IN THE NAME OF THE ALMIGHTY

Cardiovascular Disease in Dialysis Patients

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- Epidemiology
- Risk factors
- Hypertension
- Cardiovascular disease screening
- Coronary artery disease (CAD)
- Congestive Heart Failure
- Valvular Disease
- Pulmonary Hypertension

- Cardiovascular disease (CVD) is the **major cause of morbidity and mortality** in patients with end-stage renal disease (ESRD) on haemodialysis (HD).
- In this population, mortality due to CVD is **٢٠ times higher than in the general population** and the majority of maintenance HD patients have CVD

- The prevalence of **LVH** increases at each stage of CKD, reaching ٧٥% at the time of dialysis initiation, and the modifiable risk factors for LVH include anemia and systolic blood pressure, which are also worse at each stage of kidney disease.
- At least ٣٥% of patients with CKD have evidence of an **ischemic event** (myocardial infarction or angina) at the time of presentation to a nephrologist.

- CV risk factors among haemodialysis patients
  - **Traditional factors (**non-specific to kidney disease but more prevalent**)**
  - **Disease-related risk factors (**specific to ESRD**)**
  - **Dialysis-specific factors**
    - in HD patients, **dialysis catheters**, **membrane exposure**, **endotoxaemia** (from intestinal hypoperfusion or dialysis water) and more rapid loss of residual kidney function may contribute to **inflammation**, **oxidative stress** and **myocardial stunning**, which may ultimately increase the risk of CVD

Traditional	Non-traditional
Hypertension*	Anaemia*
Diabetes*	Oxidant stress*
Smoking	Chronic inflammation*
Older age (>45 in males; >55 in females)*	Albuminuria*
Obesity*	Chronic kidney disease*
Sedentary lifestyle*	Hyperhomocysteinaemia*
Premature family history of CVD	Chronic fluid overload*
Dyslipidaemia*	Poor sleep*
Male gender	CKD-MBD*
Mental stress and depression*	Malnutrition*
Race (African Americans, South Asians)*	Elevated fibrinogen*
Alcohol	Low testosterone*
Menopause	Lipoprotein A*
Left ventricular hypertrophy*	Hyperuricaemia*
	Uraemic toxins (e.g. indoxyl sulphate, p-cresyl sulphate)*
	Endotoxaemia*

*Risk factors that are prevalent in the dialysis population.
CVD, cardiovascular disease; CKD-MBD, chronic kidney disease mineral and bone disease. Modified from [19].

Table 1. Traditional and non-traditional cardiovascular risk factors.

- **Dialysis-specific factors**
  - dialysis catheters
  - membrane exposure,
  - endotoxemia (from intestinal hypoperfusion or dialysis water)
  - more rapid loss of residual kidney function

inflammation, oxidative stress and myocardial stunning

- the intermittent nature of HD associated with heightened risks of cardiovascular mortality, particularly **sudden cardiac death**, towards the end of the long inter-dialytic interval over weekends, possibly related to **fluid overload** and **electrolyte disturbances**

- PD patients may experience inflammation and oxidative stress as a result of exposure to PD catheters, bio-incompatible PD solutions and PD-related peritonitis.
- ABNORMALITIES IN SERUM POTASSIUM CONCENTRATIONS, PARTICULARLY **HYPOKALAEMIA**, ALSO DISPROPORTIONATELY INCREASE THE RISK OF DEATH IN PATIENTS RECEIVING PD

- **Excessive exposure to glucose** in PD solutions (up to ٢٠٠ g/day) has also been linked to atherogenic lipid profiles, metabolic syndrome and ultimately increased CVD risk

Hypertension

Hypertension

- Guidelines define hypertension as
  - **pre-dialysis blood pressure (BP) > ١٤٠/٩٠ mmHg**
  - **post-dialysis BP > ١٣٠/٨٠ mmHg**
  - **inter-dialytic ambulatory BP measures ≥ ١٣٥/٨٥**

Hypertension

- **Ambulatory BP monitoring (ABPM)** provides information on circadian variation, is reproducible and remains **the most reliable method to diagnose hypertension in the dialysis population**

mechanisms of hypertension

- Volume and sodium overload
- Increased arterial stiffness
- Renin-angiotensin-aldosterone
- Sympathetic hyperactivity
- Endothelial dysfunction
- Sleep apnoea
- use of erythropoiesis-stimulating agents (ESAs)

Treatment of Hypertension

- Non-pharmacological
- Pharmacological

Non-pharmacological treatment of hypertension

- **sodium and fluid restriction** (Ultrafiltration, sodium removal and reduction of dry weight result in normalization of the BP in ~٢٠% of chronic dialysis patients)

Non-pharmacological treatment of hypertension

- **Increased duration of dialysis** afford a **slower rate** of ultrafiltration, improves BP control and reduces the incidence of intra-dialytic hypotension.

Non-pharmacological treatment of hypertension

- **Minimization of inter- and intra-dialytic sodium gain** is essential to management.
- KDOQI guidelines advocate a **low dietary sodium intake (<٢–٣ g/day),**
- **avoidance of a positive sodium balance during dialysis** is also key
- **Dialysate sodium concentrations should not exceed that of pre-dialysis serum sodium**.

