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Workshop on Cardiovascular Disease in Chronic Kidney Disease: Options for Intervention

MARCH 10-11, 2003

→ → Final Report

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Workshop on Cardiovascular Disease in Chronic Kidney Disease:

Options for Intervention

REPORT OF THE PLANNING COMMITTEE

Andrew S. Levey, MD, Chairman
Alfred K. Cheung, MD
Bertram L. Kasiske, MD
Patrick S. Parfrey, MD
Mark J. Sarnak, MD

MARCH 10-11, 2003

→ → **LIAISON MEMBERS**
John W. Kusek, PhD (NIDDK)
Jeffrey A. Cutler, MD, MPH (NHLBI)

THE WORKSHOP PLANNING COMMITTEE

Alfred K. Cheung, MD
Professor of Medicine
Department of Medicine
Nephrology and Hypertension
University of Utah
Dialysis Program
85 N. Medical Drive East
Salt Lake City, UT 84112-5350
Phone: (801) 581-6427
Fax: (801) 585-3830
Email: Alfred.Cheung@hsc.utah.edu

Jeffrey Cutler, MD, MPH
Senior Scientific Advisor
National Heart, Lung, and Blood Institute
Division of Epidemiology
and Clinical Applications
National Institutes of Health
6701 Rockledge Drive, Room 8130
Bethesda, MD 20892-7936
Phone: (301) 435-0413
Fax: (301) 480-1773
Email: cutlerj@nhlbi.nih.gov

Bertram L. Kasiske, MD
Director, Division of Nephrology
Department of Medicine
Hennepin County Medical Center
701 Park Avenue
Minneapolis, MN 55415-1623
Phone: (612) 347-5871
Fax: (612) 347-2003
Email: kasis001@umn.edu

John W. Kusek, PhD
Clinical Trials Program Director
Division of Kidney, Urologic and
Hematologic Diseases
National Institute of Diabetes and
Digestive and Kidney Diseases
National Institutes of Health
6707 Democracy Boulevard, Room 617
Bethesda, MD 20817
Phone: (301) 594-7735
Fax: (301) 480-3510
Email: kusekj@extra.niddk.nih.gov

(continued)

Andrew S. Levey, MD
Dr. Gerald J. and Dorothy R. Friedman
Professor of Medicine
Tufts University School of Medicine
Chief, William B. Schwartz, MD
Division of Nephrology
Tufts-New England Medical Center
750 Washington St., Box 391
Boston, MA 02111
Phone: (617) 636-5866
Fax: (617) 636-8329
Email: alevey@tufts-nemc.org

Patrick S. Parfrey, MD
Department of Medicine
Memorial University of Newfoundland
H1418
St John's, Newfoundland, A1C 5S7 Canada
Phone: (709) 777-7261
Email: pparfrey@mun.ca

Mark Sarnak, MD
Department of Medicine
Division of Nephrology
Tufts-New England Medical Center
750 Washington St., Box 391
Boston, MA 02111
Phone: (617) 636-5866
Fax: (617) 636-8329
Email: msarnak@tufts-nemc.org

CONTENTS

GOALS OF THE WORKSHOP

The burden of cardiovascular disease (CVD) in chronic kidney disease (CKD) is substantial. To reduce the burden of CVD in CKD, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute (NHLBI) sponsored a workshop on March 10-11, 2003. The goals of the workshop were to design and prioritize possible interventions to be evaluated in randomized clinical trials and observational studies in patients with kidney failure and earlier stages of CKD, including diabetic kidney disease, non-diabetic kidney disease, and kidney transplant recipients.

Break-out sessions were designed to obtain broad input on study designs and prioritization for clinical studies. To put these proposals into context, internationally recognized scientists critically evaluated recent clinical trials and the latest information concerning ongoing studies. The workshop was highlighted by state-of-the-art lectures on the burden of CVD in CKD, atherosclerosis, and cardiomyopathy.

The Workshop participants concluded the following:

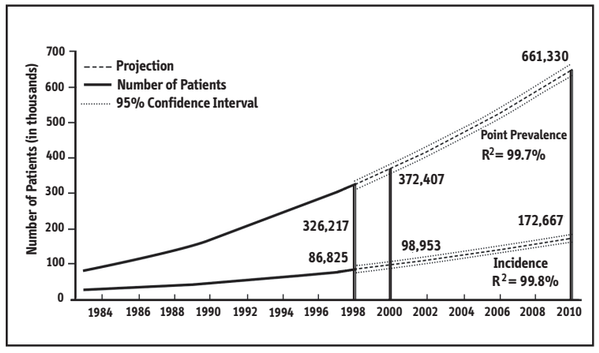
1. There is a high burden of CVD in CKD.
2. There are a large number of traditional and non-traditional CVD risk factors in CVD that could be targeted for intervention.
3. Recently completed and ongoing studies have demonstrated the feasibility of conducting clinical trials on CVD outcomes in CKD.
4. NIDDK and NHLBI should develop initiatives for clinical studies to evaluate strategies to reduce CVD in CKD.
5. All target populations should be considered (diabetic kidney disease, non-diabetic kidney disease, kidney transplant recipients, and dialysis patients).
6. The process used to develop and prioritize ideas during the Workshop worked well to produce a number of high-quality suggestions for clinical studies that should be further considered.

MAGNITUDE OF THE PROBLEM

CVD in Kidney Failure

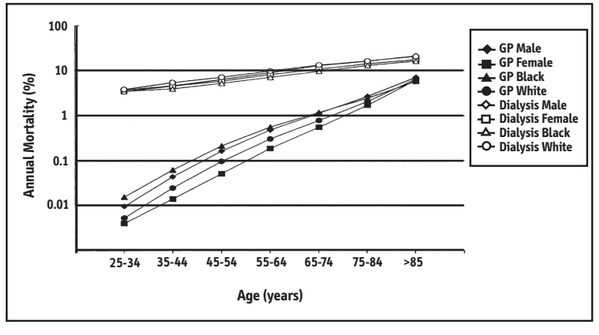
There is a growing incidence and prevalence of kidney failure, the end-stage of chronic kidney disease, as shown from data on patients treated by dialysis and transplantation, reported by the U.S. Renal Data System (USRDS) (Figure 1) [1].

Figure 1. Kidney Failure in the US



The primary cause of death in kidney failure is CVD. Across the age spectrum, the rates of CVD mortality in patients treated by dialysis ranges from 10 to 100 times greater than in the age-matched general population (Figure 2) [2-3]. The high mortality rate reflects a high prevalence of CVD, as well as a high case fatality rate.

Figure 2. Cardiovascular Disease Mortality in the Patients Treated by Dialysis Compared to the General Population (GP)



CVD in Earlier Stages of CKD

CKD can be detected and treated before the stage of kidney failure. The National Kidney Foundation (NKF) Kidney Disease Quality Outcomes Initiative (K/DOQI) Clinical Practice Guidelines on Chronic Kidney Disease provide an operational definition of CKD, irrespective of cause (Table 1) [4].

Table 1. Criteria for the Definition of Chronic Kidney Disease

1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*:
   → Pathological abnormalities; or
   → Markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests
2. GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage

The prevalence of earlier stages of CKD is far greater than the prevalence of kidney failure. Using elevated albumin-to-creatinine ratio as a marker of kidney damage, and glomerular filtration rate (GFR) estimated from serum creatinine and the Modification of Diet in Renal Disease (MDRD) Study Equation, the prevalence of earlier stages of CKD was estimated from data from the Third National Health and Nutrition Examination Survey (NHANES III) (Table 2) [4]. It is estimated that more than 20 million adults in the US, approximately 11% of the adult population, have CKD.

