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K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients

K/DOQI Disclaimer

Section I: Use of the Guidelines

These Guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care, and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these Guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

The recommendations for research contained within this document are general and do not imply a specific protocol.

Section II: Development of the Guidelines

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Acronyms and Abbreviations

ABPM	ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACLS	advanced cardiac life support
ACS	acute coronary syndromes
ADA	American Diabetes Association
AEDs	automatic external defibrillators
AGEs	advanced glycation end-products
AHA	American Heart Association
AI	adequate intake
ALE	advanced lipoxidation end products
AMDRs	Acceptable Macronutrient Distribution Ranges
AOPP	advanced oxidation protein products
apo(a)	apolipoprotein(a)
ApoE	Apolipoprotein E
ARBs	angiotensin-receptor blockers
ASA	acetylsalicylic acid
ASCVD	atherosclerotic cardiovascular disease
BDI	Beck Depression Inventory
BIA	bioimpedance
BMI	body mass index
CAB	coronary artery bypass
CAD	coronary artery disease
CAPD	continuous ambulatory peritoneal dialysis
CBS	cystathionine synthase
CBV	central blood volume
CBVD	cerebrovascular disease
CCB	calcium-channel blockers
CHF	congestive heart failure
CKD	chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
CRP	C-reactive protein
CT	cardiothoracic
CVD	cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DEXA	dual energy X-ray absorptiometry
DHA	docosahexenoic acid
EBCT	electron-beam computerized tomography
ECG	electrocardiogram
EMS	Emergency Medical Services
EPA	eicosapentaenoic acid
FSH	follicle-stimulating hormone
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
HD	hemodialysis
HGS	handgrip strength
HHCY	hyperhomocysteinemia
HRT	hormone replacement therapy
hs-CRP	high-sensitive C-reactive protein
IDH	intradialytic hypotension

IHD	ischemic heart disease
IL-6	interleukin-6
IOM	Institute of Medicine
IVC	inferior vena cava
JNC	Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure
LDLs	low-density lipoproteins
LH	leutinizing hormone
Lp(a)	lipoprotein(a)
LNA	alpha-linolenic acid
LV	left ventricular
LVH	left ventricular hypertrophy
MAP	mean arterial pressure
MDA	malondialdehyde
MI	myocardial infarction
MMPI	Minnesota Multiphasic Personality Inventory
MPO	myeloperoxidase
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MS	methionine synthase
MTHFR	5,10-methylene tetrahydrofolate reductase
nPCR	normalized protein catabolic rate
PCI	percutaneous coronary intervention
PD	peritoneal dialysis
PEM	protein-energy malnutrition
PP	pulse pressure
PTH	parathyroid hormone
PUFAs	polyunsaturated fatty acid
PVD	peripheral vascular disease
PVR	peripheral vascular resistance
PWV	pulse wave velocity
RDA	Recommended Dietary Allowance
rhEPO	recombinant human erythropoietin
RRT	renal replacement therapy
SCD	sudden cardiac death
SGA	subjective global assessment
STAI	State-Trait Anxiety Inventory
STAXI	State-Trait Anger Expression Scale
SVAs	supraventricular arrhythmias
TIA	transient ischemic attack
UKPDS	United Kingdom Prospective Diabetes Study
USRDS	United States Renal Data System
VF	ventricular fibrillation
VHD	valvular heart disease
VT	ventricular tachycardia
WHI	Women’s Health Initiative

Cardiovascular Disease in Dialysis Patients

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Foreword

The treatment of patients with cardiovascular disease (CVD) on dialysis remains suboptimal due to the lack of evidence of treatment efficacy, exclusion of this population from most major cardiovascular trials, and an attitude of therapeutic nihilism on the part of clinicians towards this population.

These guidelines are organized to facilitate the evaluation, identification, and treatment of patients on dialysis with CVD, recognizing that all patients on dialysis are at increased risk for CVD. They are designed for use by cardiologists, nephrologists, primary-care physicians, and nurse practitioners. CVD in these guidelines is defined as coronary artery disease (CAD), cardiomyopathy, valvular heart disease, arrhythmia, cerebrovascular disease (CBVD), or peripheral vascular disease (PVD). Some or all of these entities may co-exist in the same individual, or develop sequentially over time.

The intention of this Work Group was not to rewrite existing guidelines or textbooks of cardiovascular medicine. Instead, we have attempted to highlight those aspects of CVD care that are different or have been construed to be different in dialysis patients compared to the general population, either as a consequence of the kidney disease or the dialysis procedure.

For each guideline, the recommended action (guideline statement) for the management of CVD is first described, with the strength of recommendation (A, B, or C, with A being the strongest) provided for each statement. This is followed by the synopsis of a comprehensive review of literature on that particular topic, with the primary focus on the literature that is specific to the dialysis patients. This review provides the rationale for the guideline statement and the strength of recommendation. The strength of evidence (strong, moderately strong, or weak) of the rationale is provided within this section. The final section on research recommendations in each guideline attempts to define those questions that the Work Group believes need to be answered in order to improve the care of patients on dialysis, and in order to update these guidelines in the next 3-5 years based on new data.

In addition to the guidelines, there are a number of topics that the Work Group felt were important, but the available data do not support the establishment of specific guidelines. For these topics, comprehensive literature reviews were performed and individual summaries are presented as state-of-the-science chapters in the second part of this document.

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OVERVIEW OF EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE

CARDIOVASCULAR DISEASE is the major cause of morbidity and mortality in patients with chronic kidney disease (CKD) Stage 5.[1,2] Although there have been significant improvements in management of CVD in the general population, it is not known if these interventions result in similar benefits for patients with CKD Stage 5. Subtle differences in the types, distribution, mortality and pathophysiology of CVD in patients with CKD Stage 5 suggest that generalization of data from patients without kidney disease should be extrapolated with caution.

Cardiovascular risk factors among patients with CKD Stage 5 may be divided into those that are nonspecific to kidney disease but are more prevalent, and those that are specific to CKD Stage 5. There is increased prevalence of many traditional factors for cardiovascular risk (age, male gender, hypertension, diabetes, dyslipidemia, and physical inactivity). In addition, patients with CKD Stage 5 have disease-related risk factors such as anemia, hyperhomocysteinemia, hyperparathyroidism, oxidative stress, hypoalbuminemia, chronic inflammation, prothrombotic factors, among others. Data suggest that uremic factors, or factors related to renal replacement therapy (RRT)/dialysis may be implicated in the pathogenesis of heart disease in patients treated by dialysis, because cardiovascular survival improves after transplantation even in high-risk patients.[3,4] Conversely, aspects of the dialysis treatment itself may contribute to CVD.

Target Population

- Patients with CKD Stage 5 requiring chronic RRT
- Exclusion—patients after transplantation

Cardiovascular Disease Risks in This Population

- Cardiovascular disease is the leading cause of death in patients with CKD Stage 5.
- Cardiovascular mortality is markedly greater in patients treated by RRT than in the age-matched general population.
- The unique pathophysiology of CKD Stage 5 and its treatment results in differences in the incidence and prevalence of various CVD processes noted at the time of death in dialysis patients compared to the general population.

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RATIONALE

Definitions

Within years of the first clinical experience with hemodialysis, cardiovascular mortality was found to be very high.[5] Current literature substantiates a high mortality from CVD, compared to the general population.[1] Cardiovascular disease includes the specific diagnoses: myocardial infarction (MI), pericarditis, atherosclerotic heart disease (AHD), cardiomyopathy, arrhythmia, valvular heart disease (VHD), congestive heart failure (CHF), CBVD, and PVD. In addition, patients with CKD Stage 5 have a unique excess of sudden death from cardiac arrest.[1,2] This is somewhat confusing, as the USRDS classification is "cardiac arrest, cause unknown" (47% of cardiac death) and includes a separate category for arrhythmia (13% of cardiac death).

Strength of Evidence

Cardiovascular disease is the leading cause of death in patients with end-stage kidney failure. **(Strong)** The United States Renal Data System (USRDS) annual data (abstracted from prevalent patients in the years 1998-2000) shows that 75.47 (42.2%) of the 178.92 deaths per 1,000 patient years at risk have cardiovascular causes. Of these deaths 36.51 (46%) were recorded as cardiac arrest.[2]

Cardiovascular mortality is markedly greater in patients treated by RRT than in the age-matched general population. **(Strong)** Direct comparisons between patients with CKD Stage 5 and the general population are difficult. However, many studies use Framingham data for reference. Some researchers have developed a Sensitivity Analysis method for contrasting car-

diovascular mortality in the general population and in patients with CKD Stage 5—matching for such factors as sex, race, age and the presence of a diagnosis of diabetes.[1,6] Their results show that cardiovascular mortality is 5- to 100-fold greater in CKD Stage 5 than in specific reference groups. However, patients with CKD Stage 5 who develop cardiac events have a greatly increased mortality compared to patients with normal renal function.[7,8] A limited number of autopsy studies are instructive in their support of the clinical data. There is a widely accepted hypothesis that increased cardiovascular risk is caused by accelerated atherogenesis.[5] While atherosclerosis is widespread, anatomically documented MI is only present in approximately 8%-12% of patients at autopsy.[9-12] Both coronary artery and valvular calcifications are common; however, there is no direct connection between advanced coronary lesions (as graded by the degree of calcification) and cause of death.[11] There is a high incidence of subclinical pericarditis. In addition, the frequent autopsy finding of ventricular hypertrophy emphasizes the importance of primary cardiac muscle dysfunction (e.g., CHF, cardiomyopathy, etc.) in patients with CKD Stage 5 (see Guideline 7). As the number of cardiovascular comorbidities increases, the risk of complications rises. Thus, the severity of comorbid factors may play a role in the morbidity and mortality of CVD in CKD Stage 5. There is good evidence that the current population of patients starting RRT is older and sicker (i.e., more severe comorbidities) than in earlier years. The unique pathophysiology of CKD Stage 5 and its treatment results in differences in the incidence and prevalence of various cardiovascular disease processes noted at the time of death in RRT patients compared to the general population.

Patients who survive more than 7-10 years demonstrate a complex picture. In general the long-term survivors have lower risks (younger, women, lower phosphorus), which can be interpreted as a "survivor effect". But when adjustments for comorbidity are made, mortality remains about the same as in patients on RRT for shorter periods of time. **(Weak)**

Comparison of dialysis modalities is a serious research need in this field. The current literature suggests that peritoneal dialysis (PD) is more effective in controlling fluid-volume status than hemodialysis (HD); however, there is higher mortality for cardiovascular events. Selection bias, "informative censoring" of healthier patients receiving transplantation, and the inherent difference in techniques make comparisons very difficult

LIMITATIONS

Much of the confusion in this literature stems from a lack of uniform and standardized approaches to gathering data. In many papers, adequate detail about comorbid conditions is missing. Standard dialysis management has changed with time. It is rare to find clear information about dialysis adequacy or a specific dialysis therapy. Because of selection bias, it is very difficult to compare the effects of HD and PD on CVD, and equally difficult to compare the U.S. experience with that of other countries. This section reviews papers based on clinical, nontechnological diagnosis. Papers using diagnostic testing to define diagnoses or risks were intentionally excluded (see Sections II and IV). Therefore, specific diagnostic modalities (EKG or echocardiography) are likely to provide more accurate measures for determining treatment outcomes.

RESEARCH RECOMMENDATIONS

There is a marked paucity of detail about causes of sudden death in patients with CKD Stage 5. A recent study shows an increased risk of death on Monday and Tuesday compared to other days of the week in patients treated by HD.[13] This study focuses attention on the 3-day hiatus between hemodialysis treatments that is part of current standard management. At present, it is unclear if the associated risks of hyperkalemia, the rate of change in potassium with dialysis treatment, and fluid overload are the cause of the increased mortality. Careful studies of dialysis-specific risks and outcomes in CVD are likely to yield important insight into this problem.

OVERVIEW OF EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN CHILDREN

CARDIOVASCULAR DISEASE is a major cause of morbidity and mortality in pediatric patients on chronic dialysis; it is now reported as either the first or second most common cause of death in series evaluating mortality in children on chronic dialysis (Tables A and B).[2,14-17] Children and young adults on chronic dialysis have traditional factors leading to cardiovascular risk (hypertension, dyslipidemia, and physical inactivity). In addition, they have uremia-related risks such as anemia, volume overload, hyperhomocysteinemia, hyperparathyroidism, hypoalbuminemia, inflammation, and left ventricular hypertrophy (LVH) (Table C). Large-scale, multicenter studies of risk factor outcomes for CVD in patients on chronic dialysis have not been carried out in the pediatric population. Guidelines for routine screening and monitoring of many of these risk factors are not in place for pediatric chronic dialysis patients. The data presented here support the need for prevention as well as greater recognition and treatment of CVD and CVD risk factors in children and young adults on chronic dialysis.

Target Population

The Work Group considered whether to include children and adolescents in these guidelines as the majority of guidelines were directed to symptomatic atherosclerotic CVD. Children who are dialysis-dependent (Stage 5 CKD) are at risk of CVD; however, the spectrum of CVD does differ from that in adults. The guidelines proposed for children and adolescents under age 18 address the current state of knowledge in pediatric CKD Stage 5. If there are guidelines already provided for specific cardiovascular conditions or risk factors, we refer to the appropriate recommendations.

RATIONALE

Data from the USRDS suggest that children aged 0-19 years make up 1% of known chronic dialysis patients in the U.S.[17] Between 1998 and 2001 there were, on average, 2,199 children each year on chronic dialysis. Recent studies have shown that pediatric chronic dialysis patients bear a significant CVD burden and that CVD-associated mortality is 1,000 times higher in pediatric chronic dialysis patients than the nationally reported pediatric cardiovascular death rate.[14] The highest cardiovascular death rate occurs in young children on dialysis who are <5 years of age. Transplantation in children lowers the risk of cardiovascular mortality by 78%; however, the rate of CVD mortality continues to be greater than that in the general pediatric population.[14] The leading cause of mortality in the general pediatric population is accidents.[18] Strategies to reduce CVD morbidity and mortality are clearly warranted in the pediatric CKD Stage 5 population.

Cardiovascular Disease Mortality (Strong)

In the 2002 USRDS data, CVD (defined as acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease) exceeded infection as the leading cause of death in 8,549 pediatric chronic dialysis patients, accounting for 27% of deaths.[2] An additional 6% of deaths in pediatric chronic dialysis patients were caused by CBVD. Infection was the second largest known cause of death in these patients, accounting for 20% of the patient deaths.[2] A retrospective analysis of cardiovascular mortality in Medicare-eligible CKD Stage 5 patients who died at ages 0-30 years and who had participated in a USRDS special study as children (age 0-19 years) demonstrated that, of a total of 1,380 deaths between the years 1990 and 1996, 980 deaths were in the chronic dialysis patients. Cardiac causes accounted for 28% of all deaths in the dialysis patients and was second only to infection.[14] Cardiac deaths occurred in 34% of 331 black compared with 25% of 649 white dialysis patients. For both the chronic dialysis and transplant groups, the risk of cardiac death increased by 22% with every 10-year increase in age.[2] The dialysis arm of the North American Pediatric Transplant Cooperative Study (NAPRTCS) registry includes data on 4,546 patients <21 years of age. Of 205 deaths reported

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Table A. Cardiovascular Mortality in Pediatric CKD Stage 5

Author	Year Published	Years Data Collected	No. of Subjects	Total Deaths	% Cardiovascular Deaths
USRDS Annual Data Report [2]	2002	1998-2000 (Prevalent Patients)	8, 549 Dialysis Patients	244 Deaths	27%
Parekh [14]	2002	1990-1996 (USRDS)		980 Deaths	28%
Chavers [15]	2002	1991-1996 (USRDS)	1,454 Dialysis Patients	107 Deaths	38%
Groothoff [16]	2002	1972-1992 (Dutch Registry)		38 Deaths	45%
Honda [20]	1999	1981-1997 (Japanese Registry)	807 PD* Patients	87 Deaths	30%
Verrina [21]	1999	1986-1997 (Italian Registry)	297 Patients	21 Deaths	57%
Reiss [22]	1996	1969-1992	231 Patients	36 Deaths (26 HD†, 10 PD*)	14% cardiac failure 22% other cardiac
Hisano [23]	1990	1968-1988	96 Patients	28 Deaths	39%
Neu [19]	2002	1992-2001	4,546 Patients	205 Deaths	22%

*PD = peritoneal dialysis, †HD = Hemodialysis
There are no large scale direct comparisons of the general and chronic dialysis pediatric populations

to the NAPRTCS dialysis registry, cardiopulmonary events were the second leading cause of death (44/205, 22%).[19]

In a retrospective USRDS study of 1,454 Medicare-eligible incident pediatric chronic dialysis patients identified from 1991 to 1996, 107 deaths were noted during the follow-up period (each cohort was followed for 3 years). Of those, 41 (38%) were cardiac-related.[15] Cardiac deaths occurred in a greater percentage of blacks (5%) compared with whites (2%). The cardiac death rate did not decrease during the study period; (14.4 and 14.5 per 1,000 patient years for the 1991 and 1996 cohorts, respectively).

Similar mortality data have been reported for European and Asian pediatric CKD Stage 5 patients with cardiac deaths ranging from 30%-57% of all deaths.[16,20-24] Overall mortality in Dutch children with CKD Stage 5 was reported to be 30 times higher than in the general Dutch age-and gender-matched pediatric population.[16] Young age, black race, hypertension, and a prolonged period of dialysis have been associated with increased cardiac mortality in chronic pediatric CKD Stage 5 patients.

Cardiovascular Disease Events (Moderately Strong)

In the USRDS study noted above, CVD events were examined in the six incident pediatric chronic dialysis cohorts from 1991 to 1996.[15] All patients were <20 years of age at the start of dialysis and each cohort was followed for up to 3 years. Of the 1,454 incident pediatric patients who started chronic dialysis between 1991 and 1996, 452 (31%) developed CVD.[15] Arrhythmia was the most common

Table B. Autopsy Studies of Cardiac Pathology in Pediatric CKD Stage 5

Author	Year	No. of Subjects	Autopsy Findings
Pennisi [30]	1976	12	Coronary artery intimal thickening 50%, intimal collagenization 83%
Litwin [36]	2001	8	Calcified cardiac valves 50% Ventricular hypertrophy 88%

The number of autopsy studies is extremely limited. However, these two papers are instructive in their support of the previously summarized clinical data.

cardiac event and it developed in approximately 20% of the study patients. Other cardiac-related events were vascular heart disease (VHD) (12%), cardiomyopathy (10%), and cardiac arrest (3.0%). The frequency of a diagnosis of cardiomyopathy was noted to double during the USRDS study period. Arrhythmias, including sinus tachycardia, premature ventricular contractions, and heart block have been reported in pediatric chronic dialysis patients.[25-28] The 2002 USRDS Annual Data Report lists cardiac arrhythmia (hyperkalemia excluded) as the cause of death in 4% (14% of all cardiac–related deaths) of pediatric chronic dialysis patients for 1998 to 2000. Data on the incidence and prevalence of nonfatal MI, angina, and LVH were not reported.

Atherosclerosis. There is a paucity of data pertaining to atherosclerosis in children; this includes the general pediatric as well as the chronic pediatric dialysis populations. The 2002 USRDS ADR states that 10%-15% of prevalent pediatric chronic dialysis patients have a diagnosis of AHD. Musculoelastic intimal thickening is considered an early stage in the development of atherosclerosis and it has been reported in a small series of pediatric hemodialysis patients.[29] In this study, a biopsy of the recipient iliac artery was performed at the time of kidney transplantation in 12 pediatric hemodialysis patients aged 11-17 years. Five (42%) arteries had fibroelastic intimal wall thickening, two (17%) had microcalcification in the intimal layer, and two (17%) had

Table C. Prevalence of Cardiovascular Risk Factors in Pediatric CKD Stage 5

Author	Year	No. of Subjects	Risk Factor Examined	Prevalence of risk factors
Goodman [32]	2000	39	Coronary artery calcification	36%
Oh [34]	2002	37	Coronary artery calcification Valvular calcification Aortic valve calcification	92% 34% 32%
Gruppen [35]	2003	30	Aortic valve calcification	30%
Mitsnefes [37]	2000	64 (26 HD†, 38 PD*)	Left ventricular hypertrophy	75% HD† 68% PD*

†HD = hemodialysis, *PD = peritoneal dialysis

fibroatheromatous plaques (14). Six of the twelve patients had uropathy as the primary cause of CKD Stage 5 and atherosclerotic changes were present in the vessel sample obtained from all six of these patients. In contrast, only one of six patients with a diagnosis of glomerulonephritis as the cause of CKD Stage 5 had atherosclerotic changes. Serum phosphorus and the calcium-phosphorus product were higher in the uropathy group. The duration of CKD Stage 5 was, on average, 2 years longer in the uropathy group.[29] *(Weak)*

Coronary artery disease. Limited data are available in pediatric patients. One group reported accelerated coronary artery disease at autopsy in 12 CKD Stage 5 patients <20 years of age.[30] Intimal thickening was present in 50% of the CKD Stage 5 patients compared to 25% of 16 autopsy specimens obtained from pediatric patients without CKD Stage 5. Musculoelastic collagenous changes of the intima were present in 83% of CKD Stage 5 autopsy specimens compared to 25% of the control specimens. Indirect methods of determining coronary atherosclerotic disease have been studied in children. Coronary artery calcification has been studied by electron-beam computed tomography (EBCT) in 39 young adults (mean age 19 years) on chronic dialysis; the presence of coronary calcification was found in association with older age, a longer period of chronic dialysis, a higher mean phosphorus level, a higher daily calcium intake, and a higher mean calcium-phosphorus product.[31,32] Confirmation of CAD in these patients was not done with the gold standard of coronary angiography. In addition, there were limited data available on traditional cardiovascular risk factors and the association of elevated coronary calcium. A study reported findings of soft-tissue calcification at autopsy in 72 of 120 (60%) pediatric patients with CKD Stage 5 treated from 1960 to 1983.[33] Of the 120 patients, 54 (45%) were on chronic dialysis at the time of death. Soft-tissue calcification was present in 76% of the patients who had undergone chronic dialysis and 61% had severe systemic calcification. Coronary calcification by helical CT and intimal medial thickness by Doppler ultrasound have been studied in a cross-sectional analysis of 39 young adults (mean age 27 years) with CKD Stage 5 (13 chronic dialysis, 26 transplant) since childhood. Coronary artery calcification was present in 34 of 37 patients (92%) scanned, and did not correlate with worsening intimal medial thickness.[34] Coronary artery calcification was associated with higher levels of C-reactive protein, plasma homocysteine, and intact PTH, as well as a higher calcium-phosphorus product.[34] Coronary calcification may represent arteriosclerosis and not necessarily atherosclerosis in children on chronic dialysis. The distinction is usually made on autopsy material. Clearly, whether or not coronary artery and other vascular diseases are accelerated in children and young adults on chronic dialysis requires further study. *(Weak)*

Valvular heart disease/aortic valve calcification. A recent study examined the prevalence of aortic valve calcification in young adults who had experienced CKD Stage 5 since childhood. In this study, 30 of 140 Dutch patients who had onset of CKD Stage 5 at age 0-14 years (years 1972 to 1992) were on chronic dialysis (19 HD, 11 PD) at the time of cardiac evaluation in 1998 to 2000.[35] Aortic valve calcification was determined by echocardiography. Aortic valve calcification was present in nine patients (30%) and by multiple regression analysis was associated with a prolonged period of peritoneal dialysis.[35] At autopsy, it was found that four out of eight chronic pediatric dialysis patients had Moenckeberg-type arteriosclerosis and diffuse vascular and cardiac valve calcification.[36] *(Weak)*

Hypertension/left ventricular hypertrophy. Hypertension is commonly seen in 49% of children with CKD[37] and 50%-60% of patients on dialysis.[38] Left ventricular hypertrophy, left ventricular dilatation, and systolic and diastolic dysfunction have been documented using echocardiography in studies of children on maintenance dialysis.[39,40] Left ventricular hypertrophy is a known risk factor for CVD and mortality in adults on chronic dialysis but this has not been proven in children. The prevalence of LVH by echocardiography in 64 children on maintenance dialysis was 75%.[40] Some authors report increased severity of LVH in pediatric hemodialysis compared to peritoneal dialysis patients.[40,41] Established LVH has been reported at the initiation of maintenance dialysis in 20 of 29 (69%) patients aged 4-18 years.[42] The results of this

study implied that LVH begins to develop in children with earlier stages of CKD Stage 5. Left ventricular hypertrophy was found to progress in 14 of 29 patients who had LVH on initial evaluation. Progression in these patients was associated with increased systolic blood pressure. In the Litwin study of patient survival and mortality in 125 children from Poland on chronic dialysis, CVD accounted for 11 of 16 (69%) patient deaths.[36] Five of the eleven patients who died of cardiac disease underwent autopsy and were found to have LVH. Screening for LVH by electrocardiogram in children is not recommended due to the very low sensitivity of the test.[43,44] Echocardiogram is a more reliable measure of LVH in children and adolescents. *(Weak)*

RECOMMENDATIONS

Summary of Pediatric Clinical Recommendations

Guideline 1.2. Children commencing dialysis should be evaluated for the presence of cardiac disease (cardiomyopathy and valvular disease) using echocardiography once the patient has achieved dry weight (ideally within 3 months of the initiation of dialysis therapy). (C) Children commencing dialysis should be screened for traditional cardiovascular risk factors such as dyslipidemia and hypertension. (C)

Guideline 5.3. Children with VHD should be evaluated by echocardiography. Management of valvular disease should follow recommendations provided by the ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease VI.[45] (C)

Guideline 6.4. Children should be evaluated for the presence of cardiomyopathy (systolic and diastolic dysfunction) using echocardiographic testing. (C)

Guideline 8.1.c. All dialysis units caring for pediatric patients need to have on-site external automatic defibrillators and/or appropriate pediatric equipment available. Automated external defibrillators may be used for children 1-8 years of age, and should ideally deliver pediatric doses and have an arrhythmia detection algorithm.[46-48] (C)

Guideline 11. Determination and management of children with diabetes should follow recommendations provided by the American Diabetes Association.[49] (C)

Guideline 12.5. Determination and management of blood pressure in children should follow recommendations by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[50] (C)

12.5.a: Optimal systolic and diastolic blood pressure should be $<$95% for age, gender, and height. (B)

12.5.b: Management of hypertension on dialysis requires attention to fluid status and antihypertensive medications, minimizing intradialytic fluid accumulation by (C):

- education by dietitians every 3 months
- low salt intake (2 g/day sodium intake)
- increased ultrafiltration
- longer dialysis duration
- intradialytic sodium modeling to minimize intradialytic hypotension
- more than 3 dialysis treatments per week
- antihypertensives: consider if medications are cleared on dialysis.

Guideline 13. Management of dyslipidemias for prepubertal children with CKD and CKD Stage 5 should follow recommendations by National Cholesterol Expert Panel in Children and Adolescents. Postpubertal children or adolescents with CKD Stages 4 and 5 should follow the recommendations provided in the K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease.[51] (C)

Guideline 15. All children on dialysis with anemia should follow the K/DOQI Guidelines for Treatment of Anemia.[52] (C)

Guideline 16. There are no data available from large-scale studies of risk modification on which to make evidence-based recommendations. Two small studies in young adult chronic dialysis patients have shown coronary artery calcification to be associated with a higher calcium-phosphorus product. Although clinical practice guidelines for management of bone metabolism and disease in pediatric patients with CKD will be forthcoming, we recommend maintaining the corrected total calcium and phosphorus levels within the normal range for the laboratory used and the calcium-phosphorus prod-

uct below 55 mg^2/dL^2 in children on chronic dialysis. (C)

Research Recommendations

Longitudinal studies to determine the magnitude of CVD and identify cardiovascular disease risk factors are needed in pediatric chronic dialysis patients, studies are needed to quantify the magnitude of risk, identify modifiable risk factors, and identify possible interventions. Cardiovascular risk factors are likely to be similar to those in adults and include high blood pressure, dyslipidemia, obesity, physical inactivity, anemia, calcium and phosphorus abnormalities, family history of CVD and its risk factors, genetics, inflammation, malnutrition, oxidative stress, hyperhomocysteinemia, and smoking (in adolescents).

SECTION I. GUIDELINES ON EVALUATION AND MANAGEMENT OF CARDIOVASCULAR DISEASES

THE ASSESSMENT and treatment of both risk factors and end organs are essential in the management of cardiovascular diseases. The first section will deal with the end organs and will focus on cardiac, cerebrovascular and peripheral vascular diseases. Cardiac diseases have justifiably received the most attention because they are by far the most common cause of cardiovascular deaths in dialysis patients. Cerebrovascular diseases and peripheral vascular diseases, however, also lead to substantial morbidity and mortality and have often been overlooked by practitioners and clinical researchers.

The workgroup has faced dilemma in the scope and depth of the coverage of end organ diseases. There has been only one small randomized trial that demonstrated beneficial effects of specific cardioprotective drugs (namely, carvedilol) published in dialysis patients. Therefore, most guidelines described in this section are referred from published guidelines in the general population. Nonetheless, there are unusual features in the dialysis patients that the practitioners need to be aware of. For example, the pathophysiology and rate of progression of cardiac valvular calcification appear to be different from those in the general population. Surveillance and treatment strategies should take these caveats into consideration. On the other hand, the implant of tissue valves is proscribed in the existing ACC/AHA guidelines. More recent and stronger evidence, however, suggest that tissue valves are associated with equivalent outcomes in dialysis patients. These similarities, not only differences, between dialysis patients and the general population also need to be emphasized.

The section on end organ diseases is written for not only the nephrologists, but also the general practitioners, cardiologists, vascular surgeons and other practitioners.

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GUIDELINE 1: EVALUATION OF CARDIOVASCULAR DISEASE IN ADULT AND PEDIATRIC PATIENTS

Cardiovascular disease is prevalent in patients receiving dialysis therapies, and it affects long-term outcomes as well as the ability to deliver dialysis in some situations. Thus, it is important to evaluate the extent of all aspects of CVD in dialysis patients. In those patients with limited life expectancy due to severe noncardiac comorbidity, evaluation and therapy should be individualized.

1.1 At the initiation of dialysis, all patients—regardless of symptoms—require assessment for cardiovascular disease (CAD, cardiomyopathy, valvular heart disease, CBVD, and PVD), as well as screening for both traditional and nontraditional cardiovascular risk factors. (C)

1.1.a Echocardiograms should be performed in all patients at the initiation of dialysis, once patients have achieved dry weight (ideally within 1-3 months of dialysis initiation) (A), and at 3-yearly intervals thereafter (see Guideline 6). (B)

1.2 Children commencing dialysis should be evaluated for the presence of cardiac disease (cardiomyopathy and valvular disease) using echocardiography once the patient has achieved dry weight (ideally within 3 months of the initiation of dialysis therapy). (C) Children commencing dialysis should be screened for traditional cardiovascular risk factors such as dyslipidemia and hypertension. (C)

GUIDELINE 2: CORONARY ARTERY DISEASE

Ischemic heart disease (IHD) due to atherosclerotic CAD is common in dialysis patients. While its evaluation and treatment are important components of the ongoing care of dialysis patients, there are special considerations for both the evaluation and treatment in dialysis patients due to the issues of preservation of kidney function, vascular access, and bleeding tendencies.

2.1 The evaluation of CAD in dialysis patients depends on individual patient status. (C)

2.1.a If the patient is on the kidney transplant waitlist and is diabetic (and initial evaluation is negative for CAD), then evaluation for CAD every 12 months is recommended.

2.1.b If the patient is on the transplant waitlist but is not diabetic and is classified as "high risk,"* then evaluation for CAD every 24 months is recommended.

2.1.c If the patient is on the transplant waitlist and is classified as not high risk,* then evaluation for CAD every 36 months is recommended.

2.1.d If the patient is on the transplant waitlist with known CAD (and not revascularized), evaluation for CAD should be performed every 12 months.

2.1.e If the patient is on the transplant waitlist and has a history of PTCA or coronary stent, evaluation for CAD should be performed every 12 months.

2.1.f If the patient has "complete" coronary revascularization (i.e., all ischemic coronary vascular beds are bypassed), the first re-evaluation for CAD should be performed 3 years after coronary artery bypass (CAB) surgery, then every 12 months thereafter.

2.1.g If the patient has "incomplete" coronary revascularization after CAB surgery (i.e., not all ischemic coronary beds are revascularized), then evaluation for CAD should be performed annually.

2.1.h If there is a change in symptoms related to IHD or clinical status (e.g., recurrent hypotension, CHF unresponsive to dry weight changes, or inability to achieve dry weight because of hypotension), evaluation for CAD is recommended.

2.1.i Dialysis patients with significant reduction in LV systolic function (EF<40%) should be evaluated for CAD.

2.1.j Evaluation for heart disease should occur at initiation of dialysis and include a baseline electrocardiogram (ECG) and echocardiogram (see Cardiomyopathy guideline for echocardiography after dialysis initiation). Both of these tests provide information pertinent to, but not restricted to, CAD evaluation. Annual ECGs are recommended after dialysis initiation.

2.2 In patients fulfilling 2.1.a-2.1.i above, CAD evaluation should also include exercise or pharmacological stress echocardiographic or nuclear imaging tests. "Automatic" CAD evaluation with stress imaging is currently not recommended for all dialysis patients (i.e., patients not fulfilling 2.1.a-2.1.i). Stress imaging is appropriate (at the discretion of the patient's physician) in selected high-risk dialysis patients for risk stratification even in patients who are not renal transplant candidates. (C)

2.3 Patients who are candidates for coronary interventions and have stress tests that are positive for ischemia should be referred for consideration of angiographic assessment. (C)

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* High-risk (more than 20% per 10 years cardiovascular event rate risk) according to Framingham data includes those with two or more "traditional" risk factors, a known history of coronary disease, LV ejection fraction ≤40%, or PVD.[53]

2.4 Special considerations in dialysis patients regarding CAD evaluation include the following: (C)

2.4.a To minimize the risk of potential volume overload from the performance of angiographic studies, iso-osmolar radiocontrast media (e.g., iodixanol) should be used.

2.4.b Some dialysis patients have residual renal function; there are no data on the value of "nephroprotective" strategies to reduce the potential risk of contrast nephropathy in these patients. The use of *N*-acetylcysteine (and iodixanol) is appropriate in dialysis patients with residual renal function, as both may offer benefit without known harm. Sodium bicarbonate and hydration are not routinely recommended, as intravascular volume expansion may pose risk to dialysis patients with increased cardiac filling pressures.

2.5 In patients undergoing invasive coronary procedures, it is important to avoid internal jugular sites and to preserve brachial and radial arteries for future dialysis catheter and arteriovenous fistula creation, respectively. (C)

2.6 Patients undergoing planned invasive procedures for evaluation or treatment of CAD should be assessed for hemorrhagic risk and presence of anemia, as anticoagulants and/or antiplatelet agents may be administered adjunctively for percutaneous coronary intervention. (C)

RATIONALE

At least a third of incident dialysis patients have a history of CAD.[54] In some patients, the development of left ventricular (LV) dysfunction or clinically evident CHF may be a reflection of underlying IHD. Evaluation for CAD should be considered even in dialysis patients who are not candidates for kidney transplantation, since they have high event rates for CAD, early hazard of acute myocardial infarction (MI) after initiation of chronic dialysis, and high mortality rate following acute MI. The purposes of using stress imaging modalities for CAD evaluation are risk stratification (i.e., prediction of likelihood of future events related to CAD), detection of obstructive CAD, and assessment of myocardial ischemic burden after coronary revascularization and/or medical therapy.

Diagnostic Techniques

The optimal modality is strongly dependent on individual institutional expertise. Exercise ECG is not recommended because of poor exercise tolerance in general, and high prevalence of left ventricular hypertrophy (LVH) in dialysis patients, although published data have suggested a lower accuracy for CAD detection in dialysis patients using stress nuclear or echocardiographic imaging techniques, compared to the general population.[55]

Stress echocardiography can be performed in different ways. Similar to exercise ECG, exercise echocardiography is, in general, unsuitable for the majority of dialysis patients due to noncardiac exercise limitations. Echocardiography, in conjunction with stress by dobutamine, is a standard method. However, it should be cautioned that this method may be associated with approximately 2%-4% risk of transient atrial fibrillation in dialysis patients, compared to only 0.5% in the general population.[56] Stress echocardiography can also be performed in conjunction with a vasodilator, such as adenosine or dipyridamole. The accuracy of this method in dialysis patients is poorly defined. The combination of dobutamine and a vasodilator has also been advocated for stress echocardiography, but there are no published data on this technique in the dialysis population. An advantage of echocardiography is that prestress imaging can provide additional information on LV ejection fraction and dimensions, valvular disease, pulmonary artery pressure, and volume status, as well as associated pericardial disease (e.g., pericardial effusion). *(Weak)*

The same techniques of stress can be applied to nuclear scintigraphy. Stress by exercise poses the same problem as exercise ECG and exercise echocardiography because of the limited noncardiac exercise tolerance in dialysis patients. Stress by adenosine and dipyridamole in conjunction with nuclear scintigraphy is a standard method recommended by the American College of Cardi-

ology (ACC)/American Heart Association (AHA) guideline on imaging. Data on dobutamine-induced stress scintigraphy in dialysis patients are very limited. Combined stress using exercise and a vasodilator produced promising results in a single-center study of dialysis patients,[57] but it has not been well examined in diabetic dialysis patients (only 14% of Dahan's study cohort had diabetic CKD). For the purpose of risk stratification, the published data suggest that the accuracy of dobutamine echocardiography and vasodilator-induced stress nuclear scintigraphy are comparable in kidney transplant candidates. A meta-analysis that grouped both techniques together found that stress imaging was predictive of future cardiac death and MI in kidney transplant candidates.[58] *(Weak)*

For the purpose of detecting obstructive CAD in dialysis patients, the available data suggest that vasodilator-induced stress nuclear scintigraphy is less sensitive than dobutamine echocardiography. These data are predominantly derived from diabetic dialysis patients who were being evaluated for kidney transplantation, as these patients have been the focus of clinical studies on noninvasive CAD screening. This distinction may be important in monitoring patients for the detection of occult re-stenosis after percutaneous coronary intervention.

Ultrafast cardiothoracic (CT) scan or electron-beam computerized tomography (EBCT) can detect calcification of the coronary arteries. Limited data suggest that, while EBCT has a potential role in risk stratification in dialysis patients, the physiological consequences of coronary calcification cannot be assessed by EBCT. The correlation between coronary calcification and luminal diameter in dialysis patients is less certain than in the general population, since vascular calcification in this population is often the result of medial calcification rather than atherosclerosis. At the present time, EBCT (or other ultrafast CT) is not recommended for the diagnosis of CAD in dialysis patients. Experience with cardiac magnetic resonance imaging (MRI) in dialysis patients is very limited and the technique is not widely available. *(Weak)*

LIMITATIONS

- Most studies deal with patients who are eligible for kidney transplantation. There are only sparse data on general dialysis patients.
- The specific noninvasive screening method for CAD is dependent on the institution.
- No decision analysis has been done on the trade-off of performing angiography versus further diminution of residual kidney function.

IMPLEMENTATION ISSUES

- The diagnosis of obstructive CAD in patients who do not have symptoms of myocardial ischemia may raise difficult therapeutic issues in some patients, as the choice of subsequent treatment is predominantly opinion-based. Additional costs and potential risks of therapy could be incurred with the diagnosis of previously unsuspected CAD through screening.

RESEARCH RECOMMENDATIONS

- Prospective trials are needed to examine the accuracy of noninvasive imaging in dialysis patients and its utility for clinical management.

GUIDELINE 3: ACUTE CORONARY SYNDROMES

The diagnosis of acute coronary syndromes (ACS) in dialysis patients and in the general population is usually based on the triad of symptoms, ECG findings, and cardiac biomarkers. The outcomes of patients on dialysis with ACS are often poor, which may be related to the lack of a consistent and standard approach to the treatment of ACS.

3.1 All dialysis patients presenting with ACS should be treated as in the nondialysis population, with the exception of specific attention to drugs that have altered clearances in kidney failure (e.g., low molecular weight heparin). These therapies include percutaneous coronary intervention (PCI), CABG, antiplatelet agents, beta-blockers, thrombolytic therapy, and lipid-lowering agents. (C)

3.1.a Dialysis patients with ST-segment elevation MI should receive acute reperfusion therapy (as do patients in the nondialysis population). With the potential for increased hemorrhagic risk associated with thrombolytic therapy, emergent PCI is the preferred treatment if it is available. (C)

3.2 The timing of dialysis in the first 48 hours after ACS should take into account individual risk factors. (C)

RATIONALE

There are no data regarding the safety or risk associated with HD in the first 48 hours after ACS. Collaboration between nephrology teams and cardiology teams caring for these patients should take into consideration volume status, electrolyte disturbances, and bleeding potential. Dialysis prescriptions should be adjusted to maximize benefits while reducing the risk of hypotension during this vulnerable period.