Non-pharmacological treatment of hypertension

- **Dry weight** has been defined as the **lowest tolerated post-dialysis weight, achieved gently and gradually**, at **which patients experience minimal signs or symptoms of dysvolaemia**

Pharmacological treatment of hypertension

- Importantly, pharmacological treatment of hypertension has been shown to modify CVD outcomes in the dialysis population
- In a **systematic review** and meta-analysis of ٨ randomized, controlled trials (RCTs) involving ١٦٧٩ dialysis patients and ٤٩٥ cardiovascular events (CVE), lowering BP with medication was associated with decreased risks of CVE (RR ٠,٧١, ٠,٥٥–٠,٩٢, p = ٠,٠٠٩), all-cause mortality (RR ٠,٨٠, ٠,٦٦–٠,٩٦, p = ٠,٠١٤) and cardiovascular mortality (RR ٠,٧١, ٠,٥٠–٠,٩٩, p = ٠,٠٤٤) .

Pharmacological treatment of hypertension

- **Angiotensin receptor blockers (ARBs)** have been shown to reduce CVE in ESKD
- Suzuki et al. found that HD patients randomised to candesartan, valsartan or losartan had fewer fatal and non-fatal CVE (hazard ratio (HR) ۰.۵۱, ۰.۳۳–۰.۷۹, p = ۰.۰۰۲) .
- Similar results were seen with telmisartan in HD patients with congestive heart failure—with reductions in all-cause mortality (HR ۰.۵۱, ۰.۳۲–۰.۸۲, p < ۰.۰۱), cardiovascular mortality (HR ۰.۴۲, ۰.۳۸–۰.۶۱, p < ۰.۰۰۰۱) and hospital stay (HR ۰.۳۸, ۰.۱۹–۰.۵۱, p < ۰.۰۰۰۱).

Pharmacological treatment of hypertension

- **Angiotensin-converting enzyme inhibitors (ACEi)** have not been shown to reduce CVE compared with standard therapy
- Zannad et al. found no significant benefit of fosinopril in HD patients after adjusting for independent predictors of CVE .
- Li et al. showed that ramipril, whilst slowing residual kidney function decline in PD patients, did not reduce the risk of CVEs .
- In a prospective, open-label RCT of lisinopril versus atenolol reported that lisinopril-based therapy resulted in higher rates of serious CVE (incidence rate ratio [IRR] ۲,۳۶, ۹۵% CI ۱,۳۶–۴,۲۳) and all-cause hospitalizations (IRR ۱,۶۱, ۹۵% CI ۱,۱۸–۲,۱۹)

Pharmacological treatment of hypertension

- Given the small sample sizes and generally poor quality of published trials, the relative benefits and harms of **Mineralocorticoid antagonists (MCAs**), for preventing CVD in dialysis patients remain **uncertain.**
- Quach et al recently reported a systematic review and meta-analysis of ۹ RCTs involving ۸۲۹ dialysis patients (peritoneal dialysis or haemodialysis).Compared with control patients, those treated with MCAs had a significantly lower cardiovascular mortality (risk ratio [RR] ۰,۳۴, ۹۵% CI ۰,۱۵–۰,۷۵) and all-cause mortality (RR ۰,۴۰, ۹۵% CI ۰,۲۳–۰,۶۹), although these benefits were offset by a significantly increased risk of hyperkalaemia (RR ۳,۰۵, ۹۵% CI ۱,۲۱–۷,۷۰).

Pharmacological treatment of hypertension

- **The roles of other specific anti-hypertensive agents also remain uncertain.**
- Tepel et al. found that whilst **amlodipine** did not significantly reduce all-cause mortality, it may reduce CVE (composite secondary end-point, HR ۰,۵۳, ۰,۳۱–۰,۹۳, *p*
- Cice et al. showed that **carvedilol** improved LV function and reduced all-cause mortality (HR ۰,۵۱, ۰,۳۲–۰,۸۲, $p < ۰,۰۱$), cardiovascular mortality (HR ۰,۳۲, ۰,۱۸–۰,۵۷, $p < ۰,۰۰۰۱$) and hospital admissions (HR ۰,۴۴, ۰,۲۵–۰,۷۷, $p < ۰,۰۰۵$) in ۱۱۴ HD patients with dilated cardiomyopathy over ۲ years at a single centre= ۰,۰۳) in HD patients .

target BP in dialysis patients.

- The current KDOQI and ISPD recommendations of a BP target goal < ١٤٠/٩٠ mmHg are extrapolated from studies in the non-dialysis population .
- **There have been no published prospective, randomized trials to date evaluating the target BP in dialysis patients**.

Cardiovascular disease screening

Cardiovascular disease screening

- Despite the considerable burden of CVD in the ESKD population, **screening in asymptomatic individuals is not routine in clinical practice**, except those being evaluated for transplantation.
- This may in part be due to the **uncertainty** regarding whether early detection and intervention improves outcomes in this population.