Table 2. NKF-K/DOQI Classification and Prevalence of Stages of Chronic Kidney Disease

STAGE	DESCRIPTION	GFR (mL/min/1.73 m^2)	PREVALENCE*	
			N (1000s)	%
	At increased Risk	≥60 (with CKD risk factors)	–	–
1	Kidney damage with normal or · GFR	≥90	5,900	3.3
2	Kidney damage with mild , GFR	60–89	5,300	3.0
3	Moderate , GFR	30–59	7,600	4.3
4	Severe , GFR	15–29	400	0.2
5	Kidney failure	<15 (or dialysis)	300	0.1

It is now becoming apparent that there is a high prevalence of CVD even in the earlier stages of CKD, and that CKD is a risk factor for CVD [5]. Figure 3 shows the 5-year probability of CVD events according to the baseline level of estimated GFR, as observed in 45-64 year old individuals enrolled in the Atherosclerosis Risk in Communities (ARIC) Study [6]. The large increase in risk for individuals with baseline GFR <60 ml/min/1.73 m^2 is apparent. The increased risk is attenuated after adjustment for other known risk factors, but remains statistically significant.

Figure 3. Risk of CVD According to Baseline Estimated GFR in the General Population (Ages 45-64)

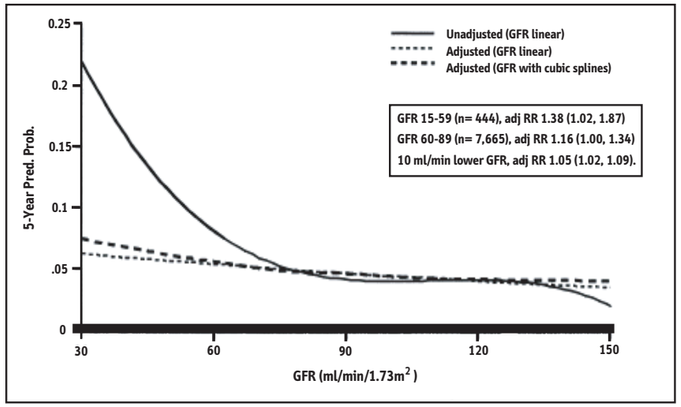
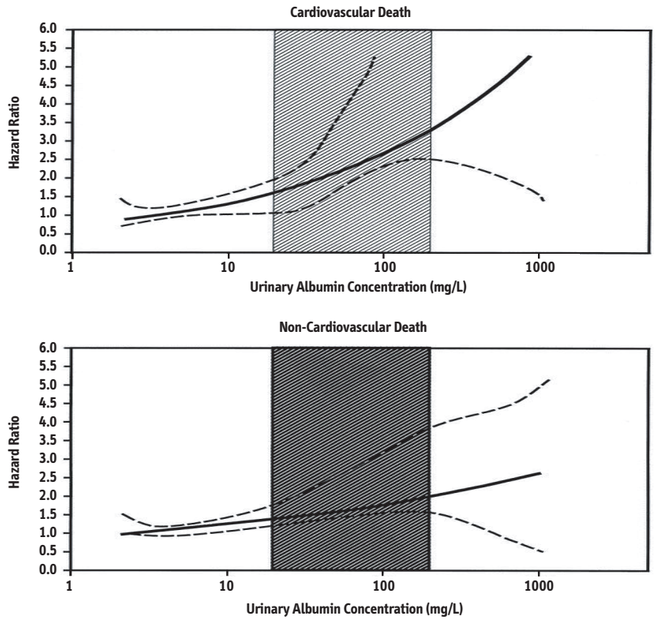


Figure 4 shows adjusted hazard ratios (solid lines) and 95% confidence intervals (dotted lines) for death due to CVD (upper panel) and other causes (lower panel) according to baseline urine albumin concentration in the city of Groningen, the Netherlands [7]. The increased risk of death due to CVD is elevated in individuals with urinary albumin concentration in the microalbuminuria range.

Figure 4. Risk of CVD and Non-CVD Death According to Baseline Urine Albumin Concentration



These studies indicate that the onset of increased risk for CVD occurs during or before the earlier stages of CKD. Figure 5 is a model of the stages of progression of CKD [4]. Shaded ovals indicate stages of CKD. White ovals indicate antecedent stages, complications (including CVD) and death. Horizontal arrows indicate factors ("risk factors") associated with transitions between susceptibility (black), initiation (dark gray), progression (light gray) and death (white). Table 3 defines and provides examples of risk factors for adverse outcomes of CKD. Therapeutic interventions for each stage are also indicated. Interventions should be cumulative, meaning that interventions appropriate for preceding stages should be continued in later stages.

Figure 5. Stages in Progression of Chronic Kidney Disease and Interventions To Improve Outcomes

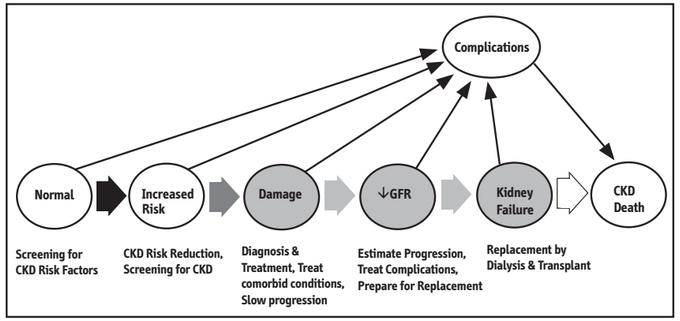


Table 3. Risk Factors for Adverse Outcomes of CKD

	DEFINITION	EXAMPLES
SUSCEPTIBILITY FACTORS	Increase susceptibility to kidney damage	Older age, family history
INITIATION FACTORS	Directly initiate kidney damage	Diabetes, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity
PROGRESSION FACTORS	Cause worsening kidney damage and faster decline in kidney function after initiation of kidney damage	Higher level of proteinuria, higher blood pressure level, poor glycemic control in diabetes, smoking
END-STAGE FACTORS	Increase morbidity and mortality in kidney failure	Lower dialysis dose (Kt/V), temporary vascular access, anemia, low serum albumin, late referral

Figure 6 is a model of the stages of progression of CVD, emphasizing the similarities to stages of progression of CKD [4]. Figure 7 shows a schematic diagram of the population with CKD and CVD, emphasizing similarities in stages of progression, shared risk factors, and the much larger number of individuals with earlier vs. later stages of disease [8]. In each stage, CVD is the leading cause of death. As shown in this diagram, kidney failure and CVD are "competing risks" in CKD.

