Home dialysis: Why and Why Not an Evidence-Based Perspective

Joanne M Bargman
Professor of Medicine, University of Toronto
Director, Peritoneal Dialysis Program University Health Network

DISCLOSURES

- Consultant: Baxter Healthcare, DaVita Healthcare Partners, Akebia, Baxter Canada
- Speakers' Bureau: DaVita Healthcare Partners, Akebia, Baxter Canada

OUTCOMES OF INTEREST

- Survival
- Patient-reported Outcomes and Quality of Life

Survival

- USRDS data on 43,000 deaths in dialysis patients prevalent on January 1, 1987/8/9
- Adjusted for age, race, sex, diabetes, and < or > 1 year of followup
- 19% overall increase in mortality in patients on PD
- Amplified in older patients and diabetics

ARTICLES

A Comparison of Mortality Between Patients Treated With Hemodialysis and Peritoneal Dialysis[1]

Wendy E. Bloembergen,[2] Friedrich K. Port, Elizabeth A. Mauger, and Robert A. Wolfe

Patient Group	All Patients	
	RR	*P* Value[a]
All patients	1.19	<0.001
Patients on Dialysis <1 yr[c]	1.14[d]	<0.001
Patients on Dialysis >1 yr[c]	1.21[d]	<0.001

J Am Soc Nephrol 1995

The study was based on Medicare data

- 90 day censorship from start of dialysis
- so early deaths not reported
  - early deaths much more common on HD than PD

After publication of the Bloembergen study, incidence of PD in US and Canada started falling

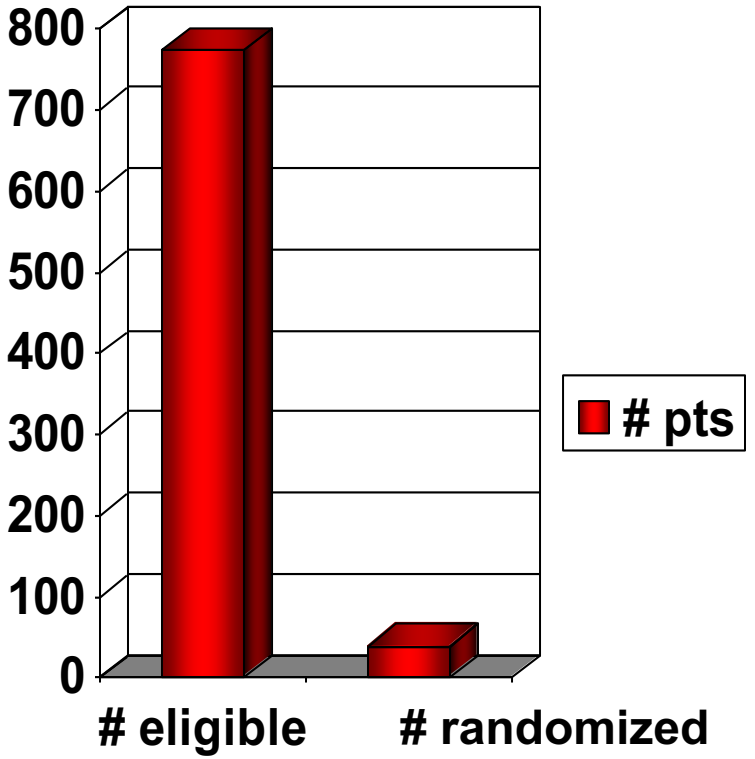
- cause and effect?
- more HD spots were opening?
- may have been falling even before the publication of this data

Observational Studies of Survival by Dialysis Modality

- Difficult to avoid flaws
- How do you control for
  - co-morbidity?
  - wanting to be at home?
  - recruitment bias?
- Best way to study this would be a randomized, controlled study

Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: A randomized controlled trial

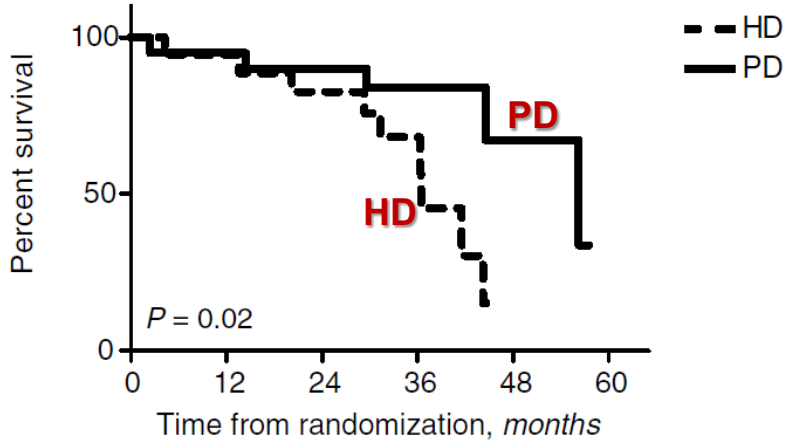
JOHANNA C. KOREVAAR, G.W. FEITH, FRIEDO W. DEKKER, JEANNETTE G. VAN MANEN, ELISABETH W. BOESCHOTEN, PATRICK M.M. BOSSUYT, and RAYMOND T. KREDIET FOR THE NECOSAD STUDY GROUP[1]



- of 773 pts eligible for the study, 735 *wanted to choose* between PD and HD
- only 38 patients were randomized into the study

Kidney Int 2003

- Hazard ratio for HD versus PD was 3.8 (p=0.03) but lost statistical significance when adjusted for age, co-morbidity and primary renal disease
- no difference in Quality-Adjusted Life Years
- authors concluded that an RCT difficult to do



Number at risk						
HD	18	16	12	6	0	–
PD	20	19	18	12	2	0

Fig. 2. Survival of patients randomized to hemodialysis (HD) and peritoneal dialysis (PD), intention-to-treat (ITT) analyses.

Korevaar Kidney Int 2003

- A second RCT was attempted in China
- 36 sites
- Originally planned as a survival study
  - too few events to determine outcome
  - re-fashioned into a quality of life study HD vs PD
  - non-inferiority of PD compared to HD
  - *many patients dropped out of their assigned modality*

Yu et al ISPD Congress 2018

- it looks like a randomized, controlled trial will never happen
- we are stuck with observational studies
- need to control for co-morbidity and avoid recruitment bias

Comparing the Risk for Death with Peritoneal Dialysis and Hemodialysis in a National Cohort of Patients with Chronic Kidney Disease

Bernard G. Jaar, MD, MPH; Josef Coresh, MD, PhD; Laura C. Plantinga, ScM; Nancy E. Fink, MPH; Michael J. Klag, MD, MPH; Andrew S. Levey, MD; Nathan W. Levin, MD; John H. Sadler, MD; Alan Kliger, MD; and Neil R. Powe, MD, MPH, MBA

- 1995-8, about 1000 patients
- self-reported baseline characteristics, including urine output
- deaths reported in unadjusted and multivariate and propensity-adjusted models

Jaar Ann Int Med 2005

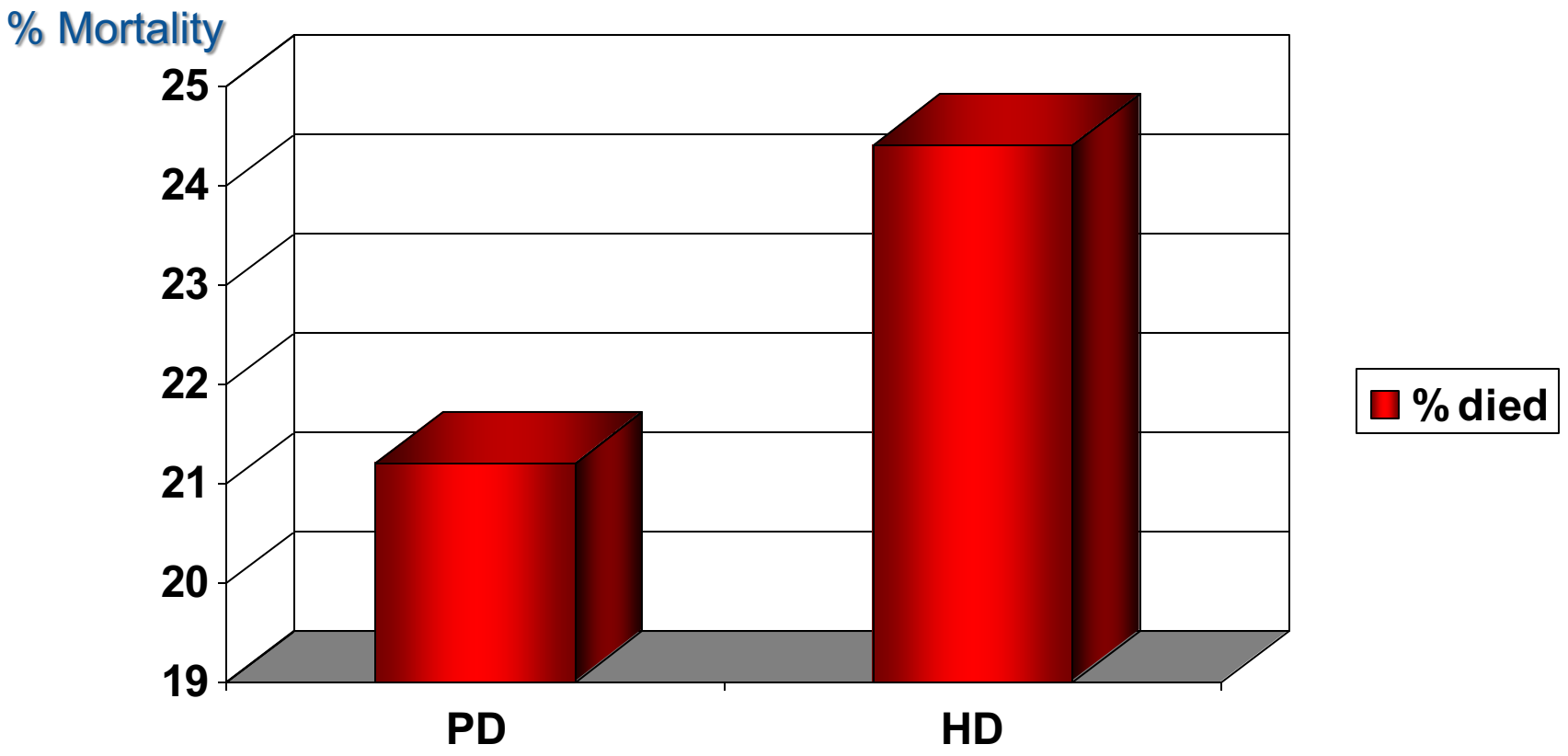
So What was the Mortality Rate?

