JOURNAL OF THE INTERNATIONAL SOCIETY FOR PERITONEAL DIALYSIS
Peritoneal Dialysis INTERNATIONAL

Supplemental Materials for

ISPD CARDIOVASCULAR AND METABOLIC GUIDELINES IN ADULT PERTIONEAL DIALYSIS PATIENTS

PART II – MANAGEMENT OF VARIOUS CARDIOVASCULAR COMPLICATIONS

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PART II – MANAGEMENT OF VARIOUS CARDIOVASCULAR COMPLICATIONS

SECTION 1. CORONARY ARTERY DISEASE

Guideline 3.1.1: We recommend serial measurements of cardiac troponins be used to evaluate acute myocardial infarction and acute coronary syndrome in peritoneal dialysis patients with acute symptoms (chest pain), along with electrocardiographic changes or other clinical evidence suggestive of acute myocardial ischemia. (1B). A rise in troponin level of >20% within 4 – 6 hours with at least 1 value above the 99th percentile should be diagnosed as acute myocardial infarction or acute coronary syndrome. (1C)

Rationale

Troponin I (TnI) or Troponin T (TnT) levels are frequently elevated in dialysis patients. Whilst there may be changes in the removal of troponins or fragments by residual renal function or different dialysis modalities, the consensus is that elevated levels represent a increased 'leak' of these markers from myocytes (1). Whilst there are subtle differences between TnI and TnT in renal failure these are unlikely to be clinically relevant. It is difficult to define a reference range in the normal population, and even more difficult in dialysis patients, thus a single elevated value of Tn without clinical correlates is unlikely to be helpful, apart from indicating enhanced vascular risk (2). A rise in serial markers along with appropriate clinical context is the currently accepted definition of an acute coronary syndrome (ACS) (3). The difficulty is in the definition of how much change constitutes a significant change. A 20% serial change is taken as ~3 standard deviation of change and assumes an analytical coefficient of variation of up to 7% (4).

Guideline 3.1.2: We suggest asymptomatic peritoneal dialysis patients incidentally found to have high cardiac troponins without dynamic changes be considered as having an elevated cardiovascular risk (2B) and may benefit from investigation for underlying cardiac disease such as cardiac hypertrophy, dysfunction or occult coronary artery disease (ungraded).

Rationale

The rapid development and refinement of assays for troponins, the lack of standardization among assays, the variability of decision limits and changing reference ranges has contributed to confusion around the interpretation of an elevated TnT or TnI in patients with renal dysfunction (3).

'Standard' ranges of TnT/TnI have been defined for a reference population with normal renal function, and elevations above the 99th percentile of this range provide both sensitive and specific indices of myocardial damage in those with a high pre-test probability of a cardiac event (6). Interestingly there appears to be only moderate correlation between hs-cTnT and hs-cTnI (7), but most physicians regard

TnI and TnT as clinically interchangeable. It is however probable that there are subtle differences in release and metabolism which may make the interpretation of different patterns of release helpful at some point, but since these differences are largely unexplored (especially in the dialysis population) it is unhelpful at this time to consider them separately. In addition many hospitals have decided to use one or the other and rarely use both.

Defining a 'normal' or reference range is also difficult since the upper limit appears to reduce when ever more stringent exclusion of pathology and sex differences are considered (8). However, it is well established that many, if not most, patients with renal dysfunction including those on dialysis, will have higher levels of these biomarkers, especially if one uses the high sensitivity assays(9)(10). There is also uncertainty about whether intra- and inter individual variation in dialysis patients is similar to that seen in normal individuals, although again this may be test specific (11).

There are a small amount of data suggesting that TnI may be slightly more sensitive to an acute myocardial infarction (AMI) than TnT, indicating that perhaps the latter is the preferred biomarker for an AMI (12). However TnT may be a better predicative marker for mortality (13), where TnI has not been established as a prognostic biomarker (14). In the dialysis population there is emerging evidence that the hs-TnT assay may be slightly superior to the standard TnT assay in its ability to predict outcomes(15), but these data are not yet robust, and any modern Tn assay appears to perform well as a prognostic tool.

Is Tn elevated because of increased release?

Cardiac troponins are subunits of the actin-myosin complex (16) that are found in the systemic circulation after release from the cardiac myosite and have better sensitivity and specificity than older markers like creatine kinase-MB or myoglobin (17). Although most cardiac troponin is released by cardiac myosites, it is possible to get skeletal muscle to re-express cTnT (for example potentially under uremic conditions), although most agree that cTnI is more cardiospecific (18). There does appear to be a correlation between circulating Tn and left ventricular (LV) mass (19), so it is important to examine whether this finding might explain the adverse prognosis implied by an elevated Tn. In support of this, there is a correlation of TnT with fluid overload in hemodialysis (HD) patients ($r=0.325$, $P<0.001$) (20). In another study of peritoneal dialysis (PD) patients cardiac congestion was predicted by TnT, and this association was not attenuated by the presence of left ventricular hypertrophy (LVH) or C-reactive protein (CRP), suggesting that TnT is independent of LV mass (21).

Nevertheless there is continued debate as to why most dialysis patients have levels of Tn that are above the 99th percentile of the reference range. The prevailing consensus is that the uremic state induces subclinical myocardial changes (e.g. LVH, shear stress enhanced permeability and systolic dysfunction) leading to Tn leak from the myocardium and true elevations in blood levels (1).

In patients with stable coronary artery disease and minimal renal dysfunction (creatinine <2 mg/dL/172micromol/L), hs-cTnT levels are detectable in 98% of patients and there is a strong and graded increase in risk of cardiovascular death/heart failure even after multivariate analysis which is continuous below the limits of detection of the conventional assays (~0.01 mcg/L for TnT) (22). In a study comparing 51 asymptomatic PD patients, the median TnI was 0.9 ng/mL (IQR 0.7-0.9) and this was significantly higher than HD patients (0.7 (IQR 0.6-0.8) (23). Similarly in dialysis patients, there may not be a threshold value of Tn at which risk starts to increase, rather there appears to be a graded risk with increasing levels. The associations of Tn and hard outcomes are well established in HD patients (12,24–30) and those studies available including PD patients are shown in Evidence Review Table 1, and show a similar pattern. Surrogate end-point studies are shown in Evidence Review Table 2.

Is there evidence of reduced Tn clearance?

There is contradictory evidence on whether the circulating half-life of immunoreactive troponins is prolonged in renal dysfunction. Intact troponin fragments may be too large to be cleared by glomerular filtration, but fragments may be amenable to renal clearance. Nevertheless some data suggest that most of the immunoreactive circulating TnT is in the form of the intact protein (31) or as complexes (32). Nevertheless, some Tn fragments may be affected by residual renal function (33), which adds a layer of complexity to the analysis because the detection will be determined by the specificity of the capture antibody.

Contradictory data exist with respect to the half-life ($t_{½}$) of the troponins; Ellis *et al* reported that TnI does not have a significantly prolonged $t_{½}$ in dialysis patients (34). In contrast Wiessner reported the $t_{½}$ of TnT to be prolonged with progressive renal impairment (35). In two chronic kidney disease (CKD) studies TnI levels were higher in the lower estimated glomerular filtration rate (eGFR) strata (36) or correlated with creatinine (37). The most compelling argument *against* residual renal function playing a significant role in Tn clearance is the demonstration that TnT levels did not seem to be significantly affected by transplantation despite good early graft function, arguing against a major role for renal clearance of Tn (38). However other data showed that TnT levels if elevated, did reduce within 3 weeks of successful transplantation (38), but whether this is due to improved hemodynamics and a better milieu for the myocardium, or reduced TnT from renal excretory/metabolic function remains to be elucidated (39). Another study suggested that if TnT does not normalize post transplantation, then this implies an elevated cardiac risk (38), as it does pre transplant (40).

In summary there is insufficient evidence to know whether renal function significantly effects levels of Tn by enhanced removal or improves myocardial performance. The workgroup felt that the current available evidence is insufficient to draw any recommendation in relation to which troponin to use and whether residual renal function contributes to clearance.

Does the Tn level differ with dialysis modality?

Many assays give upper reference limits defined as the 99th percentile of the normal range and are used for identification of patients who are likely to have suffered a myocardial insult. Two issues arise in setting a decision limit for patients on dialysis, firstly these values vary greatly between assays (6). Secondly different dialysis techniques may change the reference range, for example in one study TnI increased in some patients after HD, and this may be identifying patients at higher cardiovascular risk because of myocardial stunning (41,42). High flux dialysis clears troponins more efficiently than low flux (43) and more frequent HD lowers TnT (44) Hemodiafiltration may increase Tn removal but the reinfusion buffer used may be also important (45). In a crossover study, hemodiafiltration caused a reduction in TnT compared with conventional HD where a small rise was seen (46).

In PD, no changes in troponins have been observed after exchanges (47). Nevertheless, immunoreactive TnT can be found in PD fluid effluent (48) and at least one study suggests that TnI levels are significantly lower in PD patients than HD patients (49), suggesting that PD clearance may play a part in determining plasma levels.

A number of studies in PD patients show that it is rare for PD patients to have TnI levels >0.1 ng/mL (23,50–52) or TnT >0.1 ng/mL (53). The workgroup felt that the current available evidence is insufficient to draw any recommendation in relation to differential troponin ranges on different modalities.

Using paired values for the diagnosis of acute myocardial infarction/acute coronary syndrome

An increase in cardiac troponin I (TnI) or T (TnT) over >6hrs is the currently accepted as a test to diagnose an AMI or ACS (3,54). Using paired values make it possible to define a value of a reference change value (RCV). This is the value by which troponin must increase to accurately diagnose AMI/ACS, which in individuals with normal renal function is between ~40 and 90%. However for patients on dialysis this has not been calculated, and may be affected by the assay. However, the National Academy of Clinical Biochemistry (NACB) suggests that a 20% change is used based upon a ~3 standard deviation change, and assuming an up to 7% analytical coefficient of variation (4).

There are now a number of studies looking at the role of troponins in patients with end-stage renal disease, but most patients in these studies have been on HD and the studies have been performed across several decades where methodology has been changing rapidly. However, in a meta-analysis of 39 studies in 2004, Needham *et al* found a specificity of TnI in diagnosing an AMI of 96% (confidence interval: 94–98%) in HD patients, while TnT compared less favorably (71% (64-77)) (55). Two small studies considered asymptomatic PD patients and suggested using a single value of TnI to diagnose an acute event. Here 24/28 PD patients had TnI levels <0.1 ng/mL and none had levels >0.3 ng/mL and suggested that perhaps a single level of TnI >0.4 ng/mL may be diagnostically useful for acute events (50). One study (56) identified

high risk HD patients based upon TnT levels ≥0.7ng/mL, of whom a number had subclinical myocardial infarction (MI) on cardiac Magnetic resonance imaging (MRI).

In the short term, the usefulness of a single elevated troponin value may simply rest in its implication of a worse cardiovascular prognosis in patients with moderate to severe CKD(2), for patients on dialysis (14) or with a kidney transplant(40). The diagnosis of acute MI, AMI or ACS should rest on demonstrating an increase in either TnT or TnI of >=20% over 6-9 hrs(4).

Some units advocate prospectively collecting troponin levels as 'baseline' values with which to compare 'acute' serum levels. The value of this practice is unproven, and whether an elevated risk implied by a high Tn value can be ameliorated by intervention (e.g. coronary artery bypass or angioplasty) is also currently unknown. However we suggest asymptomatic PD patients incidentally found to have high cardiac troponins without dynamic changes may benefit from investigation for underlying cardiac disease, which may include occult or overt coronary artery disease. The workgroup felt that the current available evidence is insufficient to draw any recommendation in relation to monitoring troponin levels prospectively.

Evidence Review Table 1. Studies of peritoneal dialysis patients that examined the association of cardiac troponin with hard outcomes

Reference	Population	Patient number	Design	Assay	Outcome	Follow-up duration	Results	Study quality
Hassan et al 2014 (53)	HD 275 PD 118	393	Prospective cohort	hsTnT (Elecsys, Roche) 5th gen	MI M	59 weeks	Per 25 ng/L hs-TnT Combined (HD & PD) M:uHR 1.10(1.04-1.16)** M:aHR 1.07(1.01-1.15)+ MI: uHR1.16 (1.08-1.23)** MI: aHR 1.14(1.06-1.22)** PD M uHR1.14 (1.04-1.23)* M: aHR 1.15 (1.04-1.27)** MI uHR 1.21 (1.11-1.31)** MI aHR 1.21 (1.11-1.33)**	B
Han et al 2009 (57)	PD 107	107	Prospective cohort	TnT (Roche)	CVE	3 years	Risk of CVS event TnT >1.1 ng/mL HR 5.89 (CI 1.24-28)*	B
Mcgill et al 2010 (15)	PD 31 HD 112	143	Prospective cohort	hscTnT	M	46.7 months	M Per 2.7 nag/L increase in shunt Lon hesitant HR 1.404 (1.001-1.968)+	C
Doman et al 2005 (58)	PD 65	65	Prospective cohort	cant (Roche-Eleusis) catnip (immolate; PDC Corp)-	M CVM	2 years	TnT ≥0.035 ng/mL independently predicted; All-cause mortality OR 4.31 (1.16-16.04)* CV mortality OR 8.94 (2.23-35.88)*. Other TnT correlated with LVMI TnI did not significantly correlate with mortality.	C
Hickman et al 2009 (59)	PD 31 HD 112	143	Baseline cross-sectional with prospective	TnT (Roche elecysis) cTnI (Abbott Diagnostics)	M	30 months	All-cause mortality Detectable Tent (>0.01 nag/mol) OR 11.33 (1.48-86.79)*	C

			cohort follow up				Detectable Tin (>0.01 nag/mol) 6.37 OR, (0.82-49.58)(p=ns)	
Ishii et al 2001 (13)	HD 92 PD 8	100	Prospective cohort	catnip (Access Immunoassay) cant (Eleusis, Roche)	M	2 years	All-cause mortality was predicted by; Tent RR 3.71(2.66-4.77)* Adverse outcomes associated with; TnT≥0.1 = OR 5.14 * ¶ TnI≥0.1 OR 1.1¶	C
Haceks et al 2006 (60)	HD 550 PD 295	845	Prospective cohort (NECOSAD)		M, CVM and CVS mortality	?	All-cause mortality Tent>0.05-0.1 ng/mL uHR 2.2 (CI 1.7-2.8) aHR 1.2 (CI 0.9-1.7) TnT>0.1 uHR 3.3 (CI 2.5-4.5) aHR 2.2 (CI 1.5-3.3) CVS mortality TnT>0.05-0.1ng/mL uHR 1.9 (1.2-3.0) aHR 1.0 (0.6-1.7) TnT>0.1ng/ml uHR 3.4(2.1-5.7) aHR 1.9 (0.9-3.7)	B
Ryu et al 2011 (61)	HD 247 PD 37	284	Retrospective review of cases diagnosed with ACS	cTnT (Roche - Elecsys)	CVM	6 years	CV mortality (vs TnT≤0.01 ng/mL) Overall uHR 1.12(1.06-1.18)** aHR 1.12 (1.03-1.22)* TnT 0.01-0.1ng/mL uHR 4.11 (1.41-11.96)* aHR-ns TnT 0.1-0.35 ng/mL uHR 7.81(2.77-22.03)* aHR=ns TnT ≥ 0.35 ng/mL uHR 13.27(4.57-38.53)* aHR 8.65(1.01-74.01)+	C

Wang et al 2007 (62)	PD 238	238	Prospective cohort	cTnT (Roche 3rd generation elctrochemiluminescence)	M CVE	3 years	All-cause mortality aHR 4.43(1.87-10.45)* CVS death aHR 4.12(1.29-13.17)* Non-cardiovascular death aHR 8.06 (CI 1.86-35.03)* Fatal/nonfatal CVS events aHR 3.59 (CI 1.48-8.7)*	B
Lowbeer et al 2003 (63)	PD 26	26	Prospective cohort	cTnT (Enzymum-test Troponin T)	M	4 years	All-cause mortality: TnT≥0.04 µg/L: OR 3.43 ¶	C
Wang et al 2010 (64)	PD 130	130	Prospective cohort	cTnT (Elecsys, Roche)	SCD	5 years	SCD per 0.1ng/mL increase in TnT uHR 1.25 (1.13-1.38)** aHR 1.14 (0.99-1.30 9)(p=ns)	B

(Note µg/L and ng/mL are synonymous; therefore ng/mL used)

¶ Insufficient data given to calculate confidence interval. *p<0.05

HD = hemodialysis; PD = peritoneal dialysis; MI = myocaridial infarction; M = mortality; RR = relative risk; HR = hazard ratio (unadjusted (i.e. univariate) uHR, adjusted (i.e. after multivariable adjustment) aHR) (given with 95% confidence intervals in brackets if available); OR = odds ratio (with 95% confidence limits if available); LVMI = left ventricular mass index. MVA = multivariate analysis; SCD = sudden cardiac death; cTnT = cardiac troponin T; cTnI = cardiac troponin I; CVS = cardiovascular surgery; CVM = cardiovascular mortality; CVE = cardiovascular event; ACS = acute coronary syndrome.

Evidence Review Table 2. Studies of peritoneal dialysis patients with surrogate end-points of cardiovascular disease

Reference	Population	Patient number	Design	Outcomes of interest	Assay	Follow up duration	Results	Study quality
Wang et al 2006 (65)	PD 222	222	Prospective cohort	Cardiovascular congestion, Left ventricular mass	TnT (Roche)	3 years	TnT independently predicted congestion (per 1ug/L) HR 2.98 (CI 1.19-7.42)* TnT correlated with LV mass index (Spearman r=0.44**)	B
Caliskan et al 2012 (66)	PD 37	37	Point prevalence	Carotid intimal medial thickness (CIMT) Pulse wave velocity (PWV) Coronary flow reserve (CFR)	TnT (Roche electrochemiluminescence)	-	TnT correlated with CIMT (r^2=0.557)* PWV (r^2=.186)* CFR (r^2=0.192)*	C
Taskapan et al 2007 (67)	HD 26 PD 26	52	Point	Brain natriuretic peptide (BNP)	TnI (Abbott)	-	BNP correlated with TnI (r=0.405)* HD Mean TnI 0.05ng/ml (SD 0.07)) PD Mean TnI =0.02 (SD 0.02))* TnT or TnI did not correlate with QT dispersion	C
Zapolski 2012 (68)	HD73 PD 57	120	Point prevalence	Aortic stiffness Index (ASI)	cTNT(Roche)	-	TnT correlated with ASI PD beta 0.33 ** (HD beta 0.443)**	C
Park et al 2009 (69)	PD 30	30	Point prevalence	TnT (Roche) LV mass index by echo		-	TnT did not correlate with LV mass index	C

PD = peritoneal dialysis; HD = hemdodialysis; cTnT = cardiac troponin T; cTnI = cardiac troponin I; HR = hazard ratio; CI = confidence interval; LV = left ventricular

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Guideline 3.1.3: We recommend a thorough history and physical examination in all patients initiating peritoneal dialysis therapy to identify any significant cardiac conditions including coronary artery disease, recent myocardial infarction, decompensated heart failure, significant arrhythmias, and severe valvular disease for further specific management.

Guideline 3.1.4: We suggest noninvasive stress testing be considered in peritoneal dialysis patients who are kidney transplant candidates and without active cardiac conditions but on the basis of presence of 3 or more coronary artery disease risk factors: diabetes mellitus, prior cardiovascular disease, >1 year on dialysis, left ventricular hypertrophy, age >60 years, smoking, hypertension, and dyslipidemia. (2C)

Rationale

Coronary artery disease (CAD) is under-diagnosed and under-treated in patients with CKD, therefore identifying treatable disease is desirable. The expected benefits must weigh against the costs and risks associated with screening. Screening can be justified only when the burden of asymptomatic disease is high and when intervention after active screening and diagnosis improves clinical outcomes. The major factors that drive the high prevalence of CAD in the dialysis population are age and the high prevalence of diabetes. In contrast to the general population, a large majority of dialysis patients with CAD are asymptomatic. In addition, acute MI or unstable angina can develop in individuals with non-obstructive CAD, probably as a result of plaque rupture or destabilization.

Whether or not percutaneous coronary intervention or coronary artery bypass grafting improves outcomes of asymptomatic dialysis patients with CAD is unclear. Population-based randomized controlled trials (RCTs) have excluded patients with CKD. However, observational studies suggest

that interventions may be associated with survival benefit compared to conservative management [1,2]. This issue becomes even more critical for patients on the waiting list for transplantation, who are at risk of intra- or post-operative death from MI. Cardiac evaluation could also be used to deny transplantation to high-risk patients if they are deemed to have sufficiently short life expectancy to make transplantation a poor use of scarce donated organs.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), United Kingdom - National Institute for Health and Care Excellence (UK-NICE) and American Heart Association/ American College of Cardiology (AHA/ACC) have therefore come up with guidelines for evaluation for CAD in the dialysis population and those awaiting transplantation [3-5]. All the guidelines acknowledged the lack of high quality evidence in non-dialysis CKD and dialysis patients to inform guideline development (Table 1).

Nevertheless, the major justification for advocating screening in this population is the high prevalence of asymptomatic CAD [Evidence Review Table 2]. In a community-based study of patients hospitalized with acute MI, patients with underlying kidney disease were less likely to report chest pain and more likely to report shortness of breath compared with patients without kidney disease in the setting of acute MI. [6] Using multidetector row computed tomography, Lee et al identified CAD in 32% asymptomatic incident dialysis patients [7]. The majority of dialysis patients with angiographically documented CAD are asymptomatic. Braun et al. [8] reported that 75% of diabetic HD patients with confirmed coronary artery stenosis had no symptoms. In two other studies, 74% and 67% of dialysis patients with CAD were asymptomatic at the time of angiography. [9,10] In a recent study from Japan, the prevalence of unidentified CAD in dialysis patients declined from 69% to 25% from 1993 to 2010 [11]. PD patients exhibit a higher prevalence of cardiovascular disease (CVD) risk factors [12] and poor survival compared to HD patients [13]. In a preliminary report of 256 percutaneous coronary interventions performed in 111 patients, silent myocardial ischemia, defined as the absence of chest pain in response to balloon dilatation of the affected vessel, was present in 59.1% of subjects with CKD versus 29.1% of subjects without CKD. [14] However, the value of routine screening in asymptomatic patients that will benefit from revascularization has not been defined.

Exercise tolerance was suggested the main clinical parameter to be included in the testing algorithm suggested in the “ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. [15] Self-reported poor exercise tolerance was associated with twice as many perioperative cardiovascular complications compared to those with better functional status. [16] However, this simple clinical tool has not been validated at all in the CKD or dialysis population.

Noninvasive testing for CAD has imperfect sensitivity and specificity in patients with end-stage renal disease (ESRD). Evidence Review Table 3 summarizes studies examining the associations between non-invasive cardiac stress testing and occlusive coronary artery lesions on angiography in patients with ESRD. Abnormal myocardial perfusion scintigraphy (MPS) and dobutamine stress echocardiography (DSE) results have been associated with an increased risk of adverse cardiac events and mortality in the ESRD population. In a meta-analysis of 12 studies involving either thallium-201 scintigraphy or DSE, patients with ESRD with inducible ischemia had ≈6 times the risk of an MI and 4 times the risk of cardiac death as patients without inducible defects. [17] Moreover, patients with fixed defects had nearly 5 times the risk of cardiac death. Among 485 patients with advanced kidney disease, the percentage of ischemic segments by DSE was an independent predictor of mortality and offered prognostic information beyond clinical characteristics alone. [18] Also complicating the issue is the fact that the association of CAD demonstrated by angiography with subsequent survival in ESRD is inconsistent [11,19], likely because plaque instability is more

important for risk of major adverse coronary events than angiographic stenosis and many plaque ruptures producing MIs are not localized to sites of angiographic stenosis. [20,21]
The AHA/ACC guidelines [4] suggest using aggregate CAD risk factors for targeted screening to identify those with the highest pretest likelihood of prognostically significant CAD. Presence of "active cardiac conditions" listed above (unstable angina, recent MI, decompensated heart failure, significant arrhythmia, and severe valvular heart disease) qualifies as major risk. If none of these are present, the patient is then risk stratified on the basis of functional capacity. If the functional status is estimated as ≥4 METS, then that patient is deemed low risk and no further testing is advocated. If functional capacity is <4 METS, it is difficult to know whether the low level of exertion is preventing manifestation of an active cardiac condition or whether cardiac conditions are truly absent. Such patients are considered to be of indeterminate cardiac risk and are further risk stratified according to the presence or absence of risk markers, namely, ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, and cerebrovascular disease. Because the presence of any of these risk markers is associated with an increased likelihood of CAD among patients with poor functional status, the diagnostic yield of noninvasive stress testing theoretically improves as one acquires more risk factors.
As for risk stratification among potential kidney transplant candidates, the 2012 AHA guidelines [4] recommend risk-factor based stratification regardless of functional status. Another set of risk factors were defined specifically for the transplant population in the 2007 Lisbon Conference [22]. Compared to ACC/AHA, the Lisbon strategy improves the sensitivity and specificity in identifying significant CAD (sensitivity, 94% versus 77%; specificity, 33% versus 24%) and to reduce the overall frequency of testing. [23] The Lisbon Conference on the care of the kidney transplant recipient identified diabetes mellitus, prior cardiovascular disease, >1 year on dialysis, LVH, age >60 years, smoking, hypertension, and dyslipidemia as risk factors for CAD for prospective kidney transplant recipients [22]. The NKF-KDOQI approach would have identified all patients with abnormal stress tests and revascularizations but this comes with significant additional costs and unclear outcome benefits. Compared to the NKF-KDOQI approach, the ACC/AHA guideline approach would decrease the rate of stress test significantly by 80% but this approach would have identified only 24% of patients who had an abnormal stress test and only 40% of patients who underwent revascularization. The Lisbon approach would result in an intermediate rate in recommending preoperative cardiac evaluation in 68% of subjects. Even though the ACC/AHA guideline would have missed some of the patients with single vessel disease, the benefit of percutaneous coronary intervention beyond medical therapy has not been evaluated in randomized studies in dialysis patients and has remained uncertain. Thus, summarizing the current recommendations given by the various guidelines group and with the lack of high quality evidence in this aspect, the work group would suggest a more targeted approach and screen only PD patients with relevant risk factors for CAD including diabetes mellitus, prior cardiovascular disease, >1 year on dialysis, LVH, age >60 years, smoking, hypertension, and dyslipidemia with non-invasive stress testing.