Figure 6. Stages in Progression of Cardiovascular Disease and Interventions To Improve Outcomes

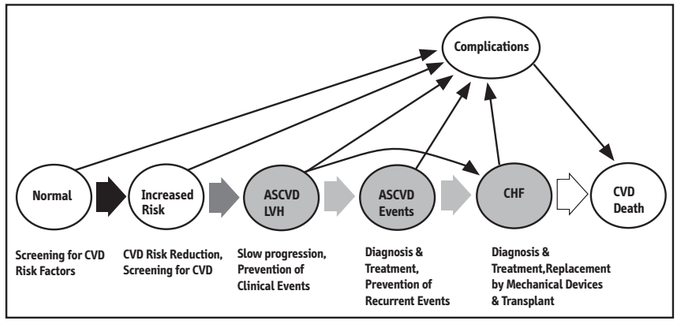
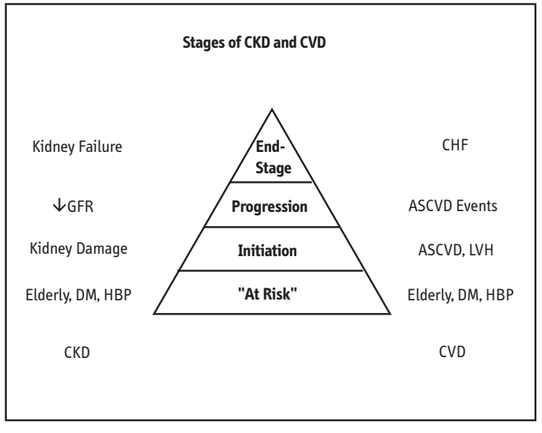


Figure 7. Schematic Diagram of Population With CKD and CVD



Differences Between CVD in CKD vs. CVD in the General Population

Arterial vascular disease and cardiomyopathy are the primary types of CVD (Table 4) [5]. In CKD, it is useful to consider two subtypes of arterial vascular disease, namely atherosclerosis and arteriosclerosis or large vessel remodeling. Atherosclerosis is an intimal disease characterized by the presence of plaques and occlusive lesions. There is a high prevalence of atherosclerosis in CKD. Atherosclerotic lesions in CKD are frequently calcified, as opposed to fibroatheromatous, and have increased media thickness in comparison with lesions in the general population.

Patients with CKD also have a high prevalence of arteriosclerosis and remodeling of large arteries. Remodeling may be due either to pressure overload, which is distinguished by wall hypertrophy and an increased wall to lumen ratio, or flow overload, which is characterized by a proportional increase in arterial diameter and wall thickness.

Patients with CKD also have a high prevalence of cardiomyopathy. Analogous to remodeling of large vessels, pressure overload leads to increased ratio of LV mass to diameter (concentric LVH), while volume overload leads to a proportional increase in LV mass and LV diameter (LV dilatation with LVH).

Table 4. Spectrum of CVD in CKD

TYPES OF CVD	PATHOLOGY	SURROGATES	CLINICAL PRESENTATIONS OF CVD
Arterial Vascular Disease	Atherosclerosis	Inducible ischemia, carotid IMT, EBCT (may be less useful than in the GP for atherosclerosis because of medial rather than intimal calcification), ischemia by ECG	IHD (myocardial infarction, angina, sudden cardiac death), Cerebrovascular disease, PVD, HF
	Arteriosclerosis: Dilated and non-compliant large vessels	Aortic pulse wave velocity, calcification of the aorta, LVH (indirectly), increased pulse pressure	IHD, HF
Cardiomyopathy	Concentric LVH, LV dilatation with proportional hypertrophy	LVH, systolic dysfunction, and diastolic dysfunction by echocardiogram. LVH by ECG	HF, hypotension, IHD

IMT intima-media thickness, EBCT electron beam computerized tomography; IHD ischemic heart disease; HF heart failure; GP general population, LVH left ventricular hypertrophy, PVD peripheral vascular disease, EKG electrocardiogram, CVD cardiovascular disease, CKD chronic kidney disease

CVD Risk Factors in CKD

Table 5 shows hypothesized traditional and non-traditional risk factors for CVD in CKD [5]. Traditional risk factors defined as those in the Framingham Heart Study that have been used to estimate the risk of developing symptomatic ischemic heart disease. Most of the traditional CVD risk factors, such as older age, diabetes mellitus, systolic hypertension, LVH, and low HDL cholesterol are highly prevalent in CKD. The cardiovascular risk conferred by many traditional risk factors, such as diabetes, older age, and LVH, largely parallels the relationships described in the general population. However, some important differences have been noted with regard to other risk factors. For example, "U" shaped relationships exist between all-cause mortality and both blood pressure and total cholesterol levels in dialysis patients.

Several studies have suggested that the Framingham risk equation is insufficient to capture the extent of CVD risk in subjects with CKD [9-12]. One explanation for these findings is that traditional risk factors may have qualitatively and/or quantitatively different risk relationships with CVD in CKD, as compared to the general population. For example, individuals with CKD may have had a longer and more severe exposure to hypertension than subjects without CKD. In addition, subjects with CKD may have been treated for hypertension. The Framingham risk equation does not include the duration of exposure to risk factors nor treatment.

Another explanation is that other factors ("non-traditional" risk factors), which are not included in Framingham risk equations, may play an important role in promoting ischemic heart disease in subjects with CKD. Of note, many of the hypothesized non-traditional risk factors are related to CKD.

Table 5. Hypothesized Traditional and Non-Traditional Risk Factors for CVD in CKD

TRADITIONAL CVD RISK FACTORS	NON-TRADITIONAL CVD RISK FACTORS
Older Age Male gender Hypertension Higher LDL cholesterol Lower HDL cholesterol Diabetes Smoking Physical inactivity Menopause Family history of CVD Left ventricular hypertrophy	Type of CKD Decreased GFR Albuminuria Homocysteine Lipoprotein (a) and apo (a) isoforms Lipoprotein remnants Anemia Abnormal calcium/phosphate metabolism Extracellular fluid volume overload Electrolyte imbalance Oxidative stress Inflammation Malnutrition Thrombogenic factors Sleep disturbances Altered nitric oxide/endothelin balance

FRAMEWORK FOR CONSIDERING INTERVENTIONS TO REDUCE RISK OF CVD IN CKD

In principle, interventions should be directed at modifiable risk factors for CVD in CKD. Table 6 shows possible explanations for the increased risk of CVD in CKD and interventions to reduce risk of CKD and CVD outcomes in CKD.

Table 6. Explanations and Interventions for Increased Risk of CVD in CKD

POSSIBLE REASONS FOR THE INCREASED RISK OF CVD IN CKD	POSSIBLE INTERVENTIONS TO REDUCE CKD AND CVD OUTCOMES IN CKD
Increased prevalence of CVD risk factors in CKD	
→ Shared risk factors for susceptibility, initiation, and progression between CKD and CVD (older age, hypertension, diabetes, smoking)	Treatment of CKD and CVD risk factors in patients at increased risk to reduce CKD and CVD events
→ CVD causes CKD (atherosclerosis, heart failure)	Treatment of CVD to reduce CKD events
→ CKD causes CVD risk factor levels to rise	
• Traditional risk factors (blood pressure, decreased HDL)	Treatment of traditional CVD risk factors in CKD to reduce CVD events
• Non-traditional risk factors (anemia, dyslipidemia, calcium x phosphorus concentration product, homocysteine)	Treatment of non-traditional CVD risk factors in CKD to reduce CVD events
CKD is an independent risk factor for CVD	
→ Proteinuria	Treatments to lower proteinuria in CKD to reduce CKD and CVD events
→ Decreased GFR	Treatments to slow GFR decline in CKD to reduce CKD and CVD events

Clinical studies in the general population have demonstrated unequivocal benefit of some interventions in reducing CVD risk, leading to widespread adoption of clinical practice guidelines for CVD risk reduction. However, few patients with CKD have been included in most observational studies, and clinical trials have usually excluded patients with CKD. Table 7 compares the evidence derived from studies in the general population to evidence derived from studies in CKD [2-3].