The mortality after acute MI (Fig 1) in dialysis patients has been reported to be approximately 75% in 2 years, in part due to inadequate post-MI treatment.[7] Prophylactic care that is considered to be standard in the general population may improve upon this very poor outcome in dialysis patients. Therefore, the use of aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and thrombolytic therapy are recommended although controlled trials in dialysis patients are lacking. These therapies have been found to be protective in retrospective observational studies in various stages of CKD.[8,59-61] Abciximab and tirofiban (glycoprotein platelet [GP] IIb/IIIa inhibitors) should also be considered as adjunctive therapy in ACS in dialysis patients. The use of adjunctive antithrombotic and antiplatelet agents during PCI presents special problems in dialysis patients, because of the increased risk of hemorrhage. Bivalirudin is a direct thrombin inhibitor specifically studied in dialysis patients with dosing recommendations and should be preferentially considered. When a GPIIb/IIIa antagonist is used, abciximab and tirofiban should be considered preferred agents, since no dosing changes are required for abciximab, and dialysis-specific dosing recommendations are available for tirofiban. Abciximab is typically used for PCI, as the clearance of the drug is not altered in dialysis patients. There are CKD—but not dialysis—patient studies dealing with this issue. One study reported safety of abciximab for Cr >2.0 mg/dL,[62] while another showed no increase in bleeding for renal failure versus no renal failure for abciximab in PCI.[63] However, increased bleeding with abciximab in renal failure has been reported.[64] Increased bleeding but reduced in-hospital mortality in CKD patients with ACS treated with IIb/IIIa antagonists has also been shown.[65] *(Weak)*

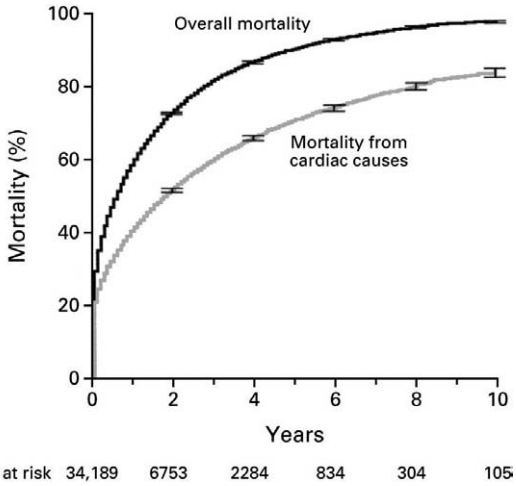

Fig 1. Estimated mortality of dialysis patients after acute MI. Reproduced with permission.[7]

LIMITATIONS

- There have been very few dialysis-specific clinical trials.
- It is difficult to assess bleeding diathesis, and therefore risk associated with GPIIb/IIIa inhibitors, in individual dialysis patients.

IMPLEMENTATION ISSUES

- There may be reluctance of clinicians to employ fibrinolytic agents for ACS in dialysis patients due to concerns with hemorrhage. The risk of hemorrhage in dialysis patients will be higher with fibrinolytic, antithrombotic, and antiplatelet agents.

RESEARCH RECOMMENDATIONS

- Clinical trials of ACS treatment are required that specifically target all ranges of CKD, including dialysis patients.

GUIDELINE 4: CHRONIC CORONARY ARTERY DISEASE

The processes by which atherosclerotic disease may be exacerbated by the uremic milieu, and the outcomes of patients on dialysis with established CAD, are worse than outcomes in the general population.

4.1 The medical management of chronic CAD in dialysis patients should follow that of the general population. In particular, patients should receive acetylsalicylic acid (ASA), beta-blockers, nitroglycerin, ACE inhibitors or angiotensin receptor blockers (ARB), statins, and/or calcium-channel blockers (CCB) as indicated. Dose adjustments are required for medications that are renally excreted or dialyzed. (C)

4.2 Unique aspects of management in the dialysis population include:

4.2.a Maintenance of hemodynamic dry weight. (C)

4.2.b Maintenance of hemoglobin levels in accordance with K/DOQI Guidelines.[52] (B)

4.2.c Modification of dosing regimens so that cardiovascular medications do not adversely impact the delivery of dialysis and ultrafiltration. Nocturnal dosing of medications should be considered. (C)

4.2.d Loop diuretics to increase urine output may be helpful for those patients with substantial residual renal function. (C)

4.3 In patients with obstructive CAD lesions, PCI and CABG are appropriate revascularization techniques. (C)

4.3.a Drug-eluting or conventional stents should be implemented according to local practice. The incidence of restenosis after PCI with drug-eluting stents is reduced in the nondialysis population. As the risk of restenosis is higher in dialysis patients, the use of drug-eluting stents is favored.

4.3.b Patients with three-vessel and/or Left main disease should undergo CABG as preferred therapy. (C)

RATIONALE

Management of CAD (Weak)

Maintenance of target dry weight is important for the management of heart disease. Target dry weight should be periodically assessed because it may change over time. This is particularly true for diabetic and elderly patients, since their muscle mass may decline over time. Caution should be exercised when using nitrates in low preload states (e.g., hypovolemia at the end of HD session), as these states may potentiate the hypotensive effect of the drug. The hemodynamic and electrophysiological effects of CCBs are markedly different from each other, and these differences should be evaluated when selecting a suitable therapy.

Clopidogrel is approved in the general population for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events, including CAD. Most dialysis patients would theoretically be candidates for long-term clopidogrel therapy. It should be prescribed for all patients with coronary stents and considered in other patients with stable CAD or established ASCVD. All dialysis patients with CAD who are not allergic to ASA should receive ASA. The efficacy-to-risk ratio of ASA in combination with clopidogrel—compared to ASA alone—for the secondary prevention of ASCVD events is unknown in dialysis patients; one undefined risk is hemorrhage. There are data indicating a two-fold relative hemorrhagic risk with ASA + clopidogrel versus placebo alone.[66] Since it may significantly increase the risk of hemorrhage, clopidogrel should be withheld (typically for 1 week) before major elective surgery. In contrast, withholding ASA before surgery is usually unnecessary. Since the use of clopidogrel is mandatory for at least 30 days after coronary stent placement, elective major surgery—including renal transplantation—should generally be postponed to allow for discontinuation of clopidogrel before surgery. For this reason, in the immediate poststent period (when clopidogrel is required), it may be appropriate to temporarily suspend the active waitlist status of patients awaiting cadaveric renal transplantation until the clopidogrel can be discontinued. This decision should be made by consultation of the patient's nephrologist, cardiologist, and transplant surgeon (with

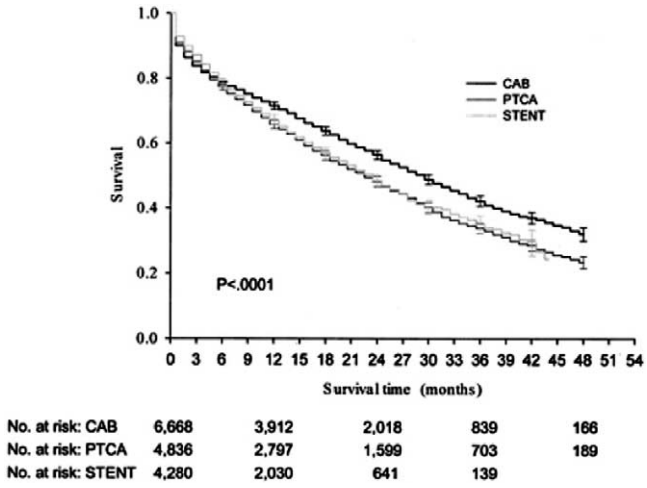

Fig 2. Estimated all-cause survival of dialysis patients after CABG, PTCA, and stenting. Bars indicate SEMs. Reprinted with permission (http://lww.com)[67]

attention to the clinical profile of the particular patient).

Coronary Revascularization (Weak)

The short-term and long-term mortality after coronary revascularization procedures in dialysis patients is considerably higher than those in the general population. Coronary revascularization can be performed with either surgical or percutaneous approaches. In diabetic dialysis patients, there is no difference in survival between percutaneous angioplasty with and without stenting. In contrast, stents offer better outcomes than angioplasty without stents in nondiabetic dialysis patients. In either diabetic or nondiabetic patients, the mortality at 6-9 months in retrospective studies is higher after PCI, compared to coronary bypass surgery, although the mortality after PCI is lower within 90 days after the procedure (see Fig 2 and Table 1).[55,67] Observational studies support the conclusion that surgical coronary revascularization is associated with better outcomes than percutaneous coronary intervention in dialysis patients.[67-69] The survival advantage of surgical coronary bypass over PCI in dialysis patients is attributable to the use of internal mammary artery bypass grafts.[70] Therefore, dialysis patients most likely to benefit from coronary bypass surgery are those who are suitable candidates for internal mammary graft utilization. In dialysis patients not receiving internal mammary grafts, there is no apparent survival advantage compared to PCI, but there is still a reduced rate of repeat coronary revascularization. There are currently no data on the impact of coronary brachytherapy or drug-eluting stents on re-stenosis after PCI in dialysis patients, but these techniques may improve the long-term outcome of dialysis patients after PCI.

These general trends notwithstanding, the selection of coronary artery revascularization techniques should also be guided by local institutional experience, since a wide variety of outcome data from single centers has been reported in the literature.

The risk of re-stenosis after percutaneous coronary angioplasty and stent placement is higher in dialysis patients than in the general population (see Table 1).[55,71] The failure rate of various types of coronary grafts has not been studied in angiographic series in dialysis patients. In addition, re-stenosis in dialysis patients may not be clinically apparent, since dyspnea and angina can occur in the setting of volume overload. Therefore, in all dialysis patients who have undergone PCI, provocative stress imaging should be considered to detect clinically silent re-stenosis 12-16 weeks after PCI. This latter recommendation may be modified as more data on drug-eluting stents in dialysis patients become available.

LIMITATIONS

- All published studies are retrospective analyses. There are no randomized controlled trials comparing PCI and surgical bypass of coronary arteries in dialysis patients.

Table 1. Comparison of Surgical Interventions for CAD To Prevent Future Cardiovascular Outcomes

Author, Year	Mean Study Duration	No. of Subjects[a]	Applicability	Surgical Treatments	Cardiovascular Outcome	Results[b] (Univariate)	Results[b] (Multivariate)	Quality
Herzog 2002 [67]	18 mo	15,784[c]	↑↑↑	CABG vs PTCA	All-cause death	**CABG**	**CABG**	●
				CABG vs Stent		**CABG**		
				Stent vs PTCA		⇔	**Stent**	
Herzog 1999 [68]	21 mo	14,306[d]	↑↑↑	CABG vs PTCA	All-cause death	**CABG**	**CABG**	●
Hase 2001 [72]	17 mo	103	↑↑	Stent[e] vs PTCA	Cardiac death	⇔		●
Rinehart 1995 [73]	28 mo	84	↑↑	CABG vs PTCA	All-cause death	CABG		●
Agirbasli 2000 [74]	1 yr	252	↑↑	CABG vs PTCA	All-cause death	⇔		○
Herzog 2002 [67]	18 mo	15,784[c]	↑↑↑	CABG vs PTCA	Cardiac death	**CABG**	**CABG**	●
				CABG vs Stent		**CABG**		
				Stent vs PTCA		⇔	**Stent**	
Herzog 1999 [68]	21 mo	14,306[d]	↑↑↑	PTCA vs CABG	Cardiac death	**CABG**	**CABG**	●
Hase 2001 [72]	17 mo	103	↑↑	Stent[e] vs PTCA	Cardiac death	⇔		●
Rinehart 1995 [73]	28 mo	84	↑↑	PTCA vs CABG	Cardiac death	CABG	CABG	●
Herzog 1999 [68]	21 mo	14,306[d]	↑↑↑	CABG vs PTCA	Cardiac death or myocardial infarction	**CABG**	**CABG**	●
Hase 2001 [72]	17 mo	103	↑↑	Stent[e] vs PTCA	Death or event	**Stent**		●
Rinehart 1995 [73]	28 mo	84	↑↑	CABG vs PTCA	Cardiac death or event	**CABG**	**CABG**	●
Koyanagi 1996 [75]	2.3 yr	43	↑↑	CABG vs PTCA	Cardiac death or event	**CABG**		○
Herzog 1999 [68]	21 mo	14,306[d]	↑↑↑	CABG vs PTCA	Myocardial infarction	**CABG**	**CABG**	●
Hase 2001 [72]	17 mo	103	↑↑	Stent[e] vs PTCA	MACE	**Stent**	**Stent**	●
Rinehart 1995 [73]	28 mo	84	↑↑	CABG vs PTCA	Myocardial infarction	CABG	**CABG**	●
Agirbasli 2000 [74]	1 yr	252	↑↑	CABG vs PTCA	Myocardial infarction	⇔		○
Hase 2001 [72]	17 mo	103	↑↑	Stent[e] vs PTCA	Repeated intervention	**Stent**		●
Agirbasli 2000 [74]	1 yr	252	↑↑	CABG vs PTCA	PTCA or CABG	**CABG**		○

Abbreviations: CABG, coronary artery bypass graft; MACE, major adverse cardiac events; PTCA, percutaneous transluminal coronary angioplasty.

a Combined HD and PD.

b CABG = Nonsignificant outcome benefit for CABG; **CABG** = Statistically significant outcome benefit for CABG; **Stent** = Statistically significant outcome benefit for coronary artery stenting; ⇔ = Procedures resulted in similar outcomes.

c First coronary revascularization procedure occurring after initiation of renal replacement therapy from January 1995 to December 1998.

d First coronary revascularization procedure occurring after initiation of renal replacement therapy from January 1978 to June 1995.

e Either coronary stenting with balloon angioplasty or with rotational atherectomy.

- There have also been no studies in the dialysis population on the newest generation of drug-eluting stents (e.g., stents eluting sirolimus or paclitaxel).

IMPLEMENTATION ISSUES

- There is concern over the potential effects of antianginal agents on intradialytic hemodynamics.
- The increased risk of hemorrhage associated with ASA + clopidogrel therapy may deter its use, especially before major surgery.
- Higher in-hospital postoperative mortality in dialysis patients, compared to PCI, might discourage some institutions from performing coronary bypass surgery, although the long-term outcome could be better with surgery. This early mortality could be a concern for quality assurance entities, as in-hospital and 30-day mortality are traditionally used as benchmarks. As in-hospital mortality for PCI is considerably less than CABG (and the benefit of CABG is only apparent at greater than six months post-procedure), it is plausible that PCI could appear more attractive by commonly used benchmarks. The cost for drug-eluting stents is also a potential concern.

RESEARCH RECOMMENDATIONS

- Randomized trials of PCI are required, using sirolimus-eluting or paclitaxel-eluting stents compared to coronary bypass surgery.

GUIDELINE 5: VALVULAR HEART DISEASE

The presence of valvular heart disease (VHD) impacts long-term outcomes, as in the general population. In addition, VHD in dialysis patients may impair the ability to adequately deliver dialysis, which, in turn, may limit ultrafiltration and toxin removal, resulting in exacerbation of CVD.

5.1 Evaluation of VHD in dialysis patients:

5.1.a Patients should be evaluated for the presence of VHD and for follow-up of VHD in the same manner as the general population except for frequency of follow-up for aortic stenosis. (C)

5.1.b Special considerations for echocardiographic evaluation in dialysis patients:

5.1.b.i Dry weight optimization should be achieved prior to testing, to enhance the interpretation of results. (B)

5.1.b.ii The interpretation of repeat echocardiographic evaluations should be done with consideration of the relationship between the echo exam and either the HD treatment or the presence or absence of PD fluid in the peritoneal cavity. (B)

5.2 Management of VHD in dialysis patients:

5.2.a Published recommendations for the management of VHD in the general population should be followed. (C)

5.2.b Both mechanical and tissue valves can be used for replacement, with similar outcomes, in dialysis patients. (B)

5.2.c Asymptomatic dialysis patients on the transplant waitlist with moderate or more severe aortic stenosis (aortic valve area $\leq$1.0 cm^2) should have annual Doppler echocardiograms (as aortic stenosis progresses faster in dialysis patients than general population). The same frequency of follow-up is appropriate in other dialysis patients who would be suitable candidates for aortic valve replacement based on overall clinical status. (C)

5.2.d Newly or increasingly symptomatic (e.g., displaying dyspnea, angina, fatigue, and unstable intradialytic hemodynamics) patients with VHD should be (re)-evaluated for VHD severity by echocardiography (and referred to a cardiologist for further evaluation if the patient is deemed suitable for intervention on clinical grounds). (C)

5.3 Children with VHD should be evaluated by echocardiography. Management of valvular disease should follow recommendation provided by the ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease VI.[45] (C)

RATIONALE

Medical Treatment

Cardiac calcification, including that of heart valves, occurs at a faster rate in dialysis patients compared to the general population. The rate of progression of aortic stenosis is faster in dialysis patients.[76,77] A rate of aortic stenosis progression of 0.23 cm^2/year versus 0.05-0.1 cm^2/year has been reported in the general population.[77] This is presumably a complication of the metabolic milieu of uremia, which includes hyperparathyroidism and high calcium-phosphate product (see the K/DOQI Bone Metabolism and Disease Guidelines).[78-80] It is uncertain whether pharmacological agents can alter the rate of progression of this process, although sevelamer has been shown to retard coronary arterial and aortic calcification specifically in the dialysis population, based on clinical data utilizing EBCT.[81] In addition, statins have been suggested to inhibit calcification and bone formation in cardiac valves, currently the subject of a proposed clinical trial in the general population. *(Weak)*

Cardiac filling pressures are greatly affected by intravascular volume. The maintenance of dry weight is a critical part of the management of valvular heart disease.

***Operative Treatment* (Weak)**

Balloon valvuloplasty is not recommended for aortic stenosis in the general population because of poor long-term results due to re-stenosis, and it is also not recommended for dialysis patients. Severe mitral calcification (and mitral insufficiency) is quite common in dialysis patients, making mitral valvuloplasty inappropriate for many dialysis patients. Percutaneous balloon valvuloplasty of the mitral valve in dialysis patients should be performed only in centers with experienced operators.

The risk of in-hospital and long-term mortality associated with aortic and/or mitral valve replacement is considerably higher in the dialysis population compared to the general population. In the U.S., the in-hospital mortality of dialysis patients with valvular replacement surgery is almost 20% and the two-year mortality is approximately 60%.[67]

The selection of the type of prosthetic heart valve is the only practice guideline related to valvular heart disease that is at significant variance from the current ACC/AHA guidelines. The current ACC/AHA practice guidelines proscribe the use of bioprosthetic (i.e., tissue) heart valves for HD patients (Class III: "conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful and in some cases may be harmful"). This proscription is based only on four cases collected over two decades ago, which led to the perception that bioprosthetic valves were associated with accelerated calcification and failure in HD patients. The more recent epidemiological data on 5,825 dialysis patients (4,545 were HD only, and there was no difference in the HD subset) undergoing cardiac valvular surgery from the USRDS found that approximately 900 patients had bioprosthetic valves. Similar findings are reported in smaller series on the noninferiority of bioprosthetic valves in dialysis patients (Table 2). There was no difference in two-year mortality (60%) in patients who received bioprosthetic valves (relative risk = 1.00) and those who received mechanical valves (Fig 3). Therefore, both tissue

Table 2. Effect of Tissue versus Nontissue Valve Replacement on Prevention of Future Cardiovascular Outcomes

Author, Year	Mean Study Duration	No. of Subjects	Applicability	Surgical Treatments	Cardiovascular Outcome	Results[a] (Univariate)	Results[a] (Multivariate)	Quality
Herzog 2002 [70]	19 mo	5858	↑↑↑	Tissue vs nontissue valves (all)	All-cause death	⇳		⊕
				Tissue vs nontissue AV			⇳	
Kaplon 2000 [82]	Up to10 yr	42	↑↑	Tissue vs nontissue valves (all)	All-cause death	⇳		⊕
Herzog 2002 [70]	19 mo	5858	↑↑↑	Tissue vs nontissue valves (all)	Cardiovascular death	⇳		⊕
				Tissue vs nontissue AV			⇳	
Lucke 1997 [83]	32 mo	19	↑	Tissue vs nontissue valves (all)	Stroke	Tissue		⊕

Abbreviation: AV, aortic valve.
a **Tissue** = Statistically significant outcome benefit for tissue valve graft; ⇳ = Valve types resulted in similar outcomes.

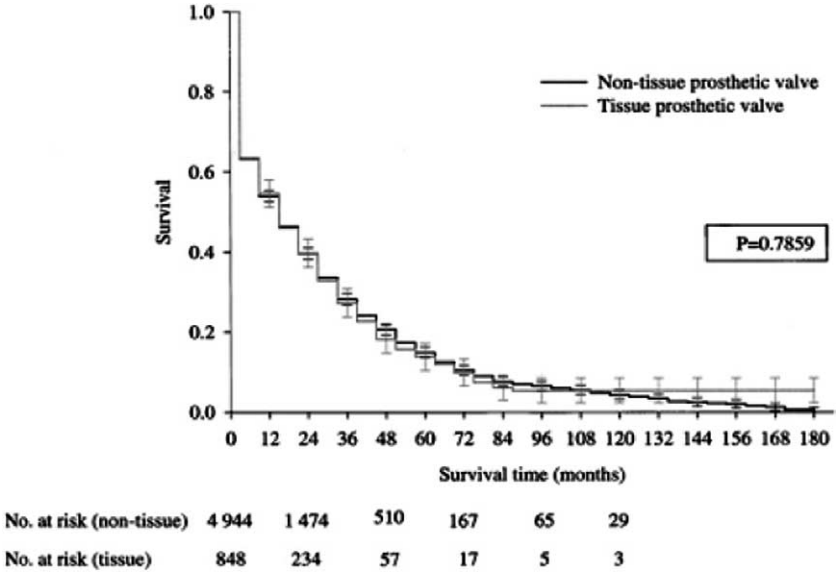

Fig 3. Estimated all-cause survival of dialysis patients after heart valve replacement surgery with tissue and nontissue prosthetic valves. Bars indicate standard errors. Reprinted with permission (http://lww.com).[70]

(bioprosthetic) and nontissue (mechanical) prosthetic heart valves are appropriate for dialysis patients. In dialysis patients with a history of life-threatening hemorrhage and no other indications for chronic anticoagulation, bioprosthetic valves may even be preferable.

LIMITATIONS

- The mortality risk of nonintervention or delayed intervention is not known.

IMPLEMENTATION ISSUES

- The current guideline provided by the AHA/ACC task force could be a deterrent to this new K/DOQI Guideline for the use of bioprosthetic valves. Ideally, the ACC/AHA guideline on this particular issue would be changed.

RESEARCH RECOMMENDATIONS

- Observational studies of the newer generation of bioprosthetic valves (e.g., stentless valves) are required.
- Studies on the timing of valve replacement in relation to survival will provide valuable information (e.g., do clinicians wait too long to refer patients for surgery?).

GUIDELINE 6: CARDIOMYOPATHY (SYSTOLIC OR DIASTOLIC DYSFUNCTION)

The prevalence of systolic or diastolic dysfunction, or overt LVH, is estimated to be at least 75% at dialysis initiation (see also Guideline 1). *De novo* and recurrent heart failure occurs in a substantial proportion of patients on dialysis, and impacts on morbidity and mortality, as well as the ability to deliver adequate dialysis.

6.1 Evaluation of cardiomyopathy (systolic or diastolic dysfunction) in dialysis patients:

6.1.a Dialysis patients should be evaluated for the presence of cardiomyopathy (systolic or diastolic dysfunction) in the same manner as the general population, using echocardiographic testing. (C)

6.1.b Patients should be re-evaluated if there is change in clinical status (e.g., symptoms of CHF, recurrent hypotension on dialysis, post-cardiac events) or considered for kidney transplant. (C)

6.1.c Echocardiograms should be performed in all patients at the initiation of dialysis, once patients have achieved dry weight (ideally within 1-3 months of dialysis initiation) (A), and at 3-yearly intervals thereafter. (B)

6.1.d As in the general population, dialysis patients identified with significant reduction in LV systolic function (EF <40%) should be evaluated for CAD (if not done previously). This evaluation may include both noninvasive testing (stress imaging) and invasive testing (coronary angiography). In patients at high risk for CAD (e.g., those with diabetic CKD), coronary angiography may be appropriate, even in patients with negative stress imaging tests, due to lower diagnostic accuracy of noninvasive stress imaging tests in CKD patients. (C)

6.2 The treatment of cardiomyopathy in the dialysis population is similar to that in the nondialysis population, with the important exception of potential effects of therapeutic agents (e.g., ACE inhibitors or beta-blockers) on intrahemodialytic hemodynamics. (C; B for carvedilol)

6.2.a Congestive heart failure unresponsive to changes in target dry weight may also be a complication of unsuspected VHD or IHD; clinical re-evaluation should be considered in these patients. (C)

6.2.b Dosing of therapeutic agents may need to be empirically individualized to hemodialysis schedules (in hypotensive patients). (C)

6.2.c The consistent maintenance of euvolemia is a cornerstone of treatment of CHF in dialysis patients. (C)

6.3 Target "hemodynamic dry weight" may need to be adjusted to compensate for hemodynamic effects of therapeutic agents. (C)

6.4 Children should be evaluated for the presence of cardiomyopathy (systolic and diastolic dysfunction) using echocardiographic testing. (C)

RATIONALE

Diagnosis (Moderately Strong)

Congestive heart failure in dialysis patients is a complex condition. It often reflects the interaction of hypertensive heart disease (resulting in LVH and noncompliant vasculature), hypervolemia, anemia, IHD, and—to a lesser extent—VHD. In addition, there are abnormalities of the myocardial ultrastructure (e.g., fibrosis) that may make the dialysis patient particularly vulnerable to ischemia and, importantly, sudden cardiac death (SCD), the single largest cause of death in this population. Left ventricular hypertrophy, LV systolic dysfunction (decreased ejection fraction), and CHF are independent predictors of poor survival in dialysis patients, as in the general population. In one prospective cohort study[84] abnormal LV systolic function and LV geometry were independently associated with mortality. Other studies also suggest the prognostic importance of echocardiographically-defined LV sys-

tolic dysfunction[85,86] and LV mass[84-88] as predictors of cardiovascular outcome (Table 3, Table 4). Left ventricular hypertrophy and systolic dysfunction cannot be accurately assessed solely by history, physical examination, or chest X-ray. Left ventricular systolic performance, however, can be accurately measured by echocardiography, gated nuclear scintigraphy, ultrafast CT, contrast ventriculography, or cardiac MRI.

Echocardiography (M-mode, 2-D, or Doppler) provides information on LV function, chamber dimension and geometry, presence of LVH, pulmonary artery systolic pressure, VHD, and volume status. No other single imaging modality provides this potential wealth of data in the screening of noncoronary heart disease.

Treatment (Moderately Strong)

The consistent maintenance of euvolemia and normal blood pressure is a goal of treatment. Good volume control is a cornerstone of antihypertensive therapy and cardiac management. Clinicians must be alerted to the changing lean body mass in these patients and adjust the target dry weight accordingly, on a periodic basis. When CHF appears to be refractory, ultrafiltration with simultaneous direct-pressure monitoring using right-heart catheterization (e.g., a pulmonary artery catheter) may be helpful to define the optimal intravascular volume. Echocardiography can provide key, noninvasive measurement of cardiac filling pressures and volume status with Doppler imaging for estimation of pulmonary artery pressure, pulmonary vein (and diastolic transmitral), qualitative assessment of pulmonary venous and left atrial pressure, and inferior vena cava (IVC) imaging for estimation of right atrial pressure. Optimal blood pressure in HD patients has not been defined clearly, and should probably incorporate predialysis and postdialysis systolic and diastolic blood pressures. Quotidian long-duration dialysis may be more effective in optimizing fluid volume in patients who have difficulty attaining presumed dry weight with conventional, thrice-weekly HD.

In the general population, large multicenter studies have validated the efficacy of certain agents for the treatment of CHF in patients with impaired LV systolic function. Agents that are known to improve cardiovascular outcome in clinical trials (e.g., beta-blockers) are preferred.

Table 3. Presence of Systolic Dysfunction on Echocardiogram as a Predictor of Future CVD Outcomes[a]

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	Results (Univariate)	Results (Multivariate)	Quality
Harnett 1995 [85]	41 mo	432		↑↑	All-cause death	⇧		○
Foley 1995 [84]		420					↑	
Harnett 1995 [85]		432			New onset congestive heart failure	↑	⇧	
Parfrey 1996 [86]		336	168		New onset ischemic heart disease	↑	↑	
Harnett 1995 [85]		432			Recurrent congestive heart failure	⇧	↑	

a All analyses from same set of patients.

Table 4. Increased LV Mass Index on Echocardiogram as a Predictor of Future Cardiovascular Outcomes

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	Results (Univariate)	Results (Multivariate)	Quality
Zoccali 2001 [87]	29 mo	203	51	↑↑	All-cause death	↑		●
Harnett 1995 [a 85]	41 mo	432		↑↑	All-cause death	⇧		○
Foley 1995 [a 84]		420					⇧	
De Lima 2001 [88]	79 mo	103		↑↑↑	All-cause death	↑	↑	○
Blacher 1998 [92]	25 mo	79		↑↑↑	All-cause death	⇳	⇳	○
Zoccali 2001 [87]	29 mo	203	51	↑↑	Cardiovascular death	↑		●
Blacher 1998 [92]	25 mo	79		↑↑↑	Cardiovascular death	⇳	⇳	○
Zoccali 2001 [87]	29 mo	203	51	↑↑	Cardiovascular event	⇳		●
Blacher 1998 [92]	25 mo	79		↑↑↑	Cardiovascular event	⇳		○
Harnett 1995 [a 84]	41 mo	432		↑↑	New onset congestive heart failure	↑	⇧	○
Parfrey 1996 [a 86]	41 mo	336	168	↑↑	New onset ischemic heart disease	↑		○
Harnett 1995 [a 85]	41 mo	432		↑↑	Recurrent congestive heart failure	⇳	⇳	○

a Same set of patients.

Special dosing regimens may be necessary to facilitate the delivery of HD and ultrafiltration. Among all the medications used to treat CHF in the general population, only carvedilol has been shown to be effective in a randomized trial in the dialysis population. In a single, small study of dialysis patients with dilated cardiomyopathies, carvedilol was found to improve LV function and decrease hospitalization, cardiovascular deaths and total mortality.[89,90] The degree of improvement was comparable to that observed in the general population. Other beta-blockers may have effects similar to carvedilol, but there are no studies to confirm or refute this hypothesis. Pending further data, carvedilol should be the preferred beta-blocker for the treatment of dialysis patients with severe dilated cardiomyopathy. *(Moderately Strong)*

Angiotensin-converting enzyme inhibitors have been used extensively in the general population for the treatment of CHF. In randomized placebo-controlled trials, ACE inhibitors have been shown to improve survival in patients with depressed LV function and symptomatic heart failure, and to improve survival in asymptomatic patients with depressed LV function. However, minimal data exist on the use of ACE inhibitors in dialysis patients with CHF. Nonetheless, the Work Group recommends that these agents be used in patients with CHF and impaired LV function. The dosing schedules may need to be individualized for each dialysis session in order to avoid intradialytic hypotension. One randomized prospective study, employing a 2×2 design on simvastatin and enalapril, found a 30% 6-month drop-out rate as a result of hypotension in the enalapril arm.[91] *(Weak)*

Digitalis glycosides (e.g., digoxin) should be considered as third-line therapy for CHF. A major indication for this class of agent is ventricular rate control in patients with atrial fibrillation. In most dialysis patients, diuretics are ineffective and not indicated for removing excess volume. There is a paucity of data on the use of spironolactone or eplerenone in dialysis patients with CHF. Serum potassium levels have been reported to increase in dialysis patients receiving spironolactone and potassium loading. Pending further safety data, this agent should be used with great caution, or not at all. *(Weak)*

LIMITATIONS

- There is only a single, small trial for carvedilol in dialysis patients.
- There are no data on the use of ACE inhibitors in dialysis patients with potential hypotension.
- The longitudinal cohort study on echocardiographic changes in chronic HD patients by Foley and Parfrey was conducted in patients recruited from 1982-1991, mostly before the use of erythropoietin.[84] Despite the newer therapies that became available since then, cardiac events are still the major cause of death and cardiac mortality increases with years on dialysis, according to USRDS data.[2] Long-term echocardiographic surveillance of dialysis patients in the modern treatment era is lacking. The appropriate time interval for re-evaluation in chronic dialysis patients is therefore uncertain.

IMPLEMENTATION ISSUES

Although echocardiography is widely available, the cost is not low, and this may deter its use. Further, the detection of cardiac abnormalities (such as LV dysfunction) may increase the necessity for other diagnostic tests, such as stress imaging or contrast angiography, for the assessment of CAD.

RESEARCH RECOMMENDATIONS

- More clinical trials on treatment of CHF in dialysis patients are required. A randomized, prospective trial on primary beta-blocker therapy to reduce the risk of CHF and death would be a worthwhile project in dialysis patients, especially in diabetics.
- Valuable information may be derived from a large longitudinal cohort study of echocardiographic changes in the incident chronic HD and PD populations, in the modern era of cardiac therapeutics.
- Further large cross-sectional studies are required to examine the prevalence of cardiomyopathy in the chronic HD and PD populations.

GUIDELINE 7: DYSRHYTHMIA

Patients on maintenance dialysis are at increased risk for dysrhythmias, cardiac arrest, and SCD. The risk of SCD or cardiac arrest increases with age and dialysis duration.

7.1 Evaluation of dialysis patients:

7.1.a All dialysis patients, regardless of age, should undergo a routine 12-lead ECG at the initiation of dialysis. (C)

7.1.b Patients with dysrhythmias should be treated in the same manner as the general population with regard to antiarrhythmic agents (including beta-blockers) and pacing devices (including internal defibrillators). Refer to Table 5 for dosage adjustments and drugs to be avoided. (C)

RATIONALE

Risk Factors

Patients on maintenance dialysis therapy are at increased risk for dysrhythmias, cardiac arrest, and SCD. Dialysis patients with underlying structural or functional CVD are at much higher risk for these dysrhythmias and cardiac arrest because of increased dysrhythmogenicity due to dynamic changes in electrolytes, volume status, blood pressure and the use of multiple medications. Even nondiabetic dialysis patients have a markedly increased cardiac event rate and decreased event-free survival as compared to the general population.[93] *(Moderately Strong)*

Ischemic heart disease is present in many patients even at the time of initiation of dialysis. CKD Stage 5 patients with either symptomatic or asymptomatic coronary artery disease are at increased risk for dysrhythmias and SCD.[94-97] This risk is potentiated with concomitant presence of anemia[98] and left ventricular hypertrophy[99] or increased left ventricular mass index, often present in CKD patients at the initiation of dialysis therapy.[100,101] *(Weak)*

The prevalence of baseline ECG abnormalities and the development of new dysrhythmias and silent myocardial ischemia is related to the concomitant presence of CAD, and is also directly proportional to the duration of dialysis.[102-105] Potentially life-threatening ventricular dysrhythmias and silent myocardial ischemia were noted in 29% and 36%, respectively, on Holter monitor performed 24 hours before, during HD, and continued for 20 hours after dialysis in a small cohort of 38 HD patients.[105] Furthermore, atrial dysrhythmias were noted in 10% of patients in a cohort of 106 maintenance HD patients[106] and 76% of patients demonstrated varying degrees of ventricular dysrhythmias in a cohort of 127 maintenance dialysis patients.[102] The risk of new onset dysrhythmias was shown to increase in patients on peritoneal dialysis (PD), with ventricular dysrhythmias increasing from 30% to 43% and supraventricular dysrhythmias (SVA) increasing from 40% to 57%, respectively, during a mean follow-up period of 20 $\pm$4 months.[107] *(Moderately Strong)*

Risk factors for increased arrhythmogenicity include compromised myocardium (due to either underlying CAD, decreased coronary reserve blood flow, or the consequences of uremia on myocardial function and structure), increased QTc interval or dispersion, electrolyte abnormalities, intradialytic hypotension, concomitant presence of LVH (present in almost 80% patients on dialysis), and autonomic dysfunction (with or without diabetes).[108-110] *(Moderately Strong)*

Dialysis patients have frequent electrolyte abnormalities such as fluctuating levels of potassium, ionized calcium, magnesium, and other divalent ions.[111] Due to the intermittent nature of the dialysis procedure, patients on HD have wide fluctuations in volume status, and potassium and bicarbonate levels, in between dialysis treatments.[97,112] These fluctuations are partly driven by the level of potassium and calcium in the dialysate fluid used during the prior session of treatment, and wide variability in eating habits due to varying adherence to dietary modifications necessary to control the calcium-phosphate product.[112-115] All these factors culminate in an dysrhythmogenic diathesis. *(Weak)*

Atrial fibrillation (A.fib) is perhaps the most commonly diagnosed dysrhythmia in the general population, and also in the dialysis population.[106] A historical cohort study of the USRDS DMMS Wave 2 revealed that A.fib was more common in dialysis patients than in the general population, although the study did not show

Table 5. Dosage Adjustments and Drugs To Be Avoided

Antiarrhythmic Class	Name of the Drug	What To Do in Patients with Renal Failure?
Class Ia agents	*Procainamide*: Normally 50% of procainamide is excreted unchanged by kidneys. Procainamide is metabolized to NAPA in different proportions based on the acetylator status, e.g., 16%-22% in slow acetylators and 24%-30% in rapid acetylators is converted to NAPA. Two-thirds of NAPA is eliminated by the kidneys.	Procainamide should be avoided in dialysis patients. NAPA levels should be monitored every 6-8 hours. Procainamide-induced lupus anticoagulants may increase the risk of thrombosis, including the thrombosis of the dialysis access.
	Disopyramide: The elimination half-life is 6-9 hours and renal excretion accounts for 40%-60% of elimination of the unchanged drug; an additional 30% is excreted as metabolites. Protein binding is highly variable, ranging from 40%-90%, and with higher doses and higher plasma concentration, greater concentration of the drug remains unbound resulting in an increased risk for toxicity.	The pharmacokinetics of disopyramide on dialysis is not known. The dose modification is required if used in dialysis-dependent patients. Great caution should be exercised in patients with pre-existing heart failure, as the use of disopyramide is associated with worsening of CHF. There may be an increased risk of developing torsades de pointes with the use of disopyramide in dialysis patients.
Class Ib agents	*Tocainide*: It is an amine analogue of lidocaine, thus allowing oral administration. Bioavailability is almost 100% following oral administration. Some 40% is excreted unchanged in urine and between 10%-50% is bound to plasma proteins.	The dose of tocainide should be reduced in dialysis patients with an aim to maintain the trough levels of tocainide between 4-10 µg/mL.
Class Ic agents	*Flecainide*: It is a derivative of procainamide. The fraction of flecainide excreted unchanged in the urine is 30% (range 10%-50%) and the rest of the drug is metabolized in liver. The relationship between flecainide elimination and creatinine clearance is poorly understood.	Dose reductions are necessary in patients with renal failure but the magnitude of the clearance by dialysis is not known. However, it is prudent to decrease the dose by 50% of the normal recommended dose (100 mg every 12 hours) in patients with renal and liver failure and to maintain the trough level of 0.2-1.0 µg/mL. Also, flecainide should be used with caution in patients with CHF.
Class II agents	*Acebutolol*: After an oral dose, 40% of the drug is converted to the major metabolite (diacetolol) that is equally active but more cardioselective than the parent compound. Another 40% of the parent drug is eliminated by the kidneys and almost all of the diacetolol is cleared by the kidneys. Both acebutolol and diacetolol are hydrophilic and hence cleared by dialysis therapy.	Patients with advanced renal failure and not on dialysis will need dose reduction to avoid the accumulation of diacetolol. On the contrary, patients on dialysis should be advised to take acebutolol at the end of dialysis therapy and patients on daily dialysis will need a supplemental dose at the end of dialysis.
Class III agents	*Sotalol*: After oral administration, bioavailability varies from 60%-100%. It is not protein bound and 75% of the administered dose is excreted unchanged; hence it accumulates in patient with renal failure. No active or inactive metabolites have been found.	Dosage reduction is necessary in patients with impaired renal function. Its use should be avoided in dialysis patients.
	Dofetilide: Bioavailability is >90% after an oral dose. Eighty percent of the drug is excreted in urine unchanged and the remaining is excreted in the form of various metabolites. Dofetilide use is associated with prolongation of the Q-T interval, and the prolongation of Q-T interval is directly related to the plasma concentration of dofetilide.	Dofetilide is contraindicated in patients with creatinine clearance of <20 mL/min. The dose is reduced to 125 µg twice a day, 250 µg twice a day, and 500 µg twice a day in patients with estimated creatinine clearance of 20-40 mL/min, 40-60 mL/min and >60 mL/min, respectively. Its use should be avoided in dialysis-dependent patients.
	Tedisamil: About 60% of the drug is absorbed after oral administration, 96% of the drug is protein bound and is excreted by the kidney as an active drug. Plasma concentration and half-life are increased in patients with renal disease.	Dose modifications are necessary if Tedisamil is used in patients with renal impairment. Due to lack of PK data in dialysis patients, it may be prudent to monitor QTc interval and the drug use should be stopped if QTc increases more than 550 ms.
Miscellaneous group	*Magnesium*: Only 1% of total magnesium is found in the serum and the kidney is the principal organ responsible for the maintenance of magnesium homeostasis. Progressive increase in magnesium concentration results in hypotension, prolongation of PR, QRS intervals and peaked T waves. At a level of 5 mmol/L, areflexia, respiratory paralysis, and cardiac arrest may occur.	Dialysis patients if treated with intravenous magnesium should have continuous electrocardiographic monitoring and frequent estimation of serum magnesium levels to avoid the development of hypermagnesemia.

whether A.fib was related or unrelated to valvular disease.[116] *(Weak)*

Treatment

There is strong evidence for the use of different interventions either for primary or secondary prevention of arrhythmias and cardiac arrest in the high-risk general population (patients with CAD,[117-120] CHF[121,122] and near-fatal cardiac events[123-126]). Since dialysis patients are at increased risk for CV events, it is reasonable to assume that these interventions will be effective, despite the lack of evidence in the dialysis population. Pending further research, there is presently no reason to withhold these interventions in dialysis patients. *(Moderately Strong)*

The use of beta-blockers in nondialysis patients is recommended for the primary prevention of SCD,[127] and improves outcomes in patients with CHF.[128,129] Similarly, the USRDS Wave 3 and 4 study showed decreased risk of death in patients who were on beta-blockers.[130,131] A small study demonstrated that dialysis patients may not tolerate sotalol due to an increased risk of torsade de pointes.[132,133] *(Weak)*

The use of novel agents such as Ximelagatran, direct thrombin inhibitor, fixed-dose therapy without coagulation monitoring as an alternative to coumadin therapy for the prevention of strokes in patients with nonvalvular A.fib, has been demonstrated to be effective in the general population.[134-136] However, the use of Ximelagatran in dialysis patients has not been studied. *(Weak)*

LIMITATIONS

- Although there is an existing and evolving body of evidence about the primary and secondary prevention of cardiac events in the form of arrhythmias in the general population, such evidence is apparently lacking from the growing population of CKD and dialysis-dependent patients.
- Without definitive evidence from prospective trials in the dialysis population, there may remain an increased concern over the safety and efficacy of interventions.

IMPLEMENTATION ISSUES

The use of internal defibrillators may be precluded due to:

- lack of data in the dialysis population;
- invasive nature; and
- potential interference with dialysis catheters.