The specific number of risk factors that should be used to initiate stress testing remains to be determined but ≥ 3 is regarded a reasonable threshold and in keeping with the ACC/AHA guideline. These include diabetes mellitus, prior cardiovascular disease, >1 year on dialysis, left ventricular hypertrophy, age >60 years, smoking, hypertension, and dyslipidemia.
The workgroup felt that current available evidence does not allow recommendation to be drawn on the frequency of repeat screening or stress testing for PD patients who are on transplant waiting list. The 2005 NKF-KDOQI guidelines recommended repeat stress testing once a year among patients on the transplant list. [5] However, the cardiac event rate (cardiac death or nonfatal MI) was only 0.6% over 2 to 3 years in 7376 patients with a normal myocardial perfusion stress

(MPS), suggesting that the “warranty” on a normal myocardial stress perfusion is at least 2 years in a general population; [24] however, only 10% of participants in this study were diabetic. Data suggest that the event rate is higher in subjects with diabetes, and increases in a graded manner with declining renal function. [24,25]

Table 1: Existing guidelines for testing for coronary artery disease in asymptomatic kidney transplantation candidates

2012 AHA/ACC Consensus document [4]

- Risk-factor based noninvasive stress testing regardless of functional status (Class IIb, Level of Evidence C)
- Risk factors: diabetes mellitus, prior cardiovascular disease, ≥1 y on dialysis, LVH, age ≥60 y, smoking, hypertension, and dyslipidemia (3 or more)

2010 UK Renal Association Guidelines [3]

- Dialysis patients should have unimpeded access to a full range of cardiac investigations including exercise and stress echocardiography, radio-isotopic cardiac scans and coronary angiography. (2D)
- There should be no clinically important delay for pre-dialysis and dialysis patients in receiving assessment by cardiology colleagues for their suitability for transplantation. (2D)

2007 ACC/AHA Guidelines [15]

- Risk-factor based noninvasive stress testing if functional status <4 METS or unknown clinical risk factors : Ischemic heart disease, Compensated or prior heart failure, Diabetes mellitus, Renal insufficiency, Cerebrovascular disease
- Recommendations stronger if ≥3 clinical risk factors are present but may be considered in those with 1–2 risk factors

2007 Lisbon Conference [22]

- Noninvasive and/or invasive testing should be considered in highest-risk patients with Diabetes mellitus, Prior cardiovascular disease, Multiple cardiac risk factors such as ≥1 y on dialysis, LVH, age ≥60 y, smoking, hypertension, and dyslipidemia

2005 NKF/KDOQI Guidelines [26]

- Noninvasive stress testing for all patients with diabetes, All patients with prior CAD (repeat annually);
- If prior PCI, repeat annually;
- If prior CABG, repeat after first 3 y and then every annually;
- Repeat every 24 mo in "high-risk" nondiabetic patients defined as ≥2 traditional risk factors (known history of CAD, LVEF ≤40%, Peripheral vascular disease)

2001 AST Guidelines [27]

- Noninvasive stress testing for "high risk" patients defined as diabetes, history of ischemic heart disease, or ≥2 risk factors
- Coronary angiography for patients with a positive stress test
- Revascularization for patients with critical coronary lesions

2000 European Best Practice Guidelines [28]

- Thallium scanning for patients with history of myocardial infarction or "high-risk" clinical features
- Coronary angiography recommended if thallium scanning positive
- Revascularization if lesions are suitable

LVH = left ventricular hypertrophy; CAD = coronary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction

Evidence Review Table 2. Studies examining prevalence of coronary artery disease in patients with end stage renal disease

Reference	Population	Patient number	Study design	Intervention (coronary artery disease definition)	Coronary artery disease prevalence	Follow-up duration	Association with clinical events	Study quality
De Lima et al (2003) [29]	Kidney transplant candidates	106	Prospective	>70% stenosis in 1 or more arteries	1-,2-and 3-vessel CAD in 19%,16% 7%	1, 2, and 4 years	Unadjusted probability of MACE at was higher with angiographic CAD (p<0.001): 13%, 39%, and 46% versus 2%, 6%, and 6%	C
Sharma et al (2005) [30]	Kidney transplant candidates	125	Prospective	Severe >70%, moderatae 50-70%, mild <50%	Severe, moderate, and mild CAD in 29%, 14%, and 21%	2 years	Unadjusted 2-y survival lower with CAD (85% versus 100%; p=0.005)	C
Gowdak et al (2007) [31]	Kidney transplant candidates	301	Prospective	>70%	45% significant CAD	1.8 year median	MACE higher (45% v 18%, p<0.001)	D
Gowdak et al (2007) [32]	Kidney transplant candidates	288	Prospective	>70%	43% significant CAD		MACE higher in nondiabetic (HR 4.3, 95% CI 2.4-7.9; p<0.001). No difference in diabetics	C
Hage et al (2007) [33]	Kidney transplant candidates, positive stress test or known CAD	260	Retrospective	>50% narrowing, LAD considered 2-vessel disease	1,2,3 vessel CAD in 16,13 and 33%	2 year	Presence and severity of CAD not associated with survival	C
Hickson et al (2008) [34]	Kidney transplant candidates	132	Retrospective	Mild <50%, moderate 50-70%, severe >70%	Mild 25%, mod erate10%, severe 56%	6 months	Severity not associated with survival	C

CAD = coronary artery disease; MACE = major adverse cardiac events; HR = hazard ratio; CI = confidence intervals; LAD = left anterior descending

Table 3: Accuracy of noninvasive testing for detection of coronary artery stenosis in end-stage renal disease patients

Reference	Study population	Patient number	Stress test	Endpoint: Coronary stenosis	Endpoint prevalence	Sensitivity	Specificity	PPV	NPV
de Lima et al. (2003) [29]	100% KT candidates	89	DSE	CAS ≥70%	0.38	0.44	0.87	0.53	0.60
Sharma et al. (2005) [30]	100% KT candidates Mean age 52±12 years 39% had diabetes mellitus 55% were on dialysis	125	DSE	CAS >70%	0.29	0.89	0.94	0.86	0.95
Ferreira et al. (2007) [35]	100% KT candidates Mean age 52±9 years 27% had diabetic nephropathy	148	Dobutamine/tropine echocardiography	CAS >50%		0.53	0.87		

PPV = positive predictive value; NPV = negative predictive value*;* KT = kidney transplant; SPECT = single-photon emission computed tomography; *DES* = dobutamine stress echocardiograph; CAS = coronary artery stenosis

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Guideline 3.1.5: We suggest peritoneal dialysis patients with ischemic heart disease be treated with antiplatelet agents. (2D)

Rationale

Medical management of CAD, both ACS and chronic stable CAD, has been extensively studied in the general population leading to evidence-based clinical practice guidelines. Landmark trials have firmly established roles for reperfusion and primary percutaneous coronary intervention (PCI), antiplatelet and anticoagulant therapies, beta blocker therapy, and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy for ACS in the general population. Unfortunately, the majority of these trials have excluded patients with moderate-to-severe renal impairment have, leading to unanswered concerns about efficacy and safety, and consequently significant underuse of these therapeutic options in CKD patients, including those on PD [1-4]. In a prospective cohort study examining the effect of aspirin, beta blocker, ACEI and statin use on 12-month mortality in CKD patients with heart failure and angiographically proven CAD [5], aspirin use was significantly lower amongst CKD patients (including 466 dialysis patients) and those on aspirin had a lower 12-month mortality (OR 0.69, 95% CI: 0.57 - 0.85).

Efficacy

There are no RCTs specifically examining the efficacy of aspirin alone or clopidogrel alone for the management of chronic stable CAD in PD patients.

The ATC (Antithrombotic Trialists' Collaboration) meta-analysis of randomized trials of anti-platelet therapy for the prevention of death, MI and stroke in high risk patients [6] included 2632 HD patients in 14 trials of anti-platelet agents used for maintenance of access patency. Anti-platelet therapy was associated with a 41% reduction in risk of serious vascular events. In contrast, aspirin prescription was associated with an increased risk for any cardiac event (RR 1.08, 95% 1.02, 1.14) and MI (RR 1.21 95% CI 1.06, 1.38) but a reduced risk for stroke (RR 0.82, 95% CI 0.69, 0.98) in the DOPPS (Dialysis Outcomes and Practice Patterns Study). [7] In an observational study of 41,425 HD patients, aspirin as was clopidogrel prescription was associated with an increased risk of all-cause mortality (RR 1.06, 95% CI 1.01, 1.11 and RR 1.24, 95% CI 1.13, 1.35 respectively) [8].

In a post-hoc analysis of HOT (Hypertension Optimal Treatment) study[9], the addition of low dose aspirin (75 mg/day) to antihypertensive treatment reduced major cardiovascular events in 18,790 hypertensive patients with CKD (RR 0.595 ,95% CI 0.387, 0.913), with no significant increase in major bleeds (RR 1.50, 95% CI 0.67, 3.34). This effectively translates to preventing 12.9 events at the cost of 2 bleeds per 1000 patient years of aspirin treatment [10]. Another post-hoc analysis of the same study showed that aspirin therapy produced greater reduction in major cardiovascular (CV) events than in patients with normal eGFR, with a RR of 0.34 (95% CI 0.17, 0.67) for patients with a baseline eGFR of <45 mL/min. [11] Major bleeding was not significantly different in the lower eGFR group. By this analysis, treating 1000 patients for 3.8 years would prevent 76 events at the cost of 27 major bleeds.

The efficacy and safety of clopidogrel has not been examined in dialysis patients. In a RCT for prevention arteriovenous fistula failure in HD patients, clopidogrel use alone was not associated with any reduction in atherosclerotic events over a 6 month follow up [12].

The efficacy of adding clopidogrel to aspirin for ACS in CKD was examined in post-hoc analyses of 2 major studies [13,14]. In the CURE study (Clopidogrel in Unstable Angina to Prevent Recurrent Events), addition of clopidogrel to aspirin for unstable angina was associated with reduced risk of cardiovascular death, non-fatal MI or stroke at 1 year compared to aspirin and placebo [13]. The risk reduction was dependent on eGFR, but the confidence interval just crossed 1 in the lowest eGFR tertile (<64 mL/min). In CREDO (Clopidogrel for Reduction of Events During Observation) study, addition of clopidogrel to aspirin in patients undergoing percutaneous coronary intervention did not show any benefit in lower eGFR tertiles. Recent data suggest that some of this lack of activity could be explained by variable clopidogrel bioavailability in advanced CKD [15]. The newer faster acting thienopyridine, prasugrel, shows less variability, but needs to be tested in CKD patients.

The effect of aspirin therapy after MI has been examined in registry data.[16,17] Combined aspirin and beta blocker use was associated with a lower in-hospital mortality rate amongst 1724 patients, 47 of whom were on dialysis (RRR 78% for dialysis patients). In another study, use of aspirin, beta blocker and ACEI therapy post-acute MI was associated with a lower RR (RR 0.64, 95% CI: 0.50 - 0.80) of 30-day mortality in 1025 dialysis patients.

In another registry analysis [18], clopidogrel reduced death and primary endpoints (combined outcomes of death, non-fatal MI and stroke at 12 months) for CKD population (HR 0.35, 95% CI: 0.21–0.61 and HR 0.48, 95% CI: 0.30–0.77, respectively,). Patients with clopidogrel(−)/CKD(−), clopidogrel(+)/CKD(+) and clopidogrel(−)/CKD(+) had 2.4, 3.0 and 10.4 fold risk to have primary endpoints compared with those receiving clopidogrel treatment without CKD (all p<0.01). Clopidogrel treatment was not associated with increased in-hospital bleeding risk in CKD population.

Safety

The safety of aspirin and clopidogrel combination has not been examined in PD patients. In a trial of prevention of arteriovenous graft thrombosis in HD patients [19], the combination was associated with increased risk of major bleeding (HR 1.98 95% CI 1.19, 3.28). In a systematic review of 16 studies, combination anti-platelet therapy (clopidogrel and high dose aspirin; and aspirin with ticlopidine, sulfinpyrazone, dipyramidole or warfarin) increased the risk for major bleeding in HD patients [20]. Methodological weaknesses, however, limited the conclusions from this review.

The UK-HARP-1 (Heart and Renal Protection) study [21] examined the safety of simvastatin and aspirin in CKD patients. Treatment with 100 mg/day of aspirin was not associated with an excess of major bleeds, albeit there was a 3-fold excess of minor bleeds (RR 2.81, 95% CI 1.49, 5.28). The ATC meta-analysis and DOPPS also did not show increased bleeding risk with anti-platelet therapy in dialysis patients. Both CURE and CREDO studies did not show significant increase in bleeding risk with clopidogrel use. However, disaggregated safety data are not available for the dialysis population.

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Revascularization in CAD

Although rates of MI and stroke are higher in patients with CKD than in the general population, subjects with CKD have been commonly excluded from clinical trials involving either stable atherosclerosis or ACS [1]. As a result, evidence for specific treatment modalities in this population is limited. It has been shown that all types of therapy for CAD are safe in subjects with CKD. Patients with advanced CKD are more likely to present with acute MI than with stable angina. [2] CKD patients who present with ACS have more extensive CAD; have higher risk for reinfarction, heart failure, and death; have more atypical and delayed presentations; and are less likely to receive evidence-based therapy than are patients without CKD [3]. Out of 109,169 Medicare patients with MI, fewer patients with CKD received thrombolytic therapy, and those with the worst kidney disease waited the longest for therapy [4], despite the adjusted odds ratio (OR) for bleeding events in ESRD being lower than in patients with normal kidney function (OR 1.84 vs 2.28, respectively). SWEDEHEART reported in 23,262 consecutive cases of NSTEMI, that the utilization of coronary angiography and revascularization decreased as eGFR declined. [5] Even though CKD are less likely to be offered coronary angiography in the setting of ACS, observational studies suggest they benefit from revascularization with a reduced mortality. [6,7] Wong et al. [8] showed a benefit with revascularization even in those with severe CKD.

Modality of revascularization for PD patients with CAD (Evidence Review Table 4)

The most appropriate method of revascularization in dialysis patients remains a matter of debate [9]. Advances have been made in coronary artery bypass graft (CABG) surgery, with consequent reduction in operative morbidity and mortality [10]. CABG may be preferred over percutaneous coronary intervention (PCI) with left main disease or disease of left descending artery, although a recent randomized trial in the general population suggested that survival and major cardiovascular events were similar following PCI or CABG [11], but the need for repeat revascularization was higher in patients receiving PCI [12].

Indeed, there have been several randomized trials comparing CABG with PCI, including those with multivessel disease. However, none of the trials included patients on dialysis and so far no randomized trials comparing CABG versus PCI were conducted in the dialysis population. Recommendations for the general population may not simply be applicable to dialysis population as the morphology of coronary artery disease in dialysis patients was different from the general population. It is difficult to make evidence-based decisions for the management of coronary artery disease in patients who have severe kidney disease, since the risk/benefit ratio in this patient population differs significantly from that seen in patients with normal or mildly impaired kidney function.

A previous systematic review [13] examined whether CABG or PCI may be better in dialysis patients. They included 17 retrospective, observational studies from five countries with a total of 32,388 dialysis patients. In total, 15,175 patients underwent CABG, and 17,213 patients underwent PCI but drug-eluting stents were not used in any of the studies. With the exception of two studies, which each followed over 14,000 patients, other studies had small sample size including 25 to 452 patients. Importantly, the dialysis modality was not always reported. In this meta-analysis, patients receiving CABG were more likely to have multivessel CAD (85% versus 53%) and left main disease (14% versus 8%), reflecting selection bias inherent to the choice of intervention modality. Data on short-term 30 days in-hospital mortality showed a higher risk after CABG compared to PCI. The pooled absolute increase in short-term death with CABG compared with PCI was 5.2% (absolute rates 10.6% versus 5.4%). The unadjusted relative risk (RR) of short-term mortality was 1.91 (95% confidence interval [CI] 1.44 to 2.52; $P < 0.001$) for CABG versus PCI. The long-term (≥ 1 year) mortality was no different between CABG and PCI in 13 of the 16 studies, and 3 showed a lower risk of mortality after CABG compared to PCI. The overall cumulative mortality was 51.6% after CABG versus 59.5% after PCI (unadjusted RR 0.93, 95% CI 0.88 to 0.98; $P = 0.01$). The point estimate of the risk of cardiac events was lower after CABG compared to PCI (20.3% versus 32.4%; absolute difference 12.1%; RR 0.50, 95% CI 0.37 to 0.68; $P < 0.01$). However, none of the studies considered the competing event of death when examining cardiac events. MI (RR 0.62, 95% CI 0.51 to 0.75; $P < 0.00001$) and need for revascularization (RR 0.21, 95% CI 0.13 to 0.35; $P < 0.00001$) were lower after CABG compared to PCI. There were several confounders in the studies. As expected, individuals receiving CABG compared with those receiving PCI had important baseline differences, which were adjusted for only in four studies. In general, patients who received CABG had worse coronary anatomy but if these patients were too ill to undergo CABG, and received PCI, this could confound the results. The studies included surgery with or without cardiopulmonary bypass could also have a significant effect on the surgical results.

Using data from the United States Renal Data System, Chang et al [14] compared the results of CABG and PCI performed between 1997 and 2009 for multivessel disease in 21,981 maintenance dialysis patients. In addition to mortality, a composite of death or MI was examined as outcome of interest in their analysis. Over a median follow-up time of 1.7 years (interquartile range [IQR]=0.5–

3.6), CABG was associated with a lower risk of death (HR=0.87, 95% CI=0.84–0.90) and lower composite risk of death or MI (HR=0.88, 95% CI=0.86–0.91). Results were similar using a propensity score-matched cohort analysis. The benefit was maintained irrespective of age groups, gender, presence or absence of diabetes, dialysis vintage or modality (HD vs PD).

These findings were similar to two previous studies using data from the USRDS that included patients with single as well as multi-vessel disease. The first study [15] examined dialysis patients undergoing initial coronary revascularization between 1990 and 1995 and showed an 8% lower risk of death (CI=3%–14%) associated with CABG compared with PCI. The second study examined revascularizations between 1995 and 1998and found a 20% lower risk of death with CABG (CI=16%–26%) versus PCI [16].

Another meta-analysis [17] compared PCI using drug eluting stents (DES) versus bare metal stents (BMS) in seven nonrandomized controlled cohort studies with 869 dialysis patients (range, 54–204 patients) and relatively short follow-up duration (9–12 months, except in one study that followed patients for three years). There was no difference in the risk of all-cause mortality or MI. However, a significant reduction was observed in the incidence of target lesion/vessel revascularization (TLR/TVR) (odds ratio [OR], 0.55; CI: 0.39–0.79) and composite endpoint of death, TLR/TVR and recurrent MI (major adverse coronary events, MACE) (OR 0.54; CI: 0.40–0.73); and a trend towards lower OR for all-cause mortality (OR 0.68; CI: 0.45–1.01) was observed in the DES treated patients compared to BMS treated patients. No significant differences were noted between the groups in the relative or absolute risk of MI. The absolute risk reduction with DES use was -0.09 (CI: -0.14 to -0.04; numbers needed to treat [NNT] = 11) for TLR/TVR, -0.13 (CI -0.19 to -0.07; NNT 8) for MACE. The procedural success with DES was similar to that encountered with BMS.

Two other studies, however, provided results different from this meta-analysis. In a small retrospective review [18] that reported the outcome of 58 dialysis patients who underwent CABG and 67 who received PCI with DESs, the overall survival rates at one, three, and five years were 84.2%, 64.7%, and 56.2% in CABG group and 88.2%, 75.5%, and 61.7% in DES group, respectively ($p = 0.202$). The rates of freedom from cardiac-related events at one, three, and five years were 76.6%, 68.1%, and 48.6%, and 63.0%, 31.4%, and 0% in CABG and DES groups ($p < 0.001$), respectively, including seven (10%) late thrombosis in the DES group. Although the risk-adjusted analysis showed no significant difference for overall and cardiac death rates, the rates of cardiac-related events and graft/stent failure were significantly higher in the DES group. However, sample size of this study was regarded small and the study was retrospective design. In another study [19], 29 HD patients underwent CABG, and 75 patients underwent PCI with DES: the 2-year survival rate was 84.0% for CABG and 67.6% for PCI (p 0.0271). The cardiac death-free curve at 2 years was 100% for CABG and 84.1% for PCI (p 0.0122). The major adverse cardiac events-free rate at 2 years was 75.8% for CABG and 31.5% for PCI ($p < 0.0001$). The DES carried a higher risk for sudden death, which might be associated with stent thrombosis.

In another meta-analysis of 5 non-randomized studies, comprising 641 patients (279 DES, and 362 BMS) with follow-up between 9 and 12 months, in-hospital clinical outcomes were similar between the two groups. At follow-up, there was a trend towards lower TLR (OR 0.50, CI, 0.27-0.93, P=0.011) and trend towards decreased late luminal loss (P=0.09) in patients treated with DES. There was no difference in the rates of all-cause mortality (OR 0.66, CI, 0.40-1.08, P=0.070), and MI (OR 1.35, CI 0.52-3.52, P=0.53) between the two groups.

In light of these results, it is not possible to recommend DES over BMS. In addition, several types of DESs are now available, and it remains uncertain whether one type of DES may be more

effective than the other [Evidence Review Table 5]. There are no prospective randomized trials currently underway according to a recent search of the Clinical Trials database [20].

Until randomized data become available for patients receiving dialysis including those on PD, the workgroup felt that strong recommendations on the modality of revascularization cannot be made in PD patients. The workgroup suggests that the modality of revascularization be individualized and selected on the basis of the extent and severity of lesions, assessment of risk versus benefit in individual patients and availability of expertise.

PD patients with acute coronary syndrome

Patients with CKD who develop ACS are less likely to receive guideline recommended therapies including coronary angiography or revascularization. This treatment disparity is likely caused by concerns for higher procedural complications, increased bleeding risk with long-term anti-platelet therapy, increased likelihood of restenosis and need for repeat revascularization and hastening the loss of residual renal function. The benefits in terms of reducing MI and cardiovascular morbidity with an initial invasive strategy followed by early revascularization in ACS patients has been shown in RCTs [Evidence Review Table 6]. However, majority of the studies have excluded patients with advanced CKD. The number of CKD patients included in the registries were small. In a recent analysis of 23,262 consecutive non-ST-elevation MI patients in the SWEDEHEART registry [5], significantly fewer patients at lower levels of renal function were treated invasively (CKD 1:62%; 2: 55%; 3:36%; 4: 14%; and 5: 15%; P<0.001). The overall 1-year mortality, however, was 36% lower (hazard ratio 0.64, 95% confidence interval 0.56 to 0.73, P<0.001) with an invasive strategy. Furthermore, while the magnitude of survival difference was similar in normal renal function to-moderately impaired renal function groups, the benefit diminished with decreased renal function, with no difference in mortality in patients on dialysis (hazard ratio 1.61, 95% confidence interval 0.84 to 3.09, P=0.15). In the most recent 2012 update of the American College of Cardiology Foundation/American

Heart Association (ACCF/AHA) guidelines for management of unstable angina/ non–ST-segment elevation myocardial infarction (UA/NSTEMI), the role of early revascularization in the CKD subpopulation with ACS was considered uncertain and deemed an important of research and future investigation [21].

In a recent meta-analysis that included 7 reports enrolling 23,234 patients, of whom 6276 received early revascularization vs. 16,958 received initial medical therapy, early revascularization was associated with a significant reduction in 1-year mortality (OR = 0.46, 95% CI 0.26–0.82, P = 0.008) among ACS patients with estimated GFR < 60 mL/min/1.73 m^2. The mortality reduction with early revascularization occurred upfront (short term mortality OR = 0.69, 95% CI 0.56–0.87, P = 0.001)) and persisted at 3 years (OR = 0.54, 95% CI 0.31–0.96, P = 0.037), and was evident across all CKD stages (including dialysis patients), and was independent of the influence of any single study. Among those with ESRD, there was 40% reduction in the odds of 1-year mortality. The magnitude of reduction in mortality with early revascularization, however, diminished with worsening degree of CKD [22]. It is important to note, however, that patients with ESRD derived more survival benefit in terms of absolute risk reduction in 1-year mortality with early revascularization compared to the group with at least moderate CKD (21.3% vs. 16.6%). This implies that even though hazards for death are inversely related to renal function in those with ACS, the benefit- of early coronary revascularization is incremental with worsening renal disease severity. Thus, given the current lack of randomized controlled trials and high degree of uncertainty of risk versus benefits for early revascularization in dialysis patients, the work group suggest PD patients who develop ACS be referred promptly to cardiologists and be assessed for suitability of early revascularization and the recommendation was ungraded. We felt that this is an area that requires further research and randomized trials for confirmation.

