Heart and Kidney

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High Prevalence of CVD in CKD & ESRD

	CAD (Clinical)	LVH (Echo)	CHF (Clinical)
GP	5-12*	20†	5‡
CRI	NA	25-50 (varies with renal function)§	NA
HD	40	75¶	40
PD	40	75¶	40
RTR	15#	50**	NA

Foley RN et al, AJKD 1998; 32(suppl 3):S112-9

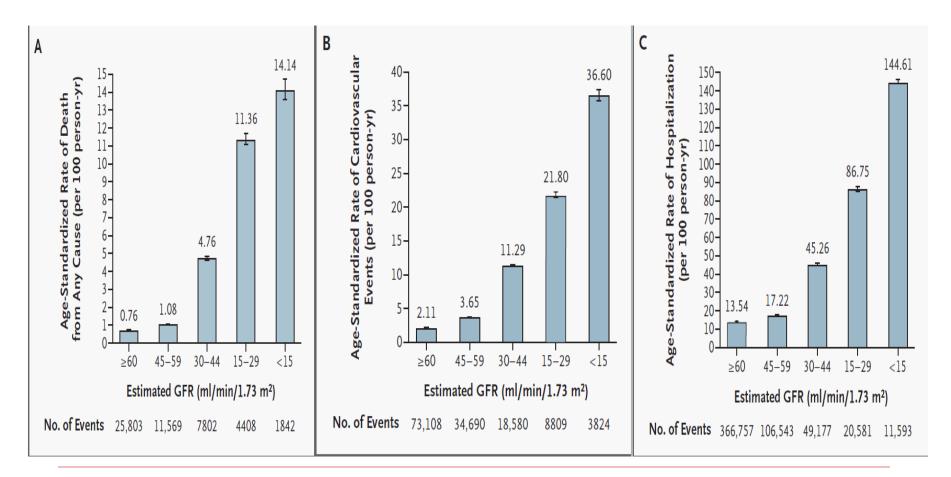
High CV Mortality in ESRD

All Men Women White Black Diabetic Nondiabetic

0.28 0.28 0.27 0.29 0.23 0.80 0.26 GP 7.78 9.12 9.38 8.83 11.18 6.68 11.09 HD 10.76 6.07 8.14 9.24 10.27 13.22 7.09 PD RTR 0.54 0.59 0.43 0.53 0.56 1.11 0.39

Foley RN et al, AJKD 1998; 32(suppl 3):S112-9

CKD Increased Risks of Death, CV Events & Hospitalization



Go AS et al, NEJM 2004;351:1296-305

CRS general definition:

Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other

Acute CRS (Type 1) Acute worsening of cardiac function leading to renal dysfunction

Chronic CRS (Type 2) Chronic abnormalities in cardiac function leading to renal dysfunction

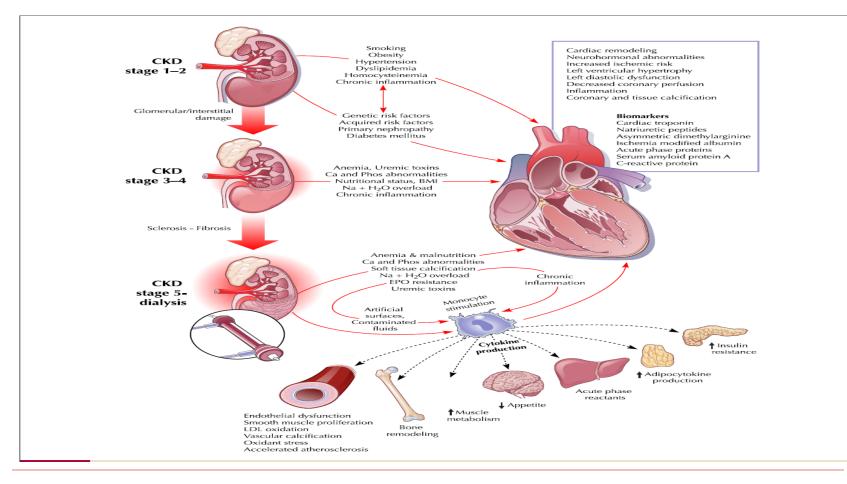
Acute Renocardiac Syndrome (Type 3) Acute worsening of renal function causing cardiac dysfunction

Chronic Renocardiac Syndrome (Type 4) Chronic abnormalities in renal function leading to cardiac disease

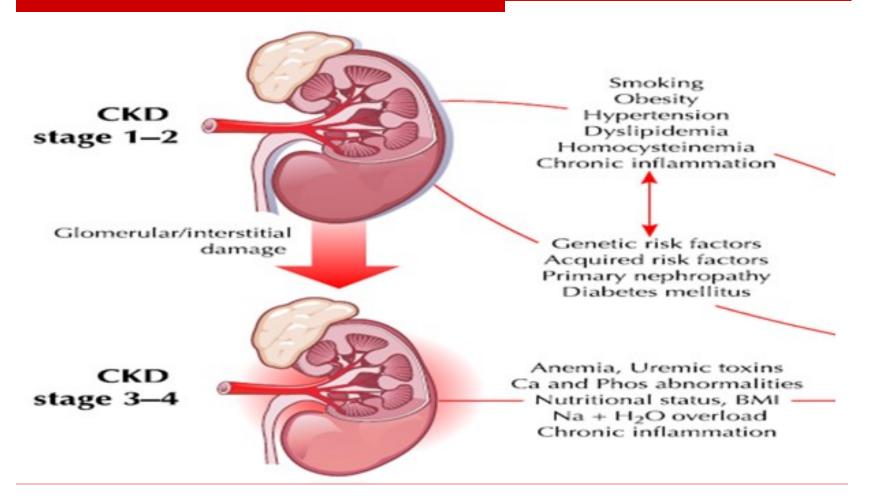
Secondary CRS (Type 5)

Systemic conditions causing simultaneous dysfunction of the heart and kidney

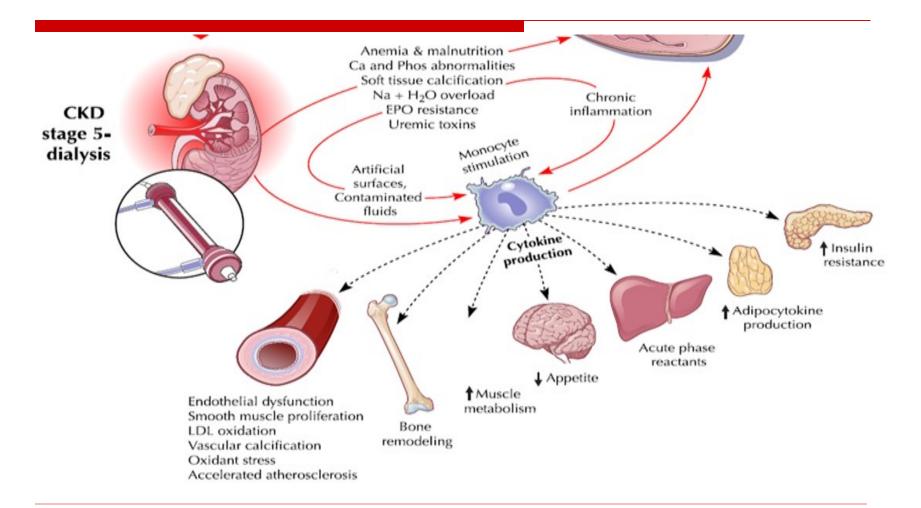
Ronco C, Contrib Nephrol. 2010;164:33-8



Ronco C et al: J Am Coll Cardiol 2008;52:1527-39



Ronco C et al: J Am Coll Cardiol 2008;52:1527-39



Ronco C et al: J Am Coll Cardiol 2008;52:1527-39

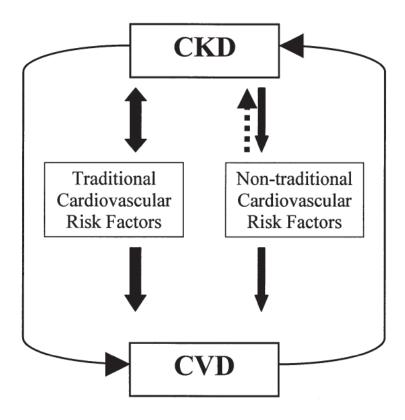
Cardiac remodeling Neurohormonal abnormalities Increased ischemic risk Left ventricular hypertrophy Left diastolic dysfunction Decreased coronary perfusion Inflammation Coronary and tissue calcification