- After a mean follow-up of 2.4 years:

PD: 21.2%
HD: 24.4%

Jaar Ann Int Med 2005

Let's See that Again:



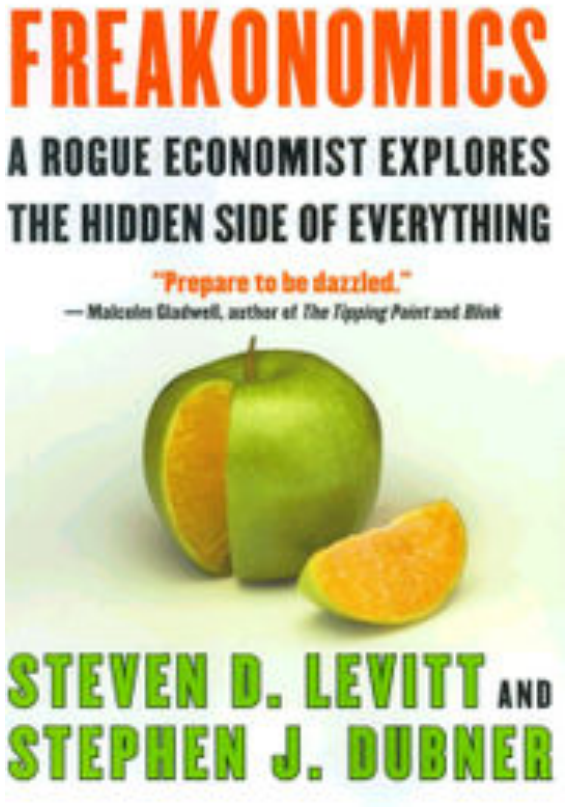
- multivariate adjustment in the second year of treatment
- no difference in survival adjusted for demographics *or* adjusted for demographics and clinical/treatment factors
- adding third adjustment for laboratory values *changed everything*

Hazard Ratio of Death PD vs HD

Second year (n = 795/478)	
Unadjusted	1.06 (0.59–1.90)
Adjusted for	
Demographic characteristics‡	0.77 (0.31–1.88)
Plus clinical/treatment factors§	0.84 (0.33–2.14)
Plus laboratory values‖	2.34 (1.19–4.59)

Jaar Ann Int Med 2005

"*It should be said that regression analysis is more art than science*."



- I would have said "*this is weird*"
- There was no difference in survival between the 2 modalities until laboratory values were added in
- A biostatistician can hand you numbers, but they have to make sense

Second year (n = 795/478)	
Unadjusted	1.06 (0.59–1.90)
Adjusted for	
Demographic characteristics‡	0.77 (0.31–1.88)
Plus clinical/treatment factors§	0.84 (0.33–2.14)
Plus laboratory values‖	2.34 (1.19–4.59)

WORSHIPPING AT THE ALTAR OF ST. COX:
WHO ADJUSTS THE ADJUSTMENTS?

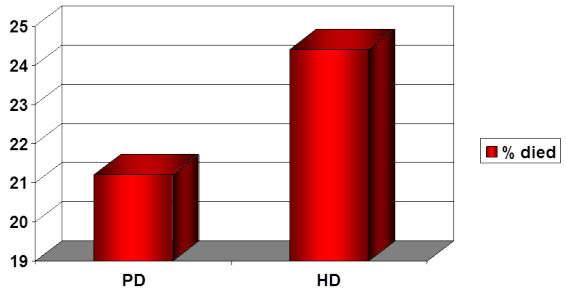
Bargman Perit Dial Int 2006

Peritoneal dialysis has higher death risk than hemodialysis

New research suggests end-stage renal disease patients who choose peritoneal dialysis rather than hemodialysis increase their death risk by 50%, according to a study published online August 1 in the *Annals of Internal Medicine*. Researchers at Johns Hopkins University followed 1,041 newly-diagnosed dialysis patients across the country for 8 years. Participants chose their dialysis method at the outset: 274 selected peritoneal dialysis, while 767 chose hemodialysis.

"My impression is that peritoneal dialysis is a good technique initially," said Bernard Jaar, MD, a lead study author and assistant professor of Medicine and Epidemiology at Johns Hopkins Medical Institutions. "The main difference is in both groups patients lose their renal function, but in hemodialysis we can compensate more easily by increasing the time on the machine." Unfortunately, PD patients use a biological membrane that can become worn out and not filter as well, said Jaar, who is also a staff nephrologist at the Nephrology Center of Maryland. "That means that over time, they will have more hypertension, more cardiovascular disease, and more complications related to poor fluid and toxin clearance. Whereas, that problem really doesn't exist on hemodialysis as long as they have a vascular access."

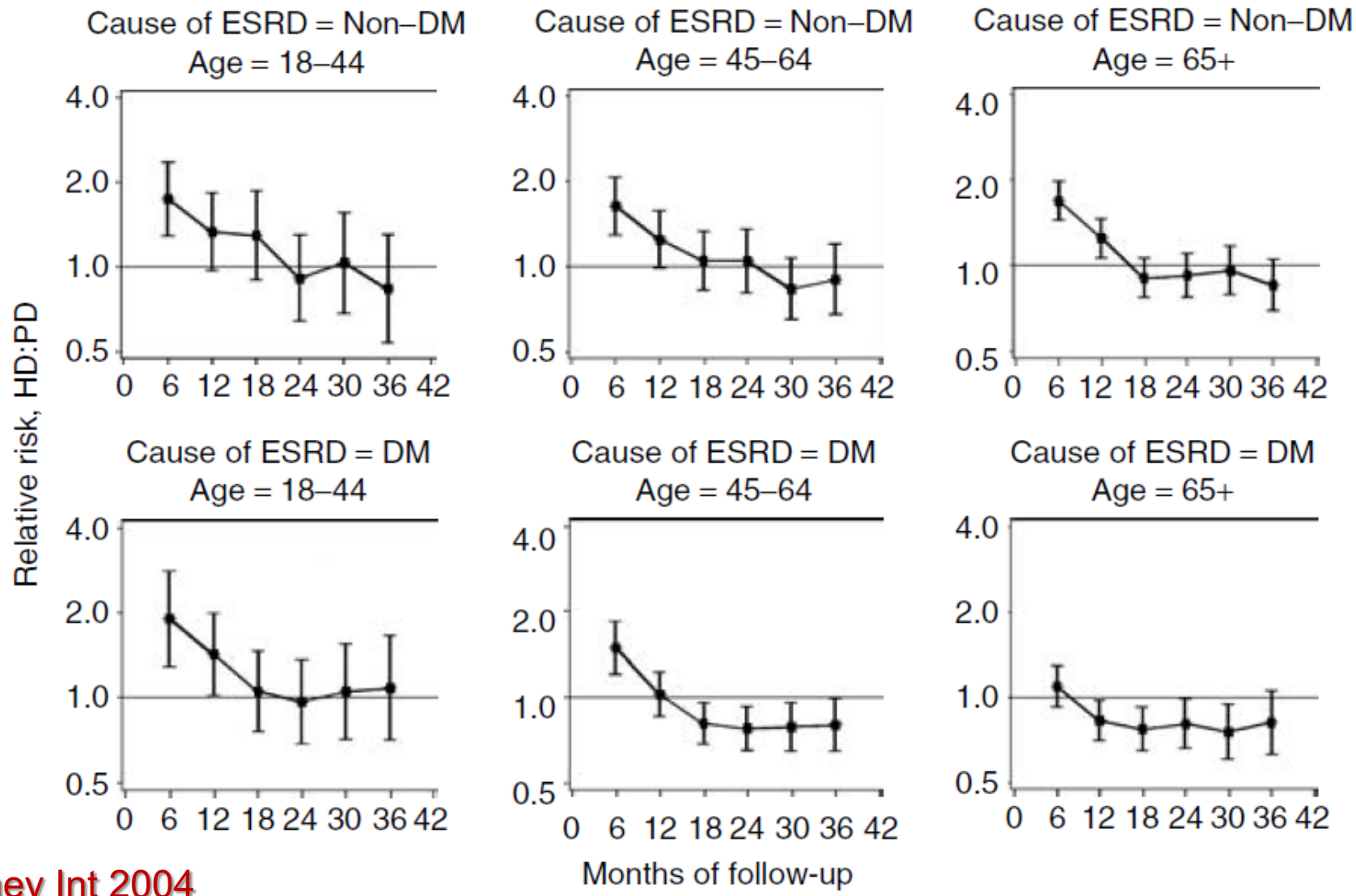
Another interesting finding was the demographics of patients on the differing dialysis types. Patients who started the study on PD were more likely to be healthier overall, have graduated from high school, be married, or have jobs while on dialysis. Jaar attributes part of this connection to the active role PD patients must take in their care. Although the findings in this study are significant, Jaar said "this is not the end of the story." He believes the debate will continue about which form of dialysis is better, and this study is merely a stepping stone towards finding out the answer.