Evidence Review Table 4: Studies that examined coronary artery bypass graft with percutaneous angioplasty and/or stenting

Reference	Population	Patient number	Study design	Intervention	Outcome	Duration of follow up	Results	Study quality
Chen et al 2013 [23]	CKD	28 studies, 38,740 patients	Meta-analysis	PCI vs CABG	Mortality	12–96 months	PCI group had lower short-term mortality (OR 0.55, 95% CI 0.41 to 0.73, P b 0.01), higher long-term all-cause mortality (OR 1.29, 95% CI 1.23 to 1.35, P b 0.01), higher cardiac mortality (OR 1.08, 95% CI 1.01 to 1.15, P b 0.05), higher incidence of late myocardial infarction (OR 1.78, 95% CI 1.65 to 1.91, P b 0.01) and recurring revascularization (OR 2.94, 95%CI 2.15 to 4.01, P b 0.01).	B
Chang et al 2013 [24]	Non dialysis CKD		Propensity score matched cohort	CABG vs PCI	Mortality	?	CABG lower adjusted rate of death than PCI: HR 0.81, 95% CI 0.68 to 1.00 for patients with eGFR ≥60; HR 0.73 (CI 0.56-0.95) for eGFR of 45 to 59; and HR 0.87 (CI 0.67-1.14) for eGFR <45	B
Shroff et al 2013 [25]	Dialysis	23, 033	Registry	CABG vs stenting	Mortality	5 years	In-hospital mortality CABG patients 8.2%; all-cause survival at 1, 2, and 5 years was 70%, 57%, and 28%, for DES patients was 2.7%; 1-, 2-, and 5-year survival was 71%, 53%, and 24%, respectively. Survival higher for IMG HR 0.83; P<0.0001	C
Chang et al 2012 [14]	Dialysis	21,981	Retrospective comparison	Multivessel CABG vs PCI	Mortality	5 year	CABG lower risks for death (HR=0.87, 95% CI=0.84-0.90) death+MI (HR=0.88, 95% CI=0.86-0.91).	B
Yeates et al 2012 [26]	Dialysis	90	Observational	PCI, CABG and medical therapy	MACE	?	stenting and coronary bypass grafting had lower risks of an adverse outcome than best medical management	C
Terazawa et al 2012 [18]	Dialysis	125	Retrospective comparison	CABG vs PCI	Death/MACE	5 years	Similar survival at 1,3,5 years were 84.2%, 64.7%, and 56.2% in CABG group and 88.2%, 75.5%, and 61.7% in DES	C

							group, (p = 0.202). The rates of freedom from MACE at one, three, and five years were 76.6%, 68.1%, and 48.6%, and 63.0%, 31.4%, and 0% in CABG and DES groups (p < 0.001),	
Ashrith et al 2010 [27]	CKD	812	Retrospective analysis	CABG vs DES	Death/MACE/TLR	2 years	CABG lower mortality (HR 0.61, 95% CI 0.36 to 1.03; p = 0.06). 2-vessel CAD similar long-term mortality risk (HR 1.12, 95% confidence interval 0.52 to 2.34; p = 0.7)	C
Sunagawa et al 2009 [19]	HD	104	Retrospective comparison	CABG vs DES	Mortality	2 years	2-year survival 84.0% for CABG and 67.6% for PCI (p = 0.0271). The cardiac death-free curve at 2 years was 100% for CABG and 84.1% for PCI (p = 0.0122). The MACE free rate at 2 years was 75.8% for CABG and 31.5% for PCI (p < 0.0001).	C
Manabe et al 2009 [28]	HD	46	Comparative	CABG vs PCI		2 years	MACE-free survival (CABG: 85.9% vs. PCI: 37.1%; p = 0.001) and angina-free survival (CABG: 84.9% vs. PCI: 28.9%; p < 0.001) higher in the CABG	C
Nevis et al 2009 [13]	Dialysis	17 studies, 32,388 patients	Systematic review	CABG vs PCI	Mortality	1 year	5.2% increase in short-term death with CABG compared with PCI was 5.2%. Relative risk (RR) of short-term mortality 1.91 (CI 1.44 to 2.52; P < 0.001). 2 y mortality lower after CABG (RR 0.93, 95% CI 0.88 to 0.98; P = 0.01). CV events were lower after CABG (RR 0.50, 95% CI 0.37 to 0.68; P < 0.01). MACE lower after CABG (myocardial infarction RR 0.62, 95% CI 0.51 to 0.75; P < 0.00001; revascularization RR 0.21, 95% CI 0.13 to 0.35; P < 0.00001).	B
Herzog et al 1999 [15]	Dialysis	14,306	Registry	CABG vs PCI	Mortality	2 years	In-hospital mortality was 5.4% for PTCA and 12.5% for CAB patients. After comorbidity adjustment, the relative risk of CAB surgery (vs. PTCA) performed 1990 to 1995 for all-cause death was 0. 91 (95% CI, 0.86 to 0.97); cardiac death, 0.85 (95% CI, 0.78 to 0. 92); myocardial	C

							infarction, 0.37 (95% CI, 0.32 to 0.43); and cardiac death or myocardial infarction 0.69 (95% CI, 0.64 to 0.74).	
Herzog et al 2002 [16]	Dialysis	15,784	Registry	CABG vs PTCA vs stent	Mortality	2 years	The in-hospital mortality 8.6% for 6668 CABG patients, 6.4% for 4836 PTCA patients, and 4.1% for 4280 stent patients. The 2-year survival 56.4+/-1.4% for CABG patients, 48.2+/-1.5% for PTCA patients, and 48.4+/-2.0% for stent patients (P<0.0001). RR for CABG (versus PTCA) patients 0.80 (95% CI 0.76 to 0.84, P<0.0001) for all-cause death and 0.72 (95% CI 0.67 to 0.77, P<0.0001) for cardiac death. For stent (versus PTCA), RR was 0.94 (95% CI 0.88 to 0.99, P=0.03) for all-cause death and 0.92 (95% CI 0.85 to 0.99, P=0.04) for cardiac death.	B

PCI = percutaneous intervention; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal angioplasty; DES = drug eluting stent; MACE = major adverse cardiac events; OR = odds ratio; CI = confidence interval; HR = hazard ratio; RR = relative risk

Evidence Review Table 5: Studies that examined different types of stents

Reference	Population	Patient number	Study design	Intervention	Outcome	Duration of follow up	Results	Study quality
Tsujita et al 2012 [30]	HD	41	Retrospective comparison	Sirolimus vs paclitaxel-eluting stents	TLR, mortality	1 year	TLR higher with SES (36.6 % vs. PES 15.8 %; P = 0.037) no difference in all-cause death, MI or MACE	C
Ishii et al 2012 [31]	HD	505	Observational	Bare vs drug eluting stent	MACE/TLR	6 years	DES lower rates of TLR beyond the 1-year follow-up after PCI (16.4% vs. 30.9%, P=0.019) and lower MACE (42.5% vs. 58.0%, P=0.036)	C
Higashitani et al 2011 [32]	HD	54	Retrospective comparison	Paclitaxel vs sirolimus-eluting stent	Restenosis/TLR	10 months	Restenosis rate was lower in PES (13.6 vs. 39.5%; p = 0.034). TLR lower in PES (9.3 vs. 26.5%; p =	C

							0.041)	
Charytan et al 2011 [33]	CKD	1,749	Registry	Drug-eluting or bare-metal stent	Death	2 years	2-year risk-adjusted mortality, MI, and TLR 39.4% versus 37.4% (risk difference, 2.1%; 95% CI, -4.3 to 8.5; P = 0.5), 16.0% versus 19.0% (risk difference, -3.0%; 95% CI, -8.2 to 2.1; P = 0.3), and 13.0% versus 17.6% (risk difference, -4.6%; 95% CI, -9.5 to 0.3; P = 0.06)	B
Abdel-Latif et al 2010 [17]	ESRD	869	Meta-analysis	BMS vs DES	TLR/MACE	2 years	DES-treated patients lower TLR/TVR (OR 0.55 CI: 0.39-0.79) and MACE (OR 0.54; CI: 0.40-0.73). ARR in TLR/TVR was -0.09 (CI: -0.14 to -0.04; NNT 11) and in MACE was -0.13 (CI: -0.19 to -0.07; NNT 8).	B
Ichimoto et al 2010 [34]	Dialysis	107	Retrospective comparison	BMS vs SES	Mortality	1 year	No difference in restenosis (30% versus 40%, P = 0.20),3-year mortality (22.5% versus 22.2%, P = 0.75), myocardial infarction (3.8% versus 4.9%, P = 0.93), target lesion revascularization (24.7% versus 31.0%, P = 0.61), and stent thrombosis rates (3.8% versus 2.4%, P = 0.73)	C
El-Menyar et al 2010 [3]	CKD	117 studies	Systematic review	BMS vs DES	MACE	?	No difference between DES and BMS	B
Rosenblum et al 2009 [35]	CKD	6220	Retrospective comparison	DES vs BMS	TLR	1 year	TLR rates lower for DES in CrCl >60 (5 vs. 9.3%; p < 0.0001). No diff in CrCl <40 mL/min or on dialysis	C
Yachi et al 2009 [36]	HD	123	Retrospective comparison	BMS vs SES	MACE	?	In-stent lumen loss SES, 0.62 +/- 0.75 mm; BMS, 1.07 +/- 0.75 mm; P = 0.003. MACElower SES, 0.62 +/- 0.75 mm; BMS, 1.07 +/- 0.75 mm; P = 0.003	C

Okada et al 2008 [37]	Dialysis	80	Retrospective comparison	BMS vs SES	Mortality	1 years	MACE 25.2% in SES and 38.2% in BMS (p=0.048). In multivariate analysis, SES independent predictor of MACE at 1 year after PCI (risk ratio 0.70, 95% CI 0.52-0.9, p=0.015)	C
Ishio et al 2007 [38]	Dialysis	123	Retrospective comparison	BMS vs SES	MACE	9 months	SES higher MLD (1.98+/-0.83 mm vs 1.50+/-0.78 mm, p<0.01). In-stent restenosis rate lower in SES (22% vs 40%, p=0.048). No difference for in-segment restenosis (31% vs 43%, p=0.3).	C
Mishkel et al 2007 [39]	CKD	2758	Retrospective analysis	BMS vs DES	Death/MACE	2 years	GFR < 60 ml per minute remained a significant predictor of 2-year mortality (p < 0.001) and MACE (p < 0.001), but not TVR (p = 0.839)	C
Halkin et al 2006 [40]	Dialysis	74	Retrospective analysis	BMS vs DES	MACE	1 year	DES associated with freedom from the composite MACE endpoint (HR = 0.24, 95% CI [0.10-0.60]; p = 0.002) and with a trend to lower all-cause mortality (HR = 0.40 [0.15-1.05]; p = 0.06	C
Das et al 2006 [41]	Dialysis	89	Retrospective comparison	BMS vs DES	TVR	9 months	Reduction in TVR (OR 0.07, 95% CI 0.006-0.844; p = 0.036); death, MI and TVR (OR 0.11, 95% CI 0.022-0.513; p = 0.005)	C

BMS = bare metal stents; DES = drug-eluting stent; SES = sirolimus-eluting stents; PES = paclitaxel-eluting stent; TLR = target lesion revascularization; TVR = target vessel revascularization; ARR = absolute risk reduction; PCI = percutaneous coronary intervention; MLD = minimum lumen diameter; MI = myocardial infarction; MACE = major adverse cardiac events; CKD = chronic kidney disease; ESRD = end stage renal disease; HD = hemodialysis; HR = hazard ratio; CI = confidence interval

Evidence Review Table 6: Studies that examined early revascularization or conservative therapy following acute coronary syndrome

Reference	Population	Patient number	Study design	Intervention	Outcome	Duration of follow up	Results	Study quality
Chu et al 2013 [29]	CKD with NSTE-ACS	834	Retrospective comparison	Early invasive vs early conservative revascularization	MACE (CV death, MI and stroke)	1,163.96 ± 19.99 days	CKD subjects receiving an EIS had the highest MACE, HF and DDA rate (all $p < 0.019$)	C
Huang et al 2013 [22]	ACS and CKD	23,234	Meta-analysis	Early revascularization vs medical therapy	Mortality	1 year	Reduced 1-year mortality (OR=0.46, 95% CI 0.26-0.82, P=0.008), persisted at 3years (OR=0.54, 95% CI 0.31-0.96, P=0.037)	B

CKD = chronic kidney disease; ACS = acute coronary syndrome; NSTE = non-ST elevation; MACE = major adverse cardiac events; CKD = chronic kidney disease; CV = cardiovascular; MI = myocardial infarction; EIS = early invasive strategy; HF = heart failure; DDA = dialysis during admission; OR = odds ratio; CI = confidence interval

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SECTION 2. LEFT VENTRICULAR HYPERTROPHY, LEFT VENTRICULAR DYSFUNCTION AND HEART FAILURE IN PERITONEAL DIALYSIS PATIENTS

Guideline 3.2.1: We suggest evaluation of left ventricular hypertrophy, dilatation, systolic and diastolic function, as well as cardiac valvular abnormalities including valvular calcification, using echocardiography in peritoneal dialysis patients after initiation of peritoneal dialysis and repeat if change in clinical status. (2C)

Rationale

Left ventricular hypertrophy (LVH) is a frequent complication in peritoneal dialysis (PD) patients. The prevalence has been estimated to range from 44% to over 90% in prevalent PD patients (1-11). The presence of LVH predicted an increased risk of all-cause and cardiovascular mortality in dialysis patients including PD (5,10). In addition, in prospective follow-up studies, LVH and systolic dysfunction have been shown to be independent predictors of heart failure in PD patients (12,13). A recent observational study reported a progressive increase in left atrial diameter and LV mass with increasing time on the transplant waiting list in dialysis patients (14). Similarly, an earlier study showed progression of LVH and worsening of systolic dysfunction in PD patients with increasing time on PD (3). Furthermore, increased left atrial diameter, LV mass index and worsening systolic function have been shown to predict an increase in mortality and cardiovascular events (14). Compared to patients who maintained a stable LV mass index, patients with greater progressive increases in LV mass index over time are associated with increased risk of mortality and cardiovascular events in dialysis patients (15). There are also data that regression of LVH was associated with improved cardiovascular outcomes in dialysis patients (16).

In a cohort of 254 asymptomatic dialysis patients, Zoccali and co-workers showed that the prevalence of systolic dysfunction, defined using endocardial fractional shortening, was 26% and increased to 48% when defined using midwall fractional shortening (17). Systolic dysfunction is a powerful predictor of mortality and adverse cardiovascular outcomes in dialysis patients (12,13,17). Another study by Yamada *et al* showed in a cohort of 1254 incident hemodialysis (HD) patients that 14.2% had reduced ejection fraction < 50%, which predicted cardiovascular mortality independent of other risk factors (18). Further deterioration in systolic dysfunction with time on dialysis has also been associated with a greater mortality and cardiovascular event risk (19). Systolic dysfunction, defined using ejection fraction < 50%, predicted an increased risk of sudden cardiac death in PD patients (20). Increased LV filling pressure defined non-invasively using the ratio of early transmitral inflow velocity (E) to tissue Doppler derived measure early diastolic mitral annular velocity (Em), as a marker of diastolic dysfunction, has been shown to provide additional predictive value for mortality and adverse cardiovascular outcomes beyond LV mass index, ejection fraction and other clinical and biochemical parameters in PD patients. In this study, 62% of the PD patients were noted to have elevated LV filling pressure (E/Em ratio >15), indicating a high prevalence of diastolic dysfunction (21). A number of other studies in HD patients also demonstrated similar prognostic value of E/Em ratio. Notably, E/Em ratio appeared to have stronger predictive value for cardiovascular events compared to other standard echocardiographic parameters (22,23).

These observational data provide an important rationale for assessing and regularly monitoring the degree of LVH, dilatation, systolic and diastolic function in PD patients. However, evidence demonstrating that regular assessment of cardiac status of dialysis patients using echocardiography guides further therapeutic strategies and impacts positively on survival and other outcomes is currently lacking in dialysis patients. Thus, the recommendation on regular

monitoring and evaluating cardiac status using echocardiography in PD patients was weak. [Evidence Review Table 1]

Guideline 3.2.2: We suggest peritoneal dialysis patients with significantly impaired systolic function be evaluated for the presence of coronary artery disease. (2C)

Rationale

Heart failure is one of the most frequent complications in dialysis patients, with an estimated prevalence ranging from 30-40% (13,24-26). In PD patients, the reported prevalence of heart failure is around 35% and is even higher (up to 60%) among patients with a background history of heart failure (12). The presence of heart failure is a powerful predictor of adverse clinical outcomes in dialysis patients. Data from the United States Renal Data System suggested that heart failure is a very frequent cause of hospitalization in dialysis patients and the mortality rate after heart failure was 83% at 3 years (27). The presence of heart failure at initiation of dialysis treatment not only increased the mortality risk within 90 days of dialysis initiation (28) but also increased risk of long-term mortality. The median survival of dialysis patients with baseline heart failure has been estimated to be around 36 months versus 62 months for those with no baseline heart failure (26). In addition, recurrent heart failure on dialysis is also associated with an increased mortality risk (29). Recent study showed that it may be important to further define the nature of heart failure in PD patients, namely whether it is heart failure with preserved or reduced ejection fraction as these two entities are associated with different long-term clinical outcomes. Heart failure with reduced ejection fraction had the worst prognosis in relation to subsequent risk of all-cause mortality, heart failure, cardiovascular death, and fatal and non-fatal cardiovascular events. Heart failure with preserved ejection fraction had better outcomes compared to those with reduced ejection fraction though was inferior when compared to patients with no heart failure at all. Patients with heart failure and reduced ejection fraction showed the highest prevalence of coronary artery disease (46%) compared to patients with heart failure but preserved ejection fraction (28%) and patients with no heart failure (10%) ($P<0.001$) (30). The presence of LV systolic dysfunction or clinically evident heart failure may reflect underlying coronary ischemia. Thus, the working group suggests PD patients with significant reduction in systolic function be referred to cardiologists for further evaluation to rule out significant coronary artery disease and this recommendation was ungraded.

Guideline 3.2.3: We suggest peritoneal dialysis patients with left ventricular hypertrophy or heart failure be considered for treatment with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. (2D)

Rationale

In uremic animal models, angiotensin converting enzyme inhibitor (ACEI) abrogates LVH and cardiomyocyte loss and ameliorates structural abnormalities of the heart and vasculature (31,32). Non-randomized studies in the 1990s showed that ACEI were associated with reduced cardiac hypertrophy in dialysis patients independent of a blood pressure lowering effect (33,34). A subsequent observational study reported a favorable association of ACEI with survival and cardiovascular outcomes in dialysis patients independent of its effect on pulse wave velocity and blood pressure (35). In a 3 year prospective randomized controlled trial (RCT) conducted in 332 HD patients with New York Heart Association (NYHA) Functional Class II and III heart failure and ejection fraction ≤ 40%, combined angiotensin receptor blocker (ARB) and ACEI significantly reduced LV end-diastolic diameter and improved ejection fraction compared to combined ACEI

and placebo treatment. The LV structural and functional parameters were secondary and not primary endpoints of the study (36). A recent meta-analysis including 6 RCTs with a total of 207 participants (123 HD and 84 PD patients) of which 107 patients received treatment with ARB versus 100 patients received non-ARB treatment (37). The ARB treated group showed greater regression in LV mass index than for the non-ARB group (P=0.002) but no significant difference was observed in LV ejection fraction. In the subgroup analysis of HD (P=0.009) and PD patients (P=0.03), ARB treatment was associated with greater LV mass regression than non-ARB treatment. However, it is noteworthy that the sample size of individual trials in this systematic review was below 50 subjects. On the other hand, another placebo-controlled RCT comparing enalapril and simvastatin versus placebo in 107 dialysis patients (including both HD and PD) showed no significant difference in LV mass or dimensions between the two groups (38). Given the very limited evidence available in the dialysis population, the level of recommendation for using ACEI and ARB treatment in PD patients with LVH is therefore weak [Evidence Review Table 2].

Inhibition of the activated renin-angiotensin system by an ACEI (or ARB) has long been established as a standard therapy for the general population with heart failure (39) and has been shown to reverse LV dilatation in asymptomatic patients with LV systolic dysfunction (40) and confer survival benefit in different high risk populations including patients with heart failure, myocardial infarction (MI), diabetes with nephropathy, or strokes (41-45). Evidence Review Table 3 presents a summary of the clinical trials that examined the effects of ACEI or ARBs in dialysis patients in relation to hard outcomes. So far, no RCT has examined *de novo* or recurrent heart failure as the primary outcome. In the double-blind placebo-controlled RCT by Zannad *et al* (46) that examined the effect of fosinopril on cardiovascular events in 397 HD patients with LVH over 24 months, a 7% reduction in cardiovascular events was observed in the intention to treat analysis and was insignificant. A secondary per-protocol analysis suggested a trend towards benefit in the composite cardiovascular endpoint (of which 6.5% were heart failure hospitalization) with fosinopril treatment (adjusted relative risk = 0.79, 95% confidence intervals, 0.59-1.1 P=0.099). The study did not demonstrate survival benefit with an ACEI in HD patients. Another small open-labeled RCT in 80 HD patients showed that the ARB candesartan significantly reduced cardiovascular events (16.3% vs 45.9%) and mortality (0% vs 18.9%) compared to placebo. However, this study excluded patients with background symptomatic cardiac disease including heart failure (47). The 3 year prospective RCT by Cice *et al* demonstrated significant long-term survival and cardiovascular benefits as well as reduction in hospitalization for heart failure by combining an ACEI with an ARB in HD patients with class II-III heart failure and systolic dysfunction (36). There is so far no adequately powered RCT that examined hard outcomes in relation to the use of ACEI or ARBs in PD patients with heart failure. Given the rather limited evidence in HD patients and lack of evidence in PD patients, even though there are convincing data of benefit of ACEI or ARB in the general population, the strength of recommendation for the use of ACEI or ARB in PD patients with heart failure is weak [Evidence Review Table 3].

Guideline 3.2.4: We suggest peritoneal dialysis patients with left ventricular hypertrophy, dilated cardiomyopathy, or systolic heart failure be considered for treatment with a beta blocker. (2C)

Rationale

Cice *et al* examined the effects of carvedilol in a randomized placebo-controlled trial of 114 HD patients with dilated cardiomyopathy (48,49) (Table 4). Carvedilol showed a significant reduction in LV volumes with improved LV ejection fraction and NYHA functional class and the improvement was maintained up to 24 months follow-up. However, there are so far no randomized trials examining the effect of beta blockers in regressing LVH in PD patients.

Beta blockers are the standard therapy for general population with ischemic heart disease as well as in patients with heart failure (50) as it has been shown to reduce heart failure symptom score, improve NYHA class, increase LV ejection fraction and most importantly improve survival in the general population with heart failure (51-54). The beneficial effects of beta blockers are partly related to their effect on blocking sympathetic overactivity which is considered deleterious in patients with heart failure. Sympathetic overactivity plays an important role in the genesis of hypertension in chronic kidney disease (CKD) (55) and pathogenesis of cardiac hypertrophy (56). Chronic elevation of plasma norepinephrine levels predict adverse cardiovascular outcomes in long-term dialysis patients (57) as well as in heart failure patients (58). A number of observational studies demonstrated improved survival or cardiovascular benefit with beta blockers in dialysis patients (27,59-61). The cardiovascular benefit of beta blockers was also demonstrated in the Dialysis Outcomes and Practice Patterns Study (DOPPS) which included a representative cohort of HD patients. A significant and independent reduction in the risk of cardiovascular mortality was observed with beta blocker treatment (relative risk = 0.87, *P* = 0.004) (62).

There is so far only one prospective RCT evaluating the cardiovascular effects of beta blocker treatment in long-term dialysis patients. The study was of 12-months duration recruiting 114 HD patients with NYHA Class II-III heart failure and LV ejection fraction < 30% on echocardiography, carvedilol treatment was associated with a significant improvement in LV ejection fraction as well as NYHA class (48). Subsequent 24-month extended follow-up of the same cohort suggested survival benefit with carvedilol treatment compared to placebo (51.7% died in carvedilol group vs 73.2% in placebo group; P<0.01). There were significantly fewer cardiovascular deaths (29.3% vs 67.9%; P<0.0001) and all-cause hospital admissions (34.5% vs 58.9%; P<0.005) among the carvedilol than the placebo group. Secondary endpoint analyses revealed lower fatal MIs), fatal strokes, and hospital admissions for worsening heart failure in carvedilol as compared to placebo group. A reduction in sudden deaths and pump-failure deaths was observed in the carvedilol group versus the placebo group, though this did not reach statistical significance (49). This preliminary data suggested cardioprotective benefits of beta blockers in long-term dialysis patients with systolic heart failure. However, the study was small and underpowered and the study included a highly selected group of HD patients with dilated cardiomyopathy. Given that there are no RCTs in PD patients and this is the only trial conducted in dialysis patients with heart failure, the level of recommendation for using beta blockers in PD patients with heart failure is therefore weak. As in the general population with systolic heart failure, treatment with beta blockers should be initiated at a very low dose and titrated upwards slowly to minimize negative inotropic effects. Patients should also be monitored closely to avoid hypotension [Evidence Review Tables 4 and 5].

