

New Exams and Drugs in Hemodialysis Patients

New Diagnostic Approach of Cardiovascular Disease in HD Patients

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Introduction

- Although maintenance dialysis prevents death from uremia, but patient survival remains an important issue
- Mortality and morbidity due to infectious disease is increasing at present.
- But, ESRD patients on Hemodialysis have mortality due to Cardiovascular disease 10 -30 times more than general population

Foley RN et al. J Am Soc Nephrol 1998;9(Supple 12):S16-S23
Am J Kidney Dis. 2010; 55(Suppl 1):S1 S269-280

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Introduction

- Due to increased prevalence
 - Diabetes mellitus
 - Hypertension
 - Left ventricular hypertrophy
 - Hyperlipidemia
 - Hyperphosphatemia
 - Anemia
- 40-50% of deaths are attributable to CV disease

de Jager DJ, et al. JAMA 2009
Am J Kidney Dis. 2010; 55(Suppl 1):S1 S269-280

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Introduction

- Overall and across causes, mortality is highest in the third month of dialysis and then falls back to levels close to or lower than those in month one

Am J Kidney Dis. 2010; 55(Suppl 1):S1 S269-280

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Introduction

- Thus, the diagnosis and management of cardiovascular disease(CVD) has become the most challenging clinical issue in dialysis patients
- Also, cardiovascular evaluation during the early periods of hemodialysis initiation were important.

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Problems in HD pts

- CAD, LV dysfunction and LVH more than normal population.
- But, asymptomatic Pts. more than symptomatic Pts.
- Limitation for diagnosis of cardiovascular disease in asymptomatic Pts

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Limitation of noninvasive test

Noninvasive screening test	Limitations in ESRD patients
Cardiac troponin measurement	Prognostic significance of high-sensitivity assays unknown
Exercise tolerance test	Poor exercise performance
	High proportion of baseline ECG abnormalities
	Low sensitivity reported
Myocardial perfusion scintigraphy	
Dobutamine stress echocardiography	Operator dependent
	Adequate acoustic windows not possible in up to 20%
Quantification of coronary calcium score	No correlation calcification score—stenosis in ESRD
CT coronary angiography	Contrast exposure
	Low specificity due to high coronary calcium burden
Cardiac PET	No data in patients with ESRD
Cardiac MRI	Not widely available
	Inability to use gadolinium
	Technical problems

An S, De Vriese et al, Kidney International (2012) 81, 143-151;

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Ischemic Heart Disease in Dialysis Pts

- Asymptomatic myocardial ischemia is not uncommon in patients on maintenance hemodialysis
- Coronary artery disease in dialysis patients is often asymptomatic or presents non-specific symptoms.

Joki N et al, Nephrol Dial Transplant 1997;12:718-23
Ohtake T et al, J Am Soc Nephrol 2005;16:1142-8

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Ischemic Heart Disease in Dialysis Pts

- Significant coronary stenosis was noted in 50% or more of asymptomatic dialysis patients at the introduction of dialysis

All eligible patients with CKD starting RRT for 3 years

Table 2. Prevalence of CAS by CAG among 30 asymptomatic CKD patients^a

	DM	Non-DM	PCI
CAS positive, n (%)	16 (53.3)	10	6
One vessel, n (%)	10 (62.5)	5	5
Two vessel, n (%)	4 (25.0)	3	1
Three vessel, n (%)	2 (12.5)	2	0

Ohtake T, et al, J Am Soc Nephrol 2005;16:1141-8

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Ischemic Heart Disease in Dialysis Pts

- Prevalence of CAD (stenosis of at least 75%) in 54% of asymptomatic patients

Table 5. Prediction of the presence of coronary artery disease (CAD) by evaluation of chest symptoms using discriminant function analysis

Chest symptoms	CAD		n
	Present	Absent	
Present	8	3	11
Absent	7	6	13
Total	15	9	24

- Need a active screening for ischemic heart disease starting from the initiation of dialysis

Joki N, et al, Nephrol Dial Transplant 1997;12:718-23

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Ischemic Heart Disease in Dialysis Pts

- In the presence of clear symptoms of angina pectoris → refer to a cardiologist
- In the absence of clear symptoms of angina pectoris
 - Non-specific Sx : SOB, palpitation, epigastric pain...
 - De novo heart failure ; not responding to a reduction in the dry weight.
 - Hypotension ; repeated hypotension during HD