Cardiovascular disease screening

- The **prediction of CAD risk** is limited by traditional risk estimate tools, including the **Framingham risk model**, which can underestimate risk in ESKD by ٥٠%

Biomarkers

- The search for a novel predictive **biomarker has not yielded** many successful results.
- The most promising biomarker appears to be the **cardiac troponin assay.**

Biomarkers

- meta-analysis of ~۴۰۰۰ asymptomatic ESKD patients found that an elevated **troponin T** level (>۰,۱ ng/ml) was significantly associated with **increased allcause mortality** (RR ۲,۶۴, ۲,۱۷–۳,۲۰) and **CVD mortality** (RR ۲,۵۵, ۱,۹۳–۳,۳۷)
- The American College of Cardiology Foundation highlighted the value of troponin for prognostication in ESKD but also **its current limitations in guiding clinical practice** This may be in part related to the lack of specificity of troponin, elevated in more than a third of patients with ESKD

Biomarkers

- **B-type natriuretic peptide (BNP)** and **N-terminal pro-BNP (NT pro-BNP)** may also have a role in predicting CVD and all-cause mortality in ESKD
- a prospective cohort study of ۱۱۳ HD patients found that an annual increase in serum BNP of ۴۰% predicted all-cause and cardiovascular death in the subsequent year
- in a study of ۱۵۰ HD patients, serum NT pro-BNP had a strong graded relationship with all-cause mortality (HR ۱,۵۴, $p < ۰,۰۱$) and cardiovascular mortality (HR ۲,۹۹, $p < ۰,۰۱$) [۱۷۱].

Exercise stress test

- A poor screening tool in the dialysis population due to
  - The high prevalence of baseline **ECG abnormalities**,
  - **Limited exercise tolerance** due to non- Cardiac co-morbidities,
  - **A blunted chronotropic response** from autonomic dysfunction—ultimately only ٧–٥٣% of patients achieve the target heart rate

Myocardial perfusion scintigraphy (MPS)

- The same limitations of exercise stress testing exist with exercise-MPS in dialysis patients, **necessitating the use of pharmacological stressors.**
- The **low sensitivity** in dialysis patients has been attributed to equally distributed diminished coronary flow ('balanced ischaemia') and an impaired vasodilatory response.
- In one prospective study of ١٥٠ dialysis patients, an abnormal MPS result was more predictive of mortality than the number of narrowed coronary vessels

Dobutamine stress echocardiography (DSE)

- **DSE is a valid screening test** as it not only provides information on the location and extent of CAD, but also on ventricular hypertrophy, volume status and valvular disease.
- Its sensitivity and specificity appear similar to that of MPS

Coronary artery calcium score

- Coronary calcium scores do predict mortality in dialysis patients, but **have poor correlation with angiogram findings**.
- Though not the best tool to predict future need for coronary intervention,
- low or negative coronary calcium scores have been shown to have **good negative predictive value**

CT coronary angiogram

- CT coronary angiogram is presently used in the general population to evaluate CAD in low to intermediate risk patients.
- Its utility has not been extensively assessed in the dialysis population.
- Given its **high negative predictive value**, Hakeem et al. concluded that ‘the potential role of CT coronary angiogram likely rests in **serving as a gatekeeper for invasive angiography** in patients with submaximal, equivocal or mildly abnormal stress tests’

limitations of screening tests

Non-invasive screening test	Limitations in ESKD
Exercise stress test	Poor exertional tolerance
	High prevalence of baseline ECG abnormalities
Myocardial perfusion scintigraphy	Low sensitivity
Dobutamine stress echocardiography	Operator dependent
	Adequate acoustic windows not possible in up to 20% of cases
Coronary artery calcium score	No correlation between score and CAD
CT coronary angiogram	Contrast exposure
	Low specificity due to high coronary calcium burden
Cardiac MRI	Inability to use gadolinium

Adapted from [164].

Table 2. Limitations of non-invasive screening methods in ESKD patients.

Coronary angiography

- Coronary angiography remains the ***gold standard*** for the diagnosis of CAD in dialysis patients.
- Coronary intervention does not appear to improve survival in asymptomatic individuals in the general population

Cardiovascular disease screening

- As for any screening program, the **expected benefits should outweigh the costs and side effects.**
- Screening can only be justified when there is high asymptomatic disease prevalence within the cohort and with evidence that early intervention improves overall outcomes
- **Hakeem et al.** proposed an **algorithm for CAD screening and risk stratification** in asymptomatic ESKD