Guideline 3.2.5: We suggest peritoneal dialysis patients already receiving an angiotensin converting enzyme inhibitor or angiotensin receptor blocker be considered for treatment with a mineralocorticoid receptor antagonist. (2B)

Rationale

Aldosterone is well recognized to have an important contribution to sodium and fluid retention in patients with heart failure and plays a key role in myocardial remodeling and promoting collagen deposition, cardiac and kidney fibrosis. Angiotensin converting enzyme (ACE) inhibition suppresses aldosterone production but both aldosterone and angiotensin II may escape the effects of long-term ACE inhibition, resulting in rebound of aldosterone levels (63,64). Thus, giving low dose aldosterone receptor antagonist provides more complete inhibition of the activated renin-angiotensin-aldosterone system in patients with heart failure. This is supported by a number of

large RCTs conducted in the general population showing clear survival benefits, significant reduction in cardiovascular events and death as well as hospitalization with the addition of an aldosterone receptor antagonist in patients with moderate to severe LV systolic dysfunction and heart failure (65,66). There is one prospective RCT conducted in 112 patients with stage 2 -3 CKD showing a significant improvement in LV mass, augmentation index and aortic pulse wave velocity with spironolactone treatment independent of central and peripheral blood pressure reduction versus placebo (67). A very recent open-label RCT in PD patients showed that spironolactone significantly reduced the rate of change in LV mass index at 6 month and the benefit persisted at 18 and 24 months compared to controls. Furthermore, the rate of change in LV ejection fraction also improved significantly at 24 weeks with spironolactone compared to controls (68). This is so far the first RCT in PD patients evaluating mineralocorticoid receptor antagonist on echocardiographic parameters [Evidence Review Table 2]. Given the very encouraging quality evidence, a weak recommendation statement was drawn on the use of aldosterone receptor antagonists in regressing LVH in PD patients. Given that PD patients appear to have a higher risk for hypo- rather than hyperkalemia, aldosterone receptor antagonists may potentially be safer in the PD compared to HD population. A recent prospective open-label RCT conducted in 309 oligoanuric HD patients already receiving an ACEI or ARB showed that adding spironolactone to ACEI or ARB treatment significantly lowered the risk of reaching primary composite endpoint of death from cardiovascular and cerebrovascular events and hospitalizations due to cardiovascular and cerebrovascular events. Spironolactone treatment was also associated with a reduced risk of secondary endpoint, namely death from all causes (69) [Evidence Review Table 6]. Given the good quality evidence from this RCT that demonstrated significant cardiovascular benefits of spironolactone in HD patients, the workgroup felt that a recommendation statement should be drawn on the use of mineralocorticoid receptor antagonist additional to ACEI or ARB in PD patients. However, since there are so far no similar studies in PD patients and specifically in relation to reducing the risk of heart failure in PD patients. The recommendation was therefore graded as 2B.

Guideline 3.2.6: We suggest peritoneal dialysis patients with heart failure and anemia receive treatment for anemia and have target hemoglobin no different from peritoneal dialysis patients without heart failure. (2D)

Rationale

Anemia has been shown in an observational study to be an important predictor of clinical and echocardiographic cardiac disease, namely LV dilatation, development of *de novo* and recurrent heart failure as well as mortality in end stage renal disease (ESRD) patients (70). An earlier uncontrolled study in HD patients reported an improvement in LVH and geometry after 7 months of erythropoietin treatment (71). However, the studies that examined the echocardiographic effects of erythropoietin were mostly of very small sample size and uncontrolled and did not fulfill the inclusion criteria for evidence review [Evidence Review Table 7]. There are so far no RCTs that examined the use of erythropoiesis stimulating agents as a treatment strategy for retarding LVH, improving LV function and reduce heart failure in PD patients. In an RCT by Foley and co-workers, 146 HD patients with either concentric LVH or LV dilatation were randomized to receive erythropoietin to achieve hemoglobin of 10 g/dL or 13.5 g/dL for 48 week, normalization of hemoglobin did not regress established LVH or dilatation (72). Another prospective RCT recruiting 596 incident HD patients with anemia and without symptomatic cardiac disease found no beneficial effect on cardiac structure, namely LV volume index and LV mass index with normalization of hemoglobin to 13.5 -14.5 g/dL with erythropoietin treatment compared to partial

correction of anemia to a hemoglobin of 9.5 – 11.5 g/dL for 96 weeks (73). A previous meta-analysis including 15 eligible studies involving 1731 CKD and ESRD patients showed a reduction in LV mass index with treatment of severe anemia (namely, patients with hemoglobin <10 g/dL) to conventional hemoglobin target (≤12 g/dL). However, in moderate anemia (that is, hemoglobin level ≥10 g/dL), treating anemia to a target hemoglobin >12 g/dL did not show a significant beneficial impact on LV mass index compared to conventional hemoglobin target (≤12 g/dL) (74). Taken together, the current evidence does not support correction of anemia as a therapeutic strategy for regressing LVH and dilatation or preventing heart failure in dialysis (PD) patients. Treatment of severe anemia to conventional hemoglobin target of ≤12 g/dL may improve LV mass but these studies lacked control groups. There is no RCT that examined whether treatment of anemia may improve hard outcomes in PD patients with heart failure. The workgroup felt that treatment of anemia in PD patients should follow that recommended by the Kidney Disease Improving Global Outcomes Guidelines [Evidence Review Table 7].

Other Potential Therapies

Salt restriction

Circulatory congestion is a highly prevalent complication in PD patients (13). Observational studies have reported an important positive relationship between circulatory congestion and volume overload with LVH and abnormal LV geometry in PD patients (9,75,76). Reversing hypervolemia and underlying positive sodium balance as well as improving blood pressure control remain a key management strategy in PD patients with heart failure and circulatory congestion (77). This is based on non-randomized, interventional studies showing how aggressive sodium and fluid removal, stringent control of salt intake and lowering of dialysate sodium concentration may reduce hypertension, retard LVH and dilatation without the need of anti-hypertensive drugs in both HD and PD patients (78,79). However, the sample size of these studies was very small (<50 subjects) and we lack RCTs to confirm whether aggressive salt and fluid restriction may confer any 'hard outcomes' benefit in dialysis patients with and without heart failure including PD patients. Nevertheless, taking into consideration data from the general population and also experimental data (80) and given that this management strategy has virtually no cost and represents lifestyle modification, we have given a strong level of recommendation on restricting salt intake in all PD patients (Guideline 1.2), in keeping with the Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. This recommendation is of course applicable to patients with heart failure, in line with the Practice Guidelines of the American College of Cardiology Foundation/American Heart Association Task Force (ACCF/AHA) on Diagnosis and Management of Heart Failure in Adult General population 2009 (50).

Volume control

There are 2 RCTs that examined the use of icodextrin as a treatment strategy in improving volume control and only 1 study examined the effects of icodextrin on LV structural abnormalities in PD patients. A study by Davies and co-workers recruited PD patients with urine output less than 750 mLs per day and with high peritoneal membrane transport status, either treated hypertension or untreated hypertension, or a requirement of equivalent of all 2.27% glucose PD solutions. The study did not examine change in LV mass as one of the study outcomes though an improvement in fluid status and fluid removal was observed in the icodextrin treated group after 6 months (81). Another study by Konings *et al* observed a significant reduction in LV mass, increase in daily ultrafiltration volume and reduction in extracellular water 4 months after icodextrin compared to

control group using 1.5% PD solutions (82). However, both studies were of very small sample size and very short duration (≤6 months) and did not examine corresponding cardiac functional changes and most importantly hard outcomes. In addition, the majority of patients in the study by Konings still had significant residual renal function and did not have ultrafiltration failure. There were also some concerns that some patients actually developed a decline in residual renal function after icodextrin treatment and secondary analysis showed that these patients were actually underhydrated. Thus, even though the preliminary findings appear favorable, the effects of icodextrin on LV mass and function remained to be confirmed in adequately powered studies. The impact of icodextrin on hard outcomes in PD patient subgroups such as those with diabetes, high transport status or heart failure has also not been studied. Thus, even though the effects of icodextrin in improving fluid removal and blood pressure control in patients with high transport status or low urine volume are promising, it remains premature to make recommendations on the generalized use of icodextrin as a therapeutic strategy for retarding LV structural and functional abnormalities in PD patients with or without heart failure. Please see also fluid management section. [Evidence Review Table 8]

Activated vitamin D

There is emerging data that activated vitamin D plays a role in cardiovascular disease beyond its effect on calcium and phosphorus homeostasis. 25-hydroxyvitamin D deficiency has been associated with impairment of cardiac contractile function (83,84), increased myocardial collagen content and mass (85,86) in different experimental studies which may further predispose to heart failure. Studies in HD and PD patients reported similar associations between low 25-hydroxyvitamin D status and poor LV function (87,88). In addition, a low serum 25-hydroxyvitamin D level predicts an increased risk of cardiovascular events including heart failure (87). However, 2 recent prospective RCTs comparing activated vitamin D treatment at a dose that effectively suppressed secondary hyperparathyroidism versus placebo failed to show any significant regression in cardiac magnetic resonance imaging measured LV mass index (primary endpoints in both studies) in stages 3 -5 CKD patients (89,90) [Evidence Review Table 9]. There is currently an ongoing RCT examining the effect of 25-hydroxyvitamin D supplementation and volume control on cardiac magnetic resonance imaging-determined LV mass index in PD patients and results not available yet. Thus, no recommendation can be made with the use of activated vitamin D as a cardioprotection strategy in PD patients.

Cardiac resynchronization therapy

Ventricular mechanical dyssynchrony is frequently observed in the general population with heart failure and results in suboptimal ventricular filling, reduced cardiac output (91) and predicts an increased mortality (92,93). Cardiac resynchronization therapy (CRT) improves ventricular contraction and reduces the degree of secondary mitral regurgitation and when added to optimal medical therapy, has been shown to improve health-related quality of life, functional class, exercise capacity and LV ejection fraction in patients with systolic heart failure (94-96). In two meta-analyses of CRT trials in patients with reduced LV ejection fraction, prolonged QRS interval and NYHA class III or IV symptoms, CRT has been shown to reduce hospitalizations for heart failure by 32% and all-cause mortality by over 20%, with benefits most pronounced in patients with class III and IV symptoms and driven largely by a reduction of death due to progressive heart failure (97,98). These data clearly support the use of CRT in systolic heart failure patients with ventricular dyssynchrony. However, the effects of CRT in dialysis (including PD) patients with systolic heart failure on hard outcomes as well as surrogate outcomes have so far not been investigated and thus recommendation cannot be made in this population.

Evidence Review Table 1. Studies that examined prevalence and importance of cardiac structural and functional abnormalities in dialysis patients.

Reference	Population and number of patients	Study design	Outcomes of interest	Follow-up duration (if applicable)	Prevalence and outcome results	Study quality
Greaves et al AJKD 1994 (1)	54 prevalent CAPD, 30 HD	Cross-sectional	LVH Systolic dysfunction	-	46% had LVH 36% had LV systolic dysfunction	C
Silaruks et al PDI 2000 (99)	66 prevalent non-diabetic CAPD patients without dilated cardiomyopathy	Prospective follow-up study	Mortality	24 months	21% mild LVH; 25% severe LVH Severe LVH associated with higher mortality 1 year survival: 72% vs 100% for severe LVH vs normal echo patients (P=0.03)	C
Zoccali et al JASN 2001 (5)	254 prevalent dialysis patients (203 HD & 51 PD)	Prospective follow-up study	All-cause mortality, CV mortality	29 ± 12 months	Gender-independent criteria - LVH by BSA: 57.1%; LVH by height $^{2.7}$: 70.1% Gender-specific criteria – LVH by BSA: 70.1%; LVH by height $^{2.7}$ 77.2% Geometric pattern – BSA based: Concentric LVH 30.7%, eccentric LVH 26.4% Height based: Concentric LVH 37.4%. eccentric LVH 32.7% Concentric LVH by the height$^{2.7}$ index was an independent predictor of all-cause mortality (HR, 2.96, 95% CI, 1.40 to 6.26], *P* =0.004) as well as of CV outcomes (HR, 2.20 [1.12 to 4.30], *P* =0.02). Eccentric LVH by this criterion predicted all-cause death (HR, 2.48, 95% CI, 1.16 to 5.33, *P*= 0.02) but failed to predict CV outcomes (*P* = 0.19)	B

Stack et al AJKD 2002 (4)	2584 incident new ESRD patients	Retrospective database review from Dialysis Morbidity and Mortality Study Wave 2	Mortality	24 months	LVH: 16.4% The impact of LVH on subsequent mortality was greatest in the first 6 months of follow-up (RR, 1.61; confidence interval [CI], 1.17 to 2.22) and became less pronounced thereafter (RR, 1.36; CI, 1.07 to 1.89; RR, 1.29; CI, 1.07 to 1.56 at the end of 1 and 2 years, respectively).	C
Enia et al NDT 2001 (2)	51 prevalent CAPD, 201 HD	Cross-sectional	LVH	-	LVH: 86% in PD, 62% in HD	C
Wang et al Kidney Int 2002 (11)	158 prevalent non-diabetic PD patients	Cross-sectional	LV mass index	-	LVH: 92.4%	C
Toprak et al NDT 2003 (9)	69 prevalent CAPD patients	Cross-sectional	LVH and LV geometric pattern	-	Concentric LVH: 28%, eccentric LVH: 46%, Normal geometry: 14%, concentric remodeling: 12%	C
Zoccali et al JASN 2004 (17)	254 asymptomatic dialysis patients	Prospective observational study	Fatal or non-fatal CV events	41 ± 22 months	Systolic dysfunction: 26% by endocardial fractional shortening; 48% by mwFS LV systolic function independently predicts CV events. Every 1% ↓ in LVEF, adjusted HR, 1.04 (1.02 – 1.07), P=0.001 in relation to CV events Every 1% ↑ in mwFS, adjusted HR, 1.11 (1.03 – 1.19), P=0.002 in relation to CV events	B
Zoccali et al KI 2004 (15)	161 prevalent HD patients	Prospective longitudinal study	CV events	29 ± 13 months	Echo twice 18 ± 2 SD months apart. Every 1 $g/m^{2.7}$/month increase in LVMI was associated with a 62% increase in the incident risk of fatal and nonfatal CV events [adjusted HR, 1.62 (95% CI 1.13-2.33), P= 0.009].	B
Wang et al JASN 2004	231 prevalent PD patients	Prospective longitudinal	Mortality and fatal or non-fatal CV	30 ± 14 months	LVMi, C-reactive protein and loss of residual renal function were each independently associated with mortality and CV events. Compared with patients with none of the three risk factors, those with all three risk	B

(10)		study	events		factors had an adjusted HR of 6.94 (*P* = 0.001) and 5.43 (*P* =0.001) for all-cause mortality and cardiovascular mortality, respectively. In conclusion, inflammation, RRF, and LVH are interrelated and combine adversely to increase mortality and CV death risk of PD patients.	
Zoccali et al JASN 2006 (19)	191 prevalent dialysis patients	Prospective longitudinal study	CV events	27 ± 13 months	Changes in mwFS over 17 ± 2months maintained an independent association with CV events (adjusted HR, 0.49; 95% CI, 0.27 to 0.88; *P* = 0.02) than in those who had a decrease in mwFS.	B
Wang et al Kidney Int 2006 (13)	222 prevalent PD patients	Prospective longitudinal follow-up study	Circulatory congestion	3 years	LV Mass index [adjusted HR, 1.006, 95% CI, 1.000 – 1.011, P-value = 0.05] and ejection fraction [adjusted HR, 0.97, 95% CI, 0.94 – 0.99, P=0.014] independently predicts circulatory congestion.	B
Tian et al Renal Fail 2008 (6)	48 HD, 62 PD prevalent	Cross-sectional	LVH	-	LVH: 68.8% in HD, 45.2% in PD	C
Wang et al Hypertension 2008 (21)	220 prevalent PD patients	Prospective longitudinal study	Mortality and fatal or non-fatal CV events	Mean FU: 48 months	E/Em ratio elevated > 15 in 62% of patients E/Em ratio emerged as an independent predictor of all-cause mortality [adjusted HR, 1.027, 95% CI, 1.003 – 1.051; P=0.026] and cardiovascular death [adjusted HR, 1.033, 95% CI, 1.002 – 1.065; P=0.035]. In addition, the E/Em ratio added significant incremental prognostic value for all-cause mortality [P=0.035] and cardiovascular death [P=0.035] beyond the standard clinical, biochemical, dialysis parameters and echocardiographic measurements.	B
Cheng et al 2009 (7)	237 prevalent dialysis patients (49 HD and 188 PD)	Cross-sectional	LVH	-	LVH: BSA-based definition – HD: 44.8% Male and 80% female PD: 47.6% male and 65.1% female Height based definition – overall 62.8%	C
Yamada et al CJASN 2010 (18)	1254 incident patients starting HD	Prospective longitudinal follow-up study	All-cause death & CV death	4.2 ± 2.4 years	Reduced LV EF predicts all-cause and CV mortality independent of other risk factors and have additional prognostic value beyond other risk factors All-cause mortality: P<0.0001 EF; AHR (95% CI) < 0.3 7.28 (3.06 – 7.34);	B

					0.3-0.4 4.00 (2.02 – 7.92); 0.4-0.5 1.26 (1.01 – 1.85); 0.5-0.6 1.02 (0.8 – 1.42) >0.6 reference Adding LV EF increase C-statistics from 0.751 to 0.768 (0.729 -0.809), P=0.001 CV mortality (P<0.0001); <0.3 9.42 (3.82 – 23.3); 0.3-0.4 4.99 (1.91 – 13.0); 0.4-0.5 2.58 (1.19 – 5.06); 0.5-0.6 1.20 (0.65 – 2.21) >0.6 reference Adding LVEF increase C-statistics from 0.750 to 0.789 (0.715 – 0.863). P=0.0049	
Wang et al Hypertension 2010 (20)	230 prevalent PD patients	Prospective longitudinal follow-up	Sudden cardiac death	5 years	Reduced LV EF independently predicts sudden cardiac death Every 1% reduction in EF was independently associated with 7% reduction in the risk of sudden cardiac death (95% CI, 0.89-0.97, P=0.0012). Its importance outweighed LV mass index.	B
Wang et al CJASN 2011 (12)	220 prevalent PD patients	Prospective longitudinal follow-up study	Heart failure	4 years	LV mass index predicts heart failure independently [adjusted HR, 1.004, 95% CI, 1.001 – 1.007, P= 0.003] in multivariable Cox regression model including also previous history of heart failure. LV EF predicts heart failure independently [adjusted HR, 0.97, 95% CI, 0.95 – 1.00, P=0.02] in the multivariable Cox regression model not including previous history of heart failure.	B
Yilmaz et al Kidney Blood Press Res 2012 (8)	87 prevalent PD patients	Cross-sectional	LVH	-	LVH: 44%, Normal LV geometry: 50.6%	C
Rocha et al J Nephrol 2012 (14)	79 prevalent dialysis patients (63 patients on waiting list)	Prospective follow-up	Adverse CV events	31 ± 19 months	Time on transplant waiting list associated with progressive increase in left atrial diameter and LV mass. LA diameter (HR, 8.84, 95% CI, 1.95 – 40.53, P=0.005), systolic dysfunction (Fractional shortening) (HR, 0.74, 95% CI, 0.59 – 0.92; P=0.007) and LV Mass index (HR, 1.023, 95% CI, 1.005 – 1.041, P=0.013)	C

					predicts adverse CV events	
Iwabuchi et al. Intern Med 2012 (22)	161 prevalent HD patients with preserved systolic function	Prospective follow-up	CV events	4 years	Tissue Doppler derived measure E/Em ratio predicted CV events in HD patients better than other parameters (P=0.0016) E/Em ratio in relation to CV events, adjusted HR, 1.07 (95% CI, 1.019 – 1.118; P=0.0078)	C
Dogan et al. Eur Rev Med Pharmacol Sci 2012 (23)	45 prevalent HD patients	Prospective follow-up	Combined all-cause mortality and CV events	52 ± 26months	Tissue Doppler derived measure E/Em ratio predicted combined mortality and CV events (adjusted HR, 1.20, 95% CI, 1.03 – 1.39; P=0.018)	C

CAPD = continuous ambulatory peritoneal dialysis; HD = hemodialysis; LVH = left ventricular hypertrophy; LV = left ventricular; CV = cardiovascular; HR = hazard ratio, RR = relative risk; CI = confidence intervals; SD = standard deviation; mwFS = midwall fractional shortening; EF = ejection fraction; E/Em = ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity; LA = left atrial; pts. = patients.

Evidence Review Table 2. Studies that examined the effects of renin-angiotensin aldosterone system blockers on left ventricular structural and functional abnormalities in dialysis patients.

Reference	Patient type, number	Treatment arm	Study design	Follow-up duration	Primary endpoints	Results	Study quality
Cice et al JACC 2010 (36)	332 HD patients with HF, NYHA class II to III, EF≤ 40%	Telmisartan + ACEI vs Placebo + ACEI	Prospective RCT	3 years	All-cause mortality; CV mortality; and HF hospital stay.	Secondary endpoints: Sig. reduction in LV end-diastolic diameter [-0.12 ± 0.6 vs -0.04 ± 0.3 cm/m^2; P<0.0001] and improved LV EF [5.8 ± 6.7% vs 3.1 ± 4.4%; P<0.0001] in carvedilol treated group vs placebo	B
Edwards et al JACC 2009 (67)	112 patients with stage 2 & 3 CKD with good BP and already on ACEI or	Spironolactone vs placebo	Prospective RCT	40 weeks	Change in MRI determined LV mass	Spironolactone sig. reduced MRI determined LV mass and improves arterial stiffness. Prevalence of LVH decreased by 50% with spironolactone but unchanged with placebo	B

	ARBs						
Edwards et al Am J Cardiol 2010 (100)	112 patients with stage 2 & 3 CKD with good BP and already on ACEI or ARBs	Spironolactone vs placebo	Prospective RCT	40 weeks	Change in MRI determined LV mass	Secondary endpoints: Spironolactone improved LV long-axis systolic function (Sm 8.2 ± 1.4 vs 7.7 ± 1.3 cm/s, p <0.05), torsion (7.77 ± 1.61° vs 6.77 ± 1.48°, p <0.05), and myocardial deformation (strain rate -1.14 ± 0.24 vs -1.09 ± 0.20 s(-1), p <0.05) compared to placebo, without a change in the ejection fraction. Markers of LV relaxation (E/e' ratio 7.2 ± 2.3 vs 8.5 ± 2.3, p <0.05) and suction (M-mode propagation velocity 56 ± 12 vs 50 ± 12 cm/s, p <0.05) were also improved. Spironolactone reduced NTproBNP (24.8 pmol/L [range 0.4 to 122.4] vs 39.4 pmol/L [range 10.8 to 102.4], p <0.01) and attenuated an increase in aminoterminal propeptide of type III procollagen observed with placebo.	B
Yang et al Am J Med Sci 2013 (37)	Meta-analysis of 6 RCTs including total 207 participants (sample size of individual trials < 50 subjects) Total: 107 ARB vs 100 non-ARB HD: 63 vs 60 (ARB vs. non-ARB) PD: 44 vs 40 (ARB vs. non-ARB)	ARB vs non-ARB	Meta-analysis of 6 RCTs	-	LVMi	ARB group had greater regression of LVMi than non-ARB group (P = 0.002) in dialysis patients but no significant difference in LV EF (P =0.30). The ARB group had a non-significantly greater therapeutic value on LVMi and LVEF when compared with ACEI; P 5 0.74 and 0.49, respectively). No significant alterations were observed in LVMi and LVEF between the combination of ARBs and ACEIs and ARBs group (P =0.43 and 0.24, respectively). Greater LV mass regression was observed with ARB vs. non-ARB in HD pts (P=0.009) Greater LV mass regression was observed with ARB vs. non-ARB in PD pts (P=0.03)	C
Robson et al Nephrol 1997 (38)	107 CAPD or HD patients	Enalapril + Zocor vs placebo	Placebo-controlled RCT	6 months	LV mass	No statistically significant difference in LV mass or dimensions between patients assigned enalapril vs. placebo	C

Ito et al Am Soc Nephrol 2014 (68)	158 PD patients already receiving ACEI or ARB	Spironolactone vs control	Open-label prospective RCT	2 years	Change in LV Mass index	Rate of change in LV mass index assessed by echo (study primary endpoint) improved significantly at 6 (P=0.03), 18 (P=0.004) and 24 (P=0.01) month in spironolactone group compared to control. Rate of change in LV ejection fraction improved significantly at 24 wks with spironolactone compared to control (P=0.02). Benefit of spironolactone was clear in patients with reduced residual renal function.	B

HD = hemodialysis; HF = heart failure; ACEI = angiotensin converting enzyme inhibitor; LV = left ventricular; CKD = chronic kidney disease; RCT = randomized controlled trial; MRI = magnetic resonance imaging; LVH = left ventricular hypertrophy; BP = blood pressure; Sm = systolic mitral annual velocity; E/Em = ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity; ARB = angiotensin receptor blocker; NT-pro-BNP = N-terminal pro-brain natriuretic peptide; LVMi,= left ventricular mass index; EF = ejection fraction; CAPD = continuous ambulatory peritoneal dialysis; PD = peritoneal dialysis.