Table 7. Comparison of Evidence in the General Population (GP) and in CKD on Risk Factor Reduction for CVD

EVIDENCE RELATING RISK FACTORS TO OUTCOME	GP	CKD
Prevalence of Risk Factor	✓	✓
Relationship to CVD	✓	✓
Effect of Treatment		
→ Effect on risk factor level	✓	✓
→ Effect on CVD outcomes	✓	
→ Effect on CVD mortality	✓	
→ Effect on total mortality	✓	
Side-effects of treatment	✓	✓
Effect with 2-5 years in GP	✓	
Additional side-effects in CKD		✓
Effect on CKD outcomes		✓

*** Check mark indicates strong evidence; absence of check mark indicates absence of strong evidence; shaded areas indicate non-applicable.**

Thus, the evidence base favoring CVD risk factor reduction in CKD is not as strong as it is in the general population. It is important to ask whether observational studies and clinical trials that have been conducted in the general population need to be repeated in CKD, or can guidelines based on the results of studies in the general population be extrapolated to CKD? Some would argue that no guideline statements should be made in the absence of evidence on clinical outcomes in the target population. The 1998 Report of the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease recommended the following criteria for extrapolating evidence from the general population to the patients with CKD [2-3]:

1. The mechanisms and expression of CVD in CKD should be similar to those observed in the general population. Specifically, the features of CVD, the relationship of CVD outcomes to risk factors, the mechanism of risk factor alterations, and the responsiveness of risk factors to therapies should be similar in patients with and without CKD.

2. Therapies in patients with CKD should be as safe, or nearly so, as in the general population. In particular, there should not be additional adverse effects of a specific therapy that limits its usefulness in patients with CKD, either because of altered pharmacokinetics, drug interactions, or increased risk of toxicity to the kidney.

3. The duration of therapy required to improve CVD outcomes in the general population should not exceed the life expectancy of patients with CKD. In other words, it should not already be too late to intervene in this generally elderly, sick, and frail population. Determining whether patients with CKD can survive for long enough to gain the benefit of therapy for CVD is a difficult question. Numerous studies show a dramatically shortened life expectancy for patients with CKD, especially patients with kidney failure. For example, the USRDS has estimated that the average life expectancy of 60-64 year old patients treated by dialysis ranges from 3.6-5.1 years, depending on gender and race. On the other hand, the most common cause of death in kidney failure is CVD, and numerous studies of CVD in the general population have shown a benefit of interventions within 2-5 years, with greater and earlier benefits in patients at highest risk. Thus, it is likely that patients with kidney failure could benefit from more effective treatment of CVD. Because of their longer life expectancy, patients with earlier stages of CKD might be most likely to benefit.

Although these criteria provide a framework to develop guidelines for some CVD risk-reduction interventions in CKD, the Planning Committee and Workshop attendees recommended that at least some clinical trials of CVD risk reduction interventions need to be repeated in CKD. If the results of these studies are similar to the results in the general population, it would strengthen the conclusion that extrapolation from the general population to CKD is appropriate. In addition, there are a large number of hypothesized risk factors which have not been adequately tested in the general population.

TARGET POPULATIONS FOR CLINICAL STUDIES

Table 8 gives a simple classification of causes of kidney disease, which is useful in clinical practice and in clinical studies. This classification was used in developing recommendations for clinical studies during this Workshop.

Table 8. Classification of Chronic Kidney Disease by Diagnosis and Prevalence Among Patients With Kidney Failure

DISEASE	MAJOR TYPES (EXAMPLES*)	PREVALENCE**
Diabetic kidney disease	Type1 and type 2 diabetes	33%
Nondiabetic kidney diseases	Glomerular diseases (autoimmune diseases, systemic infections, drugs, neoplasia)	19%
	Vascular diseases (renal artery disease, hypertension, microangiopathy)	21%
	Tubulointerstitial diseases (urinary tract infection, stones, obstruction, drug toxicity, idiopathic)	4%
	Cystic diseases (polycystic kidney disease)	6%
Diseases in the kidney transplant	Allograft nephropathy (chronic rejection)	-NA
	Drug toxicity (cyclosporine or tacrolimus)	
	Recurrent diseases (glomerular diseases)	
	Transplant glomerulopathy	

* Examples of some causes for specific pathologic types. ** Approximate, based on USRDS Annual Data Report 1998. Prevalence varies with age. NA, not available, not recorded in USRDS.

Table 9 compares target populations for clinical trials of interventions for CVD risk reduction. In general, it is reasonable to consider clinical trials in hemodialysis (HD) patients. The large number of patients available, treatment in specialized centers, and frequent contact with health care providers facilitate recruitment and adherence to interventions. There is a wealth of preliminary data available through the USRDS and recently completed clinical trials. CVD events rates are very high, enabling sufficient statistical power within a follow up of 3-5 years or less for many conditions. However, ascertainment of CVD and CVD risk factors can be difficult because of non-steady-state onditions, frequent hypotension, false-positive serum markers for myocardial ischemia, and difficulty in recognition of heart failure. In addition, there is a high level of comorbidity, and some speculate that it may be “too late” to intervene.

Many characteristics in peritoneal dialysis (PD) patients are similar to those in HD patients, but with steady-state conditions. Metabolic abnormalities due to glucose-based dialysate provide additional opportunities to intervene. Fewer patients are available.

Most kidney transplant recipients are classified as having CKD, according to the K/DOQI definition. Their treatment in specialized centers, frequent contact with health care providers, and high rates of adherence facilitate recruitment and adherence to interventions. There is adequate preliminary data on CVD available through UNOS and large single-center studies. In addition, many kidney transplant recipients have had a thorough evaluation for CVD prior to transplantation, providing better characterization of CVD at entry into the clinical trial. As in other kidney diseases, GFR declines over time in the transplant, and necessitating ascertainment of CKD as well as CVD outcomes. Variation across centers and over time in immunosuppression may confound the interpretation of the trial.

Numerous clinical trials have been performed successfully in diabetic kidney disease. Although there are a large number of patients, treatment occurs in physicians' offices, making recruitment difficult. There is a large body of preliminary data and CVD event rates are high. In addition, GFR decline is relatively fast, necessitating ascertainment of CKD as well as CVD outcomes. Ethical issues may arise, because it may be difficult to withhold from the control group interventions that are effective in diabetes without CKD.

It is most difficult to conduct clinical trials in non-diabetic kidney disease. These patients are the most difficult to recruit, because CKD is often not recognized. Preliminary data is scant, but CVD event rates are probably lower than in other subgroups. Specific treatment is available for some diseases, for example lupus nephritis, which may complicate treatment regimens. Heterogeneity among the causes of CKD may lead to variation in treatment effects, thereby reducing statistical power. As in diabetic kidney disease, ethical issues are likely to arise from withholding interventions from the control group that have been proven to be effective in the general population. Despite these difficulties, it is important to study this subgroup because it represents the largest subgroup of CKD.