The Industry of Survival Analyses

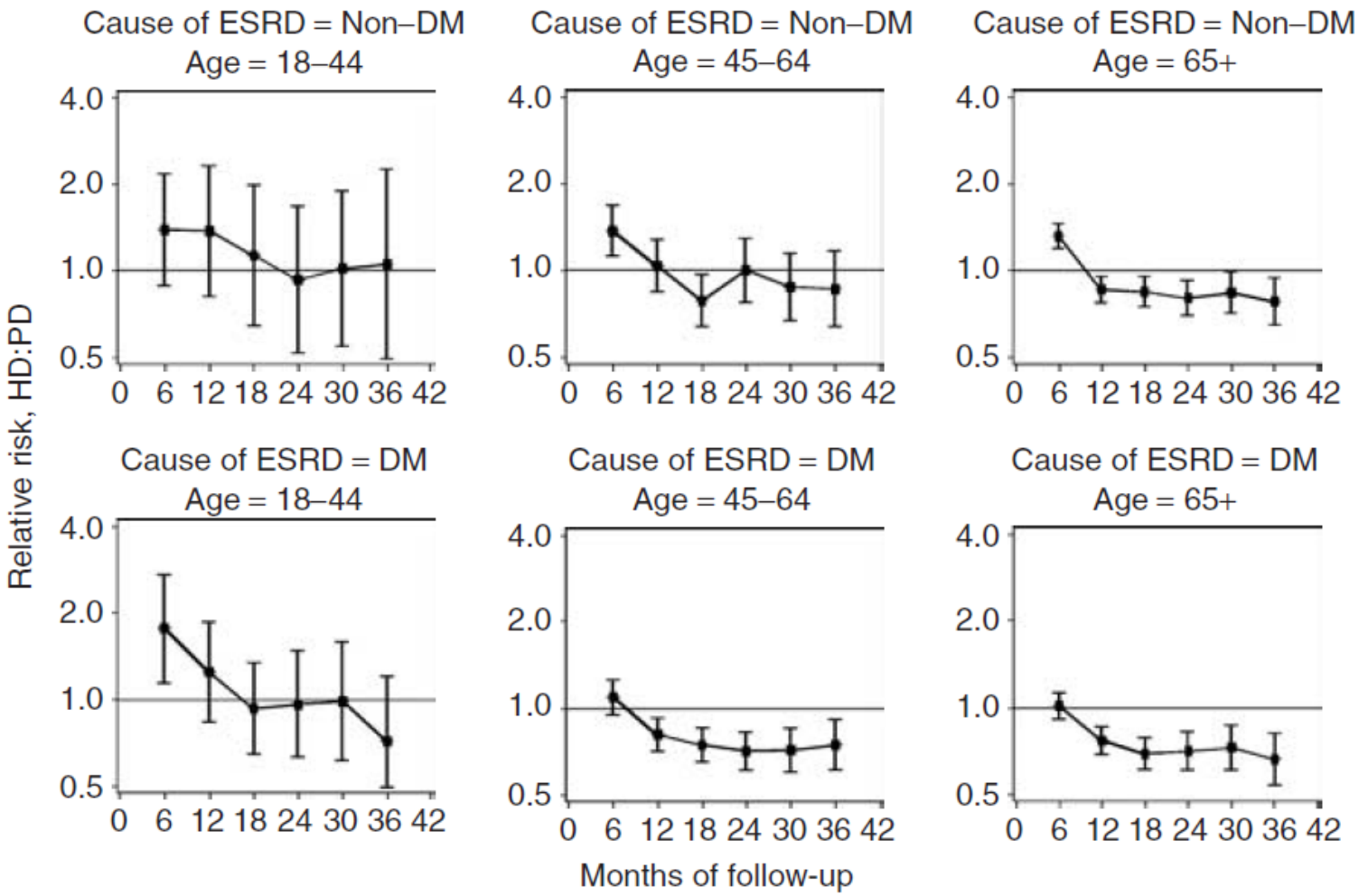
- The 1990's and early 2000's saw a number of studies focusing on survival differences between PD and conventional HD

RR of Death HD:PD *(no reported comorbidity)*



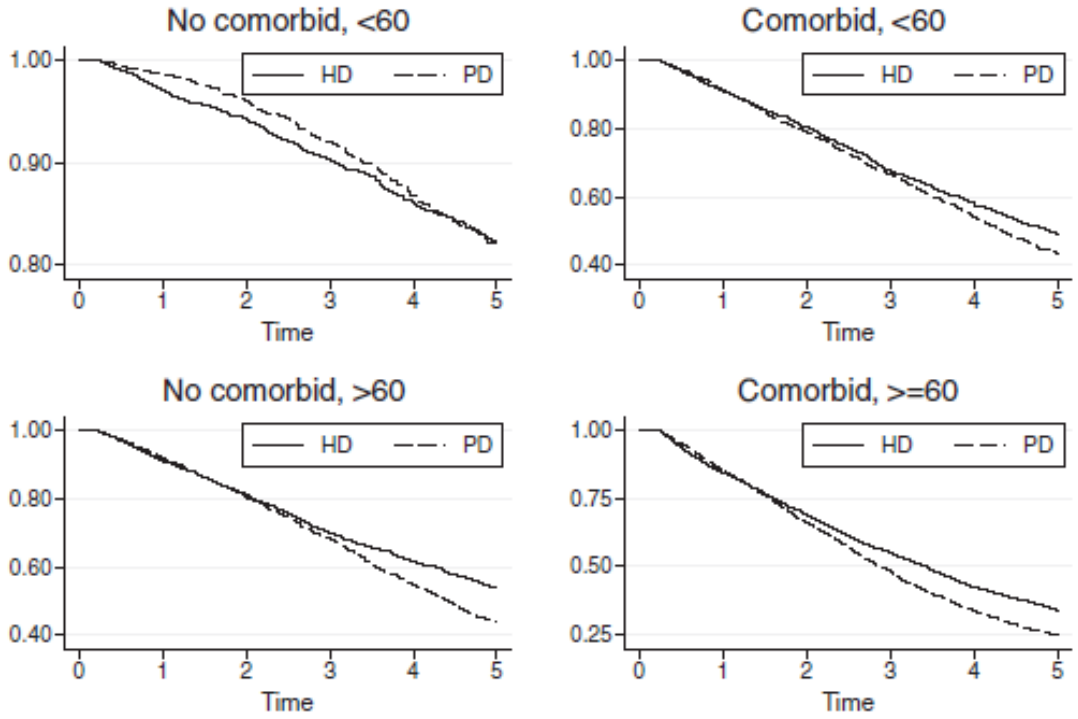
Vonesh Kidney Int 2004

RR of Death HD:PD *(at least 1 reported comorbidity)*



Vonesh Kidney Int 2004

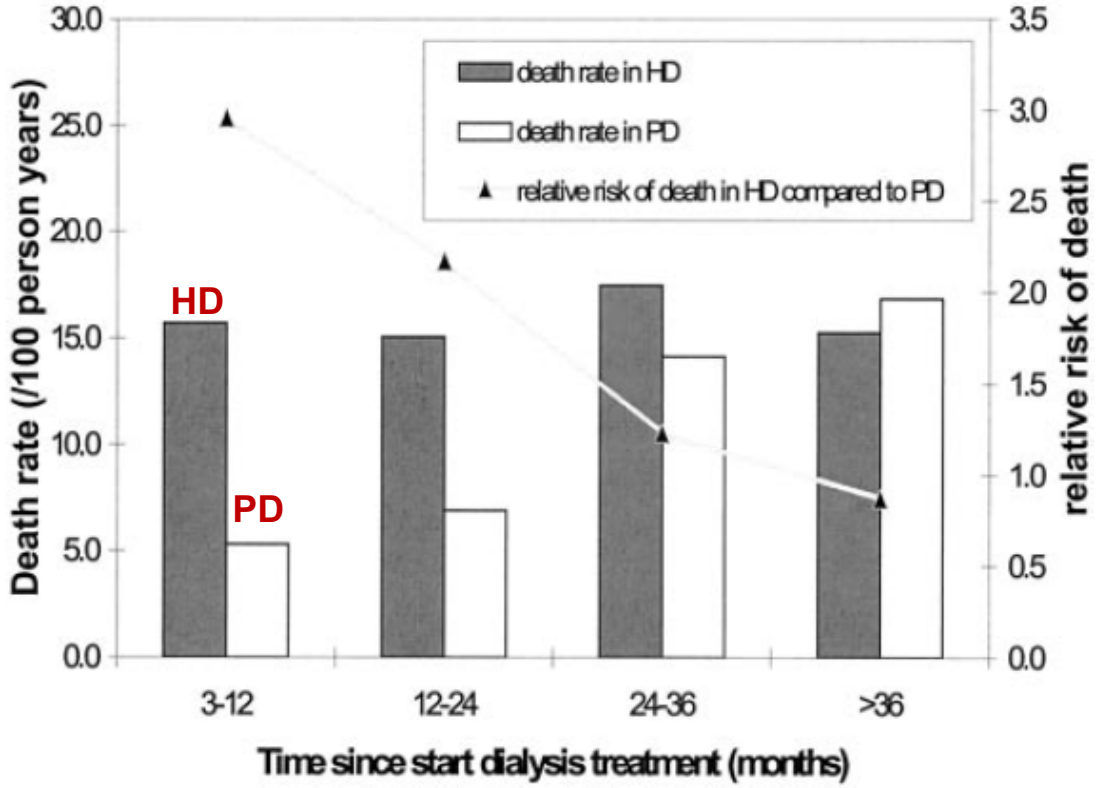
- Registry data 1991-2005
- 1 year survival advantage for PD, followed by survival advantage for HD
- Effect modified by age and comorbidity