Evidence Review Table 3. Studies that examined angiotensin converting enzyme inhibitor or angiotensin receptor blocker in relation to clinical outcomes of dialysis patients

Reference	Population and number of patients	ACEI/ARB	Study design	Primary endpoints	Follow-up duration	Results	Study quality
Zannad et al Kidney Int 2006 (46)	397 HD patients with LVH	ACEI vs placebo	Prospective placebo-controlled RCT	CV event (defined as a composite of CV death, nonfatal myocardial infarction, unstable angina, stroke, revascularization, hospitalization for heart failure, and resuscitated cardiac arrest)	24 months	AHR, 0.93 (95% CI, 0.68–1.26), P= 0.35 in the intention to treat analysis AHR, 0.80 (95% CI, 0.59–1.1), P= 0.099 in the per protocol analysis	B
Takahashi et al NDT, 2006 (47)	80 HD pts with no clinical evidence of heart disease	ARB vs no treatment	Open-label RCT	Cardiovascular events (including fatal/nonfatal myocardial infarction, unstable angina pectoris, congestive heart failure, severe arrhythmia	19.4 ± 1.2 months	AHR, 0.23 (95% CI, 0.08–0.67), P<0.01	C

				and sudden death)			
Cice et al JACC 2010 (36)	332 HD patients with NYHA class II – III heart failure, EF ≤40%	Telmisartan + ACEI vs placebo + ACEI	Prospective placebo-controlled RCT	Primary endpoints: All-cause mortality, hospital admissions for heart failure, all CV death Secondary endpoints: Nonfatal MI and nonfatal stroke, pump failure deaths, sudden cardiac deaths	3 years	All-cause mortality: AHR, 0.51 (0.32–0.82), P=0.004 Hospital admissions for heart failure: AHR, 0.38 (0.19–0.51), P=0.00007 All cardiovascular death: AHR, 0.42 (0.38–0.61), P=0.00009 Nonfatal MI and nonfatal stroke: NS Exploratory analysis – Pump failure deaths: AHR, 0.45 (0.25 – 0.66), P=0.0004 Sudden cardiac deaths: AHR, 0.53 (0.33 – 0.68), P=0.008 Permanent treatment withdrawal: AHR, 1.3 (1.1 – 1.6), P=0.008	B
Akbari et al PDI 2009 (101)	PD patients (total n = 154 Combining all 4 trials)	ACEI vs placebo or ARB vs placebo	Systematic review of 4 RCTs (all small sample size <50)	Mortality and CV events not primary endpoints in all these 4 trials	12 months in 3 studies and 24 months in 1 study	Mortality : OR, 1.56 (95% CI, 0.24 – 10.05) for ACEI vs. placebo CV events: OR, 1.00 (95% CI, 0.19 – 5.40) for ACEI vs placebo Insufficient evidence to recommend use of ACEI or ARB in lowering hard outcomes in PD patients.	C

HD = hemodialysis; PD = peritoneal dialysis; CVD = cardiovascular disease; ACEI = angiotensin converting enzyme inhibitor; CCB = calcium channel blocker; ARB = angiotensin receptor blocker; CV = cardiovascular, AHR = adjusted hazard ratio; CI = confidence intervals; RCT = randomized controlled trial; NYHA = New York Heart Association; MI = myocardial infarction; OR = odds ratio.

Evidence Review Table 4. Studies that examined the effect of beta blocker on left ventricular structural and functional abnormalities in dialysis patients.

Reference	Patient type, number	Beta blocker	Study design	Follow-up duration	Primary endpoints	Results	Study quality
Cice et al JACC 2001 (48)	114 HD patients with dilated cardiomyopathy	Carvedilol vs placebo	Prospective placebo controlled RCT	12 months	Changes in LVEDV, LVESV and LVEF at 1, 6 and 12 months, and changes in symptoms of heart failure 6 and 12 months	Significant increase in LV EF (from 26.3% to 34.8%, $P < 0.05$ vs basal and placebo group) and reduction of both LV EDV (from 100 mL/m^2 to 94 mL/m^2, $P < 0.05$ vs basal and placebo group) and LV ESV (from 74 mL/m^2 to 62 mL/m^2, $P < 0.05$ vs basal and placebo group) reached statistical significance after six months, compared with baseline and corresponding placebo values, and remained significant at one year ($p < 0.05$ vs basal and placebo group).	B
Cice et al JACC 2003 (49)	114 HD patients with dilated cardiomyopathy	Carvedilol vs placebo	Prospective placebo controlled RCT (but unblended at 1 year)	24 months	Changes in LVEDV, LVESV and LVEF at 1, 6 and 12 months, and changes in symptoms of heart failure 6 and 12 months	Significant reduction in LV volumes and improvement in LV ejection fraction with carvedilol but not placebo LVEDV: 100 ± 9 mL/m^2 at baseline to 94 ± 5 mL/m^2 at 24 months (carvedilol group) vs. 97 ± 8 ml/m^2 at baseline to 100 ± 5mL/m^2 at 24 months (placebo group)($P<0.05$ vs. baseline and vs. placebo group) LV EF: 26 ± 8% vs. 37 ± 10% (baseline vs. 24 months)(carvedilol group) vs. 26 ± 8% vs. 24 ± 10% (baseline vs 24 months)(placebo group)($P<0.05$ vs. baseline and vs placebo group) Cardiovascular mortality: AHR, 0.18 (95% CI, 0.06 to 0.55)	B

HD = hemodialysis; RCT = randomized controlled trial; LV = left ventricular; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; NYHA = New York Heart Association; AHR = adjusted hazard ratio; CI = confidence intervals.

Evidence Review Table 5. Studies that examined beta blockers in relation to hard outcomes in chronic kidney disease and dialysis patients.

Reference	Patient type, number	Beta blocker	Study design	Study endpoints	Follow-up duration	Results	Study quality
Cice et al JACC 2003 (49)	114 HD patients with dilated cardiomyopathy	Carvedilol vs placebo	Prospective placebo controlled RCT	Primary: LV EDV, LVESV, EF and clinical status Secondary: All-cause mortality, all CV mortality, All-cause hospitalizations, non-fatal MIs, combined endpoint, Hospital admission for worsening heart failure	24 months	All-cause mortality: AHR, 0.51 (95% CI, 0.32 to 0.82) All CV mortality: AHR, 0.32 (95% CI, 0.18 to 0.57) All-cause hospitalizations: AHR, 0.44 (95% CI, 0.25 to 0.77) Non-fatal MIs: AHR, 0.81 (95% CI, 0.61 to 1.34) Combined endpoint: 0.76 (95% CI, 0.47-1.22) Hospital admission for worsening heart failure: AHR, 0.19 (95% CI, 0.09 – 0.41)	B
Wali et al Circ Heart Failure 2011 (102)	4217 patients with systolic LV dysfunction with/without symptoms of HF, NYHA class I – III (2566, 60.8% with CKD)	Carvedilol	Meta-analysis of 2 RCTs CAPRICORN – 1959 patients within 21 days after AMI with LVEF ≤0.4 with or without symptomatic HF	Primary: All-cause mortality Secondary: CV mortality, HF mortality, first hospitalization for heart failure, composite of CV mortality or HF hospitalization, sudden cardiac death	Median, 13.5 months and Mean ± SD, 13.6 ± 7.9 months	Post-hoc analysis: All-cause mortality: AHR, 0.76 (95% CI, 0.63-0.93) CV mortality: AHR, 0.76 (95% CI, 0.62 – 0.94) HF mortality: AHR, 0.68 (95% CI, 0.52 - 0.88) First hospitalization for HF: AHR, 0.74	B

			COPERNICUS – 2289 patients with LVEF ≤0.25 and severe chronic HF of ischemic/non-ischemic etiology			(95% CI, 0.61 – 0.88) Composite of CV mortality or HF hospitalization: AHR, 0.75 (95% CI, 0.65 – 0.87) Sudden cardiac death: AHR, 0.76 (95% CI, 0.56 – 1.05)	

CKD = chronic kidney disease; PD = peritoneal dialysis; HD = hemodialysis; LV = left ventricular; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; CV = cardiovascular; AHR = adjusted hazard ratio; CI = confidence intervals; RCT = randomized controlled trial; AMI = acute myocardial infarction; HF = heart failure; NYHA = New York Heart Association

Evidence Review Table 6. Studies that examined aldosterone receptor antagonist treatment in relation to hard outcomes in dialysis patients.

Reference	Patient type, number	Aldosterone R antagonists	Study design	Study endpoints	Follow-up duration	Results	Study quality
Matsumoto et al JACC 2014 (69)	309 oligoanuric HD patients	Spironolactone 25 mg daily vs control	Open label prospective RCT	Primary - composite of death or hospitalization from cardiovascular and cerebrovascular events Secondary – death from all causes	3 years	Reduced primary endpoint in spironolactone versus control group before (HR, 0.404, 95% CI, 0.202 – 0.809, P=0.017) and after adjustment for confounding covariates (adjusted HR, 0.379, 95% CI, 0.173 – 0.832; P=0.016). Reduced secondary endpoint (death from all causes) in spironolactone versus control group (6.4% vs 19.7%, HR, 0.355, 95% CI, 0.191 – 0.662; P=0.002) and (adjusted HR, 0.335, 95% CI, 0.162 – 0.693; P=0.003) before and after adjustment, respectively.	B

HD = hemodialysis; RCT = randomized controlled trial; HR = hazard ratio; CI = confidence intervals.

Evidence Review Table 7. Studies that examined the effects of erythropoietin stimulating agent on left ventricular structural and functional abnormalities in dialysis patients.

Reference	Patient type, number.	Treatment arm	Study design	Primary endpoints	Follow-up duration	Results	Study quality
Parfrey et al CJASN 2009 (74)	15 eligible studies involving 1731 CKD & ESRD patients (5 assigned cohorts using RCT design, 6 compared lower HB vs higher HB target	-	Meta-analysis	LVMi	4 months to 4.4 years (mean, 16 months)	In severe anemia (Hb <10 g/dL), conventional Hb targets for EPO therapy are associated with a reduction in LVMi, but that in moderate anemia (Hb ≥10 g/dL), target Hb >12 g/dL does not have a beneficial impact on LVMi compared with conventional targets.	C
Macdougall et al NDT 2007 (103)	197 pre-dialysis CKD	Eprex at early stage of anemia to maintain Hb at 11 ± 1 g/dL (N=65) vs to fall to ≤9 g/dL before starting Eprex (n=132)	Prospective open-label randomized trial	LV mass	3 years	LV mass did not differ between early vs late intervention of anemia, time to death/dialysis also not differ between early vs late intervention of anemia	C
Ritz et al AJKD 2007 (104) (ACORD study)	172 patients with CKD stage 1-3, T1 or 2 diabetes mellitus, mild to moderate anemia	Hb correction to either target of 13-15 g/dL vs 10.5-11.5 g/dL	Multi-center randomized open-label parallel study, 64 centers	LVMi	15months	Correction to a Hb target level of 13-15 g/dL does not decrease LVMi vs those with Hb level of 10.5-11.5 g/dL	B
Ayus et al KI 2005 (105)	40 anemic CKD pts vs 61 non-anemic CKD patients Non-DM, CrCl 10-30 mL/min.	rhEPO given to those with anemia	Open-label trial	LVMi	6 months	LVMi decreased in anemic pts receiving rhEPO with an increase in Hb vs no change in LVMi among controls (P=0.001)	C

	DM, CrCl 20-40 mL/min.						
Levin et al AJKD 2005 (106)	172 CKD pts, mean age 57 years, 38% DM, 70% men (eGFR: 28 vs 30 mL/min)	SC Eprex to achieve Hb 12-14 g/dL vs delayed treatment group (Hb of 9 ± 0.5 g/dL before Eprex, then target level 9 to 10.5 g/dL)	Prospective randomized trial	Change in LVMi	24 months	No statistically significant difference between the two groups for the change in LVMi over 24 months	B
Parfrey et al JASN 2004 (73)	596 incident HD patients without symptomatic heart disease	Randomized to receive Eprex to higher (13.5-14.5 g/dL) vs lower (9.5 to 11.5 g/dL)	Prospective randomized double blind trial	LV volume index	96 weeks	LV volume index as well as LVMi did not differ between higher target vs lower target group. Normalization of Hb does not have beneficial effect on cardiac structure compared with partial correction.	A
Roger et al JASN 2004 (107)	155 CKD patients (CrCl 15-50 ml/min), Hb 11-12 g/dL (female) or 11-13 g/dL (male)	Randomized to receive SC Eprex to maintain Hb between 12-13 g/dL or 9-10 g/dL	Prospective randomized trial	LVMi	24 months	Similar effects on LVMi between the two groups. Either maintenance level of Hb did not affect the development or progression of LV hypertrophy	B
Foley et al KI 2000 (72)	146 HD patients with either concentric LVH or LV dilatation	Randomized to receive Eprex to achieve Hb of 10 or 13.5 g/dL	Prospective randomized trial	Change in LVMi in those with concentric LVH and change in LV volume index in those with LV dilation	48 weeks	In pts with concentric LVH, change in LVMi similar between normal and low target Hb groups. In patients with LV dilatation, changes in cavity volume index similar between normal and low target Hb groups . Normalization of Hb does not regress established concentric LV hypertrophy or LV dilatation.	B

CKD = chronic kidney disease; HD = hemodialysis; LVMi = left ventricular mass index; EPO = erythropoietin; Hb = hemoglobin; LV = left ventricular; SC = subcutaneous; DM = diabetes mellitus; rhEPO = recombinant human erythropoietin; CrCl = creatinine clearance; LVH = left ventricular hypertrophy.

Evidence Review Table 8. Studies that examined the effect of icodextrin on left ventricular structural abnormalities in peritoneal dialysis patients.

Reference	Patient type, number.	Treatment arm	Study design	Primary endpoints	Follow-up duration	Results	Study quality
Davies S et al JASN 2003(81) *	50 PD patients with urine output <750 mL/day, high solute transport, and either treated hypertension or untreated BP >140/90 mmHg, or a requirement for the equivalent of all 2.27% glucose exchanges	Icodextrin vs 2.27% glucose as long dwell	Multi-center Randomized double-blind placebo controlled trial	Fluid removal and fluid status	6 months	Icodextrin improved fluid removal and fluid status as reflected by body weight, total body water and extracellular water by BIA (primary endpoint) compared to control LV mass not reported	C
Konings et al KI 2003 (82) *	40 PD patients (32 completed study)	22 – icodextrin, 18 – control	Open label randomized study	Fluid status	4 months	Icodextrin resulted in a significant increase in daily ultrafiltration volume (744 +/- 767 mL vs. 1670 +/- 1038 mL; P = 0.012) and a decrease in ECW (17.5 +/- 5.2 L vs. 15.8 +/- 3.8 L; P = 0.035). Change in ECW between controls and patients treated with icodextrin was significant (-1.7 +/- 3.3 L vs. +0.9 +/- 2.2 L; P = 0.013). LVM (not primary endpoint) decreased significantly in the icodextrin (241 +/- 53 g vs. 228 +/- 42 g; P = 0.03), but not control group.	C

*Both studies were not specifically done in PD patients with heart failure.

PD = peritoneal dialysis; LV = left ventricular mass; BIA = bioimpedance analysis; ECW = extracellular water

Evidence Review Table 9. Studies that examined the effect of activated vitamin D on left ventricular structural abnormalities in chronic kidney disease.

Reference	Patient type, number.	Treatment arm	Study design	Follow-up duration	Primary endpoints	Results	Study quality
Thadhani et al JAMA 2012 (89)	221 CKD stage 3-4 patients	Paricalcitol vs placebo	Multi-national Prospective double-blind RCT	48 weeks	LV mass index by cardiac MRI	No significant difference between paricalcitol vs placebo arm in primary endpoint and other echocardiographic LV structural and functional parameters over 48 weeks	B
Wang et al JASN 2013 (90)	60 CKD 3-5 patients	Paricalcitol vs placebo	Prospective double-blind RCT	52 weeks	LV mass index by cardiac MRI	No significant difference between paricalcitol vs placebo in primary endpoint and other echocardiographic LV structural and functional parameters over 48 weeks	B

CKD = chronic kidney disease; LV = left ventricular; MRI = magnetic resonance imaging; RCT = randomized controlled trial

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SECTION 3. STROKE

Guideline 3.3.1: We suggest carotid duplex ultrasonography be performed in peritoneal dialysis patients with transient ischemic attack or acute thromboembolic stroke to identify presence of significant carotid artery stenosis. (ungraded)

Rationale

There is very limited evidence to guide routine screening for cerebrovascular disease in dialysis patients. One prospective observational study of carotid duplex screening in 123 patients undergoing hemodialysis (HD) via permanent tunneled cuffed catheter identified ≥60% carotid stenosis in 12 (10%) patients and 70–99% carotid stenosis in 8 (7%) patients (1). However, there is so far no study showing how early screening of carotid artery stenosis may improve clinical outcomes or reduce stroke risk in dialysis or specifically peritoneal dialysis (PD) patients. In the absence of good quality evidence, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI 2005) Guidelines on evaluation and management of cardiovascular diseases recommend following the American Heart Association (AHA) Guidelines for the evaluation of stroke. Specifically, the AHA guidelines recommend that computed tomography of the brain should be performed to evaluate patients with transient ischemic attack (TIA) or acute stroke in order to localize the site of stroke and establish the cause (whether hemorrhagic or non-hemorrhagic) and carotid duplex scan to identify significant carotid stenoses in patients with a history of TIA or stroke (2). Given the lack of evidence in dialysis patients including PD patients, the workgroup suggests following a similar approach recommended by the AHA in managing PD patients with TIA or stroke and the statement was ungraded. [Evidence Review Table 1]

Guideline 3.3.2: We suggest peritoneal dialysis patients not be routinely prescribed antiplatelet therapy for primary prevention of cerebrovascular disease. (2C)

Rationale

The AHA Guidelines for Primary Prevention of Stroke for the general population recommend the use of low-dose aspirin for the primary prevention of stroke in the general population for those considered to be at high cardiovascular risk, but not for those at low risk (3). However, the role of aspirin for primary prevention of stroke in PD patients is uncertain. A recent Cochrane review evaluating the effects of antiplatelet therapy on cardiovascular events, mortality and bleeding in 11,701 patients with chronic kidney disease (CKD) and with either stable or no cardiovascular disease found that antiplatelet therapy was associated with uncertain effects on stroke (10 trials, 9133 participants; RR, 0.66 [CI, 0.16 to 2.78]), a significantly increased risk of minor bleeding (RR 1.70, 95% CI 1.44-2.02) but had uncertain effects on major bleeding (RR, 1.29 [CI, 0.69 to 2.42]) (4). Given the uncertain benefit of antiplatelet therapy for primary stroke prevention and risk of bleeding in patients with CKD, the working group felt that PD patients should not routinely be prescribed antiplatelet therapy for primary prevention of cerebrovascular disease. [Evidence Review Table 2].

Guideline 3.3.3: We suggest individualization of warfarin prescription for prevention of stroke in peritoneal dialysis patients with atrial fibrillation in view of an increased risk of bleeding and uncertain effects on cerebrovascular outcomes. (2D)

Rationale

Although antithrombotic therapy is recommended by the AHA Guidelines for prevention of stroke for patients with atrial fibrillation in the general population (5), all the trials upon which this recommendation was based excluded dialysis patients. The risk to benefit ratio of warfarin for stroke prevention in dialysis patients with atrial fibrillation has remained uncertain. A systematic review of eight studies (included case series, cohort studies and randomized controlled trials (RCTs) evaluating warfarin therapy in HD patients found that the rates of major bleeding episodes ranged from 0.1 to 0.54 events/patient-year with warfarin exposure and were approximately twice the rate expected in HD patients receiving either no warfarin or subcutaneous heparin (6). Furthermore, a systematic review and meta-analysis of 25 studies (included cross sectional and cohort studies) by Zimmerman in 2012 evaluating outcomes of stroke in dialysis patients with atrial fibrillation found that, while the incidence and prevalence of atrial fibrillation was higher than that found in the general population and associated with about a two-fold increased risk of stroke and mortality, overall, warfarin use did not appear to decrease the risk of the combined outcome of hemorrhagic and ischemic stroke, especially in the larger studies (7). While there have been further population-based, retrospective and observational studies published recently on this topic, they all have limitations, including lack of information on monitoring of the international normalized ratio (INR) with the usual target of between 2 and 3, and confounding by indication bias (patients who were most likely to have strokes possibly being preferentially treated with warfarin) and these studies have, thus, not been included for review in this section.

The NKF-KDOQI 2005 Guidelines caution that “dialysis patients are at an increased risk of bleeding and careful monitoring should accompany intervention”(9.2a) with thrombolytics for atrial fibrillation (8). The *Kidney Disease: Improving Global Outcomes* (KDIGO) 2011 Clinical Update, given the lack of RCTs and uncertain outcomes of primary prevention of stroke in HD patients, questioned the efficacy of the use of routine anticoagulation for primary prevention of stroke in CKD patients with atrial fibrillation on dialysis (9). While, for secondary prevention of stroke, they felt that the NKF-KDOQI 2005 Guidelines should be followed. Presumably this caution of increased bleeding risk with use of thrombolytics in HD patients also extends to PD patients. However, the KDIGO 2011 Clinical Update also suggested that, unlike HD patients who receive systemic heparin for anti-coagulation during HD, PD patients do not routinely receive systemic heparin and, thus, the risk to benefit ratio for warfarin use in PD patients may be modified compared to HD patients. The working group felt that warfarin prescription for prevention of stroke in PD patients with atrial fibrillation should be individualized by considering not only the cerebrovascular risk but also the bleeding risk. The strength of this recommendation was weak, given the uncertainty of the risk to benefit ratio of routine anticoagulation for patients on PD with atrial fibrillation. [Evidence Review Table 3]

Guideline 3.3.4: We do not recommend the use of novel oral anticoagulants to prevent stroke in atrial fibrillation in peritoneal dialysis patients. (1D)

Rationale

While new oral anticoagulants are now available to prevent stroke in patients with atrial fibrillation, all these new oral anticoagulants are mostly cleared by the kidney. There is very little

data from clinical trials or clinical experience on patients on dialysis or close to dialysis with these drugs and they are contraindicated in patients with CKD stage 5 on dialysis (10,11). Thus, we do not recommend use of these new oral anticoagulants for stroke prevention in patients on PD with atrial fibrillation.

Guideline 3.3.5: We suggest caution with administration of thrombolytic therapy to peritoneal dialysis patients with acute ischemic stroke in view of uncertainty regarding whether benefits outweigh risks. (ungraded)

Rationale

In the absence of high level evidence in dialysis patients, the NKF-KDOQI 2005 Guidelines recommend following the AHA Guidelines for the treatment of TIA or stroke in dialysis patients, with the exception of the use of thrombolytic therapy, where the NKF-KDOQI 2005 Guidelines recommend that the use of thrombolytic therapy should be considered on an individual basis (8). The more recently published KDIGO 2011 Clinical Update pointed out that the safety of IV thrombolytic therapy for treatment of acute ischemic stroke in patients on dialysis still has not been defined (9). A recent e-published ahead of print retrospective analysis of 82,142 patients with an acute ischemic stroke in the United States who received IV thrombolytics found that in the 1072 (1.3%) patients who were on dialysis (1007 on HD and 65 on PD), there was an almost two-fold higher rate of in-hospital mortality (odds ratio, 1.92; 95% CI, 1.33-2.78, p = .0005) compared to those not on dialysis. Of note, there was no significant difference in intracerebral hemorrhage rates between those on dialysis and those not on dialysis. The study could not determine whether the higher mortality rate was related to the IV thrombolytic therapy or the pre-existing comorbidities in those patients on dialysis (12). The workgroup felt that the current available evidence is insufficient to draw any recommendation in relation to the use of thrombolytic agents as a treatment of acute ischemic stroke. Nevertheless, the workgroup felt that a very careful assessment of risks versus benefits must be undertaken before administering intravenous thrombolytics for treatment of acute ischemic stroke in dialysis patients, including PD patients. [Evidence Review Table 4]

What is the evidence for prevention of recurrent stroke in patients on peritoneal dialysis?

There are few studies examining the safety and effectiveness of antiplatelet therapy to reduce the risk of recurrent stroke in patients on dialysis. One large retrospective study from Taiwan of 1936 dialysis patients (included both HD and PD patients) with a first-time ischemic stroke found that those treated with aspirin only (763) were less likely to be readmitted for recurrent ischemic stroke than those not treated with aspirin (aHR: 0.715; P = 0.002). Moreover, there was no increase in risk of readmission for bleeding in those patients treated with aspirin only compared to those not treated with aspirin (aHR: 0.885; 95% CI: 0.705-1.11; P=0.291). However, for those dialysis patients treated with clopidogrel only (146), there was no significant difference in risk of readmission for ischemic stroke compared to those not treated with clopidogrel. The authors felt that aspirin was safe and effective for patients on dialysis to prevent recurrent stroke; but advised that this retrospective study only included Han Chinese, thus, generalization of these results to other racial or ethnic groups has to be made with caution. Also, since the study was retrospective, certain data such as smoking history or history of bleeding were not available. Unfortunately, the study authors did not differentiate between outcomes for patients on HD versus those on PD (13).

While the AHA Guidelines recommend daily aspirin for patients who have a TIA or stroke to reduce the risk of recurrent stroke and an antiplatelet agent such as clopidogrel for patients who are

intolerant to aspirin or who have had a stroke while on aspirin (2), the NKF-KDOQI 2005 Guidelines note that dialysis patients are at risk for bleeding and caution should be taken when prescribing antiplatelet or anticoagulant therapy in these patients (8). The more recently published KDIGO 2011 Clinical Update (9) suggests that, until new evidence becomes available, the previous 2005 NKF-KDOQI recommendations remain valid. The workgroup felt that there is not enough quality evidence to recommend routine use of anti-platelet agents for secondary prevention of ischemic stroke in all PD patients. The decision on anti-platelet agent prescription for secondary prevention of stroke in PD patients should be individualized and balanced against the bleeding risk. The workgroup also suggest careful monitoring of bleeding-related complications if an anti-platelet agent is indeed prescribed for stroke prevention in PD patients and the statement was ungraded; however, as a group we decided against this recommendation being part of the guidelines.

