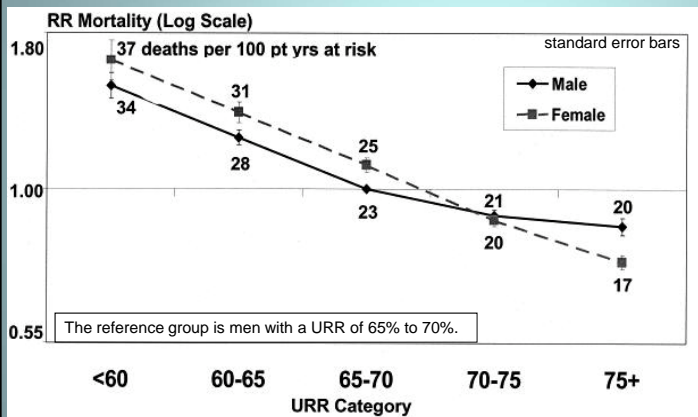
Mortality in the high-flux group was 8 percent lower (95% CI, -5 to 19; P=0.23) than that in the low-flux group (Panel B).



No. AT Risk	0	6	12	18	24	30	36	42	48	54	60
Low Flux	851	750	632	525	446	383	307	250	203	149	
High Flux	860	761	635	537	473	399	335	269	212	160	

Eknoyan, G. et al. N Engl J Med 2002;347:2010-2019

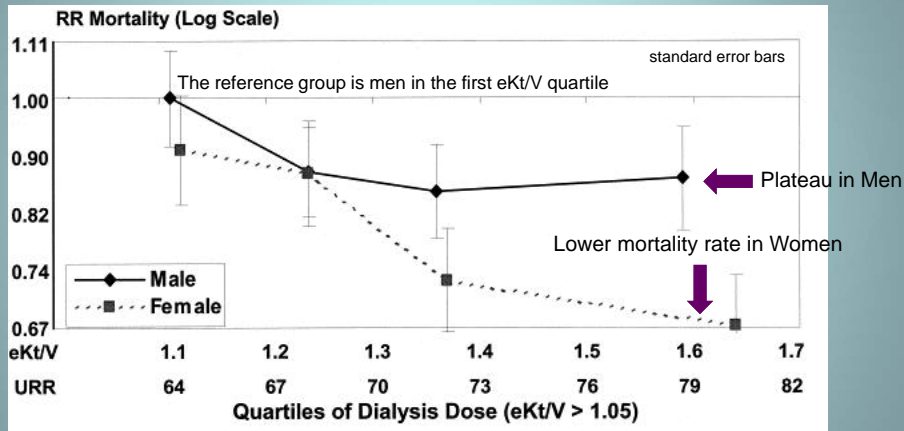
Adjusted Mortality in ESRD Patients by Sex and Dialysis Dose



Data from 74,120 US HD patients were classified into 1 of 5 categories of urea reduction ratio (URR), and their relative risk (RR) for mortality was evaluated by using Cox proportional hazards models. Similar analyses using equilibrated Kt/V were completed for 10,816 HD patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) in 7 countries.

Port FK, et al. High dialysis dose is associated with lower mortality among women but not among men. Am J Kidney Dis. 2004 Jun;43(6):1014-23.

Adjusted Mortality by Sex & Dialysis dose, by eKt/V for DOPPS Patients. (Quartiles of patients with eKt/V ≥ 1.05)



Port FK, et al. High dialysis dose is associated with lower mortality among women but not among men. Am J Kidney Dis. 2004 Jun;43(6):1014-23.

Effect of gender on the mortality response to dialysis dose

Relative Risk of Mortality: high dose & standard dose; women vs. men

Size parameter used to control the effect of gender	Effect of gender on response to high dose controlling for size parameter Ratio of RR	P value
None	0.71	0.014
Weight kg	0.73	0.023
Height cm	0.69	0.039
Vw L	0.70	0.047
Modeled V L	0.74	0.052
Body surface area m ²	0.70	0.019
BMI kg/m ²	0.75	0.037
Black race	0.74	0.032

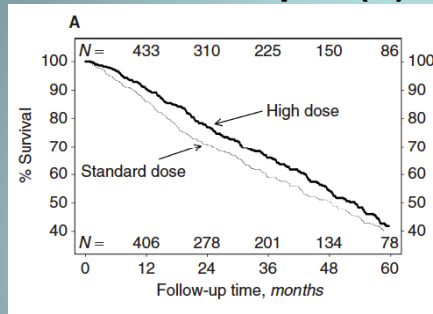
Shown in the second column are the ratios of relative mortality risk (RR) in the high vs. standard dose groups in women compared with men after adjustment for the interaction of dose group with the specified size parameter. Ratios of RR <1 indicate a greater trend towards a benefit of the high dose in women than in men. All RRs were adjusted for the other six prespecified baseline covariates. P values are not adjusted for multiple comparisons.