Biomarkers

Cardiac troponin Natriuretic peptides Asymmetric dimethylarginine Ischemia modified albumin Acute phase proteins Serum amyloid protein A C-reactive protein

Ronco C et al: J Am Coll Cardiol 2008;52:1527–39

Traditional and Nontraditional Risk Factors of CVD in CKD

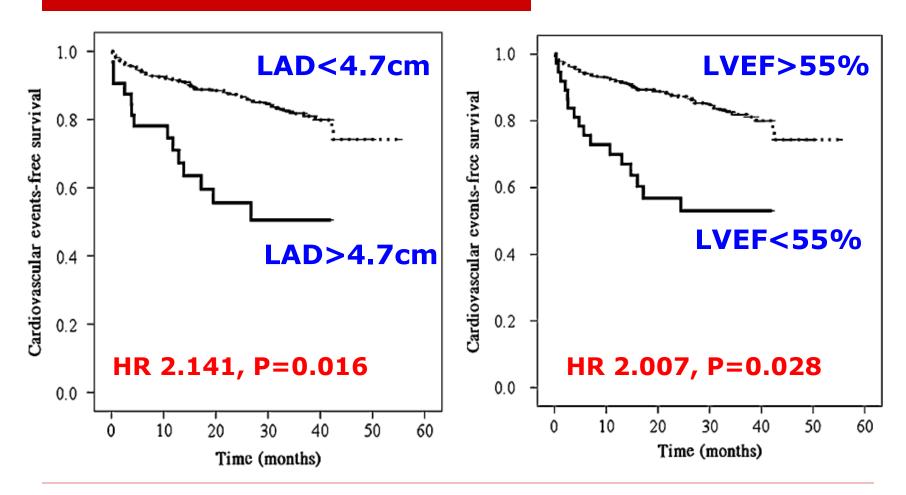


Traditional Risk Factors	Nontraditional Risk Factors
Older age	Albuminuria/proteinuria
Male sex	Homocysteine
Hypertension	Lipoprotein(a) and
Higher LDL cholesterol	apolipoprotein(a) isoforms
Low HDL cholesterol	Lipoprotein remnants
Diabetes	Anemia
Smoking	Abnormal calcium-phosphate
Physical inactivity	metabolism
Menopause	Extracellular fluid overload
Family history of CVD	Oxidative stress
Left ventricular	Inflammation (C-reactive protein)
hypertrophy	Malnutrition
	Thrombogenic factors
	Sleep disturbances
	Altered nitric oxide/endothelin
	balance

Our Findings of Some Traditional and Nontraditional CV Risk Factors in CKD

- Cardiac structural changes Heeart Echo Parameters, Surface ECG P wave
- bPEP/bET (brachial pre-ejection period/ejection time)
- Ankle-Brachial Index
- Arterial stiffness baPWV (Pulse wave velocity)
- Heart rate variability
- Four limb BP
- Anemia
- Volume status & Lipid profile

Increased LA Diameter & Decreased LVEF are Associated with Increased CV Events in CKD



N=505, Stage 3-5

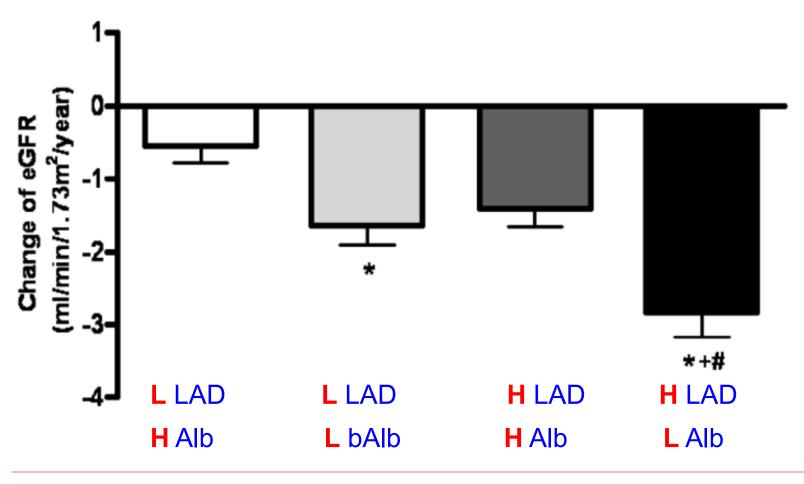
Chen & Chen, NDT 2012;27:1064-70

Increased LAD & Decreased LVEF are Associated with Rapid Renal Function Decline

Echocardiographic data	(· ·)			
aortic root diameter (cm)	0.05 (-0.59, 0.68)	0.88	—	—
LA diameter (cm)	-0.97 (-1.38, -0.56)	< 0.01	-0.5 (-0.89, -0.11)	0.01
LV relative wall thickness	1.36 (-0.71, 3.43)	0.20	—	—
LV geometry				
non-LVH	Reference		Reference	
concentric LVH	-1.03 (-1.70, -0.35)	0.03	_	_
eccentric LVH	-1.02(-1.64, -0.4)	0.01	_	_
observed/predicted LVM (%)	-0.01(-0.01,0)	0.02	—	_
inappropriate LVM	-0.53(-1.13, 0.07)	0.08	_	_
LVEF (%)	0.09 (0.07, 0.11)	< 0.01	0.06 (0.03, 0.08)	< 0.01
mwFS (%)	0.14 (0.06, 0.22)	0.01	—	_
E/A < 1	-0.09 (-0.76, 0.59)	0.80	—	-

N=415, Stage 3-5, Follow 27.3m Chen & Chen, CJASN 2011;6:2750-8

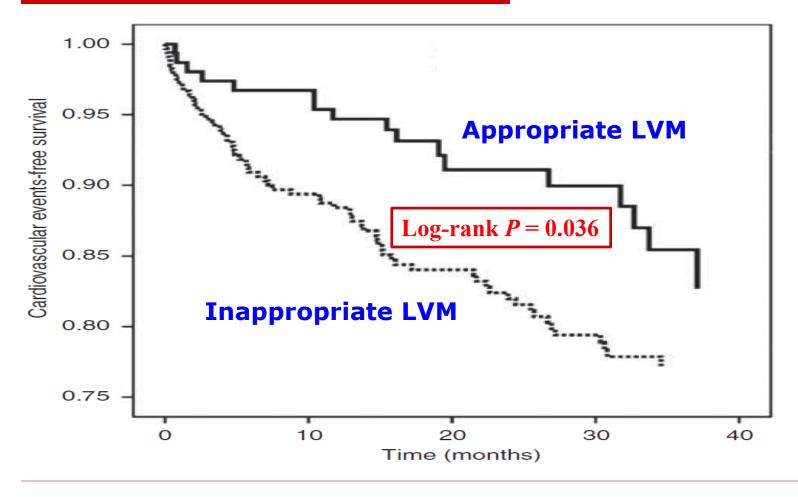
Combination of High LAD & Low Albumin is Associated with Renal Function Decline and Dialysis



