LESSONS LEARNED FROM NEPHROLOGY TRIALS WITH RESPECT TO HEART FAILURE

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Disclosure of Interests

Consultant for:

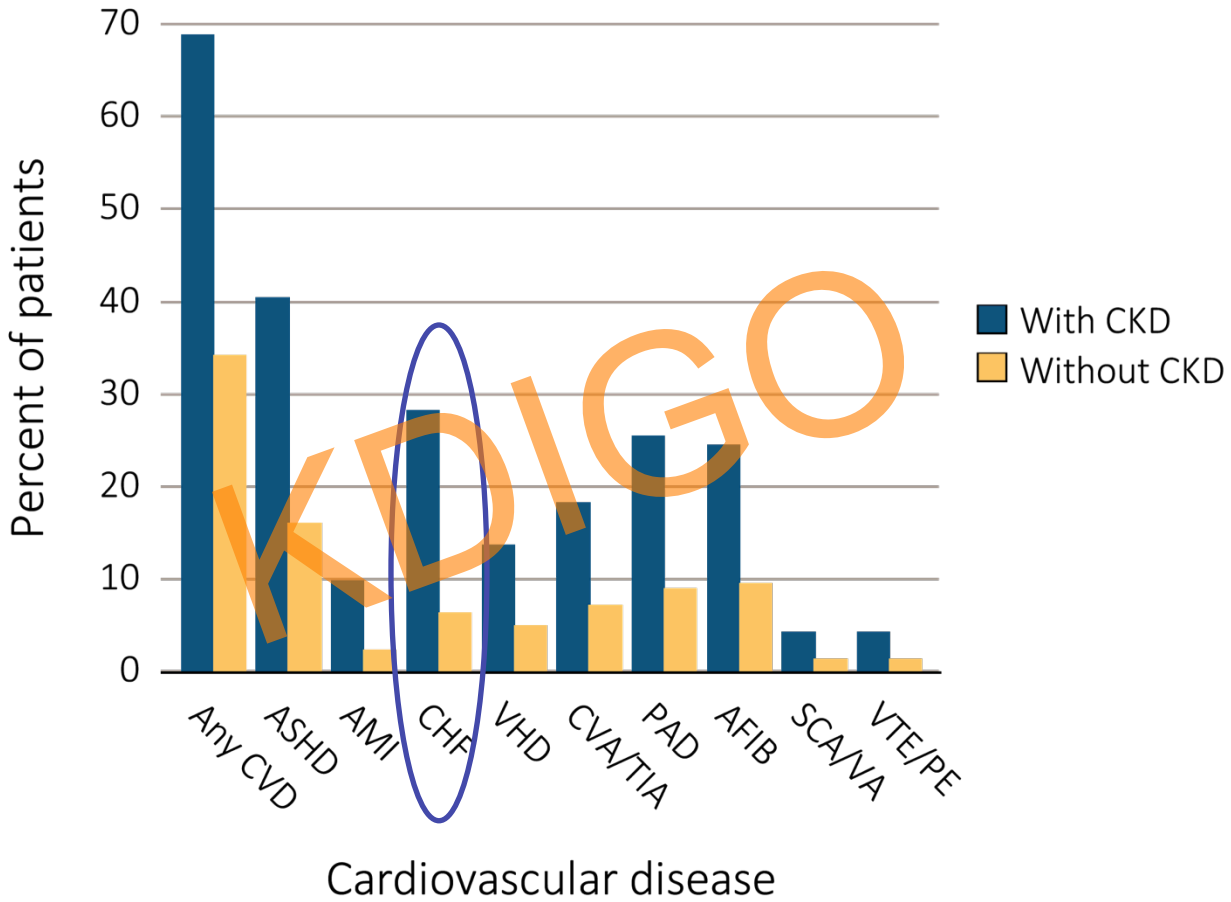
- Baxter
- NxStage
- Medtronic
- Intelomed

Objectives

To Review Available Studies and Trials with CKD and ESRD patients on Heart Failure Related Endpoints

- Definition
- Medical Therap(ies)
- Dialysis Interventions
  - Prescription
  - Dialysate Properties
- Outcomes
- Unmet Needs

Prevalence of cardiovascular diseases in patients with or without CKD



Data Source: Special analyses. Medicare 5 percent sample. Abbreviations: AFIB. atrial fibrillation: AMI. acute myocardial infarction: ASHD, atherosclerotic heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVA/TIA, cerebrovascular accident/ transient ischemic attack; CVD, cardiovascular disease; PAD, peripheral arterial disease; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; VHD, valvular heart disease; VTE/PE, venous thromboembolism and pulmonary embolism.

CKD adversely impacts on heart failure mortality (Swedish Heart Failure Registry)

Eu J Heart Failure 2017

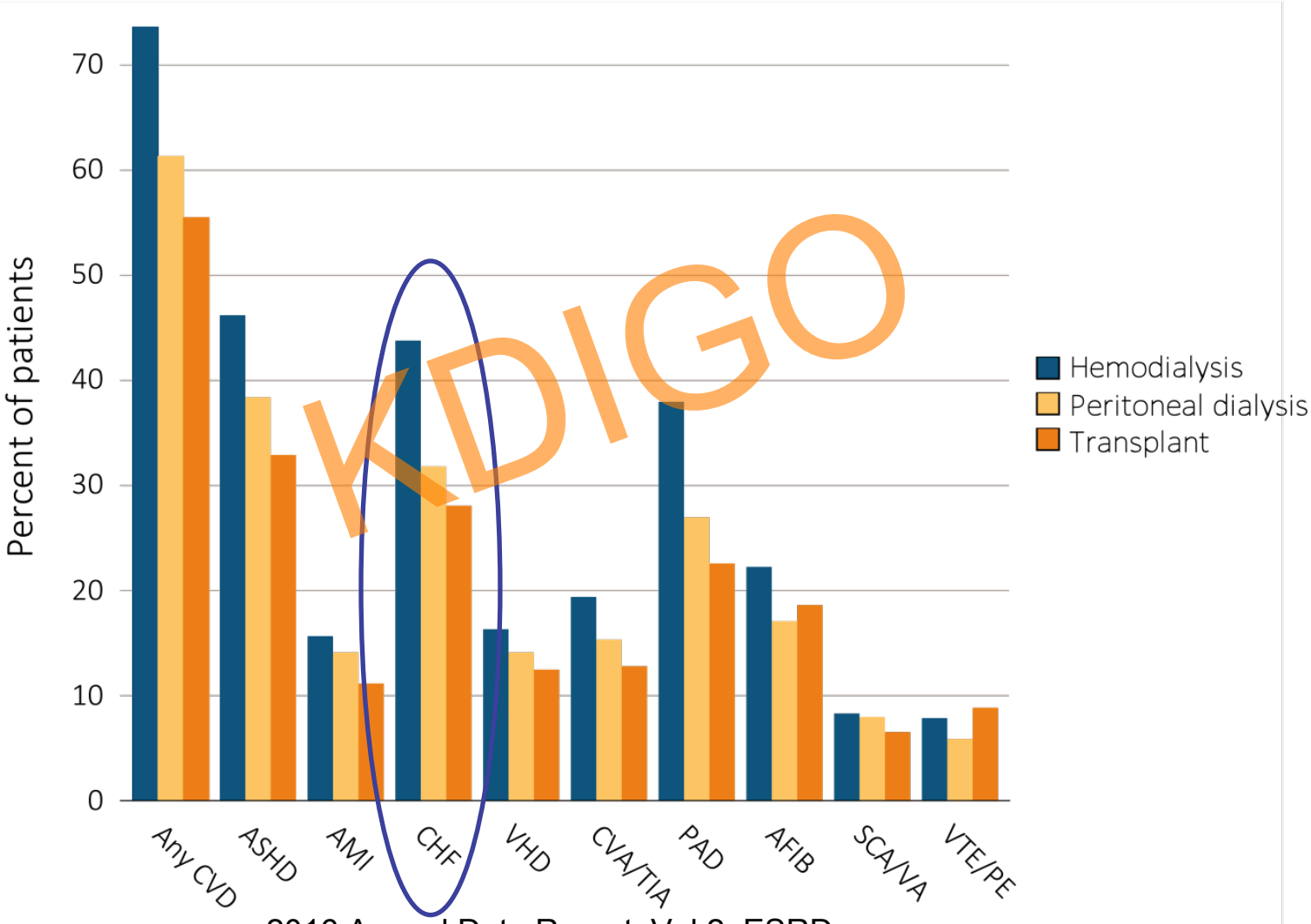
Table 3 Mortality in heart failure with preserved (HFpEF), mid-range (HFmrEF), and reduced ejection fraction (HFrEF) according to absence or presence of chronic kidney disease

	HFpEF ($n = 8860$)		HFmrEF ($n = 8350$)		HFrEF ($n = 22\,953$)	
	eGFR ≥60	eGFR <60	eGFR ≥60	eGFR <60	eGFR ≥60	eGFR <60
1-year mortality	13.4%	22.6%*	7.8%	22.4%*	8.0%	23.0%*
5-year mortality	41.8%	67.1%	32.0%	63.1%	31.1%	63.7%
Deaths/100 patient-years, *n*	2.79	4.41	2.23	4.79	2.04	4.49

eGFR, estimated glomerular filtration rate.