McDonald J Am Soc Nephrol 2009

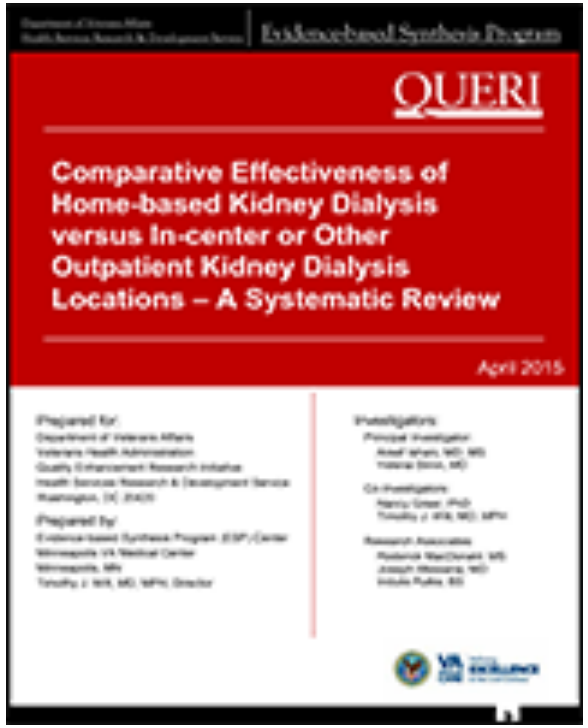
- Dutch registry of dialysis patients
- HD patients averaged 10 years older than PD patients and with more comorbidity
- Survival advantage for PD for the first 2 years, then advantage for HD after that

Relative Risk of Death HD vs PD



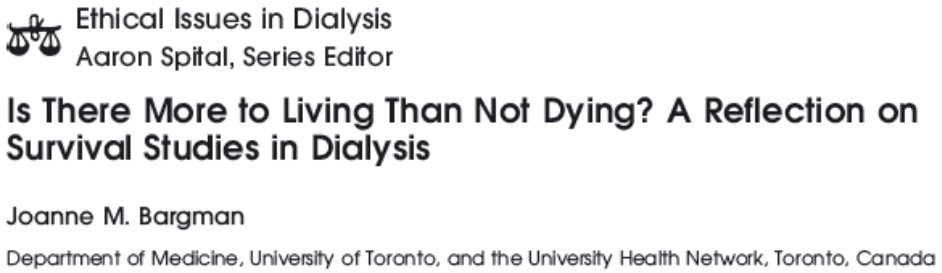
Termorshutzen J Am Soc Nephrol 2003

- Looking at only US/Canada/Australia/NZ/Europe/UK:
  - 27 registry studies
  - 1 RCT
  - 2 clinical cohort studies
- Of 22 registry studies that reported mortality
  - 12 no difference between PD and HD
  - 4 survival benefit for PD
  - 6 survival benefit for HD



Ishani et al
Evidence-Based Synthesis Program
Department of Veterans Affairs (US): 2015

- Even if you were to accept the premise that the RR of death is higher in PD than in HD
  - does that mean that patients shouldn't go on PD?
  - is life just about maximizing survival?



Ethical Issues in Dialysis
Aaron Spital, Series Editor

Is There More to Living Than Not Dying? A Reflection on Survival Studies in Dialysis

Joanne M. Bargman

Department of Medicine, University of Toronto, and the University Health Network, Toronto, Canada

Seminars in Dialysis 2007

Setting Research Priorities for Patients on or Nearing Dialysis

Braden Manns,[*†‡§] *Brenda Hemmelgarn,*[*†‡§] *Erin Lillie,*[‖] *Sally Crowe P.G. Dip,*[¶] *Annette Cyr,*[**] *Michael Gladish,*[††] *Claire Large,*[‡‡] *Howard Silverman,*[§§] *Brenda Toth,*[‖‖] *Wim Wolfs,*[¶¶] *and Andreas Laupacis*[‖***]

Clin J Am Soc Nephrol 2014

Setting Research Priorities for Patients on or Nearing Dialysis

Braden Manns,[*†‡§] *Brenda Hemmelgarn,*[*†‡§] *Erin Lillie,*[‖] *Sally Crowe P.G. Dip,*[¶] *Annette Cyr,*[**] *Michael Gladish,*[††] *Claire Large,*[‡‡] *Howard Silverman,*[§§] *Brenda Toth,*[‖‖] *Wim Wolfs,*[¶¶] *and Andreas Laupacis*[‖***]

Most Important Issues for *Patients*

- how to get the most effective HD in the shortest possible time?
- cause, prevention and treatment of itch
- treatment of low energy
- ability to travel

Clin J Am Soc Nephrol 2014

Setting Research Priorities for Patients on or Nearing Dialysis

Braden Manns,[†‡§] Brenda Hemmelgarn,[*†‡§] Erin Lillie,[‖] Sally Crowe P.G. Dip,[¶] Annette Cyr,[**] Michael Gladish,[††] Claire Large,[‡‡] Howard Silverman,[§§] Brenda Toth,[‖‖] Wim Wolfs,[¶¶] and Andreas Laupacis[‖***]*

Most Important Issues for *Caregivers*

- how to prevent or slow progression of CKD
- how can dialysis improve quality of life?
- how to reduce wait times for transplant?
- what happens when dialysis isn't appropriate?

Clin J Am Soc Nephrol 2014

Setting Research Priorities for Patients on or Nearing Dialysis

Braden Manns,[†‡§] *Brenda Hemmelgarn,*[*†‡§] *Erin Lillie,*[‖] *Sally Crowe P.G. Dip,*[¶] *Annette Cyr,*[**] *Michael Gladish,*[††] *Claire Large,*[‡‡] *Howard Silverman,*[§§] *Brenda Toth,*[‖‖] *Wim Wolfs,*[¶¶] *and Andreas Laupacis*[‖***]

Most Important Issues for *Physicians*

- grafts versus fistulae versus catheters?
- complications of calcium/P homeostasis?
- Does modality of dialysis affect survival?
- Cause, prevention of itching?

Clin J Am Soc Nephrol 2014

- The fall-off in PD in 1995 was attributed to the Bloembergen USRDS paper
- Some nephrologists would not place older diabetic women on PD because of the increased mortality in registry studies
  - (yet have no problem with putting a younger man with GN onto HD although that associates with the same incremental risk…)

Risk of Mortality	HD	PD
Older diabetic women		↑
Younger nondiabetic men	↑	

The Lay of the Land After the Vonesh USRDS Studies

- There's an early survival advantage with PD compared to HD
- After 1-2 years, this advantage dissipates and survival on HD is better than PD after that
- Promotion of "integrated care" to ride this wave: start with PD and then transition to HD in the second year to take advantage of the better HD survival

That “Surfing” Never Made Sense to Me

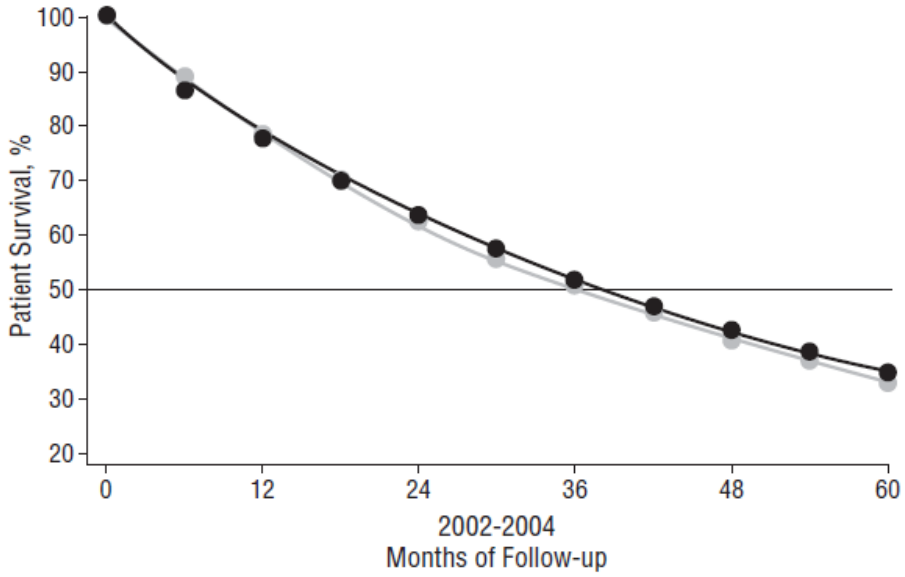
Have your baby in Iceland (lowest birth mortality rate)

Then move to Australia (lowest under 5 mortality rate)

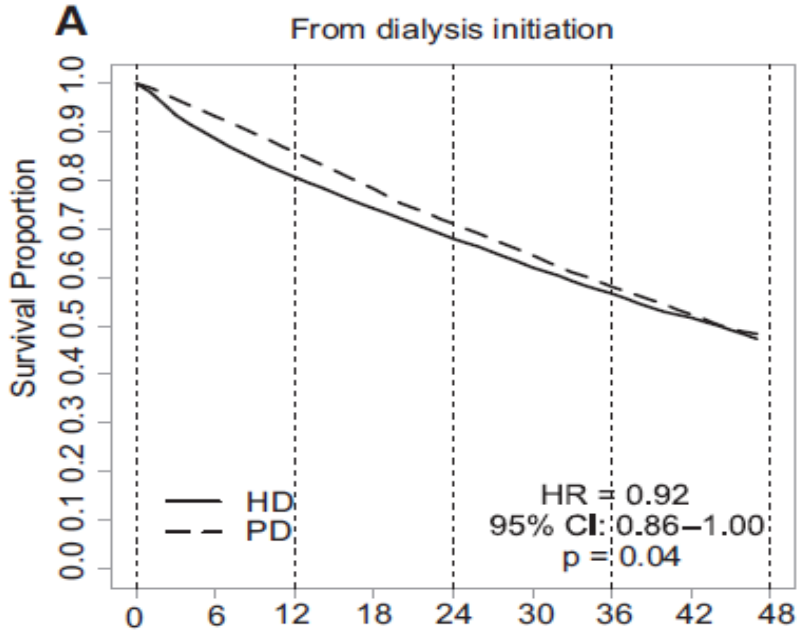
Then move to Andorra (lowest mortality rate ages 5-14)