→ EKG and chest X-ray
→ Resting echocardiography

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Symptoms and Findings suggestive of Ischemic Heart Disease

- Symptoms
 - Non-specific symptoms
Shortness of breath on exertion, palpitation, discomfort of the chest, epigastric region, and back, languidness of lower limbs, etc.
 - De novo heart failure
 - Heart failure not responding to a reduction in the DW
 - Repeated hypotension during dialysis
 - Sustained hypotension
- New abnormalities detected by regular ECG
 - ST-T changes (including non-specific changes)
 - Appearance of Q waves
 - Arrhythmias
- New abnormalities detected by regular chest radiography
 - An increase in the cardiothoracic ratio ($\geq 5\%$)
 - Pulmonary congestion
 - Interstitial pulmonary edema (Kerley's A, B, C lines)

Hirakata et al, Therapeutic Apheresis and Dialysis 2012; 16(5):387-435

Ischemic Heart Disease in Dialysis Pts

- Changes in Sx or signs and test findings caused by
 - Inappropriate setting of DW
 - Excessive internal shunt flow
 - Valvular heart disease advanced by valve calcification
 - Pericardial fluid retention from uremic pericarditis
 - Pulmonary hypertension
 - Left ventricular hypertrophy
- By performing resting echocardiography
 - differentiate the causes of these changes

Diagnostic processes for IHD in HD Pts

Hirakata et al, Therapeutic Apheresis and Dialysis 2012; 16(5):387-435

Further evaluation for CVD

- Myocardial perfusion scintigraphy
- Stress test
 - Exercise ECG(TMT)
 - Stress echocardiography
 - Exercise Echocardiography
 - Dobutamine stress Echo.
- Coronary CT

Myocardial Perfusion Scintigraphy

- Dipyridamole MPS shows widely varying sensitivities and specificities have been reported
- MPS is a functional test that measures coronary blood flow, whereas coronary angiography provides only anatomical information.

Author	n	Stress	Criterion %	Sensitivity	Specificity	Accuracy
Otte et al ²⁵	20	Dipyridamole	50	73	100	85
Boutrou et al ²⁶	80	Dipyridamole	70	86	79	83
Marrick et al ²⁷	45	Dipyridamole	50	37	73	58
			70	29	68	56
Vandenberg et al ²⁸	47	Dipyridamole/adenosine	50	53	73	63
			70	62	76	71
Dahbi et al ²⁹	76	Dipyridamole+exercise	70	92	89	90
Schmidt et al ³¹	55	Dipyridamole	70	80	37	59
De Wiese et al ³³	62	Dipyridamole	70	62	54	58

→ **Wide and low sensitivity**

An S. De Vriese et al, Kidney International (2012) 81, 143-151;

Stress Test

Indication

- Change in symptoms related to ischemic heart disease
- LVEF < 40 %
- Kidney transplant waitlist patients with DM, have a high Framingham risk score, known CAD or PCI Hx at least 1yr ago
- History of complete coronary revascularization with CABG at least 3yrs ago
- History of incomplete coronary revascularization with CABG at least 1yr ago

K/DOQI Workgroup, Am J Kidney Dis. 2005;45(4 Suppl 3):S1

Stress Test

- **Exercise ECG test and Exercise echocardiography**
 - Poor exercise capabilities in the dialysis population
 - Autonomic dysfunction
 - blunted chronotropic response
 - High prevalence of baseline ECG
 - difficult interpretation of exercise test

→ Not generally recommended

Am J Kidney Dis. 2005;45(4 Suppl 3):S1
An S. De Vriese, et al, Kidney International (2012) 81, 143–151

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Stress Test

- **Dobutamine stress echocardiography appears to be more sensitive than other non-invasive tests**

Nephrol Dial Transplant. 2005;20(10):2207.

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Stress Test

- **Sensitivity and specificity of dobutamine stress echocardiography was approximately more than 80 percent**

Test Result	Sensitivity (%)	Specificity (%)
Chest Pain	~65	~65
Abnormal ECG	~75	~65
Positive Exercise Test	~65	~40
Positive DSE	~85	~85

Nephrol Dial Transplant. 2005;20(10):2207.

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Stress Test

- **But, DSE may be associated with a relatively increased risk of transient atrial fibrillation**

Herzog Caet al, Am J Kidney Dis. 1999;33(6):1080.