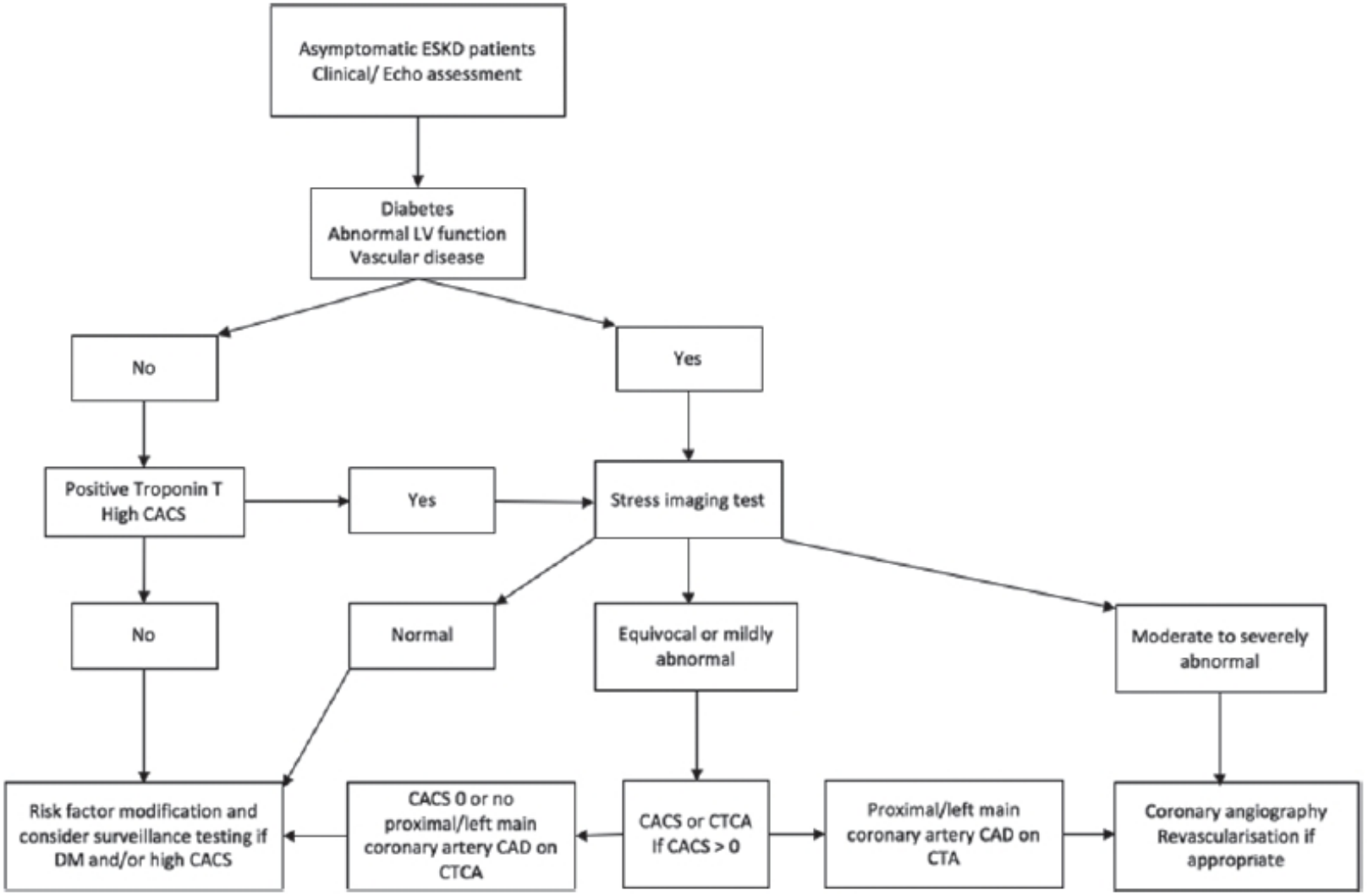


Figure 1. Proposed algorithm for CAD screening. Modified from [165]. ESKD, end-stage kidney disease; LV, left ventricular; CACS, coronary artery calcium score; CTCA, CT coronary angiogram.

Coronary artery disease (CAD)

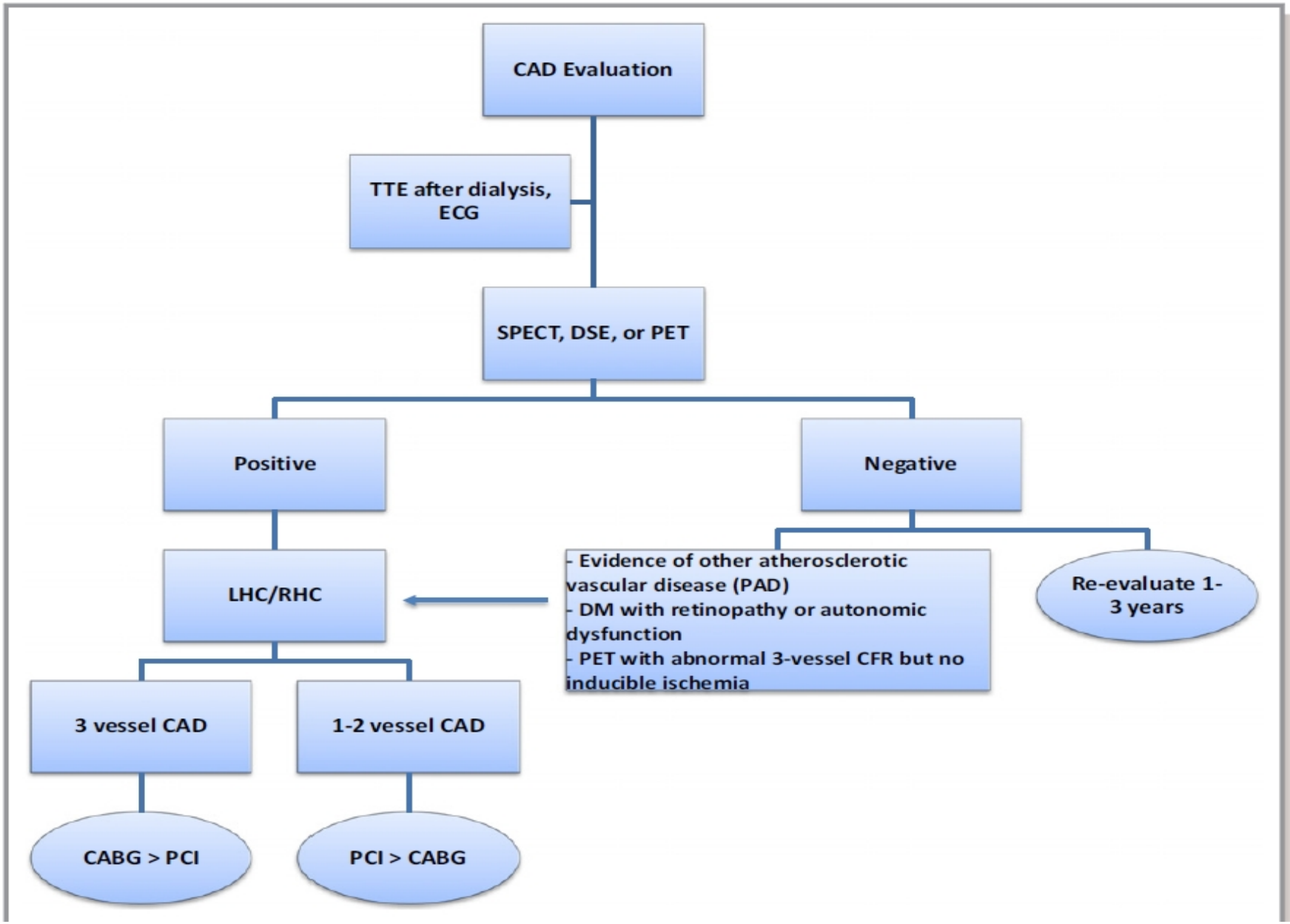
- The incidence of CAD in patients initiating dialysis is up to ٣٨%.
- CAD is highly prevalent in patients with ESRD because of
  - presence of comorbidities (hypertension, diabetes mellitus, dyslipidemia, obesity, and tobacco)
  - uremic environment
  - inflammatory process