N=395, Stage 3-5

Chen & Chen, Int J Med Sci 2013;10:575-84

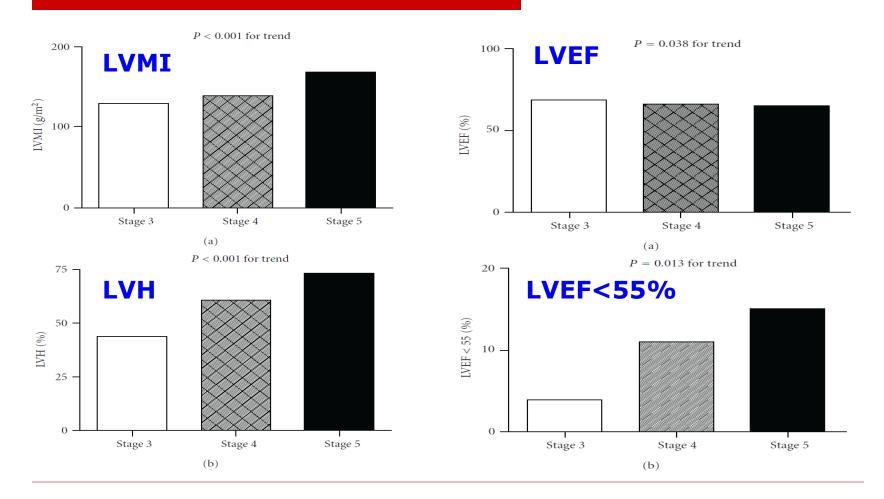
Inappropriate LVM is Associated with Increased CV Events in CKD



N=485, Stage 3-5

Chen & Chen, Hypertens Res. 2012;35:832-8

Increased LVMI & Decreased LVEF Correspond with CKD Stages in DM



N=285, DM Stage 3-5

Chen & Chen, Exp Diabetes Res 2012;2012:789325

High UA & LVMI are Associated with Rapid Renal Progression & Dialysis

	commencement of	dialysis	rapid renal progression		change of eGFR	
Parameters	Hazard ratio (95% Cl)	Р	Odds ratio (95% Cl)	Р	Unstandardized coefficient β (95% CI)	Р
Lower UA and LVMI	1	P = 0.23 (df = 3)	1	P = 0.20 (df = 3)	-0.080 (-0.512, 0.351)	0.72
Higher UA and lower LVMI	1.180 (0.531, 2.624)	0.68	1.799 (0.793, 4.081)	0.16	–1.651 (–2.190, –1.111)	< 0.001
Lower UA and higher LVMI	1.027 (0.499, 2.111)	0.94	2.032 (0.919, 4.493)	0.08	–1.414 (–1.959, –0.870)	< 0.001
Higher UA and LVMI	1.830 (1.007, 3.326)	0.048	2.231 (1.058, 4.705)	0.04	–2.363 (–2.795, –1.931)	< 0.001

Multivariate model: adjusted for age, diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, 4 study groups, mean arterial pressure, albumin, log triglyceride, total cholesterol, baseline eGFR, proteinuria (negative, 1+, and > 1+), LVEF < 50%, and medications including ACEIs and/or ARBs, diuretics, and hypouricemic agents. The study patients were stratified into 4 groups according to sex-specific median values of UA (male: 7.9; female: 7.45 mg/dL) and LVMI (male: 134.7; female: 132.5 g/m²). Abbreviations are the same as in Table 1.

N=540, Stage 3-5, Follow 33.4m, Rapid progressor: eGFR >-3/y

Chen & Chen, Am J Hypertens 2013;26:243-9

Combination of Lower BMI & Higher LVMI is Associated with CV Events in CKD

Parameters	Unadjusted		Multivariate adjus	sted (1)	Multivariate adjusted (2)		
	hazard ratio (95% CI)	р	hazard ratio (95% CI)	р	hazard ratio (95% CI)	р	
Higher BMI and lower LVMI	1		1		1		
Lower BMI and LVMI	1.060 (0.490-2.293)	0.882	1.465 (0.646-3.322)	0.361	2.006 (0.768-5.240)	0.155	
Higher BMI and LVMI	2.146 (1.094-4.206)	0.026	1.965 (0.973-3.966)	0.060	2.058 (0.900-4.710)	0.087	
Lower BMI and higher LVMI	3.178 (1.645-6.140)	0.001	3.511 (1.744-7.072)	< 0.001	3.553 (1.494-8.450)	0.004	

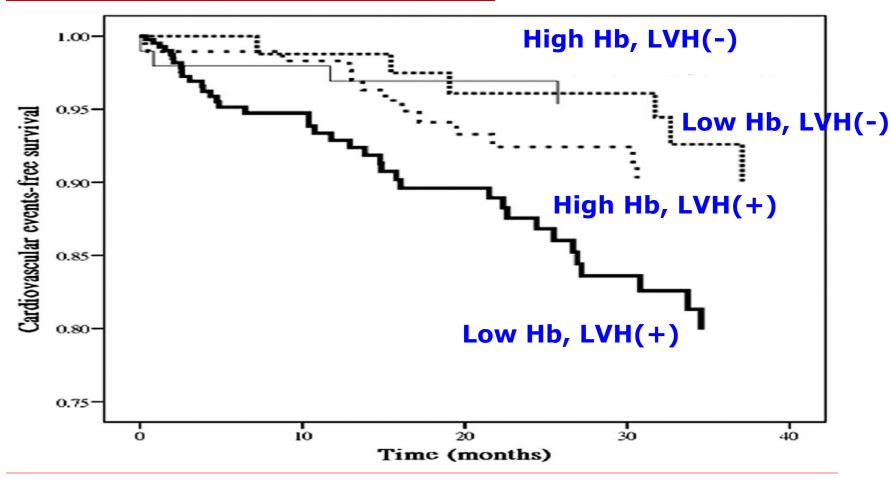
Multivariate model (1): adjusted for age, diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, systolic blood pressure, and pulse pressure.

Multivariate model (2): model (1) + albumin, fasting glucose, log triglyceride, total cholesterol, hemoglobin, eGFR, proteinuria, and ACEI and/or ARB use.

N=523, Stage 3-5

Chen & Chen, Am J Med Sci. 2016 351:91-6

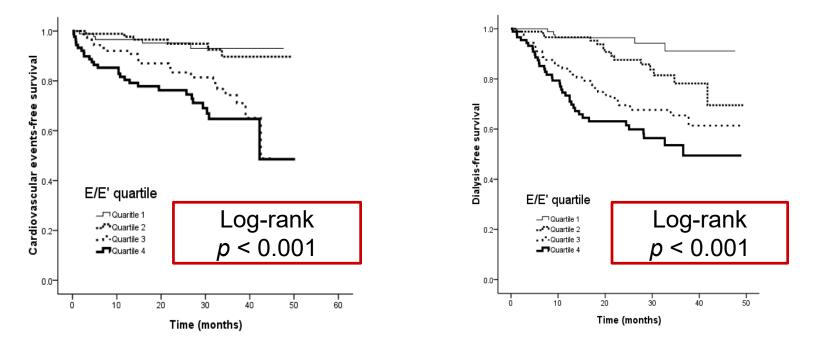
Anemia & LVH are Associated with Renal Function Decline & CV Events