RESEARCH RECOMMENDATIONS

- Modifications in the CMS form are required to increase the accuracy of data capture for arrhythmias and near-fatal cardiac arrest in dialysis patients.
- Studies are needed to assess the outcome and the effectiveness of different preventive and treatment strategies to improve the dismal outcome of near-fatal arrhythmias in dialysis patients.
- There is a strong need to evaluate the mechanisms of sudden death in this population.

GUIDELINE 8: EXTERNAL DEFIBRILLATION

The capability for effective, rapid defibrillation (with negligible risk of inappropriate treatment) is widely available with the development of automatic external defibrillators (AEDs). Given the high prevalence of dysrhythmias (see Guideline 7), the availability of AEDs in dialysis facilities may impact the outcomes of patients who experience cardiac events during dialysis therapy.

8.1 All dialysis units should have on-site capability for external cardiac defibrillation. Automatic external defibrillators are the simplest, most cost-effective means to achieving this guideline, as they do not require advanced life support training by staff for operation, require minimal maintenance, and are designed for use by nonmedical personnel. (A)

8.1.a Basic life support (CPR) training for dialysis unit staff is recommended as an enhancement to the effectiveness of AEDs, as it includes instruction in use of AEDs, airway and circulatory support during cardiorespiratory arrest, and management of noncardiac emergencies (such as choking). (B)

8.1.b Non-automatic defibrillators are also appropriate devices for providing on-site defibrillator capability, but they require more maintenance and operators certified in advanced cardiac life support (ACLS). (B)

8.1.c All dialysis units caring for pediatric patients need to have on-site external automatic defibrillators and/or appropriate pediatric equipment available. Automated external defibrillators may be used for children 1-8 years of age, and should ideally deliver pediatric doses and have an arrhythmia detection algorithm.[46-48] (C)

8.1.d The goal should be the availability of AEDs in all dialysis units within 12 months of the publication of these Guidelines. (C)

RATIONALE

Sixty-one percent of all cardiac deaths in dialysis patients have been attributed to arrhythmic mechanisms.[17] The rate of cardiac arrest during HD has been reported to be 7 events per 100,000 dialysis sessions.[95] The mortality rate immediately following cardiac arrest in the general population is 7%-10% per minute, and survival is unlikely if defibrillation does not occur within 10 minutes. Therefore, rapid defibrillation is essential for improving survival in dialysis patients experiencing cardiac arrest. The safety and efficacy of AEDs have been validated in diverse settings, such as airports, casinos, and commercial aircraft. They are designed to be used even by nonmedical personnel, and do not require advanced training or advanced cardiac life support (ACLS) certification. *(Moderately Strong)*

In a study based on Emergency Medical Services (EMS) data in Seattle and King County from 1990-1996, there were 47 cardiac arrests in dialysis centers, with an annual incidence per center of 0.746.[137] There were 41 witnessed events, and bystander CPR was administered in 41 patients. In 29 patients (62%) the cardiac rhythm was ventricular fibrillation (VF) or ventricular tachycardia (VT). While the overall survival to hospital discharge was 30%; it was 38% for the VT/VF patients. These data reflect the expertise of EMS crews in Seattle/King County and make a compelling case for on-site defibrillator capability in all dialysis units.

Pediatric-modified, FDA-approved AEDs are now commercially available; thus the official AHA Guidelines 2000 on Resuscitation, which do not support the use of AEDs in smaller children are no longer current.[138] Evidence for this recommendation is provided by studies in children[46,48] It is anticipated that all AEDs approved for sale in the U.S. will be equipped with optional modules or other electrode modifications suitable for pediatric use (children <25 kg and <8 years old) by the time these Guidelines are published, but it is recommended that individual dialysis units verify the AED capabilities of on-site units. The Commissioner of Health, New York State, has issued an official advisory (effective 7/01/02) promoting the safe and effective use of pediatric-modified AEDs in children under age 8.

Dialysis centers providing care for smaller children will need to establish their own protocols consistent with accepted pediatric practice guidelines for pediatric resuscitation. It is recommended that a pediatric nephrologist helps formulate center practice guidelines for this special group of patients. “Standard” AEDs (designed for use in patients 8 years or older) could thus be used with these removable pediatric modifications. These pediatric-modified devices deliver 50 Joules of electricity (compared to 200 Joules for standard AEDs). *(Moderately Strong)*

LIMITATIONS

- Automatic external defibrillators are easy to operate and the operator does not require medical training, but AEDs need to be widely available.

IMPLEMENTATION ISSUES

- All dialysis staff should be encouraged to attempt the use of AEDs in the event of cardiac arrest, regardless of the availability of other types of defibrillators or certified ACLS personnel.
- While an AED is available at a rather moderate cost, it is still an additional expense for the dialysis unit.
- Some units may be concerned about staff training and the maintenance of AEDs.

RESEARCH RECOMMENDATIONS

- Observational studies are required to examine mortality trends after the implementation of this guideline.

GUIDELINE 9: CEREBROVASCULAR DISEASE

Stroke is the third leading cause of death in the general population in the U.S. and many other countries, with large economic and human burdens as a consequence. Patients with CKD are at increased risk for stroke relative to the general population.

9.1 All dialysis patients should follow the AHA Guidelines for the prevention, screening and evaluation, and treatment of stroke. A summary of the AHA guidelines with any caveats related to dialysis patients is shown in Table 6. (C)

9.2 Special considerations in dialysis patients include:

9.2.a Anticoagulation in nonvalvular atrial fibrillation: Dialysis patients are at increased risk for bleeding and careful monitoring should accompany intervention. (C)

9.2.b Acute stroke in dialysis patients: Given that acute stroke syndromes can be due to either thrombotic or bleeding events in dialysis patients, the immediate goal of localization and cause is particularly important in dialysis patients because of increased risk of bleeding associated with anticoagulants in this population. Therefore, imaging with established methods should be undertaken. (C)

9.3 Treatment of stroke and transient ischemic attack (TIA):

9.3.a Treatment of TIAs and strokes should follow the same principles used in the general population for both medical management and surgical management, with the exception of thrombolytics in HD patients. (C)

9.3.a.i Assessment of the risk of bleeding in patients recently receiving heparin on dialysis should be conducted when considering the use of thrombolytics. (B)

RATIONALE

Prevention

Few studies have identified risk factors for stroke in the dialysis population. The available data suggest that high blood pressure, markers of poor nutrition, age, diabetes, and ethnicity place patients at greatest risk. Of these factors, only blood pressure and nutrition are potentially modifiable. The largest study assessing risk factors for stroke used data from the United States Renal Data System (USRDS). Several factors were found to be associated with stroke.[139] African-Americans with a history of CVD had a lower risk for incident stroke than Caucasians. Lower serum albumin, subjective malnutrition and lower weight were associated with a higher risk for stroke. Higher blood pressure, older age, and diabetes were also associated with a higher risk for stroke. There was no association between incident stroke and cholesterol, calcium, phosphorus, or parathyroid hormone. Measures of malnutrition and diabetes were not associated with hemorrhagic stroke, while polycystic kidney disease, African-American race without a history of CVD, and male gender were associated with a higher risk for hemorrhagic stroke. Data from Japan identified polycystic kidney disease, higher blood pressure, higher ECG voltage, and lower KT/V as risk factors for cerebral hemorrhage.[140] A small study from Japan demonstrated that hypertension was a risk factor for stroke.[141] Factors not found to be associated with stroke included male gender, age, diabetes, smoking, dyslipidemia, and duration of dialysis. However, a survival analysis was not performed and statistical power was limited. The epidemiology of stroke is different in Japan and caution should be used when generalizing these data to U.S. dialysis patients.

Screening/Evaluation

There are some data to suggest that dialysis patients have higher measures of subclinical vascular disease[142] and that these measures predict cardiovascular events and death. Carotid ultrasound measurements of elasticity or arterial stiffness measured in the common carotid artery assessing incremental modulus of elasticity have demonstrated a positive relationship between arterial stiffness and cardiovascular mortality.[92]

Table 6. AHA Guidelines for the Prevention, Screening and Evaluation, and Treatment of Stroke, with K/DOQI Modifications

	AHA Guideline	K/DOQI Modification
Prevention		
General	Regular screening for HTN and appropriate management as summarized in JNC VII. Encourage patients to stop smoking. Provide counseling, nicotine replacement and formal programs when available. In diabetics, careful control of HTN is important. Glycemic control is recommended to reduce microvascular complications. *Diet/Nutrition*: A healthy diet containing at least five servings of fruits and vegetables may decrease the risk of stroke and is therefore encouraged.	Target BP in dialysis patients is less certain than in the general population. See Guideline X in this document. In addition, see caveats in Guideline X on tobacco use, diet, and diabetes.
Asymptomatic Carotid Stenosis	Endarterectomy may be considered in patients with high-grade asymptomatic carotid stenosis. Careful patient selection guided by comorbid conditions, life expectancy, patient preference, as well as other factors, including gender followed by a thorough discussion of the risks and benefits of the procedure is necessary. Patients should also be thoroughly evaluated for other treatable causes of stroke.	
Atrial Fibrillation	Antithrombotic therapy (warfarin and aspirin) should be considered for patients with nonvalvular atrial fibrillation, based on an assessment of their risk of embolism and risk of bleeding complications.	Dialysis patients are at increased risk for bleeding and careful monitoring should accompany intervention.
Screening/Evaluation		
TIA	*Imaging of the brain*: Patients with symptoms suggesting a TIA should receive a CT scan of the head in the initial diagnostic evaluation to exclude a rare lesion such as a subdural hematoma or brain tumor. A CT scan may also demonstrate an area of brain infarction appropriate to TIA symptoms that may influence subsequent management. Substitution of MRI for CT, for the evaluation of TIA, is not warranted.	
	Imaging of the vessels: Magnetic resonance angiography (MRA) provides sufficient images for evaluation of vertebrobasilar ischemia. Duplex ultrasonography is a screening tool that can be used to determine those with significant stenosis of the carotid arteries. This should be followed by arteriography to determine vessels best suited for intervention.	
Acute Stroke	*Imaging*: The immediate goal in an acute stroke is localization and exclusion of other causes for symptoms. A CT scan without contrast is recommended as the primary tool for evaluation for an acute stroke. A follow-up CT in 2-10 days is recommended for negative CT scans when further documentation is necessary or when the provider suspects that transformation to hemorrhage has occurred. MRI is useful for posterior circulation strokes, small hemorrhages, or when dating the hemorrhage is needed, but it is not recommended for routine use. Imaging vessels is not necessary in acute stroke. Techniques such as ultrasound or MRA may serve as a screening procedure for considering carotid angiography and monitoring of vascular abnormalities.	

Table 6. AHA Guidelines for the Prevention, Screening and Evaluation, and Treatment of Stroke, with K/DOQI Modifications (Cont'd)

	AHA Guideline	K/DOQI Modification
Treatment:		
TIA	*Antiplatelet agents*: Daily aspirin should be used for patients who have had an atherothrombotic TIA to reduce the risk of recurrent stroke. *Ticlopidine*: Ticlopidine is limited by its side effects and should be used in patients intolerant to aspirin or who have had a major ischemic event despite aspirin. *Clopidogrel*: Clopidogrel is limited by its side effects and should be used in patients intolerant to aspirin or who have had a major ischemic event despite aspirin. *Anticoagulants*: Warfarin is recommended for subjects with atrial fibrillation who have a TIA. A target INR of 2.5 is recommended. Warfarin is also recommended for patients who are at high risk for other sources of cardioembolism. Aspirin may be used for those that have contraindications to oral anticoagulation.	Dialysis patients are at high risk for bleeding, and adequate precautions should be taken to prevent bleeding associated with antiplatelet agents and anticoagulants.
	Surgical management of carotid disease: Patients with a recent TIA or nondisabling stroke with an ipsilateral carotid stenosis >50% may benefit from surgery. Benefits vary by risk factors and are greatest among men, nondiabetics, and those with hemispheric symptoms and angiographically demonstrated ulcers.	
	Angioplasty and stent placement: Not currently recommended.	
Stroke	Intra-arterial thrombolysis should be considered investigational. Intravenous tissue plasminogen activator is recommended within 3 hours after the onset of ischemic stroke. This should be done in the setting of a stroke confirmed by CT. It should not be used if the patient has had heparin during the prior 48 hours.	The stipulation of excluding patients who have had heparin during the 48 hours prior to thrombolysis was not designed to address dialysis patients on intermittent dialysis, and would eliminate the majority of dialysis patients on thrombolytics. Therefore, the use of thrombolytics in dialysis patients should be considered on an individual basis.
	Heparin therapy is not recommended as thrombolytic therapy.	
	Surgery: Emergent carotid endarterectomy is not recommended.	

Greater carotid intimal medial thickness has also been shown to be associated with a greater risk for cardiovascular events.[143] Carotid artery incremental elastic modulus has been associated with an increased risk for cardiovascular events. Each one standard deviation increase was associated with a 1.7-fold increased risk for cardiovascular events.[92] There are no studies that have assessed whether these measures predict stroke specifically, or if screening decreases events. Routine screening using carotid ultrasound is not recommended in asymptomatic patients.

LIMITATIONS

- There are extensive data from the general population regarding risk factors, screening and treatment of stroke. However, the epidemiology of stroke is different in the dialysis population. In addition, exposures related to dialysis may alter the effectiveness and complications associated with treatment. All recommendations regarding screening and treatment are opinion-based and should be taken with caution.
- There are limited data regarding stroke that are specific to the dialysis population. Data addressing the association between risk factors and stroke are scant. Data supporting screening for stroke are based on limited and weak data, while data addressing treatment do not exist.
- There are no data in the dialysis population regarding medical or surgical management of

stroke. However, due to the high risk of bleeding in the CKD population, caution should be used when treating with antiplatelet agents.

IMPLEMENTATION ISSUES

- Altering modifiable risk factors can be implemented and has been shown to be effective in the general population. Screening and treatment of stroke is routine in the general population, and should therefore be possible to implement effectively in the dialysis population.

RESEARCH RECOMMENDATIONS

- Stroke risk is very high in the CKD population. Effective screening strategies do not exist, nor do studies assessing interventions. Studies addressing these issues are greatly needed.

GUIDELINE 10: PERIPHERAL VASCULAR DISEASE

Both diabetic and nondiabetic dialysis patients are at risk for peripheral vascular disease (PVD),[144,145] with approximately 15% of incident patients having a clinical diagnosis of PVD.

10.1 Diagnosis of PVD:

10.1.a At the time of dialysis initiation, all patients should be evaluated for the presence of PVD. (C)

10.1.b Evaluation should include physical examination including assessment of arterial pulse and skin integrity. (C)

10.1.c Further specialized studies, such as duplex studies or invasive testing, should be undertaken if abnormalities are detected upon physical examination and interventions are considered. (C)

10.2 Approach to therapy of PVD: (C)

10.2.a Patients with PVD should be treated in the same manner as the general population in regard to smoking cessation, lipid-lowering therapy, glycemic control, blood pressure control, and the use of ACE inhibitors and antiplatelet agents. In addition, supervised exercise regimens and medications to increase vasodilation should be considered in patients with claudication and without critical leg ischemia. Established national guidelines, similar to those for stroke, are not available for PVD in the general population.

RATIONALE

Screening for PVD (Weak)

Ankle brachial index (ABI) (ankle systolic blood pressure divided by brachial systolic blood pressure) is a simple method of screening for PVD. However, ABI might be falsely elevated in dialysis patients because of vascular calcification.[146] Toe brachial index (TBI) is not affected by vascular calcification.[146] Even though ABI and TBI are simple, inexpensive, noninvasive methods, further studies are warranted to determine whether screening for asymptomatic PVD with these tests improve limb survival.

Checking arterial pulses and assessing skin integrity should be part of a physical examination, particularly in diabetic dialysis patients. As PVD is a strong predictor of cardiovascular mortality in the general and dialysis population,[147,148] early diagnosis of PVD and aggressive medical therapy (smoking cessation, lipid-lowering therapy, glycemic control, blood pressure control, and the use of ACE inhibitors and antiplatelet agents) might improve cardiovascular survival in dialysis patients (Table 7).

Therapy of PVD (Weak)

There are no randomized, controlled trials for PVD in dialysis patients that establish the efficacy of any pharmacological agents or other interventions. In the absence of evidence to the contrary, it might be reasonable to extend the therapy of PVD in the general population to the dialysis population. The therapy of PVD depends upon the presence of claudication and critical leg ischemia in the general population.[149]

When compared to the general population, outcomes after revascularization for PVD in dialysis patients are inferior.[150,151] The problems with revascularization in PVD in dialysis patients include: high perioperative and 1-year mortality; decreased wound healing; loss of limb despite patent graft; and prolonged hospital stay and poor rehabilitation.[152-156] Therefore, some authors have argued for the liberal use of primary amputation in dialysis patients.[157]

However, careful patient selection for revascularization in dialysis patients might result in acceptable outcomes. A study of 44 HD patients who underwent revascularization reported a 2-year survival rate of 48%, perioperative mortality of 9%, primary graft patency at 1 year and 2 years of 71% and 63%, respectively and limb salvage at 1 year and 2 years of 70% and 52%, respectively.[158] In this study, an aggressive approach to limb salvage was favored when pa-

Table 7. Association of Low Ankle-Arm Brachial Index with Risk of Cardiovascular Outcomes

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	AABI Threshold	Cardiovascular Outcome	Results (Univariate)	Results (Multivariate)	Quality
Fishbane 1996[147]	1 yr	132		↑↑↑	0.9	All-cause death	↑	↑	⊙
Fishbane 1996[147]	1 yr	132		↑↑↑	0.9	Cardiovascular death	↑	↑	⊙
Oishi 2000 [159]	Cross-sectional	116		↑↑	—	Prevalent peripheral vascular disease	⇔		○
						Prevalent atherosclerotic disease	↑		
						Prevalent coronary artery disease	↑		
						Prevalent cerebrovascular disease	↑		

— Analyzed as a continuous variable (no threshold analyzed).

tients were found to be ambulatory or able to use the affected extremity for purposes of weight bearing or transfer. Attempted limb salvage was not advocated for patients who were chronically bedridden, or those with uncontrolled infection or tissue necrosis precluding a reasonable expectation of limb salvage.

Therefore, symptomatic PVD in dialysis patients should not automatically result in amputation in all patients. Revascularization (surgical or angioplasty with stent) might be the preferred method of treatment of symptomatic PVD in selected dialysis patients. Extensive tissue necrosis in nonweight-bearing limbs and preoperative infection might be indications for primary amputation.

LIMITATIONS

- There are no randomized, controlled trials of any of the interventions for therapy of PVD in dialysis patients.
- The above recommendations are based on retrospective, observational studies in dialysis patients. Further large, prospective observational studies and randomized, controlled trials are warranted.

RESEARCH RECOMMENDATIONS

- Further studies are warranted to examine the feasibility and effectiveness of ankle:brachial or toe:brachial indices as screening tests for asymptomatic PVD in reducing limb amputation rates.

SECTION II. GUIDELINES ON MANAGEMENT OF CARDIOVASCULAR RISK FACTORS

Traditional risk factors—such as diabetes, hypertension, dyslipidemia—and those specific to dialysis patients (anemia and mineral metabolism abnormalities) require regular assessment and treatment as per current recommendations. The relative importance and weight of each of these risk factors in the dialysis population is not known and, in the absence of controlled trials in this population, current recommendations from existing organizations should be followed, with special consideration given to potential risks.

Furthermore, lifestyle issues such as smoking, physical activity, depression, and anxiety are the cornerstones of therapy as in the general population. The treatment options are often similar, but the impact of these factors is potentially more profound in dialysis patients. These factors are all discussed in this section. Special attention will be paid to the difference between the usual recommendations and those for dialysis patients.

GUIDELINE 11: DIABETES

11.1 All dialysis patients who have diabetes should follow the American Diabetes Association guidelines.[49,160] (C)

RATIONALE

Glycemic Control (Weak)

The rationale for this ADA recommendation is based on substantial evidence from the Diabetes Control and Complications Trial (DCCT),[161,162] and the U.K. Prospective Diabetes Study (UKPDS)[163,164] that the careful control of blood glucose has a significant effect on decreasing the complications of diabetes. Combined with substantial observational evidence of the link between prolonged hyperglycemia and complications, the recommendation has strong evidence-based support. However, these relationships have not been validated specifically in dialysis patients. Tight control has potential problems for patients on dialysis, and there is some evidence that hemoglobin A_{1C} may not be as predictive of glycemic control in patients on dialysis.

The ADA recommendation indicates that extremely tight control may increase the incidence of hypoglycemic events, and may produce weight gain. Hypoglycemia may be worsened by nausea and the inability to eat, as well as by longer duration of drugs and increased half-life of insulin. Therefore, care should be taken to prevent hypoglycemic episodes in patients on dialysis who experience significant nausea or gastrointestinal complaints. In addition, if excellent glycemic control gradually increases a patient's solid weight, it should be reflected in the adjustment of dry weight for the purpose of postdialysis weight targets.

There is evidence that hemoglobin A_{1C} is not as representative of glycemic control in patients on HD[165] or PD.[166,167] Through decreased metabolism, anemia, and shorter life of red cells, the hemoglobin A_{1C} may under-represent glycemic control, and a level $>7\%$ in a dialysis patient may represent glycemic control similar to a non-dialysis patient with a hemoglobin A_{1C} $<7\%$. The precise target of hemoglobin A_{1C} that is associated with the best outcome in dialysis patients has not been clearly established. Clinicians are cautioned that insulin doses and oral hypoglycemic doses may change substantially during the transition from earlier stages of CKD to dialysis. The decrease in insulin catabolism associated with the further loss of kidney function may reduce insulin requirements. On the other hand, the glucose contained in the dialysate (especially peritoneal dialysate) may increase the requirement of hypoglycemic agents.

The use of newer insulin regimens and insulin preparations (with properties that are closer to normal physiology) should be encouraged, possibly in consultation with a specialist in diabetes management. There are some oral hypoglycemic agents that either should be used with caution, or not used at all, in dialysis patients (see Table 8).

Nutritional Therapies and Care (Weak)

The rationale for metabolic and nutritional management in diabetes comes primarily from a review by the ADA of the existing evidence, which supports nutritional interventions in the control of diabetes and its complications.[160,168] In contrast, although health and dietary habits for diabetics are generally consistent with those for dialysis patients, there are special dietary considerations for patients on dialysis. The level of dietary protein recommended for dialysis patients exceeds the ADA recommendation for pa-

Table 8. Oral Hypoglycemic Agents Contraindicated or To Be Used with Caution in Dialysis Patients

Medication		Rationale
Metformin	Contraindicated	Decreased clearance; possibility of lactic acidosis
Glyburide, glipizide, glimepride, tolazamide, chlorpropamide	Use with Caution	High risk of persistent hypoglycemia due to low clearance of sulfonylurea class drugs and their metabolites

Table 9. Antihypertensive Agents Contraindicated or To Be Used with Caution in Dialysis Patients

Medication		Rationale
Sotalol	Contraindicated	Decreased clearance, not indicated in advanced kidney disease
Spironolactone Antagonists	Use with Caution	The risk of hyperkalemia is uncertain in dialysis patients

tients with diabetic nephropathy not requiring dialysis, because the prevention of malnutrition is a primary concern for dialysis patients. In patients not requiring dialysis, the slowing of progression of CKD is a major concern in which protein restriction probably has a role. High-protein diet may also cause more electrolyte imbalance and retention of nitrogenous waste products in nondialysis patients. On the other hand, dietary phosphorus restriction is often necessary to decrease hyperphosphatemia in dialysis patients. For more detailed recommendations, see the K/DOQI Guidelines on Nutrition,[169] and the sections on nutrition and calcium-phosphorus product in this document.

Exercise (Weak)

Patients who are on dialysis may have to modify their exercise routines to match their dialysis schedule, since postural hypotension, dizziness, and washout sensations are not uncommon, and exercise immediately after dialysis may be poorly tolerated.

Hypertension Control (Weak)

The rationale for these recommendations derives from extensive reviews of the link between hypertension and cardiovascular morbidity and mortality for the general population and the statement of the Seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.[170] The optimal blood pressure for dialysis patients, however, has not been firmly established (see Guideline 12 in this document). Although the JNC VII recommendation for blood pressure control in patients with CKD is <130/80 mm Hg, blood pressure control in patients on HD is complicated by the volume and electrolyte shifts surrounding dialysis procedure that acutely changes blood pressure. Diabetic patients on dialysis may be more prone to postural hypotension and labile blood pressure than nondiabetic dialysis patients. A higher supine blood pressure may be necessary in order to prevent symptomatic postural hypotension. Individual judgment and patient evaluation is required to match goals with symptoms.

Antihypertensive Therapy (Weak)

The use of diuretics in patients on HD cannot be recommended for blood pressure control, unless there is substantial residual kidney function that responds to diuretics.[171,172] The choice of initial pharmacological therapy for hypertension in dialysis patients is otherwise similar to those not on dialysis; however, the kidney-protective effect of ACE inhibitors and ARBs are less of a concern. Limited data suggest that ARBs may protect residual kidney function for patients on chronic PD. There is weak evidence that some beta-blockers may hinder peritoneal transport in patients on PD,[173,174] but this evidence is not sufficient to warrant withholding the use of beta-blockers in dialysis patients when they are clearly indicated.

Finally, as detailed in Table 9, there are some antihypertensive agents that should not be used, or should be used only with care, in dialysis patients.

Cardiac Disease Screening (Weak)

The NKF K/DOQI Guidelines support the need for cardiac screening in patients on dialysis, especially since the combination of diabetes and advanced kidney disease substantially increases the likelihood of coronary disease. The techniques for screening and their caveats in dialysis patients are described in Guideline 2 in this document.

LIMITATIONS

- Many of the recommendations supported by the ADA on the care of diabetes are based on large clinical studies that provide strong evidence for the particular recommendation, but those studies do not target dialysis patients.

RESEARCH RECOMMENDATIONS

- Long-term, randomized controlled trials are needed to strengthen the evidence for the direct application of the ADA recommendations to patients on dialysis.
- More research is needed on the effect of renal dietary restrictions in diabetic patients.

GUIDELINE 12: BLOOD PRESSURE

The management of blood pressure is an important component of CVD risk management for all aspects of CVD: CAD, cardiomyopathy, VHD, CBVD, and PVD. There are unique challenges in both the measurement and management of blood pressure in dialysis patients.

12.1 Measurement of blood pressure:

12.1.a In patients who have undergone multiple surgical procedures for vascular accesses in both arms, blood pressure should be measured in the thighs or legs. However, health-care professionals should use appropriate cuff size and measure blood pressure only in the supine position. (B)

12.2 Predialysis and postdialysis blood pressure goals should be <140/90 mm Hg and <130/80 mm Hg, respectively. (C)

12.3 Management of blood pressure by adjustment of dry weight:

12.3.a Management of hypertension in dialysis patients requires attention to both management of fluid status and adjustment of antihypertensive medications. This requires close collaboration among health-care providers. (B)

Excessive fluid accumulation between dialysis sessions should be managed with: (B)

- **Education and regular counseling by dietitians**
- **Low sodium intake (2-3 g/day sodium intake)**
- **Increased ultrafiltration**
- **Longer dialysis**
- **More than 3 dialysis treatments per week**
- **Drugs that reduce salt appetite**

12.4 Management of hypertension with drugs in dialysis patients:

12.4.a Drugs that inhibit the renin-angiotensin system, such as ACE inhibitors or angiotensin II-receptor blockers should be preferred because they cause greater regression of LVH, reduce sympathetic nerve activity, reduce pulse wave velocity, may improve endothelial function, and may reduce oxidative stress. (C)

12.4.b Antihypertensive drugs should be given preferentially at night, because it may reduce the nocturnal surge of blood pressure and minimize intradialytic hypotension, which may occur when drugs are taken the morning before a dialysis session. (C)

12.4.c In patients with difficult-to-control hypertension, the dialyzability of antihypertensive medications should be considered (see Table 10). (C)

12.5 Determination and management of blood pressure in children should follow recommendations by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[50] (C)

12.5.a Optimal systolic and diastolic blood pressure should be <95% for age, gender and height. (B)

12.5.b Management of hypertension on dialysis requires attention to fluid status and antihypertensive medications, minimizing intradialytic fluid accumulation by (C):

- **education by dietitians every 3 months**
- **low salt intake (2 g/day sodium intake)**
- **increased ultrafiltration**
- **longer dialysis duration**
- **intradialytic sodium modeling to minimize intradialytic hypotension**
- **more than 3 dialysis treatments per week**
- **antihypertensives: consider if medications are cleared on dialysis.**

Table 10. Removal of Antihypertensive Drugs with Dialysis

	Percent Removal with Dialysis	
	HD	PD
ACE Inhibitors		
Benazepril	Yes	?
Enalapril	35	?
Fosinopril	2	?
Lisinopril	50	?
Ramipril	Yes	?
Calcium Channel Blockers		
Amlodipine	?	?
Diltiazem	?	?
Nifedipine	Low	Low
Nicardipine	?	?
Felodipine	?	?
Verapamil	Low	Yes
β-Blockers		
Atenolol	75	53
Alebutolol	70	50
Carvedilol	None	None
Labetalol	<1	<1
Metoprolol	High	?
Antiadrenergie Drugs		
Clonidine	5	?
Guanabenz	None	None
Methyldopa	60	30-40
Vasodilators		
Hydralazine	None	None
Minoxidil	Yes	Yes
Angiotensin Receptor Blockers		
Losartan	None	None
Cardesartan	None	?
Eprosartan	None	None
Telmisartan	None	?
Valsartan	None	None
Irbesartan	None	None

RATIONALE

Definitions

Hypertension. The Seventh Report of the Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) has defined hypertension in adults in the general population as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg, and has defined normal blood pressure <120/80 mm Hg.[170]

Orthostatic Hypotension. This is defined as a fall in blood pressure of at least 15 mm Hg systolic and 10 mm Hg diastolic after standing for at least 2 minutes. Although these levels of decline in blood pressure are usually associated with symptoms of cerebral anoxia, some patients may remain asymptomatic. By contrast, some patients may become symptomatic with lesser decreases in blood pressure. Thus, any quantitative definition of orthostatic hypotension may be misleading, and orthostatic hypotension should be diagnosed whenever the patient manifests symptoms of brain hypoxia upon standing. Heart rate variability during orthostasis is impaired in many CKD patients due to the coexistence of autonomic dysfunction. *(Moderately Strong)*

Blood Pressure and CVD

Blood pressure and cardiovascular events. Hypertension is very prevalent among dialysis patients (50%-60%, when hypertension is defined as blood pressure >150/90 mm Hg for HD patients). The prevalence would be even higher if we were to use the JNC VII definitions above. In a study of 2,535 HD patients, only 14% were normotensive on no drugs and among the hypertensive patients, only 30% were controlled.[175]

Cardiovascular disease is the leading cause of death in patients receiving maintenance HD, especially in the first year of treatment. A history of long-lasting arterial hypertension is associated with an increase in cardiovascular deaths in these patients. Hypertension is the single most important predictor of coronary artery disease in uremic patients, even more so than cigarette smoking and hypertriglyceridemia.[176] Although a direct relationship between levels of blood pressure and cardiovascular events has not been clearly established by controlled studies, hypertension in dialysis patients should be considered a major cardiovascular risk factor. The lack of a significant correlation between blood pressure and cardiovascular events in dialysis patients may be due to poor ventricular function, leading to lower blood pressure in some patients, when the follow-up duration is relatively short. *(Weak)*

It was found that, after adjusting for age, diabetes, IHD, hemoglobin and serum albumin, each 10 mm Hg rise in mean arterial blood pressure was independently associated with a progressive increase of concentric LVH, the development of *de novo* cardiac failure and *de novo* ischemic heart disease.[177] Other studies however, have not shown a consistent association between blood pressure and subsequent mortality in the dialysis population. A “U-shaped” relationship between blood pressure and mortality was observed, with excess mortality risk in patients with the lowest and with the highest levels of blood pressure.[178] Systolic blood pressure >180 mm Hg was associated with poor outcomes.[179-181] It has been suggested that observations longer than 5 years are required to see the

beneficial effect of blood pressure control. In a cohort study of 432 CKD patients (261 HD and 171 PD) followed prospectively for an average of 41 months, each 10 mm Hg rise in MAP increased the relative risk of LVH by 48% on follow-up echocardiography, increased the risk of *de novo* CHF by 44%, and the risk of *de novo* IHD by 39%. Interestingly, in this study low mean arterial pressure was independently associated with mortality.[182] *(Weak)*

A substantial body of evidence indicates that increased pulse pressure (PP), particularly in middle-aged and older subjects, is an independent predictor of risk of coronary heart disease, compared with mean arterial pressure (MAP). Pulse pressure represents the pressure increase during systole over diastolic blood pressure. It may be related to increased LV mass, decreased aortic compliance, and small-vessel remodeling,[183-185] and is associated with reduced coronary vasodilator capacity.[186] Reducing PP in hypertension may normalize small artery structure.[187] In a recent study of a large cohort of nondiabetic patients on chronic HD, pulse pressure was found to be an independent predictor of total mortality,[188] and was superior to systolic and diastolic blood pressure in predicting total mortality. Arterial stiffness can be measured noninvasively using the pulse wave velocity (PWV) technique, which is also an independent marker of cardiovascular risk in the general population.[189] Epidemiological studies have shown that PWV is increased in CKD patients and it is an independent marker of cardiovascular risk in these patients.[190] Aortic stiffness depends on the arterial wall structure and function, which can be influenced by blood pressure and aging.[191] A recent prospective cohort study of 180 CKD patients on maintenance HD, followed for a mean duration of 52 $\pm$ 36 months, has shown that carotid pulse pressure and aortic PWV were strong independent predictors of all-cause (including cardiovascular) mortality. Brachial blood pressure, including pulse pressure, had no predictive value for mortality.[192] *(Moderately Strong)*

Pulse wave velocity frequently improves when blood pressure is reduced, particularly when ACE inhibitors[193] or CCBs[194] are used. In CKD patients, the failure of PWV to improve in response to decreased blood pressure is associated with worse cardiovascular outcome. Moreover, the use of ACE inhibitors may have a favorable effect on all-cause mortality and cardiovascular mortality that is independent of blood pressure changes.[195] *(Weak)*

Measurement of Blood Pressure in CKD Patients

Methods. Blood pressure should be measured according to existing guidelines.[196-198] The dialysis personnel should be trained and regularly retrained. The patient must be seated quietly for at least 5 minutes in a chair, with feet on the floor, and arm supported at heart level. Blood pressure should be measured at least 5 minutes before the needles for dialysis access are placed, as this may cause substantial stress in some patients. Blood pressure should also be measured in the standing position (at least 2 minutes) and the arm should be supported at heart level. Blood pressure should be measured both before and at the end of dialysis. Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. The auscultatory method of blood pressure measurement should be used and the disappearance of Korotkoff sounds should define diastolic blood pressure. Appropriate cuff size should be selected so that the cuff bladder encircles at least 80% of the arm. The equipment should be regularly inspected and validated considering that, in one study, automated blood pressure recordings overestimated blood pressure by 14/7 mm Hg before dialysis.[199] *(Moderately Strong)*

In patients who have undergone multiple surgeries for vascular accesses in both arms and blood pressure is technically not measurable in the arms, blood pressure could be measured in the thighs or legs. However, health-care professionals need to be properly trained, and should use appropriate cuff size and measure blood pressure only in the supine position. It must be kept in mind that blood pressure in the lower limb does not represent blood pressure measured in the arm. Systolic blood pressure and pulse pressure are amplified from the aorta towards peripheral arteries and amplification increases with the distance from the heart. Therefore, lower limb blood pressure is higher than brachial pressure. The difference is usually expressed as ankle-arm-pressure index. In young subjects the ankle pressure could be higher than arm pressure by as

much as 30%. In older subjects, ankle and arm pressure tend to be the same. Therefore, the reference value for systolic blood pressure of 140 mm Hg is valid only for brachial pressure; the reference value for lower limb blood pressure is basically unknown. *(Moderately Strong)*

In patients with severe vascular calcifications, indirect measurements of blood pressure may be inaccurate. Intra-arterial measurements of blood pressure could provide true blood pressure, but this is not feasible in most dialysis units. *(Weak)*

Predialysis vs. postdialysis blood pressure. **(Weak)** It is unclear which blood pressure reading should be used as the guide for therapy and control of CVD. Some data suggest that predialysis systolic blood pressure correlates best with LVH.[200] Another report suggests that postdialysis blood pressure is the most representative of mean interdialytic blood pressure measured by ambulatory blood pressure monitoring (ABPM).[201] Others have suggested that an average of predialysis and postdialysis blood pressure may be a better predictor of mean interdialysis blood pressure.[202] In reality, neither is a particularly good predictor of interdialytic blood pressure.[203] This issue is complicated by the known fall in blood pressure during dialysis in a large number (40%-50%) of patients, and by the fact that this fall is short-lived (12-24 hours). Thus, perhaps ABPM or self-measured home blood pressure are better markers of interdialytic blood pressure load; however, for practical and financial reasons, these tools cannot be applied to the totality of dialysis patients.

Circadian blood pressure variability and cardiovascular risk. **(Weak)** Ambulatory blood pressure monitoring has improved the existing knowledge of the relationship between circadian variability of arterial blood pressure and end-organ damage. Normally, blood pressure tends to be the highest during the morning, and gradually decreases during the course of the day to reach the lowest levels at night.[204-207] Some hypertensive patients (approximately 10%-25% of patients with essential hypertension) fail to manifest this normal nocturnal dipping of blood pressure, defined as a night-time blood pressure fall of $>$10%. These patients are called "nondippers,"[208,209] whereas those with a normal circadian rhythm are called "dippers." Among patients with advanced renal disease,[210] and those on maintenance HD,[211-214] the lack of diurnal variation in blood pressure and of the nocturnal dipping of blood pressure can affect as many as 74%-82% of patients. At times, in these patients, nocturnal blood pressure can be greater than blood pressure measured during the day. Because blood pressure is usually measured during the day, this may lead to the erroneous impression of good antihypertensive control.[215] Using ABPM, it was observed that, in HD patients, blood pressure decreased after dialysis and during the first night, but by the next morning reached predialysis levels and it did not decrease during the second night.[216]

The phenomenon of nondipping can be improved with volume depletion and, perhaps, by dosing drugs at night rather than in the morning.

The mechanisms responsible for the abnormal circadian rhythm of blood pressure in patients with renal failure remain elusive. Autonomic dysfunction,[217] reduced physical activity,[218] sleep disordered breathing[219,220] and volume overload[221] have all been implicated. Since the phenomenon of nondipping is more prevalent among salt-sensitive patients with essential hypertension, and since this disturbance improves with salt restriction,[222,223] one would predict that volume expansion would play a major role in HD patients. However, not all evidence supports a primary role of volume expansion in the phenomenon of blood pressure nondipping.[224-226]

The correlation between blood pressure measured in the physician's office and cardiovascular end-points is usually weak. A large body of evidence from subjects with essential hypertension has shown that average 24-hour ambulatory blood pressure correlates with incident cardiovascular events[227-231] better than office blood pressure. Ambulatory blood pressure monitoring has better long-term reproducibility than casual blood pressure measurement in HD patients.[232]

A relationship also seems to exist between the absence of nocturnal dipping of blood pressure and the severity of cardiovascular target organ damage.[209] In a study of 57 treated hypertensive HD patients, it was observed that after an average follow-up of 34.4 $\pm$ 20.4 months and after adjusting for age, gender, and previous cardiovascular events, an elevated nocturnal and 24-hour PP, and low office diastolic blood pressure predict cardiovascular mortality.[233] However, one

Table 11. Factors Implicated in the Pathogenesis of Hypertension in Dialysis Patients

1. Sodium and volume excess
2. Increased activity of vasoconstrictors
   - The renin-angiotensin-aldosterone system
   - The sympathetic nervous system
   - Endothelin
   - Ouabain-like substances
3. Decreased activity of vasodilators
   - Nitric oxide
   - Kinins
   - Atrial natriuretic peptide
4. Erythropoietin use
5. Divalent ions and parathyroid hormone
6. Structural changes in the arteries
7. Pre-existent essential hypertension
8. Renovascular disease
9. Miscellaneous: anemia, AV fistula, vasopressin, serotonin, calcitonin gene-related peptide

has to remember that among HD patients there is a substantial day-to-day variability in the day-night blood pressure profile.[212] Moreover, nocturnal blood pressure measurements predict cardiovascular outcome only in patients with reproducible blood pressure profiles.[234]

Pathophysiology of Hypertension in Dialysis Patients

The pathogenesis of hypertension in CKD patients is complex and multifactorial. (Table 11).

Role of sodium and volume status. **(Moderately Strong)** Excessive intravascular volume is a major pathogenic factor of hypertension in patients with CRF. However, the relationship between weight gain during two dialyses and hypertension is unclear. Some studies have established that volume gain affects interdialytic blood pressure, whereas other studies have not shown such a relationship.[235]

The HEMO study observed that volume status influenced both predialysis and postdialysis blood pressure.[236] However, the intradialytic reduction in body weight (or interdialytic fluid gain) is helpful but insufficient to describe volume status and to predict blood pressure changes in HD patients.

The strongest evidence supporting a role for extracellular volume expansion derives from observations that, when excessive body fluids are removed with slow dialysis (8 hours × 3 times weekly) and "dry-weight" is achieved, blood pressure normalizes in more than 90% of dialysis-dependent patients.[237] It is of interest that whilst the normalization of the extra-cellular volume was achieved in the first month of dialysis treatment, blood pressure continued to decrease for another 8 months, despite the withdrawal of antihypertensive medication. The reasons for long, slow dialysis achieving a more effective blood pressure control may be due to more effective control of the ECV expansion with a low rate of hypotension episodes. Moreover, dry weight is probably more difficult to achieve with short dialysis than with long, slow HD.