Recommendations for Management of CAD

- Careful **clinical history** and **baseline ECG** should be performed in all patients.
- **Echocardiography** to assess ventricular dimensions and function.
- **Dobutamine stress echocardiogram** or, preferably, **nuclear stress imaging with SPECT or PET** are the initial tests that we use to screen for the presence of CAD.

- Patients with evidence of ischemia on stress test should be referred for **left heart catheterization** to identify prognostically significant CAD.
- Revascularization by PCI or CABG for ٣-vessel disease should be pursued if indicated.

- **Patients with multiple risk factors** for CAD (≥٣ risk factors: diabetes mellitus, prior cardiovascular disease, >١ year on dialysis, LVH, peripheral arterial disease, age >٦٠ years, smoking, hypertension, dyslipidemia) **should be considered for *further imaging or cardiac catheterization* despite a negative stress test in some instances.**


CAD Evaluation
TTE after dialysis, ECG
SPECT, DSE, or PET
Positive
Negative
LHC/RHC
- Evidence of other atherosclerotic vascular disease (PAD)
- DM with retinopathy or autonomic dysfunction
- PET with abnormal 3-vessel CFR but no inducible ischemia
Re-evaluate 1-3 years
3 vessel CAD
1-2 vessel CAD
CABG > PCI
PCI > CABG

Congestive Heart Failure

- It is estimated that up to ۳۶% of all patients with ESRD have CHF at the initiation of dialysis.
- ۲۵% of patients on dialysis develop de novo CHF with an incidence of ۷% per year.

- The underlying causes of CHF in patients with ESRD are similar to those in the general population including **advancing age, diabetes mellitus,** and **ischemic heart disease.**
- **Toxins from the uremic milieu** may affect myocardial contractility and function.
- **Anemia** secondary to CKD is associated with a higher incidence of CHF in this population.
- **Chronic volume overload** and **poorly controlled hypertension** are also major risk factors for CHF in patients with CKD and ESRD

- Medical treatment of CHF in patients with advanced CKD is similar to patients without renal disease
- Beta blocker therapy lowered all-cause and cardiovascular mortality
- ACE inhibition, however, has been shown to be effective at preventing progression of CKD in patients with an estimated glomerular filtration rate of **≥٢٠ mL/min.**
- A drop in estimated glomerular filtration rate of >٢٥% or development of hyperkalemia (>٥,٥ mmol/L) is an indication for discontinuing therapy