Table 9. Strengths and Weaknesses of Target Populations for Clinical Trials of CVD Risk Reductions

CHARACTERISTICS	KIDNEY FAILURE TREATED BY HD (STAGE 5)	KIDNEY FAILURE TREATED BY PD (STAGE 5)	KIDNEY DISEASE IN THE TRANSPLANT (STAGES 1-4)	DIABETIC KIDNEY DISEASE (STAGES 1-4)	NON-DIABETIC KIDNEY DISEASE (STAGES 1-4)
NUMBER OF PATIENTS	Large	Few	Moderately large	Large	Largest
LOCATION	Specialized centers	Specialized centers	Specialized centers	Physicians' offices	Physicians' offices
PATIENT CONTACT	Frequent	Frequent	Frequent	Less frequent	Infrequent
PRELIMINARY DATA	USRDS, HEMO	USRDS, CANUSA, ADEMEX	UNOS, USRDS single-center reports	CSG, DCCT/EDIC, IDNT, RENAAL	MDRD, AASK, AIPRD
CVD EVENT RATE	Highest	Highest	High	High	Moderate
PRIOR EVALUATION FOR CVD	No	No	Yes	No	No
CVD ASCERTAINMENT	Difficult	Usual	Usual	Usual	Usual
COMORBID CONDITIONS	Most	Most	Many	Many	Least
TREATMENT COMPLICATIONS	Fluid shifts, solute shifts, access complications, extracorporeal circuit, anticoagulation	Access complications, frequent changes in modality, glucose load	Immunosuppression	Diabetic regimens	Heterogeneous diseases and treatments
NEED FOR COMPOSITE OUTCOMES	No	No	Yes, changes in kidney function	Yes, changes in kidney function	Yes, changes in kidney function

COMPLETED AND ONGOING STUDIES IN CKD

Tables 10a and 10b provide a summary of data that was presented on clinical trials that have been completed in subjects with CKD. Table 11 provides a summary of data on ongoing studies that were presented at the workshop.

Table 10a. Randomized Controlled Trials of Interventions to Improve Clinical Outcomes in CKD: Interruption of Renin–Angiotensin System

STUDY	YEAR	PATIENTS
RENAAL [13]	2001	Type II DM, hypertensive, serum creatinine 1.3–3.0 mg/dl and proteinuria
IDNT [14, 15]	2001 , 2003	Type II DM hypertensive, serum creatinine 1.0–3.0 mg/dl
AIPRD Metaanalysis [16]	2001	11 RCTS in nondiabetic renal disease
AASK [17]	2002	Black Americans, GFR 20-65 ml/min/1.73^2 No diabetes, proteinuria, or heart failure
HOPE [18]	2001	Age > 55, CVD or DM + CV risk, Excluded if serum creatinine > 2.3 mg/dl
SAVE	Not Published	Post MI, left ventricular enlargement
ALLHAT [19]	2002	Hypertensive, at high risk for coronary event, ≥ 55 years, serum creatinine ≥ 2mg/dl excluded

***Legend for Tables 10a and 10b**

IDNT, Irbesartan Diabetic Nephropathy Trial; AASK African American Study of Kidney Disease and Hypertension, HOPE Heart Outcomes Prevention Evaluation; CARE Cholesterol and Recurrent Events; HPS Heart Protection Study Collaborative Group; SPACE Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease; ALLHAT Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial; HEMO Hemodialysis Study; SAVE Survival And Ventricular Enlargement; RENAAL The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan; ADEMEX Adequacy of Peritoneal Dialysis in Mexico; AIPRD ACE Inihibition Progressive Renal Disease Study Group

(Table 10a continued)

INTERVENTION	PRIMARY OUTCOME	NUMBER	CONCLUSION
Losartan v. Placebo	Doubling of serum creatinine	1512	Losartan slowed kidney disease progression and hospitalization for heart failure
Irbesartan v. Amlodipine v Placebo	Doubling of serum creatinine	1715	Irbesartan reduced kidney disease progression, but not CV events
ACEI v. non-ACEI regimens	Doubling of serum creatinine	1860	ACEI reduced kidney disease progression. More in patients with proteinuria
Ramipril v. Amlodipine v Metoprolol	Decline in GFR	1094	Ramipril slowed kidney disease progression. No additional benefit with lower BP goal.
Ramipril v. Vitamin E v Placebo	CV events	1287	Ramipril reduced CVD risk, similar risk reduction by ramipril in those with and without kidney disease
Captopril v. Placebo	CV events	2184	Captopril reduced CV risk, greater benefit in those with GFR <60 than ≥ 60 ml/min
Lisinopril v. Amlodipine v. Doxazosin v. Chlorthalidone	Fatal CAD/MI	42, 418	Doxazosin arm stopped early because of adverse events, chlorthalidone had similar or better CV outcomes than lisinopril or amlodipine

Table 10b. Randomized Controlled Trials of Other Interventions to Improve Clinical Outcomes in CKD

STUDY	YEAR	PATIENTS	INTERVENTION
CARE [20]	2003	MI 3-20 months post MI, cholesterol < 240 mg/dl, excluded if serum creatinine > 1.5 mg/dl	Pravastatin v. Placebo
HPS [21]	2002	Patients with CVD or DM, excluded serum creatinine > 2.3 mg/dl	Simvastatin v. Placebo
USA normalization of hematocrit trial [22]	1998	Hemodialysis with symptomatic heart disease	Normalization of hematocrit with erythropoietin v. partial correction of anemia
Canadian normalization of hemoglobin trial [23]	2001	Hemodialysis without symptomatic cardiac disease	Normalization of hemoglobin with erythropoietin v. partial correction of anemia
Scandinavian normalization of hemoglobin trial [24]	2003	Predialysis, hemodialysis, peritoneal dialysis	Normalization of hemoglobin with erythropoietin v. partial correction of anemia
Metaanalysis [25]	2003	14 RCTs in hemodialysis	Antiplatelet therapy
Treat to Goal Working Group [26]	2002	Hemodialysis	Sevelamer v. calcium-based phosphate binders
SPACE [27]	2000	Hemodialysis, preexisting vascular disease	Vitamin E v. placebo
ADEMEX [28]	2002	Peritoneal dialysis	Target peritoneal clearance of 60 l/wk/1.73 m^2 v. 4 daily exchanges
HEMO [29]	2002	Hemodialysis	High dose of dialysis v. conventional; high flux dialyzers v. low flux

***Legend for Tables 10a and 10b**

IDNT, Irbesartan Diabetic Nephropathy Trial; AASK African American Study of Kidney Disease and Hypertension, HOPE Heart Outcomes Prevention Evaluation; CARE Cholesterol and Recurrent Events; HPS Heart Protection Study Collaborative Group; SPACE Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease; ALLHAT Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial; HEMO Hemodialysis Study; SAVE Survival And Ventricular Enlargement; RENAAL The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan; ADEMEX Adequacy of Peritoneal Dialysis in Mexico; AIPRD ACE Inihibition Progressive Renal Disease Study Group

(Table 10b continued)

PRIMARY OUTCOME	NUMBER	CONCLUSION
CV Events	4014	Pravastatin reduced CV events, similar in patients with GFR >75 and ≤ 75 ml/min
CV Events	20,536	Simvastatin reduced CV events including sub group with serum creatinine 1.4–2.3 mg/dl
Death/MI	1233	Normalization of hematocrit did not reduce death/MI and increases the risk of vascular access loss
LV volume index/LV mass index	146	Normalization of hemoglobin did not induce regression of established LV dilatation but may present its development
Mortality	416	Normalization of hemoglobin did not improve survival, but improved quality of life
CV Events	2632	Antiplatelet agents reduced CV events
EBCT measured aortic and coronary calcification	200	Sevelamer reduced vascular calcification scores
CV Events	196	Vitamin E reduced CV events
Survival	965	Increases in small solute peritoneal clearance did not improve patient survival
Survival	1846	Higher dialysis dose or high flux dialyzers did not improve survival