In dialysis patients, normal blood pressure can be achieved independently of the duration and dose of dialysis, provided that the control of the postdialysis ECV is adequate. Decreased ECF expansion is responsible for a significant portion of HTN control in HD regardless of modality, but variability in achieved ECV is significant.[238]

Longer and more frequent dialysis. **(Weak)** Long, slow dialysis was shown to achieve a better blood pressure control and survival.[239] Other investigators have also shown better regression of LVH with slow dialysis.[240] Several studies have shown that short, daily HD treatment may be associated with a significant reduction of blood pressure, reduced use of antihypertensive medications, and lowered LV mass index.[226,241,242] In other studies, daily dialysis (short diurnal or nocturnal) improved blood pressure control, but only short daily HD resulted in lower ECV.[243]

The improvement of blood pressure observed with short, daily HD is not necessarily due to less

postdialysis ECFV. Unchanged postdialysis ECFV has been reported after the conversion to nocturnal HD and after excellent blood pressure control was achieved.[244] Some have suggested that short daily HD may decrease SNS activity.

In patients who remain hypertensive despite intense ultrafiltration, sodium and volume excess may play only a secondary role. The lack of correlation between exchangeable sodium and/or extracellular volume and blood pressure in these patients supports this notion.[245,246]

Role of CAPD. **(Weak)** Since CAPD allows for more consistent control of extracellular fluid volume than HD, it has been suggested that CAPD may provide better control of blood pressure than HD. Within 12 months of starting CAPD, between 40%-60% of hypertensive patients no longer required antihypertensive drugs.[247]

Better blood pressure control achieved during the first 2 months appears to be volume-related. After the initial 6 months of CAPD treatment, the sustained reduction in blood pressure does not correlate any longer with changes in volume and it is more likely related to removal of pressor hormones, although precise measurements of blood volume have not been performed.[248] After 1-2 years of CAPD treatment, blood pressure may rise again, and so does the need for antihypertensive drugs, presumably due to fluid retention related to sclerosis of the peritoneum, decreased efficiency of the peritoneal membrane in removing fluids, and reduced kidney function.

Role of erythropoietin. **(Moderately Strong)** The advent of recombinant human erythropoietin (rhEPO) has substantially improved the management of anemia and the quality of life in patients with chronic renal failure. However, increasing the hematocrit with rhEPO can lead to several adverse side effects, including worsening of hypertension.

During studies in dialysis and pre-phase III multicenter trials of rhEPO in dialysis patients, an increase in diastolic blood pressure of more than 10 mm Hg and/or a need to increase antihypertensive therapy occurred in 88 of 251 (35%) of previously hypertensive patients. A similar increase in blood pressure was noted in 31 of 71 (44%) of normotensive patients; in 32% of these patients, antihypertensive therapy had to be instituted.[249,250] This adverse rise in blood pressure has not been noted in patients receiving rhEPO for other reasons, suggesting that renal disease may confer a particular susceptibility[251] to the hypertensive action of rhEPO. The rise in blood pressure during rhEPO administration usually occurs within 2-16 weeks, although some patients may experience a rise in blood pressure several months after the initiation of therapy.

Patients who are at greater risk for developing hypertension during rhEPO therapy are those with severe anemia, those in whom anemia is corrected too rapidly, and those with pre-existing hypertension.

Management of Blood Pressure in Dialysis Patients

Target blood pressures. Despite the obvious importance of defining an ideal goal blood pressure for HD patients, this issue has not been resolved. According to JNC VII recommendations, normal blood pressure is <120/80 mm Hg.[170] In patients with essential hypertension, receiving antihypertensive therapy, the recommended goal blood pressure is <135/85 mm Hg. This recommendation is largely based on the HOT study.[252] The same study indicated that, in diabetic patients, the goal blood pressure should be set lower and should probably be below 130/80 mm Hg.

In patients with renal disease, particularly those with proteinuria greater than 1 g per 24 hours, a goal blood pressure of 125/75 mm Hg provides maximum protection against progression of renal disease.[253] This recommendation, however, does not apply to African-Americans with hypertension and renal disease in whom no difference in progression of renal disease was observed between MAP of 107 and 92 mm Hg.[254] Furthermore, these studies did not address the effect of different levels of blood pressure control on CVD.

It has been suggested that blood pressure of less than 150/90 mm Hg is a reasonable goal for most patients undergoing HD. The Work Group on chronic renal failure and renovascular hypertension, however, recommended a goal blood pressure of <130/85 mm Hg.[255] In the only prospective study so far performed in the dialysis population, a blood pressure of 140/90 mm Hg minimized the occurrence of LVH and death.[182]

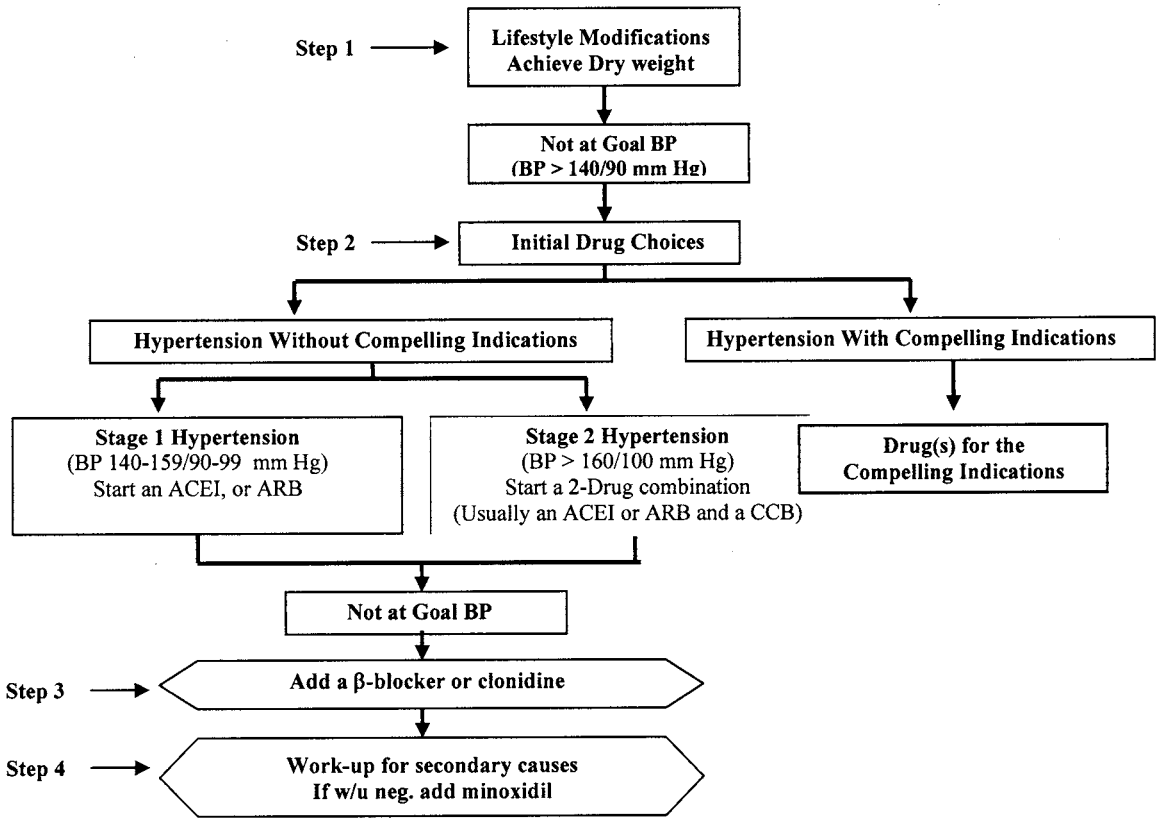

Fig 4. Hypertension treatment algorithm in dialysis patients.

It is the opinion of this Work Group that, in HD patients, a reasonable goal is predialysis blood pressure <140/90 mm Hg (measured in the sitting position), provided there is no substantial orthostatic hypotension and these levels are not associated with substantial and symptomatic intradialytic hypotension. *(Weak)*

Treatment algorithm. **(Weak)** The management of hypertension in dialysis patients is frequently challenging and it requires the knowledge of the pharmacokinetic and pharmacodynamic properties of all the agents used. We propose an algorithmic approach to the management of hypertension in dialysis patients (Fig 4).

Lifestyle modifications should be an integral part of the management of hypertensive CKD patients. The importance of salt restriction should be continuously emphasized. Achievement of dry weight and reduction of ECFV should be pursued, although this is not easy to monitor or accomplish, and it may not be effective in every patient.

If those measures are unsuccessful (and frequently they are), antihypertensive drugs should be initiated. As a first line of treatment in the majority of patients, we propose the use of ACE inhibitors or ARBs. The latter also reduce LVH in HD patients, and may be more potent than ACE inhibitors.[195,256-258] In an observational study, the use of an ACE inhibitor has been associated with decreased mortality in cohorts of CKD Stage 5 patients.[259]

Table 12 describes some of the criteria to be used in the selection of antihypertensive drugs in dialysis patients based on compelling indications.

In patients with previous myocardial infarction or with well-established coronary artery disease, β-blockers should be preferred. Exposure to beta-blockers is associated with decreased mortality in CKD (see also Guideline 6).[130] Calcium channel antagonists and anti–alpha-adrenergic drugs should be an integral part of the management of hypertension to achieve control if necessary. Observational studies sug-

Table 12. Antihypertensive Drug Therapy in Dialysis: Guidelines for Selection

Clinical Situation	Preferred	Relatively or Absolutely Contraindicated
Angina pectoris	β-Blockers, CCBs	Direct vasodilators
Post-MI	Non-ISA β-blockers	Direct vasodilators
Hypertrophic cardiomyopathy with diastolic dysfunction	β-Blockers, diltiazem, verapamil	Direct vasodilators, α_1-blockers
Bradycardia, heart block, sick sinus syndrome		β-blockers, labetalol, verapamil, diltiazem
Heart failure (decreased LV ejection fraction)	ACE inhibitors, ARBs, β-blockers	CCBs
Peripheral vascular disease		β-blockers
Diabetes mellitus	ACE inhibitors, ARBs	
Asthma/COPD		β-blockers
Cyclosporine-induced hypertension	CCBs, labetalol	Nicadipine,[a] verapamil,[a] diltiazem[a]
Liver disease		Labetalol, methyldopa
Erythropoietin-induced hypertension	Calcium antagonists	ACE inhibitors[b]

a May increase serum levels of cyclosporine
b May increase erythropoietin requirement

gest that CCBs are associated with decreased total and cardiovascular mortality.[260] In the most severe forms of hypertension, multiple antihypertensive drugs are needed, including minoxidil. If full doses of one agent are ineffective, a second or a third drug should be added. If blood pressure is not controlled with dialysis and three antihypertensive agents of different classes, the patient should be evaluated for potential secondary causes of resistant hypertension. If no evident cause for resistant hypertension is found, and the patient remains hypertensive after a trial with minoxidil, one should consider treating the patient with continuous ambulatory peritoneal dialysis (CAPD). If CAPD proves ineffective, surgical or embolic nephrectomy should be considered.

Resistant hypertension. **(Weak)** In dialysis patients, hypertension is considered resistant if blood pressure in a compliant patient remains above 140/90 mm Hg after achieving dry weight, and after an adequate and appropriate triple-drug regimen. In elderly patients with isolated systolic hypertension, resistant hypertension is defined as the failure of an adequate regimen to reduce systolic blood pressure to less than 140-150 mm Hg. The regimen should include nearly maximal doses of at least three different pharmacological agents selected from ACE inhibitors, calcium antagonists, β-blockers, antiadrenergic agents, or direct vasodilators, such as hydralazine or minoxidil.

Several factors can cause resistant hypertension, including patient noncompliance, inadequate regime, drug-to-drug interactions, pseudoresistance, secondary hypertension, and unrecognized pressor mechanisms (Table 13).

Paradoxical rise of blood pressure during dialysis. **(Weak)** Hypertension induced by HD is a topic that has received little attention. It occurs in a small number of patients during HD. The causes of this phenomenon have not been well worked out. Sometimes it is precipitated by removal of certain antihypertensive drugs during dialysis.

Hemodialysis reduces blood levels of some ACE inhibitors (enalapril, ramipril) but not others (benazepril, fosinopril, methyldopa, atenolol, acebutolol, nadolol, minoxidil and nitroprusside); by contrast, levels of clonidine, carvedilol, labetalol, CCBs and ARBs do not change significantly (see Table 12). At times, excessive volume depletion may result in hypertension rather than in hypotension. This has been attributed to excessive stimulation of the renin-angiotensin system precipitated by the decrease in blood volume. An alternative possibility, which has not been properly investigated, is that this might be the result of excessive activation of the sympathetic nervous system and resulting vasoconstriction.

In a recent study of seven patients with this characteristic, all with marked cardiac dilation, intense ultrafiltration reduced blood pressure and

Table 13. Causes of Resistant Hypertension in Dialysis Patients

Patient nonadherence to the prescribed treatment
Dietary (excessive sodium intake or alcohol consumption, inability to reduce excessive body weight)
Drug regimen
Inadequate regimen
Drug-to-drug interaction
Administration of epoetin, steroids, cyclosporine, NSAIDs
Secondary hypertension (renovascular, primary aldosteronism or other mineralocorticoid excess syndromes, pheochromocytoma, hypothyroidism, hypercalcemia, sleep apnea)
Pseudoresistance
Drug abuse (cocaine, amphetamines, methylphenidate, etc.)

cardiac dilation and eliminated the paradoxical elevation of blood pressure during dialysis.[261] The explanation of this phenomenon remains elusive.

LIMITATIONS

- One major limitation of these guidelines is the lack of large-scale clinical trials correlating levels of blood pressure with cardiovascular disease events. Particularly puzzling is the U-shaped relationship between systolic blood pressure and cardiovascular morbidity and mortality, and the apparent lack of high blood pressure effects on cardiovascular disease events until systolic blood pressure reaches approximately 180 mm Hg. The increase mortality in patients with lower blood pressure could be related to poor ventricular function. The lack of effects of blood pressure on cardiovascular events over a wide range of blood pressure between 100-180 mm Hg could be related to variable ventricular function, and to "survival bias," whereby high-risk patients with higher blood pressure may not have survived to be entered into the study.
- Another limitation of these guidelines is related to the great variability of blood pressure with dialysis and the lack of firm criteria on definition of hypertension in this patient population.
- Another major limitation of these guidelines is the lack of controlled studies on the effect of different blood pressure goal and different therapeutic intervention on CVD events. Most of the recommendations are based on inference from studies performed in the general population with normal renal function. Other studies were performed in patients with various degrees of kidney disease, but not on dialysis therapy, and the outcomes were deterioration of renal function but not CVD.

IMPLEMENTATION ISSUES

- Measurement and recording of blood pressure is already implemented in most HD programs. Not all dialysis programs, however, routinely measure blood pressure in the sitting and upright position both before and after dialysis. Further definition and evaluation of the associated costs and benefits are required to determine the need for and implementation of 24-hour ABPM.
- Longer and/or more frequent short dialysis may be necessary to achieve control of blood pressure and fluid/volume status in many patients. However, current Medicare reimbursement policies, and patient resistance to more frequent and/or longer dialysis renders the implementation of these recommendations difficult.

RESEARCH RECOMMENDATIONS

- More studies are necessary to better determine goal blood pressures in dialysis patients.
- Studies are needed to determine which antihypertensive drugs are best suited for dialysis patients.
- More studies are necessary to determine optimal dosing (dose and time of administration) of antihypertensive drugs in dialysis patients.
- Further studies are needed to ascertain the potential advantage of daily dialysis over dialysis performed 3 times weekly to achieve better blood pressure control and better cardiovascular outcomes.

GUIDELINE 13: DYSLIPIDEMIA

Since the NKF K/DOQI Clinical Practice Guidelines for Managing Dyslipidemia in Chronic Kidney Disease Patients were established only recently,[51] we refer to those guidelines. However, we add the information on four recent studies that provide some new insights on the inverse association between cholesterol level and mortality, as well as further indirect evidence of the beneficial effects of lipid-lowering therapy. Furthermore, unpublished results of the recently completed "4D Trial" on the effect of statins in chronic HD patients recently became available and will be discussed.

Management of dyslipidemias for prepubertal children with CKD and CKD Stage 5 should follow recommendations by National Cholesterol Expert Panel in Children and Adolescents. Postpubertal children or adolescents with CKD Stages 4 and 5 should follow the recommendations provided in the K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease.[51]

RATIONALE

Association between Dyslipidemia and CVD in Dialysis Patients (Weak)

The previous guidelines listed the studies, which investigated an association between cholesterol levels and CVD, and discussed the often-observed "paradoxical association" between dyslipidemia and CVD in HD patients, i.e., that higher cholesterol levels are apparently associated with better outcomes in HD patients. As one of several explanations it was mentioned that none of the previous studies was a long-term, prospective cohort study and that illness, inflammation, and poor nutrition might have confounded the relationship between dyslipidemia and CVD. This was recently observed in a study investigating the association of cholesterol levels with all-cause and CVD mortality in a prospectively followed cohort of 823 patients who initiated dialysis treatment.[262] During a median follow-up of 2.4 years, 324 deaths (including 159 CVD deaths) occurred. Average serum cholesterol level was lower in the presence of inflammation/malnutrition than in its absence. A higher baseline total serum cholesterol level was associated with a decreased risk of all-cause mortality overall and in the presence of inflammation/malnutrition. In contrast, a higher serum cholesterol level was associated with an increased risk in the absence of inflammation/malnutrition. For CVD mortality, an inverse trend was not statistically significant in the presence of inflammation/malnutrition, and a positive association was evident in the absence of inflammation/malnutrition. The authors concluded that the inverse association of total cholesterol level with mortality in dialysis patients is likely due to the cholesterol-lowering effect of systemic inflammation and malnutrition, not to a protective effect of high cholesterol concentrations. These findings would support the treatment of hypercholesterolemia in dialysis patients.

Indirect Evidence for Lipid-Lowering Therapy in Kidney Disease (Weak)

Even if the present guidelines focus on dialysis patients, further indirect evidence for the beneficial effect of lipid-lowering intervention comes from three additional studies. A multicenter, randomized, double-blind, placebo-controlled trial of 40-80 mg fluvastatin was conducted in 2,102 kidney transplant recipients followed for 5-6 years.[263] Fluvastatin reduced LDL cholesterol concentrations by 32%. Risk reduction for the composite primary endpoint including myocardial infarction, cardiac death and cardiac interventions did not reach significance although the fluvastastin group experienced a third fewer cardiac death and nonfatal MI than the placebo group. Coronary intervention procedures and other secondary endpoints were not significantly different between the two groups.

Another study was performed in more than 19,000 hypertensive patients with at least three other CVD risk factors.[264] Patients with nonfasting cholesterol concentrations of 6.5 mmol/L or less were randomly assigned additional atorvastatin 10 mg or placebo. A prespecified subgroup analysis in 6517 patients with kidney dysfunction revealed a significantly lower risk for the primary endpoint (nonfatal MI or cardiac death) in the atorvastatin group when compared to placebo.

A randomized trial of pravastatin versus placebo in 4,159 patients with previous MI and total plasma cholesterol level <6.21 mmol/L performed a *post hoc* analysis in 1,711 patients with

CKD.[265] After a median follow-up of almost 5 years, the incidence of the primary end point (coronary death or nonfatal MI) was lower in patients receiving pravastatin than in those receiving placebo, suggesting that pravastatin is effective for secondary prevention of cardiovascular events in persons with mild chronic kidney insufficiency.

4D Trial

Together with the Heart Protection Study,[266] all four studies support the hypothesis that lipid-lowering intervention might be beneficial in patients with kidney insufficiency.

The latest results came from the "4D Trial" (Deutsche Diabetes Dialyse Studie) which have not yet been published. It was a randomized, placebo-controlled study in 1,255 type 2 diabetic patients on chronic HD.[267] Out of those patients, 619 were treated with 20 mg atorvastatin compared to 636 matched controls treated with placebo for a median of 4 years. The statin was safe and effective in reducing the median serum LDL cholesterol level by 42% throughout the study period. However, the primary endpoint—defined as the composite of cardiac death, nonfatal MI, and fatal or nonfatal stroke—was only reduced by 8% which was not statistically significant (Christoph Wanner for the 4D Study investigators, American Society Nephrology 37th Annual Meeting, October 2004). This was in distinct contrast to the recently published CARDS trial (Collaborative Atorvastatin Diabetes Study) in type 2 diabetic patients who had not yet developed significant kidney disease.[268] In that study, atorvastatin reduced the rate of acute coronary events by 36%, coronary revascularization by 31%, stroke by 48%, and death by 27%. The 4D investigators concluded that the negative results might have been due to the advanced cardiovascular diseases in the chronic HD patients, and because statin therapy was initiated too late. Therapy might better be started during the early stages of disease progression as demonstrated by the CARDS study. There are, of course, other potential explanations for these results, which would warrant further studies. Whether the effect of statin reported in the 4D Trial on diabetic dialysis patients is different in nondiabetic dialysis patients or chronic PD patients needs to be further investigated.

Recent NCEP Report on ATP III Guidelines

A recent report from the National Cholesterol Education Program (NCEP) discussed the implications of clinical trials on the Adult Treatment Panel III (ATP III) guidelines.[269] Results from the Heart Protection Study and the PROVE IT Study suggested that additional benefit may be obtained by reducing LDL cholesterol levels to substantially below 100 mg/dL. Since other studies are underway to prove the efficacy of lowering LDL to very low levels, the NCEP report stated that "until these trials are completed, prudence requires that setting an LDL-C goal of $<$70 mg/dL for high-risk patients must be left as a therapeutic option on the basis of clinical trial evidence, whereas a goal of $<$100 mg/dL can be retained as a strong recommendation. Factors that favor a decision to reduce LDL-C levels to $<$70 mg/dL are those that place patients in the category of very high risk."

GUIDELINE 14: SMOKING, PHYSICAL ACTIVITY, AND PSYCHOLOGICAL FACTORS

While there are few data specific to CVD in dialysis patients regarding smoking, physical activity, and psychological factors (depression, anxiety, and hostility), the evidence in the general population is clearly in favor of addressing each of these issues. In order to ensure that clinicians caring for dialysis patients do not overlook the importance of each of these factors, we have dedicated an entire guideline to them.

14.1 All dialysis patients should be counseled and regularly encouraged to stop smoking. (A) Referral to smoking cessation specialists is recommended. (C)

14.1.a Special consideration should be given to cessation of smoking in depressed individuals with little ability to engage in physical activity. (C)

14.2 All dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity. (B)

14.2.a Unique challenges to exercise in dialysis patients need to be identified in order to refer patients appropriately (e.g., to physical therapy or cardiac rehabilitation) and to enable the patients to follow regimens successfully. Such challenges include orthopedic/musculoskeletal limitations, cardiovascular concerns, and motivational issues. (C)

14.3 Measurement of physical functioning:

14.3.a Evaluation of physical functioning and re-evaluation of the physical activity program should be done at least every 6 months. (C)

14.3.b Physical functioning can be measured using physical performance testing or questionnaires (e.g., SF-36). (C)

14.3.c Potential barriers to participation in physical activity should be assessed in every patient. (C)

14.4 Physical activity recommendations:

14.4.a Many dialysis patients are severely deconditioned and therefore may need a referral for physical therapy to increase strength and endurance to the point where they are able to adopt the recommended levels of physical activity.

14.4.a.i Patients who qualify for cardiac rehabilitation should be referred to a specialist. (C)

14.4.a.ii The goal for activity should be for cardiovascular exercise at a moderate intensity for 30 minutes most, if not all, days per week. Patients who are not currently physically active should start at very low levels and durations, and gradually progress to this recommended level. (C)

14.4.b Follow-up:

14.4.b.i Physical functioning assessment and encouragement for participation in physical activity should be part of the routine patient care plan. Regular review should include assessment of changes in activity and physical functioning. (C)

14.5 Depression, anxiety, and hostility should be identified and treated in dialysis patients. (B)

14.5.a Every dialysis patient should be seen by the dialysis social worker at initiation of dialysis, and at least biannually thereafter, to assess the patient's psychological state, with specific focus on the presence of depression, anxiety, and hostility. (C)

14.5.b Dialysis patients should be treated for depression, anxiety, and hostility if they are experiencing these psychological states. (C)

RATIONALE

Definitions

Physical activity. Bodily movement that is produced by the contraction of skeletal muscle and that substantially increases energy expenditure.

Regular physical activity. Accumulation of at least 30 minutes of moderate-intensity physical activity on most—and preferably all—days of the week. Moderate intensity is at levels appropriate to the capacity, needs, and interest of the individual.

Physical functioning. Ability of the individual to participate in required activities of living.

Physical capacity. Measured ability to perform specific tasks, such as performance testing and exercise testing.

Major Depression is typically characterized by having a depressed mood and a significant loss of interest in all activities that persists for a minimum of 2 weeks and is accompanied by a minimum of four of the following symptoms: appetite or sleep disturbances; psychomotor retardation or agitation; fatigue; feeling guilty or worthless; problems with concentration; or suicidal ideation.[270] Because many of the somatic symptoms associated with depression are also symptoms of uremia, the cognitive symptoms may be better used when assessing depression in dialysis patients.

Anxiety has both physiological and psychological symptoms. The psychological aspects, which may be more relevant when assessing those with pre-existing medical problems, include: feelings of powerlessness; a sense of impending danger; exhaustive alertness; self-absorption that interferes with ability to effectively problem-solve; and extreme doubts about a threatening occurrence and one's ability to deal with it; and worries that are difficult to control and may interfere with functioning. The concerns may be with or without cause, are pervasive, and last longer than would be expected.[271]

Hostility involves negative behavior and feelings, often directed at interpersonal relationships. It includes such characteristics as anger, cynicism, and lack of trust.[270]

Smoking (Moderately Strong)

Cigarette smoking is universally recognized as an independent risk factor for CVD. Smoking, therefore, should also be discouraged in patients with CKD. However, this recommendation is even more compelling, considering the relationship between smoking and poor outcomes in dialysis and transplant patients (Table 14). The frequency and duration of contact with dialysis health-care providers should facilitate concerted and serious efforts directed towards assisting patients to discontinue smoking.

Physical Activity (Weak)

Dialysis patients have extremely low levels of physical functioning and exercise capacity, and are often physically inactive. Physical inactivity is known to be a risk factor for CVD and overall mortality[272] as well as increasing risk for developing several chronic conditions, including diabetes[273,274] and hypertension.[275] In the general population, regular physical activity: reduces high blood pressure in persons with hypertension; reduces depression and anxiety; helps to control weight; helps to maintain healthy bones, muscles, and joints; helps older adults become stronger and better able to move about without falling; and promotes psychological well-being. This evidence is clearly documented in the U.S. Surgeon General's Report on Physical Activity and Health.[276] Several other national guidelines recommend regular physical activity as part of treatment for cardiovascular-related risk factors, specifically, the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[277] and the National Cholesterol Education Project Adult Treatment Guidelines III.[278] In fact, in both of these documents, lifestyle change (which includes regular physical activity) is the first recommendation.

Data in dialysis patients indicate that *self-reported* physical functioning is highly predictive of outcomes such as hospitalizations and death, even when corrected for case mix and comorbidity.[279] Likewise, a recent study has

Table 14. Association of current smoking with risk of cardiovascular outcomes

Author, Year	Mean study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	Results (Univariate)	Results (Multivariate)	Quality
Zimmermann, 1999 [1436]	24 mo	280		↑↑↑	All cause death	⇧		●
Foley, 2003 [10192]	2.2 yr	~1721	~1640	↑↑↑	All cause death	⇔	⬆	●
Kestenbaum, 2002 [10005]	~18 mo	3716		↑↑↑	All cause death	⇔	⇧	○
Bloembergen, 1996 [2540]	~2 yr	2479		↑↑↑	All cause death		⇧	○
Tepel, 2002 [10155]	18 mo	188		↑↑↑	All cause death	⬆		○
Fishbane, 1996 [2748]	1 yr	132		↑↑↑	All cause death	⇩	⇔	○
Blacher, 1998 [1637]	25 mo	79		↑↑↑	All cause death		⇔	○
Fleischmann, 2001 [117]	2 yr	453		↑↑	All cause death	⇔	⇔	○
Kimura, 1996 [2475]	54 mo	195		↑↑	All cause death	⬆	⇔	○
Zimmermann, 1999 [1436]	24 mo	280		↑↑↑	Cardiovascular death	⇧		●
Mallamaci, 2002 [10153]	29 mo	175		↑↑	Cardiovascular death	⇔		●
Benedetto, 2001 [106]	30 mo	91	47				⇔	
Fung, 2002 [10133]	~5 yr	5058		↑↑↑	Cardiovascular death		⬆	○
Kestenbaum, 2002 [10005]	~18 mo	3716		↑↑↑	Cardiovascular death	⬇	⇔	○
Bloembergen, 1996 [2540]	~2 yr	2,479		↑↑↑	Cardiovascular death Coronary artery disease death Other cardiac death	⇩ ⇧ ⇧		○
Brown, 1994 [3215]	4 yr	305		↑↑↑	Cardiovascular death	⬆		○
Fishbane, 1996 [2748]	1 yr	132		↑↑↑	Cardiovascular death	⇧	⇧	○
Blacher, 1998 [1637]	25 mo	79		↑↑↑	Cardiovascular death		⇔	○
Rostand, 1982 [6378]	29 mo	320		↑↑	Ischemic heart disease	⇔		○
Foley, 2003 [10192]	2.2 yr	~1003	~1221	↑↑↑	Ischemic heart disease	⇔	⇔	●
Foley, 2003 [10192]	2.2 yr	~960	~1168	↑↑↑	Congestive heart failure	⬆	⬆	●
Foley, 2003 [10192]	2.2 yr	~1284	~1562	↑↑↑	Cerebrovascular disease	⇔	⇔	●
Foley, 2003 [10192]	2.2 yr	~1183	~1663	↑↑↑	Peripheral vascular disease	⬆	⬆	●

shown that *objective laboratory measures* of physical fitness are independently predictive of mortality, with patients with low maximal oxygen uptake (<17 mL/kg/min) showing significantly higher mortality.[280] It is not known whether improving exercise capacity and/or increasing physical activity will result in reduction in hospitalizations or death in dialysis patients.

Although no randomized clinical trials have been performed to assess the effects of physical activity on cardiovascular risk in patients with renal failure, the preponderance of evidence and existing guidelines for physical activity for other populations at high risk for CVD suggest similar implementation of physical activity for patients with renal failure. The well-documented literature on low levels of physical functioning in this population, and evidence that it can be improved with exercise training, warrants attention to this lifestyle issue.[281-297]

Psychological Factors (Moderately Strong)

The purpose of this guideline is to identify those individuals at increased risk for developing or worsening CVD due to their psychological state. There is a strong association between depression, anxiety, and hostility, and CVD in the general population. No research was identified that addressed the association of psychological state *per se* with CVD in dialysis patients. However, since there is a high prevalence of depression and anxiety, as well as documented hostility, in this population, it is reasonable to recommend assessment and treatment of these conditions that are known elsewhere to be highly associated with CVD.

Depression. In the 1980s, two meta-analyses of the research literature evaluating psychological functioning and CVD found conflicting results. One strongly suggested that depression relates to CAD, including its development, while the other found that depression did not predict the occurrence of CAD.[298,299] Another study of 498 men found that depression was only slightly associated with incidence of CHD.[300] However, recent evidence from 13 rigorously designed research studies linking patients exhibiting depressive symptoms or experiencing major depression with higher cardiovascular morbidity and mortality suggests depression may be an independent risk factor in CVD progression.[270,301] A meta-analysis of 11 epidemiological studies found that the relative risk for developing CHD was 1.64 in depressed individuals.[300] Multiple studies that followed patients with coronary heart disease for up to 2 years found that depression predicted the occurrence of angina pectoris, MI, and angioplasty and/or coronary artery bypass surgery.[302] Depression also resulted in more than a fourfold increased independent risk of mortality, giving it the same prognostic value as a prior history of MI.[302]

Rates of depression of 30%-50% have been reported in dialysis patients who use self-reported measures of depressive symptoms, although lower rates have been reported when DSM III-R criteria are used to assess for major depression.[303] HD patients' mean depression score has been documented to be significantly higher than that of normal subjects.[304] In one study of 128 dialysis patients, 25.7% exhibited symptoms of depression and 26.6% scored within the range of clinical depression. Approximately 50% of participants scored within the range that indicated a potentially clinically significant depression.[305] A more recent study found that approximately 25% of the 1,000 HD patients studied were depressed.[279] Forty-three percent of 9,382 hemodialysis patients scored within the depressed range of the Center for Epidemiological Studies Depression Screening Index.[306] Multiple studies have demonstrated that depression is associated with decreased overall survival in dialysis patients. It has not been established whether depression is an independent risk factor or if depression affects other variables, such as adherence, that may impact survival.[303]

Anxiety. Most early studies suggested that anxiety was, at the most, only slightly related to CVD.[298,299] An exception was a 5-year prospective study of 10,000 adult men which found that not only was anxiety an independent contributor to the development of angina pectoris, but the likelihood of developing angina increased as the level of anxiety rose.[307] Later evidence from three research studies, one involving 34,000 healthy subjects, further documented a significant association between anxiety and the development of cardiac events and SCDs.[270] Others have shown that social anxiety both significantly predicts CHD development as well as increases its incidence.[300] Multiple studies have established that those who experienced both depression and anxiety had a compounded cardiac risk.[270] Other research has documented the relationship between anxiety and cardiac events, including MI[302,308,309] and SCD.[310]

Approximately 45% of 128 dialysis patients in one study exhibited clinical anxiety.[305] As with depression, the mean anxiety score of HD patients has been found to be significantly higher than that of normal subjects.[304]

Hostility. Research evaluating the relationship of hostility with CVD has shown mixed results in the general population. Three prospective, controlled studies representing 1,250 subjects in the general population, which used the Cook-Medley Hostility Inventory as a measure of hostility, demonstrated that the presence of hostility predicted CAD events and overall mortality.[298] Further support for hostility being an independent risk factor for CAD comes from a meta-analysis of 45 research studies.[311] Data from the Western Collaborative Group Study showed that potential for hostility was a significant predictor for developing CHD.[299] Additional studies revealed that hostility was independently related to coronary atherosclerosis and significantly predicted the development of CHD.[299] It was found that patients with documented hostility had a 1.9 risk ratio for experiencing MI, angina, and cardiac death after controlling for other traditional risk factors.[302]

The intensity of anger, which is a component of hostility, has also been associated with CVD. In a prospective study of 1,305 individuals, those

who experienced a higher level of anger were found to have a 3.2 times higher risk of having a fatal or nonfatal coronary event compared to those who reported the lowest level of anger.[310] Another study documented that the relative risk of experiencing another MI was 2.3 within 2 hours of an anger episode in 1,623 post-MI patients.[302]

The Kellner Symptom Questionnaire, which was administered to female subjects, showed that not only were dialysis patients more depressed, they were also more hostile than the healthy control group.[312] A study of dialysis patients and their partners documented that those on dialysis experienced a variety of psychological reactions, including anger.[313]

Physiological factors associated with depression, anxiety, and hostility. **(Weak)** Depression, anxiety, and hostility may be associated with CVD through several mechanisms. For example, these factors may lead to nonadherence with the dialysis or diet regimen, which may impair cardiovascular functioning. In addition, a patient who is experiencing any of these psychological states may be more prone to engage in high-risk behaviors, such as smoking, that could have a negative impact on cardiovascular health.

Additionally, there are pathophysiological effects when a person experiences depression, anxiety, or hostility. Depression has been associated with impaired platelet functioning, hypercortisolemia, heightened plasma and urinary catecholamines, increased heart rate, altered vagal control, and a reduction in the variability of the heart rate. Each of these may have a negative impact on the prognosis of CHD.[301] Patients experiencing depression have exhibited sympathoadrenal hyperactivity, and it has been suggested that this may contribute to the development of CVD due to the cathecholamines' effects on cardiac functioning and platelets.[301] Depression has also been associated with the inflammatory response, and consequent CAD progression.[302] Other physiological changes associated with depression that negatively impact cardiovascular function are hypercoagulability, systemic and localized inflammation, and cardiac rhythm alterations.[314]

Some patients with anxiety have exhibited decreased heart rate variability, which may result in pathological alterations in cardiac autonomous tone. This could involve either increased sympathetic stimulation or impaired vagal control, both of which have been linked to mortality.[270] Sympathetic-adrenal medullary and adrenal cortical activity are higher when anxiety is present, and this may also be a contributor to CVD.[307] Anxiety may also result in coronary vasospasm that can cause atherosclerotic plaques to rupture.[302]

People who exhibit hostility and are exposed to certain stimuli, such as mental tasks, have been shown to have higher blood pressure and heart rates than those who are not hostile,[270,298] as well as other physiological changes that are linked to CVD.[270,302]

Assessment and suggested treatment of depression, anxiety, and hostility. **(Weak)** Although there are no studies specifically addressing the relationship between psychological factors and CVD in dialysis patients, the prevalence of these factors, as discussed earlier, makes treatment an important issue. There is documented evidence that psychological and social interventions, in addition to standard cardiac rehabilitation, can significantly reduce mortality and morbidity and have positive influences on cholesterol, blood pressure, and heart rate.[302]

Adequate dialysis and anemia control are important contributors to overall well-being and quality of life for dialysis patients. These factors, combined with an assessment of the patient's physical health and potential side effects of medication, should first be evaluated as possible contributors to depression and anxiety.

Typically, referral to a psychologist may be necessary for psychometric testing, although quality-of-life assessments, which include depression, have become routine in many dialysis facilities. Several instruments measure levels of depression, anxiety, and hostility (Table 15). The Beck Depression Inventory (BDI), which is used frequently, is a well-validated instrument.[303] The BDI Fast Screen is a self-report instrument that was developed specifically to measure depression in patients who have medical illness.[315] The Cognitive Depression Index, a subset of the BDI, controls for the possible impact of somatic symptoms, which may artificially inflate depression rates when assessing the dialysis population.[303] The SF-36 has also been established as a good

Table 15. Pyschometric Testing Instruments

Test	Factors Measured	Reliability/Validity	Reference
Beck Depression Inventory (BDI)	Depression, includes somatic symptoms	Good	Kimmel, 1993[303]
BDI Fast Screen	Depression, without somatic symptoms	Good	Benedict, 2003[315]
Cognitive Depression Index of the BDI (CDI)	Depression, without somatic symptoms	Good	Kimmel, 1993[303]
SF-36	Depression	Good	DeOreo, 1997[279]
World Health Organization Quality of Life-100 (WHOQOL-100)	Depression, anxiety	Good	WHOQOL, 1998[316]
WHOQOL-100 BREF	Depression, anxiety	Good	WHOQOL, 1998[316]
State Trait Anxiety Inventory (STAI)	Anxiety	Good	Alarcon, 1982[317]
State Trait Anger Expression Scale (STAXI)	Anger Anger suppression Anger expression	Good	Mayne, 1999[318]
Cook-Medley Hostility Inventory (from MMPI)	Hostility Predicts CAD events and mortality	Good	Goldstein, 1992[298]

screening tool for depression with center HD patients.[279] The World Health Organization Quality of Life-100 (WHOQOL-100) and its abbreviated version, WHOQOL-BREF, were developed for use throughout the world in a variety of cultures. These instruments contain a psychological domain that assesses depression and anxiety.[316] The State-Trait Anxiety Inventory (STAI) has been commonly used and is considered to be one of the best standardized tests to measure anxiety.[317] Similarly, the State-Trait Anger Expression Scale (STAXI) has also been used extensively. It has predictive validity and vast normative data, and distinguishes between the suppression and the expression of anger.[318] Another measure of hostility is the Cook-Medley Hostility Inventory, which is taken from the Minnesota Multiphasic Personality Inventory (MMPI). This instrument has been found to predict CAD events, CHD mortality and overall mortality.[298,319]

Social support has been shown to lower depression in the general population.[303] Poor social support has also been associated with an increased incidence of CAD.[270] Group counseling that focused specifically on modifying Type A personality traits, such as hostility, was found not only to reduce Type A characteristics, but also to significantly reduce cardiac deaths in a controlled study of over 800 post-MI participants. Group instruction that included stress reduction techniques was also found to lower hostility, as well as cardiac deaths.[270]

The use of cognitive-behavioral therapy was found to lower anxiety and reduce depression in the general population,[311] and has also effectively reduced hypertension and the morbidity and mortality from CVD that is associated with hypertension.[318] Relaxation techniques were also equal to or more effective than other psychological interventions in lowering physiological arousal in persons with CVD. Biofeedback, one form of relaxation, lowered hypertension in 60% of study participants with CVD.[318] Other techniques, such as controlled breathing, have been found to be significantly associated with reduction in MIs, as well as all-cause mortality.[270] Chronic HD patients who were taught simple progressive relaxation exercises had significantly lowered anxiety levels, while a control group remained unchanged.[317] Multiple studies with the general population have documented that anger is also treatable using a variety of different interventions.[311,318]

Patient education has been documented to impact psychological state. Patients who participated in an educational program about CKD (which included information on its treatments and potential impact on quality of life) prior to beginning dialysis were found to have significantly lower levels of anxiety and improved moods compared to a control group. This differ-

ence remained for the first six months after initiating dialysis.[320] As discussed earlier in this guideline, physical activity can also significantly impact the dialysis patient's well-being.

If patients exhibit depressive or anxiety symptoms that do not respond to other treatments, psychotropic medication should be considered. Selective serotonin reuptake inhibitors or atypical antidepressants, such as nefazodone or buproprion, may be considered for use in CVD patients who are depressed. These antidepressant medications may have fewer potential negative cardiovascular effects than many other antidepressants.[301] Studies have documented that pharmacological intervention has had positive effects on the psychological functioning of patients with CKD.[321]

LIMITATIONS

Smoking

- Cessation of smoking in dialysis patients may be difficult to achieve, as in the general population.
- There are no comprehensive studies of the use of the pharmacotherapies recommended for smoking cessation in dialysis patients.

Physical Activity

- There are no randomized trials in dialysis patients of the effects of exercise on cardiovascular risk profile; however, there are randomized trials in dialysis patients that demonstrate the effects of exercise training on physical functioning. Many patients are severely debilitated and will require lower levels of rehabilitation efforts. These levels may not be sufficient to modify cardiovascular risks; however, they will prove adequate to improve physical functioning.

Psychological Factors

- Research studies have produced conflicting data that may be due to using different definitions of the constructs, examining components within a construct rather than using the entire construct, or using varying methods of measuring psychological constructs. Additional problems in some studies included small sample sizes, large percentages of a study population lost to follow-up, and not controlling for variables that could affect the outcome.
- This guideline is largely based upon observational studies, meta-analyses, and review articles. No research could be found that evaluated the association between psychological factors and CVD in dialysis patients.