N=415, Stage 3-5

Chang & Chen, Am J Med Sci 2014; 347:183-9

High E/Ea is Associated with CV Events and Dialysis in CKD

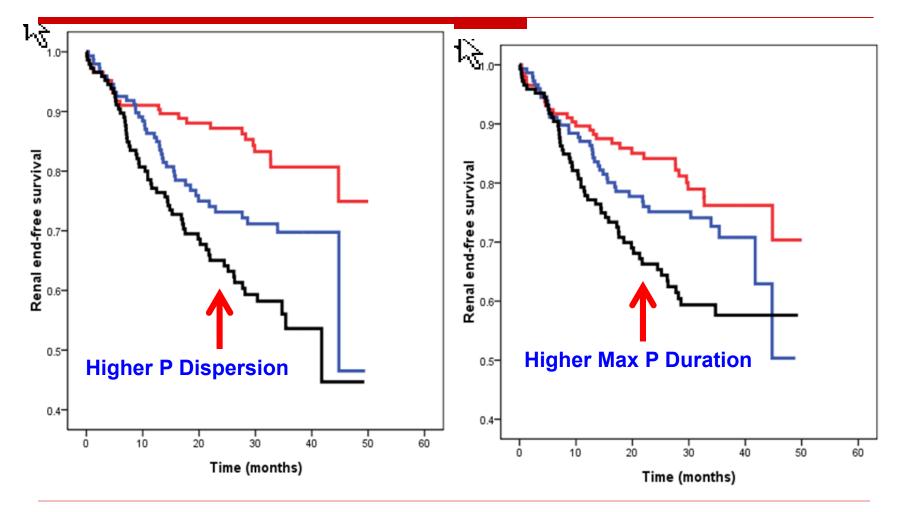


Transmitral E-wave velocity (E)/ Early diastole mitral annulus velocity (Ea): LV diastolic function, the higher the worse.

N=356, Stage 3-5, Follow 24m

Chen & Chen, Nephron Clin Pract 2013;11;123:52-60

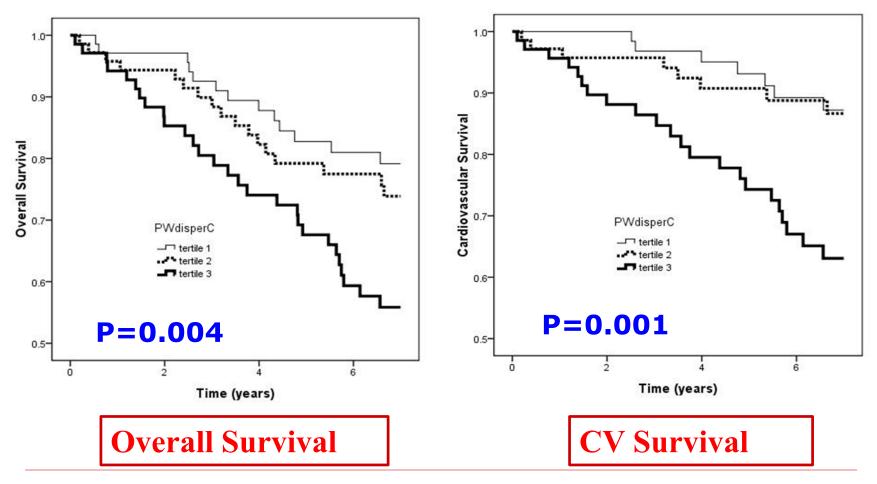
High ECG P Wave Dispersion & Maximum P Wave Duration are Associated with Progression to Dialysis & Death in CKD



N=439, Stage 3-5

Chen & Chen, PLoS One. 2014;9:e101962

High P wave Dispersion is Associated with Overall and CV Mortality in HD



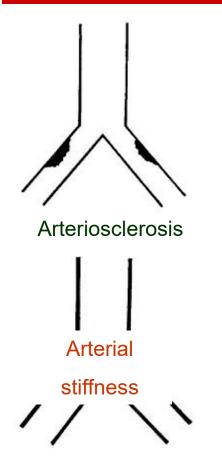
N=209 HD, Follow 5.4yrs Chen & Chen, Am J Nephrol 2015;42:198-205

Colin VP System





VP1000 - ABI, baPWV, bPEP/bET



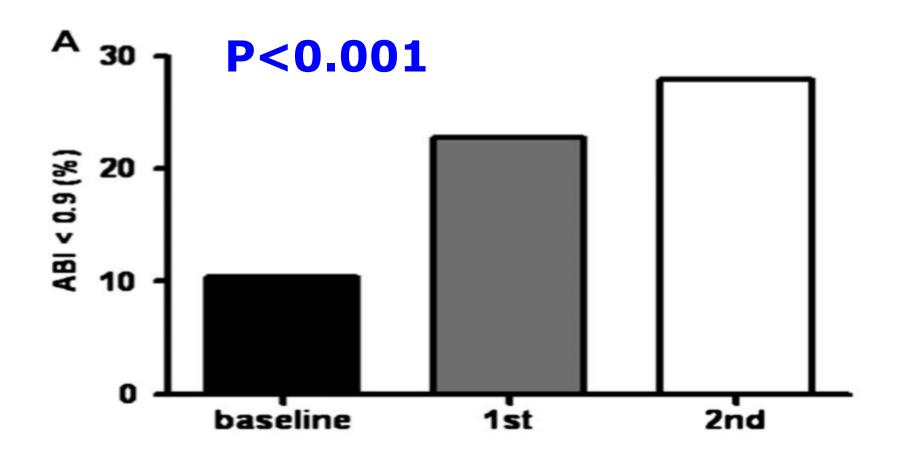
1.ABI/API (Ankle Brachial Pressure Index)— Lower extremity artery stenosis

2. baPWV (Brachial-

(Brachial-Ankle Pulse Wave Velocity) Artery stiffness

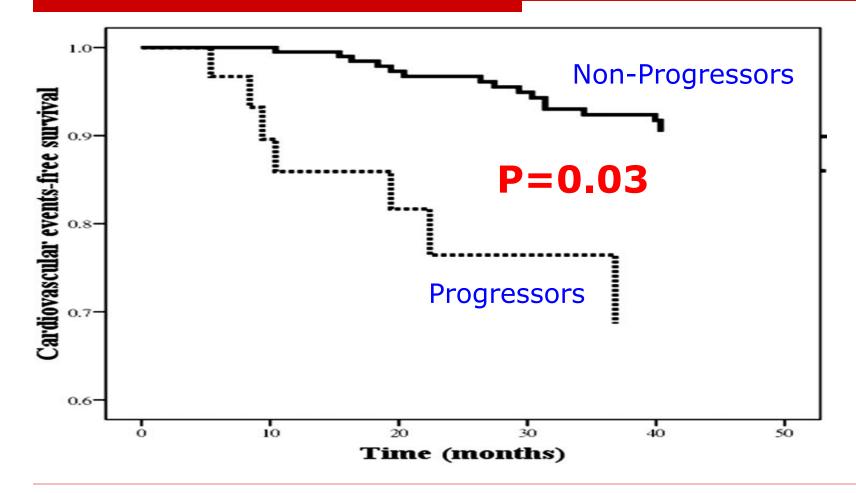
3. bPEP/bET(brachial pre-ejection period/brachilal ejection time) Systolic time interval (STI)

Increasing Prevalence of Peripheral Arterial Occlusive Disease (ABI<0.9) after Initiating HD