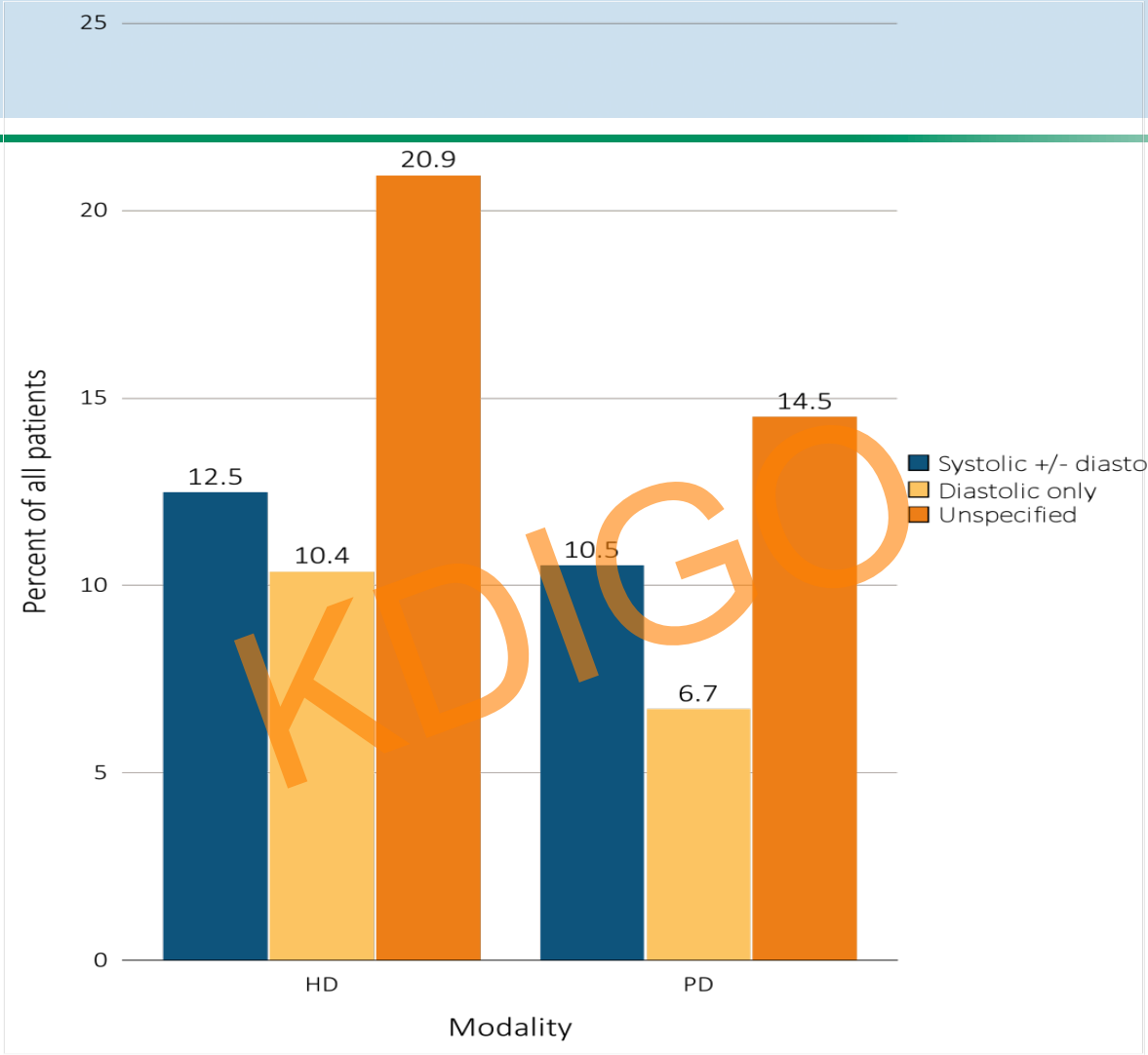
*$P < 0.001$, comparing eGFR ≥60 vs. <60 mL/min.1.73 m^2 within each ejection fraction group.

Prevalence of cardiovascular diseases in adult ESRD patients, by treatment modality



2016 Annual Data Report, Vol 2, ESRD, Ch 9 Cardiovascular disease

Figure 9.5 Heart failure in adult ESRD patients by modality, 2014



Data Source: Special analyses, USRDS ESRD Database. Point prevalent hemodialysis and peritoneal dialysis patients aged 22 and older, with Medicare as primary payer on January 1, 2014, who are continuously enrolled in Medicare Parts A and B from January, 1, 2013 to December 31, 2013,and ESRD service date is at least 90 days prior to January 1, 2014. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis.

Table 6.2 Unadjusted percentages of deaths due to cardiovascular disease (CVD), infection, other specified causes, and with missing data, by modality among ESRD patients, 2012

	Cause-specific mortality			
	CVD	Infection	Other cause	Missing cause
Modality				
ESRD	39%	9%	26%	26%
Dialysis	41%	9%	27%	23%
Transplant	11%	6%	16%	68%

Data Source: Special analyses, USRDS ESRD Database. Adjusted (age, race, sex, ethnicity, and primary diagnosis) all-cause mortality among 2012 prevalent patients. Ref: period prevalent ESRD patients, 2011. Abbreviations: CVD, cardiovascular disease; ESRD, end-stage renal disease.

Proposal for a Functional Classification System of Heart Failure in Patients With End-Stage Renal Disease

Proceedings of the Acute Dialysis Quality Initiative (ADQI) XI Workgroup

Lakhmir S. Chawla, MD,* Charles A. Herzog, MD,† Maria Rosa Costanzo, MD,‡ James Tumlin, MD,§ John A. Kellum, MD,|| Peter A. McCullough, MD, MPH,¶# Claudio Ronco, MD,** for the ADQI XI Workgroup

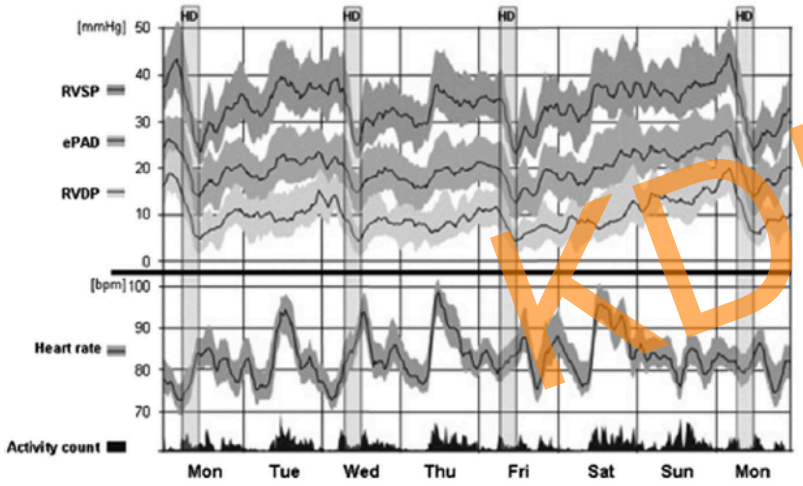
Questions

- What are the current classification system for HF in dialysis patients?
- What are the critical features of a staging system (for diagnostic and therapeutic approaches)?
- How can a new heart failure staging system specifically address the unique nature of nonphysiological periodic volume removal?

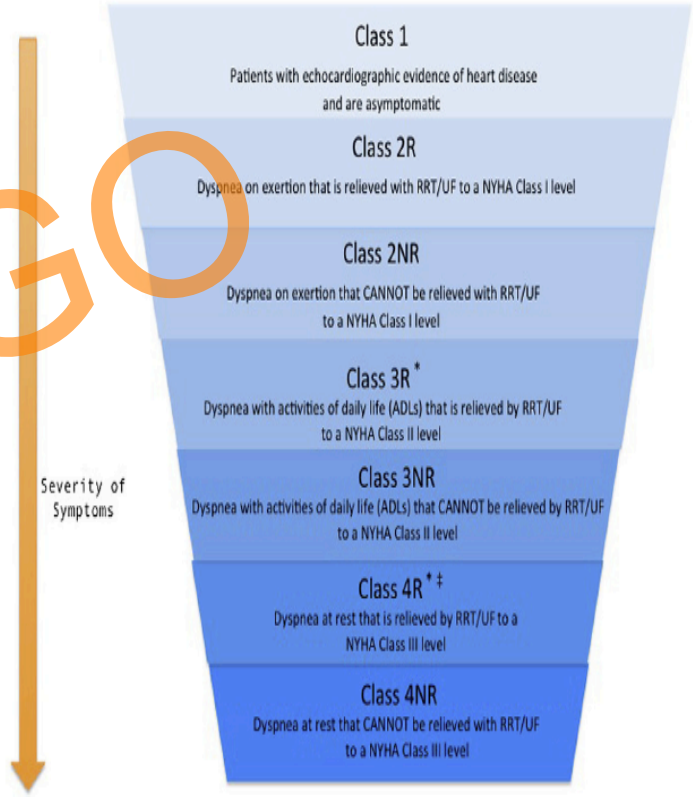
Proposed Staging System

- Standardized echo evidence for:
  - Structural
  - Functional abnormalities
- SOB occurring in the absence of primary lung disease (including pulmonary hypertension)
- Response of congestive symptoms to RRT/UF

JACC Vol. 63, No. 13, 2014
April 8, 2014:1246–52



Changes in Right Heart Pressures Over 8 Days in Patients Undergoing Hemodialysis



ADQI Heart Failure in ESRD Classification System

JACC Vol. 63, No. 13, 2014
April 8, 2014:1246–52

Chronic Fluid Overload and Mortality in ESRD

Zoccali et al – JASN 2017 (in press)