IMPLEMENTATION ISSUES

Psychological Factors

- In the U.S., regulations governing dialysis facilities mandate that Masters-prepared social workers with clinical specialization perform a psychological and social assessment of patients when they begin dialysis. Social workers, as part of the multidisciplinary team, are also mandated to reassess stable patients every six months and unstable patients as part of team care planning.
- Nephrologists and other dialysis health-care providers may not routinely assess dialysis patients' psychological functioning. They may not feel confident in assessing psychological function and may think that this task falls outside their area of expertise. They may also not be aware of the prevalence of these psychological traits in the dialysis population, the positive associations between these traits and CVD, or the interventions that have been shown to reduce psychological distress.
- The various interventive techniques discussed for psychological factors could be implemented by the dialysis facility social worker or by referral to an outside mental health professional. Medicare will cover 50% of the charges for outpatient mental health treatment, after a deductible is met, if it is provided by an approved Medicare provider.

RESEARCH RECOMMENDATIONS

Smoking

- Studies are required in CKD patients to examine the pharmacokinetics/safety of pharmacotherapies known to be effective in smoking cessation.
- Randomized trials are needed to determine the most effective interventions for smoking cessation in dialysis patients.

- Randomized, controlled trials are needed to determine the effects of smoking cessation on cardiovascular and all-cause outcomes in dialysis patients.

Physical Activity

- Randomized clinical trials are needed to study the effects of exercise training on cardiovascular risk in dialysis patients.
- Studies are required to determine the optimal exercise prescription and to develop practical ways of incorporating physical activity and assessment of physical functioning into the routine care of dialysis patients.
- Studies are needed to define the barriers to exercise in dialysis patients and to develop motivational strategies to increase participation in regular physical activity.
- Studies are required to determine how to effectively incorporate physical activity into the routine care of dialysis patients.

Psychological Factors

- Research is needed to study the presence of psychological distress in dialysis patients.
- Further studies are required to examine the impact of psychological distress on cardiovascular functioning and outcomes in dialysis patients.
- Studies are required in dialysis patients to examine the impact of therapeutic interventions, which are used to treat psychological conditions associated with CVD, on psychological states and cardiovascular events.

GUIDELINE 15: ANEMIA

The impact of anemia on CVD (specifically, LVH) and exacerbation of CAD is well described in the dialysis population. Given the prevalence of anemia in the dialysis population, and its association with poor outcomes, anemia is considered a "uremia-specific" CVD risk factor.

15.1. All dialysis patients with anemia should follow the K/DOQI Guidelines for Treatment of Anemia.[52]

RATIONALE *(Weak)*

Anemia results in decreased peripheral vascular resistance and plasma viscosity, and increased venous return. A reduced hemoglobin level lowers oxygen delivery, resulting in increased heart rate and venous tone. These factors cause increased cardiac output, which increases arterial volume and LV wall tension. The cumulative effect is LVH, arterial hypertrophy, and arteriosclerosis. Guidelines have been previously developed by the K/DOQI Anemia Work Group.[52]

Observational studies have demonstrated an association between anemia and adverse cardiovascular outcomes in CKD patients. One such study demonstrated that a hemoglobin level $<$8.8 g/dL was independently associated with LV dilation, cardiac failure, and total mortality.[331] Other studies have supported these findings, and are reviewed in the previous anemia guidelines.[52]

It is not known if treatment of anemia prevents cardiovascular events in CKD patients. The Normal Hematocrit Trial randomized 1,200 patients with heart failure or ischemic heart disease to a target hematocrit of 30% or 42%, and assessed time to first myocardial infarction or death.[332] Although there was no significant difference in outcome between groups, the trial was stopped early due to a trend suggesting poorer outcomes among those with higher hematocrit levels.

The Canadian Normalization of Hemoglobin Trial randomized 146 CKD patients with either concentric LV hypertrophy or LV dilation[333] to receive doses of erythropoietin to achieve a hemoglobin of either 10 or 13 g/dL (100 or 130 g/L). In the patients with concentric LVH, changes in LV mass index were similar between groups. In the patients with LV dilation, changes in volume index were also similar between groups. However, those with concentric LVH were less likely to develop progressive LV dilation if they were assigned to the high hemoglobin group.

LIMITATIONS

- There is a clear association between poor outcomes and low hemoglobin, but there are little data to suggest that hemoglobin levels $>$13 g/dL are associated with improved outcomes. The data supporting an association between anemia treatment and improvements in CVD are limited.

IMPLEMENTATION ISSUES

- Identification and treatment of anemia can be easily implemented, making it readily amenable to intervention. The use of erythropoietin to treat anemia is currently a standard care practice and is feasible.

RESEARCH RECOMMENDATIONS

- Studies are needed to determine the most appropriate hemoglobin value to reduce the risk of nonatherosclerotic heart disease.

GUIDELINE 16: ARTERIAL STIFFNESS, VASCULAR AND VALVULAR CALCIFICATION, CALCIUM, PHOSPHORUS AND PTH

The role of abnormalities of calcium, phosphorus, and PTH in contributing to arteriosclerosis, subsequent arterial stiffness, calcification and cardiac valve calcification is an area of intense research. The importance of these parameters to CVD outcomes and the biological plausibility of these variables in CVD processes require attention to them as "uremia-related" risk factors.

16.1 All dialysis patients should have pulse pressure (PP) determined monthly before dialysis.

16.1.a For PP >60 mm Hg and systolic blood pressure >135 mm Hg, it is recommended that PP be reduced by achieving ideal body weight and the use of antihypertensive medication with the target PP being 40 mm Hg. (B)

16.2 Identification and treatment of calcification:

16.2.a If arterial calcification is identified by plain radiography in any of the following sites (abdominal aorta, carotid arteries, ileo-femoral axis or femoropopliteal axis), identification of calcification at another site should be sought. (C)

16.2.b If vascular calcification is present in two or more sites, consideration should be given to prescription of a non-calcium-containing phosphate binder. (B)

16.3 All dialysis patients should follow current K/DOQI Guidelines for treatment of calcium, phosphate, and PTH.[78]

16.3.a Serum phosphorus should be maintained between 3.5-5.5 mg/dL (1.13-1.78 mmol/L). (B)

16.3.b PTH should be measured every 3 months using an intact PTH assay (first-generation immunoradiometric assay). (C)

16.3.b.i. For prevention of CVD, the target PTH value should be between 150-300 pg/mL (16.5-33.0 pmol/L). (B)

16.3.b.ii. Treatment strategies for PTH values <150 pg/mL (16.5 pmol/L) and >300 pg/mL (33.0 pmol/L) should be developed according to the K/DOQI Bone Disease Guidelines.[78] (B)

RATIONALE

Arterial Stiffness (Weak)

Increased arterial stiffness in dialysis patients is the result of chronic flow/volume overload, uremia-induced endothelial dysfunction, fibroelastic intimal thickening, increased extracellular matrix, and medial calcification.[334] Arterial stiffness may cause CVD because it increases LV after-load and decreases the diastolic pressure, resulting in a decrease in coronary perfusion. Arterial stiffness can be assessed by measurement of PWV using B-mode ultrasonography. However, pulse wave velocity is not easily measured in clinical practice. In contrast, PP can be easily measured and is an attractive surrogate for PWV. Pulse pressure, the difference between systolic and diastolic blood pressure, reflects LV ejection and aortic elasticity. Similar to PWV, increased PP has been associated with increased all-cause mortality in nondiabetic HD patients.[188] Others have reported that pre- and post-dialysis blood pressures have independent associations with mortality in a manner that implicates wide pulse pressures.[130] *(Moderately Strong)*

Patients who had a decrease in PWV with a decrease in blood pressure also had regression in LVH.[335] Further, it has been shown that patients whose PWV could be decreased by correcting hypertension had better survival rates than those whose PWV did not change with blood pressure decrease.[195] Whether a decrease in PP would also identify those with better survival is not known. In a study of 22 HD patients with type 2 diabetes, there was an improvement in PWV among patients treated with fluvastatin.[336] Whether the improved PWV associated with

statins would improve cardiovascular outcomes requires further study. *(Weak)*

The evidence supporting an association between arterial stiffness and increased risk of death in dialysis patients is derived from prospective cohort studies using PWV as the estimate for arterial stiffness. A study of 243 chronic HD patients with a PWV >12.0 mL/sec compared to <9.4 mL/sec had an odds ratio of 5.4 for all-cause mortality and 5.9 for cardiovascular mortality.[190] The evidence supporting an association between pulse pressure and mortality in dialysis patients is based on two prospective cohort studies. The first study cohort consisted of 1,243 chronic HD patients followed for 9 years.[188] During the mean follow-up of 76 months, the mortality rate among those with PP <59 mm Hg was 28%, compared to 38%, 46%, and 60% for those with PP 60-79, 80-99 and >100 mm Hg respectively. Using multivariate analysis for non-diabetic patients, there was an 8% increase in the relative risk for all-cause mortality associated with each 10 mm Hg increase in pulse pressure. The second study cohort consisted of a random sample of 11,142 subjects followed from 1994-2000.[130] Higher systolic and lower diastolic blood pressure were associated, in a multivariate analysis, with an increased risk of death. The associations are strong and consistent. *(Moderately Strong)*

Vascular Calcification

The calcium content in coronary arteries of dialysis patients is much higher than that found in age-gender-matched controls and in nonuremic patients with CAD.[337] Moreover, there is an association between the Agatston[338] score and the prevalence of atherosclerotic disease in HD patients.[339] However, the ACC/AHA did not recommend EBCT for the diagnosis of obstructive coronary disease due to the low specificity of this test.[340] However, EBCT remains a valuable surrogate outcome when used in the tightly controlled environment of the randomized clinical trial. For clinical practice, spiral CT may be a feasible alternative[341] but there are insufficient data to recommend routine use of this technique. *(Weak)*

A valid and reproducible estimate of vascular calcification that is easily applied in clinical practice is required. The method of Guerin[342] uses ultrasound and soft-tissue radiographs to estimate arterial calcification in the common carotid arteries, abdominal aorta, iliofemoral axis and femoro-popliteal axis. The overall score ranges from 0-4 based on the number of calcified sites. Good inter-observer reproducibility has been reported. It is a valid predictor of all-cause mortality and cardiovascular mortality.[343] However, the Work Group felt that the experience with this technique was limited, and that there would be major barriers to its acceptance and implementation. *(Weak)*

The recommendation made by the K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in CKD was that a non-calcium-based binder be used if there was evidence for severe vascular calcification.[78] While the diagnosis is based on an incidental finding of vascular calcification on plain radiography, no suggestion is made for frequency of diagnostic evaluation nor is there a definition for severe vascular calcification.

Young dialysis patients with detectable coronary artery calcification had a mean daily calcium carbonate dose of 6,456 mg compared to 3,325 mg among those who had no detectable calcium.[32] Older age, male gender, diabetes, dialysis vintage, higher serum calcium, and higher serum phosphorus have been associated with higher coronary artery calcification scores.[339] Prevention of hyperphosphatemia is critical, but dietary phosphorus restriction and conventional HD are often not adequate. An orally administered phosphate binder is required. An alternative to calcium-based phosphate binders is desirable. One currently available alternative is sevelamer hydrochloride. In a randomized clinical trial, subjects treated with sevelamer for 12 months did not have a statistically significant increase in the coronary artery or in the aortic calcification scores while those treated with calcium carbonate or calcium acetate had a continued increase.[81] The serum phosphorus values were well controlled in both groups. The incidence of hypercalcemia (16% vs. 5%) and the prevalence of an undesirable suppression of PTH at the end of the study (57% vs. 30%) were greater in the calcium-treated group. *(Moderately Strong)*

The calcification score at which to initiate treatment with a non-calcium-based phosphate

binder is unclear. Ideally, calcium-based binders should be avoided entirely, but there are cost considerations as the currently available non-calcium-based binder (sevelamer hydrochloride) is considerably more expensive. The Work Group recommends that, if vascular calcification is noted in one part of the vascular tree (either carotids, aorta, ileo-femoral or femoropopiteal) and the calcium-phosphorus product exceeds 55, plain radiographs of the other areas should be made. If positive in one other area, a non-calcium-based phosphate binder should be considered. It is recognized that vascular calcification on plain radiographs does not disqualify arteriosclerosis (which may respond to reduction in calcium-phosphorus product) from atherosclerosis (which is unlikely to respond). *(Weak)* (Table 16)

Lanthanum carbonate is a non-calcium-based phosphate binder but there are insufficient published data on its efficacy and safety.[344]

Valvular Calcification

Valvular calcification was found to be much more common in CKD patients treated with HD than in age-matched and gender-matched controls.[345] There is an increased prevalence of valvular insufficiency with calcification of the mitral (29% vs. 6%) and aortic valves (22% vs. 6%). Using EBCT, calcification was reported in 45% of the mitral and 34% of the aortic valves in HD patients, compared to an expected 3%-5% in controls.[339] Others found significant increases in valvular calcium estimated by EBCT over a 12-month period.[337] There is no convincing evidence linking valvular calcification to abnormalities in serum calcium, phosphorus, or PTH. Valvular calcification is associated with a worse survival, perhaps mediated by increased LVH, for those with aortic valve calcification. There is also an increased risk for death among PD patients with valvular calcification (Table 17).[346] *(Weak)*

Serum Phosphorus

Observational studies in HD patients show a statistically significant increase in the risk for all-cause and cardiovascular mortality with serum phosphorus >6.5-6.6 mg/dL (2.10-2.13 mmol/L) (Table 18).[347,348] The evidence linking increased serum phosphorus to vascular calcification is based on the observation that vascular

Table 16. Association of Low Serum Calcium Level with Risk of Cardiovascular Outcomes and Markers

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	Ca Threshold (mg/L)	Results (Univariate)	Results (Multivariate)	Quality
Block 1998 [347]	2 yr	2,669		↑↑↑	All-cause death	--		⇳	●
Parfrey 1996 [86]	44 mo	264	169	↑↑↑	Ischemic heart disease	--	⇳		●
Karnik 2001 [95]	Case Control	>77,000		↑↑↑	Cardiac arrest	--	⇳		○
Kronenberg 2003 [357]	12 mo	106	49	↑↑	Vascular calcification progression	--	⇳		●
De Lima 1995 [358]	5-80 mo	74		↑↑↑	Ventricular arrhythmia	--	⇳		○

-- Analyzed as a continuous variable (no threshold analyzed).

Table 17. Association of Elevated Serum Calcium-Phosphorus Product with Risk of Cardiovascular Outcomes and Markers

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	Ca-P Threshold (mg^2/dL^2)	Results (Univariate)	Results (Multivariate)	Quality
Zoccali 2001 [a 359]	33 mo	225		↑↑	All-cause death	--	⇧	⇔	●
Ganesh 2001 [348]	2 yr	12,833		↑↑↑	All-cause death	--		⬆	○
Block 1998 [347]	2 yr	2,669		↑↑↑	All-cause death	72		⬆	○
Mallamaci 2002 [a 327]	29 mo	175		↑↑	Cardiovascular death	--	⇔		●
Benedetto 2001 [a 143]	30 mo	91	47					⬆	
Ganesh 2001 [348]	2 yr	12,833		↑↑↑	Coronary artery disease death	--		⬆	○
					Sudden death			⬆	
					Stroke death			⇧	
					Other cardiac death			⇧	
Lundin 1980 [360]	14 yr	24		↑	Cardiovascular death	--	⬆		○
Zoccali 2001 [a 359]	33 mo	225		↑↑	Fatal and nonfatal cardiac events	--	⇔	⇔	●
Kronenberg 2003 [357]	12 mo	106	49	↑↑	Vascular calcification progression	--	⇔		○
Fernandez-Reyes 1995 [361]	1-9 yr		76	↑↑↑	Mitral annular calcification	40 / 50 / 60 / 70	⇔		○

-- Analyzed as a continuous variable (no threshold analyzed).
a Same set of patients.

Table 18. Association of Elevated Serum Phosphorus Level with Risk of Cardiovascular Outcomes and Markers

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	PO_4 Threshold (mg/dL)	Results (Univariate)	Results (Multivariate)	Quality
Ganesh 2001 [348]	2 yr	12,883		↑↑↑	All-cause death	6.5 (2.1 mmol/L)		↑	○○○○
Block 1998 [347]	2 yr	6,407		↑↑↑	All-cause death	--		⇧	○○○○
						6.6 (2.13 mmol/L)		↑	
Owen 1998 [362]	6 mo	1,054		↑↑↑	All-cause death	--	⇧	↑	○○○○
Ganesh 2001 [348]	2 yr	12,883		↑↑↑	Coronary artery disease death	6.5 (2.1 mmol/L)		↑	○○○○
					Sudden death			↑	
					Stroke death			⇧	
					Other cardiac death			⇧	
Parfrey 1996 [86]	44 mo	264	169	↑↑↑	Ischemic heart disease	--	⇧		○○○○
Karnik 2001 [95]	Case Control	>77,000		↑↑↑	Cardiac arrest	--	→		○○○
Kronenberg 2003 [357]	12 mo	106	49	↑↑	Vascular calcification progression	--	⇧		○○○○
De Lima 1995 [358]	5-80 mo	74		↑↑↑	Ventricular arrhythmia	--	⇧		○○○

-- Analyzed as a continuous variable (no threshold analyzed).

calcification is an active process of ossification.[349] Prior to the deposition of calcium in medial smooth muscle cells, bone matrix proteins are detectable. The linkage of hyperphosphatemia to development of vascular calcification is based on the observation that phosphorus can induce the production of bone-forming proteins in the vascular smooth muscle.[350] The *in vitro* evidence for the role of inorganic phosphorus in the pathogenesis of vascular calcification has been reviewed.[351] Exposure of cultured human aortic smooth muscle cells to concentrations of phosphorus similar to those found in CKD patients increased the expression of osteogenic factors. An additional mechanism by which hyperphosphatemia might cause cardiac disease is increased cardiac fibrosis.[352] The progression of vascular calcification in coronary arteries has been associated with high doses of calcium-based phosphate binders[32] and there is progression in patients prescribed a mean dose of 1,500 mg elemental calcium daily.[81] *(Moderately Strong)*

The strategies to treat hyperphosphatemia and the evidence for the use of non-calcium-based phosphate binders are described in the K/DOQI Bone Disease Guidelines.[78]

PTH

It is common to consider hyperparathyroidism as a traditional risk factor for CVD (Table 19). The relative risk for all-cause mortality was 1.18 in the quintile with PTH values >511 pg/mL (56.2 pmol/L) compared to the referent quintile of PTH values 34-91 pg/mL (3.7-10.0 pmol/L) in an observational study.[347] In another study, the relative risk for sudden death was 1.06 in the quintile with PTH values >496 pg/mL (54.6 pmol/L) compared to the reference quintile with PTH values 91-197 pg/mL (10.0-21.7 pmol/L).[348] *(Weak)*

Patients with histological evidence for adynamic bone disease have decreased ability to buffer exogenous calcium loads than do patients with high-turnover bone disease or those with mixed uremic osteodystrophy.[353] Intact PTH has been used as a surrogate marker for bone metabolic activity. In PD patients, a prevalence of 63.2% for biopsy-proven low-turnover bone disease was reported.[354] An intact PTH value <200 pg/mL (22.0 pmol/L) has been used to define relative hypoparathyroidism in HD patients.[355] *(Weak)*

Table 19. Association of Serum PTH Level with Risk of Cardiovascular Outcomes and Markers

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	PTH Threshold (pg/mL)	Results (Univariate)	Results (Multivariate)	Quality
Zoccali 2001 [363]	26 mo	212	34	↑↑	All-cause death	--	⇔	⇔	●
Block 1998 [347]	2 yr	2,087		↑↑↑	All-cause death	>**511** (56.2 pmol/L)		↑	○
Tepel 2002 [324]	18 mo	188		↑↑↑	All-cause death	--	⇔	⇔	○
Guh 2002 [355]	10 yr	101		↑↑↑	All-cause death	< 65 (7.1 pmol/L) > 200 (22 pmol/L)	↑ ↓	↑ ↓	○
Blacher 1999 [190]	53 mo	241		↑↑	All-cause death	--		⇔	○
Zoccali 2001 [363]	26 mo	212	34	↑↑	Cardiovascular death	--		⇔	●
Ganesh 2001 [348]	2 yr	6643		↑↑↑	Sudden death	< 33 (3.6 pmol/L) 33-495 (3.6-54.5 pmol/L) > 495 (54.5 pmol/L)		⇑ ⇔ ↑	○
					Stroke death	--	↑		
					Other cardiac death	--	↑		
Blacher 1999 [190]	53 mo	241		↑↑	Cardiovascular death	--		⇔	○
Karnik 2001 [95]	Case Control	>77,000		↑↑↑	Cardiac arrest	--	⇔		○
Kronenberg 2003 [357]	1 yr	106	49	↑↑	Vascular calcification progression	--	⇔		○
Fernandez-Reyes 1995 [361]	1-9 yr		76	↑↑↑	Mitral annular calcification	>150 (16.5 pmol/L)	⇔		○

– Analyzed as a continuous variable (no threshold analyzed).

Factors suppressing PTH include hypercalcemia, increased vitamin D levels, diabetes mellitus and increasing age. Despite being associated with these risk factors for CVD, hypoparathyroidism was found to be an independent predictor of mortality.[355] In several studies, low PTH levels do not show a convincing association with a variety of markers of cardiovascular outcomes.

There are several intact PTH assays available, the most frequently used currently being the Nichols assay. This assay measures both active PTH and PTH fragments which might be either inactive or inhibitory. This assay has been used in the majority of studies reported in the literature. The measurement of serum PTH and the target values for CKD patients are discussed in the K/DOQI Bone Disease Guidelines.[78]

LIMITATIONS

Arterial Stiffness

- The data addressing the relationship between increased PP and increased mortality rates are robust, while data relating high pulse pressure with medial calcification are less robust. The data supporting the efficacy of interventions to decrease the pulse pressure and to improve clinical outcomes are relatively weak. Earlier interventions that prevent the development of noncompliant blood vessels might be more effective than the treatment of established vascular stiffness in dialysis patients.

Serum Phosphorus

- The evidence linking hyperphosphatemia to an increased risk of all-cause and cardiovascular mortality is based on observational data. The evidence linking hyperphosphatemia with vascular calcification is based on empirical data that are consistent with clinical observations. The randomized clinical trial comparing sevelamer to calcium-containing phosphate binders showed a convincing decrease in the rate of vascular calcification.[81] However, the demonstration of improved clinical outcomes awaits longer-term studies.
- The mechanisms by which vascular calcification leads to specific cardiovascular events are not clear, and further studies are required.

IMPLEMENTATION ISSUES

Arterial Stiffness

- Measurement and recording of PP can be easily implemented. Therefore, PP could be identified as a risk factor amenable to intervention. The interventions (targeted ideal body weight, lowering of blood pressure and use of statins) are also feasible.

Serum Phosphorus

- The regular measurement of serum phosphorus and the prescription of diets containing 800-1,000 mg phosphorus are common practices in most dialysis units. The limitation on the dose of oral calcium-containing phosphate binders is new and will require a change in prescribing habits. There may be fiscal barriers to the use of sevelamer. This might be alleviated by the use of a combination of calcium-based binders and sevelamer.[356]

PTH

- The discussion of hypoparathyroidism is based on relatively new concepts from a small number of articles published since 2001. The credibility of aggressive therapy for treating relative hypoparathyroidism will be greeted with skepticism, given the long-term focus on hyperparathyroidism. The association of relative hypoparathyroidism with worse outcomes may be confounded by the relationship with age and diabetes. There will be continued reliance on PTH as a surrogate for bone turnover but this may be clarified with the introduction of intact PTH assays.

RESEARCH RECOMMENDATIONS

- Further studies are required to examine the use of statins in patients with PP $>$60 mm Hg.
- Evaluation of interventions is needed that might prevent or reverse the decrease of vascular compliance in patients with increased PP.
- The validity of the semi-quantitative estimation of vascular calcification as a predictor of survival requires confirmation in other centers. Evaluation of alternative methods for estimation of coronary artery calcification (e.g., multislice CT) is needed.

SECTION III. STATE OF THE SCIENCE: NOVEL AND CONTROVERSIAL TOPICS IN CARDIOVASCULAR DISEASES

The following sections have been prepared to ensure that the state of the art and science related to CVD includes novel concepts, therapeutic strategies, and emerging areas of pathophysiological and practical importance to the care of dialysis patients.

The reader will notice that the format of this section is different, reflecting its different perspective: namely, the relative lack of evidence on which to base plausible guideline statements. The evidence that does exist, and is cited in this section, is either completely in nondialysis populations, or is purely associative information, with no intervention in any population yet tested. Thus, it would be a problem to include guideline statements or recommendations.

Nonetheless, this section describes the current status of knowledge with respect to risk factors and biomarkers, and represents an overview of key areas for future clinical trials. The reader is encouraged to review this section, and examine his or her current understanding and practice within the context of these highlights.

The literature review has been conducted using the same systematic strategy as for the previous guidelines in this document. The reviews presented here have been thoughtfully constructed so that clinicians can adopt different practices based on them. However, for reasons cited above, the ability to truly recommend or suggest changes in practice would be premature at this time.

INTRADIALYTIC HYPOTENSION

Introduction

Intradialytic hypotension (IDH) is defined as a decrease in systolic blood pressure by ≥20 mm Hg or a decrease in MAP by 10 mm Hg associated with symptoms that include: abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; and anxiety. It impairs the patient's well-being, can induce cardiac arrhythmias, predisposes to coronary and/or cerebral ischemic events. In addition, IDH precludes the delivery of an adequate dose of dialysis, as hypotension episodes lead to the compartment effect and result in suboptimal Kt/V_{urea}.

Cardiovascular complications of IDH include: ischemic (cardiac or neurological) events; vascular access thrombosis; dysrhythmias; and mesenteric venous infarction.[364] Long-term effects of IDH include: volume overload due to suboptimal ultrafiltration and use of fluid boluses for resuscitation; LVH, with its associated morbidity and mortality; and interdialytic hypertension.

Discussion

Evaluation of risk. During the past 10 years, despite improvements in dialysis technology, the frequency of IDH has remained unchanged at about 25% of all HD sessions.[365] In addition, the incidence of IDH will continue to increase as an increasing number of elderly patients will develop CKD, and also due to the progressive increase in the number of diabetic patients with CKD. Patient subgroups most likely to have IDH include those with diabetic CKD, CVD, poor nutritional status and hypoalbuminemia, uremic neuropathy or autonomic dysfunction, severe anemia, age ≥65, and predialysis systolic blood pressure <100 mm Hg.

There are no large-scale, epidemiological studies to define the risk factors that are associated with the risk of developing IDH, although IDH appears to be more common in patients with diabetes and predialysis hypotension. Both normotensive or hypertensive dialysis patients can develop IDH. The degree of IDH in the same patient may vary from time to time or may have seasonal variations.

A small group of patients (5%-10%) may have low systolic blood pressure (<100 mm Hg) at the initiation of dialysis.[364] This group includes anephric patients, those who are on dialysis for a longer period, and diabetic patients with persistent orthostatic hypotension due to autonomic dysfunction. Patients on dialysis with autonomic dysfunction show an exaggerated drop in systolic and diastolic blood pressures and MAP, compared to those without underlying autonomic dysfunction.[366] Other risk factors include older age (>60 years), female sex, diabetes mellitus, presence of CAD, and the use of nitrates before a dialysis session.

Patients with CKD have defective reactivity of the resistance vessels as well as the capacitance

Table 20. Factors Related to IDH Treatment

Patient-Related Factors
Assess and maintain dry weight as close to the target as possible. May need some means of objective assessment of dry weight in difficult cases.
Counsel and educate patients to minimize interdialytic weight gain.
Discontinue antihypertensive medications prior to the scheduled dialysis.*
Avoid the use of long-acting vasodilators.
Avoid eating just before or during the treatment session.
Evaluate by echocardiography to rule out valvular or pericardial disease, and LV systolic and diastolic function.
Dialysis-Related Factors
Avoid aggressive ultrafiltration to achieve the preconceived dry weight; consider the use of isolated UF, UF modeling, or sodium modeling to achieve the desired dry weight.

* IDH is often attributable to Bezold-Jarisch reflex physiology—particularly in patients with marked LVH—a state in which beta-blockers should actually be beneficial, as the trigger is stimulation of posterior LV wall stretch receptors. Beta-blockers will attenuate this effect.

vessels during the HD sessions.[367,368] The exact mechanism of this poor vascular responsiveness is not known; however, recent data from isolated ultrafiltration and hemodiafiltration have shown that vascular responses remained intact as these modalities are not associated with increase in core body temperature.[369]

The following subgroups of chronic HD patients should be evaluated carefully for the risk of developing IDH:

- Patients with diabetic CKD Stage 5
- Patients with CVD:
  - LVH and diastolic dysfunction with or without CHF
  - LV systolic dysfunction and CHF
  - Patients with valvular heart disease
  - Patients with pericardial disease (constrictive pericarditis or pericardial effusion)
- Patients with poor nutritional status and hypoalbuminemia
- Patients with uremic neuropathy or autonomic dysfunction due to other causes
- Patients with severe anemia
- Patients requiring high volume ultrafiltration; more than expected interdialytic weight gain
- Patients with predialysis SBP of $<$100 mm Hg
- Patients 65 years or older age.

Routine measures for the treatment of IDH include the use of Trendenlenburg's position and saline boluses to increase the systolic blood pressure to 100-110 mm Hg. In addition, it is advisable to assess for the signs of orthostatic hypotension before the patient is discharged from the dialysis unit. Additional factors relating to IDH treatment are presented in Table 20.

Dialysis Interventions

Dialysate temperature modeling. During standard dialysis, an increase in core body temperature is usual and increases the risk for IDH. The increase in body temperature is either related to heat load from the extracorporeal system, or secondary to volume removal. Volume removal is associated with increased metabolic rate with decreased thermal losses either directly, or secondary to peripheral vasoconstriction[370] and impaired convective mechanisms of heat loss.

Temperature monitoring is difficult in dialysis patients due to variability in room, core body, and dialysate temperatures, as well as the lack of sensitive equipment to monitor the dialysate-blood temperature gradient. The use of low-temperature dialysate (i.e., lower than the patient's core temperature) compared with standard dialysate-temperature (37-38°C)[371,372] decreases the frequency and intensity of symptomatic hypotension. Low-temperature dialysis improves the reactivity of capacitance and resistance vessels, and is associated with improvement in cardiac contractility.[373,374]

Isothermic dialysis. Maintenance of isothermic dialysis involves keeping the temperature constant during the dialysis treatment. Each percent change in ultrafiltration-induced body weight requires removal of 6% heat to prevent an increase in core body temperature.[370] It was shown that differences in vascular reactivity in patients

with standard HD, hemodiafiltration, or isolated ultrafiltration remained unchanged if energy transfer was similar.[369,375]

In a recent multicenter analysis, the impact of thermoneutral dialysis (preventing any transfer of thermal energy between dialysate and extracorporeal circulation) on hemodynamic stability in selected hypotension-prone patients was compared to isothermic dialysis (keeping the predialysis body temperature unchanged) by using blood-temperature monitoring. The frequency of intradialytic morbid events decreased by 25% with isothermic HD.[376] During isothermic treatments, body temperature was maintained at predialysis temperature settings and was tolerated without adverse effects, as compared to a simple decrease in dialysate temperature that often leads to rigors and shivering.[377]

Dialysate calcium modeling. The long-term hemodynamic and osseous consequences associated with the use of different levels of dialysate calcium need careful evaluation. The use of low-calcium dialysate has been associated with decreased LV contractility and a corresponding decrease in blood pressure.[378,379] It was further associated with a significant intradialytic decrease in blood pressure in both healthy and cardiac-compromised HD patients and patients with decreased LV ejection fraction.[378,380] Significant changes in blood pressure,[380] myocardial contractility[378,380,381] and changes in intradialytic blood pressure in cardiac compromised patients[382] have been associated with the changes when dialysate calcium concentration is $\leq$2.5 mEq/L. A dialysate Ca of 3.5 mEq/L may lead to hypercalcemia and decreased bone turnover.[78] Furthermore, limited studies have shown only marginal benefit on the frequency of IDH episodes with the use of dialysate Ca $>$3.0 mEq/L.

Dialysate sodium modeling. Sodium profiling is based on the principle that there is a linear relationship between the changes in plasma sodium concentration and blood volume (BV). The intradialytic decrease in plasma volume can be as much as three-fold greater with dialysate sodium of 134 mEq/L than with a dialysate sodium of 144 mEq/L.[383-386] In this technique, the dialysate sodium concentration at the beginning of treatment is hypertonic, and during the final hours of dialysis is progressively reduced, reaching almost normal levels before the end of dialysis.

Sodium modeling prevents the development of IDH by: a) an increased ECF sodium level at the time of peak UF rate improves shift of water from ICF to the ECF compartment with improved venous refill and prevention of the Bezold-Jarisch reflex;[387,388] and b) hypertonic dialysate—to a greater extent—accelerates urea equilibration between ICF and ECF while urea removal is at its peak during the first hour of dialysis.[389]

Limitations of dialysate sodium modeling include the following: a) there is poor temporal correlation between the time of onset of IDH and an antecedent decrease in blood volume;[390] b) there is a significant interdialysis and interindividual variation in serum sodium, and for any given level of serum sodium, the amount of diffusible plasma water varies based on total body water, serum proteins and other nondiffusible elements in the plasma;[391] and c) the development of postdialysis hypernatremia can be associated with thirst, dysphoria, hypertension, and increased interdialytic weight gain.[384] In some instances, a reverse sodium profile is prescribed, in which the dialysate sodium concentration increases toward the end of the session when plasma volume is lowest. Various profiles of ultrafiltration modeling can also be used to decrease the incidence of hypernatremia.

Pharmacological Interventions

Midodrine. Midodrine prevents IDH by maintaining the central blood volume (CBV) and cardiac output, and a marginal increase in peripheral vascular resistance (PVR). A single dose of midodrine (5 mg) administered 30 minutes before the dialysis session was associated with an improvement in intradialytic and postdialytic systolic and diastolic blood pressures and MAP, compared to dialysis sessions without the use of Midodrine.[392] Others have reported the continued efficacy of midodrine use for more than 8 months without development of adverse events.[393]

Midodrine is effectively cleared by HD and its half-life is reduced to 1.4 hours by HD.[394] Such pharmacokinetic data are not available in PD patients at the time of writing these guidelines. Midodrine has minimal cardiac and central ner-

vous system effects, due to its specificity for α1 receptors, and it does not cross the blood-brain barrier. The most frequent side effects of midodrine are piloerection, scalp itching or tingling, nausea and heartburn, urinary urgency, headache, nervousness, and sleep disturbance. Long-term use has been associated with supine systolic hypertension in less than 10% of patients; this side effect warrants cessation of therapy.[395] Patients should also be monitored for bradycardia, as midodrine is associated with reflex parasympathetic stimulation.[396] Since midodrine is administered on the days of dialysis, both prodrug and active metabolite are removed effectively by HD; therefore, the risk of developing supine hypertension is possible, but very rare.

Midodrine should be used cautiously in patients with CHF and in those using other negative chronotropic agents such as beta-blockers, digoxin and nondihdropyridine CCBs. Concomitant use with other α-adrenergic agents—such as ephedrine, pseudoephedrine and phenylpropanolamine—should be avoided, as this may aggravate supine hypertension. Midodrine can also antagonize the actions of α-adrenergic blockers (such as terazosin, prazosin and doxazosine) and could result in urinary retention.

The combination of cool dialysate and predialysis doses of midodrine may lead to decreased frequency and intensity of symptoms of IDH without side effects.

Carnitine. Hemodialysis therapy for more than 6 months is associated with reduction of plasma and tissue levels of carnitine and carnitine esters. Carnitine deficiency is associated with several metabolic defects, defined as dialysis-related carnitine disorders, including IDH.[397] A multicenter trial of intravenous L-carnitine therapy at 20 mg/kg into the dialysis venous port with each session of dialysis was associated with reduced frequency of IDH and muscle cramps (44% versus 18% and 36% versus 13%, respectively), as compared with the placebo group.[397-399] The reasons for this beneficial effect are not clear, but could be due to improvement in vascular smooth muscle and cardiac muscle function.

Sertraline. Sertraline is a selective serotonin reuptake inhibitor and has been shown to improve symptoms in patients with neurocardiogenic syncope,[400] idiopathic orthostatic hypotension,[401] and IDH.[402] These disorders share a common pathogenic mechanism with IDH: a paradoxical withdrawal of central sympathetic outflow, resulting in sudden decrease in blood pressure with bradycardia. Both retrospective and prospective studies in small number of patients demonstrated that treatment with sertraline hydrochloride was associated with an improvement in the hemodynamic parameters in patients with IDH.[402-404] Side effects of sertraline include dizziness, insomnia, fatigue, somnolence, and headache.

Resistant IDH. Resistant cases of IDH should be treated with a combination of modalities, such as combination of midodrine and dialysate temperature profiling, combination of dialysate temperature profiling and 3 mEq/L dialysate calcium, or combination of dialysate temperature modeling and sodium modeling. Such patients should also be offered alternative measures to prevent and treat IDH. For example, isolated ultrafiltration and other techniques providing a high convective solute transport (such as hemofiltration and hemodiafiltration) are associated with decreased incidence of IDH and improved hemodynamic stability compared to conventional HD, due to improved plasma refill and appropriate neurohormonal response to loss of intravascular volume.[236,405-407]

There are limited data to make any recommendation about the benefit of extended daily dialysis or nocturnal HD to prevent the development of IDH. However, these two modalities of dialysis therapy have the advantage of slow ultrafiltration rate and the possibility to prevent the activation of Bezold-Jarisch reflex and subsequent cardiodepressor response. However, more clinical studies are needed to prove the efficacy and cost-effectiveness of these two modalities in the treatment of IDH.[408-410]

Limitations. It is unclear if episodes of IDH, *per se*, are associated with increased morbidity and mortality. The data supporting the effectiveness of various therapeutic options for the treatment of IDH are available in the form of case series and case reports. Very few multicenter randomized studies have been published.

Objective assessment of dry weight using such methods as IVC sonography, or bioimpedance or tissue impedance techniques, have not been rigorously tested in relation to IDH and long-term clinical outcomes.

Research Recommendations

A randomized study in patients with IDH is needed to assess the safety, efficacy, and cost-effectiveness of automated feedback systems that continuously adjust ultrafiltration rate, dialysate sodium, and dialysate temperature. Controlled studies are also needed to examine the use of continuous on-line hematocrit monitoring to calculate the rate of ultrafiltration and blood volume and impedance measurements in the assessment of actual dry weight and desired goal for ultrafiltration.

Conclusions

Patients with CKD who are at risk for IDH may require evaluation for the presence of underlying cardiovascular and autonomic function. The patients' medications list should be verified very carefully to avoid the use of short-acting anti-hypertensive medications and peripheral vasodilators immediately before the dialysis session.

Hemodialysis patients at risk for, or predisposed to, IDH may benefit from lowering dialysate temperature, dialysate sodium modeling, and maintaining dialysate calcium at 3 mEq/L. Further benefits may be derived from treatment with pharmacological agents that prevent the development of IDH.

If modifications in dialysis prescription and adjustments in antihypertensive medications do not improve IDH, these patients should be considered for extended daily dialysis or nocturnal HD. If no improvement is seen after these measures, patients may be counseled for living-donor kidney transplantation.

BIOMARKERS

TROPONIN

Introduction

The diagnosis of acute coronary syndromes in dialysis patients and the general population is usually based on the triad of symptoms, electrocardiographic findings, and cardiac biomarkers. The presence of a time-dependent elevation in serum cardiac troponin T or I levels in the setting of acute coronary syndromes is associated with increased cardiovascular morbidity and mortality.

Discussion

An emerging indication for the measurement of cardiac troponins is risk stratification in asymptomatic HD patients, in the absence of other signs and laboratory tests suggestive of acute coronary syndromes (Table 21,Table 22). Several published studies have demonstrated that the presence of elevated serum cardiac troponin T, and—to a lesser extent—troponin I, is a powerful predictor of mortality in HD patients. In a prospective study of 733 asymptomatic outpatients on chronic HD, serum troponin was highly predictive of all-cause mortality (Fig 5).[411] Patients without detectible troponin T had a 2-year 8% mortality, with progressively higher mortality predicted by increasing ranges of the biomarker. Patients with troponin T >0.1 μg/L had a 2-year mortality of approximately 50%. Another study found a significant correlation between the increase in serum troponin T levels and the severity of CAD in a subset of asymptomatic HD patients.[412] It is plausible that the elevation in serum cardiac troponins in asymptomatic dialysis patients is a reflection of silent IHD and nonischemic cardiomyopathy, and troponin levels have been related to LV mass.[413] Troponin elevation (as seen in dialysis patients, i.e., not following a time-appropriate rise and fall after an index ischemic event) has been reported in patients with severe nonischemic cardiomyopathy. Regardless, it is clear that these elevations in cardiac troponin levels in dialysis patients are not spurious findings. The clearance of troponins may be altered in dialysis patients, but the source is cardiac.

The potential clinical duality of troponin testing in dialysis patients needs to be recognized. The diagnosis of acute coronary syndromes and risk stratification in nonischemic settings are discrete, but complementary tasks. It is a key issue that a time-appropriate rise and fall of the cardiac biomarker occurs in acute coronary syndromes; as serum troponin elevation is prognostically important, but not necessarily indicative of acute coronary syndrome. The operational characteristics of different-generation troponin assays vary widely and—unfortunately, as new assays become available—nullify conclusions attributable even to recent data. Although troponin I may "currently" be the best cardiac biomarker for diagnosis of acute coronary syndrome (see Fig 5B; only 45 of 733 [6%] asymptomatic dialysis patients had *any* detectible troponin I), based on "specificity" criteria, this may not necessarily be correct for the next generation of troponin I and T assays.

Research Recommendations

A prospective, randomized clinical trial on troponin testing and clinical decision-making would provide valuable information. There is a need for prospective cohort studies on the correlation between troponin levels and the burden of CAD, as well as fatal and nonfatal CAD-related and non–CAD-related events.