Secular Trend in Overlapping Survival of PD and Conventional HD

- USRDS data
- Adjusted survival over time shows essentially no difference by the most recent study period



Mehrotra Arch Intern Med 2011

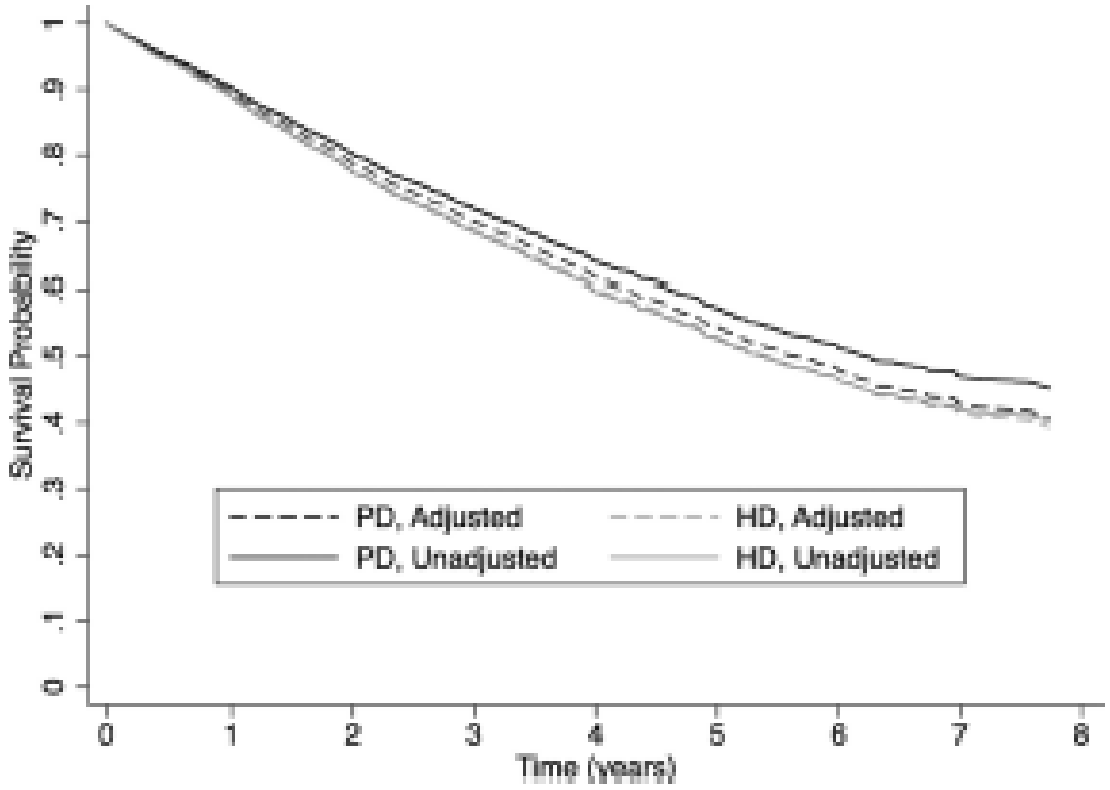


Weinhandl J Am Soc Nephrol 2010

Selection Bias Explains Apparent Differential Mortality between Dialysis Modalities

Robert R. Quinn,*† Janet E. Hux,‡§‖¶ Matthew J. Oliver,§‖¶ Peter C. Austin,‡‖** Marcello Tonelli,††‡‡ and Andreas Laupacis‡§ §§

- Patients who had > 4 months of predialysis care and had an elective outpatient start
- Ontario, Canada data
- 6500 patients: 4500 HD starts, and 2000 PD starts
- *No difference in adjusted survival between HD and PD starts*

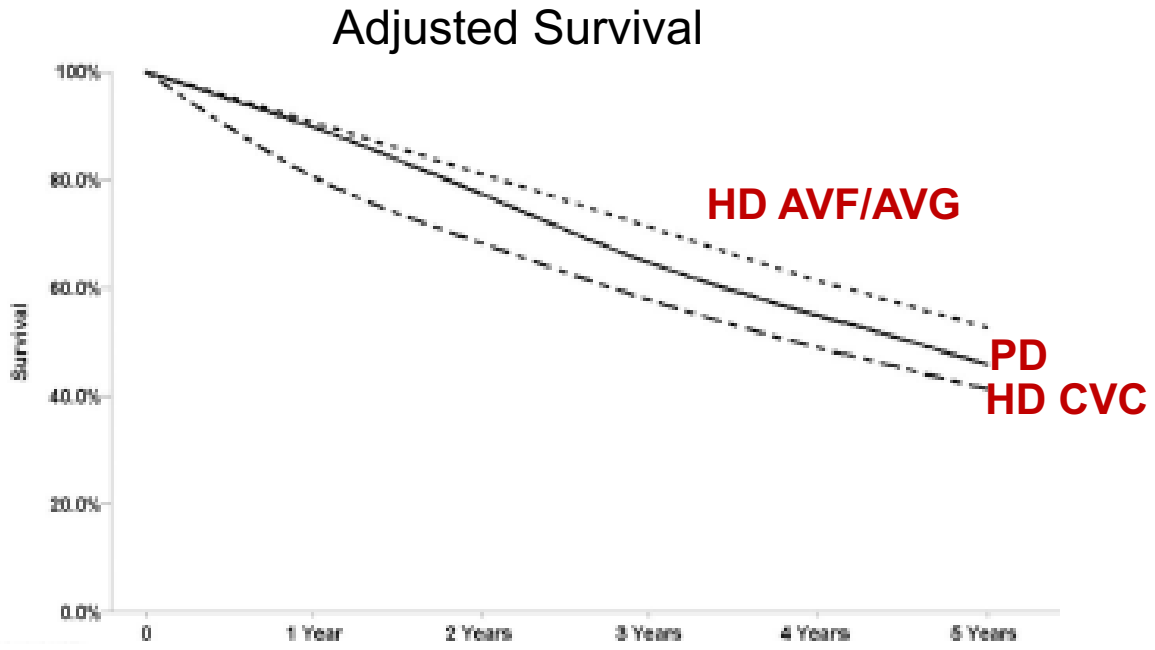


Quinn J Am Soc Nephrol 2011

Hemodialysis Vascular Access Modifies the Association between Dialysis Modality and Survival

Jeffrey Perl,[*†] Ron Wald,[*†] Philip McFarlane,[*†] Joanne M. Bargman,[†‡] Edward Vonesh,[§] Yingbo Na,[‖] S. Vanita Jassal,[†‡] and Louise Moist[¶]

- Canadian Organ Replacement Registry 2001-2008
- 40,000 new dialysis starts
  - 7400 PD starts
  - 6663 HD starts with a fistula or a graft
  - 24437 HD starts with a CVC (permcath)



Perl J Am Soc Nephrol 2011

- There isn’t an early survival advantage to PD: there is an early survival *disadvantage* to HD
  - unprepared starts
  - urgent starts
  - the CVC itself
  - HD as a CV “stress test”

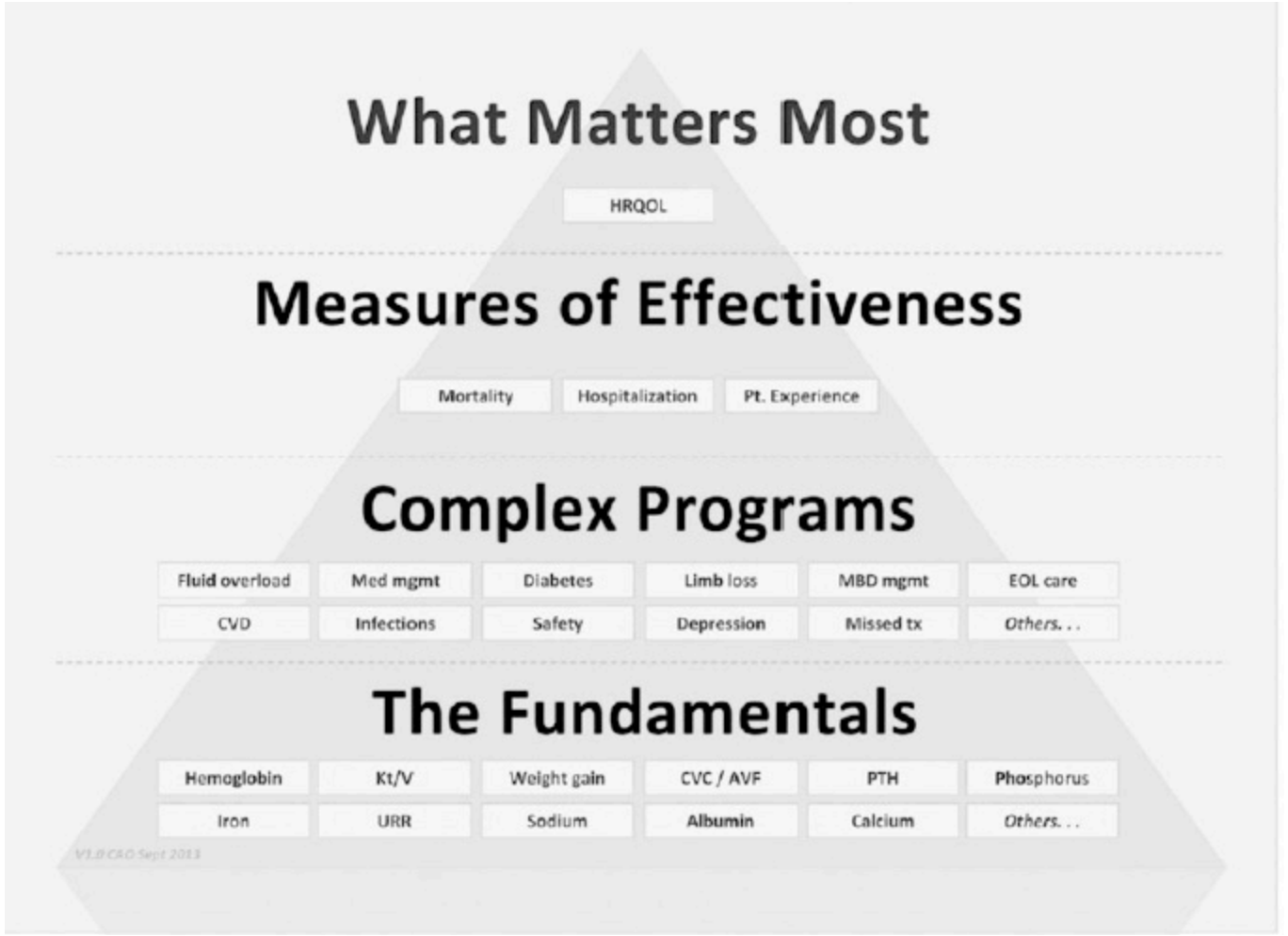
- I was asked to review yet another study comparing survival by dialysis modality
- I thought "*Enough already!*"

Commentary

Survival by Dialysis Modality—Who Cares?