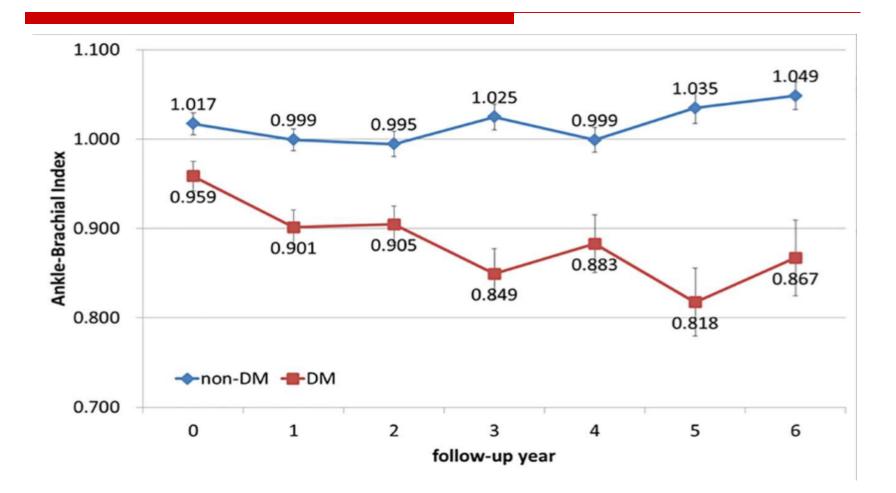
N=237 HD, Follow 2yrs Chen & Chen, AJMS 2012 ;343:440-5

Faster Decrease in ABI over time is Associated with Higher CV Mortality



N=234 HD, Follow 37.8m Chen & Chen, AJMS 2012 ;344:457-61

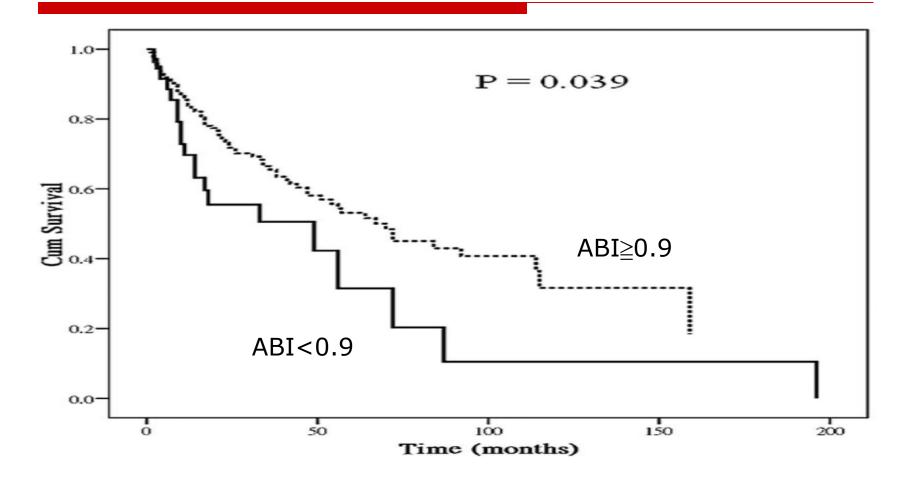
DM is Associated with Faster Decline in ABI



N=296 HD, Follow 6yrs

Chen & Chen, Plos One 2017 https://doi.org/10.1371/journal.pone.0175363

ABI <0.9 is Significantly Correlated with Increased Vascular Access Failure



N=222 HD, Follow 42.2m Chen & Chen, CJASN 2009 ;4:128-34

Either ABI<0.9 or \geq 1.3 is Associated with LVH in CKD

Characteristics	Normal (n = 244)	Concentric remodeling (n = 58)	Eccentric LVH (n=284)	Concentric LVH (n = 98)	Ρ
ABI					
≥0.9 to<1.3 (%)	87.7	87.7	80.4*	74.2*	0.001
<0.9 in either leg (%)	5.8	10.8	9.6	10.4	0.041
\geq 1.3 in either leg (%)	6.5	1.5	10.0	15.3	0.018

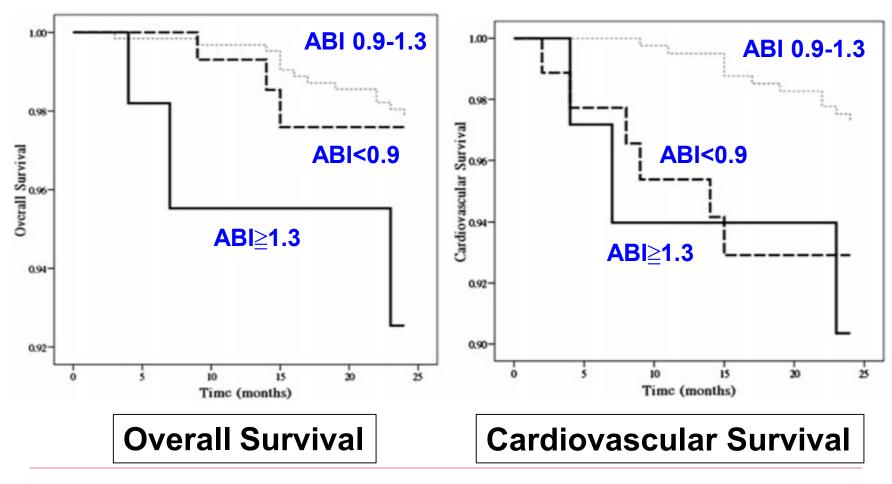
Table 4. Determinants of LVMI in study patients.

Parameter	Univariate	Multivariate (Forward)		
	Standardized coefficient β	Ρ	Standardized coefficient β	Р
ABI (versus \geq 0.9 to <1.3)	Reference		Reference	
<0.9 in either leg	0.123	0.001	0.099	0.004
\geq 1.3 in either leg	0.154	<0.001	0.143	<0.001

N=684, Stage 3-5

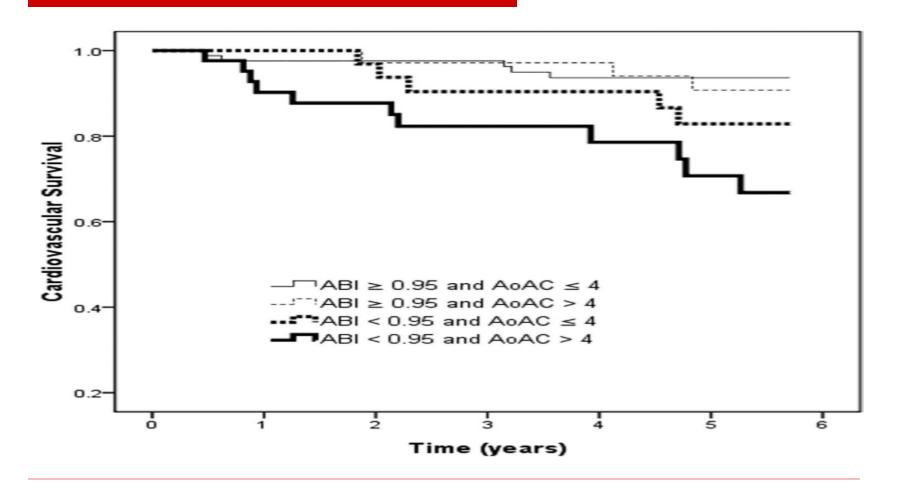
Su & Chen, PLoS One 2012;7(9):e44732

Both ABI<0.9 & \geq 1.3 are Associated with Overall and CV Mortality in HD and CKD



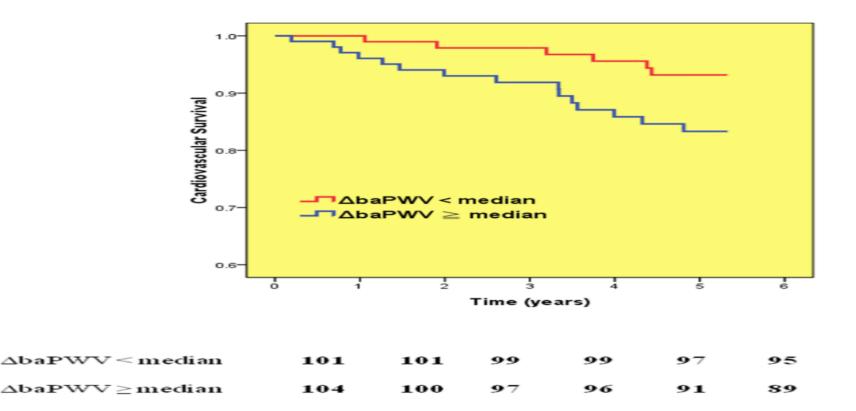
N=69, Stage 3-5, HDN=231 Chen & Chen, Nephrology 2010;15:294-9