Conclusions

Therefore, serum troponin T levels should be considered for risk stratification in chronic dialysis patients. In HD patients, the blood samples should be collected before dialysis. The utility of troponin T for risk stratification in PD patients has not been reported, but there is no obvious reason to suspect that these patients differ from HD patients in this regard. The assay for troponin T is widely available. However, it is currently unclear how this information can be utilized. For example, should an elevated serum troponin T level be followed by another diagnostic test (e.g., stress imaging) or therapeutic intervention (e.g., the administration of beta-blockers)? To determine the appropriate therapeutic consequences, understanding of the precise causes of death in dialysis patients with elevated serum troponin

Table 21. Association of Elevated Random Troponin I Levels with Risk of Cardiovascular Outcomes

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	TnI Threshold (μg/L)	Cardiovascular Outcome	Results (Univariate)	Results (Multivariate)	Quality
Apple 2002 [411]	1.6 yr	733		⇑⇑⇑	0.1	All-cause death, 1 yr	⇕	⇕	●
						All-cause death, 2 or 3 yr	⇑	⇑	
Ishii 2001 [414]	2 yr	91	8	⇑⇑	0.1	All-cause death	⇑ Sn 50% Sp 83%	⇕	○
Lang 2001 [415]	2 yr	100		⇑⇑⇑	0.4	All-cause death	⇕ Sn 5% Sp 93%		○
Ishii 2001 [414]	2 yr	91	8	⇑⇑	0.1	Cardiac death	⇑ Sn 50% Sp 93%	⇕	○
Lang 2001 [415]	2 yr	100		⇑⇑⇑	0.4	Cardiac death	⇕ Sn 8% Sp 93%		○
Porter 2000 [416]	2 yr	27		⇑⇑	0.4 *	Cardiac death or event	Sn 9% Sp 88%		○
					0.5 *		Sn 18% Sp 88%		
Roppolo 1999 [417]	6 mo	48	1	⇑⇑	0.5	Cardiac event	Sn 50% Sp 100%		○
Lang 2001 [415]	2 yr	100		⇑⇑⇑	0.4	Myocardial infarction	⇕ Sn 7% Sp 93%		○

Abbreviations: Sn, sensitivity; Sp, specificity.
* Separate tests using different manufacturers' kits.

levels, and the underlying pathophysiological mechanisms, must be improved.

A credible case can be made for recommending the measurement of serum cardiac troponins in dialysis patients for the purpose of risk stratification (distinct from the diagnosis of acute coronary syndrome). Indeed, in May 2004 the U.S. Food and Drug Administration approved the measurement of troponin T in patients with chronic renal failure (i.e., dialysis) for the express purpose of risk stratification (i.e., prediction of mortality). The K/DOQI Work Group has not designated this as a practice guideline, however, because of uncertainty at the present time regarding appropriate clinical strategies using this information.

INFLAMMATION

Introduction

Patients arrive at CKD Stage 5 with significant cardiovascular risk factors and, once on dialysis, they die at a more rapid rate than would be predicted by their Framingham risk factors alone. Recently, much interest has focused on the role of nontraditional risk factors for atherosclerosis, such as an excessive inflammatory response. Although the concept that inflammation plays a central role in the pathophysiology of atherosclerosis has gained a lot of recent interest, we do not know yet whether inflammation reflects vascular injury or is instead a cause of vascular injury. However, recent data suggest that inflammatory biomarkers, such as interleukin-6 (IL-6) and the archetypal acute phase reactant C-reactive protein (CRP), are not only markers but also mediators of atherothrombotic disease in man. In the general population, high-sensitive C-reactive protein (hs-CRP) appears to be the best inflammatory biomarker employed to detect enhanced absolute risk of CVD. Moreover, there is evidence supporting the use of CRP in primary prevention of CVD; in fact, CRP may be a stronger predictor of cardiovascular events than the LDL-cholesterol level. It has been speculated that a persistent inflammatory response may mediate malnutrition (i.e., wasting) and progressive atherosclerotic CVD by a number of pathogenic mechanisms.

Table 22. Association of Elevated Random Troponin T Levels with Risk of Cardiovascular Outcomes

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	TnT Threshold (μg/L)	Cardiovascular Outcome	Results (Univariate)	Results (Multivariate)	Quality
Apple 2002 [411]	1.6 yr	733			0.01	All-cause death, 1, 2 or 3 yr	↑	↑	●
					0.04		↑	↑	
					0.1		↑	↑	
Ooi 1999 [418]	12 mo	172			0.1	All-cause death	↑		○
Dierkes 2000 [419]	2 yr	102			--	All-cause death	↑		○
					0.04		Sn 45%		
					0.05		↑	↑	
					0.10		↑ Sn 83%	↑	
Ishii 2001 [414]	2 yr	91	8		0.1	All-cause death	↑ Sn 48% Sp 91%	↑	○
Lang 2001 [415]	2 yr	100			0.1	All-cause death	⇧ Sn 39% Sp 82%		○
Ooi 1999 [418]	12 mo	172			0.1	Cardiac death	⇔		○
Dierkes 2000 [419]	2 yr	102			0.05	Cardiovascular death		↑	○
Ishii 2001 [414]	2 yr	91	8		0.1	Cardiac death	↑ Sn 28% Sp 96%	↑	○
Lang 2001 [415]	2 yr	100			0.1	Cardiac death	⇔ Sn 38% Sp 82%		○
Dierkes 2000 [419]	2 yr	102			--	Fatal and non-fatal cardiovascular events	↑		○
					0.05		⇧	⇧	
Porter 2000 [416]	2 yr	27			0.1	Cardiac death or event	Sn 82% Sp 88%		○
Roppolo 1999 [417]	6 mo	48	1		0.1	Cardiac event	Sn 100% Sp 56%		○
					0.2		Sn 83% Sp 91%		
Lang 2001 [415]	2 yr	100			0.1	Cardiac death	⇔ Sn 36% Sp 80%		○

Abbreviations: Sn, sensitivity; Sp, specificity.
-- Analyzed as a continuous variable.

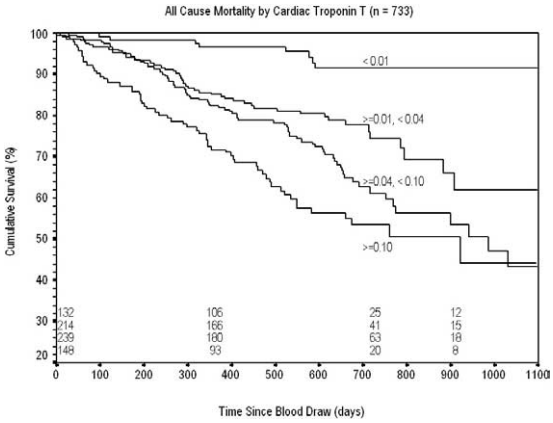

Fig 5. Kaplan-Meier survival curves by baseline troponin levels. The number of patients at risk at baseline, 1 year, 2 years, and 2.5 years for each cutoff is shown at the bottom of the graph. The 99th percentile refers to the normal reference limit. The 10% CV refers to the lowest concentration that demonstrates a 10% total precision. The ROC cutoff refers to concentrations optimized for the sensitive and specific detection of MI. Reproduced with permission (http://lww-.com).[411]

Discussion

Whereas chronic inflammation is a common phenomenon in European[420] and North American[421,422] CKD patients, the prevalence of inflammation seems to be lower in Asian CKD patients (Table 23).[423,424] This suggests that genetic factors and/or cultural habits (such as food intake) may affect the inflammatory response in dialysis patients. Recent studies suggest that a reduction of kidney function *per se* may be associated with an inflammatory response, both in mild CKD[425] and advanced kidney failure.[426,427] Factors common in dialysis patients, such as clotted access grafts,[428] failed kidney grafts[429] atherosclerosis,[430] and persistent infections[431,432] may contribute to an acute-phase response, thus elevating inflammatory biomarkers such as CRP and IL-6.

A recent evaluation of a historical cohort of 393,451 U.S. dialysis patients demonstrated that septicemia was associated with increased cardiovascular death risk.[433] Although the association between CVD and inflammation is well documented in CKD patients,[434,435] we do not know if the acute-phase response merely reflects established atherosclerosis or if acute-phase reactants are actually involved in the initiation and progression of atherosclerosis. However, an increasing body of evidence suggests that CRP may be directly involved in atherothrombogenesis that extends beyond its previously accepted role as an inflammatory marker. Thus, CRP and other biomarkers of inflammation, such as IL-6, TNF-α, and fibrinogen, may contribute to atherogenesis.[436] The circulating calcification inhibitor, fetuin-A, has recently attracted interest as its level decreases during chronic inflammation, and patients with low serum fetuin-A levels showed a significantly poorer survival rate compared to those with normal or high-normal values.[437] Several studies have shown that elevated CRP predicts all-cause and cardiovascular mortality in both HD[322,422,424] and PD[423,438,439] patients. Moreover, in PD patients, elevated CRP was independently shown to predict nonfatal myocardial infarction[440] and increased incidence of CVD.[438] Also, recent data from the MDRD study (n=801) showed that, after adjusting for traditional CVD risk factors, the odds of CVD were 1.73 times greater in patients with high CRP levels.[421] Further support for linking inflammation to poor outcomes is evident from two recent large studies of 7,719[441] and 25,661[442] HD patients, respectively, showing a direct association between neutrophil counts and mortality.

In the current evaluation (Table 23), we have defined inflammation as elevated CRP (usually defined as a serum level >5-10 mg/L). In some studies, other inflammatory markers such as IL-6, have been used to assess the presence of inflammation. Most studies with high applicability did show that elevated CRP predicted *all-cause* mortality in dialysis patients.[322,359,422,438,439] Notably, in the only study in which no significant relationship was observed between the odds risk of death and CRP,[362] the observation period was only 6 months. Most studies with high applicability[322,422,439] also showed that elevated CRP predicted *cardiovascular* mortality in CKD. The majority of papers with a lower level of applicability also show that elevated CRP predicts all-cause mortality and/or are associated with cardiovascular disease. Taken together, the presence of inflammation predicts both all-cause and cardiovascular mortality in CKD patients.

Limitations

There is no consensus in the literature with regard to the optimal "cut-off" point of CRP used to define the presence of inflammation in CKD

Table 23. Association of Elevated Serum CRP Level with Risk of Cardiovascular Outcomes and Markers

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	CRP Threshold (mg/L)	Results (Univariate)	Results (Multivariate)	Quality
Zimmermann 1999 [322]	24 mo	280		↑↑↑	All-cause death	--	↑	↑	●
Ducloux 2002 [438]	41 mo		240	↑↑↑	All-cause death	--	↑	↑	●
						3.2 – 7		⇧	
						> 7		↑	
Yeun 2000 [422]	34 mo	91		↑↑↑	All-cause death	--		↑	●
						2.6	↑	↑	
Benedetto 2001 [a 143]	30 mo	91	47	↑↑	All-cause death	--		↑	●
Owen 1998 [362]	6 mo	1054		↑↑↑	All-cause death	--	⇔	⇔	○
Blacher 2001 [343]	53 mo	110		↑↑↑	All-cause death	--	↑	⇔	○
Haubitz 2001 [444]	69 mo	34		↑↑↑	All-cause death	1.5 / --	↑		○
Stenvinkel 2002 [445]	37 mo	87 [b]	113 [b]	↑↑	All-cause death	10 (all)	↑	↑	○
						10 (men)	↑	↑	
						10 (women)	⇧	⇔	
Iseki 1999 [424]	Up to 7 yr	163		↑↑	All-cause death	6	↑		○
						10	↑	↑	
Qureshi 2002 [446]	36 mo	128		↑↑	All-cause death	15	↑	↑	○
Noh 1998 [423]	24 mo		105	↑↑	All-cause death	8 / --	↑	↑	○
Herzig 2001 [440]	36 mo	50		↑↑	All-cause death	6	⇧	⇧	○
Herzig 2001 [440]	36 mo	50		↑↑	Death or myocardial infarction	6		↑	○
Zimmermann 1999 [322]	24 mo	280		↑↑↑	Cardiovascular death	--	↑	↑	●
Yeun 2000 [422]	34 mo	91		↑↑↑	Cardiovascular death	--		↑	●
Mallamaci 2002 [a 327]	29 mo	175		↑↑	Cardiovascular death	--	⇔		●
Zoccali 2001 [a 359]	33 mo	225						⇔	
Blacher 2001 [343]	53 mo	110		↑↑↑	Cardiovascular death	--	⇧	⇔	○
Iseki 1999 [424]	Up to 7 yr	163		↑↑	Cardiac death	10	↑		○
Herzig 2001 [440]	36 mo	50		↑↑	Myocardial infarction death	6	⇧	⇧	○
Ducloux 2002 [438]	41 mo		240	↑↑↑	Cardiovascular event	>3.2 / --	↑	↑	●
Haubitz 2001 [444]	69 mo	34		↑↑↑	Coronary artery disease	1.5 / --	↑		○
Herzig 2001 [440]	36 mo	50		↑↑	Myocardial infarction	6	↑	↑	○
					Congestive heart failure		⇔		
					Stroke		⇔		
					Peripheral vascular disease		⇔		

-- Analyzed as a continuous variable (no threshold analyzed).
a Same set of patients.
b 6 subjects unaccounted for. 206 subjects analyzed for CRP.

patients. Moreover, most studies have used only a single determination of CRP (or IL-6), which may be problematic since inflammatory biomarkers vary with time in dialysis patients.[443] Difficulties and differences in the definition of cardiovascular mortality may also limit the applicability of the present studies. Also, there are no controlled studies in which the effects of various anti-inflammatory treatment strategies have been evaluated in this patient population. Finally, the cost-effectiveness of CRP screening in dialysis patients has not been evaluated.

Research Recommendations

Future research should aim at finding the optimal "cut-off" point at which elevated CRP predicts outcome in CKD. Studies are needed to investigate the possible interactions between the presence of inflammation and both traditional risk factors (such as dyslipidemia) and nontraditional risk factors (such as oxidative stress, vascular calcification, advanced glycation end-products and endothelial dysfunction) for atherosclerosis. Research is also required to investigate the impact of age, gender, physical activity, diet, race and genetic factors on the prevalence of inflammation in CKD. Nonpharmacological and pharmacological interventions for patients with signs of inflammation should be developed and evaluated for efficacy in reducing inflammation and improving clinical outcomes in this patient group. The independent role of potential proatherogenic inflammatory biomarkers such as CRP, fetuin-A, and IL-6, in the processes of atherogenesis and progression, need to be tested in the uremic milieu.

Conclusions

Based on the studies reviewed, CRP predicts outcomes and improves risk prediction. Therefore, it would be beneficial to assess CRP levels in dialysis patients on a regular basis, and to seek sources of infection or inflammation. A highly sensitive method for measuring CRP is recommended. Various causes of inflammation may be identified in dialysis patients. Overt and occult infectious processes (such as clotted arteriovenous grafts) require appropriate treatment. Factors associated with dialysis treatments that may provoke an inflammatory response include impure dialysate (due to endotoxin or bacterial contamination), back-filtration, and bioincompatible dialysis membranes.

OXIDATIVE STRESS

Introduction

Oxidative stress is defined as the tissue damage resulting from the imbalance between an excessive generation of oxidant compounds and antioxidant defense mechanisms. It should be recognized that the generation of oxidative compounds is an important mechanism of normal physiology, playing a role in both inflammation and tissue repair processes. Thus, oxidative stress represents part of the defense mechanisms against invading micro-organisms and malignant cells, as well as a signal for tissue healing and remodeling. However, in a pathological situation, chronic activation of oxidative processes may contribute to cell and tissue injury.

As oxidants are highly reactive species with a half-life of only seconds, *in vivo* determination is generally not feasible. However, some lipids, proteins, carbohydrates and nucleic acids are modified by oxy-radicals and have lifetimes ranging from hours to weeks. Therefore, these markers may serve as clinical surrogate markers of oxidative stress (Table 24). As oxidative stress occurs when the production of oxidants exceeds local anti-oxidant capacity, the prevention of the harmful effects of reactive oxygen systems—by both enzymatic and nonenzymatic antioxidant systems—are of major importance.[447,448] Several deficiencies in different components of antioxidant defense mechanisms have been demonstrated in CKD. These include reduced levels of vitamin C, increased levels of oxidized vitamin C, reduced intracellular levels of vitamin E, reduced selenium concentrations, and deficiency in the glutathione scavenging system.[448]

Discussion

Increased generation of oxidants in CKD. In the human body, oxidative activity is generated in the mitochondrial respiratory chain and in the phagocyte NADPH oxidase system.[447,448] Among phagocyte-derived oxidants, chlorinating reactions catalyzed by myeloperoxidase (MPO) may be the most important. Activation of polymorphonuclear cells and secretion of MPO may link oxidative stress to both inflammation and endo-

Table 24. Markers That Could Be Used To Assess Oxidative Stress in CKD

Lipids
Malondialdehyde (MDA)
Oxidized low-density lipoproteins (LDL)
Exhaled alkanes
Advanced lipoxidation end products (ALE)
Arachidonic acid derivatives
F_2-isoprostanes
Isolevuglandins
Carbohydrates
Reactive aldehydes
Reducing sugars (ascorbate, ribose, etc.)
Amino acids
Cysteine/cystine
Homocysteine/homocystine
3-chlorotyrosine
3-nitrotyrosine
Modified proteins
Thiol oxidation
Carbonyl formation
Advanced oxidation protein products (AOPP)
3-nitrotyrosine
Advanced glycation end-products (AGEs)
DNA
8 hydroxy 2′deoxyguanine

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thelial dysfunction in CKD patients.[449] The clinical importance of MPO activation is further underscored by the fact that both elevated leukocyte and blood MPO levels are associated, in the general population, with signs of CAD.[450] Furthermore, in patients with acute coronary syndromes, MPO serum levels predicted subsequent cardiovascular events[451] and identified patients at risk for cardiac events.[452]

Available evidence suggests that the balance between pro- and anti-oxidant capacities is shifted towards an increased oxidative stress in uremia.[447,448] Factors contributing to increased prooxidant activity in CKD may include typical characteristics of the CKD patient population, such as advanced age and diabetes, uremia, chronic inflammation, malnutrition and factors associated with the dialysis treatment *per se*. Indeed, several recent studies have shown that various indicators of oxidative stress are increased in patients with CKD.[453-455] Although some groups have reported a normal lipid peroxidation,[456] most investigators[457-459] have reported increased lipid peroxidation in CKD. Proteins and amino acids may also be elective targets of oxidant-mediated injury, and an increased formation of 3-chlortyrosine (a specific marker of MPO-catalyzed oxidation) has been demonstrated in HD patients.[460] Moreover, increased levels of advanced oxidation protein products (AOPP) in CKD patients have been demonstrated.[461] Oxidative compounds may also interact with nucleic acids to form 8-hydroxy-2′-deoxyguanosine, which has been used to evaluate leukocyte DNA damage. Significantly elevated levels of this marker of oxidative stress have been documented in CKD.[462]

Consequences of increased oxidative stress in CKD. In the general population, increased vascular oxidative stress was shown to predict cardiovascular events in those with CAD.[463] Several recent studies indicate that increased oxidative stress may contribute to the excessive burden of cardiovascular morbidity and mortality also in CKD. It was shown that the serum anti-oxLDL antibody titer is an independent predictor of cardiovascular mortality in CKD patients.[464] An association between AOPP and carotid arteriosclerosis was reported in HD patients.[465] This finding was corroborated by a recent study showing that AOPP was an independent risk factor for CAD in the general population.[466] Moreover, whereas oxidative stress was related to impaired endothelial function in a group of 37 CKD patients with moderate renal dysfunction,[467] another group found that endothelial dysfunction is unrelated to LDL oxidation in a cross-sectional analysis of 23 dialysis and 16

nondialysis CKD patients.[468] Clearly, the relationship between oxidative stress and endothelial dysfunction in CKD needs to be addressed in larger patient groups. The relationship between malonyldialdehyde (MDA) levels as an indicator of oxidative stress and the development of atherosclerosis was recently demonstrated in a cross-sectional study of 76 HD patients.[469] Finally, two recent studies have demonstrated that two surrogate markers of oxidative stress, oxLDL[470] and plasmalogen[471] were associated with increased cardiovascular mortality in patients with advanced CKD. It is also notable that other complications in dialysis patients, such as amyloidosis, anemia, hypertension and malnutrition may be linked to increased oxidative stress.[447,448] Although increased oxidative stress seems to be associated with many complications of CKD, no large, prospective epidemiological studies have yet demonstrated a link between oxidative stress and patient outcome.

Linking oxidative stress to inflammation and malnutrition. As increased oxidative stress, inflammation, and malnutrition all are common features of CKD, it has been speculated that there may be significant associations between them.[449] Indeed, several recent clinical studies suggest links between oxidative stress, inflammation and malnutrition. The presence of inflammation and the duration of dialysis are the most important determinants of oxidative stress in HD patients.[472] Associations between F_2-isoprostanes and CRP levels have been reported in HD patients.[453,454] A significant positive correlation is found between acute-phase proteins and markers of oxidative stress in a group of 64 predialysis patients.[473] It has also been demonstrated that AOPPs act as mediators of oxidative stress and monocyte respiratory burst, which points to monocytes as both targets and actors in the immune deregulation associated with CKD.[461] Different isoforms of vitamin E may have different activities. Thus, the administration of γ-tocopherol (in contrast to α-tocopherol) to patients with CKD results in a decrease in circulating levels of CRP.[474] Finally, evidence suggests that malnourished CKD patients have increased oxidative stress compared to well-nourished patients,[475] which is of interest as S-albumin can act as a binding protein for products of oxidation of carbohydrates, lipids and proteins,[476] and redox active metals. Thus, it could be speculated that malnutrition, which is interrelated to chronic inflammation,[434] may further contribute to cardiovascular morbidity and mortality by reducing both antioxidant defenses due to poor nutritional intake. Taken together, these observations may provide one explanation why hypoalbuminemia and inflammation so strongly correlate with cardiovascular mortality in both the general population[477,478] and CKD patients.[322,479]

Treatment strategies for increased oxidative stress in CKD. Although epidemiological data suggest that the intake of vitamin E is inversely related to the development of CVD, large, prospective, randomized controlled trials all have failed to show that vitamin E supplementation improves cardiovascular outcomes in the general population.[480] Moreover, a recent study showed that, whereas vitamin E supplementation did reduce circulating oxidized LDL, it did not reduce the progression of atherosclerosis in the general population.[481] On the other hand, a study has shown positive results of vitamin E supplementation on outcome[482] and the combination of vitamin E and C slowed the progression of carotid artery lesions in another study.[483] As discussed elsewhere[484] there may be a number of reasons why vitamin E supplementation failed to improve survival in these patient groups. In CKD patients, oral vitamin E supplementation has been shown to reduce the oxidative susceptibility of LDL,[485] and to prevent the oxidative stress associated with anemia therapy or improve erythropoietin responsiveness.[486] The SPACE trial tested the effect of vitamin E (800 IU/day) on a combined cardiovascular endpoint in 196 HD patients with pre-existing CVD, and showed a significant benefit from vitamin E supplementation.[487] In contrast, a recent study reported no survival benefit of vitamin E in patients with mild to moderate CKD.[488] In another recent study, treatment with the antioxidant acetylcysteine was associated with a reduced number of cardiovascular events in patients undergoing HD.[489] Moreover, vitamin C supplementation in chronic HD patients can reduce the lymphocyte 8-OHdG levels and the production of intracellular reactive oxygen species.[490] Based on these results, larger trials that are sufficiently powered to assess the effects of antioxidants on mortality appear highly desirable in CKD patients.

As the interaction between dialysis membranes and blood neutrophils can trigger oxidative stress[491] direct scavenging at the membrane site is another attractive therapeutic approach. Thus, specific dialysis techniques (such as vitamin E-modified cellulose membranes) have been introduced in an attempt to reduce oxidative stress. However, although some studies have demonstrated beneficial effects of vitamin E-coated dialyzers on markers of oxidative stress,[492] endothelial dysfunction,[493] and cytokine induction,[494] no study yet has, to the best of our knowledge, demonstrated any benefit of these expensive dialyzers on cardiovascular morbidity or mortality. Other modifications of the dialysis procedure may also reduce oxidative stress. Recently, it was shown that high-flux HD was associated with an improvement in some measures of protein oxidation.[495] Another aspect of the management of CKD with potential clinical implications for oxidative stress is the treatment of anemia. As red blood cells contain high levels of antioxidants (in particular, reduced glutathione), it is possible that a rise in red cell mass may increase the total antioxidative capacity.[496] On the other hand, the intravenous injection of iron may induce an increase in protein oxidation[465,497] and carotid atherosclerosis.[465] Therefore the relationship between anemia management and oxidative stress may be complicated.

Research Recommendations

Studies are needed to determine which surrogate marker of oxidative stress best predicts outcome in CKD patients. Further research is required to investigate the possible interactions between the presence of oxidative stress and both traditional risk factors (such as dyslipidemia) and non-traditional risk factors (such as inflammation, vascular calcification, advanced glycation end-products and endothelial dysfunction) for atherosclerosis. Studies are also needed to determine which oxidative stress pathway (i.e., nitrosative, chlorinated or carbonyl stress) is quantitatively the most important in CKD patients. Nonpharmacological (such as diet) and pharmacological (such as vitamin E and acetylcysteine) interventions for CKD patients with signs of increased oxidative stress should be developed and evaluated for efficacy in reducing oxidative stress and improving clinical outcomes in this patient group.

Conclusions

Oxidative stress, which is an important part of the host defense mechanism, may play a crucial role in the pathogenesis of atherosclerosis in CKD. Associations exist between increased oxidative stress, inflammation and endothelial dysfunction, which may contribute to increased risk of cardiovascular disease. As oxidants have very short half-lives they cannot be reliably evaluated in the clinical situation. Thus, the determination of oxidative stress relies on the use of more stable surrogate markers. Oxidative stress appears to play an important part in the pathogenesis of CVD in CKD patients. However, the benefit of antioxidant treatment strategies in this patient group remains undefined.

NUTRITIONAL AND METABOLIC FACTORS

BODY WEIGHT AND MANAGEMENT

Introduction

The Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults were published in 1998 to address the increasing problem of overweight and obesity in the United States.[498] This document reports strong evidence that overweight and obesity increases morbidity from hypertension, dyslipidemia, type 2 diabetes, CHD, stroke, gall bladder disease, osteoarthritis, sleep apnea and respiratory problems, and endometrial, breast, prostate and colon cancers. Overweight and obesity also increase all-cause mortality.

There is strong evidence that weight loss in overweight and obese individuals reduces risk factors for diabetes and CVD. Weight loss has been associated with reductions in blood pressure, reductions in triglycerides, total cholesterol and LDL cholesterol, increases in HDL cholesterol, reductions in blood glucose in overweight and obese persons without diabetes, and reductions in blood glucose and Hb_{A1c} in some patients with type 2 diabetes. No prospective trials exist to show that weight loss changes mortality.

In the NIH Guidelines, the definition of overweight is a body mass index (BMI) of 25-29.9 Kg/m^2 and obesity as a BMI of >30 Kg/m^2. The panel also suggested that waist circumference should be used as a marker of abdominal fat, with measurements of >102 cm in men and >88 cm in women indicating high risk. These measurements are not direct measures of body composition (i.e., fat mass and lean body mass), which are more accurately measured using total body water, total body potassium, bioelectrical impedance, dual energy X-ray absorptiometry (DEXA) (see the chapter on Malnutrition in this document), MRI, and computed tomography. In epidemiological studies, BMI is the favored measure of excess weight to estimate relative risk of disease, since it is a simple, rapid and inexpensive measure that can be applied generally to adults. Likewise, CT and MRI are more accurate measures of abdominal fat, but impractical for clinical use; thus, the recommendation for measurement of waist circumference.

Discussion

In contrast to the general population, higher BMI is associated with better outcomes in dialysis patients, even when overall health status is considered. The preponderance of associative evidence suggests this BMI paradox in dialysis patients confers a survival advantage.[499-502]

However, BMI may be an inappropriate measure of body composition in patients with renal failure, since it is complicated by excess fluid weight and muscle wasting, and may be related to malnutrition. A recent study measured lean body mass and thus was able to evaluate the association of body composition (i.e., muscle mass as indicated by 24-hour urinary creatinine excretion) in addition to BMI, and cardiovascular and overall outcomes.[503] This study showed that, as in other studies, patients with high BMI (>27 Kg/m^2) had lower all-cause and cardiovascular death rates than those with normal BMI. However, the survival advantage of a high BMI was only confined to those with low body fat; even in the low BMI group, high body fat and low muscle mass were associated with increased risk of death.

Thus, in terms of body composition, it appears that maintenance of muscle mass and lowering of body fat are important in reducing cardiovascular risk. Evidence suggests that exercise training (aerobic exercise and resistance training) increases muscle mass, as does nandrolone decanoate in dialysis patients.[504] There are no randomized clinical trials to determine the effects of either of these interventions, or caloric restriction to lower body fat, on cardiovascular or all-cause mortality in dialysis patients.

Clinical Applications

The following considerations are based on the NIH Clinical Practice Guidelines.[498] Clearly special attention related to nutritional status is necessary for patients with renal failure. The BMI data that have established the theory of the "BMI paradox" in dialysis patients have resulted in few, if any, interventions for weight management in dialysis patients. Certainly, no randomized clinical trials have been conducted to test stan-

dardized approaches to weight management in dialysis patients. Likewise, the confounding factors of nutritional deficiency and those of determining lean body mass, fat mass, and fluid weight complicate goal setting and monitoring of any programs. Nonetheless, reduction in fat mass and maintenance of muscle mass may be important in dialysis patients.

Weight loss. While the recommended weight loss goal for the general population is to reduce body weight by approximately 10% from baseline, the safety and efficacy of weight loss in the overweight dialysis patient is unknown, as is the potential benefit to CVD outcomes. Therefore, weight loss in the dialysis patient should be approached with close monitoring by a registered dietitian and physician. Further weight loss can be attempted, if indicated, through further assessment to ensure fat loss and not muscle loss. Until weight loss studies are completed in dialysis patients, rates of weight loss should be individually determined.

Dietary therapy. For the general population, lowering caloric intake and increasing exercise are recommended for weight loss in overweight and obese persons. Reducing fat as part of a low-calorie diet is a practical way to reduce calories. Weight loss for the dialysis patient requires an individualized meal plan that is determined by a registered dietitian working with the patient. Such a diet plan would need to meet the nutritional recommendations for dialysis patients in regards to micro- and macro-nutrients (see the NKF-K/DOQI Nutrition Guidelines[169]) while decreasing total calories appropriately. Monitoring of laboratory values and food intake during a weight loss diet is critical due to the paucity of information regarding weight loss in dialysis patients. It is important to avoid the popular diets that could induce adverse metabolic complications. Examples include high protein types, food-combining diets, and diets that encourage unusually large portion sizes of fruits and vegetables.

Physical Activity. Exercise is recommended as part of a comprehensive weight loss therapy and weight control program because it 1) modestly contributes to weight loss in overweight and obese adults; 2) may decrease abdominal fat; 3) increases cardiorespiratory fitness; and 4) may help with maintenance of weight loss. Physical activity should be an integral part of weight-loss therapy and weight maintenance, and should be undertaken in combination with behavioral therapy that assesses the patient's motivation levels and other factors that contribute to the success of an exercise program. For additional information, see Guideline 12.

Special Treatment Groups

Smokers. All smokers, regardless of their weight status, are likely to benefit from smoking cessation while minimizing weight gain. If weight gain does occur, it may be treated through dietary therapy, physical activity, and behavioral therapy, maintaining the primary emphasis on the importance of abstinence from smoking.

Older adults. A clinical decision to forego obesity treatment in older adults should be guided by an evaluation of the potential benefits of weight reduction for day-to-day functioning and reduction of the risk of future cardiovascular events, as well as the patient's motivation for weight reduction. Care must be taken to ensure that any weight reduction program minimizes the likelihood of adverse effects on bone health or other aspects of nutritional status.

Conclusions

Strong evidence in the general population has shown that overweight and obesity are associated with increasing risks of a variety of cardiovascular complications, and with higher all-cause mortality. However, no studies have examined standardized approaches to weight management in dialysis patients. Overweight or obese patients are likely to benefit from weight reduction, but plans will need to be carefully individualized and monitored for each patient.

OMEGA-3 FATTY ACIDS

Introduction

Fatty acid biochemistry. There are four families of polyunsaturated fatty acids in mammalian tissue: ω-3, ω-6, ω-7 and ω-9 (Fig 6). The fatty acids that are considered to be essential to human health belong to the first two families: 18:3, ω-3; 18:2, ω-6; and arachidonic acid (20:4, ω-6).[505] The main dietary sources of ω-3 fatty acids are cold-water fish, canola oil, soybeans, walnuts, flaxseeds, and their products. Omega-6 fatty acids are found predominantly in all other veg-

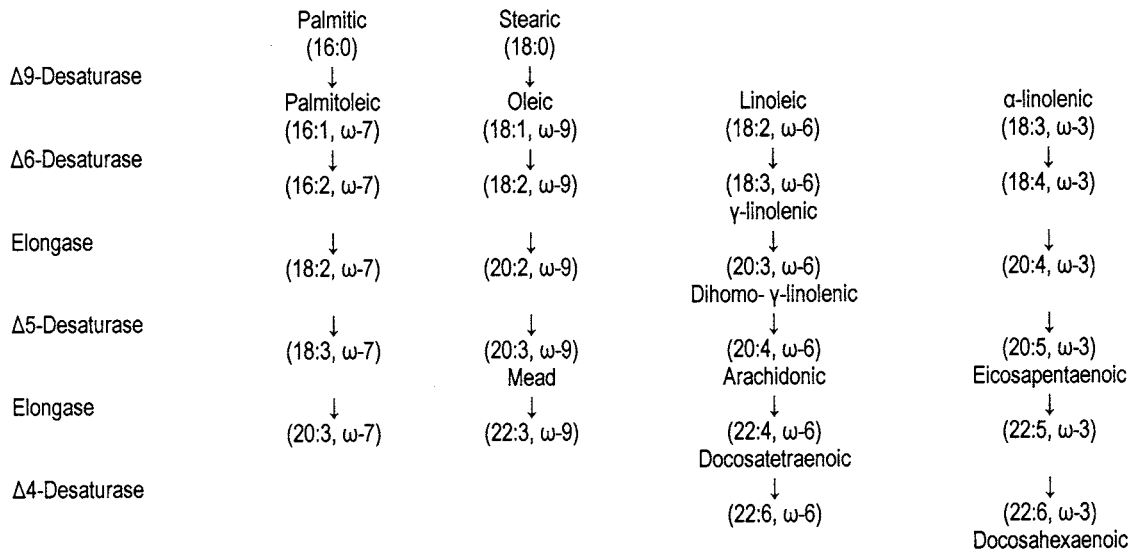

Fig 6. Desaturation and elongation of the major families of polyunsaturated fatty acids. Reproduced with permission.[8]

etable oils and foods prepared with them, while ω-9 fatty acids are predominantly found in olives and olive oil.

Inter-relationship between ω-3 fatty acid biochemistry and CVD. The beneficial effects of ω-3 fatty acids on CVD risk appear to be related to their impact on several risk factors identified to have a role in the development of CVD. These include: systemic inflammation, thrombotic tendency, lipid levels, endothelial function, reduction of proinflammatory responses, cardiac rhythm, and—to a lesser extent—hypertension.[506-509] Mechanisms thought to be responsible for the beneficial effects of ω-3 fatty acids on CVD risk and treatment are listed in Table 25. The results from these studies have been analyzed and summarized for review elsewhere (1, 6, 7, 11, 12).[506-508,510,511]

The effect of ω-3 fatty acids on some of these risk factors has been demonstrated by partial substitution of ω-3 fatty acids for arachidonic acid in the sn-2 position of cell membrane phospholipids. The replacement of the ω-3 fatty acid eicosapentaenoic acid (20:5, ω-3) for the 20:4, ω-6 arachidonic fatty acid alters the proinflammatory thromboxane-prostanoid balance by attenuating the rate of dienoic eicosanoid production, results in a decrease in triglyceride levels, and confers antithrombotic and anti-inflammatory properties.[505,509,512] Omega-3 fatty acids have been reported to decrease platelet activation, and improve vascular tone[513] and endothelium-mediated vasodilation.[511,514] Recent studies indicate that ω-3 fatty acids also impact the metabolism of adhesion molecules and cytokines (see Table 25).[515,516]

Table 25. Potential Effects of ω-3 Fatty Acids on CVD Risk Factors

Hypotriglyceridemic Effect
Reduction in platelet aggregation
Enhanced fibrinolysis
Dose-Dependent Hypotensive Effect
Dependent on degree of hypertension
Enhancement of fibrinolysis
Inhibition of New Plaque Development
Alteration of metabolism of adhesion molecules: VCAM-1, ICAM-1
Inhibition of proinflammatory mediators: IL-6, IL-1, TNF-α
Stabilizing Effect on Myocardium
Improved endothelial function
Increased arterial compliance

Hypotheses regarding the role of ω-3 fatty acids on decreasing sudden death and arrhythmias relate to inhibition of the fast, voltage-dependent sodium current and the L-type calcium channels, inhibition of thromboxane production, and beneficial effects on factors that affect heart-rate variability.[517,518]

Diet and risk reduction. The role of diet in risk reduction of CVD in the general population has been debated for over 100 years. Early animal studies demonstrated that diets high in cholesterol and saturated fat resulted in atherosclerosis. Human studies in the 1950s showed that diets high in cholesterol and saturated fatty acids

Table 26. Summary of Effects of Fatty Acid Types on Lipid Classes

Fatty Acid Type	Effect on Serum Lipid
Saturated fatty acids	↑ Total and low-density lipoprotein (LDL) cholesterol levels
Trans fatty acids	↑ Total and LDL cholesterol levels
Omega-9	Neutral or ↓ LDL levels
Omega-3	↓ Triglyceride levels
Omega-6	↓ Cholesterol

increased serum cholesterol levels. Epidemiological data indicated that elevated serum cholesterol levels predicted the risk of CHD.[507,509] As a result of these studies, initial dietary recommendations focused on lowering dietary cholesterol intake to 300 mg or less, decreasing saturated fatty acids to <10% of fat calories and total fat to <30% of total caloric intake.[519] The application of these guidelines to the diet were accomplished by cutting back on animal fat intake, replacing butter with margarine, and using corn and other vegetable oils in food preparation and salads rather then partially hydrogenated fats and lard.

Advancing research over the years has now identified that CVD has many metabolic components, of which several are modifiable by dietary fatty acids. In addition to affecting serum lipid levels (Table 26),[269] dietary fatty acids—specifically those of the ω-3 class—attenuate proinflammatory mediators and mechanisms that have been identified to have a role in the development of CVD.[506,508,520]

As a result of the growing abundance of literature including epidemiological and randomized clinical trials evaluating omega-3 fatty acids, the American Heart Association (AHA) and the Institute of Medicine (IOM) have recently included a recommendation for inclusion of ω-3 fatty acids in the diets of Americans for the purpose of prevention and treatment of cardiovascular disease.[506,508] Prudent application of these new guidelines should be considered for the potential of prevention and treatment of CVD for the kidney patient on renal replacement therapy until data specific for this patient population become available.

Discussion

While there is an abundance of literature on ω-3 fatty acids and kidney disease,[521-530] no randomized clinical trials have been completed that evaluate the effectiveness of ω-3 fatty acids on CVD risk factors and surrogate markers in dialysis patients.

One recent study reports the effect of fish intake in dialysis patients.[531] In a cohort of 216 incident dialysis patients, those who reported fish consumption were 50% less likely to die compared to those who did not report fish intake during the study interval ($p=0.02$). Multivariate analysis indicated that younger age, black race, and high mental health scores at baseline were also associated with a lower mortality risk. Omega-3 fatty acid substitution was not objectively documented in this study. Despite this limitation, the results suggest a beneficial effect of ω-3 fatty acids via fish consumption and further studies are warranted.

Fatty acid guidelines for general health maintenance. The IOM recently published Acceptable Macronutrient Distribution Ranges (AMDRs) that have been established for protein, carbohydrate, fat, ω-6 and ω-3 fatty acids.[506] The AMDRs are based on the results of epidemiological studies and a literature review that evaluated associations between diet intake and risk of chronic disease. The AMDR for fat is 20%-35% of calories, 5-10% of calories for linoleic acid (ω-6 polyunsaturated fatty acids, PUFAs) and 0.6%-1.2% of energy for alpha-linolenic acid (ω-3 PUFAs). Up to 10% of the AMDR for ω-3 fatty acids can be consumed as eicosapentaenoic acid (EPA) and/or docosahexenoic acid (DHA); 0.06%-0.12% of energy. It is important to avoid excessive intake of ω-3 fatty acids as there have been reports of adverse effects on immune function and a potentially increased risk of excessive bleeding and hemorrhagic stroke.[506] An intake of <3 g/day is unlikely to cause clinically significant bleeding.[508]

The IOM also has introduced a new reference value, Adequate Intake (AI), for the general population. It is defined as the recommended

average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate. This value is used when the Recommended Dietary Allowance (RDA) cannot be determined.[506]

The AI for alpha-linolenic acid is 1.6 g and 1.1 g for men and women, respectively. Up to 10% can be consumed as EPA and/or DHA. This amount of ω-3 fatty acid can be obtained by eating at least two servings of fatty fish per week or by taking supplements. For linoleic acid, the AI is 17 g/day for adult men and 12 g/day for adult women. Table 27 identifies amounts of ω-3 fatty acids provided by selected food sources and supplements.

Clinical Applications

Overall approach. The AHA Guidelines for CVD prevention include encouraging the intake of fruits, vegetables, grains, low-fat or nonfat dairy products, fish, legumes, poultry, and lean meats. Food choices should be modified to reduce saturated fats (<10% of calories), cholesterol (<300 mg/dL) and trans-fatty acids by substituting grains and unsaturated fatty acids from fish, vegetables, legumes, and nuts. Salt intake should be limited to <6 g/day. Alcohol intake should also be limited (≤2 drinks per day in men and women) among those who drink.[508]

Response to therapy. Routine review of dietary intake and laboratory values should be sufficient to monitor tolerance to the inclusion of foods enriched in ω-3 fatty acid at least twice per week.