- **Adequate acoustic windows may not be obtained in up to 20% of the tests**

Herzog CA et al, Am J Kidney Dis 1999; 33: 1080–1090.

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Coronary CT : calcium score

- **Coronary calcium scores in dialysis patients do not appear to correlate well with angiographic findings**

Sharples EJ et al, Am J Kidney Dis 2004; 43: 313–319

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Coronary CT : calcium score

- **Coronary calcium scores predict mortality in dialysis patients**

Shantouf

- **N=166, asymptomatic**
- **Calcium score for mortality**

Months	0	12	24	36	48	60	72
Number at risk	166	145	133	120	9	5	2
CAC 0	48	47	37	20	10	6	0
CAC 1-100	29	23	14	10	9	2	0
CAC 101-400	72	59	44	16	9	2	0

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Coronary CT angiography

- Has not been studied extensively in dialysis Pts.
- Coronary CT angiography may be inappropriate for dialysis patients due to
 - Problem of volume loading by the contrast
 - may affect residual renal function
 - Difficult in diagnosis of CAD in dialysis patients with marked coronary artery calcification

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Coronary CT angiography

- Few small sized studies show..
- MDCT is a useful and non-invasive approach for excluding CAD in patients undergoing dialysis

Justin M, et al, Cardiol J 2010;17, 4: 349-361
Park et al. Nephrology 2011;16(3):285-289

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Acute coronary syndrome in HD Pts

- Development of acute myocardial infarction in ESRD
 - Heart failure such as dyspnea and cough rather than left shoulder pain, chest pain, back pain, Q waves are observed infrequently on ECG

Factor	Symptoms	Unadjusted Odds Ratio (95% confidence interval)	Multivariate Odds Ratio (95% confidence interval)
1*	Arm pain and/or shoulder pain, left arm pain, right arm pain, numbness/tingling in arm or hand	0.35 (0.30-0.41)	0.52 (0.42-0.64)
2*	Left shoulder pain, right shoulder pain	0.46 (0.37-0.58)	0.53 (0.40-0.72)
3	Abdominal pain, nausea, vomiting, weakness/fatigue	1.13 (1.00-1.29)	1.11 (0.94-1.32)
4*	Chest pain, chest pressure, sweating/diaphoresis	0.23 (0.20-0.40)	0.27 (0.60-0.70)
5	Dizziness/light-headedness, loss of consciousness, syncope	0.97 (0.81-1.16)	1.08 (0.86-1.37)
6*	Arm pain, neck pain	0.49 (0.40-0.60)	0.54 (0.41-0.70)
7*	Cough, shortness of breath/dyspnea	1.52 (1.33-1.74)	1.36 (1.13-1.62)
8	Back pain, palpitations/rapid heart rate, chest discomfort/heaviness/tightness/burning	0.80 (0.69-0.92)	0.88 (0.73-1.06)
9	Chest tightness	0.72 (0.69-0.88)	0.87 (0.66-1.13)
10	Headache, indigestion	0.63 (0.50-0.81)	0.75 (0.54-1.04)

*Significant after adjusting for the presence of selected demographic and clinical factors and Bonferroni factor.

Sosnov J et al. Am J Kidney Dis 2006;47:378-84.

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Acute coronary syndrome in HD Pts

- Acute heart failure in dialysis patients should be differentiated from acute coronary syndrome.
- Biomarkers : Troponin-I, Troponin-T, CM-MB..

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Biomarkers in HD Pts.

- Troponins T, I, are the gold standard approach in diagnosing acute myocardial necrosis
- Cardiac troponin T, I are frequently elevated in the absence of acute coronary syndrome with dialysis pts.
- So, difficult accurately interpreting for elevations in cardiac biomarkers

Wang AY et al, J Am Soc Nephrol 2008; 19: 1643-1652.

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Troponin-T in HD Pts.

- Prevalence of cTnT elevation is reported to range from 30 to 85% in patients with ESRD

Apple FS, et al, Circulation 2002; 106: 2941-2945

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Troponin-T in HD Pts.