Ankle-Brachial Index and Aortic Arch Calcification Predict CV Mortality



N=197 HD, Follow 5.7yrs Chen & Chen, Sci Rep 2016; DOI: 10.1038/srep33164

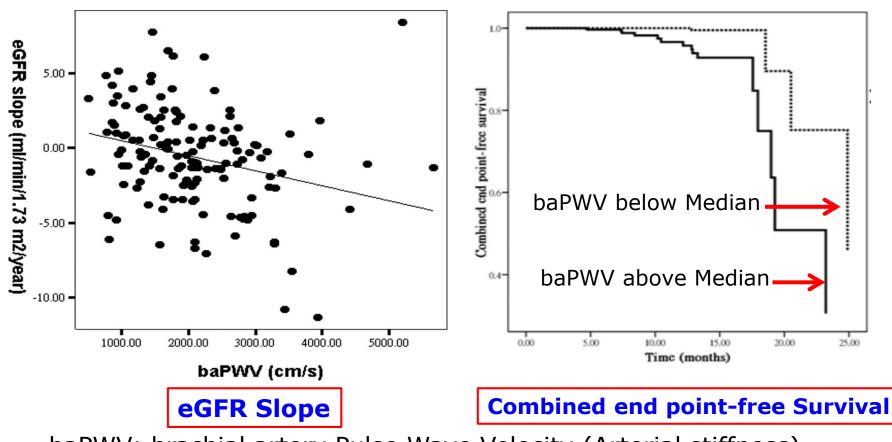
Unequal baPWV is Associated with Higher CV Mortality



baPWV: Arterial stiffness

N=205 HD, Follow 4.4yrs Wei & Chen, AJMS 2016 ;351:187-93

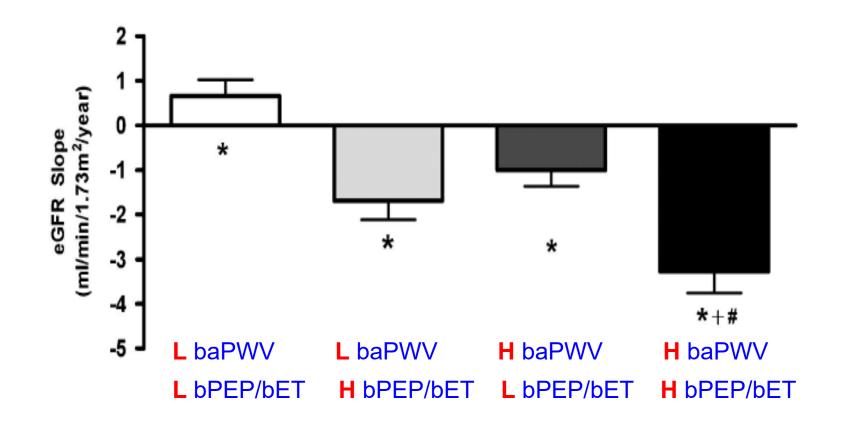
High baPWV is Associated with Rapid Renal Function Decline and Progression to Dialysis and Death in CKD



baPWV: brachial artery Pulse Wave Velocity (Arterial stiffness)

N=145, Stage 3-5, Follow 14m Chen & Chen, CJASN 2011;6:724-32

High baPWV and High bPEP/bET are Associated with Rapid Renal Function Decline and Progression to Dialysis in CKD



N=243, Stage 3-5 Chen & Chen, Hypertens Res 2012;35:1159-63

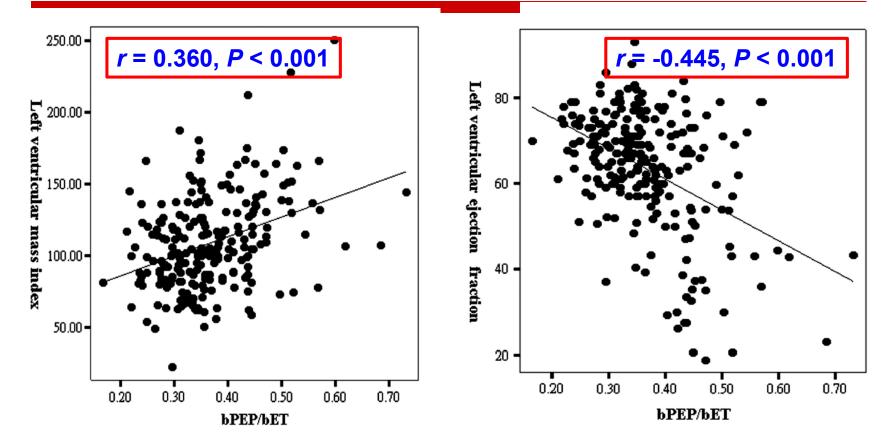
bPEP/bET is associated with Overall and CV Mortality in HD

Univariate			Multivariate Univariate			Multivariate	9		
Parameter	Hazard ratios (95% CI)	Р	Hazard ratios (95% CI)	Р	Parameter	Hazard ratios (95% CI)	Р	Hazard ratios (95% CI)	Р
Age (per 1 year) 1.025 (0.992-1.060) Male vs. female 1.035 (0.447-2.395) Operation of diabetic (per 1 month) 0.087 (0.074 0.090)		0.144 0.936	0.144 0.997 (0.949–1.048) 0.936 1.573 (0.528–4.686)		Age (per 1 year) Male vs. female Duration of dialysis (per 1 month)	1.021 (0.981–1.063) 1.086 (0.394–2.996) 0.989 (0.874, 1.003)		0.988 (0.927–1.053) 2.067 (0.519–8.238)	0.71 0.30
Overall mo	ortality			Univar	iate		Multiv	variate	
Parameter Hazard ratios(95% (CI) P	Hazard ra	atios(9	5% CI) P				
bPEP/bET(per 0.01) 1.051(1.005-1.100)		0.030	1.055(1.001-1.112) 0.047						
CV mortality			Univariate Multiv		variate				
Parameter		Н	Hazard ratios(95% CI) P		Hazard ratios(95% CI) P				
bPEP/bET(per 0.01)	1	.073(1.020-	1.128)	0.006	1.080(1.0	014-1.1	50) 0.017	
PTH (per 1 ng per 100ml) hsCRP (per 1 ng l ⁻¹) KtV (per 1.0)	0.864 (0.648-1.151) 0.999 (0.997-1.000) 1.124 (0.961-1.314) 0.868 (0.153-4.931)	0.318 0.061 0.144 0.873			Uric acid (per 1 mg per 100 ml) PTH (per 1 pg ml ⁻¹) hsCRP (per 1 mg l ⁻¹) Kt/V (per 1.0)	0.882 (0.625–1.246) 0.998 (0.996–1.000) 1.119 (0.922–1.358) 0.336 (0.040–2.836)	0.476 0.071 0.256 0.317		-
Cardiothoracic ratio > 50%	1.268 (0.550–2.925)	0.577	_	_	Cardiothoracic ratio > 50%	1.108 (0.402-3.056)	0.843	_	_
Medications Aspirin use ACEI and/or ARB use Statins use	2.863 (1.120-7.319) 2.529 (1.061-6.029) 0.376 (0.111-1.269)	0.028 0.036 0.115	1.375 (0.349-5.427) 2.087 (0.741-5.879) —	0.649 0.164 —	Medications Aspirin use ACEI and/or ARB use Statins use	1.887 (0.532–6.688) 2.949 (1.050–8.287) 0.368 (0.083–1.633)	0.326 0.040 0.189	2.361 (0.626-8.898) —	0.204