For patients with documented CHD, initial bimonthly check of bleeding times would be prudent, followed by monthly check with routine laboratory values once stable. Lipid levels, including triglycerides, should be monitored.

Patients taking 2-4 g of EPA+DHA supplements should maintain bimonthly checks of bleeding times with triglyceride monitoring as part of routine monthly laboratory values.

Follow-up. For those patients taking therapeutic doses of ω-3 fatty acids for hypertriglyceridemia, supplementation can be modified to a lower dose of 1 g/day upon normalization of the lipid profile and/or inclusion of foods enriched in ω-3 fatty acids 1-2 times per week.

Limitations. There are more questions than answers regarding essential fatty acid metabolism, oxidative stress, CVD, and diet in the dialysis patient. The lack of evidence in the dialysis population makes extrapolation of guidelines for the general population to the dialysis patient questionable. However, the abundance of evidence suggesting a beneficial effect of ω-3 fatty acids, fresh fruits and vegetables, the ongoing data that saturated and trans-fatty acids are not heart-healthy, and the continued high prevalence of CVD morbidity and mortality in this patient population justifies prudent application of healthy eating guidelines until hard data for this patient population become available.

Incorporation of fruits, vegetables, grains, and nonfat dairy products can be problematic for many dialysis patients due to the need to restrict dietary potassium intake to (on average) 2 g/day. In addition, foods enriched in alpha-linolenic acid (flaxseed, walnuts, soy) are high in potassium, and contribute dietary protein and phosphorus (Table 28). Therefore, these foods are unlikely to be a reliable source of ω-3 fatty acids for the dialysis patient. Alternatively, the oils of these foods (walnut and flaxseeds) as well as canola oil can be safely incorporated into the diet for dialysis patients.

Research Recommendations

Studies are required to identify the essential fatty acid status of CKD patients, both progressive and for those on renal replacement therapy. Studies should also evaluate the interrelationships among ω-3 fatty acid supplementation, oxidative stress, CVD and dialysis therapy. Clinical trials are needed to evaluate the role of dietary fatty acid modification on CVD risk and outcomes in CKD patients on renal replacement therapy. Further clinical trials should evaluate current nutrition recommendations for the general population modified to the diet recommendations for CKD patients.

Conclusions

Based on the available evidence, it is beneficial for well-nourished, stable dialysis patients, who have no evidence of CVD, early CVD, or established CVD, to include food sources of ω-3 fatty acids in their diet at least twice weekly.

Table 27. Amount of ω-3 Fatty Acids Provided by Selected Food Sources and Supplements

	EPA+DHA Content, g per 3-oz Serving Fish (Edible Portion) or g/g Oil	Amount Required to Provide ~1 g of EPA+DHA per day, oz (Fish) or g (Oil)
Fish		
Tuna		
Light, canned in water, drained	0.26	12
White, canned in water, drained	0.73	4
Fresh	0.24–1.28	2.5–12
Sardines	0.98–1.70	2–3
Salmon		
Chum	0.68	4.5
Sockeye	0.68	4.5
Pink	1.09	2.5
Chinook	1.48	2
Atlantic, farmed	1.09–1.83	1.5–2.5
Atlantic, wild	0.9–1.56	2–3.5
Mackerel	0.34–1.57	2–8.5
Herring		
Pacific	1.81	1.5
Atlantic	1.71	2
Trout, rainbow		
Farmed	0.98	3
Wild	0.84	3.5
Halibut	0.4–1.0	3–7.5
Cod		
Pacific	0.13	23
Atlantic	0.24	12.5
Haddock	0.2	15
Catfish		
Farmed	0.15	20
Wild	0.2	15
Flounder/Sole	0.42	7
Oyster		
Pacific	1.17	2.5
Eastern	0.47	6.5
Farmed	0.37	8
Lobster	0.07–0.41	7.5–42.5
Crab, Alaskan King	0.35	8.5
Shrimp, mixed species	0.27	11
Clam	0.24	12.5
Scallop	0.17	17.5
Capsules		
Cod liver oil*	0.19	5
Standard fish body oil	0.30	3
Omega-3 fatty acid concentrate	0.50	2
Omacor (Pronova Biocare)†	0.85	1

Data from the USDA Nutrient Data Laboratory. The intakes of fish given above are very rough estimates because oil content can vary markedly (>300%) with species, season, diet, and packaging and cooking methods.

* This intake of cod liver oil would provide approximately the Recommended Dietary Allowance of vitamins A and D.

† Not currently available in the United States.

Modified with permission. [508]

HOMOCYSTEINE

Introduction

Homocysteine is the demethylation product of the amino acid methionine. Once degraded, homocysteine enters the cysteine biosynthetic pathway (transulfuration), or is remethylated to methionine (activated methyl cycle). The controlling enzymes in these two pathways are cystathionine synthase (CBS), methionine synthase (MS) and 5,10-methylene tetrahydrofolate reductase (MTHFR), the latter of which supplies the methyl group required by MS in the methylation of homocysteine. Each enzyme requires a member

Table 28. Alpha-Linolenic Acid (LNA) and Potassium (K+) Content of Selected Foods per 100 g

Food	LNA Content (g)	K^+ Content (mg)
Oils	All listed oils contain 0 K^+	
Canola	10	
Corn	1.0	
Flax	53.0	
Soybean	6.8	
Walnut	10.4	
Fats	All listed fats contain 0 K^+	
Butter	1.2	
Margarine	1.5-3.0	
Vegetables		
Purslane	0.4	509
Soybean	2.1	515
Spinach	0.9	435
Nuts	6.8	580
Walnuts, English		
Cereal Grains		
Wheat germ	0.7	925

Source: Human Nutrition Information Service, USDA. Provisional table on the content of omega-3 fatty acids and other fat components in selected foods. HNIS/PT-103, 1988.

of the B vitamin family as a co-factor. A secondary pathway for the remethylation of homocysteine is by betaine methyltransferase, a pathway that occurs in the kidney and liver. The kidneys account for approximately 70% of plasma clearance of homocysteine. The majority of plasma homocysteine is in the protein-bound form. The normal plasma concentration of homocysteine is approximately 5-10 μmol/L. Degrees of hyperhomocysteinemia (HHCY) approximately defined as mild are 15 μmol/L, as moderate are 25 μmol/L, as intermediate are 50 μmol/L, and as severe are $>$50 μmol/L.[532-536]

In the general population, HHCY has been suggested by many studies to be a risk factor for CVD, including atherosclerosis and arterial and venous thrombosis.[537-547] It is not entirely clear whether a mild increase in plasma homocysteine contributes to the pathogenesis of vascular disease or is a marker for increased risk.[537-539] Pathogenic mechanisms that have been postulated include activation of the coagulation cascade, damage to endothelial cells either directly or through an oxidative stress response, and lipid peroxidation.[540-544] The association between HHCY and CVD has not yet been proven to be causal. Clarification of the interrelationships between HHCY and CVD will require completion of prospective, randomized intervention trials, several of which are in progress.[546] Despite the lack of a solid relationship, there is significant research activity exploring interventions for the treatment of HHCY for the prevention of CVD in both the general population and in CKD patients receiving renal replacement therapy.

Discussion

Association data. Whether the association between HHCY and CVD applies to patients receiving renal replacement therapy is unclear. Several studies have demonstrated that HHCY is an independent risk factor for CVD or a CVD outcome in HD patients.[159,327,357,435,548-561] Others have found negative or inconclusive results.[562-566] A recent study reports that in 94 HD patients taking a multivitamin, lipid peroxidation and inflammation—but not HHCY—were the main risk factors for mortality.[470]

Summaries of data pertaining to the association of HHCY and CVD in the general population are available. A literature review of 33 prospective cohort studies evaluated MI, stroke, CV morbidity, CV death, and/or all-cause mortality.[537,547] In 73% of the studies, there was a significant association between elevated homocysteine and the aforementioned outcomes; 27% of the studies were inconclusive. In CKD patients receiving maintenance dialysis, 19 studies suggested an association between elevated plasma homocysteine levels and CVD.[159,327,357,435,470,552-566] However, a causal relationship between HHCY and CVD has

not been established in either the general or CKD population.

Treatment of HHCY in the general population. Intervention studies in the general population have demonstrated that dietary supplementation with folic acid, vitamin B_{12} and/or vitamin B_6, lowers plasma homocysteine levels.[546,547,567-570] A meta-analysis of randomized trials of homocysteine-lowering vitamin supplements concluded that daily supplementation with 0.5-5.0 mg folate and 0.5 mg vitamin B_{12} would be expected to reduce homocysteine levels by 12 μmol/L to approximately 8-9 μmol/L.[567] Interventional studies designed to reduce plasma homocysteine levels and determine if this reduction modifies cardiovascular outcomes need to be completed.

Observations of HHCY in dialysis patients. Hyperhomocysteinemia is a common observation in the CKD population.[551] The prevalence of HHCY in HD patients has been reported in the range of 85%-100%, with the higher end observed in patients who were not receiving a standard multivitamin supplement.[551] Concentrations of homocysteine range from 20.4-68.0 μmol/L.[551] Mildly elevated levels of homocysteine occur in approximately 5%-7% of the general population, while severe HHCY is rare.[533,537,567] Patients without kidney failure with mild HHCY are described as asymptomatic until the third or fourth decade, when CAD and recurrent arterial and venous thrombosis develop.[533] The severe elevations of homocysteine seen in patients on maintenance dialysis therapy could be one of the nontraditional risk factors for the 50% mortality rate from CVD observed in this patient population.

Plasma homocysteine levels in HD patients have been reported to be lowered by dietary supplementation with folic acid that is given with or without vitamin B_{12} and B_6.[571-581] Other therapies that have been examined include intravenous folinic acid and MTHF. Doses of orally administered nutrients in these studies ranged from 1 mg-60 mg folic acid, with or without up to 110 mg vitamin B_6 and with or without up to 1 mg vitamin B_{12}. The higher doses of oral folate did not have a better result compared to the lower doses in terms of the post treatment plasma homocysteine levels.

These studies demonstrate that, while plasma homocysteine levels can be reduced by these nutrients, they are not normalized, and remain in the range of 15.9-29.9 μmol/L. Possible reasons for this resistance include impaired folic acid metabolism and impaired folate absorption.[551] Supplementation with betaine or serine, and with the addition of betaine to folic acid, has not demonstrated a reduction in elevated plasma homocysteine levels.[569] Results from interventional studies designed to determine whether modifying plasma homocysteine levels affect cardiovascular outcomes in dialysis patients are not available at this time.

Clinical Applications

Existing guidelines for the general population. The Canadian Task Force on Preventive Health Care completed an evidence-based review of the literature regarding both the association of elevated homocysteine levels and CAD, and the effect of lowering homocysteine levels with vitamin supplementation or diet.[546] This evaluative process yielded several results showing associations between total homocysteine levels and CAD risk, but there was insufficient evidence to make therapeutic recommendations regarding screening for, or management of, HHCY.

Applicability to the dialysis patient. There is a strong inverse correlation between serum folate levels and plasma homocysteine levels, and a weaker correlation between homocysteine levels and plasma levels of vitamins B_6 and B_{12}.[532] In the general population, administration of the deficient nutrient will correct the deficiency.[568,570,582] In the dialysis patient, the administration of folate, and vitamins B_6 and B_{12} have been reported to lower, but not normalize, plasma homocysteine levels.[567-577] It has been observed that patients who are not receiving a multivitamin supplement have higher levels of plasma homocysteine.[553] As a result, routine vitamin supplementation for the dialysis patient becomes important not only for adequate nutritional status. B vitamin supplementation is necessary to replace the losses from dialysis, and to prevent an independent, additive elevation in serum homocysteine levels that could be due to deficient or marginal intake of folate, riboflavin (vitamin B_2),[583] pyridoxine (vitamin B_6) and/or cobalamin (vitamin B_{12}).[578]

Research Recommendations

Further data are required regarding the effect of vitamin therapy on clinical outcomes.

Conclusions

As in the general population, the literature for dialysis patients is inconclusive regarding HHCY and CVD. Current studies indicate that normalization of the plasma homocysteine levels in the kidney patient population cannot be effectively obtained through folate, B6, or vitamin B12 supplementation. In addition, any lowering of the plasma homocysteine level that has been reported, has not been shown to effect CVD outcomes. However, the evidence does show that vitamin deficiency, particularly that of vitamins B_2, B_6, B_{12} and folic acid, contribute to HHCY.

Current opinion and evidence suggests that it is prudent to supplement, rather than risk deficiency, especially when supplementation is safe at the recommended levels. Therefore, dialysis patients are likely to benefit from a daily vitamin supplement that provides the recommended published vitamin profile for dialysis patients, with special attention to the inclusion of folic acid, and vitamins B_2, B_6 and B_{12}.

LIPOPROTEIN(A) AND APOLIPOPROTEIN(A) POLYMORPHISM

Introduction

Lipoprotein(a) [Lp(a)] is an LDL-like lipoprotein, consisting of an LDL particle to which the glycoprotein apolipoprotein(a) [apo(a)] is attached. Apolipoprotein(a) shows a high homology with plasminogen and competes with it for binding on plasminogen receptors, fibrinogen, and fibrin.[584] This apolipoprotein contains a heritable number of so-called kringle-IV (K-IV) repeats, providing the basis for the apo(a) K-IV repeat polymorphism.[585] The molecular weight of apo(a) increases with the number of K-IV repeats (300 kDa to >800 kDa) and is inversely related to the Lp(a) plasma concentrations. That means that individuals with high molecular-weight (HMW) or large apo(a) isoforms have, on average, low Lp(a) concentrations, and those with low molecular-weight (LMW) or small isoforms exhibit usually high concentrations of Lp(a). Depending on the population under investigation, this association explains between 30%-70% of the variability in Lp(a) levels.

Since most studies showed that lipids were not useful for atherosclerosis risk assessment in dialysis patients, many studies during the last decade focused on nontraditional lipid abnormalities. Lp(a) was a promising candidate because of the strong evidence from the general population that Lp(a) is a risk factor for CVD.[586-589]

The NKF-K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in CKD Patients[51] focused primarily on lipids, and less on those abnormalities that cannot be interventionally influenced at present. Due to the strong interest in Lp(a), this review examines the literature relating Lp(a) and/or the apo(a) polymorphism to CVD.

Discussion

Lp(a) concentrations and apo(a) size polymorphism in renal disease. In the early stages of renal disease, Lp(a) starts to increase, often long before glomerular filtration rate is decreased.[590,591] This holds true mostly for patients with HMW apo(a) isoforms and not for those with LMW apo(a) isoforms when compared to apo(a) isoform-matched controls.[322,590,592-595] This isoform-specific increase was observed in several—but not all—studies in non-nephrotic renal disease and HD patients, but not in patients with nephrotic syndrome[596,597] or in PD patients.[594] Those treatment groups showed an increase in Lp(a) in all apo(a) isoform groups, probably as a consequence of the pronounced protein loss they experience. In support of this assumption, a decrease of Lp(a) following a successful kidney transplantation can be observed in HD patients with HMW apo(a) isoforms[598,599] and in CAPD patients with all apo(a) isoform groups.[600]

There is evidence that malnutrition and/or inflammation have an Lp(a)-increasing effect.[322,434,601,602] However, the elevation of Lp(a) can be observed already in the earliest stages of renal impairment[590] as well as in HD patients[322] with HMW apo(a) phenotypes and normal CRP and/or normal serum amyloid A levels. These results suggest that CRP only modifies Lp(a) concentrations, but they fail to explain the apo(a) phenotype-specific elevation of Lp(a).

Association of Lp(a) concentrations with CVD. The association of Lp(a) with atherosclerotic complications was investigated in numerous studies in dialysis patients. The results, however, were ambiguous in prospective as well as in retrospective studies.[143,159,322,325,357,419,555,561,603-633] Most of the retrospective studies, including those with the largest patient numbers, found no association between Lp(a) levels and cardiovascular complications. The same holds true for prospective studies (Table 29). A study of 129 HD patients reported significantly higher Lp(a) concentrations in those who suffered a CVD complication during the 4-year observation period.[610] The two largest prospective studies, however, did not observe an association between high Lp(a) concentrations and CAD events[603] or total mortality,[605] respectively.

Association of the apo(a) size polymorphism with CVD. Almost all studies that did not only measure Lp(a) concentrations but also performed apo(a) phenotyping consistently showed an association between the apo(a) K-IV repeat polymorphism and CVD complications (Table 30).[357,603-605,613,617-619,624,630] A study of 167 HD patients reported the apo(a) phenotype to be a better predictor for the prevalence and the degree of carotid atherosclerosis than the Lp(a) plasma concentration.[618] Similarly, others found LMW apo(a) isoforms (besides age and oxidized LDL) to be predictive for the presence of carotid plaques in 109 predialysis patients with terminal chronic renal failure.[434] A doubling of the frequency of LMW apo(a) phenotypes was observed in those CAPD patients who had suffered a CAD event.[630] A large cross-sectional study in 607 HD patients described an association of LMW apo(a) phenotypes with CAD events.[604] Another study of 440 HD patients prospectively followed for a period of 5 years found a strong association between the LMW apo(a) phenotype and CAD events defined by stringent criteria (definite myocardial infarction, percutaneous transluminal coronary angioplasty, aortocoronary bypass or a stenosis >50% in the coronary angiography) (Fig 7).[603] Patients with LMW apo(a) isoforms had, on average, twice the number of coronary events per 100 patient-years.[603] Similarly, the CHOICE study recently reported that LMW apo(a) isoforms were associated with total mortality in an inception cohort of 864 incident dialysis patients who were followed for a median of 33.7 months; again, Lp(a) concentrations were not associated with total mortality.[605] On the other hand, when prevalent atherosclerotic CVD at the start of renal replacement therapy was investigated in the same cohort, Lp(a) concentrations were associated with prevalent disease in whites younger than 60 years, but not among blacks or those older than 60 years. In addition, apo(a) isoforms were not associated with prevalent atherosclerotic CVD.[606]

Clinical Applications

Considering all these studies, it seems that Lp(a) concentrations might not be very fruitful for risk prediction. However, from two prospective studies (total of 1,300 patients) and most of the cross-sectional studies (including more than 1,000 patients) the evidence is strong that the apo(a) size polymorphism is associated with various endpoints. The diverging results for Lp(a) concentrations might be caused, at least in part, by the methodological problems with the Lp(a) measurement, which is not standardized. The apo(a) polymorphism might be a better predictor as discussed previously.[603,634] This fact is based on the above-described apo(a) isoform-specific elevation of Lp(a).[592,594] In hemodialysis patients with only large apo(a) isoforms, Lp(a) concentrations increase and come closer to the concentrations usually seen in patients with small isoforms. Therefore, the risk for atherosclerotic complications can no longer be discriminated by means of Lp(a) concentrations. The apo(a) phenotype, however, gives approximate information about the prior contribution of Lp(a) to the risk for atherosclerosis. This is probably more important, since the predisease period (with its specific atherosclerosis risk) lasted longer in most of the patients than did the present situation. It is furthermore conceivable that patients with a LMW apo(a) phenotype and a more pronounced atherosclerosis preload develop a more rapidly-progressing atherosclerosis after commencement of renal insufficiency or hemodialysis treatment.

At present, no easily practicable method for lowering Lp(a) is available and sufficient proof is lacking that lowering Lp(a) is favorable. This holds true for the general population, as well as dialysis patients. The question remains whether the apo(a) K-IV repeat polymorphism should be determined in dialysis patients.

Table 29. Association of the Lp(a) Concentration with Risk of CVD or Markers

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	Lp(a) Threshold (mg/dL)	Results (Univariate)	Results (Multivariate)	Quality
Longenecker 2002 [605]	34 mo	700	164	↑↑↑	All-cause death	--	⇔	⇔	●
Zimmermann 1999 [322]	24 mo	280		↑↑↑	All-cause death	--	↑	⇔	●
Goldwasser 1993 [633]	12 mo	125		↑↑↑	All-cause death	57	⇔	⇔	◎
Fleischmann 2001 [325]	2 yr	453		↑↑	All-cause death	30		⇔	◎
Koda 1999 [608]	28 mo	390		↑↑	All-cause death	30	↑	⇔	◎
Dierkes 2000 [419]]	2 yr	102		↑↑	All-cause death	--	⇔		◎
Iliescu 2002 [613]	2 yr		54	↑↑	All-cause death	-- 65	⇧ ⇔	↑ ↑	◎
Koch 1997 [621]	36 mo	130		↑	All-cause death	--	⇔		◎
Zimmermann 1999 [322]	24 mo	280		↑↑↑	Cardiovascular death	--	⇧	⇔	●
Benedetto 2001 [143]	30 mo	91	47	↑↑	Cardiovascular death	--		↑	●
Koda 1999 [608]	28 mo	390		↑↑	Cardiovascular death	30		↑	◎
Dierkes 2000 [419]	2 yr	102		↑↑	Cardiovascular death	18	⇔	⇔	◎
Ohashi 1999 [609]	5 yr	268		↑	Cardiovascular death Coronary artery disease death	-- 30	↑	 ↑	○
Kronenberg 1999 [603]	5 yr	440		↑↑↑	Coronary artery disease event	--	⇔	⇔	●
Cressman 1992 [610]	48 mo	129		↑↑↑	Cardiovascular event	-- 15	↑ ↑	↑	◎
Kronenberg 2003 [357]	12 mo	106	49	↑↑	Vascular calcification progression	--	⇔	⇔	◎

-- Analyzed as a continuous variable (no threshold analyzed).

Table 30. Association of the Apo(a) Polymorphism with Risk of CVD or Markers

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	Predictor	Results (Univariate)	Results (Multivariate)	Quality
Longenecker 2002 [605]	34 mo	700	164	↑↑↑	All-cause death	K-IV repeats		↑	●
Iliescu 2002 [613]	2 yr		54	↑↑	All-cause death	K-IV repeats	⇔	↑	○
						LMW vs HMW	⇔	⇔	
Kronenberg 1999 [603]	5 yr	440		↑↑↑	Coronary artery disease event [a]	LMW vs HMW	↑	↑	●
						K-IV repeats	↑		
		389			New onset coronary artery disease [b]	LMW vs HMW	↑	↑	
						K-IV repeats	↑		
Longenecker 2003 [606]	Cross-sectional	701	170	↑↑↑	Prevalent cardiovascular disease	K-IV repeats	⇔	⇔	○
Koch 1997 [604]	Cross-sectional	607		↑↑↑	Prevalent coronary artery disease	LMW vs HMW	↑	↑	○
Gazzaruso 1996 [619]	Cross-sectional	138		↑↑↑	Prevalent coronary artery disease	LMW vs HMW	↑		○
Wanner 1995 [630]	Cross-sectional		64	↑↑	Prevalent coronary artery disease	LMW vs HMW	↑		○
Auguet 1993 [624]	Cross-sectional	101		↑	Prevalent cardiovascular disease	LMW vs HMW	⇔		○
Kronenberg 2003 [357]	12 mo	106	49	↑↑	Vascular calcification progression	LMW vs HMW	⇔		○
Kronenberg 1994 [618]	Cross-sectional	167		↑↑↑	Prevalent carotid plaques	LMW vs HMW	↑	↑	○
Kronenberg 2003 [357]	Cross-sectional	106	49	↑↑	Prevalent vascular calcification	LMW vs HMW	⇔		○

Abbreviations: HMW, high molecular weight phenotype; LMW, low molecular weight phenotype.

a All subjects regardless of previous history of coronary artery disease.

b In subjects with no previous history or coronary artery disease.

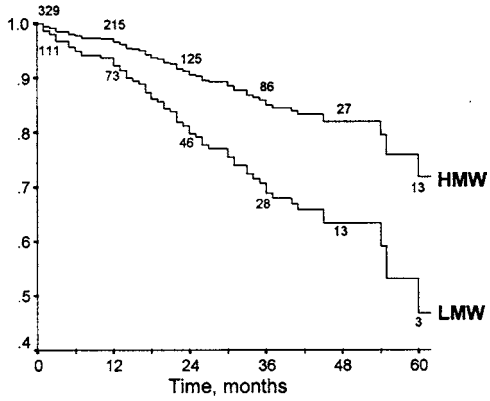

Fig 7. Coronary event-free survival and apo(a) phenotypes. Adjusted results are obtained from a multiple Cox proportional hazards regression analysis. Numbers near the survival curves represent the number of patients with HMW and LMW apo(a) phenotypes at risk at the times 0, 12, 24, 36, 48 and 60 months. Reproduced with permission (http://lww.com).[603]

Research Recommendations

Further large dialysis cohorts should investigate the value of Lp(a) concentrations and Apo(a) phenotypes for risk assessment. This question should especially be addressed in PD patients as well as in various ethnicities. A possible interaction of various apo(a) isoforms with lipids and other cardiovascular risk factors should be investigated. Experimental therapeutic strategies to lower Lp(a) should be examined in randomized, controlled clinical trials, especially in high-risk populations such as dialysis patients.

Conclusions

Although Lp(a) levels are not a suitable factor for CVD risk prediction in dialysis patients, there is strong evidence that the apo(a) size polymorphism is associated with various clinical endpoints.

MALNUTRITION

Introduction

Protein-energy malnutrition (PEM) and wasting are common among CKD patients,[635-637] and are associated with higher rates of morbidity and mortality.[169,441,635,638,639] Although various factors associated with the dialysis procedure, *per se* (such as dialyzer membrane bio-incompatibility, and nutrient losses), may contribute to PEM, recent studies have shown that malnutrition is also common before the start of dialysis.[434,638] Various factors contributing to malnutrition in CKD patients are presented in Table 31. The decline in nutritional status during the course of progressive kidney failure may be caused by disturbances in protein and energy metabolism, hormonal derangement, as well as by spontaneous reductions in dietary energy and protein intake.[640] However, as it has been demonstrated that patients treated with HD for a long time become malnourished despite adequate dialysis dose and protein intake,[641] several co-morbid conditions may also contribute to PEM among dialysis patients. In particular, chronic inflammation, CVD, diabetes mellitus, and other superimposed illnesses may produce anorexia and malnutrition. It was recently reported that diminished appetite (anorexia) was associated with higher concentrations of proinflammatory cytokines.[642] Evidence suggests that the presence of PEM is associated with inflammation in CKD patients.[421,434,643,644] Moreover, both PEM at baseline and worsening of PEM over time are associated with a greater risk for cardiovascular death in dialysis patients[328,645] and strong associations between the presence of malnutrition and CVD have been documented both in predialysis[434] and dialysis[643] populations. On the other hand, a recent study[646] documented no association between BMI and hospitalized acute coronary syndromes in a large group of incident Medicare dialysis patients. The exact mechanism(s) by which PEM may increase the risk of CVD are not known. However, as PEM and low BMI recently have been associated with both increased oxidative stress[475,647] and impaired endothelium-dependent vasodilation with reduced bioavailability of nitric oxide,[647] these may be mechanisms that contribute to the high prevalence of CVD in malnourished CKD patients. As nutritional status is so strongly associated with outcome, it is important to define which nutritional indicators to use in the clinical setting. However, the optimal protocol to diagnose and monitor the response to nutrition intervention has not yet been defined. Therefore, the current approach is to integrate parameters that have been shown to have nutritional relevance; i.e., clinical assessment, food intake, biochemical assessment, body weight, body composition, and psychosocial evaluation.

Table 31. Factors Contributing to Wasting in CKD Patients

Anorexia Due To:
Nausea, emesis, medications
Uremia/uremic state of metabolism
Underdialysis
Accumulation of uremic toxins not completely removed by dialysis
Inflammation
Contributing to anorexia
Inducing catabolism
Due to comorbidities
Related to the dialysis procedure (such as impure dialysate, backfiltration)
Metabolic Acidosis
Endocrine Disorders
Insulin resistance
Hyperparathyroidism
Impaired response to IGF-1
Comorbidity
Infections
Diabetes mellitus
CVD
Dental problems
Dialysis-Related
Inadequate doses
Bioincompatible membranes
Loss of amino acids
Reuse with bleach
Psychosocial
Depression
Low physical activity
Loneliness
Poverty

Adapted with permission.[648]

Discussion

Validity of serum albumin as a nutritional marker. Over the past few years, the process of nutrition assessment and management of the CKD patients has been presented with new challenges regarding validity and reliability. This is largely due to the fact that parameters previously relied upon for visceral stores assessment, predominantly serum albumin (and, to a lesser extent, prealbumin), are independently altered by systemic inflammation. Several studies have demonstrated that a low serum albumin concentration is strongly associated with both mortality[181,362,441,479,649] and cardiac disease[479] in CKD patients maintained on either PD or HD. Moreover, among 1,411 HD patients enrolled in the HEMO study, patients in the low albumin group had significantly greater prevalence of CHD.[650] However, in studies in which the effect of inflammation (measured by CRP levels) is also accounted for in multiple-regression analysis, low serum albumin levels tend to lose predictive power,[322,422,445] suggesting that inflammation may be a more powerful predictor of poor outcome. Indeed, in two recent studies of 7,719[441] and 25,661[442] HD patients, respectively, the risk of mortality was directly associated with the neutrophil count. The interactions between inflammation and nutritional status may be complex, as inflammation and dietary protein intake exert competing effects on serum albumin levels.[651] In fact, inflammation may cause the same changes in serum protein levels and body composition as PEM, even with adequate calorie and protein intake. Recent studies have shown that inflammatory cytokines, such as TNF-α and IL-6, are associated with protein synthesis and catabolism in the body, and downregulate albumin synthe-

Table 32. Factors That May Affect Serum Albumin Levels in CKD Patients

Inflammation
Poor energy and protein intake
Catabolic and anabolic processes
Age
Co-morbidity (CVD, diabetes mellitus)
External protein losses (urine, dialysate)
Fluid overload

sis.[652] The poor correlation documented between serum albumin and other nutritional parameters[445,653] implies that non-nutritional factors actually may be more important in determining serum albumin levels than dietary intake and nutritional status *per se* in CKD patients. Indeed, a number of factors other than protein intake and nutritional status may affect the serum albumin concentration in CKD patients (Table 32). Beside inflammation, age and co-morbidities, such as CVD and diabetes, have been shown to be strongly associated with serum albumin levels in CKD patients.[445,654,655] Moreover, external albumin losses, such as albuminuria and losses in dialysate, may significantly contribute to hypoalbuminemia in CKD.[655] Finally, over-hydration, which is a common feature in dialysis patients, may also contribute to low serum albumin levels.

Among a number of other available biochemical nutritional indicators, prealbumin and serum creatinine may have unique validity, when researchers reach a more detailed mechanistic understanding of their functions. Prealbumin is

Table 33. Assessment of Wasting in CKD Patients

Symptoms and Signs
Weight loss
Anorexia
Fatigue
Gastrointestinal symptoms
Muscle wasting
Subjective global assessment (SGA)
Anthropometrics
Body mass index (BMI)
Skinfold thickness
Midarm muscle circumference
Handgrip strength (HGS)
Waist circumference
Biochemical Methods
S-albumin
Prealbumin (transthyretin)
S-creatinine
Creatinine kinetics
Normalized protein catabolic rate (nPCR)
Transferrin
Cholesterol
Neutrophil and lymphocyte count
Sophisticated Methods
Bioimpedance (BIA)
Dual energy x-ray absorptiometry (DXA)
Total body nitrogen
Total body potassium

Table 34. Association of SGA Score >1 with Risk of Cardiovascular Outcomes and Markers

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome		Results (Univariate)	Results (Multivariate)	Quality
Kestenbaum 2002 [a 260]	~18 mo		3716	↑↑↑	All-cause death		↑	↑	○
Stenvinkel 2002 [445]	37 mo	87 [b]	113 [b]	↑↑	All-cause death	All	↑	↑	○
						Men	↑	↑	
						Women	↑	↑	
Qureshi 2002 [446]	36 mo	128		↑↑	All-cause death		↑	↑	○
Kestenbaum 2002 [a 260]	~18 mo		3716	↑↑↑	Stroke death		↑	⇧	○
Wang 2001 [667]	Cross-sectional		137	↑↑	Valve calcification		↑		●

Abbreviation: SGA, subjective global assessment.
-- Analyzed as a continuous variable (no threshold analyzed).
a SGA score implied
b 196 of 206 subjects total analyzed for SGA.

curiously misnamed, as it is not structurally related to albumin in any way, but is in fact the thyroxin-binding protein, transthyretin. Transthyretin levels are more sensitive to nutritional status than serum albumin levels. Both are suppressed when hepatic protein synthesis switches to the production of acute-phase proteins, but transthyretin levels change more rapidly. Therefore, transthyretin represents a good index of liver anabolic protein synthesis. However, the clinical picture is complicated, because transthyretin is reabsorbed and/or metabolized by the proximal tubule.[656] Therefore, serum levels of transthyretin rise as kidney function declines.[442] Nonetheless, transthyretin levels correlate strongly with serum albumin and have been shown to provide prognostic value independent of albumin in HD patients.[657] Because serum creatinine concentration reflects muscle mass, somatic protein stores, and dietary protein intake, and also predicts outcome in CKD,[181] it may be another useful marker of nutritional status in CKD. However, creatinine levels are also affected by inflammation and other factors such as age, sex, race, residual kidney function, variation in creatinine metabolism, and dialysis dose.[441,651]

Other potentially useful nutrition markers. Clearly, other nutritional indices are needed to assess nutritional status in CKD. Ideally, a nutritional marker should not only predict outcome, but it should also be an inexpensive, reproducible, and easily performed test that is not affected by such factors as inflammation, gender, age, and systemic diseases. Unfortunately, no such ideal nutritional marker is available at present. Thus, the use of a broad panel of putative indicators may best facilitate the epidemiological and clinical assessment of nutritional status (Table 33). The assessment of dietary intake has been commonly used to assess nutritional status. In particular, the normalized protein catabolic rate (nPCR) has been widely used as a measure of dietary protein intake, assuming a state of protein balance. Indeed, nPCR is much simpler to determine than dietary protein intake from diet diaries or interviews.[658] However, a recent study observed no relationship between mortality and either baseline or 6-month follow-up measurements of nPCR in 7,719 U.S. adult HD pa-

tients,[441] raising doubt about the clinical usefulness of this nutritional parameter.

Several methods have been used to monitor lean body mass in CKD, e.g., anthropometrics, creatinine kinetics, multifrequency bioimpedance (BIA) and DEXA. Of these, DEXA seems to be the most reliable, especially if serial measurements are made.[659] However, to the best of our knowledge, no studies have yet evaluated whether lean body mass (by DEXA) predicts outcomes and/or is associated with CVD. By using DEXA, a reliable estimation of the amount of body fat mass can also be done. However, as DEXA is not widely available, other nutritional indicators are needed.[660] Although measures such as BIA and handgrip muscle strength (HGS) are practical and convenient, they, too, suffer from limitations.[661-663]

Subjective global assessment (SGA), on the other hand, is widely available and seems to be a reliable predictor of poor outcome in both sexes (Table 34).[445] It is a combined subjective and objective test of the patient's medical history and physical examination, including recent weight loss, dietary intake, gastrointestinal symptoms and visual assessment of subcutaneous fat.[664,665] In addition, several large prospective studies have demonstrated that SGA is a reliable predictor of poor outcome in dialysis patients, suggesting that it provides a meaningful assessment of nutritional status.[441,635] Although SGA has several advantages, such as its low cost, rapid performance, and strong predictive value for mortality, it should be appreciated that visceral proteins are not assessed and that the sensitivity, precision and reproducibility over time of SGA have not been well studied. In a recent study, it was found that whereas SGA may not be a reliable predictor of degree of protein malnutrition (as assessed by total body nitrogen), it may differentiate severely malnourished patients from those with normal nutrition.[666]

Research Recommendations

Studies are needed to identify the incidence of hypoalbuminemia due to visceral protein store depletion vs. hypoalbuminemia due to chronic inflammation. Effective nutrition and medical management interventions need to be identified that are specific for malnutrition vs. inflammation vs. metabolic challenges. Studies are also required to examine how long-term nutritional intervention affects cardiovascular risk and specific risk factors for accelerated atherosclerosis, such as oxidative stress and endothelial dysfunction, in CKD patients.

Conclusions

Protein-energy malnutrition and wasting are strong predictors of mortality among CKD patients. Although several biochemical and anthropometric measurements correlate with nutritional status, there is not a single measurement that provides complete and unambiguous assessment. While serum albumin is a robust and well-documented indicator of mortality risk in CKD patients, its value as a nutritional marker has been questioned because levels are affected by a number of non-nutritional factors. As SGA is a simple and inexpensive indicator that predicts outcome, this test could be useful in identifying malnourished CKD patients at high risk. The utility of the SGA for nutrition assessment and management of this patient population requires further verification. At present, the use of a broad panel of nutritional indicators, such as BMI, SGA, handgrip strength (or other measure of muscle mass), waist circumference, serum albumin, and serum creatinine may be the best approach to provide useful information about the nutritional status in any given clinical situation.

RISK STRATIFICATION

OVERVIEW OF RISK STRATIFICATION

Risk stratification is the categorization of patients with a special disease into risk strata that reflect the probability to develop a certain event or an exacerbation of the disease. The categorization is based on several factors, e.g., demographic variables, comorbidities, or conditions that are already known to be associated with an increased risk for the endpoints of interest. It is, therefore, the goal of risk stratification to identify those patients who have the highest risk to develop an endpoint. The most important task of risk stratification is to improve the health status by slowing or preventing complications through early detection or appropriate intervention before a fatal or nonfatal event occurs. One opportunity to do so is to offer the patients disease management programs.

It is important to distinguish between two different kinds of stratifiers. The first kind includes those conditions that can be detected and changed by avoidance (e.g., smoking) or intervention (e.g., high blood pressure or hypercholesterolemia). Data from the general population show that these changes are associated with a lower incidence of cardiovascular events. In CKD patients, data are often rare and it is necessary to extrapolate results from the general population. On the other hand, many of these conditions are reported to show paradoxical associations in dialysis patients. For example, many studies show a higher BMI to be associated with a higher mortality risk in CKD patients, which is completely opposite to what is observed in the general population.[668-672] This association is even independent of serum albumin, clinical assessment of nutritional status, and comorbid conditions. Similar associations with mortality, which are opposite to those in the general population, were reported for cholesterol and homocysteine.[181,562,673-677] Studies that described associations opposite to what is known from the general population resulted in a discussion of a so-called reverse epidemiology in dialysis patients.[678,679] In many cases, there is an explanation for this apparent paradox on further examination of the data, as was recently shown for the reverse association between cholesterol and mortality in dialysis patients.[262]

The second kind of risk stratifiers is that that is "fixed" and cannot usually be changed. Examples are age, gender, and—in particular—genetically determined conditions. Biomarkers also belong to this category, since they cannot be changed, but they point to an already damaged cardiovascular system or to a cardiovascular system which is at high risk of future damage. Typical examples discussed earlier include troponins[411,412,414,419,680] or particular genetic variants of the apo(a) gene, the so-called LMW (or small) apo(a) isoforms.[603-605,613,617-619,624,630] Although age, gender, or special genetic variants are fixed stratifiers, they should be considered in any decision regarding intervention. For example, patients with adverse conditions should be followed more closely by noninvasive tests (e.g., ultrasound of the carotid arteries) and in shorter time intervals, since cardiovascular changes often develop rapidly. If an invasive test (e.g., coronary angiography) is indicated, these adverse conditions might support its use. However, at present, no randomized controlled studies in CKD patients are available that have investigated whether risk stratification by these fixed stratifiers is beneficial, when it is either followed by a "forced" structured disease management program or by "routine" care.

FAMILY HISTORY AND GENETICS

Introduction

Family history (Table 35) is a strong predictor of CVD in the general population. It remains predictive for CVD even after correction for measured familial risk factors such as hypertension, cholesterol, obesity and diabetes.[681-685] The familial aggregation of genes and shared environment strongly contribute to the increased frequency of a positive family history. A study of more than 120,000 families from the Health Family Tree Study and the Family Heart Study observed that 14% of the families that had a positive family history of CHD accounted for 72% of persons with early CHD (onset before age 55 for men and age 65 for women) and 48% of CHD at all ages. For strokes, 11% of families with a positive family history for stroke accounted for 86% of early strokes (before age 75)

Table 35. Approximate Definition of Categories of Family History in the General Population

Category	Description
protective	no events in a large family
average	no events in an average or small family or one event at any age in a large family
positive	one event at any age in average size families or one early event in large families
strong positive	one early event or two events at any age
very strong positive	two events at an early age

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and 68% of all strokes.[681] Family history collection is therefore a validated and inexpensive tool for family-based preventive medicine and medical research in the general population. However, there are no sufficiently powered studies in the CKD population that have investigated the value of this tool for risk assessment. Instead, several studies have examined a handful of candidate genes for CVD in dialysis patients.

Discussion

The studies on candidate genes can be stratified into three groups. Two groups were already investigated in more than three patient cohorts and showed, in the majority of the studies, either a statistically significant association with CVD endpoints in dialysis patients (e.g., the apo(a) size polymorphism and the MTHFR polymorphism) or rejected such an association (ApoE and ACE polymorphism). The third group investigated candidates mostly in one cohort, and its results need to be confirmed by further studies.

Positive Genetic Association Studies

Apo(a) size polymorphism. There is clear evidence that the apo(a) K-IV repeat polymorphism is associated with CVD in the general population, as well as in dialysis patients [see section on Lp(a) and apo(a) size polymorphism]. In brief, almost all studies found an association between LMW apo(a) phenotypes and atherosclerotic complications or total mortality (see Table 30).

677C→T polymorphism of the MTHFR enzyme. A recent meta-analysis suggested that elevated homocysteine is, at most, a modest independent predictor of IHD and stroke in the general population.[686] Interestingly, moderate increases of homocysteine are reported in subjects who are carriers of a variant of the MTHFR gene. Those with a C-to-T substitution at position 677[687] have a reduced enzyme activity and about 20% higher homocysteine concentrations,[688] especially when associated with low folate intake.[689] A meta-analysis of all case-control observational studies from the general population revealed that the TT genotype was associated with 16% higher odds of CHD compared to individuals with the CC genotype.[690] Five studies, mostly in HD patients, investigated this polymorphism in relation to various cardiovascular endpoints (Table 36).[562,565,691-693] Four of the five studies found an association with outcome in univariate and/or in multivariate analysis[562,691-693] which was not confirmed by another large study.[565] Recently, a prospective follow-up study[694] of earlier reported cross-sectional analysis in 459 patients was published.[562] In contrast to the earlier findings, the prospective follow-up study did not show an association of this mutation with CVD.[694] Taken together, it seems that there might exist an association between this mutation and CVD; however, the association is uncertain (Table 36).