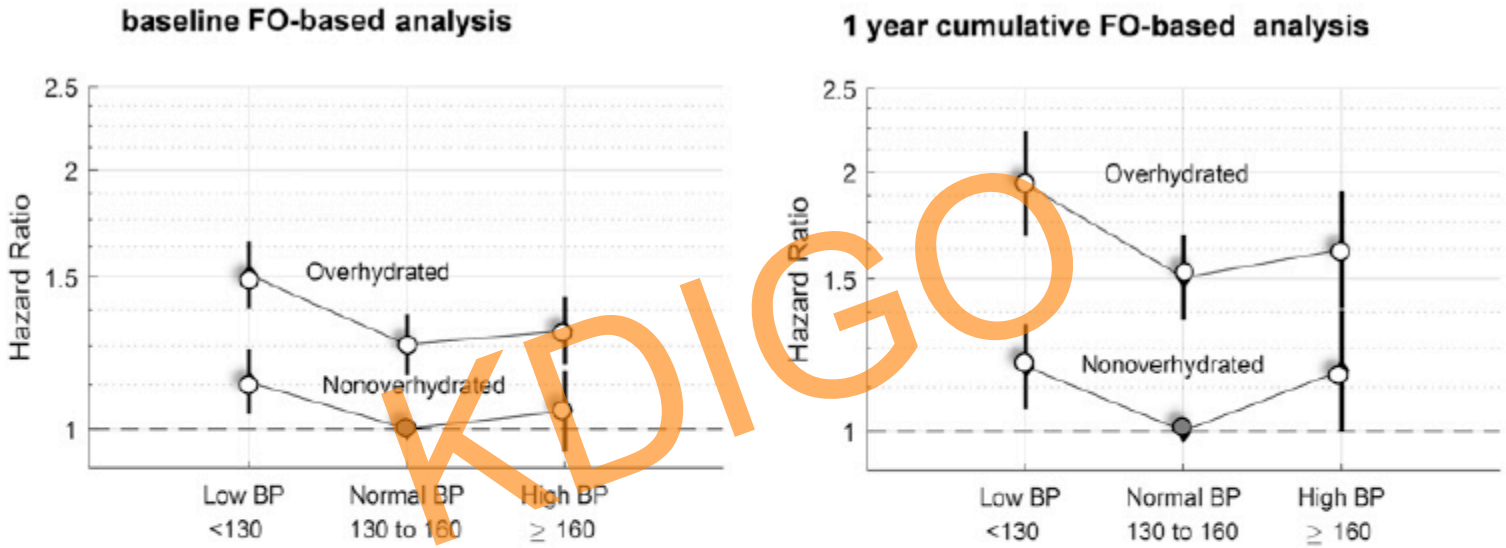
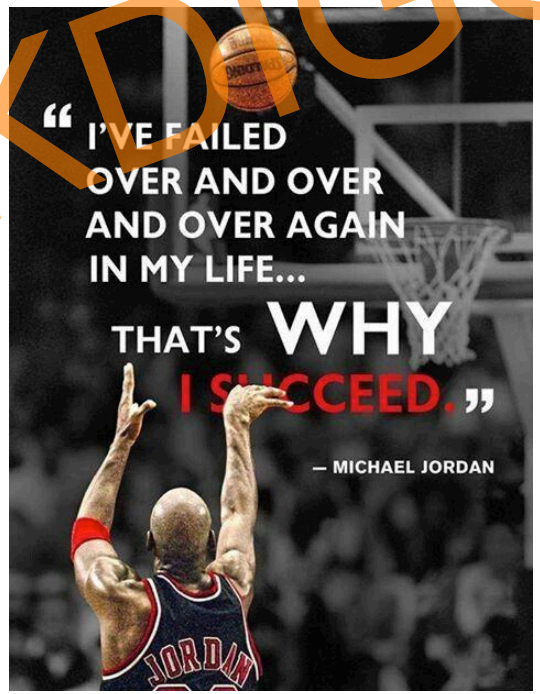


Figure 4. (Left panel) Baseline and (right panel) 1-year cumulative FO and mortality in patients stratified by predialysis systolic BP. Data are adjusted for the full list of variables in Table 1. Data are HR and 95% CIs. Fluid-overloaded patients had a significantly higher risk of death compared with nonoverloaded patients across all BP strata (all $P<0.001$).

Can we do anything about heart failure in CKD/ESRD?

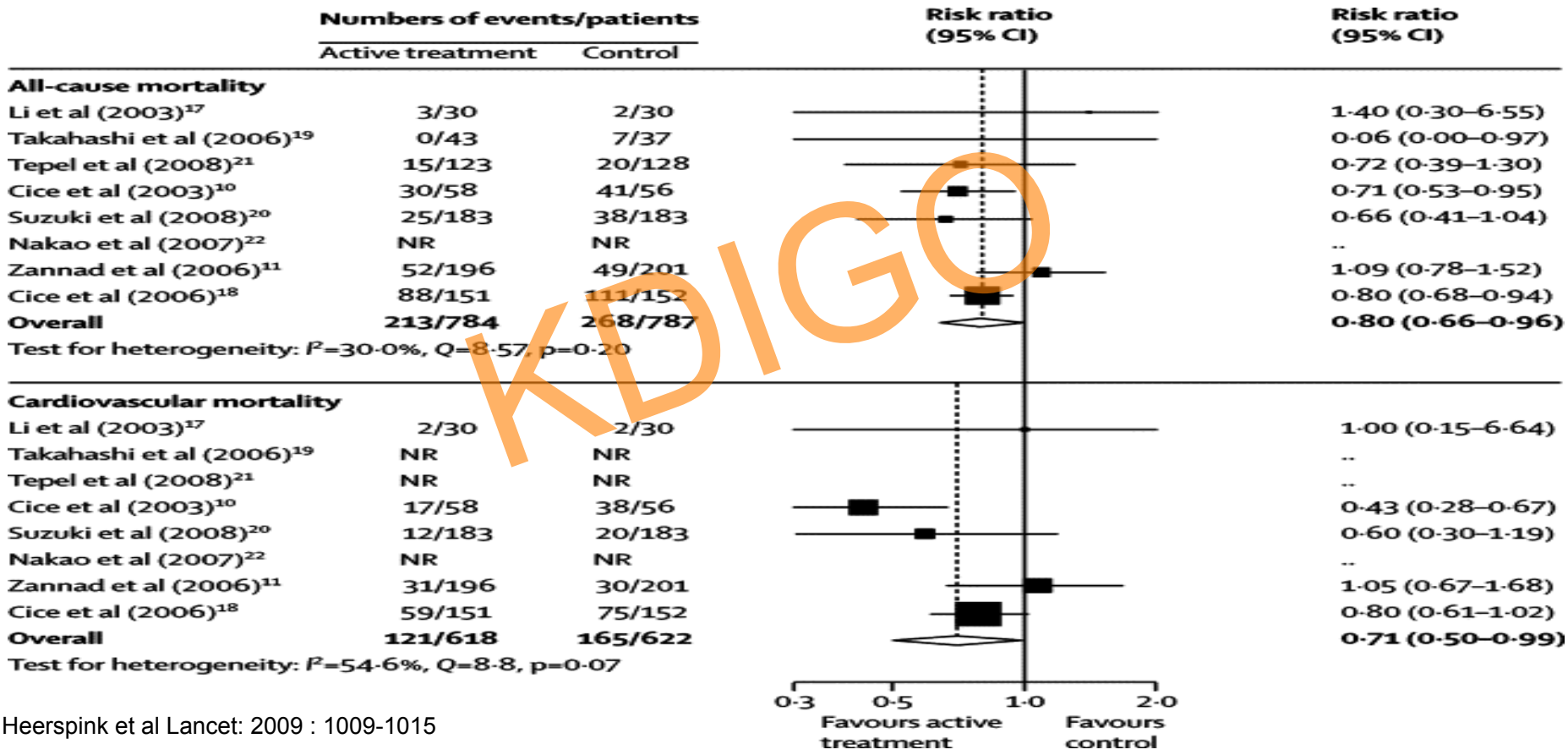


Issues…

- Paucity of trials examining HF in CKD/ESRD
- Outcomes are heterogenous
  - Functional improvement?
  - Structural improvement?
  - Conduction abnormalities?
  - CVS hospitalization?
  - CV mortality?
  - All cause mortality?

- Specific Emphasis ON:
  - Beta-Blocker
  - ACEi/ARB
  - MRA

What about vasoactive medications in ESRD?



Heerspink et al Lancet: 2009 : 1009-1015

Effect of Carvedilol in CKD (Meta-Analysis)

Table 3. Adjusted Risk (Hazard Ratios) for Primary and Secondary Outcomes in HF Patients Within CKD and Non-CKD Groups, Based on Treatment With Carvedilol

	CKD, eGFR ≤60 mL/min/1.73 m^2 (Carvedilol Versus Placebo) (n=1293 Versus 1273)		Non-CKD, eGFR >60 mL/min/1.73 m^2 (Carvedilol Versus Placebo) (n=822 Versus 829)	
Outcome	HR*	95% CI	HR*	95% CI
All-cause mortality	0.76	0.63–0.93	0.59	0.43–0.81
Cardiovascular mortality	0.77	0.62–0.94	0.59	0.42–0.82
HF mortality	0.68	0.52–0.88	0.58	0.34–0.99
First hospitalization for HF	0.74	0.62–0.88	0.83	0.63–1.09
Composite of cardiovascular mortality or hospitalization for HF	0.75	0.65–0.87	0.78	0.63–0.98
Sudden cardiac death	0.76	0.56–1.05	0.58	0.37–0.92

*HR is based on the Cox model after adjusting for treatment arm and study type.
There was no significant interaction of treatment and CKD/non-CKD for any of the outcomes.