N=212 HD, Follow 28.3m

Chen & Chen, Hypertens Res 2010;33:492-8

Higher bPEP/bET is Associated with Higher LVMI and Lower LVEF in CKD



bPEP/bET(brachial pre-ejection period/brachilal ejection time): STI

N=243, Stage 3-5

Chen & Su, NDT 2011;26:1895-902

bPEP/bET is Associated with Increassed CV Events in CKD

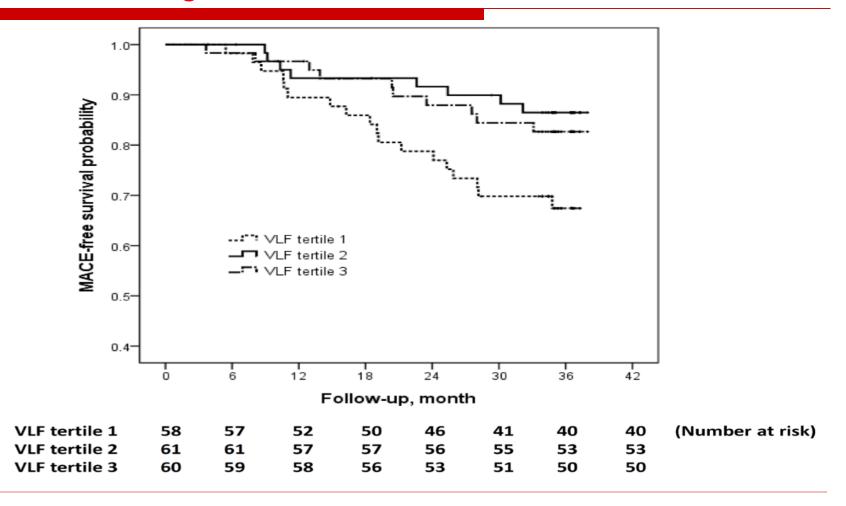
Vable 1. Comparison of Baseline Characteristics Between Patients With and Without Cardiovascular Events

Characteristics	Patients without events (n=214)	Patients with events (n=28)	All patients (n=242)
Age (years)	64.5±12.8	64.5±13.4	64.5±12.8
Male gender (%)	64.5	53.6	63.2
ABI	1.11±0.13	1.12±0.09	1.11±0.13
baPWV (cm/s)	1986.9±522.5	2043.7±436.9	1993.4±512.8
bPEP (ms)	100.3±17.9	107.4±23.9	101.1±18.8
bET (ms)	284.9±32.3	269.0±31.1*	283.1±32.5
bPEP/bET	0.36±0.08	0.41±0.11*	0.36±0.09

N=242, Stage 3-5

Chen & Chen, Circ J 2010 ;24;74:2206-10

Heart Rate Variability Predicts Major Adverse CV Events



N=179 HD, Follow 33.3m

Chen & Chen, KBPR 2017;42:76-88

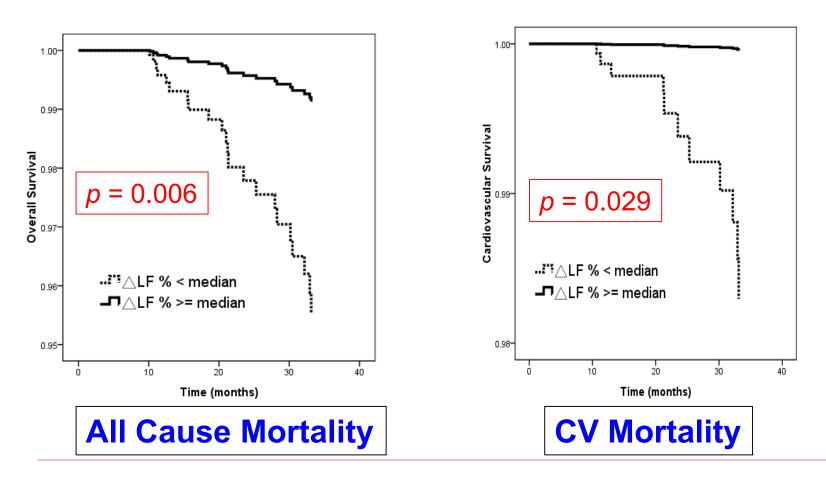
Diminished Heart Rate Variability Changes in Patients with Peripheral Artery Disease

HRV parameters (frequency domain)	Withou	It PAD	With PAD		
	Before HD	After HD	Before HD	After HD	
LF (ms ²)	2.5 ± 0.4	2.9 ± 0.5	1.6 ± 0.6	2.7 ± 0.6	
HF (ms ²)	2.3 ± 0.4	$2.7 \pm 0.4^*$	1.6 ± 0.7	2.5 ± 0.7	
LF% (nu)	42.2 ± 2.2	$47.0 \pm 2.0^{*}$	$35.3 \pm 3.$	40.4 ± 3.4	
HF% (nu)	33.0 ± 1.6	30.3 ± 1.3	33.2 ± 1.9	30.2 ± 1.9	
LF/HF	0.22 ± 0.12	$0.46 \pm 0.10^*$	-0.07 ± 0.17	0.16 ± 0.16	

N=161 HD

Chen & Chen, PLoS One 2015;10:e0120459

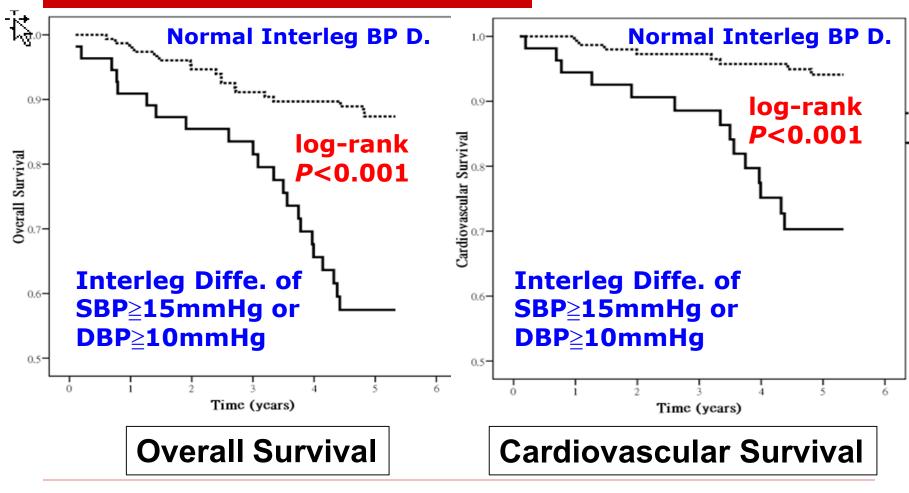
Less Change in Heart Rate Variability after Single HD is Associated with Higher CV Mortality