Evidence Review Table 1. Studies that examined the use of carotid duplex screening to assess risk for stroke

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Lin et al Vasc Endovascular Surg 2012 (1)	Patients undergoing dialysis catheter placement plus those who underwent aortorenal artery duplex study in a single centre in the United States.	123	Single centre, prospective, observational	To identify hemodialysis patients at increased risk for vascular disease (carotid, renal, and aortic).	N/A	For the 123 HD patients who underwent a dialysis catheter placement, 12 patients (9.8%) had $\geq$ 60% stenosis and 8 patients (6.5%) had 70% to 99% stenosis. For the 109 HD patients who underwent an aortorenal artery duplex study, there was only a 3.7% prevalence rate for abdominal aorta aneurysm and 4.6% for renal artery stenosis.	C

HD = hemodialysis; N/A = not applicable

Evidence Review Table 2. Studies that examined the use of antiplatelet therapy in peritoneal dialysis patients for primary prevention of stroke

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Palmer et al Ann Intern Med 2012 (4)	Systematic review of RCTs that included adults with CKD and compared antiplatelet agents with standard care, placebo, or no treatment.	9 trials (acute coronary syndrome); 31 trials (stable or no cardiovascular disease)	Systematic review and meta-analysis	The effects of antiplatelet therapy on cardiovascular events, death and bleeding	Not applicable	Among CKD patients at risk for or with stable cardiovascular disease, moderate-quality evidence showed that antiplatelet therapy reduced myocardial infarction (10 trials, 9133 participants; RR, 0.66 [CI, 0.51 to 0.87]) but had uncertain effects on stroke (10 trials, 9133 participants; RR, 0.66 [CI, 0.16 to 2.78]). There was low-quality evidence that antiplatelet therapy significantly increased minor bleeding (RR, 1.70 [CI, 1.44 to 2.02]) but had uncertain effects on major bleeding (RR, 1.29 [CI, 0.69 to 2.42]).	A

RCTs = randomized controlled trials; CKD = chronic kidney disease; RR = relative risk; CI = confidence interval.

Evidence Review Table 3. Studies that examined the use of antithrombotic therapy for peritoneal dialysis patients with atrial fibrillation

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Elliott et al Am J Kidney Dis 2007 (6)	Systematic review of case series, cohort studies and RCTs in HD patients that examined the bleeding risk associated with warfarin use compared with no warfarin or subcutaneous heparin	8 studies	Systematic review	Data for bleeding were reported as rates: number of bleeding episodes per number of patient-years of warfarin exposure or follow-up.	Not applicable	Studies of full-intensity anticoagulation and the 1 randomized controlled trial of low-intensity anticoagulation demonstrated major bleeding episode rates ranging from 0.1 to 0.54 events/patient-year of warfarin exposure. When compared to bleeding rates of HD patients who received no heparin or subcutaneous heparin, these rates were approximately doubled.	A
Zimmerman et al NDT 2012 (7)	Systematic review and meta-analysis cross-sectional and cohort studies of incidence, prevalence or selected outcomes of CKD stage 5 patients on dialysis with atrial fibrillation	25 studies	Systematic review and meta-analysis	Incidence, prevalence or selected outcomes in CKD stage 5 patients on dialysis with atrial fibrillation	Not applicable	The prevalence of atrial fibrillation was 11.6% and the overall incidence was 2.7/100 patient-years. The risk of mortality and stroke was increased in CKD stage 5 patients on dialysis with atrial fibrillation at 26.9 and 5.2/ 100 patient-years versus 13.4 and 1.9/100 patient-years compared with CKD stage 5 patients on dialysis without atrial fibrillation. The majority of studies did not support a protective effect for warfarin in CKD stage 5 on dialysis patients with atrial fibrillation.	A

RCTs = randomized controlled trials; HD = hemodialysis; CKD = chronic kidney disease

Evidence Review Table 4. Studies that examined the use of intravenous thrombolytics in peritoneal dialysis patients with acute stroke

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Tariq et al J Stroke Cerebrovasc Dis 2013 (12)	Nationwide sample of patients from the United States (2002-2009), from the National Inpatient Sample database) treated with IV thrombolytics for acute ischemic stroke	82,142 (1072 on dialysis: 1007 HD; 65 PD)	Retrospective, nationwide observational	To determine the outcomes of dialysis dependent renal failure patients who had ischemic stroke and were treated with IV thrombolytics compared to the outcomes with thrombolytic-treated patients without dialysis dependence	Median length of hospital stay - 14.24 days for dialysis patients and 7.12 days for non-dialysis patients	There was a high rate of In-hospital mortality in dialysis-dependent renal failure patients treated with IV thrombolytics for acute ischemic stroke compared to those not dialysis dependent (OR 1.92; CI 95%; 1.33-2.78, p = 0.0005)	**C**

HD = hemodialysis; IV = intravenous; OR = odds ratio; CI = confidence interval

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SECTION 4. PERIPHERAL ARTERIAL DISEASE

A. Screening

Guideline 3.4.1: We recommend peritoneal dialysis patients, particularly those with diabetes mellitus, have regular clinical evaluation for peripheral arterial disease (including inquiry of symptoms of intermittent claudication and rest pain, examination of signs for peripheral arterial disease, and palpation of peripheral arterial pulses). (1D)

Rationale

Peripheral arterial disease (PAD), defined as either asymptomatic abnormalities on non-invasive Doppler ultrasound testing, intermittent claudication, critical limb ischemia (rest pain, ischemic ulceration or gangrene) or prior revascularization or amputation for limb ischemia, is exceedingly common in patients with chronic kidney disease (CKD) and is responsible for considerable morbidity and mortality (1) [Evidence Review Table 1]. A cross-sectional study of 2229 eligible participants in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000 found that the prevalence of PAD, defined as an ABI $\leq$0.9, was markedly higher in patients with a creatinine clearance of <60 mL/min/1.73 m^2 compared with those who had a creatinine clearance >60 mL/min/1.73 m^2 (24% vs 3.7%, respectively) (2). Other observational cohort studies, using variable combinations of clinical and/or ABI diagnostic criteria, have reported PAD prevalence rates ranging from 7.4%-22% in CKD stages 3-5 (3-7), 30.6%-45.9% in hemodialysis (HD) patients (7-12) and 15-30% in renal transplant patients (9, 10). In these studies, the majority of patients with a diagnosis of PAD were asymptomatic. Nevertheless, PAD is the commonest indication for amputation in end stage renal disease (ESRD) patients. Non-traumatic lower limb amputation is approximately 10 times more common in the ESRD population compared with non-ESRD patients (1, 13). Following amputation, ESRD patients' survival remains extremely poor with reported 2-year survival rates of <33% (13, 14).

There are no studies in PD patients, or indeed in any CKD populations, examining the impact of screening versus not screening for PAD on clinical outcomes. Until recently, very few studies had evaluated peritoneal dialysis (PD) patients for PAD. Most studies have taken place in the last 2-3 years and are summarized in Evidence Review Table 1. These studies have generally been limited by small sample sizes, single centre design, small follow-up duration, ascertainment bias, Neyman bias, lack of an appropriate control group, lack of assessment against angiography or prediction of future lower limbs vascular complications. Overall, the median reported prevalence of PAD in PD patients is 28.5% (range, 4.8%-47%), with the majority (59%-84%) having subclinical PAD. PAD was most commonly independently predicted by diabetes, older age and prior cardiovascular disease and was a strong predictor of adverse clinical outcomes, including residual renal function decline, technique failure, cardiovascular mortality and all-cause mortality (including subclinical PAD).

Although there are no studies comparing routine clinical evaluation of stage 5 CKD patients for PAD versus evaluation only in response to symptoms, the National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI) guidelines recommend, on the basis of weak evidence, that all patients should be evaluated for PAD at the time of dialysis initiation, including physical assessment of arterial pulse and skin integrity and further specialized studies, such as duplex studies or invasive testing, if abnormalities are detected on physical examination (15). Alternatively, the Kidney Disease Improving Global Outcomes (KDIGO) cardiovascular guidelines state that "screening guidelines are problematic for clinicians because of the lack of clarity regarding diagnostic testing and optimal therapies for PAD in CKD" (16). Nevertheless, the KDIGO

CKD Guidelines recommend that "adults with CKD be regularly examined for signs of PAD and be considered for usual approaches to therapy (1B)" and that "adults with CKD and diabetes are offered regular podiatric assessment (2A)" (17). No recommendations are made by the Caring for Australasians with Renal Insufficiency (CARI), European Best Practice (EBPG), Canadian Society of Nephrology (CSN) or United Kingdom National Clinical Institutes of Excellence (UK-NICE) Guidelines. Given the high prevalence of PAD and subclinical PAD in PD patients, especially among the diabetics, and the very adverse clinical outcomes associated with PAD, the working group felt that a strong recommendation should be given for regular clinical evaluation of PAD in PD patients.

Guideline 3.4.2: We suggest an ankle-brachial index ≤ 0.9 be used to aid in the diagnosis of peripheral arterial disease in peritoneal dialysis patients. (2D)

Rationale

The most common screening test employed to detect PAD in studies of PD patients was an ABI [Evidence Review Table 1], which has been recommended for general population screening in at-risk patients by the American College of Cardiology (ACC)/American Heart Association (AHA) (18) or in patients with suspected PAD by the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) guidelines (19), although the United States Preventive Services Task Force (USPTF) does not advocate screening of asymptomatic individuals because of questionable risk: benefit (20). Most studies in PD patients used a cut-point of ≤0.9 to define PAD, as this threshold has been reported to have a sensitivity of 95% and a specificity of 100% for PAD detection in patients without CKD (21, 22). There are no studies examining the sensitivity and specificity of ABI in PD (or hemodialysis [HD] or CKD) patients specifically.

The working group felt that there is currently not enough evidence to support routine ABI assessment as a screening test for PAD in PD patients. Nevertheless, if ABI is performed, a cutoff ≤ 0.9 is suggested by the working group to be used to aid the diagnosis of PAD.

Guideline 3.4.3: We suggest a toe-brachial index ≤0.6 be used in addition to the ankle-brachial index to aid in the diagnosis of peripheral arterial disease in symptomatic patients in whom the ankle-brachial index is unreliable due to non-compressible vessels (such as when the ankle-brachial index ≥1.3). (2D)

Rationale

It has been suggested that the high prevalence of medial arterial calcification in the CKD population (particularly in diabetic patients) would lead to an underestimation of the true prevalence of PAD by ABI (1, 23, 24). In a prospective, cross-sectional study of 102 CKD patients (including 20 PD patients), An et al (25) reported a prevalence of vascular calcification (based on plain radiographs of the foot) of 50% and observed that ABI values were not discriminatory between those with and without vascular calcification. On the other hand, Leskinen et al (7) reported ABI measurements ≥1.3 to be suggestive of medial arterial calcification in 42% of dialysis patients. In patients with such abnormally high ABI values, the AHA/ACC and TASC II guidelines recommend measuring toe-brachial index (TBI) as toe arteries are less likely to be affected by vascular calcification compared with ankle arteries (18, 19, 26). Unfortunately, TBI has only been evaluated to a very limited extent in CKD populations and there are only 2 such studies in PD patients (7, 27) [Evidence Review Table 1]. One investigation of 146 PD patients found that ABI was highly correlated with toe brachial index (TBI) ($r=0.335$, $p<0.001$), but did not evaluate the clinical performance of these two measurements relative to color Doppler, angiography or prediction of future limb vascular complications (27). Similarly, Leskinen *et al* (7) reported low ABI

and TBI values in 31% and 19% of dialysis patients, respectively, although the addition of low TBI to low ABI did not affect the overall prevalence estimates of PAD.

There are no studies examining the sensitivity and specificity of TBI in PD (or HD or CKD) patients specifically. The cut-points recommended in this guideline are in line with those recommended in the non-CKD population by the AHA/ACC and TASC II guidelines (18, 19).

Other Potential Investigations

Other non-invasive screening tests for PAD, such as transcutaneous partial pressure of oxygen readings (28) and toe pulse volume recordings (29), have not been evaluated in the dialysis population.

Evidence Review Table 1. Studies that examined the prevalence of peripheral arterial disease on the basis of clinical manifestations and/or investigations such as ankle-brachial index, toe-brachial index, Doppler studies, vascular calcification or arteriography.

Reference	Population	Patient number	Study design	Outcomes of interest	Follow up duration (if applicable)	Results	Study quality
Tian et al, Ren Fail 2012(30)	Incident/prevalent CAPD patients >60 years old clinically stable ≥3 months at single Chinese center 2006-2009	172	Prospective, longitudinal observational cohort study	Prevalence of PAD (intermittent claudication or ABI <0.9) All-cause mortality Cardiovascular mortality	Mean 24.4 months Median 34.6 months (range 5-45 months)	Prevalence of PAD: 36% (64% in diabetics) (84% asymptomatic) PAD predicted by diabetes and cardiovascular disease PAD independently predicted all-cause mortality (adjusted HR: 2.14, 95% CI 1.11-4.13, p=0.023) and cardiovascular mortality (adjusted HR: 2.54, 95% CI 1.07-6.04, p=0.035)	C
Tian et al PDI 2012 (31)	Incident CAPD patients at single Chinese centre 2006-2007 who did not die, transfer to HD, receive treatment or transfer to other center within first 3 months	86	Prospective, longitudinal observational cohort study	Prevalence of subclinical PAD (ABI <0.9)	Mean 19 months Median 18months (range 6-30 months)	Prevalence of subclinical PAD: 28% (62% in diabetics) PAD associated with older age, diabetes mellitus, lower serum albumin, higher CRP and higher baseline GFR PAD (but not coronary artery and cerebrovascular disease) independently predicted >50% of residual renal function (adjusted HR: 2.68, 95% CI 1.35-5.30, p=0.005)	C
Webb and Brown PDI 1993 (32)	Prevalent CAPD patients at a single center in the United Kingdom	70	Cross-sectional, observational cohort study	Prevalence of PAD (using a standard cardiovascular questionnaire)	-	Prevalence of symptomatic vascular disease: 47%	C

Ng et al PDI 2003(33)	Prevalent, stable diabetic and non-diabetic CAPD patients at a single Chinese center	60 (30 diabetic, 30 age-, sex-dialysis duration-matched non-diabetic)	Prospective observational cohort study	Prevalence of PAD on the basis of ABI (<1.0, severe <0.7 or >1.3) or questionnaire screening administered by trained nurses Development of lower limb vascular complications	1 year	Prevalence of abnormal ABI: 37% (50% in diabetics)(severe 20%) Prevalence of intermittent claudication symptoms: 10% Abnormal ABI predicted by older age and diabetes mellitus Abnormal ABI independently predicted lower limb vascular complications (OR 21.0, 95% CI, 2.35-187, p=0.00064); severe (OR 27.4, 95% CI, 2.81-275, p=0.0045)	C
Martin et al PDI 1996 (34)	Prevalent CAPD patients at a single center	52	Retrospective, cross-sectional, observational cohort study	Medical records search for symptoms, arteriography and Doppler studies to determine PAD prevalence	Not applicable	Prevalence of PAD: 29% (80% in diabetics)	C
Liu et al PDI 2009 (35)	Prevalent CAPD patients stable ≥3 months at a single Taiwanese center in 2005	153	Prospective, longitudinal observational cohort study	Prevalence of PAD Predictors of PAD Patient survival Technique survival	30 months	Prevalence of PAD: 20% (33% in diabetics) (33% of PAD symptomatic) PAD associated with older age, diabetes mellitus, pre-existing cardiovascular disease, lower total Kt/V, lower renal Kt/V, lower total and renal creatinine clearance, lower serum albumin, higher serum triglyceride 30 month survival lower in PAD vs non-PAD (33.3% vs 77.0%, p<0.001) (HR 0.024, 95% CI, 0.873-0.975) 30 month technique survival lower in PAD vs non-PAD (33.3% vs 77.0%, p<0.001) (HR 0.920, 95% CI, 0.868-0.972)	B

Kuang et al Vasc Health Risk Manag 2012(36)	Point-prevalent PD patients >60 years old on PD >3 months with no heart failure, recent (within 1 month) peritonitis or atrial fibrillation at a single Chinese center	69	Retrospective, cross-sectional observational cohort study	Prevalence of PAD Predictors of PAD	-	Prevalence of PAD: 32% (47% in diabetics) (41% symptomatic) PAD independently predicted by lower serum albumin and lower residual Kt/V	C
Lee et al BMC Nephrol 2012(37)	Point-prevalent ESRD patients on either PD or HD at a single Taiwanese center in 2007	484 (104 on PD)	Retrospective, cross-sectional observational cohort study	Prevalence of PAD Predictors of PAD	-	Prevalence of PAD: 4.8% in PD, 21.8% in HD PAD independently predicted by older age and diabetes mellitus	C
Tian et al Blood Purif 30:50-5, 2010(38)	Period-prevalent CAPD population at a single Chinese center 2008-2009 (on PD >3 months)	343	Prospective observational cohort study	Prevalence of PAD Predictors of PAD	-	Prevalence of PAD: 27% (45% >70 yo) (71% in diabetics) PAD independently predicted by diabetes, diastolic blood pressure, extracellular/intracellular water ratio and lnCRP	C
Liu et al Nephrology 2011(39)	Period-prevalent CAPD population with residual GFR >1 mL/min/1.73m^2 at a single Chinese center in 2005 (on PD >3 months)	74	Prospective longitudinal observational cohort study	Residual renal function decline	1 year	Higher ABI independently predicted a slower rate of residual renal function decline (OR per 0.01 unit increase in ABI, 0.896, 95% CI 0.840-0.955)	C
An et al Int Urol Nephrol 2010(25)	Stages 3-5 CKD, HD or PD patients at a single Korean center	102 (20 PD, 58 HD, 24 CKD)	Prospective, cross-sectional observational	Vascular calcification (length of calcification of dorsalis pedis artery on plain	-	Prevalence of clinical PAD: 20% (all diabetics) Prevalence of vascular calcification: 50% (45% Score 1, 55% Score 2)	C

			cohort study	radiograph) Color Doppler ultrasonography (>30% occlusion femoral or popliteal artery) ABI		Prevalence of >30% occlusion femoral or popliteal artery: 40% (10% if no vascular calcification, 70% if vascular calcification) ABI not discriminatory between those with or without vascular calcification or clinical PAD	
Huang et al Ren Fail 2007(27)	146 ESRD patients on PD ≥4 months at a single Taiwanese center	146	Cross-sectional observational cohort study	ABI TBI	-	Prevalence of ABI <0.9: 6% Prevalence of TBI <0.6: 5% ABI correlated with TBI (p<0.001, r=0.335)	C
Leskinen et al Am J Kidney Dis 2002(7)	136 CKD patients (59 pre-dialysis, 36 dialysis, 41 renal transplant) and 59 controls (orthopedic patients) at a single Finnish center	136 (36 dialysis – PD proportion not specified)	Prospective, non-randomized, controlled study	ABI TBI Claudication questionnaire (WHO/Rose)		Prevalence of intermittent claudication: 7% (3% in dialysis patients) (33% patients with claudication did not have PAD) ABI ≤0.9: 31% in dialysis patients TBI ≤0.6: 19% in dialysis patients PAD (low ABI or TBI): 31% in dialysis patients ABI ≥1.3: 42% in dialysis patients	B

CAPD = continuous ambulatory peritoneal dialysis; PAD = peripheral arterial disease; ABI = ankle brachial index; CI = confidence interval; HR = hazard ratio; OR = odds ratio; PD = peritoneal dialysis; ESRD = end stage renal disease; HD = hemodialysis; CKD = chronic kidney disease; TBI = toe brachial index

B. Treatment – General measures

In the general population, the ACC/AHA guidelines (18) and TASC II guidelines (19) each variously recommend that individuals with PAD should receive multidisciplinary medical therapy to reduce pain, minimize cardiovascular risk and avoid limb loss, including smoking cessation, antiplatelet therapy (aspirin and/or clopidogrel), lipid lowering therapy, cilostazol and supervised exercise therapy. In the presence of critical lower limb ischemia, revascularization with either angioplasty or surgical bypass is the preferred treatment option. Although high level evidence for these interventions is lacking in CKD patients (particularly those receiving dialysis), the NKF-KDOQI guidelines recommend that CKD patients with PAD should be treated in the same manner as the general population (15). However, the KDIGO CKD Guidelines (17) and the KDIGO Cardiovascular update (16) acknowledge that evidence-based therapies for PAD are lacking in patients with CKD. This section aims to review the available evidence in CKD patients, with a particular emphasis on PD patients.

Guideline 3.4.4: We suggest peritoneal dialysis patients with non-critical peripheral arterial disease receive supervised exercise therapy. (2C)

Rationale

Exercise therapy has been found in general PAD patient populations with intermittent claudication to have equivalent effectiveness to percutaneous luminal angioplasty in a meta-analysis of 8 randomized controlled trials (RCTs)(40) and to produce significantly improved walking time, pain-free walking distance and maximum walking distance (but not mortality, amputation, peak exercise calf blood flow or ABI) compared with usual care or placebo in a meta-analysis of 22 trials involving 1200 participants (41). There are no RCTs to test the efficacy of exercise therapy in CKD patients with PAD. However, given the overall benefits of exercise in CKD patients, the working group felt that a recommendation statement, albeit weak, should be drawn on prescribing supervised exercise therapy in PD patients with non-critical PAD.

Guideline 3.4.5: **We suggest peritoneal dialysis patients with peripheral arterial disease be considered for antiplatelet therapy. (2D)**

Rationale

Although antiplatelet therapy has been shown to be beneficial in reducing the risks of cardiovascular events in patients with PAD in the general population (42), its effects in CKD patients remain uncertain due to the significant contribution of calcific arteriosclerosis as well as atherosclerosis to PAD and because of the heightened bleeding risks in this population. Indeed, a recent systematic review and meta-analysis (43, 44) of adult patients with CKD found that in individuals with acute coronary syndromes or requiring percutaneous coronary interventions, antiplatelet therapy had little or no effect on myocardial infarction, stroke, cardiovascular mortality or all-cause mortality, but was associated with an increased risk of minor bleeding and an uncertain risk of major bleeding [Evidence Review Table 1]. For CKD

patients with stable or no cardiovascular disease, antiplatelet therapy was associated with a reduction in myocardial infarction, and increased risk of minor bleeding and uncertain effects on stroke, all-cause mortality, cardiovascular mortality and major bleeding [Evidence Review Table 1]. The results of this systematic review were significantly limited by the variable definitions used for minor and major bleeding and by the fact that they were derived from post hoc analyses of trials of broader populations and are mostly hypothesis-generating. In addition, none of these studies examined the use of anti-platelet therapy as a treatment of PAD in PD patients. The NKF-KDOQI guidelines (15) recommend CKD patients with PAD should be treated with antiplatelet agents, as in the general population. However, the KDIGO Cardiovascular update (16) emphasizes that evidence is lacking and that bleeding risks may be increased. Given the current lack of RCTs and a high degree of uncertainty regarding the risk versus benefit associated with the use of antiplatelet therapy in PD patients with PAD, the workgroup felt that any recommendation on the use of anti-platelet therapy in PD patients with PAD is very weak and that patients be informed of the lack of clear efficacy on cardiovascular morbidity and mortality and a potentially increased risk of bleeding before prescribing anti-platelet therapy.

Guideline 3.4.6: We suggest peritoneal dialysis patients with peripheral arterial disease, particularly those with diabetes mellitus, receive multidisciplinary foot care involving regular foot examination, treatment by a podiatrist/chiropodist and education about home foot care (including use of hydrating lotions and appropriate foot wear). (2C)

Rationale

Diabetes is a major predictor of PAD in PD patients and the majority of diabetic PD patients have PAD (38) [Screening Section Evidence Review Table 1]. Five low quality studies of diabetic CKD patients (including 3 studies exclusively in dialysis patients) have reported reductions in amputations following institution of multidisciplinary preventive foot care programs [Evidence Review Table 2]. In the quasi-randomized controlled study by McMurray et al, use of an intensive diabetes care education and management program in the dialysis unit was associated with a statistically lower hospitalization rate for diabetes and peripheral vascular- and infection-related admissions (45). The Australian Evidence-Based Guideline on Prevention, Identification and Management of Foot Complications in Diabetes (46) recommends that “podiatry review is an important component of a foot protection program” in patients with diabetes mellitus based on evidence that such prevention strategies improved life expectancy and quality-adjusted life years reduced foot ulcer rates and amputations, and were cost-effective in intermediate and high risk feet (47). The KDIGO CKD Guidelines recommend that “adults with CKD and diabetes are offered regular podiatric assessment (2A)” (17). Given the high prevalence of PAD and subclinical PAD in diabetic PD patients, the high rates of adverse clinical outcomes in such patients and the evidence supporting regular podiatry review in the general diabetes population, the workgroup felt that a weak recommendation should be given for regular podiatry assessment for PD patients with diabetes.

Other Potential Therapies

Smoking cessation

There are no RCTs of smoking cessation in patients with PAD, either with or without CKD. A number of non-randomized studies in general PAD patient populations have variously reported associations between smoking cessation and improvements in ankle pressures, walking distance, exercise tolerance, rest pain, cardiovascular events and mortality (48-50) [Evidence Review Table 3]. Given the strong association between smoking and PAD and that smoking cessation has been shown to be also associated with other significant health benefits, the working group felt that a strong level of recommendation should be given for smoking cessation in PD patients with PAD despite the lack of RCTs to test the efficacy of smoking cessation on PAD in PD patients.