Wali et al – Circ Heart Failure 2011, 4:18-26

BLOCADE

Roberts MA et al (AJKD 2016 (67): 902-11)

- Planned to recruit 150 patients
- Of 1443 patients screened – 354 eligible, 91 consented, 72 patients entered run-in phase.
- Unable to recruit planned sample size

ACEi and ARB

Yang et al – Int J Card 2016, 350 - 357

ENDPOINT = LVMI

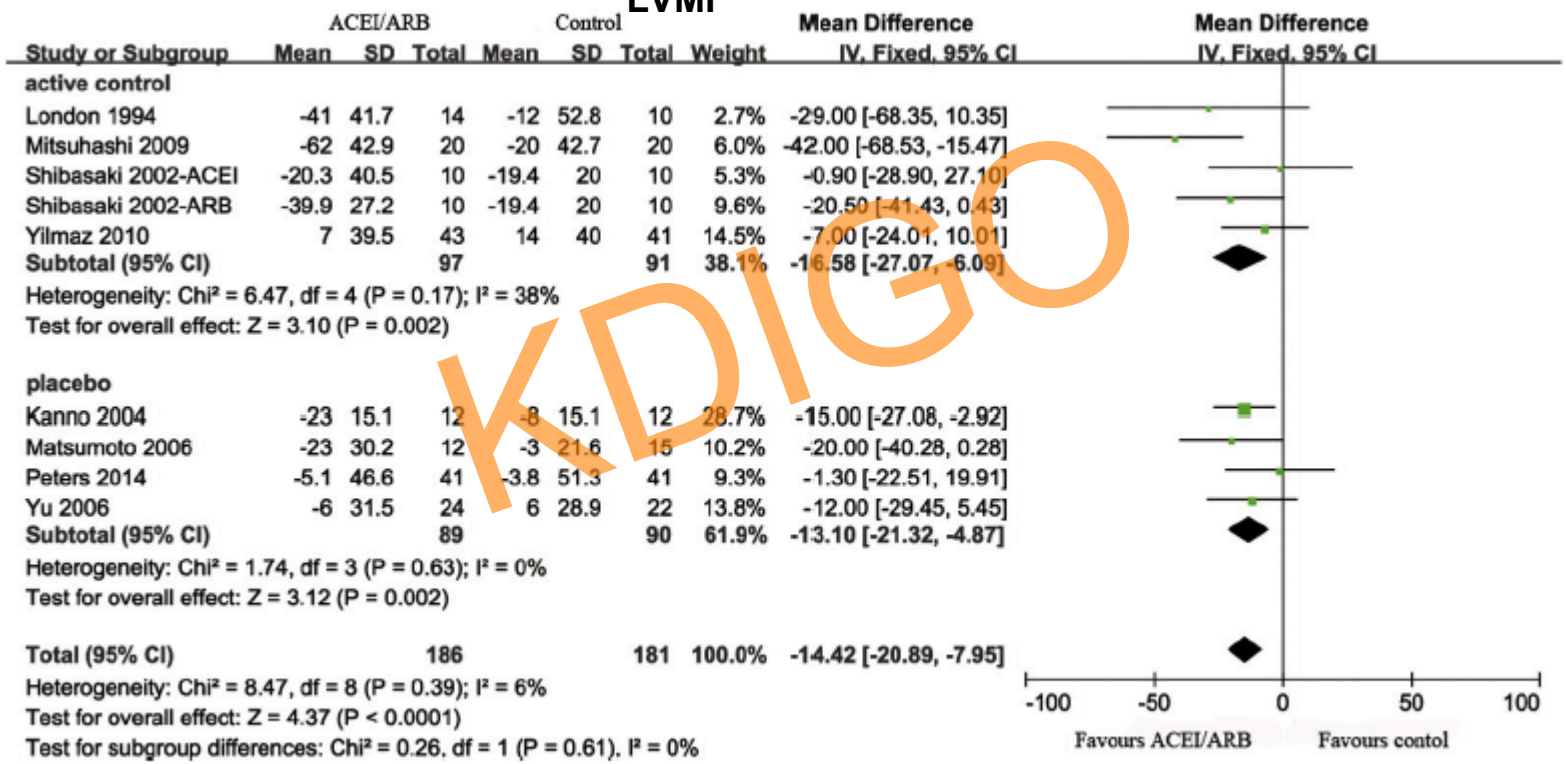


Fig. 4. Effect of RASi on LVMI. RASi: renin–angiotensin system inhibitors; LVMI: left ventricular mass index.

ACEi and ARB

Yang et al – Int J Card 2016, 350 - 357

PRIMARY ENDPOINT = LV EF

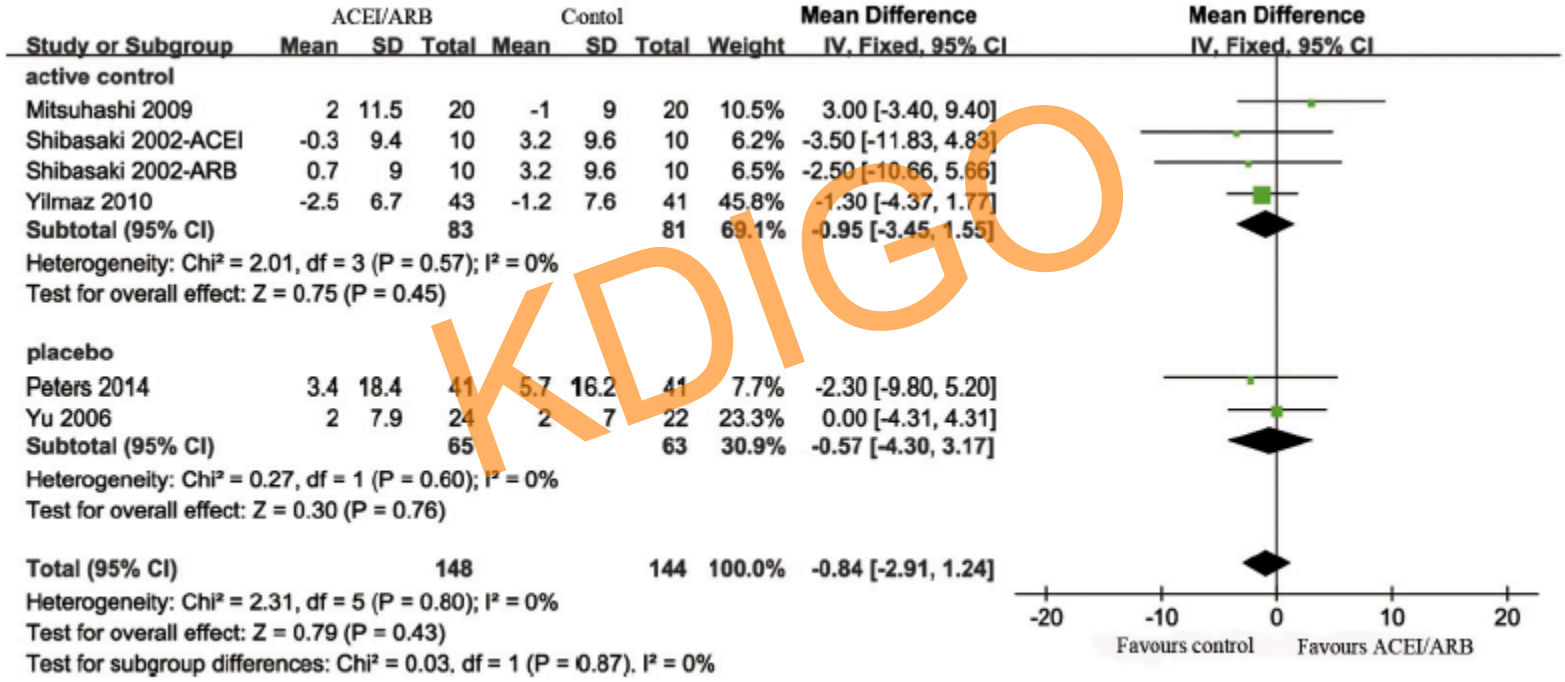


Fig. 6. Effect of RASi on EF. RASi: renin–angiotensin system inhibitors; EF: ejection fraction.