Table 11. Ongoing Randomized Trials and Observational Studies

STUDY (PRESENTER)	TARGET POPULATION	DESIGN	STUDY AIM/ QUESTION POSED
FAVORIT (Andrew Bostom)	Kidney transplant recipients with stable kidney function for ≥ 6 months with GFR ≥ 30 ml/min; Age 35-75	RCT	Effect of folic acid on reducing CVD outcomes
SHARP (Colin Baigent)	Serum Creatinine ≥1.5 mg/dl in women and ≥ 1.7 mg/dl in men, and dialysis patients	RCT	Effect of simvastatin and ezetimibe on major vascular events
ALERT (Halvard Holdaas)	Kidney transplant recipients	RCT	Effect of fluvastatin on major CVD and kidney events
4D Study (Christoph Wanner)	Type 2 diabetic hemodialysis patients	RCT	Effect of atorvastatin on major CVD events
CAN PREVENT (Adeera Levin)	Diabetic and non-diabetic kidney disease, CKD stage 3-4	RCT	In comparison to usual care does a multiple risk factor intervention protocol slow progression of CKD and CVD
CRIC (Harv Feldman)	Diabetic and non-diabetic kidney disease, GFR 20-70 ml/min/1.73 m^2 for 21-44 yrs, GFR 20-60 ml/min/1.73 m^2 for 45-64 yrs, GFR 20-50 ml/min/1.73 m^2 for 65-74 yrs	Obs	Risk factors for progression of CVD and CKD
USRDS (Charles Herzog)	Kidney failure and kidney transplant recipients (ESRD)	Obs	CVD outcomes in ESRD
CAN CARE (Adeera Levin)	Diabetic and non-diabetic kidney disease, referred to nephrologists	Obs	Describe characteristics of patients with stages 2-4 CKD referred to nephrologists and evaluate the impact of different models of care
Studies of nocturnal dialysis (Philip McFarlane)	Dialysis patients	Obs	Does nocturnal dialysis decrease CVD outcomes?

*Proposals are currently being evaluated by the NIH.

Obs, observational study; RCT, randomized controlled trial; FAVORIT, Folic Acid for Vascular Outcome Reduction in Transplantation; USRDS, United States Renal Data System; 4 D Study, Die Deutsche Diabetes Dialyse Studie; ALERT, Assessment of Lescol in Renal Transplantation; CAN CARE, Canadian Study of Elements of Care Prior to Dialysis; CAN PREVENT, Canadian Study for the Prevention of Kidney and Cardiac Outcomes; CRIC, Chronic Renal Insufficiency Cohort Study; SHARP, Study of Heart and Renal Protection.

(Table 11 continued)

n	PERIOD OF STUDY	COMMENTS AND CHALLENGES POSED TO SUCCESSFUL COMPLETION
4000	2002-2007	Recruitment, changing incidence of events, adverse events in a sick population, ascertainment of outcomes
9000	2003-2008	Too early to comment
2102	1996-2003	Recruitment, changing incidence of events, adverse events in a sick population, ascertainment of outcomes
1254	1998-2004	Uncertainty in the planning phase on prevalence and incidence of kidney failure (ESRD) as well as rates of CVD outcomes
2400	2003-2008	Feasibility (both numbers and costs) and design issues (acceptable definition of primary outcomes, randomization of patients) as well as potential contamination of the control group
3000	2002-2010	Budgetary limitations, participant burden, power and sample size considerations
US ESRD patients	Ongoing	
500	2000-2004	
		What are the appropriate controls in observational studies? Is it time for randomized trials?*

DEVELOPING A PRIORITY LIST OF RESEARCH PROPOSALS

Methods Used To Define Research Priorities

A modification of the Delphi technique was used to define and prioritize possible research topics. Originally developed by the Rand Corporation in the 1950's, the Delphi technique is a multiple, iterative, survey technique to systematically develop and refine expert opinion on a particular topic. The technique was designed to develop group consensus, while avoiding some of the problems of group dynamics, particularly the problem whereby a small number of influential members exert undue influence over the larger group. It has been used in many different situations, including the determination of research priorities [30-33], and has frequently been modified in various ways.

The Planning Committee decided that the goal of the meeting was to produce a list of approximately 20 research topics, and to select from this list approximately 5 that would be designated top research priorities. This number was selected with the recognition that funding for research is currently limited, and that the purpose of this meeting was to begin a process to develop a short list of priorities among many potentially useful proposals. On the other hand, the organizers also recognized from the outset that any technique for developing consensus would be imperfect, and it was likely that a different group of experts would produce a different, equally valid list of research priorities. Therefore, this report includes all of the topics that were selected to be of high priority, while indicating the five that were selected by the conference participants to be top priorities.

Participants were initially divided into four focus groups that were approximately equal in size, corresponding to the four target populations: 1) diabetic kidney disease, 2) non-diabetic kidney disease, 3) kidney disease in transplant recipients, and 4) kidney failure treated by dialysis. Each group was charged with producing a list of 4-5 research priorities in their area of CKD. Each focus group then presented their priorities to the whole group. Participants were then divided into four prioritization groups that each contained roughly equal numbers of individuals from the original focus groups. These prioritization groups were charged with selecting from the same list of topics developed by the focus groups, the five that should receive the highest priority. The results of each of the four-prioritization groups were then combined to produce the final list of five research priorities.

Focus Groups

As part of the meeting registration, participants indicated in which of the four areas of CKD they felt they had the most expertise. Participants were then assigned to focus groups based on their expressed expertise and the goal to have roughly equal numbers of participants in each focus group. In some cases, participants were not assigned to their first selected area of expertise. Each focus group was asked to produce a list of 4-5 possible research proposals, either observational studies or clinical trials, especially randomized controlled trials (RCT). Each group had a moderator, who had been previously instructed regarding the protocol by which the focus groups would develop a list of ideas for research projects. Specifically, the moderator called upon each member of the focus group to describe a single research proposal. When all members had been queried, the process was repeated, and repeated again, until no one in the group had any additional ideas. Each of these ideas was included in a list, and each member of the focus group was then allowed to vote on one-third of the research projects in that focus group's list. Each focus group then listed 4-5 topics in order, based on the total number of votes each topic received. Appendix II lists a few details about the top-ranked topics in each group, as well as mentioning the remainder of the topics that were proposed but not ranked at the top.

The moderator from each of the four focus groups presented the list of 4-5 topics to the whole group at a plenary session. Each of these was then briefly discussed in the plenary session. Participants were then divided into four prioritization groups that were charged with selecting from the list of 19 topics developed by the focus groups, the 5 proposals that should receive the highest priority.

Prioritization Groups

The moderator in these groups conducted a discussion of each of the 19 research proposals. Generally, members of the original focus groups (roughly equal numbers from the four focus groups were in each prioritization group) were asked to defend the topics that their focus group had recommended and to recount the rationale for these topics. At the end of this discussion, each participant in the prioritization group then voted for the topics that he/she felt should receive the top priority (Appendix III). The results of each group were then combined to give an overall ranking. The results were combined by ascribing 5 points for a 1st priority ranking, 4 points for a 2nd priority ranking, and so forth, and adding the points from all four groups (Appendix III).

PROPOSALS THAT RECEIVED THE HIGHEST OVERALL PRIORITY

1. **RCT of protocol-driven, nurse-managed, multiple risk factor intervention v. usual care in Stage 3 CKD patients with and without diabetes.**

   Background. Several interventions of proven efficacy can slow progression of kidney disease and reduce the morbidity and mortality associated with cardiovascular disease. The challenge is to identify people who will benefit from these interventions and apply them consistently. The current system, where patients largely see fee-for-service physicians for intermittent office visits with variable coordination and integration of care, is not well designed to care for chronic disease. Targeted identification, concentration of resources, and more consistent focus on appropriate use of efficacious therapy may well reduce the burden of disease and associated costs. The hypothesis proposed was that a disease management strategy will not only intervene more frequently to correct risk factors for cardiac and kidney disease, but will achieve better target levels of control. Consequently adverse cardiac and kidney disease clinical outcomes would be improved when compared to conventional therapy.