Recommendations for Management of CHF

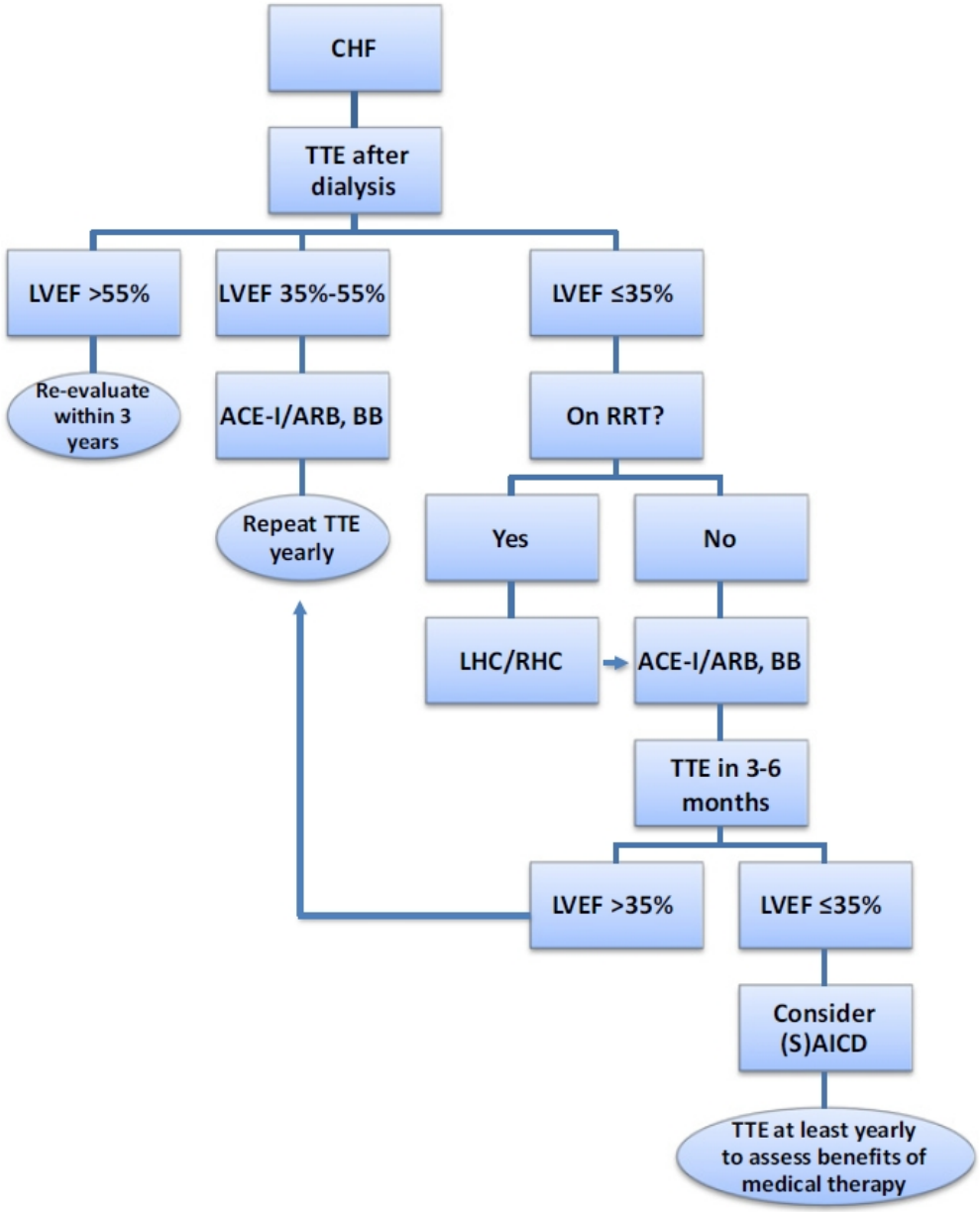
- All patients under evaluation should have baseline echocardiography at dry weight.
- For patients with an **LVEF <٣٥%**, right and left heart catheterization should be performed to assess for ischemic heart disease and targets for revascularization, with PCI or CABG performed if indicated.
- Treatments such as **beta blockers** and **ACE inhibitors** or **angiotensin receptor blockers** should be initiated to prevent cardiac remodeling and to improve LVEF

- **Side effects** such as hypotension, electrolyte abnormalities, and bradycardia should be monitored closely once therapy has begun.
- Importantly, many **angiotensin receptor blockers** are not dialyzed and are preferred over ACE inhibitors, which are dialyzable.

- If no improvement in cardiac contractility is achieved and LVEF remains <٣٥% despite optimal medical therapy, the benefits and risks of **ICD and S-ICD** for primary prevention should be discussed with the patient.

Follow up

- Cardiac evaluation should be performed **annually** for patients with LV systolic dysfunction and more frequently for patients with LVEF <٣٥% for titration of medical therapy based on guidelines for management of patients with severe LV dysfunction
- Patients with normal LVEF should be reevaluated by echocardiography within ٣ years.


CHF
TTE after dialysis
LVEF >55%
LVEF 35%-55%
LVEF ≤35%
Re-evaluate within 3 years
ACE-I/ARB, BB
On RRT?
Repeat TTE yearly
Yes
No
LHC/RHC
ACE-I/ARB, BB
TTE in 3-6 months
LVEF >35%
LVEF ≤35%
Consider (S)AICD
TTE at least yearly to assess benefits of medical therapy