Negative Genetic Association Studies

Apolipoprotein E polymorphism. The ApoE polymorphism is significantly associated with intermediate phenotypes (e.g., concentrations of ApoE, ApoB, total and LDL cholesterol)[695] and disease endpoints (coronary or peripheral atherosclerosis) in the general population.[696,697] Only a few studies have investigated the ApoE polymorphism in relation to atherosclerosis in CKD patients and reported contrasting results.[614,628,698,699] Thus, it appears that the ApoE polymorphism is not helpful for atherosclerosis risk stratification in dialysis patients (Table 37).

ACE polymorphism. A common ACE gene variant is known, with an insertion (I) or deletion (D) of a 287-bp fragment within intron 16. The D

Table 36. Association of the MTHFR 677C→T Polymorphism with Risk of Prevalent CVD or Markers[a]

Author, Year	No. of Subjects HD	PD	Applicability	Cardiovascular Outcome	Predictor Genotype (Comparators)	Results (Univariate)	Results (Multivariate)	Quality
Wrone 2001 [562]	430	29	↑↑↑	Cardiovascular disease	TT	↑	↑	○
					CT	⇔		
Morimoto 2002 [691]	168		↑↑↑	Cardiovascular disease	TT	↑		○
Kimura 2000 [565]	545		↑↑	Vascular disease	TT	⇔	⇔	○
Haviv 2002 [693]	120		↑↑	Cardiovascular disease	TT	↑	⇔	○
					CT	⇔		
Lim 2001 [692]	151		↑↑	Intima-media thickness	TT	↑	↑	○
					TT or CT		↑	

a All cross-sectional studies.

Table 37. Association of the ApoE Polymorphism with Risk of CVD or Markers

Author, Year	Mean Study Duration	No. of Subjects HD	PD	Applicability	Cardiovascular Outcome	Predictor Genotype(s) (Comparators)	Results (Univariate)	Results (Multivariate)	Quality
Imura 1999 [699]	Cross-sectional	493		↑↑↑	Prevalent cardiovascular disease complications	E2/3 vs E3/3 vs E3/4	⇔	⇔	○
Lim 1997 [698]	2 yr	119	38	↑↑↑	Stroke	E4	↑	↑	○
Güz 2000 [614]	Cross-sectional	269		↑↑	Prevalent atherosclerosis	E3/4 vs E3/3 vs E2/3	⇔		○
					Prevalent intima-media thickness		⇔		
Olmer 1997 [628]	Cross-sectional	66		↑↑	Prevalent intima-media thickness	E4	↑		○

allele is associated with increased ACE levels and the polymorphism explains about half of the variation in plasma and tissue levels of ACE. An association between the DD genotype and CAD in the general population is controversial.[700] In dialysis patients, most studies (especially the larger ones) did not reveal an association with clinical endpoints of cardiovascular disease (Table 38).[691,701-707]

Interesting candidates under investigation. The anti-inflammatory cytokine interleukin-10 (IL-10) counteracts the cascade of inflammatory factors leading to an acute-phase reaction.[708] An interesting observation was recently reported for a polymorphism in the promoter of the IL-10 gene.[709] This polymorphism, at position -1082, leads to low production of IL-10 (-1082A allele)[710]and the AA genotype is associated with a higher cardiovascular morbidity[709] compared to the GG genotype. This reflects the reduced ability of the -1082 AA genotype to downregulate inflammatory processes as compared to the -1082 GG genotype.

Myeloperoxidase is an abundant enzyme in the production of free radicals. A functional genetic variant of this enzyme in position -463 (G→A) is associated with a lower myeloperoxidase expression and a lower prevalence of CVD in HD patients.[711]

Research Recommendations

The predictive value of family history of CVD should be investigated in patients with renal disease. Further large dialysis cohorts should investigate the value of Lp(a) concentrations and apo(a) phenotypes for risk assessment. This question should especially be addressed in PD patients as well as in various ethnicities. Arising candidate genes for CVD should be investigated in dialysis patients.

Conclusions

Family history and/or genetic testing are potential tools for CVD risk assessment or risk stratification, since they examine factors that cannot be changed by intervention. At the moment, insufficient data are available to determine whether family history is as predictive for CVD in dialysis patients as it is in the general population.

Laboratory testing for genetic factors may be considered for the apo(a) K-IV repeat polymorphism. This test can be done at any time, but the time of first presentation is preferred for an early stratification. Patients with LMW apo(a) phenotypes are exposed to an increased risk for mortality and CVD. Testing for MTHFR variants does not add significant information to that already obtained by measuring homocysteine levels. Further genetic testing is not indicated at the moment.

Patients with a positive family history and/or a LMW apo(a) phenotype may be considered high risk, and they may benefit from intensive risk factor assessment and interventional management.

MENOPAUSE

Introduction

The mean age of women with CKD Stage 5 suggests that the majority of these women are postmenopausal.[17] Different patterns of abnormalities may be seen in women with CKD before and after menopause. The primary hormonal defect observed in premenopausal women with CKD is due to hypothalamic dysfunction. In women of reproductive age and normal renal function, a sustained midcycle increase in estradiol causes an increase in hypothalamic secretion of gonadotropin-releasing hormone (GnRH). This hormone then stimulates the pituitary gland to increase leutinizing hormone (LH) secretion and, with an increase in progesterone and estradiol, follicle-stimulating hormone (FSH) levels increase. This hormonal pattern leads to normal ovulation and menstruation. In the majority of premenopausal uremic women, the positive feedback mechanism of estradiol on the hypothalamus is blunted. The midcycle increase of progesterone, LH, and FSH is impaired, and anovulatory menstrual patterns predominate.[712-714] Estradiol levels in uremic women are comparable to normal in the follicular phase, but a reduced midcycle peak has been documented.[713] Hyperprolactinemia is present in approximately 70% of women with CKD due to reduced renal clearance, increased secretion by the anterior pituitary, and anterior pituitary resistance due to the downregulatory effects of dopamine.[715] Menopause occurs at a younger age among women with CKD; the median age of menopause is

Table 38. Association of the ACE Polymorphism with Risk of CVD or Markers

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	Predictor Genotype(s) (Comparators)	Results (Univariate)	Results (Multivariate)	Quality
Higashiuesato 2002 [706]	21 mo	727		♀♂	All-cause death	DD	⇔	⇔	●
Aucella 2003 [701]	29 mo	417	44	♀♂	All-cause death	DD	⇔	⇔	●
Aucella 2003 [701]	29 mo	417	44	♀♂	Myocardial infarction death	DD	⇔	⇔	●
Aucella 2003 [701]	Cross-sectional	321	20	♀♂	Prevalent coronary artery disease	DD/DI	⇔		◉
					Prevalent chronic heart failure		⇔		
Morimoto 2002 [691]	Cross-sectional	168		♀♂	Prevalent cardiovascular disease	DD	⇔		◉
Losito 2002 [702]	Cross-sectional	160		♀♂	Prevalent cardiovascular disease	DD/DI	⇔		◉
					Prevalent severe cerebrovascular disease		⇑		
					Prevalent peripheral vascular disease		⇔		
Schmidt 1996 [703]	Cross-sectional	106		♂	Prevalent coronary artery disease	DD/DI	⇔	⇔	○
Aucella 2003 [701]	Cross-sectional	321	20	♀♂	Prevalent left ventricular hypertrophy	DD/DI	⇔		◉
Losito 2002 [702]	Cross-sectional	160		♀♂	Prevalent carotid stenosis	DD/DI	⇑		◉
Schmidt 1996 [703]	Cross-sectional	106		♂	Prevalent left ventricular hypertrophy	DD/DI	⇔	⇔	○
Nergizoglu 1999 [704]	Cross-sectional	51		♂	Prevalent intima-media thickness	DD	⇑		○
						DD/DI		⇑	

50-51 years in normal women and 47 years among women with CKD.[716]

Discussion

Menopause and cardiovascular risk. In the general population, the risk of CVD increases after menopause. This is thought to be due to loss of the protective effect of estrogen on lipids and vascular function. The role menopause plays in the accelerated CVD that is characteristic of CKD is not known.

Hormone Replacement Therapy

Prevalence. Although appropriate indications for estrogen replacement therapy are controversial, 5%-11% of women with CKD over 45 years of age are treated with hormone-replacement therapy (HRT).[716,717] Younger, better-educated Caucasians are more likely to receive HRT.[717] It is not known whether reports from the Women's Health Initiative (WHI), indicating a lack of cardioprotective effect associated with HRT in healthy women, has impacted the use of HRT.

Cardioprotection. There are few reports that have assessed the impact of HRT on cardiovascular outcomes among CKD patients. In the general population, HRT is known to lower LDL cholesterol and Lp(a), and increase HDL and triglycerides. The most common lipoprotein abnormalities in CKD include reduced HDL and elevated LDL, triglycerides, and Lp(a). Since the only lipoprotein abnormality that has been associated with CVD in dialysis patients is Lp(a), it is possible that HRT has positive cardiovascular effects in CKD patients.[610]

One small study in women with CKD demonstrated an increase in HDL and ApoA-I with no change in total cholesterol, LDL, Lp(a), or triglycerides after 8 weeks of treatment.[718] Estrogen also modifies vascular function and atherosclerosis among women without CKD. In the general population, estrogen increases stroke volume, heart rate and contractility, and reduces peripheral vascular resistance in postmenopausal women.[719-721] Regression of atherosclerotic plaques has been shown to occur among women following institution of HRT.[722] Although this may, in part, be due to alterations in lipid metabolism, estrogen also inhibits vascular smooth muscle cell proliferation *in vitro*, a process that contributes to atherogenesis.[723]

The use of HRT in the general population has become increasingly controversial. Reports from the WHI have documented significant reductions in hip fracture and colorectal cancer rates among postmenopausal women treated with HRT.[724] Although estrogens have been reported to improve the lipid profile by increasing high-density lipoprotein and decreasing low density lipoprotein,[725] the WHI did not find an overall benefit among those receiving both estrogen and progesterone.[724] In addition, studies have demonstrated an increased risk of venous thrombosis among women who use estrogen.[724,725] Patients with CKD have an increased risk for pulmonary embolus and are at risk for vascular access thrombosis. The association between HRT and venous thrombosis, particularly vascular access thrombosis, among women with CKD remains unstudied.

Dosing. Previous reports have suggested that renal failure may alter the pharmacokinetics of estrogen, and that dose adjustments are necessary in patients with CKD. One study reported that, after a single dose of estradiol, serum concentrations of estradiol and estrone were 2-3 times that of the controls,[726] while another reported that urinary excretion of estradiol in men with normal renal function was 78%-83% over 4 days compared to 1.4% in men with CKD.[727] Other potential risks of estrogen, such as breast cancer, coagulopathy, or CAD, may be dose-dependent. A recent study found that estradiol serum concentrations among post-menopausal women with CKD requiring maintenance HD were over 20% greater than those among women with normal renal function, in spite of reducing the dose of β-estradiol by 50%. These data suggest that women with CKD should receive a 50%-70% lower dose of β-estradiol to achieve equivalent concentrations. Measurement of estradiol levels (and possibly FSH levels) may be of value in selected postmenopausal women with CKD receiving HRT. It is likely that any benefit would be relative to the blood concentration and not the actual dose, and there may be potential harm in having excessively high blood concentrations.

Research Recommendations

Little is known regarding cardiovascular outcomes associated with menopause. Observational studies should assess the impact of menopause on CVD risk. Given that there are over 30,000 women with CKD treated with HRT, studies should assess if the use of HRT is associated with improved CVD outcomes.

Conclusions

Given the lack of data from the CKD population, it may be prudent to follow the recently published guidelines from North American Menopause Society, which state that the treatment of menopause symptoms remains the primary indication for HRT, and that HRT not be used solely for primary or secondary prevention of CHD.[728] For those women with CKD on HRT, doses of estrogen replacement that are 50%-70% lower than those among women with normal renal function would have an equivalent effect.

PREVENTIVE FOOT CARE IN DIABETES

Introduction

In 1994, the annualized rate of amputation among Medicare diabetic and nondiabetic patients on dialysis was 11.8 and 2.3 per 100 respectively.[144] Compared to dialysis patients with glomerulonephritis as the cause of kidney failure, diabetic dialysis patients had 8.9-fold higher odds of undergoing amputation.[144] The 30-day perioperative mortality in dialysis patients who underwent amputation was 16%.[729] Thus, there is an exceedingly high risk of amputation in diabetic dialysis patients, with its attendant loss of quality of life and high perioperative mortality. Hence, it is imperative to implement measures to decrease the amputation rates in diabetic dialysis patients. Adoption of preventive care of the diabetic foot has been outlined in the American Diabetic Association (ADA) Position Statement,[730] and these recommendations, with certain modifications, may be applied to CKD patients.

Discussion

Several clinical studies in the nondialysis diabetic population have shown that coordinated programs to screen for high-risk feet and to provide regular foot care decreased lower extremity amputation rates.[731,732] In a controlled study, 45 HD patients were assigned to intensive education and care management that included preventive foot care and 38 HD patients were assigned to usual care.[733] Over the 12-month follow-up period, there were no amputations in the study group while there were five lower extremity amputations and two finger amputations in the control group.

Clinical Applications

The ADA Position Statement has discussed several measures that can be implemented for preventive foot care in diabetic patients.[730] Foot examination at the initiation of dialysis is likely to reveal high-risk foot conditions, such as peripheral neuropathy, altered biomechanics, PVD, ulcers, and severe nail pathology. Identification of any of these risk factors may necessitate further regular examinations. Minor conditions may be treatable to prevent complications; however, other conditions (e.g., increased plantar pressure) may require referral to a foot-care specialist.

A major issue will be raising the awareness of preventive foot care in diabetic dialysis patients, and patient education in preventive foot care measures is desirable as part of routine care. Education of dialysis health-care professionals is also important.

Research Recommendations

Long-term studies are warranted to examine the effectiveness of screening with ABI, and early diagnosis of PVD, on reducing the development of critical limb ischemia and the rates of amputation. Randomized, controlled trials are needed to study the effects of antiplatelet agents and statins in asymptomatic and symptomatic PVD on the development of critical limb ischemia and the rates of amputation.

Conclusions

There are no randomized controlled trials of intensive education and care management versus usual care of feet in diabetic dialysis patients. Nonetheless, diabetic dialysis patients are likely to benefit from examination of the foot as part of the routine dialysis care. In this regard, recommendations made by the ADA are applicable to the care of diabetic dialysis patients.

ASPIRIN

Introduction

There are no randomized controlled trials in dialysis patients that establish the safety and efficacy of aspirin for primary or secondary prevention of atherosclerotic events. However, since CKD patients are among the highest-risk groups for atherosclerotic events, it might be reasonable to use aspirin in dialysis patients without contraindications for aspirin therapy.

Discussion

There are no data on use of aspirin in primary prevention of CVD in dialysis patients. In an observational study of 3,374 incident dialysis patients with and without CAD in the USRDS Dialysis Morbidity Mortality Study Wave II, patients on aspirin had 2.9-fold higher hazard of acute coronary syndrome in unadjusted analysis.[734] However, this result was nonsignificant in multivariate analysis. Even though this study used Medicare data to track acute coronary syndromes, not all of the study patients were on Medicare.

In an analysis of the Cooperative Cardiovascular Project, dialysis patients who received aspirin following MI had 43% lower odds of dying within 30 days in a multivariate analysis.[735] Another observational retrospective study found that the use of aspirin and beta-blockers following MI was associated with lower mortality in patients with CKD.[61] Thus, there are reasonable data to support the use of aspirin following MI.

The major risk of aspirin therapy is gastrointestinal (GI) bleeding. A randomized controlled trial of aspirin plus clopidrogel versus placebo to prevent AV graft thrombosis was terminated early because of GI bleeding.[66] However, a retrospective observational study of USRDS data did not find increased risk of GI bleeding with aspirin.[736]

Research Recommendations

- Randomized controlled trials of aspirin as primary or secondary prophylaxis in preventing cardiovascular events with attention to GI bleeding are warranted.
- The cost-effectiveness of aspirin (risk of GI bleeding versus reduction in cardiovascular events) needs to be studied.

Conclusions

Aspirin may be useful for primary prevention of atherosclerotic disease in dialysis patients, with careful monitoring for bleeding complications. Its use following MI is warranted, based on the available evidence. Further large, prospective, observational studies and randomized controlled trials are required.

METHODS FOR REVIEW OF ARTICLES

AIMS

The overall aim of the project was to develop clinical practice guidelines for the evaluation and management of CVD in CKD patients who require either HD or PD.

The Work Group sought to develop the guidelines using an evidence-based approach. Evidence regarding the guideline topics was derived from a systematic summary of the available scientific literature on the epidemiology of CVD among dialysis patients, the evaluation and management of cardiac, cerebrovascular, and peripheral vascular disease among dialysis patients, the evaluation and management of specific risk factors for CVD among dialysis patients, and cardiovascular risk stratification among dialysis patients.

OVERVIEW OF PROCESS

Development of the guideline and evidence report required many concurrent steps to:

- Form the Work Group and Evidence Review Team that were to be responsible for different aspects of the process
- Hold meetings to discuss processes, methods, and results
- Develop and refine topics
- Define population of interest
- Create draft guideline statements and rationales
- Create draft summary tables
- Create data extraction forms
- Create and standardize quality assessment and applicability metrics
- Develop literature search strategies
- Perform literature searches
- Screen abstracts and retrieve full articles
- Review literature
- Extract data and perform critical appraisal of the literature
- Grade the evidence
- Tabulate data from articles into summary tables
- Grade the strength of the recommendations
- Write guideline statements and rationales based on literature.

Creation of Groups

The Co-Chairs of the K/DOQI Advisory Board selected the Work Group Co-Chairs and Director of the Evidence Review Team, who then assembled groups to be responsible for the development of the guidelines and the evidence report, respectively. These groups collaborated closely throughout the project.

The Work Group consisted of "domain experts," including individuals with expertise in nephrology, epidemiology, cardiology, nutrition, social work, pediatrics, and internal medicine. In addition, the Work Group had a liaison member from the Renal Physicians Association. The first task of the Work Group members was to define the overall topic and goals, including specifying the target condition, target population, and target audience. They then further developed and refined each topic, literature search strategy, and data extraction form (described below). The Work Group members were the principal reviewers of the literature, and from these detailed reviews, they summarized the available evidence and took the primary roles of writing the guidelines and rationale statements.

The Evidence Review Team consisted of nephrologists (two senior nephrologists and a nephrology fellow) and methodologists from Tufts-New England Medical Center with expertise in systematic review of the medical literature. They were responsible for coordinating the project, including coordination of meetings, refinement of goals and topics, creation of the format of the evidence report, development of literature search strategies, initial review and assessment of literature, and coordination of all partners. The Evidence Review Team also coordinated the methodological and analytical process of the report, coordinated the meetings, and defined and standardized the methodology of performing literature searches, of data extraction and of summarizing the evidence in the report. They performed literature searches, retrieved and screened abstracts and articles, created forms to extract relevant data from articles, and tabulated results. Throughout the project, and especially at meetings, the Evidence Review Team led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles and the body of evidence, and summary reporting.

Development of Topics

The goals of the Work Group targeted a diverse group range of topics, which would have been too large for a comprehensive review of the literature. Based on their expertise, members of the Work Group focused on the specific questions, and employed a selective review of evidence: a summary of reviews for established concepts (review of textbooks, reviews, guidelines and selected original articles familiar to them as domain experts); and a review of primary articles and data for new concepts.

Refinement of Topics and Development of Materials

The Work Group and Evidence Review Team developed a) draft guideline statements; b) draft rationale statements that summarized the expected pertinent evidence; and c) data extraction forms requesting the data elements to be retrieved from the primary articles. The topic refinement process began prior to literature retrieval and continued through the process of reviewing individual articles.

Data extraction forms were designed to capture information on various aspects of the primary articles. Forms for all topics included study setting and demographics, eligibility criteria, causes of kidney disease, numbers of subjects, study design, study funding source, dialysis characteristics, comorbid conditions, descriptions of relevant risk factors and cardiovascular outcomes, statistical methods, results, study quality (based on criteria appropriate for each study design, see below), study applicability (see below), and sections for comments and assessment of biases.

Training of the Work Group members to extract data from primary articles occurred at meetings, and subsequently by e-mail and during teleconferences.

Literature Search

The Work Group and Evidence Review Team decided in advance that a systematic process would be followed to obtain information on topics that relied on primary articles. Only full journal articles of original data were included. Editorials, letters and abstracts were not included. Selected review articles were included for background material. Though reports of formal studies were preferred, case series were also included. No systematic process was followed to obtain textbooks and review articles.

Studies for the literature review were identified through MEDLINE searches of English language literature conducted between March and October 2002. These searches were supplemented by relevant articles known to the domain experts and reviewers through December 2003.

The MEDLINE literature searches were conducted to identify clinical studies published from 1966 through the search dates. The primary search was designed to capture studies pertaining to all topics. Supplemental searches were made to maximize retrieval of studies pertaining to specific topics, including: anxiety and hostility, carnitine, diet, hormone replacement therapy, pediatrics, and peripheral vascular disease. Development of the search strategies was an iterative process that included input from all members of the Work Group. The text words or MeSH headings for all topics included "renal replacement therapy," end-stage renal disease and related terms. The searches were limited to studies on humans and published in English, and focused on either adults or children, as relevant.

MEDLINE search results were screened by members of the Evidence Review Team. Potential papers for retrieval were identified from printed abstracts and titles, based on study population, relevance to topics, and study size. For studies of risk factors and treatments, those with fewer than 10 subjects were excluded; for epidemiology studies, those with fewer than 30 subjects were excluded. Studies of risk factors had to evaluate a cardiovascular outcome to be included. Studies of risk factor or cardiovascular treatments, including surgery, had to be comparative; thus single-cohort case series were excluded. After retrieval, each paper was read to verify relevance and appropriateness for review, based primarily on study design and ascertainment of necessary variables. Some articles were relevant for two or more topics. Domain experts made the final decision for inclusion or exclusion of articles. All articles included were extracted and are contained in the summary tables. Numerous additional articles that did not meet the specific criteria necessary to qualify for inclusion were reviewed, with or without extraction, for use as background material.

In an iterative process, the topics for which articles would be analyzed in depth and summarized were restricted to those topics that had not been sufficiently summarized previously by other K/DOQI Work Groups or others and provided evidence for the specific guidelines. For most topics, given the small number of available studies, all comparative studies with at least 10 dialysis patients per arm were included. For certain topics with relatively large numbers of studies, stricter criteria were used. For studies of serum calcium, phosphorus, and PTH as predictors of CVD, only studies that reported that they were sufficiently powered for these predictors were included. Studies that evaluated tobacco use as a risk factor for CVD had to both define smoking use categories *a priori* and have a minimum of 100 subjects. Studies of both Lp(a) and genetic markers were required to have at least 10 subjects with CVD outcomes. For predictors with sufficient numbers of studies, only associations with CVD event outcomes were included. These included: C-reactive protein, random serum troponin levels, smoking, echocardiogram measurements, and surgical interventions for coronary artery disease. Intermediate outcomes, including vascular calcification, intima-media thickness, and ventricular arrhythmia were included for other predictors analyzed. For certain predictors, studies were also included that reported prevalent (as opposed to future) CVD. These included genetic markers and ankle-arm brachial index.

Overall, 16,691 citations were screened (9,078 from the primary search; 7,613 from supplemental searches), from which 396 articles were retrieved and reviewed. An additional 151 articles, added by Work Group members and domain experts, were reviewed. Of these, a total of 86 articles met sufficient criteria to be included in summary tables.

Format for Evidence Tables

Two types of evidence tables were prepared. Detailed tables contain data from each field of the components of the data extraction forms. These tables were used to efficiently track and transmit data about all extracted studies. They were completed by the Evidence Review Team from extraction forms filled out by Work Group members. They were then given to the Work

Table 39. Example of Format for Summary Tables

Author, Year	Mean Study Duration	No. of Subjects HD	No. of Subjects PD	Applicability	Cardiovascular Outcome	Outcome Threshold (units)	Results (Univariate)	Results (Multivariate)	Quality
Smith, 1999	2 yr	2,669		↑↑↑	All-cause death	2.6	⇧	⇧	●
Jones, 1995	44 mo	264	169	↑	Ischemic heart disease	2.0	⇳		●
Lopez, 1995	Case Control	56,000		↑↑↑	Cardiac arrest	3.0	⇳		○
Roberts, 1995	12 mo	106	49	↑↑	Vascular calcification progression	--	⬆		●
Doe, 2000	5-80 mo	74		↑↑↑	Ventricular arrhythmia	--	⇩		○

-- Analyzed as a continuous variable (no threshold analyzed).

Group members, but are not included in the report.

Summary tables describe the strength of evidence according to four dimensions: study size (of both HD and PD patients) and duration, study applicability, results and methodological quality. Within each table, the studies are first grouped by outcome type. Outcomes are ordered by all-cause death, CVD death, and CVD events. Studies with intermediate and prevalent outcomes are shaded at the bottom of the tables. Within each outcome, studies are ordered first by methodological quality (best to worst), then by applicability (most to least) and then by study size (largest to smallest). When relevant, outcome thresholds (e.g., of troponin I levels) or definitions of predictors (for genetic predictors) are included. Results are presented using summary symbols, as defined below. An example of an evidence table is shown in Table 39.

Study size and duration. The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to be generalizable; however, large size alone does not guarantee applicability. A study that enrolled a large number of selected patients may be less generalizable than several smaller studies that included a broad spectrum of patient populations. Similarly, longer duration studies may be of better quality and more applicable, depending on other factors.

Applicability. Applicability (also known as generalizability or external validity) addresses the issue of whether the study population is sufficiently broad so that the results can be generalized to the population of interest at large. The study population is typically defined primarily by the inclusion and exclusion criteria. The target population was defined to include patients with end stage renal disease (primarily those on dialysis). A designation for applicability was assigned to each article, according to a three-level scale. In making this assessment, sociodemographic characteristics were considered, as were the stated causes of chronic kidney disease, and prior treatments. Applicability referred to either the HD population or the PD population, as appropriate.

	Sample is representative of the target population, or results are definitely applicable to dialysis population irrespective of study sample.
	Sample is representative of a relevant sub-group of the target population. For example, sample is only representative of people with a narrow range of GFR, or only a specific relevant subgroup, such as elderly individuals or patients with diabetic kidney disease.
	Sample is representative of a narrow subgroup of patients only, and not well generalizable to other subgroups. For example, the study includes only patients with a rare disease. Studies of such narrow subgroups may be extremely valuable for demonstrating "exceptions to the rule."

Results. In general, the result is summarized by both the direction and strength of the association. Depending on the study type, the results may refer either to dichotomous outcomes, such as the presence of a specific genotype or a laboratory test above or below a threshold value, or to the association of continuous variables with outcomes, such as serum laboratory tests. The magnitude of the association and both the clinical and statistical significance of the associations were considered. Criteria for indicating the presence of an association varied among predictors depending on their clinical significance. Both univariate and multivariate associations are presented. Associations are generally represented according to the following symbols:

⇧	Positive association (positive predictor predicts a clinically meaningful increase in CVD or worsening of intermediate CVD outcome)
⇔	No association (predictor is not associated with CVD outcomes)
⇩	Negative association (positive predictor predicts a decrease in CVD outcomes)
⇧ or ⇩	Statistically significant association (generally $P < 0.05$)

For studies of troponin I and T, sensitivity and specificity data are included when reported. For clarity, the results for studies of surgical interventions for coronary artery disease are presented as **CABG, Stent,** or **Tissue** to indicate studies for which the intervention had significantly better outcomes, or CABG for studies where there was a trend toward better outcomes with coronary artery bypass graft.

Quality. Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of types of design were evaluated, a three-level classification of study quality was devised:

●	Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; clear description of the population and setting; clear description of an appropriate reference standard; proper measurement techniques; appropriate statistical and analytic methods; no reporting errors; and no obvious bias. Not retrospective studies or case series.
◎	Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in category above. It has some deficiencies but none likely to cause major bias.
○	Significant bias that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

Summarizing Reviews and Selected Original Articles

Work Group members had wide latitude in summarizing reviews and selected original articles for topics that were determined not to require a systemic review of the literature.

Translation of Evidence to Guidelines

Format. This document contains 14 guidelines. The format for each guideline is outlined in Table 40. Each guideline contains one or more specific "guideline statements," which are presented as "bullets" that represent recommendations to the target audience. Each guideline contains background information, which is generally sufficient to interpret the guideline. A discussion of the broad concepts that frame the guidelines is provided in the preceding section of this report. The rationale for each guideline contains a discussion of specific topics that support the guideline statements, together with a classification of the strength of evidence. The guideline concludes with a discussion of limitations of the evidence review and a brief discussion of implementation issues and research recommendations regarding the topic.

Strength of evidence. The overall guideline is, in general, graded according to the strength of evidence supporting the individual topics addressed by the guideline statements. Strength of evidence was assessed by assigning either "A," "B," or "C" (Table 41). An "A" rating indicates "it is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes, and benefits substantially outweigh harms." The "B" rating indicates "it is recommended that clinicians routinely follow the guideline for eligible patients. There is moderate evidence that the practice improves health outcomes." A "C" rating indicates "it is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence, or on the opinions of the Work Group and reviewers, that the practice might improve health outcomes."

The strength of evidence was graded using a rating system that takes into account: 1) methodological quality of the studies; 2) whether or not the study was carried out in the target population, i.e., patients with CKD on dialysis, or in other populations; and 3) whether the studies examined health outcomes directly, or examined surrogate measures for those outcomes, e.g., valve calcification instead of CVD death (Table 42). These three separate study characteristics were combined in rating the strength of a body of evidence provided by the composite of the pertinent studies.

Table 40. Format for Guidelines

Introductory Statement
- **Guideline Statement 1**
- **Guideline Statement 2**

BACKGROUND
(if appropriate)

RATIONALE
Definitions (if appropriate)
Topic 1
Supporting text
Topic 2
Supporting text
Strength of Evidence

LIMITATIONS

IMPLEMENTATION ISSUES

RESEARCH RECOMMENDATIONS

Table 41. Rating the Strength of Guideline Recommendations

Grade	Recommendation
A	It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.
B	It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.
C	It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence or on the opinions of the Work Group and reviewers, that the practice might improve health outcomes.

Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving health outcomes implies that benefits outweigh any adverse effects.

In addition, the Work Group adopted a convention for using existing expert guidelines issued for populations other than the target population. Grades assigned by the guideline-issuing bodies for the strength of evidence were adopted. When the guideline or the evidence was not graded, this Work Group assumed that the guideline would be based on at least moderately strong evidence. The extrapolation of ungraded guideline recommendations from the general populations to the target population was considered to support grade B recommendations.

Limitations of Approach

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched, and searches were limited to English language publications. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts that were missed by the literature search were included in the review.

Exhaustive literature searches were hampered by limitations in available time and resources that were judged appropriate for the task. The sensitive search strategies required to capture every article that may have had data on each of the questions frequently yielded upwards of 10,000 articles. Given the large number of topics, this approach was not feasible. The difficulty of finding all potentially relevant studies was compounded by the fact that in many studies, the information of interest for this report was a secondary finding for the original studies. We used our best judgment in developing search strategies to balance the yield of potentially useful articles and feasibility.

Table 42. Rating the Strength of the Evidence

		Methodological Quality		
Outcome	Population	Well designed and analyzed (little, if any, potential bias)	Some problems in design and/or analysis (some potential bias)	Poorly designed and/or analyzed (large potential bias)
Health outcome(s)	Target population	Strong[a]	Moderately strong[b]	Weak[h]
Health outcome(s)	Other than the target population	Moderately strong[c]	Moderately strong[d]	Weak[h]
Surrogate measure for health outcome(s)	Target population	Moderately strong[e]	Weak[f]	Weak[h]
Surrogate measure for health outcome(s)	Other than the target population	Weak[g]	Weak[g]	Weak[g,h]

Strong- [a]Evidence includes results from well-designed, well-conducted study/studies in the target population that directly assess effects on health outcomes.

Moderately strong- [b]Evidence is sufficient to determine effects on health outcomes in the target population, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; *OR* [c]evidence is from a population other than the target population, but from well-designed, well-conducted studies; *OR* [d]evidence is from studies with some problems in design and/or analysis; *OR* [e]evidence is from well-designed, well-conducted studies on surrogate endpoints for efficacy and/or safety in the target population.

Weak- [f]Evidence is insufficient to assess the effects on net health outcomes because it is from studies with some problems in design and/or analysis on surrogate endpoints for efficacy and/or safety in the target population; *OR* [g]the evidence is only for surrogate measures in a population other than the target population; *OR* [h]the evidence is from studies that are poorly designed and/or analyzed.

WORK GROUP BIOGRAPHIES

Kline Bolton, MD, FACP, is Professor of Medicine at University of Virginia in Charlottesville, where he is Chief of the Division of Nephrology and Director of the Nephrology Clinical Research Center, Kidney Center and Renal Operations. He has received special honors from organizations ranging from the American Society for Clinical Investigation to the International Society of Nephrology. He has published many articles in journals ranging from *American Journal of Kidney Diseases* and *Kidney International* to *Immunologic Renal Diseases*, and contributed to numerous textbooks, including the *Textbook of the Autoimmune Diseases* and the *Textbook of Nephrology*. Dr. Bolton is Chairman of the Renal Physicians Association Work Group on *Appropriate Preparation of Patients for Renal Replacement Therapy.* In addition, Dr. Bolton serves on the Advisory Boards for Amgen and Ortho-Biotech. His research interests are in refining the epitope(s) involved in causing Goodpasture's syndrome, treating glomerulonephritis, and disease management of CKD and ESRD.

Srinivasan Beddhu, MD, is Assistant Professor of Medicine at the University of Utah and Director, End-Stage Renal Disease Program, Salt Lake VA Healthcare System, Salt Lake City, UT. He received his medical degree from Madras University, Madras, India and completed his nephrology fellowship at the University of Pittsburgh, Pittsburgh, PA. His major area of research interest is atherosclerosis, inflammation and nutrition in chronic kidney disease. He has published several peer-reviewed articles in this area in journals such as the *Journal of American Society of Nephrology, Kidney International, American Journal of Medicine and American Journal of Kidney Disease*. He has received funding from several sources including the *Agency for Healthcare Research and Quality (AHRQ)*. He has been a reviewer for many nephrology journals and reviewed abstracts for the American Society of Nephrology meetings. He is a member of the American Society of Nephrology, National Kidney Foundation, and International Society of Nephrology.

Vito M. Campese, MD, is Professor of Medicine, Physiology and Biophysics at the Keck School of Medicine, University of Southern California in Los Angeles, where he is Chief of the Division of Nephrology and Hypertension Center. Dr. Campese received his M.D. from the University of Bari in Italy. In 1974 he came to the United States via the University of Southern California for a fellowship in hypertension and was subsequently promoted to full Professor of Medicine with tenure in 1985. His main research interests are neurogenic factors in renal hypertension and salt-sensitivity in hypertension. He is the author or co-author of more than 235 scientific publications. Dr. Campese has been active in many professional societies, including the National Kidney Foundation, the American Society of Nephrology, and the American Society of Hypertension. He is a member of the Leadership Committee of the Council for High Blood Pressure. He has served or is serving on the editorial board of several renal and hypertension journals.

Blanche M. Chavers, MD, is Professor of Pediatrics at the University of Minnesota. She is a member of the American Society of Nephrology, the American Society of Pediatric Nephrology, the American Society of Transplantation, the International Society of Nephrology, and the International Society of Pediatric Nephrology. Dr. Chavers is Deputy Director of the Cardiovascular Special Studies Center at the United States Renal Data System, NIH. Dr. Chavers is on the Public Policy Committee of the American Society of Pediatric Nephrology, she is the American Society of Nephrology's representative to UNOS, and she is a member of the American Society of Transplantation's Kidney and Pancreas Transplant Committee. Dr. Chavers is Co-editor of the *American Journal of Kidney Diseases*. She has been published numerous times in a variety of journals and books. Her areas of research and special interest include cardiovascular disease in children with kidney disease, pediatric kidney transplant outcomes, and diabetic nephropathy. Dr. Chavers has received grants from the Department of Health and Human Services for the National Health and Nutrition Survey IV (NHANES) and the United States Renal Data System.

Alfred K. Cheung, MD, is a Professor of Medicine in the Division of Nephrology & Hypertension and the Executive Director of the Dialysis Program at the University of Utah. He received his Nephrology fellowship training at the

University of California, San Diego, under the research mentorship of Dr. Lee Henderson. His research interest has focused on chronic kidney disease and HD. In addition to serving as a member of the editorial board of several journals, he has served as an Associate Editor of the four editions of the *National Kidney Foundation Primer on Kidney Diseases*, and the *Journal of American Society of Nephrology*. Dr. Cheung is the principle investigator of grants from the National Institutes of Health and the Department of Veterans Affairs for the study of novel strategies to prevent vascular access stenosis. He is also the Chair of the Kidney Disease Research Consortium, which was formed in 2003 for the purpose of performing multicenter studies related to chronic kidney disease and dialysis. In the last 15 years, he has served on a number of committees in the National Kidney Foundation and the American Society of Nephrology, and has lectured frequently in national meetings of those organizations. He is currently the Chair of the D-Subcommittee in the National Institute of Diabetes and Digestive and Kidney Diseases for grant reviews. Dr. Cheung has co-authored over 100 papers and book chapters. He is actively involved in the care of patients with chronic kidney disease and the training of fellows for clinical nephrology and research.

David N. Churchill MSc, MD, FRCPC, FACP, is Professor of Medicine in the Faculty of Health Sciences at McMaster University, Hamilton, Ontario. He was the Director of the Division of Nephrology from 1989-1999. Currently, he has a cross-appointment in the Department of Clinical Epidemiology and Biostatistics at McMaster University. He has been a member of the Scientific Advisory Board of the Kidney Foundation of Canada for 3 terms since 1987 and the National Kidney Foundation Research Review Committee since 2002. From 1995-1998, he was Chair of the ISPD Committee on International Studies. Dr. Churchill was the Vice-Chair of the original DOQI Peritoneal Dialysis Work Group and is currently a member of the KDOQI Advisory Board. He was also the Chair for the Canadian Society of Nephrology Committee on Clinical Practice Guidelines from 2000-2003. He is an Associate Editor for the Journal of the American Society of Nephrology and is a member of the Editorial Boards for Nephrology, Dialysis and Transplantation; Peritoneal Dialysis International and the Hong Kong Journal of Nephrology. Dr. Churchill's research interests include adequacy of dialysis (Co-Principal Investigator for the CANUSA group), anemia of renal disease, quality of life in ESRD, vascular access and economic analysis. He has 140 peer-reviewed publications and 9 book chapters. He is the Chair of the Amgen Canada Scientific Advisory Board and has received research funding from Amgen. He has also been a consultant for Genzyme Corporation.

Jordi Goldstein-Fuchs, DSc, RD, is Clinical Assistant Professor at the University of Nevada School of Medicine, Department of Internal Medicine and is completing a second term as Editor-in-Chief of the *Journal of Renal Nutrition*. She also works with DaVita, Inc. as a researcher and clinical dietitian in Reno, NV. Dr. Goldstein first became interested in kidney disease while studying for her Master's degree at the MGH Institute of Health Professions. Her research thesis was in the area of urea kinetic modeling. The resulting publication was awarded the Mary P. Huddleson Award by the American Dietetic Association. After working as a renal dietitian for several years, Dr. Goldstein returned to graduate school and received her Doctor of Science degree in Nutritional Sciences from Boston University. Her doctorate work was in the area of essential fatty acids and experimental kidney disease. She is the author or co-author of over 25 scientific publications and book chapters. Dr. Goldstein is now participating in research in chronic kidney disease and energy expenditure, and essential fatty acids with the Comprehensive Dialysis Study. She is the recipient of the 2003 Service Award from the National Kidney Foundation Council on Renal Nutrition. She is a member of several nutrition and kidney societies including the International Society of Renal Nutrition & Metabolism, the Council on Renal Nutrition of the National Kidney Foundation, and the American Dietetic Association. Dr. Goldstein is a reviewer for several nutrition and nephrology journals.

Charles A. Herzog, MD, is Director of the Cardiovascular Studies Center, United States Renal Data System. He has been a cardiologist at Hennepin County Medical Center (HCMC) in Minneapolis and a University of Minnesota fac-

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William Henrich, MD, is the Theodore E. Woodward Professor and Chairman of Medicine at the University of Maryland School of Medicine. He also serves as Physician-in-Chief of the University of Maryland Medical Center. Dr. Henrich joined the Department as Chairman in February of 1999. A nephrologist with special interests in end stage renal disease and analgesic-related renal disease, he received his M.D. from the Baylor College of Medicine in Houston, Texas. He then served his internship and residency in medicine at the University of Oregon Medical School Hospitals and Clinics, and fellowship in renal diseases at the University of Colorado Medical School. He is the author or co-author of over 200 scientific publications. He is also the editor of the popular dialysis textbook *The Principles and Practice of Dialysis*, just released in its third edition. Dr. Henrich has maintained an active investigative interest in heart disease in dialysis patients, hemodynamic stability during dialysis, analgesic nephropathy and the intrarenal renin-angiotensin system. He currently leads a NIH-sponsored multicenter study of the effect of analgesics on the kidney and has a leadership role as Co-Chair in a NIH multicenter trial on renal artery stenosis. Over the years he has been active in many professional societies including the American Society of Nephrology and National Kidney Foundation, and he is the recipient of the President's and Distinguished Service Awards from the National Kidney Foundation. Dr. Henrich is an elected councilor of the American Society of Nephrology and is slated to serve as President of the Society in 2006-2007. He is a member of several prestigious scientific societies including the Association of American Physicians, American Society of Clinical Investigation, the International Society of Nephrology, and the American Clinical and Climatological Association. Dr. Henrich is a reviewer and editorial board member for several renal and internal medicine journals.

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