Not ACEi+ARB

Table 4 | Mortality hazard ratios in hypertensive ESRD subjects initiated on an ACEI or ARB, followed by another concomitant antihypertensive medication

	Number of events	Unadjusted model (n=9325) HR (95% CI)	Adjusted model[a] (n=8282) HR (95% CI)
Risk of cardiovascular death			
ACEI+other anti-HTN drug	514 (7.4%)	1.00 (0.75–1.33)	0.87 (0.72–1.06)
ARB+other anti-HTN drug	107 (6.1%)	0.83 (0.60–1.16)	0.69 (0.57–0.84)
ACEI+ARB	53 (7.4%)	1.00 (ref)	1.00 (ref)

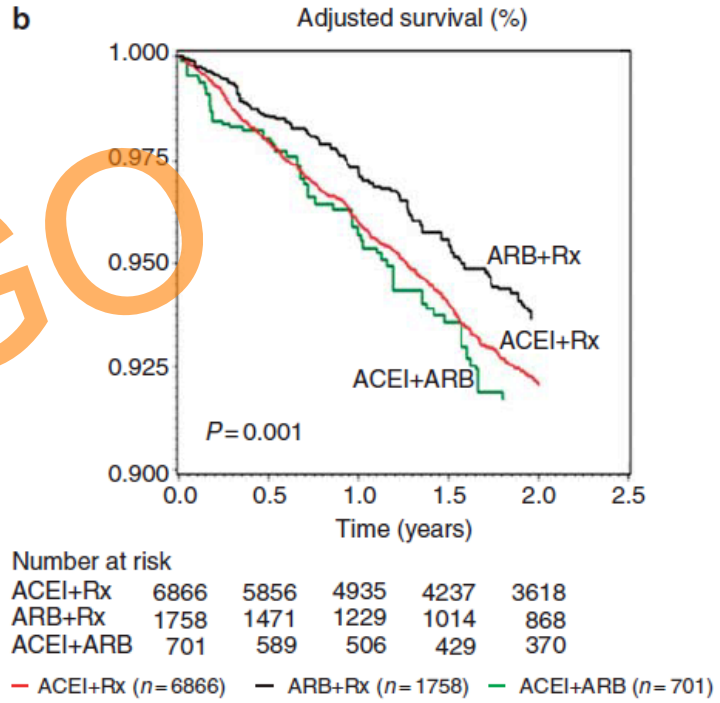
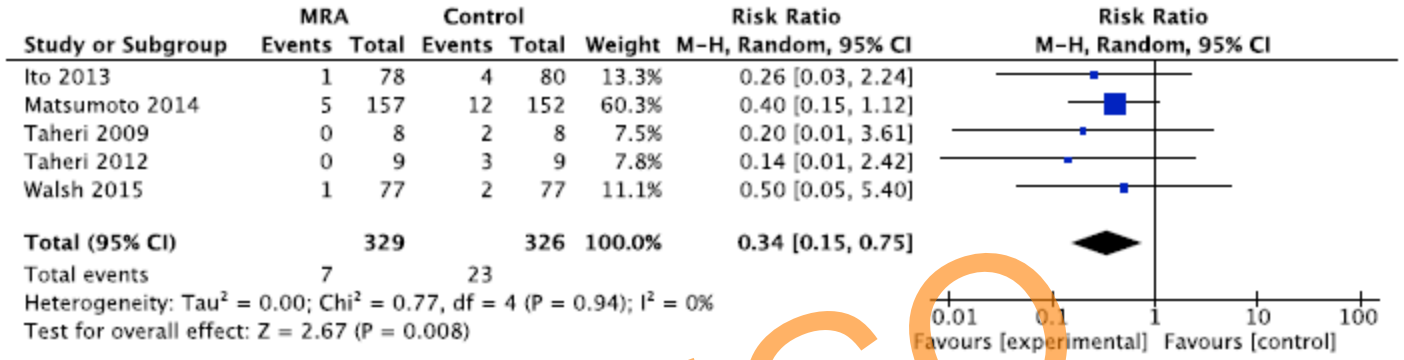


Figure 2 | Cardiovascular survival curves. (**a**) Crude and (**b**) adjusted survival curves in patients in whom treatment was initiated with an ACEI + other antihypertensive (antiHTN) medications (ACEI + Rx), an angiotensin receptor blocker (ARB) + antiHTN (ARB + Rx), or an ACEI + ARB. ACEI, angiotensin-converting enzyme inhibitor.

Chan et al, KI 2011

Mineralocorticoid Receptor Antagonist in Dialysis

Quach et al – AJKD 2016 68:591-98

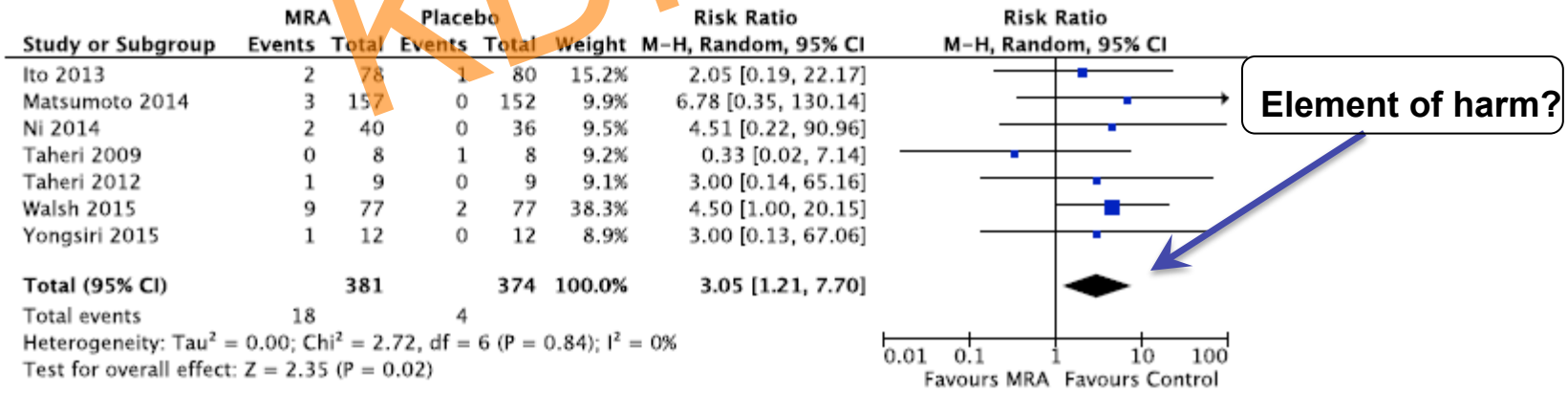


Study or Subgroup	MRA Events	MRA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ito 2013	1	78	4	80	13.3%	0.26 [0.03, 2.24]
Matsumoto 2014	5	157	12	152	60.3%	0.40 [0.15, 1.12]
Taheri 2009	0	8	2	8	7.5%	0.20 [0.01, 3.61]
Taheri 2012	0	9	3	9	7.8%	0.14 [0.01, 2.42]
Walsh 2015	1	77	2	77	11.1%	0.50 [0.05, 5.40]
Total (95% CI)		**329**		**326**	**100.0%**	**0.34 [0.15, 0.75]**
Total events	7		23			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.77$, df = 4 (P = 0.94); $I^2 = 0\%$

Test for overall effect: Z = 2.67 (P = 0.008)

Figure 2. Forest plot of the effects of mineralocorticoid receptor antagonists (MRAs) on cardiovascular mortality in dialysis patients. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.



Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Ito 2013	2	78	1	80	15.2%	2.05 [0.19, 22.17]
Matsumoto 2014	3	157	0	152	9.9%	6.78 [0.35, 130.14]
Ni 2014	2	40	0	36	9.5%	4.51 [0.22, 90.96]
Taheri 2009	0	8	1	8	9.2%	0.33 [0.02, 7.14]
Taheri 2012	1	9	0	9	9.1%	3.00 [0.14, 65.16]
Walsh 2015	9	77	2	77	38.3%	4.50 [1.00, 20.15]
Yongsiri 2015	1	12	0	12	8.9%	3.00 [0.13, 67.06]
Total (95% CI)		**381**		**374**	**100.0%**	**3.05 [1.21, 7.70]**
Total events	18		4			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.72$, df = 6 (P = 0.84); $I^2 = 0\%$

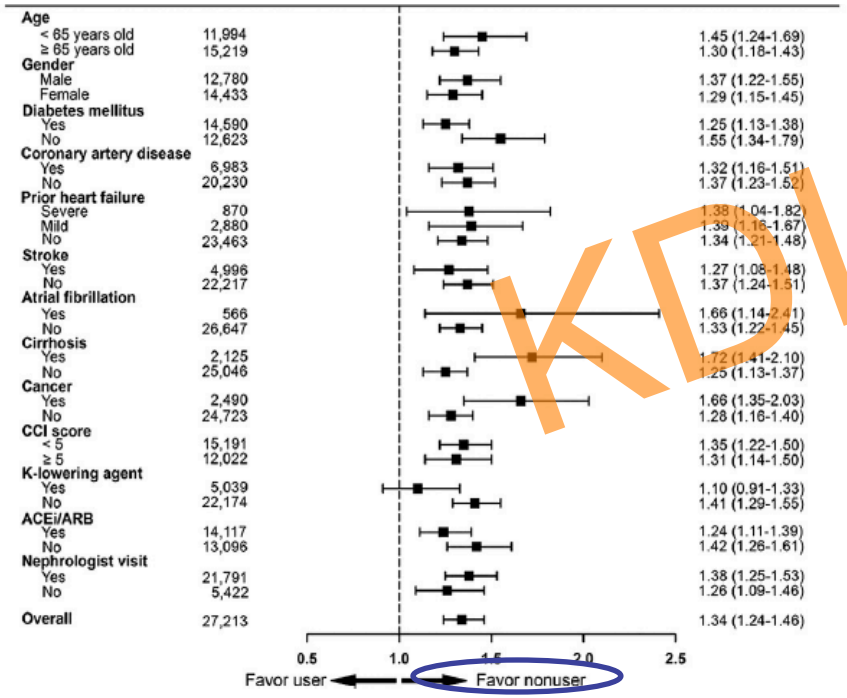
Test for overall effect: Z = 2.35 (P = 0.02)

Figure 4. Forest plot of the effect of mineralocorticoid receptor antagonists (MRAs) on hyperkalemia in dialysis patients. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Effect of spironolactone on the risks of mortality and hospitalization for heart failure in pre-dialysis advanced chronic kidney disease: A nationwide population-based study

Tseng et al – Int J Cardiology (in press)