Valvular Disease

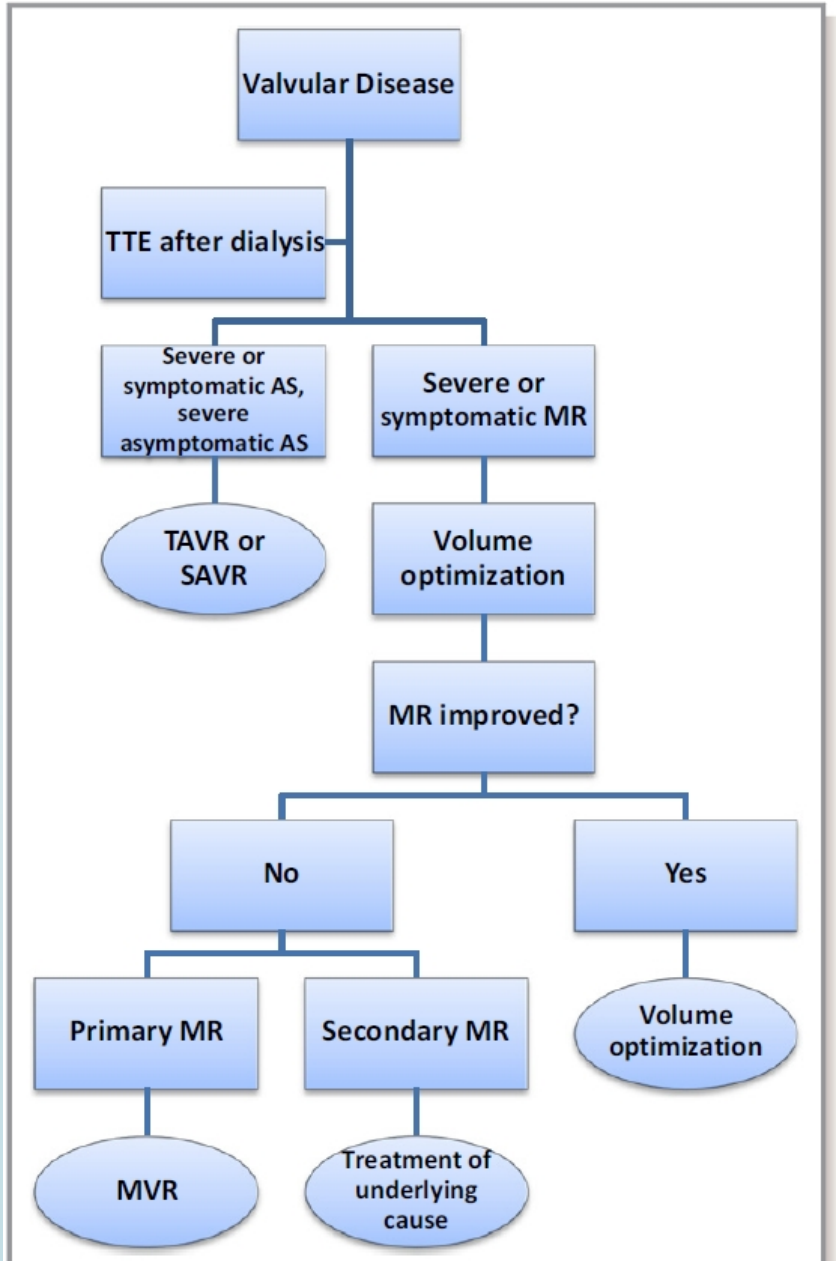
- Degenerative valvular calcification is more prevalent and progresses faster in ESRD than in the general population, likely because of
  - Abnormal calcium and phosphate metabolism
  - Secondary hyperparathyroidism
  - Vitamin D and calcium supplementation

- These metabolic abnormalities lead to increased calcium deposition in the mitral annulus and aortic valve.
- In patients on dialysis, **aortic valve calcification (AVC)** is often severe and can lead to **rapidly progressing aortic stenosis (AS).**

- ۳۶% of patients had **mitral annular calcification** that was associated with age, age at initiation of dialysis, calcium phosphate product, and time spent on dialysis.
- Progressive mitral annular calcification can cause functional impairment by encroachment to the mitral leaflets, leading to mitral regurgitation and/or mitral stenosis.

Recommendations for Management of Valvular Disease

- Patients Should considered for definitive management prior to transplantation.
- **TAVR** should be used as an alternative to **SAVR** in patients at high or intermediate risk for surgery.


Valvular Disease
TTE after dialysis
Severe or symptomatic AS, severe asymptomatic AS
Severe or symptomatic MR
TAVR or SAVR
Volume optimization
MR improved?
No
Yes
Primary MR
Secondary MR
Volume optimization
MVR
Treatment of underlying cause

Pulmonary Hypertension

- PH is common in patients with ESRD, and multiple studies have estimated the prevalence to be ۲۶% to ۴۸% depending on the mean age of the population studied and the time spent on dialysis.

- Several factors place patients with ESRD at risk for the development of PH:
  - **Placement of AVF**
  - **Chronic hypervolemia,**
  - **Anemia**
- These risk factors can lead to a state of high cardiac output, which can further contribute to the development of PH.

- **Endothelial dysfunction** caused by decreased nitric oxide production may also play a role
- An AVF flow rate ≥۲ L/min and cardiac output of ≥۸ L/min place patients at high risk of high-output cardiac failure.

- **Surgical reduction of AVF** should be considered in patients with very high cardiac output in whom improvements in cardiac output and PH by temporary AVF closure has been shown.
- The definitive treatment for PH in this population is **renal transplantation** if the etiology is secondary to high cardiac output from AVF.

- Evidence of PH on echocardiogram **(≥٤٠ mm Hg)** should be confirmed with **repeat echocardiography** following hemodialysis to ensure that PH is not simply caused by volume overload
- If pulmonary artery pressures remain elevated despite optimization of volume status by dialysis, **right heart catheterization** to assess severity and potential etiology of PH should be performed.