   Objective. To address the hypothesis that compared to usual care, a nurse supported by a nephrologist, running a multiple risk factor intervention and disease management clinic for people with moderate CKD (stage 3) identified by laboratory-based case-finding, will reduce or delay the onset of advanced kidney disease, cardiovascular events, and death.

   Outcomes. CKD progression and CVD.

2. **Prospective, observational study of living kidney donors, examining CVD risk factors over time with two-kidney siblings serving as controls.**

   Background. A growing number of observational studies suggest that mild to moderate reductions in glomerular filtration rate, and microalbuminuria, are associated with CVD. Although it is possible that this association reflects the adverse effects of CVD risk factors on the kidney, it is also possible that decreased kidney function may affect a number of CVD risk factors (e.g,. blood pressure, dyslipidemia, hyperhomocysteimemia, etc.).

   Objective. To determine whether mild reductions in kidney function, such as may occur with living donor nephrectomy, adversely affect CVD risk factors.

   Rationale. Living donors represent an ideal population for a prospective cohort study of the effects of mild reductions in kidney function on CVD risk factors. They are selected to have normal kidney function and CVD risk at baseline. They have a vested interest in learning whether their voluntary donation affects their risk for CVD. The transplant community also has an obligation to carefully assess the long-term risk of kidney donation.

   Study Design. Living unrelated kidney donors would be followed prospectively over several years, with measurement of GFR and CVD risk factors. The enrollment of donors who are not blood-relatives of transplant recipients would ensure that genetic predisposition to CKD does not bias the results. Ideally, a two-kidney control group (e.g., siblings of the donors) would also be enrolled.

   Measurements. GFR, microalbuminuria, blood pressure, lipoproteins (including remnant lipoproteins, lipoprotein(a), etc.), measurements of glucose homeostasis (e.g., measures of insulin resistance and glucose intolerance), inflammatory markers (C-reactive protein and others), homocysteine, etc.

3. **RCT of coronary artery bypass grafting v. drug-coated stents v. medical therapy in dialysis patients.**

   Background. Dialysis patients with coronary artery disease have a high cardiovascular mortality rate and are at higher risk for surgical complications than patients in the general population. Retrospective studies from the USRDS suggest that patients who undergo coronary artery bypass surgery (CABG) may have improved outcomes compared to those who undergo coronary angioplasty; however, these studies may be limited by a selection bias in that the healthier subjects may be selected to undergo CABG. In recent years improved outcomes in the general population have been noted in patients receiving stents, in particular those receiving drug-coated stents.

   Objective. To evaluate whether CABG, drug-eluting stents, or medical management is the best option for dialysis patients with symptomatic coronary disease.

   Study Design. Randomized controlled trial.

Outcomes. CVD morbidity, CVD mortality, and all-cause mortality (both short-term and long-term outcomes).

4. **RCT of a peroxisome proliferator-activated receptor agonist (PPAR) v. placebo in Stage 3-5 CKD patients with type 2 diabetes. Outcomes: proteinuria, blood pressure, CKD progression, and CVD.**

   Background. PPARs improve sensitivity to insulin in type 2 diabetes, resulting in better glucose control. PPARs may also improve dyslipidemia, inflammatory status, and blood pressure control.

   Objective. To determine whether PPARS improve glucose control and correct other abnormalities associated with insulin resistance in type 2 diabetes mellitus.

   Study Design. RCT of PPR vs placebo in diabetic patients with CKD.

   Outcomes

   - Blood pressure control.
   - Insulin resistance
   - Inflammatory markers
   - Dyslipidemia
   - Microvascular complications of diabetes such as retinopathy
   - Progression of CKD defined by reduction in GFR or proteinuria
   - Surrogates of CVD such as endothelial function
   - Macrovascular CVD outcomes

5. **RCT of beta blocker v. placebo in chronic dialysis patients.**

   Background. Dialysis patients have a high prevalence of left ventricular hypertrophy (LVH), unrecognized ischemic heart disease, increased sympathetic activity, and suffer from high rates of CVD mortality including sudden cardiac death. It therefore seems reasonable to hypothesize that beta blockers by improving ventricular remodeling and decreasing sympathetic activity may reduce CVD events in asymptomatic dialysis patients.

   Objectives. To evaluate whether beta blocker use CVD morbidity and mortality in dialysis patients without known ischemic heart disease.
   Design. Randomized controlled trial.

   Outcomes. All-cause mortality; cause-specific mortality, including sudden cardiac death; and CVD morbidity.

CONCLUSIONS

Table 12. Conclusions of the Planning Committee and Workshop Attendees

1. There is a high burden of CVD in CKD.
2. There are a large number of traditional and non-traditional CVD risk factors in CVD that could be targeted for intervention.
3. Recently completed and ongoing studies have demonstrated the feasibility of conducting clinical trials on CVD outcomes in CKD.
4. NIDDK and NHLBI should develop initiatives for clinical studies to evaluate strategies to reduce CVD in CKD.
5. All target populations should be considered (diabetic kidney disease, non-diabetic kidney disease, kidney transplant recipients, and dialysis patients).
6. The process used to develop and prioritize ideas during the Workshop worked well to produce a number of high-quality suggestions for clinical studies that should be further considered.

Because of the high prevalence and severe impact of cardiovascular diseases in the CKD population, a workshop sponsored by the NIH was appropriate and timely. The co-sponsorship of the workshop by the NIDDK and NHLBI is a testimony to the recognition of the importance of this issue by both of these funding agencies. The high incidence of CVD events, even at early stages of CKD, demands attention from not only nephrologists, but more importantly from cardiologists, the general medical community, and the public at-large. More efforts must be devoted to the education of the general public about CKD, the high incidence and prevalence of CKD, and CKD per se as a risk factor for CVD. Simultaneously, the nephrology and cardiology communities and scientists from other disciplines must intensify their efforts to unravel the mechanisms by which CKD predisposes to CVD and develop strategies to curtail this epidemic.

All patients with CKD are at increased risk for CVD. Further, there are frequent transitions among stages of CKD, with the progression of kidney disease and successful kidney transplantation; however, the burden of CVD and its risk factors may well be cumulative over time. It is therefore essential to study all target populations (diabetic kidney disease, non-diabetic kidney disease, kidney transplant recipients, as well as chronic dialysis patients) in this effort, in order to produce impact expeditiously.

Finally, the process of arriving at these proposals and conclusions involved the initiation of the concept and provision of the administrative and financial support by the NIH, formation of a Planning Committee, including liaison members from NIDDK and NHLBI, to organize the Workshop, formulation of the objectives and format of the meeting and invitations and advertisements to recruit broad representation. Keynote speakers were asked to provide overviews, recent developments, and new directions in several areas. Investigators for clinical trials that had been recently completed or are in progress presented succinctly their projects and strengths, weaknesses, and impediments associated with them. This provided ideas and insights on the practicality of clinical trials. Most importantly, all participants of the Workshop were encouraged to provide a brief synopsis of their own clinical studies and prepare for discussion and suggestions of ideas prior to the meeting. The format of the break-out sessions, which were initially separated by the target populations corresponding to stages and types of kidney diseases, strongly encouraged proposals and discussions by all participants. Presentation of the summaries of these proposals and discussions at a plenary session, followed by redistribution of participants to various break-out sessions allowed for further sharing of ideas and fair voting to prioritize the topics. The entire process appeared to function well to develop and prioritize suggestions for clinical trials, stimulate research ideas, and promote establishment of collaborations and networks. The process has also been educational to the organizers and the participants and could serve as a template for future workshops to accomplish similar goals.