All Cause Mortality



Hospitalization for Heart Failure

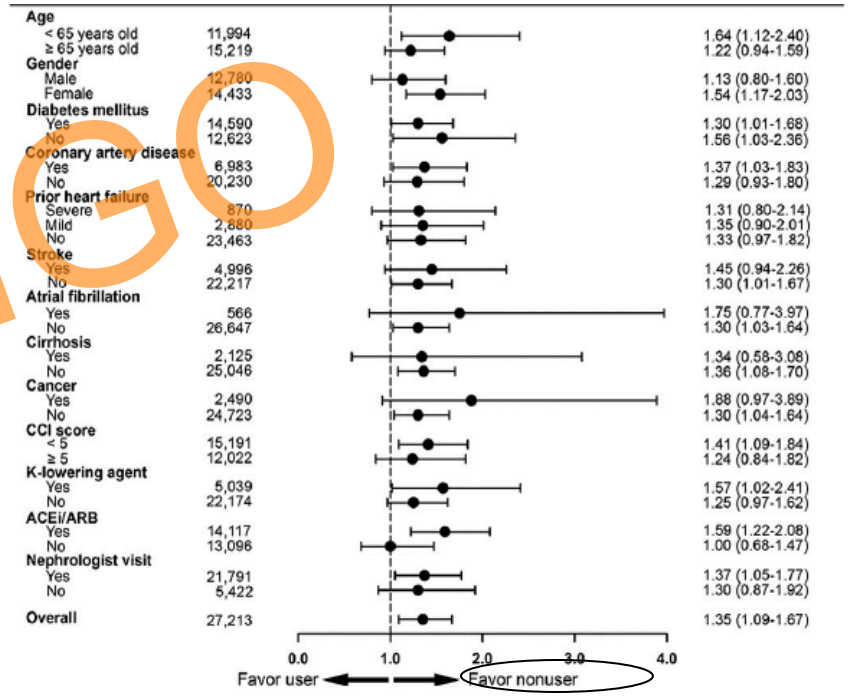


Fig. 3. Propensity-score matched adjusted hazard ratios (HRs) of (A) all-cause mortality and (B) hospitalization for heart failure among patients with predialysis stage 5 chronic kidney disease by spironolactone use. The risks of (A) all-cause mortality and (B) hospitalization for heart failure in the spironolactone user and non-user groups are shown, stratified by the baseline characteristics. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-II receptor blocker; CCI = Charlson comorbidity index; CI = confidence interval.

Summary (so far)

- Medical therapies
  - Relatively few studies
  - Beta blocker:
    - meta-analysis → favourable
    - RCT → unable to recruit to target
  - ACEi/ARB:
    - Vasoactive
    - ? Change cardiac function
  - MRA: ? Signal of harm

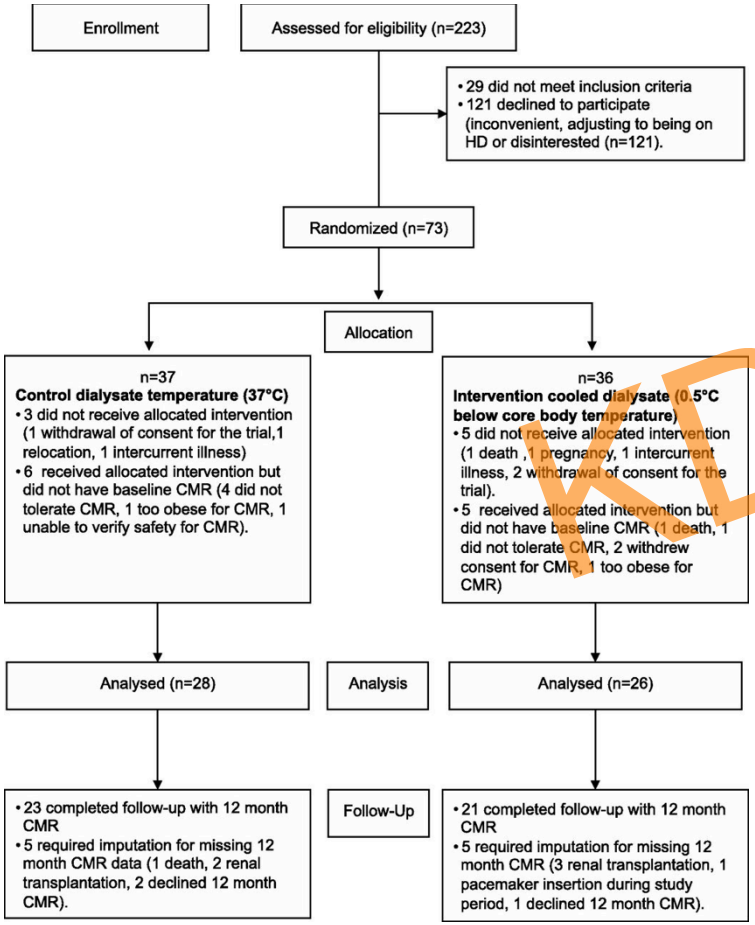
What about intra-dialytic management?

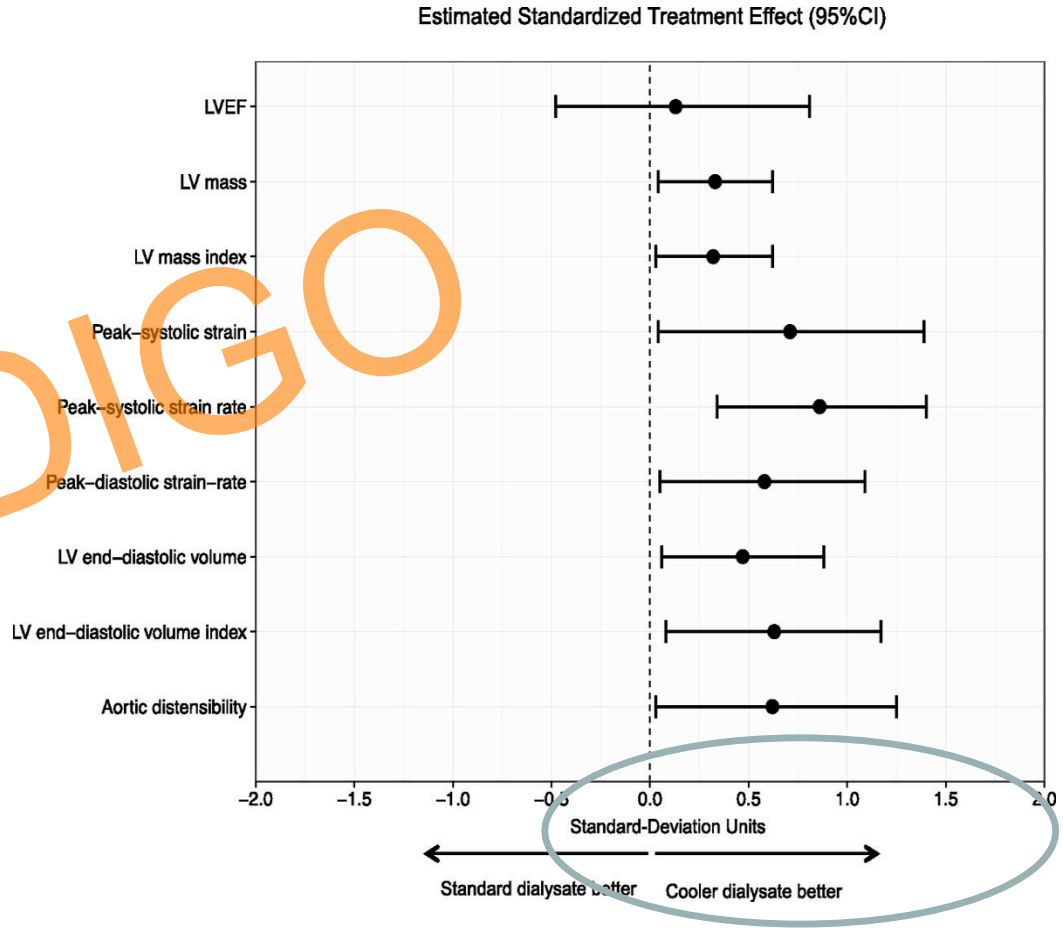
- Changes in dialysate composition
  - Na → lowering sodium is favoured
    - Hemodynamics
    - Reduced high inter-dialytic weight gain
  - K → extremes of serum K is associated with higher mortality
    - But does it improve with modifying dialysate K?
  - High Dialysate Calcium → BP control

- Intra-dialytic Medications
  - TPN → limited caloric intervention
  - Carnitine → limited support
  - BP modification → ? Symptoms

Dialysate Temp

Randomized Controlled Trial of Individualized Dialysate Cooling for Cardiac Protection in Hemodialysis Patients (Odudu et al. CJASN 2015 1408-1417)





Typical Treatment Parameters During Frequent Hemodialysis

	Conventional HD	Short Daily HD	Nocturnal HD	NxStage HD
Treatments/wk	3	5-6	5-6	6
Treatment time (hrs)	3-4	2-3	6-8	2.5-3.5
Blood Flow Rate (ml/min)	200-400	400	200-300	400
Dialysate Flow Rate (ml/min)	500-800	500-800	200-350	130