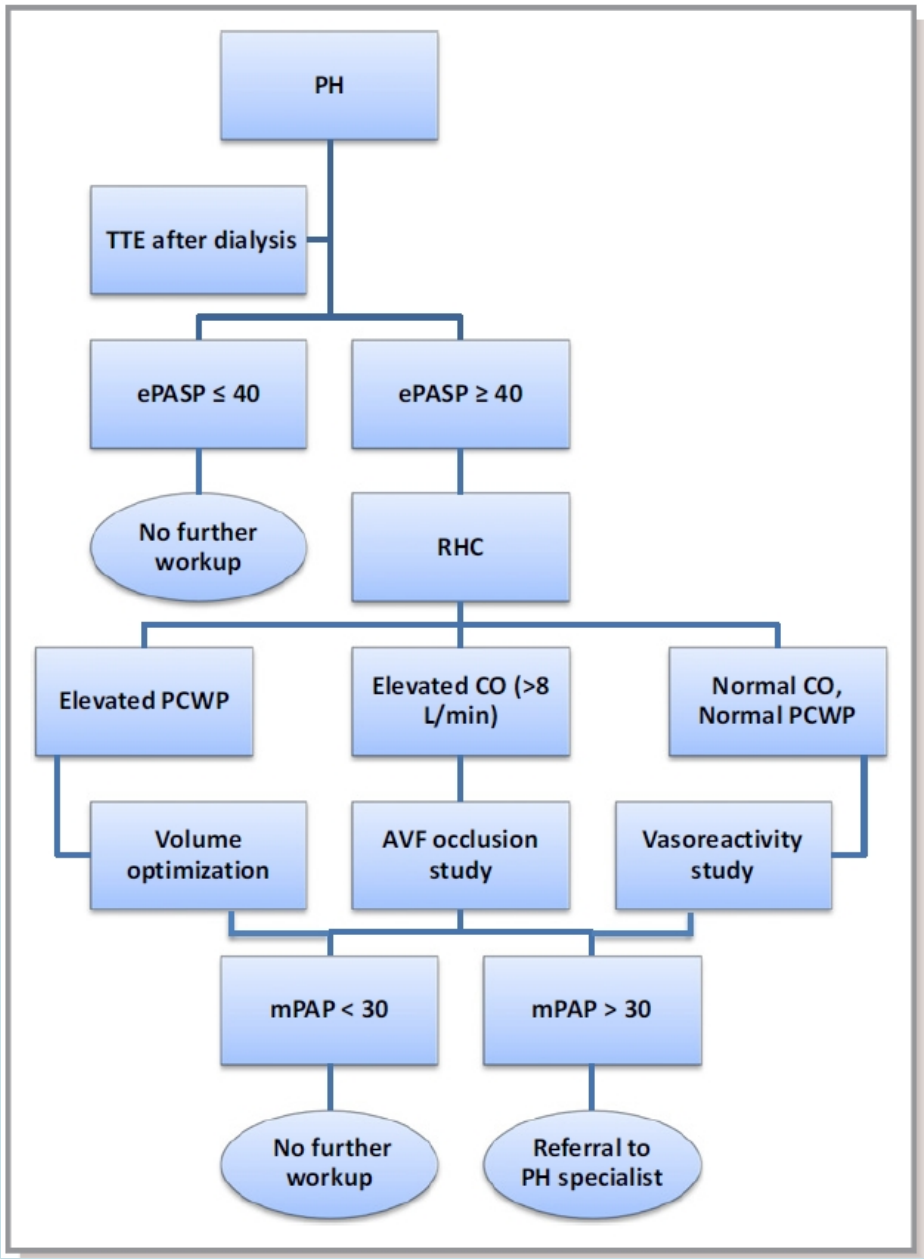
Recommendations for Management of PH

- Severe PH (mean pulmonary artery pressure ≥۴۰ mm Hg) in the setting of elevated pulmonary capillary wedge pressure (≥۱۸ mm Hg) should **be treated with more aggressive diuresis to optimize volume status,** at times requiring inpatient admission to **perform daily dialysis**.
- When PH is present in the absence of elevated pulmonary capillary wedge pressure but with high cardiac output (>۸ L/min), attention should be paid to the **AVF.**

Recommendations for Management of PH

- **Evidence of decreased cardiac output and improved pulmonary pressures acutely during AVF occlusion in the catheterization laboratory are suggestive of AVF as the etiology of PH, and surgical revision should be considered.**

- Patients with PH with normal left atrial pressures and normal cardiac output should undergo reversibility testing with intravenous and with or without **inhaled vasodilators** to determine the potential response to medical therapy


PH
TTE after dialysis
ePASP ≤ 40
ePASP ≥ 40
No further workup
RHC
Elevated PCWP
Elevated CO (>8 L/min)
Normal CO, Normal PCWP
Volume optimization
AVF occlusion study
Vasoreactivity study
mPAP < 30
mPAP > 30
No further workup
Referral to PH specialist

Cardiovascular Disease in Dialysis Patients

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Additional info
http://dx.do

Cardiovascular disease in dialysis patients

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ABSTRACT

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Nephrology Dialysis Transplantation

CONTEMPORARY REVIEW

American Heart Association | American Stroke Association

Diagnosis and Management of Cardiovascular Disease in Advanced and End-Stage Renal Disease

Navdeep K. Bhatti, MD; Keyvan Karimi Galougahi, MD, PhD; Yehuda Paz, MD; Tamim Nazif, MD; Jeffrey W. Moses, MD; Martin B. Leon, MD; Gregg W. Stone, MD; Ajay J. Kirtane, MD; Dimitri Karmpaliotis, MD; Sabahat Bokhari, MD; Mark A. Hardy, MD; Geoffrey Dube, MD; Sumit Mohan, MD; Lloyd E. Ratner, MD, MPH; David J. Cohen, MD; Ziad A. Ali, MD, DPhil

Chronic kidney disease (CKD) affects 13% of the US population.[1] Although a significant proportion of these patients progress to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT)[2] or renal transplantation, cardiovascular disease remains the most common cause of

guidelines on optimal management of cardiovascular disease in patients with advanced CKD with particular focus on coronary artery disease (CAD), congestive heart failure (CHF), valvular disease, and PH. The overall aim is to identify the subset of patients who may maximally benefit from renal


thank
you