Secondary outcomes: dose-gender

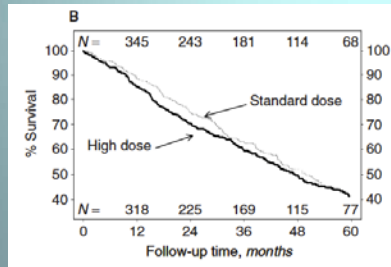
	# Events per 100 patient years	All patients			Men			Women			Interaction P value ^a
		RR	95% CI	P value	RR	95% CI	P value	RR	95% CI	P value	
All-cause mortality (acM)	871 (16.6)	0.96	(0.84-1.10)	0.53	1.16	0.94-1.43	0.16	0.81	0.67-0.97	0.02	0.014

Depner t, et al. Dialysis dose and the effect of gender and body size on outcome in the HEMO Study. Kid Int (2004) 65, 1386-1394.

Kaplan Meier Curves - Time To Death By Treatment Group in (A) Women & (B) Men



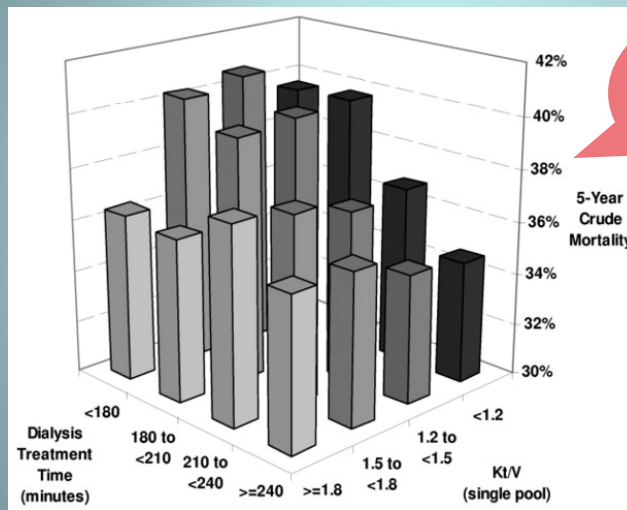
(A) Women: The high-dose group (dashed line) had a relative mortality risk of 0.81 compared with the standard dose group (solid line); 95% CI, 0.67–0.97, $P = 0.02$.



(B) Men: In contrast to women, the high-dose group (dashed line) had a relative mortality risk of 1.16 compared with the standard dose group (solid line), 95% CI, 0.94–1.43, $P = 0.16$. Numbers of patients remaining in follow-up are provided for the standard dose (top line) and high dose (bottom line).

Depner t, et al. Dialysis dose and the effect of gender and body size on outcome in the HEMO Study. *Kid Int* (2004) 65, 1386–1394.

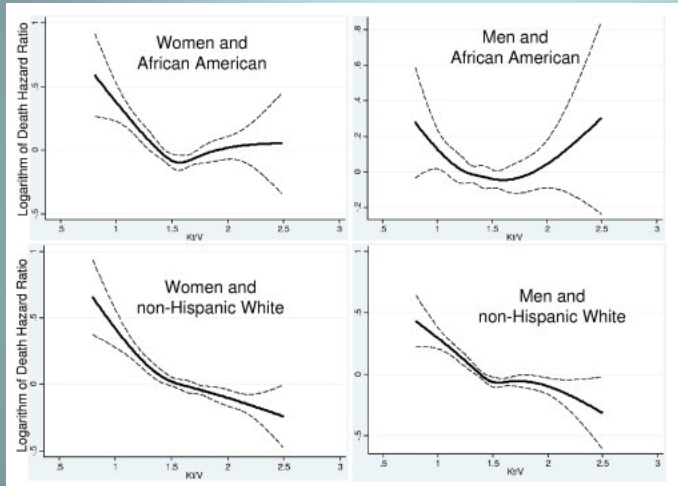
Five-year crude mortality of 88,153 HD patients across 4 groups of HD Rx times and 4 strata of Kt/V (2001-2006).



Association of HD treatment time & mortality lessens as Kt/V increases

Miller JE et al. Association of hemodialysis treatment time and dose with mortality and the role of race and sex. *Am J Kidney Dis*. 2010 Jan;55(1):100-12.

Cubic splines (solid lines) and 95% confidence levels (dashed lines) of case-mix-adjusted death hazard ratios of time-dependent quarterly varying Kt/V (single-pool) across 4 mutually exclusive sex and race categories



38,919 HD patients with averaged Kt/V of 1.54 ± 0.31 , adjusted for case-mix, body size measures, comorbid conditions, and dialysis catheter, showed similar cubic spline trends with a U-shape association in African American men, whereas non-Hispanic white women showed an almost linear survival advantage of higher Kt/V doses.

Miller JE et al. Association of hemodialysis treatment time and dose with mortality and the role of race and sex. Am J Kidney Dis. 2010 Jan;55(1):100-12.