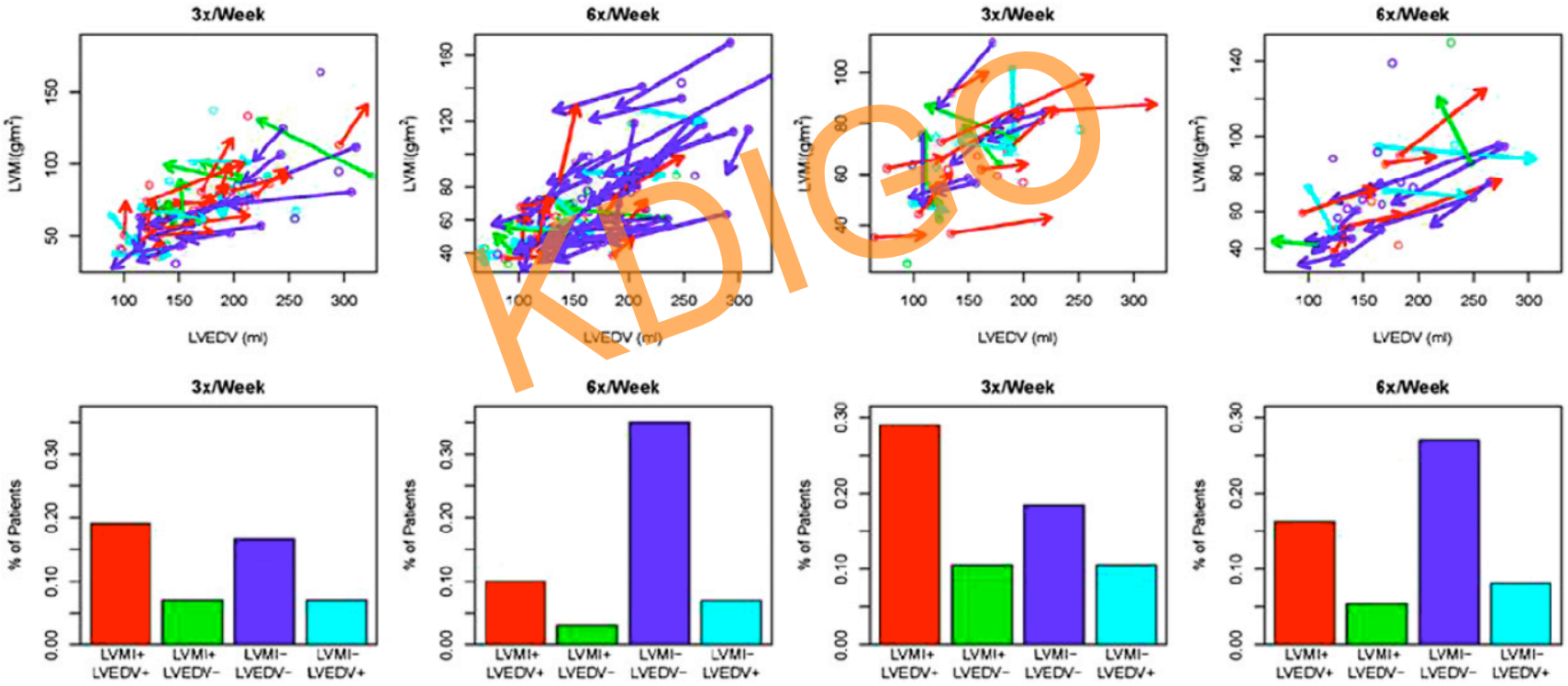
Cardiovascular Outcomes

Parameter	Number of Studies	Effect Size
Left Ventricular Mass Index (g/m2)	23 studies, 524 patients	-31.2 (-39.8 to -22.5)
Left Ventricular Mass (g)	13 studies, 335 patients	-60.5 (-90.8 to -30.2)
Left Ventricular Mass (g) [in RCTs only]	3 studies	-13.4 (-19.5 to -7.4)
Left Ventricular Ejection Fraction (%)	4 studies, 137 patients	6.7 (1.6 to 11.9)

Susantitaphong et al AJKD 2012

Effects of Frequent Hemodialysis on Ventricular Volumes and Left Ventricular Remodeling

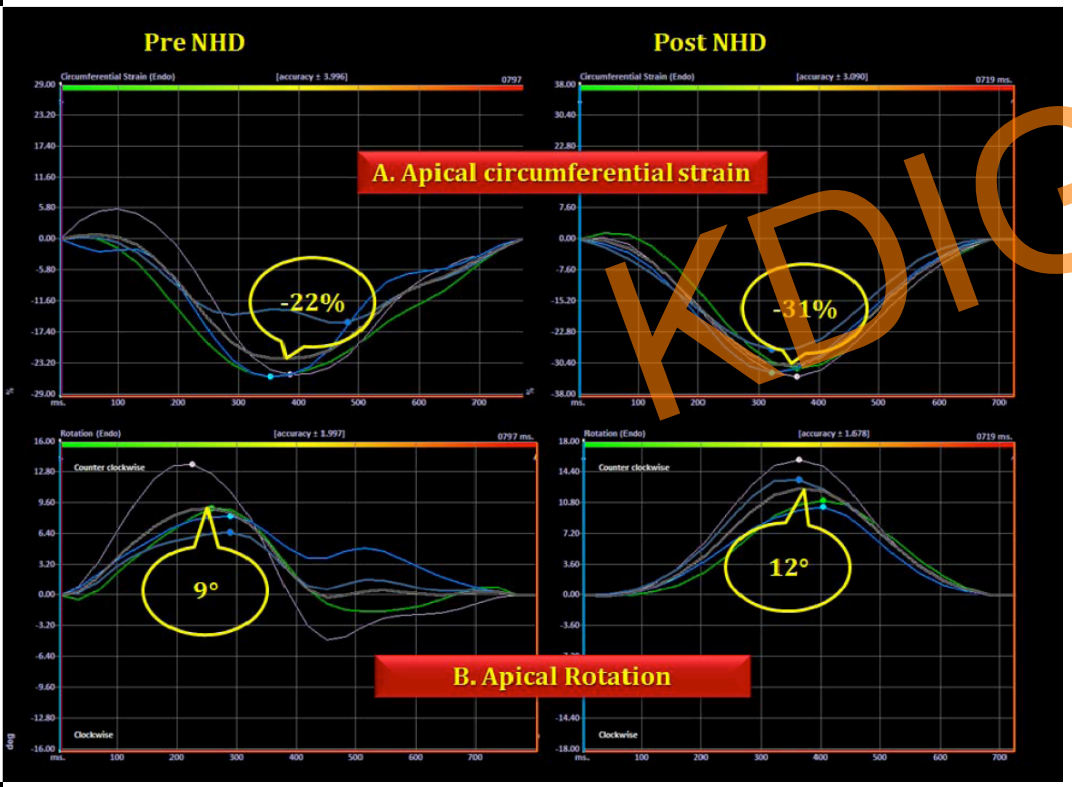
Christopher T. Chan, Tom Greene,† Glenn M. Chertow,‡ Alan S. Kliger,§ John B. Stokes,‖ Gerald J. Beck,¶ John T. Daugirdas,** Peter Kotanko,†† Brett Larive,¶ Nathan W. Levin,†† Ravindra L. Mehta,‡‡ Michael Rocco,§§ Javier Sanz,‖‖ Phillip C. Yang,‡ Sanjay Rajagopalan,¶¶ and the Frequent Hemodialysis Network Trial Group*



Chan et al CJASN 2013

Impact of Frequent Nocturnal Hemodialysis on Myocardial Mechanics and Cardiomyocyte Gene Expression

Christopher T. Chan, MD; Sara Arab, PhD; Shemy Carasso, MD; Gil Moravsky, MD; Guo Hua Li, PhD; Peter P. Liu, MD*; Harry Rakowski, MD*