Cholesterol lowering

There have been no RCTs to date which have evaluated the safety and efficacy of lipid-lowering therapies specifically in the treatment of PAD in CKD patients. In the Studies of Heart And Renal Protection (SHARP) trial (51) [Evidence Review Table 4], approximately 5% of participants were receiving PD and 15% had previous PAD [Evidence Review Table 1]. This trial demonstrated a significant benefit of ezetimibe 10 mg/simvastatin 20 mg daily on the primary composite endpoint of major atherosclerotic events compared with matching placebo (relative risk [RR], 0.83, 95% confidence intervals [CI], 0.74 - 0.94, p=0.002). Although sub-group analysis of patients undergoing PD at enrolment showed no significant effect of lipid-lowering (RR, 0.70, 95% CI 0.46-1.08), notably, this study was not adequately powered for detecting a significant difference in the subgroup of PD patients. In secondary analyses, the intervention group experienced a significant reduction in non-coronary revascularization procedures (RR, 0.79, 95% CI, 0.68 - 0.93). The other 2 major trials of lipid-lowering treatments, Die Deutsche Diabetes Dialyse Studie (4D) (52) and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) (53), involved hemodialysis patients and did not demonstrate a significant benefit of statin therapy on the primary composite cardiovascular end-point [Evidence Review Table 2]. The prevalence of prior PAD was not specified in the AURORA study, but was cited as 45.7% in the intervention arm of the 4D trial (which was comprised solely of diabetic hemodialysis patients).

A subsequent systematic review of RCTs of lipid-lowering therapy in CKD patients between 2000–2011 by Upadhyay et al (54) found that lipid lowering significantly reduced the risks of all-cause mortality, cardiovascular events and myocardial infarction. However, a more comprehensive systematic review of RCTs comparing statins with placebo, no treatment or another statin in adults with CKD from the inception of Cochrane and EMBASE databases until February 2012 found that the benefits of therapy on all-cause mortality, cardiovascular mortality, cardiovascular events and myocardial infarction was restricted to CKD patients not on dialysis, and were not evident in CKD patients receiving dialysis (55) (Evidence Review Table 2). On the basis of these findings, the KDIGO Clinical Practice Guideline for Lipid

Management in CKD, which has recently been released suggests that statins or statin/ezetimibe not be initiated in adults with CKD stage 5D (2A). The guidelines also suggest that, in patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, these agents should be continued (2C). No recommendations are made for patients with established cardiovascular disease, including PAD. On the other hand, the NKF-KDOQI Guidelines (15) recommend lipid-lowering therapy in CKD patients with PAD. Putting together the current available evidence on the efficacy of statins on cardiovascular outcomes and lack of RCTs examining specifically the efficacy of statins on PAD related outcomes, the workgroup felt that recommendation on the use of either statin or statin/ezetimibe as a standard treatment for PAD in PD patients is very weak.

Cilostazol

Cilostazol is a selective inhibitor of phosphodiesterase 3, which has vasodilatory and antiplatelet actions. It has been shown in the general PAD population to be associated with significant improvement in maximum and pain-free walking distances (56). The TASC II guidelines (19) recommend that cilostazol should be used as the first-line pharmacotherapy agent in patients with intermittent claudication. Pharmacokinetic studies in patients with mild, moderate and severe renal impairment suggest that dosage reduction is not required in CKD (57). Very few studies have examined the efficacy of cilostazol in dialysis patients with PAD and none of them were prospective RCTs [Evidence Review Table 5]. The workgroup felt that it is premature to make recommendations regarding the use of this class of drug in PD patients with PAD. In addition, caution should be exercised in patients with congestive heart failure of any grade or severity.

Naftidofuryl oxalate

Naftidofuryl oxalate is a vasodilatory agent that has also been shown in the general PAD population to be associated with significant improvement in maximum and pain-free walking distances (56). As with cilostazol, the pharmacokinetic profile of oral naftidrofuryl oxalate does not appear to be significantly influenced by renal impairment, even in patients with creatinine clearances <20 mL/min (58). There are so far no studies evaluating the safety and efficacy of naftidrofuryl oxalate in CKD patients with PAD. The work group felt that it may be premature to make any recommendations regarding the use of this drug in treating PD patients with PAD. We felt that this should form the scope of future research in PD patients with PAD.

Revascularization

Revascularization (percutaneous transluminal angioplasty $\pm$ stenting or surgical bypass) is not infrequently employed as a limb-sparing procedure in patients with critical limb ischemia. There are currently no RCTs evaluating the relative benefits and safety of angioplasty versus surgical bypass or of the timing of revascularization versus early amputation. Percutaneous angioplasty has been promoted for patients with proximal lesions and limited distal disease . Most studies have demonstrated appreciably poorer outcomes of revascularization in PAD patients with ESRD compared with those with normal kidney function, with higher rates of wound

infection, gangrene, prolonged hospitalization, peri-procedure sepsis, amputation and mortality (23). Limited evidence suggests that patients undergoing primary amputation have poorer survival than those undergoing primary revascularization (59) and that patients receiving angioplasty have worse outcomes than those receiving surgical bypass, although these results are likely confounded by indication [Evidence Review Tables 6 & 7]. The optimal management of PD patients with critical limb ischemia therefore remains unclear. We suggest that primary angioplasty, primary surgical revascularization or primary amputation are all reasonable therapeutic options for the treatment of critical limb ischemia in PD patients, depending on individual circumstances, and that the preferred management strategy remains unclear based on current available evidence (2C).

Evidence Review Table 1. Studies that examined antiplatelet therapy in relation to peripheral arterial disease outcomes of dialysis patients.

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Palmer et al Ann Int Med 2012 (43, 44)	Systematic review of RCTs comparing antiplatelet treatment with placebo or no treatment in adults with CKD who had either acute coronary syndromes or were undergoing revascularization or had stable or no cardiovascular disease from inception of Cochrane and EMBASE databases until November 2011	9 RCTs involving 9969 participants with acute coronary syndromes or undergoing percutaneous coronary intervention; 31 RCTs involving 11,701 patients with stable or no cardiovascular disease	Systematic review and meta-analysis	All-cause mortality Cardiovascular mortality Myocardial infarction Bleeding (PAD outcomes not assessed)	Not applicable	No effect on myocardial infarction in CKD patients with acute coronary syndrome or undergoing percutaneous coronary intervention (7 RCTs, 5261 participants; RR 0.89, 95% CI 0.75-1.05) but reduction in CKD patients with stable or no cardiovascular disease (10 RCTs, 9133 participants; RR 0.66, 95% CI 0.51-0.87) Uncertain effect on stroke in CKD patients with acute coronary syndrome or undergoing percutaneous coronary intervention (1 RCT, 411 participants; RR 0.51, 95% CI 0.09-2.77) and in CKD patients with stable or no cardiovascular disease (10 RCTs, 9133 participants; RR 0.66, 95% CI 0.16-2.78) No effect on all-cause mortality in CKD patients with acute coronary syndrome or undergoing percutaneous coronary intervention (8 RCTs, 9347 participants; RR 0.89, 95% CI 0.75-1.05) and uncertain effect in CKD patients with stable or no cardiovascular disease (21 RCTs, 10632 participants; RR 0.87, 95% CI 0.61-1.24) Uncertain effects on cardiovascular mortality in CKD patients with acute coronary syndrome or undergoing percutaneous coronary intervention (2 RCTs, 4498 participants; RR 0.96, 95% CI 0.79-1.16) and in CKD patients with stable or no cardiovascular disease (16 RCTs, 8706 participants; RR 0.91, 95% CI 0.60-1.36) Increased risk of major bleeding in CKD patients with acute coronary syndrome or undergoing percutaneous coronary intervention (9 RCTs, 9863 participants; RR 1.40, 95% CI 1.07-1.86) and uncertain effects in CKD patients with stable or no cardiovascular disease (18 RCTs, 10230 participants; RR 1.29, 95% CI 0.69-2.42) Increased risk of minor bleeding in CKD patients with acute coronary syndrome or undergoing percutaneous coronary intervention (9 RCTs, 9863 participants; RR 1.47, 95% CI 1.25-1.72) and in CKD patients with stable or no cardiovascular disease (18 RCTs, 10230 participants; RR 1.70, 95% CI 1.44-2.02)	A

RCTs = randomized controlled trials; CKD = chronic kidney disease; RR = relative risk; CI = confidence interval

Evidence Review Table 2. Studies that examined preventive foot care in relation to peripheral arterial disease outcomes of dialysis patients.

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Lipscombe et al Perit Dial Int (60)	PD patients with diabetes mellitus enrolled in the PD program at a Canadian centre between January 1997 and December 1999	132	Retrospective chart review	Time to first amputation or death	Not specified	Being seen by a chiropodist was protective against first amputation or death (adjusted HR 0.39, 95% CI 0.05-0.73)	C
McMurray et al Am J Kidney Dis 2002 (45)	PD or HD patients with diabetes mellitus managed at a single centre in the United States	83 (13 PD)	Quasi-RCT (allocated according to dialysis day schedule) of intensive education and care management (including regular foot checks and care) versus usual care	Foot risk category Amputations	1 year	Foot risk score unchanged in study group (2.2 to 2.0) but worsened in control group (2.7 to 3.3, $p<0.05$) Amputations significantly lower in the study group (13% vs 0%, $p<0.05$)	C
Griffiths et al Surg Gynecol Obstet 1992 (61)	Diabetic patients attending a foot clinic with foot ulcers at a single centre in the United States since 1985	171	Retrospective observational cohort study comparing patients who developed ulcers during clinic attendance (Group 1, n=21) with those who were referred with foot ulcers (Group 2, n=150)	Number of lesions Mean healing time Amputation rate	Not specified	Lower number of lesions in Group 1 (1.52 ± 0.98 vs 2.06 ± 1.33, $p<0.05$) Shorter mean healing time in Group 1 (111.9 ± 80.5 days vs 160.5 ± 151.3 days, $p<0.05$) Fewer major or partial foot amputations in Group 1	C
Foster et al Diabet Med 1995 (62)	Diabetic patients attending a special foot clinic compared with historical controls at a single centre in the United Kingdom	50	Prospective, pre- and post-intervention study	Gangrene Major amputations	Not specified	Lower number of patients with gangrene or major amputations compared with historical controls	C

Prentice et al CANNT J 2009 (63)	HD patients with foot ulcers from 3 Canadian HD units in 2005	57	Prospective, longitudinal observational cohort study following implementation of Association of Ontario Diabetic Foot Management Best Practice Guideline	Number of wounds Grade of wounds New amputations	15 months	Significant reductions in number ($p<0.05$) and grade ($p<0.01$) of wounds over time. 5 new amputations	C

PD = peritoneal dialysis; HD = hemodialysis; RCT = randomized controlled trial; HR = hazard ratio; CI = confidence interval

Evidence Review Table 3. Studies that examined smoking in relation to peripheral arterial disease outcomes of dialysis patients.

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Foley et al KI 2003(64)	Patients initiating dialysis in 1996-1997 in USRDS Dialysis Morbidity and Mortality Wave 2 (all patients initiating PD and one-fifth of patients initiating HD)	4024 (48.8% PD)	Prospective inception cohort	New-onset cardiovascular events, Death	Mean 2.2 years	Active smoking (but not former smoking) status associated with an increased risk of new-onset PAD (adjusted HR, 1.68, 95% CI 1.27-2.22, $p<0.001$)	C

PD = peritoneal dialysis; HD = hemodialysis; USRDS = United States Renal Data System; HR = hazard ratio; CI = confidence interval; PAD = peripheral arterial disease

Evidence Review Table 4. Studies that examined lipid-lowering therapy in relation to peripheral arterial disease outcomes of dialysis patients.

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Baigent et al Lancet 2011 (51)	Patients ≥40 years old with CKD (>1 prior serum creatinine ≥150 μmol/L in men or ≥130 μmol/L in women	4650 (496 or 5% on PD at enrollment; 1393 or 15% had PAD)	Multi-centre, multi-country, prospective, double-blind, parallel-arm RCT of simvastatin/ezetimibe 20/10 mg vs matching placebo	Primary composite end-point was time to first major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure)	4.9 years	17% reduction in major atherosclerotic events (RR, 0.83, 95% CI 0.74-0.94, p=0.002) No significant effect on non-fatal myocardial infarction or death from coronary artery disease (RR, 0.92, 95% CI 0.76-1.11, p=0.37) Significant reduction in non-hemorrhagic stroke (RR, 0.75, 95% CI 0.60-0.94, p=0.01) Significant reduction in arterial revascularization procedures (RR, 0.79, 95% CI 0.68-0.93, p=0.0036). Sub-group analysis of primary end-point in PD patients showed no significant effect of lipid-lowering (RR, 0.70, 95% CI 0.46-1.08) but the study was not powered for this subgroup analysis	A
Wanner et al NEJM 2005 (52)	Patients 18-80 years old with type 2 diabetes mellitus on HD < 2years at 178 centers in Germany	1255	Multi-centre, prospective, double-blind, parallel-arm RCT of atorvastatin 20 mg od vs matching placebo	Composite primary endpoint of death from cardiac causes, nonfatal myocardial infarction and stroke	4 years	No significant effect of atorvastatin on primary endpoint (RR, 0.92, 95% CI, 0.77-1.10, p=0.37) versus placebo. No significant effect of atorvastatin on individual components of primary endpoint, except an increased risk of fatal stroke (RR, 2.03, 95% CI, 1.05-3.93, p=0.04) was observed versus placebo. Significant reduction of all cardiac events (RR, 0.82, 95% CI, 0.68-0.99, p=0.03) in	A

						atorvastatin group versus placebo. No effect on cerebrovascular events (RR, 1.12, 95% CI, 0.81-1.55, p=0.49) No effect on mortality (RR, 0.93, 95% CI, 0.79-1.08, p=0.33)	
Fellstrom et al NEJM 2009 (53)	Men and women 50-80 years old with ESRD treated with hemodialysis or hemofiltration for ≥3 months at 280 centers in 25 countries	2776	Multi-centre, multi-country, prospective, double-blind, parallel-arm RCT of rosuvastatin 10 mg od vs matching placebo	Composite primary endpoint of death from cardiac causes, nonfatal myocardial infarction and nonfatal stroke	3.8 years	No significant effect on primary endpoint (HR, 0.96, 95% CI 0.84-1.11) or on any individual components of this endpoint No significant effect on all-cause mortality (HR 0.96, 95% CI 0.86-1.07)	A
Upadhyay et al Ann Int Med 2012 (54)	Systematic review of RCTs comparing ≥1 lipid-lowering agents or lifestyle modification strategies with other lipid-lowering treatments, placebo or no treatment in CKD patients from January 2000 through November 2011	18 RCTs (5 CKD, 13 CKD sub-group analyses)	Systematic review and meta-analysis	All-cause mortality Cardiovascular events Myocardial infarction Renal outcomes	Not applicable	Lipid lowering reduced all-cause mortality (15 RCTs; RR 0.91, 95% CI 0.83-0.99; p=0.031), although significant heterogeneity (I^2=59%; p=0.003) No effect on cardiovascular mortality (4 RCTs; RR 0.96, 95% CI 0.87-1.06, p=0. 41) Reduced cardiovascular events (9 RCTs; RR 0.78, 95% CI 0.71-0.86, p<0.001). Reduction of myocardial infarction (9 RCTs; RR 0.74, 95% CI 0.67-0.81, p<0.001) No effect on ischemic and hemorrhagic stroke (9 RCTs; RR 0.90, 95% CI 0.63-1.27, p=0.55). No effect on prevention of ESRD (3 RCTs; RR 0.97, 95% CI 0.90-1.05, p=0.49) No effect on composite of ESRD, ≥25% decrease in eGFR or doubling serum creatinine (7 RCTs; RR 0.91, 95% CI 0.78-	A

						1.06, p=0.21) No evidence of increased risk of adverse events	
Palmer et al Ann Int Med 2012 (55)	Systematic review of RCTs comparing statins with placebo, no treatment or another statin in adults with CKD from inception of Cochrane and EMBASE databases until February 2012	80 RCTs comprising 51,099 participants (39820 CKD patients not on dialysis; 7982 patients receiving dialysis; 3297 kidney transplant recipients)	Systematic review and meta-analysis	All-cause mortality Cardiovascular mortality Cardiovascular events Adverse events	Not applicable	Statins reduced all-cause mortality in non-dialysis CKD patients (RR 0.81, 95% CI 0.74-0.88) but not dialysis patients (RR 0.96, 95% CI 0.88-1.04) Reduced cardiovascular mortality in non-dialysis CKD patients (RR 0.78, 95% CI 0.68-0.89) but not dialysis patients (RR 0.94, 95% CI 0.82-1.07) Reduced cardiovascular events in non-dialysis CKD patients (RR 0.76, 95% CI 0.73-0.80) but not dialysis patients (RR 0.95, 95% CI 0.87-1.03) Reduced myocardial infarction in non-dialysis CKD patients (RR 0.55, 95% CI 0.42-0.72) but not dialysis patients (RR 0.87, 95% CI 0.71-1.07) No evidence of increased risk of adverse events	A

CKD = chronic kidney disease; PAD = peripheral arterial disease; RCTs = randomized controlled trials; RR = relative risk; CI = confidence interval; ESRD = end stage renal disease; eGFR = estimated glomerular filtration rate

Evidence Review Table 5. Studies that examined cilostazol in relation to peripheral arterial disease outcomes of dialysis patients.

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Shiohira et al Clin Exp Nephrol 2011 (65)	HD patients with PAD and restless legs syndrome at a single Japanese center	45 HD patients receiving cilostazol and 22 controls	Prospective, non-randomized controlled study	PAD score on self-administered questionnaire	12 months	No significant change in PAD score on multivariable analysis	C
Ishii et al Clin Ther 2010 (66)	HD patients who underwent successful percutaneous transluminal angioplasty for femoropopliteal disease at a single Japanese center	358 consecutive lesions in 174 HD patients (cilstazol 100 mg bd 121 lesions in 61 patients; controls 237 lesions in 113 patients)	Retrospective chart review (non-randomized)	Cumulative patency, as measured by event-free rate 6 years after PTA (event = restenosis >50% of vessel diameter in femoropopliteal lesions)	≤6 years	Cilostazol use associated with Higher 6-year cumulative patency (59.5% vs 50.6%, p=0.005), revascularization-free survival (65.6% vs 50.4%, p=0.013) and amputation-free survival (88.5% vs 79.6%, p=0.047)	C
Ishii et al Clin J Am Soc Nephrol 2008 (67)	HD patients who underwent successful percutaneous transluminal angioplasty for iliac and/or femora-popliteal disease at a single Japanese center	372 consecutive lesions in 193 HD patients (cilstazol 100 mg bd 130 lesions in 71 patients; controls 242 lesions in 122 patients)	Retrospective chart review (non-randomized)	5-yr patency rate (angiographic luminal diameter >50%)	5 years	Higher 5-yr patency rate in cilostazol group (52.4% vs 32.9%, p=0.0005). Cilostazol independent predictor of preventing restenosis (HR 0.50, 95% CI 0.26-0.87, p=0.014)	C

HD = hemodialysis; PAD = peripheral arterial disease; PTA = percutaneous transluminal angioplasty; HR = hazard ratio; CI = confidence interval

Evidence Review Table 6. Studies that examined angioplasty in relation to peripheral arterial disease outcomes of dialysis patients.

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Graziani et al Nephrol Dial Transplant 2007 (68)	HD patients with critical limb ischemia treated by percutaneous transluminal angioplasty	107 patients with 132 ischaemic limbs	Prospective observational cohort study	Cumulative limb salvage rate	22 months	Cumulative limb salvage rate 86% at 1 year, 84% at 2 years, 84% at 3 years and 62% at 4 years	C
Nishibe et al Int Angiol 2009 (69)	Dialysis patients with PAD and superficial femoral artery lesions treated by angioplasty and stent deployment	18 dialysis patient limbs (25 control limbs)	Retrospective observational cohort study	Primary patency Primary assisted patency Limb salvage Survival	25 +/-15 months (range, 1.0–78.2)	Comparable outcomes between the dialysis and non-dialysis patients	C
Kumada et al Nephrol Dial Transplant 2008 (70)	HD and non-HD patients who underwent successful angioplasty for PAD at a single Japanese center	118 HD patients with 205 lesions vs 108 non-HD patients with 143 lesions	Prospective, non-randomized study	5-yesr primary patency, limb salvage and survival	32±21 months	HD patients experienced significantly worse 5-yr patency (57.7% vs 68%, p=0.015), limb salvage (85% vs 97%, p=0.007) and survival (61.5% vs 84.2%, p=0.01).	C
Abularrage et al J Vasc Surg 2010 (71)	920 patients undergoing percutaneous luminal angioplasty with or without stenting at a single centre in the United States	920 patients undergoing 1075 procedures	Retrospective observational cohort study	Primary patency Limb salvage Survival	34 months	Dialysis was an independent predictor of lower 5-yr primary patency (HR 1.59, 95% CI 1.10-2.33, p=0.02), limb loss (HR 2.94, 95% CI 1.39-5.00, p=0.003) and death (HR 4.24, 95% CI 2.80-6.45, p<0.001)	C

HD = hemodialysis; HR = hazard ratio; CI = confidence interval

Evidence Review Table 7. Studies that examined surgical revascularization in relation to peripheral arterial disease outcomes of dialysis patients.

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Kimura et al Eur J Endovasc Surg 2003 (72)	ESRD patients with critical limb ischemia	28 limbs in 22 ESRD patients vs 65 limbs in 57 controls	Retrospective observational cohort study	Perioperative mortality Patient survival 2-year primary patency 2-year secondary patency 2-year limb salvage	21 (range 0–65) months	Higher peri-operative mortality in ESRD (18% vs 0%, p=0.001) Lower patient survival (45% vs 85%, p<0.001) 2-year outcomes in ESRD patients vs controls were not significantly different for primary patency (76% vs 83%, p=0.12), secondary patency (85% vs 91%, p=0.06) or limb salvage (83% vs 93%, p=0.06)	C
Whittemore et al J Vasc Surg 1993 (59)	All patients with CKD (serum creatinine >2 mg/dl) who required surgical intervention for ischemic lower limbs during a 15 year period at a single center in the United Kingdom	56 patients who underwent 70 bypass procedures vs 31 patients who underwent primary major amputation	Retrospective observational cohort study	Survival	Not specified	Patients undergoing primary amputation experienced significantly lower 5-year survival than those undergoing primary bypass (9% vs 40%, p<0.004)	C
Johnson et al J Vasc Surg 1995 (73)	ESRD patients who underwent surgical revascularization at a single center in the United States	69 reconstructions in 53 ESRD patients (including 6 PD patients)	Retrospective chart review	30 day operative mortality 2-year survival 2-year primary	Not specified	30-day operative mortality 10% 2-year survival 38% 2-year primary graft patency 68%	C

				graft patency			
Leers et al J Vasc Surg 1998 (74)	ESRD patients undergoing pedal bypass grafting at a single center in the United States	41 bypasses in 34 ESRD patients	Retrospective observational cohort study	Primary patency Limb salvage Survival	13.5 months	Primary patency 62% at 1 year and 62% at 2 years Limb salvage 56% at 1 year and 50% at 2 years Survival 64% at 1 year and 52% at 2 years	C
Lantis et al J Vasc Surg 2001 (75)	ESRD patients receiving infra-inguinal bypass graft operations at a single center in the United Kingdom 1993-1999	60 ESRD patients (4 on PD vs 481 controls)	Retrospective observational cohort study	Perioperative mortality Survival Primary patency Assisted primary patency Secondary patency Limb salvage	Not specified	ESRD patients had comparable outcomes vs controls with respect to peri-operative mortality (1.3% vs 2.3%), 4-year survival (51% vs 63%), primary patency (60% vs 64%), assisted primary patency (86% vs 77%) and secondary patency (86% vs 78%) but had significantly lower limb salvage rates (77% vs 92%, $p<0.02$).	C
Ramdev et al J Vasc Surg 2002 (76)	Dialysis patients receiving lower extremity bypass for limb salvage at a single center in the United States 1990-1999	146 (5 on PD)	Retrospective observational cohort study	In-hospital mortality Peri-operative CCF Peri-operative AMI Peri-operative arrhythmia Peri-operative wound	Not specified	In-hospital mortality 5% Peri-operative CCF 2% Peri-operative AMI 3% Peri-operative arrhythmia 5% Peri-operative wound infection 10% Survival 60% at 1 year, 18% at 3year, 5% at 5 year Primary patency 84% at 1 year, 64% at 2 years	C

				infection Survival Primary patency Secondary patency Limb salvage		Secondary patency 85% at 1 year, 68% at 3 year Limb salvage 80% at 1 year, 80% at 3 year	
Reddan et al Am J Kidney Dis 2001 (77)	ESRD patients and matched controls undergoing surgical revascularization for PAD at a single center in the United States 1992-1996	20 ESRD patients (31 procedures) and 57 controls (64 procedures)	Retrospective case-control analysis (matched for age, race, gender, diabetes mellitus and hospital setting)	Survival Time to 50% limb loss Time to 50% graft patency loss	Not specified	ESRD patients had inferior median survival (1.72 vs 5.17 years, p<0.001), time to 50% limb loss (1.24 vs 5.65 years, p<0.001) and time to 50% graft patency (0.7 vs 5.5 years, p<0.05)	C

ESRD = end stage renal disease; CKD = chronic kidney disease; PD = peritoneal dialysis; PAD = peripheral arterial disease; CCF = congestive cardiac failure; AMI = acute myocardial infarction

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SECTION 5. ARRHYTHMIA

Guideline 3.5.1: We recommend all peritoneal dialysis patients undergo a 12-lead electrocardiography at initiation of dialysis and then repeat at least annually to screen for any abnormal electrical activity of the heart including atrial fibrillation. (1C)

Rationale

In the general population, the prevalence of atrial fibrillation (AF) is estimated to be approximately 1% (1). Currently, the prevalence of AF in chronic kidney disease (CKD) patients is only available in dialysis patients. On the basis of the diagnostic categories of AF reported in the United States Renal Data System (USRDS), a prevalence of 13% in patients on hemodialysis (HD) and 7% in patients undergoing peritoneal dialysis (PD) was described. Holter monitoring longitudinal studies of patients on HD showed AF in 13 to 27% of the patients (2-5). AF is highly correlated with coronary artery disease (CAD), valvular disease (particularly due to valve calcifications), myocardiac fibrosis and left ventricular hypertrophy (LVH)(5-8). Because of the strong relationship of AF to structural heart disease, it is difficult to determine whether patients have complications related to AF or to advanced structural heart disease accompanied by AF. Fluctuating levels of electrolytes during HD, as well as sympathetic nervous system activation and modulation of the renin-angiotensin system represent additional predisposing factors for AF in dialysis patients (4-8–10).