Summary

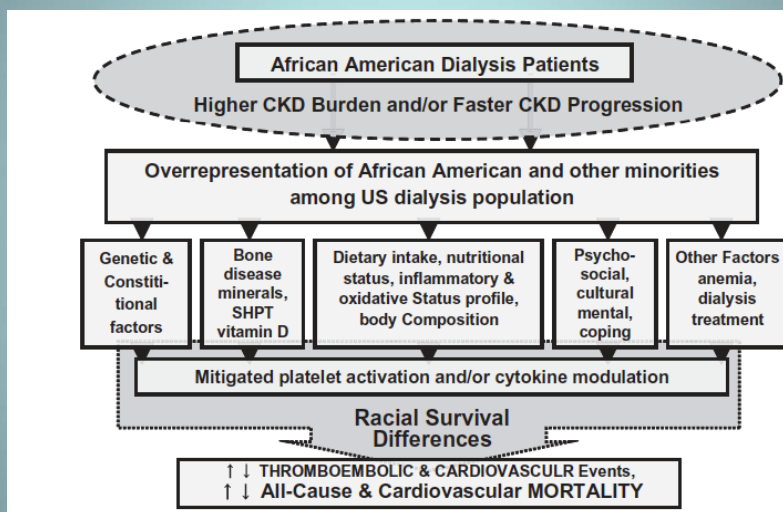
- In most large HD association studies minority groups have lower adjusted mortality rates
 - HD cancels out women's survival advantage in the GP.
 - Mechanisms of minority survival advantage remains poorly defined
 - Survival bias, reverse CV epidemiology, acute stress neurohormonal activation that provides short term protection – beneficial in a cohort with short survival.
- Dialysis Dose appears to influence mortality outcomes in women vs. men, but little effect by race/ethnicity
 - **Secondary HEMO Study analyses** suggest target equilibrated Kt/V of 1.45 is superior to 1.05 in women

Mortality, Gender and Dialysis Dose

- When normalized to body surface area rather than V, the dose of dialysis in women in the HEMO Study was substantially lower than in men.
- The lowest surface-area-normalized dose was received by women randomized to the conventional dose arm, possibly explaining the sex-specific response to dialysis dose.
- Results are consistent with the hypothesis that when dialysis dose is expressed as Kt/V, women, due to their lower V/SA ratio, require a higher amount than men.

Daugirdas JT, et al. Can rescaling dose of dialysis to body surface area in the HEMO study explain the different responses to dose in women versus men? Clin J Am Soc Nephrol. 2010 Sep;5(9):1628-36.

Potential Mechanisms Leading To Survival Disparities of African American Dialysis Patients

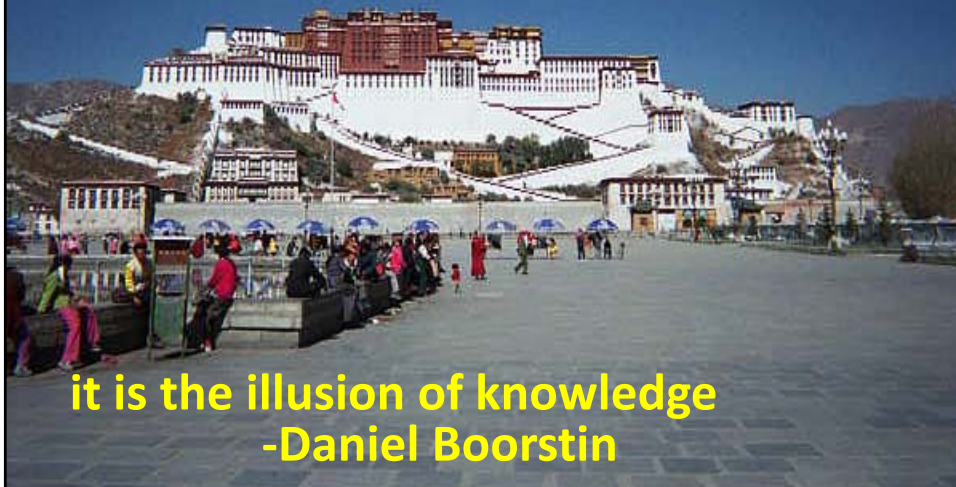


Kalantar-Zadeh K, Golan E, Shohat T, Streja F, Norris KC, and Kopple JD. Survival Disparities within American and Israeli Dialysis Populations: Learning from Similarities and Distinctions across Race and Ethnicity. Sem Dial (in press)

Conclusion

- Increased understanding of ESRD subgroup survival differences will provide unique insights for improving ESRD & CKD outcomes.
-
- Lack of definitive prospective studies precludes formal recommendation of modifying dialysis dose for subgroups.

"The greatest obstacle to discovery is not ignorance –



**it is the illusion of knowledge
-Daniel Boorstin**