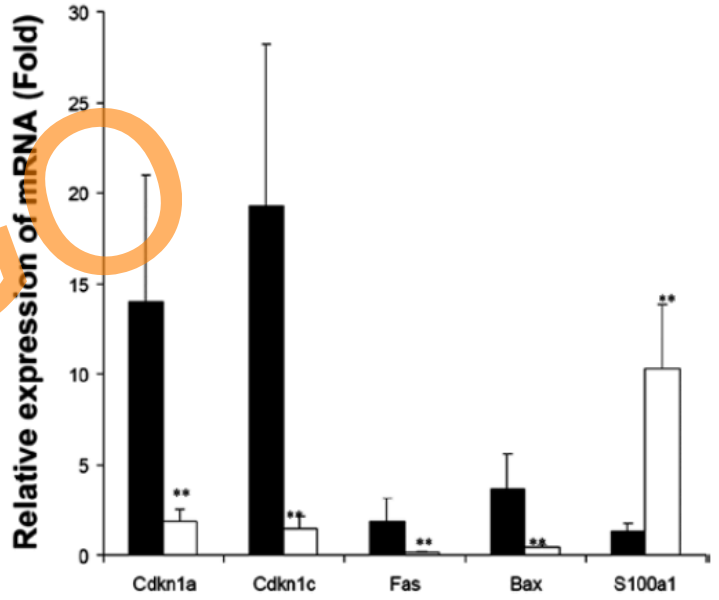
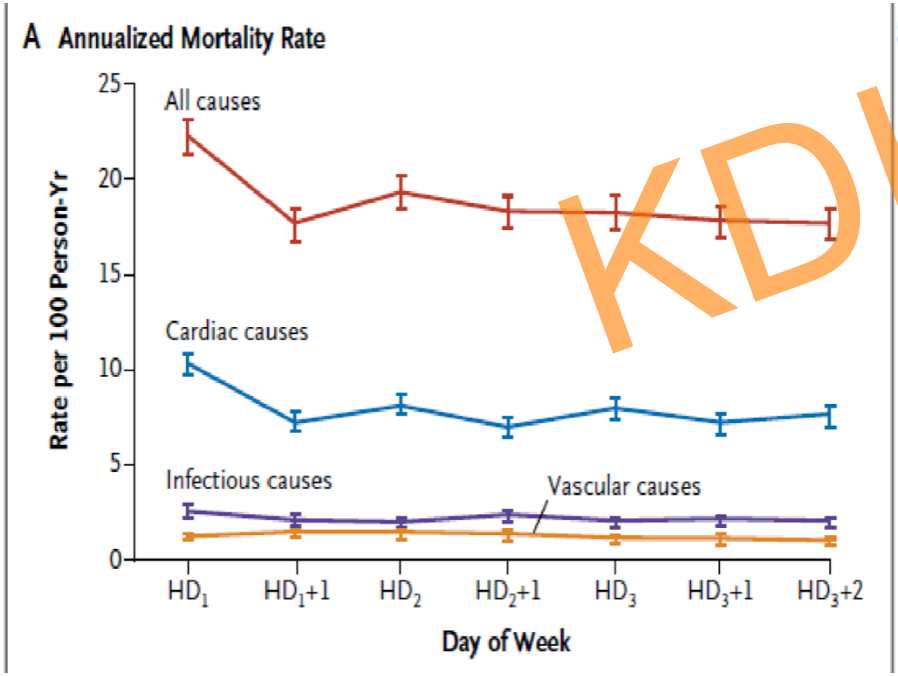
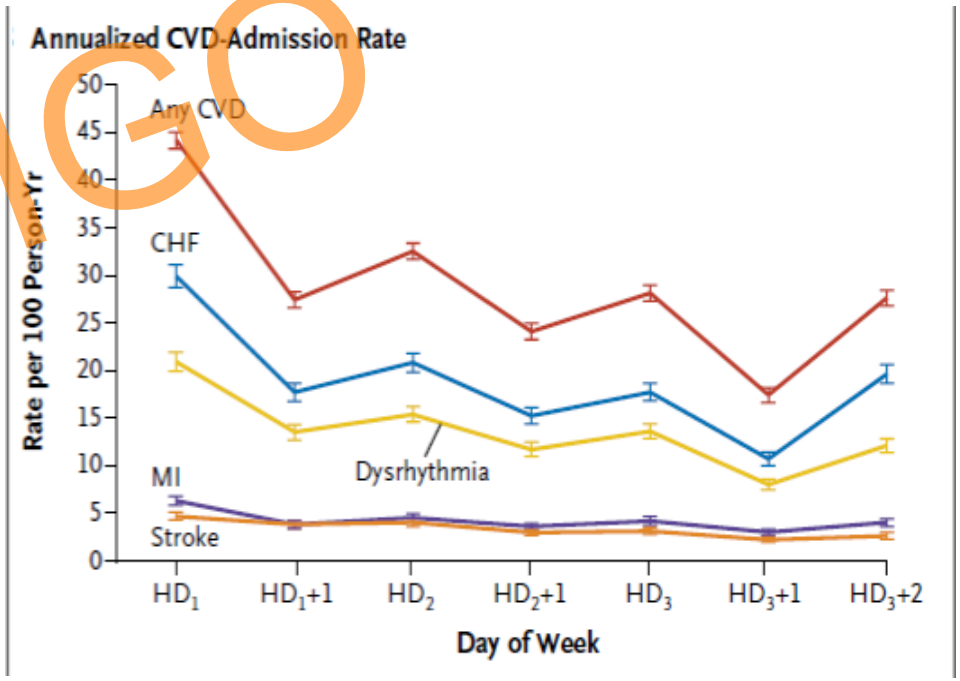


Figure 2. Real-time quantitative polymerase chain reaction confirmation of cardiomyocyte gene signature before and after conversion from conventional to nocturnal hemodialysis. Black bar indicates conventional hemodialysis. White bar indicates nocturnal hemodialysis. ***P*<0.05 between conventional hemodialysis and nocturnal hemodialysis. *Cdkn1a* indicates cyclin-dependent kinase inhibitor 1A; *Cdkn1c*, cyclin-dependent kinase inhibitor 1C; *Bax*, Bcl2-associated X protein; *S100a1*, S 100 calcium binding protein A1.

Long Interdialytic Interval and Mortality among Patients Receiving Hemodialysis

Robert N. Foley, M.B., David T. Gilbertson, Ph.D., Thomas Murray, M.S., and Allan J. Collins, M.D.





Foley et al – NEJM 2011

CVS Hospitalization: Frequent HD versus Conventional HD

Table 2. Pooled HRs of Type-Specific Hospital Admissions for Daily Home Hemodialysis Patients in Intention-to-Treat and On-Treatment Analysis

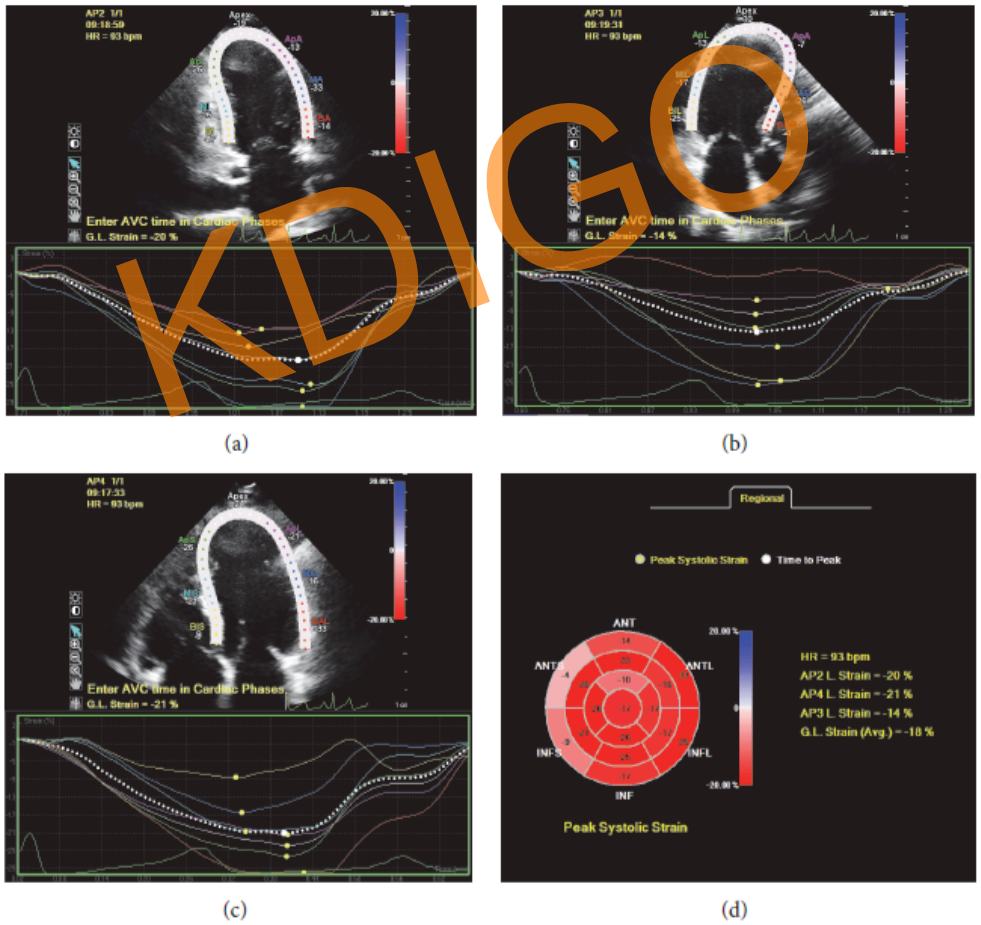
	Intention-to-Treat		On-Treatment	
	HR (95% CI)	%[a]	HR (95% CI)	%[a]
Cardiovascular disease				
Arrhythmia	0.97 (0.84-1.12)	10.4	1.00 (0.86-1.17)	11.2
Cerebrovascular disease	0.85 (0.71-1.02)	5.8	0.75 (0.60-0.93)	5.9
Heart failure, fluid overload, and cardiomyopathy	0.69 (0.62-0.77)	20.4	0.59 (0.52-0.68)	18.5
Hypertensive disease	0.88 (0.80-0.96)	24.0	0.84 (0.75-0.93)	24.4
Ischemic heart disease	0.94 (0.84-1.05)	16.6	0.91 (0.80-1.03)	16.1
Peripheral artery disease	1.06 (0.95-1.18)	16.8	1.02 (0.90-1.15)	17.5
Other cardiovascular disease	1.18 (0.98-1.41)	5.9	1.19 (0.97-1.45)	6.3

Summary

- 1. CVS medical therapy may improve HF in ESRD
- 2. Intra-dialytic management (hypothermic dialysis) may be an effective / widely applicable strategy in ESRD
- 3. Alternate dialysis strategy may improve CVS endpoints

Unmet Need 1

- Imaging of CKD/ESRD patients → Definition of Heart Failure



Unmet Need 2

- Paucity of Heart Failure Trials in CKD/ ESRD
  - Volume monitoring
    - Lung Water (recruiting)
    - Pulmonary Artery Pressure Monitoring
    - Biosensors
  - Therapeutics
    - Spironolactone (+/- K trap?)

Unmet Need 3

- The need for new therapeutics in CKD/ESRD
  - ? Anti-fibrotic therapy

Questions / Comments?