N=182 HD, Follow 35.2m

Chen & Chen, Sci Rep 2016;6:20597

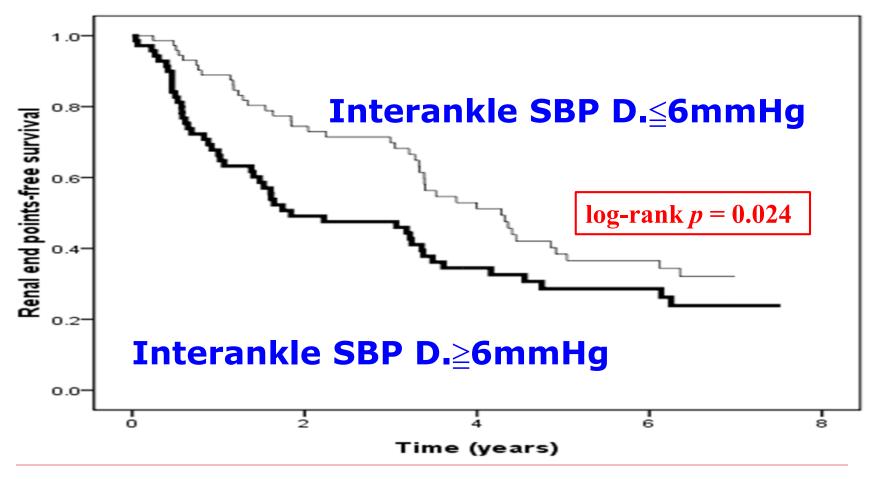
Interleg BP Difference Predicts Overall and CV Mortality in HD



N=110, Follow up $4.4\pm1.5y$ Chen 8

Chen & Chen, CJASN 2012;7:1646-53

Interankle SBP Difference is Associated with a ≧25% Decline in eGFR



N=1445, Stage 3-5, Follow 3.1y

Chen & Chen, Nephrology 2016;21:379-86

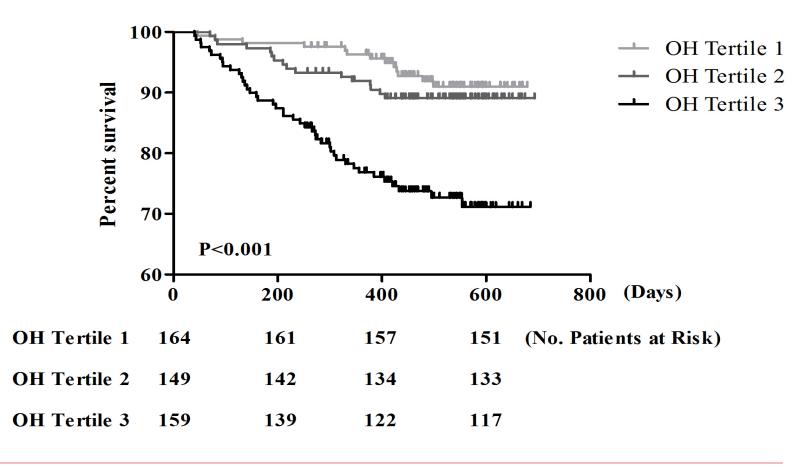
Associations of Hb (6 months after 1ST HD) with Cardiovascular Mortality in Incident HD Patients

	Categorical Hb, g/dL					Continuous Hb	
	<8	8-9	9-10	10-11	11-12	>12	per 1 g/dL
Event, n(%)	38 (23.0%)	92 (20.9%)	202 (22.6%)	106 (15.9%)	38)(10.9%)	9)(9.3%)	
Incidence rate, per 1000 patient			41.9			22.2	
years Adjusted HR (95% CI)	1.57* (1.04-2.35)		1.22	1	0.92	0.81 0.42-1.55)	

N=485, Follow up 15yrs

Hung & Chen, KMUH

Overhydration is Associated with Progression to RRT in CKD



N=472, Stage 4-5, Follow 17.3m Tsai & Chen, AJKD 2014;63:68-75

Overhydration is Associated with Overall and CV Mortality in CKD

	Entire Cohort N=478	△HS<7% N=239		P-value
Patient-year of follow-up	763.5	434.4	329.1	< 0.001
Combined outcomes per 100 patient-year (95%CI)	8.6 (6.7-11.0)	4.4(26.4-68.4)	14.3(10.5-19.0)	<0.001
Cardiovascular morbidity per 100 patient-year (95%CI)	6.7(5.0-8.8)	3.0(1.6-5.1)	11.5(8.2-15.9)	<0.001
Death per 100 patient-year (95%CI)	3.3(2.1-4.8)	1.4(0.5-3.0)	5.8(3.5-9.0)	0.008

Data are expressed as number (percentage) for categorical variables and median (25th, 75th percentile) for continuous variables, as appropriate.

Abbreviations: \triangle HS, relative hydration status

P-value was measured by comparisons between participants with \triangle HS \ge 7% and those with \triangle HS <7%.

N=478, Stage 4-5, Follow 23.2m Tsai & Chen, CJASN 2015;10:39-46

Cholesterol is Associated with Renal Outcomes in CKD

	Renal replace	ment therapy	Rapid renal progression		
	Unadjusted	Adjusted	Unadjusted	Adjusted	
Total cholesterol	HR (95% CI)	HR (95% CI)	OR (95% CI)	OR (95% CI)	
Quintile 1	1.33 (1.10, 1.61)*	1.23 (1.01, 1.49)*	1.12 (0.86, 1.46)	1.06 (0.79, 1.42)	
Quintile 2	1	1	1	1	
Quintile 3	0.90 (0.74, 1.10)	1.08 (0.88, 1.33)	1.05 (0.81, 1.38)	1.17 (0.87, 1.57)	
Quintile 4	1.15 (0.95, 1.39)	1.25 (1.02, 1.52)*	1.18 (0.90, 1.54)	1.20 (0.89, 1.61)	
Quintile 5	1.36 (1.13, 1.64)*	1.35 (1.11, 1.65)*	1.98 (1.53, 2.55)*	1.36 (1.01, 1.83)*	

p* < 0.05; *p* < 0.001 compared to quintile 2

N=3,303, Stage 3-5, Follow 2.8y Chen & Chen, PLoS One 2013;8:e55643

Proteinuria Modify the Relationship Between Lipid Profile and Mortality in CKD

All-cause	Proteinuria < 1 g/day		Proteinuria≥1 g/day		Р
mortality	Unadjusted	Adjusted	Unadjusted	Adjusted	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Total cholesterol					0.045
Quartile 1	1	1	1	1	
Quartile 2	0.75 (0.50-1.13)	1.21 (0.79-1.86)	0.71 (0.54-0.94)	0.94 (0.70-1.25)	
Quartile 3	0.78 (0.52-1.18)	1.65 (1.06-2.57)	0.60 (0.45-0.80)	0.81 (0.60-1.08)	
Quartile 4	0.93 (0.61-1.41)	2.00 (1.27-3.16)	0.57 (0.43-0.76)	0.82 (0.60-1.10)	
TC/HDL					0.029
Quartile 1	1	1	1	1	
Quartile 2	0.71 (0.45-1.11)	1.06 (0.66-1.70)	0.69 (0.52-0.93)	0.78 (0.58-1.05)	
Quartile 3	1.22 (0.81-1.82)	1.73 (1.12-2.68)	0.68 (0.51-0.91)	0.75 (0.56-1.01)	
Quartile 4	1.64 (1.09-2.48)	1.67 (1.08-2.58)	0.70 (0.53-0.92)	0.71 (0.53-0.94)	

↑TC & TC/HDL--↑Overall mortality if UPr<1g/D</p>↑TC/HDL--↓Overall mortality if UPr≧1g/D

N=3,303, Stage 3-5, Follow 2.8y Chen & Chen, CJASN 2013 ;8:1915-26



- Cardiovascular diseases are common in CKD, and CKD has been recognized as a major risk factor for CVD.
- Many nontraditional risk factors also contribute to CVD and should not be missed.
- We should recognize patients at risk and provide early prevention and treatment.

2nd International Congress of Chinese Nephrologists 第二屆全球華人腎臟病學術大會



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