Martin B. Lee* and Joanne M. Bargman†

Clin J Am Soc Nephrol 2016

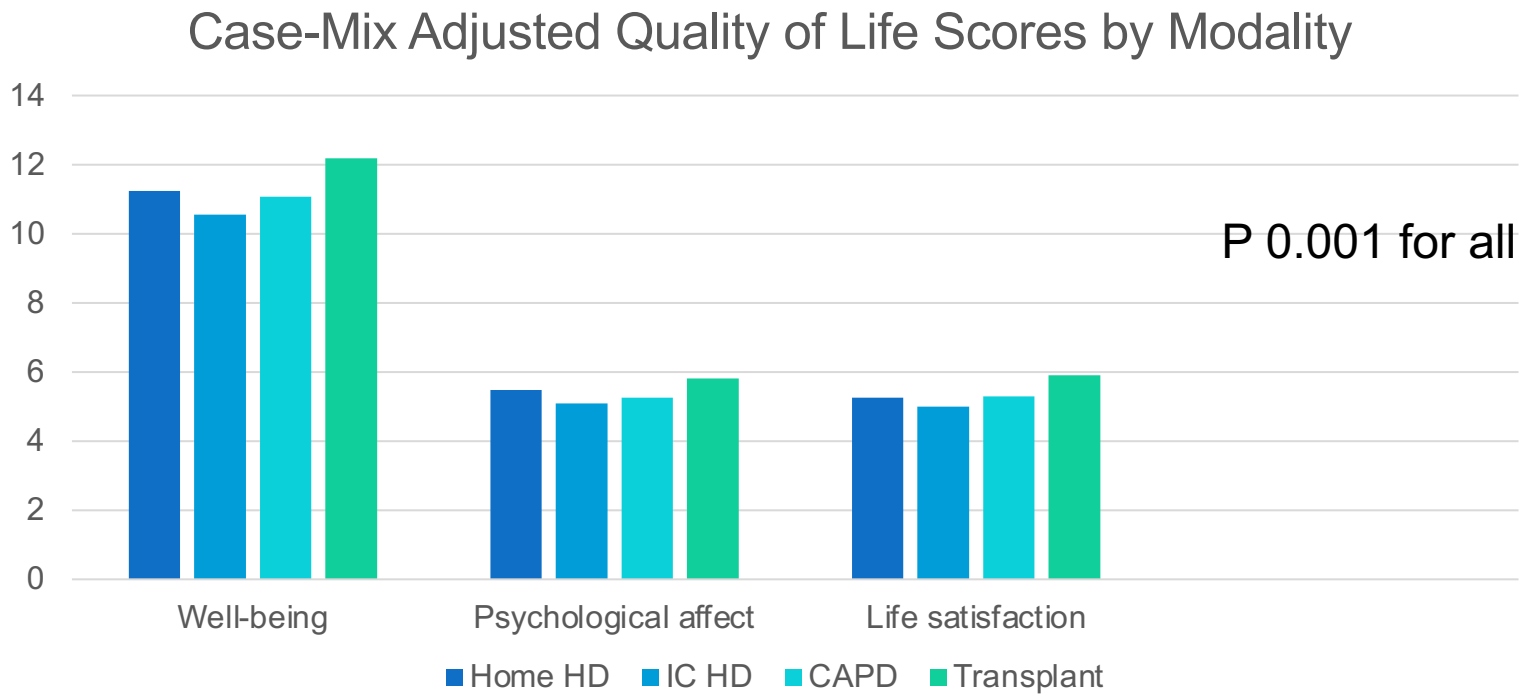


Nissenson Clin J Am Soc Nephrol 2014

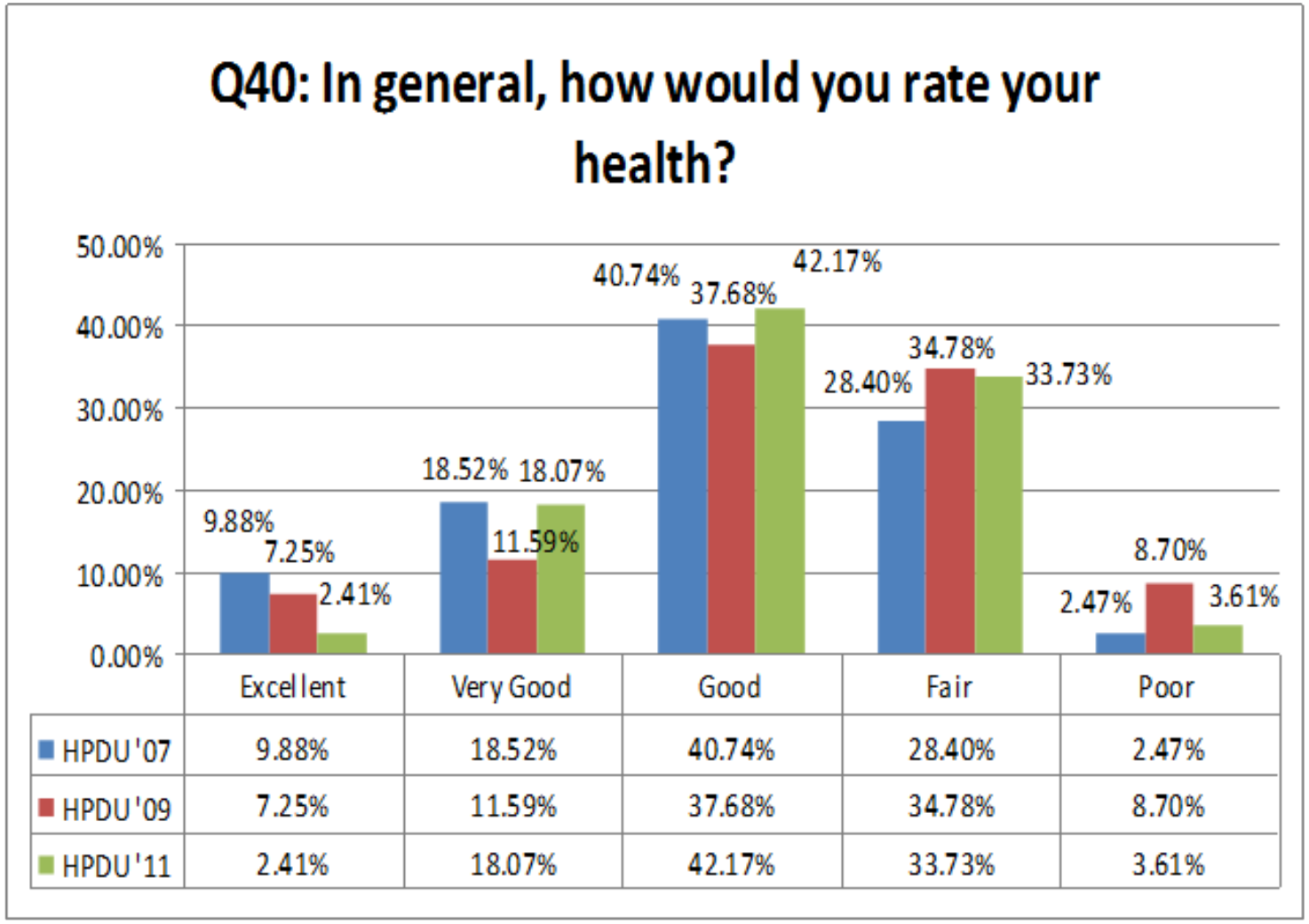
QUALITY OF LIFE / PATIENT-REPORTED OUTCOMES

THE QUALITY OF LIFE OF PATIENTS WITH END-STAGE RENAL DISEASE

ROGER W. EVANS, PH.D., DIANE L. MANNINEN, PH.D., LOUIS P. GARRISON, JR., PH.D., L. GARY HART, M.S., CHRISTOPHER R. BLAGG, M.D., ROBERT A. GUTMAN, M.D., ALAN R. HULL, M.D., AND EDMUND G. LOWRIE, M.D.