The risk of hospitalization due to AF increases linearly with the decrease in glomerular filtration rate, and it is 3.1-fold in those on dialysis compared to patients with normal renal function. The 3-year mortality rates for dialysis patients who had been hospitalized for AF were also significantly higher (53%); compared to control subjects (45%). Moreover, a longitudinal, single-center study (n = 190) reported 4-year mortality rates of 81% in dialysis patients with AF compared with 29% in those without (11). Therefore, regardless of whether AF is an independent risk factor for mortality or represents a risk predictor, we recommend that AF should be regularly screened for in all PD patients, because it indicates a markedly increased risk for comorbidities and death.

The main complication of AF is ischemic stroke. In a Japanese community-based observational study of 1,977 individuals not on dialysis (12), the hazard rate ratios for stroke in the subgroup with an estimated glomerular filtration rate between 40 and 70 ml/min was 1.9, and with <40 mL/min was 3.1 compared with those with an estimated glomerular filtration rate >70 mL/min. In the VALIANT trial that included patients with acute myocardial infarction and signs of heart failure but not on dialysis, there was a significant stepwise increase in stroke rates from 2 to 6% after 3 years with decreasing estimated glomerular filtration rate from ≥75 to <45 mL/min (13). The stroke incidence was 15% in HD patients compared with 9% in patients who had CKD and were not on HD and 2% in matched patients without. After occurrence of a stroke or transient ischemic attack, the 2-year mortality rates are dramatically increased in patients with CKD compared with those without. In a recent study, HD and PD patients had higher incidences of hospitalized ischemic stroke (102.6 and 100.1/10,000 person-years) and hemorrhagic stroke (74.7 and 59.4/10,000 person-years) in comparison to the age- and sex-matched reference cohort (42.4 and 13.0/10,000 person-years, respectively). In general, from the USRDS, there was no difference in the rates of stroke (in the presence of atrial fibrillation) between patients on HD or PD (1). However, a recent study using the HD group as the comparison group, peritoneal PD patients had a lower risk of hemorrhagic stroke (Hazard Ratio, 0.75; 95% CI, 0.58-0.96), and there was no

significant adjusted difference in risks of ischemic stroke between PD and HD patients. With regard to AF, one single-center analysis of HD patients observed thromboembolic event rates of 24% per year in those with AF compared with 5% in those with sinus rhythm, a 4.6-fold increased relative risk (11). In the USRDS (1), dialysis patients with AF had a 1.6-fold higher rate of stroke than those without AF. This was based exclusively on a 1.8-fold higher rate of ischemic strokes, whereas hemorrhagic stroke rates were similar.

Evidence Review Table 1. Studies supporting the screening for atrial fibrillation in dialysis patients

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Vazquez E, et al. Am Heart J. 2000 (3)	HD patients	190 patients	Observational	Prevalence of atrial fibrillation	1 year	In 13.6% of patients, atrial fibrillation was found; age was associated with arrhythmia (P = 0.003)	B
Abbott KC, et al. BMC Nephrol. 2003 (6)	HD and PD patients	3374 patients	Prospective, cohort study	Incidence and risk factors for hospitalized atrial fibrillation	N/A	Patients had a high incidence of atrial fibrillation.	B

HD = hemodialysis; PD = peritoneal dialysis; N/A = not available

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SECTION 6. SUDDEN CARDIAC DEATH

Guideline 3.6.1: We suggest peritoneal dialysis patients with low ejection fraction, high troponin and N-terminal pro-brain natriuretic peptide levels and those who survive a previous tachyarrhythmic cardiac arrest be considered at high risk for sudden cardiac death. (2C)

Rationale

Sudden cardiac death (SCD) is common in peritoneal dialysis (PD) patients. Within the limitations of the current definition in diagnosing SCD and difficulty in verifying death as sudden cardiac death, SCD is still the most common cause of cardiovascular death, accounting for around 25% of all deaths (1). Drawing on recommendations relating to identifying high-risk patients and therapeutic approaches in preventing SCD remain extremely challenging in PD patients, due to lack of a good understanding of the underlying etiology and lack of clinical trials that examined SCD as a primary endpoint (2). The published literature relating to chronic kidney disease (CKD) patients is very limited in general, and almost non-existent in PD patients. The situation is further handicapped by the lack of a universally applied definition of sudden cardiac death, lack of information on the type of arrhythmia and circumstances preceding SCD and a complete deficiency of randomized clinical trials (RCTs)that examined the efficacy of various therapeutic strategies in relation to SCD in this population. The lack of recurrent circulatory stress, dialysis induced cardiac ischemia (3), electrolytic shifts (4) and acute change in volume status suggest knowledge in relation to SCD in hemodialysis patients (HD) may not be applicable to PD patients.

Studies predicting the risk of SCD in PD patients are limited. One case control study containing only 24 patients with identified episodes of sudden cardiac death, identified smoking, aspirin use and low residual renal function as being associated with an increased risk of sudden cardiac death. But the study is underpowered and regarded of very low quality (5).

Heart failure is an important risk factor for SCD in both the general population and HD patients but may be difficult to differentiate from chronic volume overload in PD patients. Assessment of ventricular systolic function by ejection fraction may also be of limited use as it is affected by volume status. In addition, PD patients have a high incidence of heart failure with preserved ejection fraction (6) and heart failure with preserved ejection fraction is also associated with an increased risk of SCD (6). Wang et al. performed a 5-year prospective study in 230 end-stage renal disease patients receiving PD treatment, aiming to determine the role of echocardiography and the additional value of serum biomarkers in predicting sudden cardiac death. In the multivariable Cox regression analysis considering clinical, biochemical, dialysis, and echocardiographic parameters, left ventricular systolic dysfunction emerged as the most significant predictor of sudden cardiac death. An ejection fraction cutoff below 48% was associated with a specificity of 78.6% and a sensitivity of 57.7% in predicting sudden cardiac death. In the combined echocardiography and biomarker-based multivariable Cox regression model, N-terminal pro-brain natriuretic peptide lost significance to left ventricular ejection fraction, whereas cardiac troponin T retained significant association with SCD independent of echocardiographic parameters (7). In another study in HD patients, worsening of cardiac function was the strongest predictor of SCD(8). There is also suggestion from a post-hoc analysis of a randomized controlled trial in diabetic HD patients showing that poor glycemic control was associated with an increased risk of SCD(9). In addition, studies performed in HD patients, which may not be applicable to PD patients, showed that dialysate concentration and changes in serum calcium were associated with SCD(10). Interaction of C reactive protein and lipoproteins and also wasting (11) were associated with SCD in dialysis patients [Evidence Review Table 1].

It is unclear whether these results are applicable to PD patients. Pun et al also showed in a retrospective analysis that dialysis patients who survived an episode of tachyarrhythmic cardiac arrest had a strong indication of future risk of SCD(9), but at present it is not known the exact type of tachyarrhythmias in this setting, or whether the tachyarrhythmia is amenable to defibrillation therapy.

Guideline 3.6.2: We suggest beta blockers be considered for primary prevention of sudden cardiac death in high risk peritoneal dialysis patients. (2D)

Rationale

There are currently no randomized controlled trials that examined the effectiveness of various anti-arrhythmic agents in preventing SCD in PD patients, although some studies from CKD and HD patients suggest beta blockers may be associated with reduced rates of SCD (12, 13, 14); however, none of the studies examined SCD as the primary endpoint. The usefulness of beta blockers in preventing SCD remains to be confirmed in the PD population [Evidence Review Table 2].

Evidence Review Table 1. Studies showing the high prevalence and predictors of sudden cardiac death

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Pun P. et al. Clin J Am Soc Nephrol. 2012 (2)	HD patients	363	Retrospective cohort study	SCD	12 years	SCD common, 83% events were witnessed (p<0.001)	C
Wang AY, et al. Hypertension. 2010 (7)	PD patients	117 men 113 women	Prospective observational cohort study	SCD	5 years	Total: 115 deaths 28 deaths attributed to SCD (24%)	B
Paoletti E, et. al. Nephrol Dial Transplant 2004 (8)	HD patients	123	Cohort study	Specific factor that might be associated with a higher risk of SCD	10 years	Worsening of LVH is the strongest predictor of sudden death (p=0.0030)	C
Drechsler C, et al. Circulation 2009 (9)	HD patients	1255	Post-hoc analysis of a prospective randomized controlled trial	SCD	Median: 4 years	Glycosylated hemoglobin (every 1% increase) was strongly associated with sudden cardiac death	C
Pun PH et. al. Clin J Am Soc Nephrol 2013 (10)	HD patients	43,200	Case-control study	Influence of serum Ca, dialysate Ca, and QT interval-prolonging medications on the risk of sudden cardiac arrest	3 years	Low Ca dialysate,2.5 mEq/L (odds ratio=2.00, 95% confidence interval=1.40–2.90), higher corrected serum Ca (odds ratio=1.10, 95% confidence interval=1.00–1.30), and increasing serum dialysate Ca gradient (odds ratio=1.40, 95% confidence interval=1.10–1.80) were associated with increased risk of sudden cardiac arrest	B
Drechsler C, et. al. Am J Kidney Dis. 2011 (11)	HD patients	1,255	Prospective cohort study.	Risks of SCD, MI, stroke, combined cardiovascular events, deaths due to infection, and all-cause mortality	4 years	Patients with severe wasting had significantly increased risks of SCD (adjusted HR, 1.8; 95% CI, 1.1-3.1), all-cause mortality (adjusted HR, 1.8; 95% CI, 1.4-2.4), and deaths due to infection (adjusted HR, 2.3; 95% CI, 1.2-4.3). In contrast, MI was not	C

						affected.	

HD = hemodialysis; PD = peritoneal dialysis; N/A = not available; SCD = sudden cardiac death, LVH = left ventricular hypertrophy; Ca = calcium; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction

Evidence Review Table 2. Studies analyzing the impact of primary prevention with beta blockers

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Cice G, et al. J Am Coll Cardiol 2003 (12)	HD patients	114	Prospective, placebo-controlled trial	Sudden cardiac death (2° endpoint of study)	2 years	Carvedilol reduced morbidity and mortality in dialysis patients with dilated cardiomyopathy compared to placebo	B
Pun PH, et al. Clin J Am Soc Nephrol 2007 (13)	HD patients	729	Nested case-control	Survival after cardiac arrest	N/A	Medications may improve the chances of survival after cardiac arrest.	B
Tangri N. et al. Am J Kidney Dis. 2011. (14)	HD patients	1,747	Post hoc analysis of HEMO Study.	Beta blockers for the prevention of SCD	2 years	There was a significant interaction between beta blocker use and SCD (interaction *P* 0.03) in patients with (cause-specific HR, 0.65; 95% CI, 0.42-1.01) and without IHD (cause-specific HR, 1.61; 95% CI, 0.92-2.80).	C

IHD = intermittent hemodialysis; PD = peritoneal dialysis; N/A = not available; SCD = sudden cardiac death; LVH = left ventricular hypertrophy; HR = hazard ration; CI = confidence interval

Guideline 3.6.3: We suggest an implantable cardioverter-defibrillator be considered for secondary prevention of sudden cardiac death in peritoneal dialysis patients who survive an episode of cardiac arrest confirmed as being the result of malignant ventricular arrhythmia (except those that occur within first 48 hours post-acute myocardial infarction). (2D)

Rationale

Implantable cardioverter-defibrillators are the only intervention that appear to robustly reduce sudden cardiac death in the setting of primary or secondary prevention in the general population (excluding immediately post myocardial infarction) (15). However, data relating to their use in CKD patients are very limited and there are virtually no data in PD patients. Current guidelines for their utilization are somewhat variably applied on a global basis even in patients without CKD (16). These guidelines rely significantly on identifying patients with markedly reduced cardiac contractile function (17), immediately bringing about difficulties in implementing the currently recommended criteria for implantable cardioverter-defibrillator implantation in PD patients.

There are so far no randomized studies examining the use of implantable cardioverter-defibrillators for primary prevention of sudden cardiac death in dialysis patients. Thus, the workgroup felt that a recommendation cannot be drawn in relation to implantable cardioverter-defibrillator use for primary prevention of sudden cardiac death in high risk PD patients. However, there are data from HD patients showing that the use of implantable cardioverter-defibrillators may be associated with an improved survival in survivors of cardiac arrests (18). However, the one-year survival of patients with an implantable cardioverter-defibrillator was significantly lower in those with CKD compared to those without CKD (96.3% vs 61.2%) (18). The explanation for the relative lack of efficacy of implantable cardioverter-defibrillator use in CKD patients is not understood. Efficacy may be lower as a result of the typically higher defibrillation thresholds, rendering implantable cardioverter-defibrillator use less effective in CKD (as does advancing age >80 years) (19). Thus, if the use of implantable cardioverter-defibrillators is indeed considered in PD patients, careful attention should be paid to fine tuning the threshold of the implantable cardioverter-defibrillator devices using programmed ventricular stimulation studies in PD patients. On the other hand, the complication rates associated with implantable cardioverter-defibrillator use, such as pocket infection or pneumothorax, appeared to be significantly higher in dialysis patients compared to non-CKD patients (19). A higher incidence of appropriate shocks (37.5% vs 10.5%) is characteristic of implantable cardioverter-defibrillators that were in use in dialysis patients compared to non-CKD patients (20). Finally, in a meta-analysis of CKD studies, implantable cardioverter-defibrillator use was associated with survival benefit for patients with glomerular filtration rate ≥60 mL/min, but not for patients with < 60 mL/min (21) [Evidence Review Table 3]. Putting together the very limited evidence available, the workgroup suggests a weak recommendation statement be drawn regarding the use of an implantable cardioverter-defibrillator in PD patients who survive an episode of cardiac arrest confirmed to be resulting from malignant ventricular arrhythmia.

Evidence Review Table 3. Studies analyzing the impact of secondary prevention with implantable cardioverter-defibrillators

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Pun PH. et al. Am J Kidney Dis. 2014 (21)	CKD patients	2,867	Meta-analysis from randomized controlled trials.	Mortality, rehospitalizations, and effect modification by eGFR.	N/A	The ICD was associated with survival benefit for patients with eGFR less than 60 mL/min/1.73 m2 (adjusted HR, 0.49; 95% posterior credible interval, 0.24-0.95), but not for patients with eGFR higher than 60 mL/min/1.73 m2 (adjusted HR, 0.80; 95% posterior credible interval, 0.40-1.53).	B
Herzog CA et al. Kidney Int 2005 (9)	HD and PD patients	6042	Retrospective cohort study	Supports the use of ICDs for prevention of sudden death	N/A	ICD implantation in cardiac arrest survivors on dialysis is associated with greater survival.	B

HD = hemodialysis; PD = peritoneal dialysis; N/A = not available; SCD = sudden cardiac death; LVH = left ventricular hypertrophy; ICD = implantable cardioverter-defibrillator; eGFR = estimated glomerular filtration rate; HR = hazard ratio;

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SECTION 7. ARTERIAL STIFFNESS

Should peritoneal dialysis patients undergo regular assessment of pulse wave velocity?

Rationale

Arterial stiffness is increased in dialysis patients (1) and is principally related to arteriosclerosis involving the media of medium and large arteries (1-3). It can be measured by a variety of methods, including pulse wave velocity, augmentation index, systemic arterial compliance, arterial distensibility, arterial stiffness index and aortic distensibility using cardiovascular magnetic resonance imaging [reviewed in (1, 2)].

Of these different methods, pulse wave velocity has been the most extensively studied measure of arterial stiffness in dialysis populations and has generally been found to be independently predictive of both cardiovascular and all-cause mortality [Evidence Review Table 1]. Other measures of arterial stiffness have been studied to a more limited extent and their associations with survival outcomes have been more variable [Evidence Review Table 1]. Arterial stiffness therefore shows promise as a surrogate outcome measure for stratifying cardiovascular risk in peritoneal dialysis (PD) patients. However, there are so far no randomized controlled trials showing how reduced arterial stiffness parameters may result in an improvement in patient-level outcomes.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) cardiovascular guidelines (4) recommend that "all dialysis patients should have pulse pressures (PP) determined monthly before dialysis" and that "for pulse pressure >60 mmHg and systolic blood pressure >135 mm Hg, it is recommended that pulse pressure be reduced by achieving ideal body weight and by the use of antihypertensive medication with target pulse pressure being 40 mm Hg." In contrast, the Kidney Disease: Improving Global Outcomes (KDIGO), Caring for Australasians with Renal Impairment (CARI), European Best Practice, United Kingdom - National Institute for Health and Care Excellence (UK-NICE), Canadian Society of Nephrology and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines make no specific recommendations regarding measurement or therapeutic manipulation of arterial stiffness. Based on the fact that pulse wave velocity is not yet a validated surrogate outcome measure, the workgroup felt that it may be premature to recommend routine regular assessment of pulse wave velocity in all PD patients [Evidence Review Table 1].

Evidence Review Table 1. Studies examining the associations between arterial stiffness and cardiovascular outcomes in peritoneal dialysis patients

Reference	Population	Patient number	Study design	Outcomes of interest	Follow-up duration (if applicable)	Results	Study quality
Szeto et al Am J Nephrol 2012 (5)	Incident PD patients at a single Hong Kong center	155	Prospective, longitudinal observational cohort study	Survival	2 years	Baseline carotid-femoral PWV ≥10 m/s was associated with inferior survival compared to <10 m/s (76.1% vs 88.6%, p=0.006). Baseline carotid-femoral PWV was not an independent predictor of survival after adjustment for other cardiovascular risk factors.	B
Kato et al Ther Apher Dial 2012 (6)	HD patients <76 years old who did not have an abnormal ABI (<0.90 or ≥1.30) at a single Japanese center	135	Prospective, longitudinal observational cohort study	Cardiovascular mortality	63±4 months	Highest tertile of brachial-ankle PWV associated with a higher risk of cardiovascular mortality (adjusted HR 16.9, 95% CI, 1.1-251.8, p<0.05) Cardio-ankle vascular index was not associated with cardiovascular mortality	B
Verbeke et al. Nephrol Dial Transplant 2011 (7)	Adult patients on PD or HD >3 months from 47 European dialysis centers	1084 (31 on PD)	Prospective, longitudinal observational cohort study	Nonfatal cardiovascular events or death from any cause	2 years	Increasing carotid-femoral PWV was associated with an increased risk of cardiovascular events (adjusted HR, 1.154, 95% CI, 1.085-1.228, p<0.001) Higher tertiles of abdominal aortic calcification were associated with an increased risk of cardiovascular event (tertile 1 reference; tertile 2 HR, 3.682, 95% CI, 1.356-9.997, p=0.011; tertile 3 HR, 8.640, 95% CI, 3.528-21.158, p<0.001)	B

Siphioglu et al Perit Dial Int 2012 (8)	Patients on CAPD (not APD) ≥3 months at a single Turkish center in July 2007	156 PD patients and 28 healthy controls	Prospective, longitudinal observational cohort study	Fatal and non-fatal cardiovascular events	19.2±6.4 months	Aortic stiffness index independently predicted fatal and nonfatal CV events (HR, 1.239, 95% CI, 1.103-1.392), but not all-cause mortality in PD patients	B
El Hadj Othmane et al Orv Hetil 2010 (9)	HD patients at a single Hungarian center	98	Prospective, longitudinal observational cohort study	Cardiovascular mortality	29 (1-34 months)	Increased cardiovascular mortality predicted by increasing pre-dialysis carotid-femoral PWV (HR, 1.23, 95% CI, 1.07-1.42) and 10% lower pre-dialysis pulse pressure amplification (HR, 1.39, 95% CI, 1.02-1.89), but not by carotid augmentation index or carotid pulse pressure	B
Gao et al Perit Dial Int 2010 (10)	Prevalent PD patients at a single Hong Kong center	107	Prospective, longitudinal observational cohort study	Hospitalization for CVD	9.4±4.6 months	Carotid-femoral PWV was independently predictive of increased risk of hospitalization for cardiovascular disease (OR per m/s 1.74, p=0.041).	C
Shoji et al Atheroscleros is 2010 (11)	Prevalent HD patients at a single Japanese center	423	Prospective, longitudinal observational cohort study	Cardiovascular mortality	70 months	Higher carotid arterial stiffness parameter β was independently predictive of cardiovascular mortality	B
Othmane et al Kidney Blood Press Res 2009 (12)	Prevalent HD patients at a single Hungarian center	98	Prospective, longitudinal observational cohort study	Cardiovascular mortality	29 months (range 1-34)	Cardiovascular mortality was predicted by increased pre-dialysis carotid-femoral PWV (HR per m/s .124, 95% CI, 1.07-1.44) and 10% lower carotid-brachial pulse pressure amplification (HR 1.41, 95% CI, 1.03-1.92), but not by carotid augmentation index nor carotid pulse pressure.	C
Adragao et al Nephrol Dial Transplant	ESRD patients treated with HD >6 months	101	Prospective, longitudinal observational	Survival	43 months	Mortality was associated with a simple vascular calcification score >3 (HR, 3.308, 95% CI, 1.109-9.863, p=0.032) and a pulse pressure > 70mmHg (HR, 3.227, 95% CI, 1.114-9.347,	C

2009 (13)	at a single Portugese center		cohort study			p=0.031). Mortality in non-diabetic patients was additionally predicted by PWV >10.5 m/s (HR, 1.092, 95% CI, 1.013-8.775, p=0.047)	
Mark et al J Cardiovasc Magn Reson 2008 (14)	Stage 5 CKD patients at a single Scottish center	144 (110 on dialysis)	Prospective, longitudinal observational cohort study	Survival Composite endpoint of death or nonfatal cardiovascular event	24 months	Mortality was independently predicted by log [aortic distensibility] (HR, 0.135, 95% CI, 0.019-0.948, p=0.004) Combined endpoint was independently predicted by log [aortic distensibility] (HR, 0.066, 95% CI, 0.013-0.347, p=0.001) and log [volumetric arterial strain] (HR, 0.026, 95% CI, 0.004-0.175, p<0.001)	C
Sigrist et al Clin J Am Soc Nephrol 2007 (15)	Stage 4 or 5 CKD at a single Renal unit in the United Kingdom	134 (60 HD, 28 PD, 46 stage 4)	Prospective, longitudinal observational cohort study	Survival	24 months	Mortality was independently predicted by change in calcium score from 0-12 months (HR, 1.03, 95% CI, 1.01-1.05, p=0.03)	C
Shoji et al J Am Soc Nephrol 2001 (16)	ESRD patients treated with HD >6 months at a single Japanese dialysis center between June 1992 and December 1998	256	Prospective, longitudinal observational cohort study	Cardiovascular mortality All-cause mortality	63 months	PWV was a significant independent predictor of cardiovascular mortality (HR, 1.18, 95% CI, 1.01-1.39) and all-cause mortality (HR, 1.15, 95% CI, 1.03-1.29)	B
Blacher et al Kidney Int	HD patients at a single	242	Prospective, longitudinal	Cardiovascular mortality	78±46	Each 1 m/s increase in PWV independently predicted cardiovascular mortality (HR, 1.14, 95% CI, 1.03–1.26) and	B

2003 (17)	French center		observational cohort study	All-cause mortality	months	all-cause mortality (HR, 1.14, 95% CI, 1.05–1.24). Each 10 mmHg pulse pressure increment independently predicted all-cause mortality (HR, 1.14, 95% CI, 1.05–1.24) but not cardiovascular mortality (HR, 1.04, 95% CI, 0.92–1.18)	
Covic et al Nephrol Dial Transplant 2006 (18)	ESRD patients treated with HD ≥3 months at a single Romanian center between January 1998 and December 2001	92	Prospective, longitudinal observational cohort study	All-cause mortality	61±25 months	All-cause mortality was not independently predicted by augmentation index	C
Blacher et al Hypertension 2001 (19)	Stable ESRD treated with on HD for ≥3 months with no clinical cardiovascular disease during the previous 6 months at a single French center 1994-1998	110	Prospective, longitudinal observational cohort study	Cardiovascular mortality All-cause mortality	53±21 months	Each 1 standard deviation increase in carotid incremental elastic modulus was associated with increased risks of both all-cause mortality (HR, 1.6, 95% CI, 1.2-2.2, p<0.01) and cardiovascular mortality (HR, 1.7, 95% CI, 1.2-2.4, p<0.01).	B
Zoungas et al Am J Kidney	Stage 4-5 CKD aged 24-79 years	315	Prospective, longitudinal observational	Composite endpoint of fatal and	Median 3.6 years	An increased risk of the composite cardiovascular endpoint was independently predicted by increased aortofemoral pulse wave velocity (HR per m/s 1.12, 95% CI 1.05-1.20,	B

Dis 2007 (20)	participating in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST)		cohort study	nonfatal cardiovascular events		p=0.001), but not systemic arterial compliance, carotid-derived augmentation index or carotid intima-media thickness.	

PD = peritoneal dialysis; PWV = pulse wave velocity; HD = hemodialysis; ABI = ankle-brachial index; HR = hazard ratio; CI = confidence interval; CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis; CV = cardiovascular; CVD = cardiovascular disease; CKD = chronic kidney disease; ESRD = end stage renal disease

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