- A meta-analysis of 28 studies covering 3931 patients revealed that cTnT measured at a single time point correlated with all-cause and cardiac mortality

Study	Risk ratio (95% CI)	% Weight
Apple F (2002)	1.72 (1.36,2.13)	13.7
Chry B (2003)	6.35 (1.49,27.23)	1.6
Desmet P (2001)	4.31 (1.8,8.86)	6.1
Dierkes J (2007)	4.17 (2.87,6.76)	6.2
Hsu MC (2005)	2.61 (1.64,4.07)	9.7
Ime J (2011)	5.14 (2.8,9.16)	4.2
Lang P (2011)	2.35 (0.95,5.73)	4.2
Lombard C (2002)	2.87 (1.44,4.59)	6.7
Maldjian F (2002)	2.26 (1.65,3.08)	10.7
Musker M (1999)	0.75 (0.65,0.85)	0.8
Musker P (1999)	3.21 (1.6,6.46)	0.6
Phaner GA (2005)	4.25 (1.91,9.87)	1.6
Shaw JC (1999)	4.45 (1.63,11.89)	3.1
Wang AY (2008)	15.81 (1.95,127.63)	0.8
Wood GM (2003)	3.12 (1.8,4.45)	5.0
Yoshida (2011)	1.88 (1.37,2.59)	11.4
deFoy C (2003)	2.35 (1.76,3.09)	12.6
Overall (95% CI)	2.84 (2.17,3.20)	

Nadia A. Khan, et al, *Circulation*. 2005;112:3088-3096

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Biomarkers in HD Pts.

- Exact mechanisms that biomarker are elevated in dialysis Pts are unclear
- Possible reasons
 - Impaired renal excretion
 - Left ventricular hypertrophy
 - Endothelial dysfunction
 - Myocardial stunning
 - Stretch-mediated troponin release

Diris JH, et al, *Circulation*. 2004;109(1):23.
 Breidhardt T, et al *Clin J Am Soc Nephrol*. 2012;7(8):1285.
 Wang AY, et al, *J Am Soc Nephrol* 2008; 19: 1643-1652.

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Troponin-T in HD Pts.

- How to distinguish in elevations of cardiac troponins between ACS and chronic myocardial injury
- Obtain baseline values
- Increase above baseline levels
 - may suggest an acute problem or chronic changes.

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Troponin-T in HD Pts.

- Absence of an acute process that is known to cause elevations in cardiac troponins would be more indicative of chronic changes.
- ESRD Pts with possible ACS
 - If dynamic change in 20% after presentation
 - define acute coronary syndrome

Wang AY et al, *J Am Soc Nephrol* 2008; 19: 1643-1652.

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Optimal Time to Repeat Screening

- Out of 191, 51 CRF Pts. with normal DSE
 - cardiac event rate of 4% within 2 years
 - but increased to more than 10% at 40 months.

LR $\chi^2 = 7.5, P = 0.006$

Marwick TH et al, *J Intern Med* 1998; 244: 155-161.

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Optimal Time to Repeat Screening

- N=485, with CRF -> n=203 with normal DSE
- 12% of normal DSE died at 1yr
- 30 % at 3yrs

No. at risk	0	1	2	3
Normal DSE	203	166	117	65
Fixed wall motion abnormality	81	65	48	26
>25% Ischaemic segments	108	77	68	28
>50% Ischaemic segments	85	68	42	20

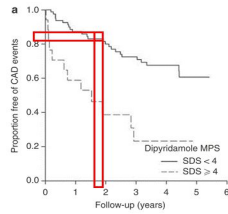
Dobutamine stress echocardiography findings and mortality over the subsequent 3 years. Log-rank test $\chi^2, 13.7; P = .003$.

Bergeron S et al, *Am Heart J* 2007; 153: 385-391.

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Optimal Time to Repeat Screening

- Normal myocardial perfusion study was associated with a 2-year cardiac event rate of 15%.



De Vriese AS et al, *Kidney Int* 2009; 76: 428–436.

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Optimal Time to Repeat Screening

- Retesting of patients with normal studies every 2 years thus seems reasonable.

An S. De Vriese et al, *Kidney International* (2012) 81, 143–151;

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Summary

- Need a active screening for ischemic heart disease starting from the initiation of dialysis.
- Important to detect change in Symptoms and Sign.

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Summary

- Resting echocardiography and stress test is most important diagnostic tools.
- Coronary CT was yet limited in dialysis Pts.

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Summary

- Acute heart failure in dialysis patients should be differentiated from acute coronary syndrome.
- Biomarkers of myocardial ischemia often show false positive results, but increasing level than baseline are meaningful findings.

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Summary

- Obtain baseline values for biomarkers.
- Retesting of patients with normal studies every 2 years.

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