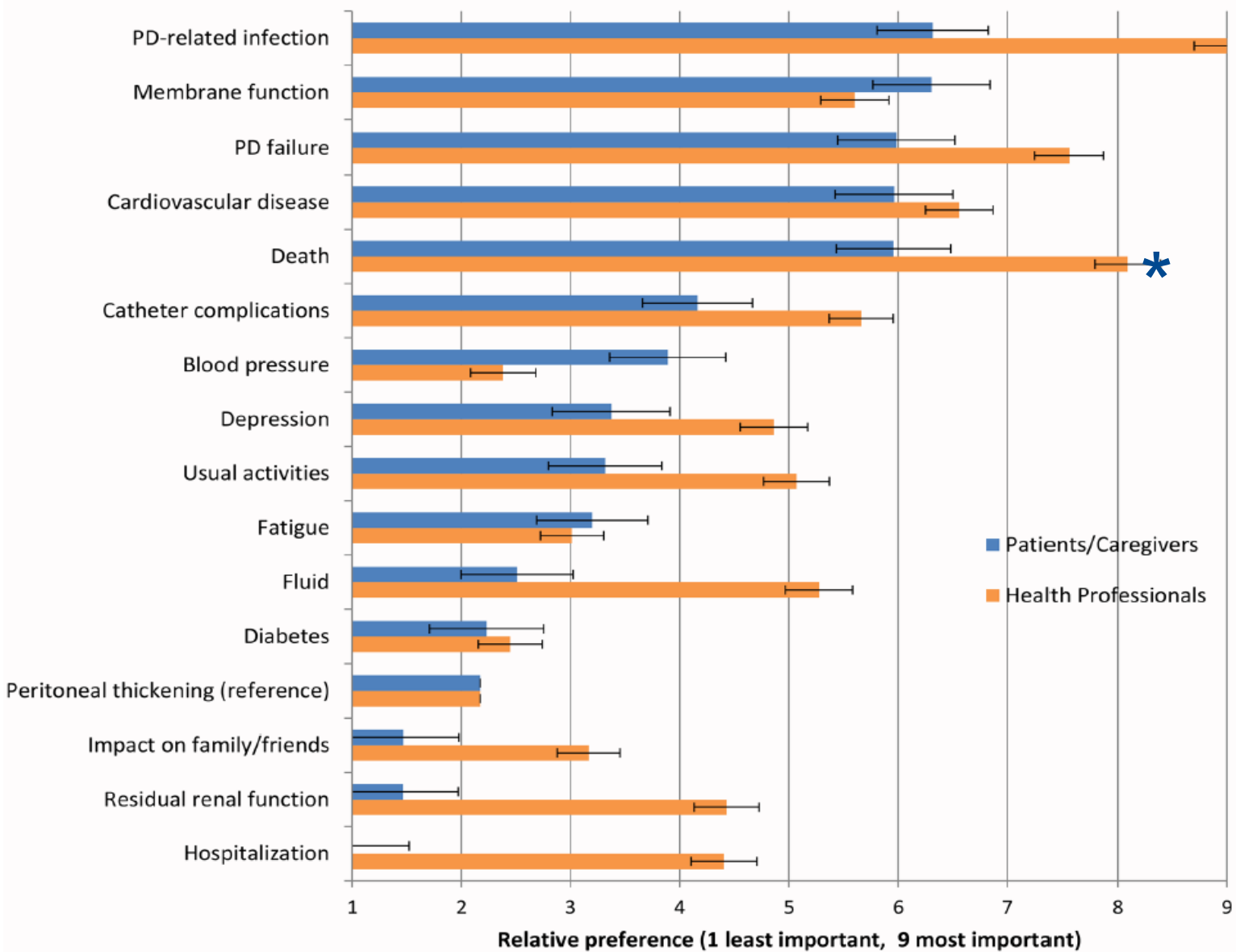


N Engl J Medicine 1985

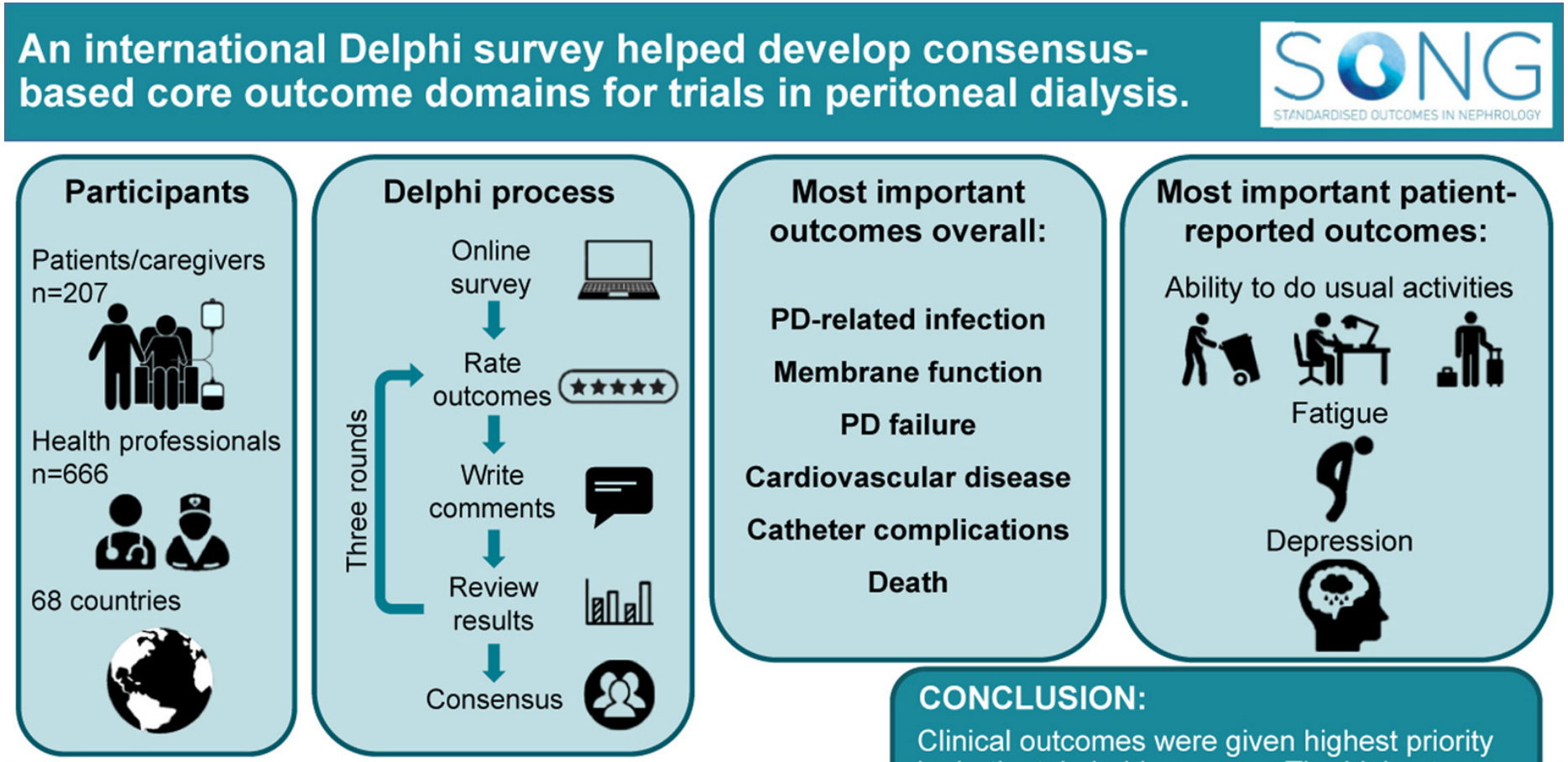


50-60% of patients rate their health as "good, very good or excellent"

3-Round Delphi Panel: Differences between Health Professionals and Patients/Caregivers *(Manera Kidney Int 2019)*



Fatigue, Depression and Ability to do Usual Activities Were Most Important Outcomes to Patients



ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY
Manera et al, 2019

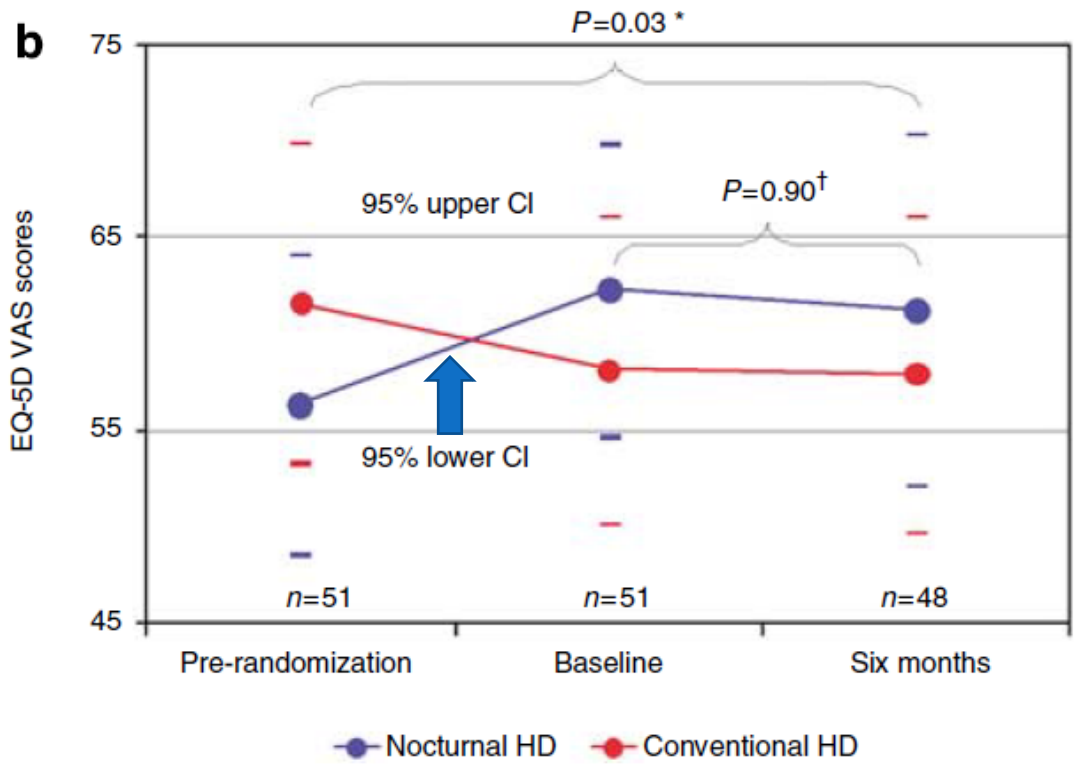
Q of L Measures in Our Program: Nocturnal Home Hemodialysis vs PD

Table 3. Comparisons of KDQOL values between NHD and PD patients

Variable	NHD		PD		*P*	
Symptom problem list	76.3 ± 2.5		71.9 ± 2.6		0.22	
Effect of kidney disease	61.5 ± 3.7		60.7 ± 2.7		0.85	
Burden of kidney disease	37.0 ± 4.4		47.0 ± 3.8	(better)	0.092	*
Work status	48.6 ± 7.6		36.0 ± 5.4		0.17	
Cognitive function	75.6 ± 4.8		81.4 ± 2.2		0.27	
Quality of social interaction	73.5 ± 3.0		75.8 ± 2.3		0.55	
Sexual function	81.7 ± 5.4	(better)	61.8 ± 9.0		0.07	*
Sleep	52.8 ± 3.9		54.1 ± 2.7		0.79	
Social support	65.7 ± 5.3		79.2 ± 2.8		0.027	
Dialysis staff encouragement	89.2 ± 2.6		85.7 ± 2.8		0.37	
Patient satisfaction	75.5 ± 4.3		79.2 ± 2.7		0.46	

Fong Clin J Am Soc Nephrol 2007

- Prevalent HD patients *expressing interest in transitioning to intensive home hemodialysis*
- Randomized to nocturnal hemodialysis or not
- Biggest improvement in Q of L occurred over randomization itself, not the next 6 months of the 2 dialysis regimens



Culleton JAMA 2007
Manns Kidney Int 2008

The Inevitable Systematic Review and Meta-Analysis

Chuasuwan Health Qual Life Outcomes 2020

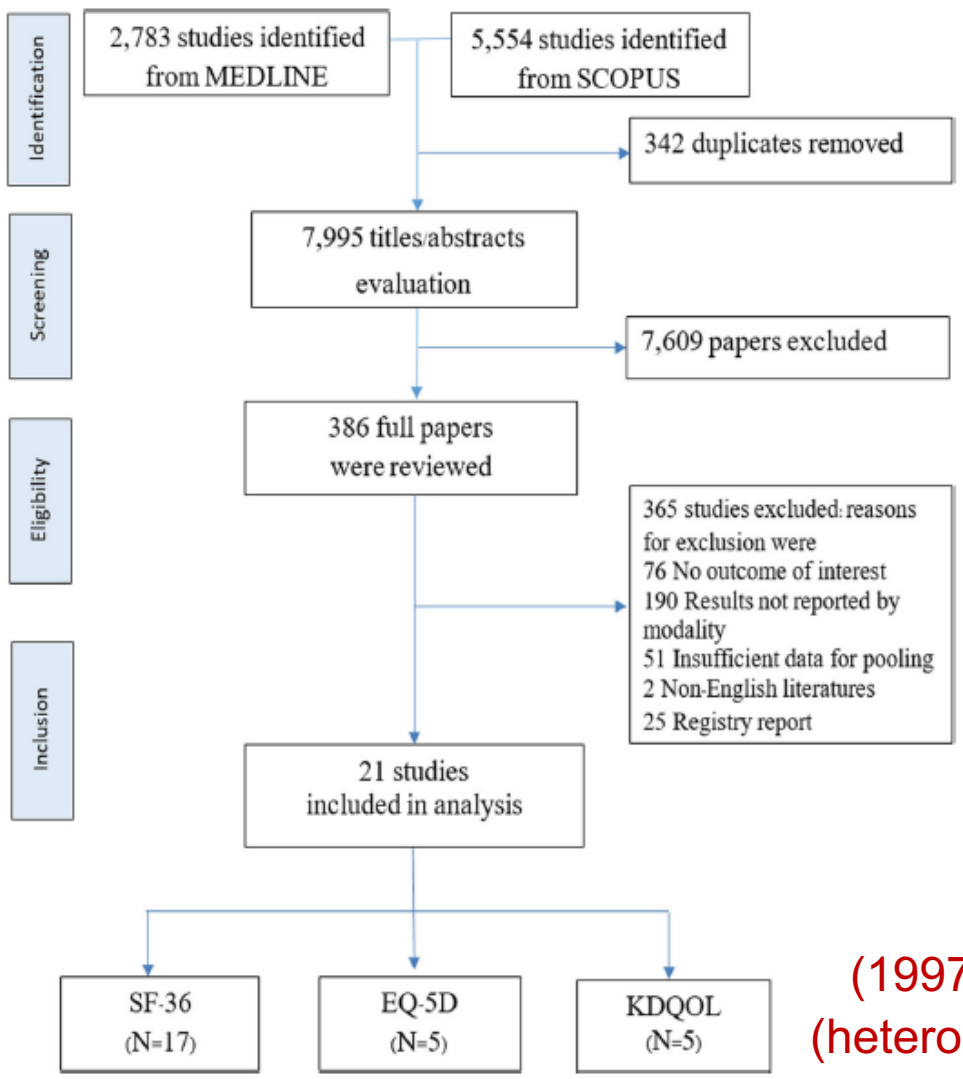


Fig. 1 Flow chart of study selection

(1997-2016)
(heterogeneity ++)

The Inevitable Systematic Review and Meta-Analysis

Chuasuwan Health Qual Life Outcomes 2020

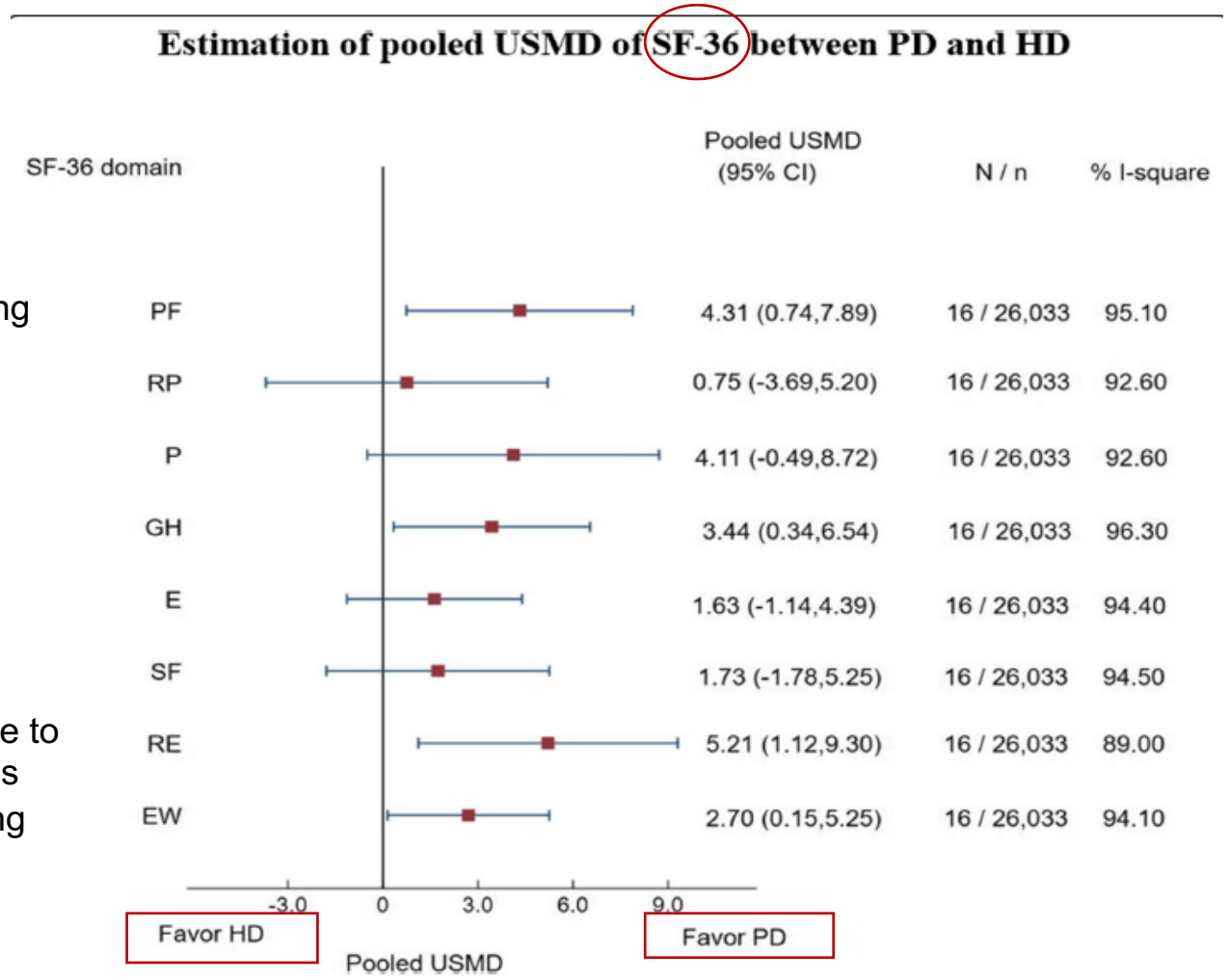


Fig. 2 Estimation of pooled USMD of SF-36 between PD and HD

- Contemporary survival studies don’t show a difference between in-centre hemodialysis and peritoneal dialysis
- The early survival benefit of PD compared to in-centre HD is likely an early survival *disadvantage* with HD, and confounded by acute starts and vascular access
- Patients themselves are more concerned about symptoms and functioning than survival
- There is a signal for better quality of life parameters in home-based dialysis compared to in-centre hemodialysis