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SPEAKERS

APPENDIX I
Speakers

Colin Baigent, BMBCh, MSc
Reader in Clinical Epidemiology
Clinical Trial Service Unit
Harkness Building, Radcliffe Infirmary
Oxford University
Woodstock Road
Oxford, OX2 6HE United Kingdom
Phone: +44 1865-404866
Fax: +44 1865-558817
Email: colin.baigent@ctsu.ox.ac.uk

Brendan Barrett, MD, MSc
Professor of Medicine
Nephrology
Health Sciences Centre
Division of Nephrology
Memorial University of Newfoundland
St John's, Newfoundland, A1B 3V6 Canada
Phone: (709) 777-8073
Fax: (709) 777-6995
Email: bbarrett@morgan.ucs.mun.ca

Andrew Bostom, MD
Director of Lipid Disorders Clinic
Rhode Island Hospital
593 Eddy Street / POB 242
Providence, RI 02903
Phone: (401) 444-6460
Fax: (401) 444-2217
Email: abostom@lifespan.org

Josephine P. Briggs, MD
Director, Division of Kidney, Urologic
& Hematologic Diseases
National Institute of Diabetes &
Digestive & Kidney Diseases
National Institutes of Health
31 Center Drive, MSC 2560
Bethesda, MD 20892-2560
Phone: (301) 496-6325
Fax: (301) 402-4874
Email: Briggs]@hq.niddk.nih.gov

Michael Bristow, MD, PhD
Head of Cardiology
Division of Cardiology B130
University of Colorado Health Sciences Center
4200 East 9th Avenue
Denver, CO 80262
Phone: (303) 315-4398
Fax: (303) 315-5082
Email: Michael.Bristow@UCHSC.edu

Robert M. Califf, MD
Professor
Medicine–Cardiology
Duke University
Duke Clinical Research Institute
2400 Pratt Street
Durham, NC 27705
Phone: (919) 668-8820
Fax: (919) 668-7103
Email: calif001@mc.duke.edu

David Churchill, MD
Professor of Medicine
Department of Nephrology
St. Joseph's Hospital
McMaster University
50 Charlton Ave E
Hamilton, Ontario, L8N 4A6 Canada
Phone: (905) 521-6049
Fax: (905) 521-6088
Email: churchil@mcmaster.ca

Harold I. Feldman, MD, MSCE
Associate Professor, Medicine and Epidemiology
Center for Clinical Epidemiology & Biostatistics
University of Pennsylvania
423 Guardian Drive, 923 Blockley Hall
Philadelphia, PA 19104-6021
Phone: (215) 898-0901
Fax: (215) 898-0643
Email: hfeldman@cceb.med.upenn.edu

Valentin Fuster, MD
Professor of Cardiology
Director, Cardiovascular Institute
Department of Medicine
Cardiovascular Biology Research Laboratory
Mount Sinai School of Medicine
Box 1030, One Gustave L. Levy Place
New York, NY 10029-6574
Phone: (212) 241-7911
Fax: (212) 423-9488
Email: vfuster@smtplink.mssm.edu

Charles Herzog, MD
Cardiovascular Special Studies Center
USRDS
914 S. 8th Street, Suite D-206
Minneapolis, MN 55404
Phone: (612) 347-3903
Fax: (612) 347-5878
Email: cherzog@usrds.org

Halvard Holdaas, MD, PhD
Consultant Nephrology
Department of Medicine
National Hospital
0027 Oslo, Norway
Phone: + 47 230 71 246
Fax: + 47 230 71 247
Email: hallvard.holdaas@rikshospitalet.no

Adeera Levin, MD, FRCPC
Director of Clinical Research and Education
Professor of Medicine
Nephrology
St. Paul's Hospital
University of British Columbia
1081 Burrard St, Room 6010A Providence Wing
Vancouver, BC V62 1Y8 Canada
Phone: (604) 682-2344
Fax: (604) 806-8120
Email: alevin@providencehealth.bc.ca

Phil McFarlane, MD
Department of Medicine
St. Michael's Hospital
30 Bond Street
Toronto, Ontario, M5B 1W8 Canada
Phone: (416) 867-3702
Fax: (416) 867-3709
Email: phil.mcfarlane@utoronto.ca

Marc A. Pfeffer, MD, PhD
Professor of Medicine
Cardiovascular Division
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115
Phone: (617) 732-5681
Fax: (617) 732-5291
Email: mpfeffer@rics.bwh.harvard.edu

Eberhard Ritz, MD
Professor
Division of Nephrology
Ruperto-Carola University
Bergheimerstr.56A
Heidelberg, 69115 Germany
Phone: 0049 6221 911244
Fax: 0049 6221 162426
Email: Prof.e.ritz@T-online.de

Christoph Wanner, MD
Department of Medicine
Division of Nephrology
University Hospital
Josef Schneider Strasse 2
Wuerzburg, 97080 Germany
Phone: + 49 931-201-36330
Fax: + 49 931-201-36502
Email: c.wanner@medizin.uni-wuerzburg.de

DETAILS OF TOP 20 PROPOSALS

APPENDIX II
Details of Top 20 Proposals

The research topics developed by each of the four focus groups were:

GROUP 1. CKD caused by diabetes.

1. RCT of protocol, nurse-managed, multiple risk factor intervention v. usual care in Stage 3 CKD patients with diabetes. Outcomes: CKD progression and CVD.
2. RCT of a peroxisome proliferator-activated receptor agonist (PPAR) v. placebo in Stage 3-5 CKD patients with type 2 diabetes. Outcomes: proteinuria, blood pressure, CKD progression, and CVD.
3. RCT of a protein kinase C inhibitor v. placebo (with patients in both groups receiving renin angiotensin system inhibition) in Stage 3-5 CKD patients with type 2 diabetes. Outcomes: proteinuria, blood pressure, CKD progression, and CVD.
4. RCT of iron and erythropoietin v. placebo in Stage 2-3 CKD patients with type 2 diabetes. Outcomes: retinopathy, peripheral vascular disease, proteinuria, and CKD progression.

Other proposals that did not receive enough votes to be prioritized:

a. Bariatric surgery in Stage 4-5 CKD patients with type 2 diabetes.
b. RCT of suppression of transforming growth factor-beta.
c. RCT of statins v. placebo in Stage 2-3 CKD patients with type 2.
d. RCT of statins & beta-blockade in Stage 3-5 CKD patients with type 2 diabetes.
e. RCT of vitamin E in Stage 3-5 CKD patients with type 2.
f. RCT of intensive diagnostic evaluation of coronary artery disease in CKD patients with type 2.
g. RCT of two blood pressure targets in CKD.
h. RCT of interventions to enhance adherence to therapies in CKD.
i. RCT of intensive counseling for high-risk offspring of patients with CKD and type 2 diabetes.
j. Effects of intensive insulin regimens on hypoglycemia episodes in CKD.

GROUP 2. CKD from causes other than diabetes.

1. RCT of a peroxisome proliferator-activated receptor agonist (PPAR) v. placebo in Stage 2-4 CKD patients. Outcomes: surrogates of inflammation and endothelial dysfunction, CVD and CKD progression
2. Observational study of ambulatory v. office blood pressure monitoring in CKD. Outcomes: surrogates of CVD and CKD, such as left ventricular hypertrophy and proteinuria.
3. Observational study in Stage 2-4 CKD patients to assess physician and patient barriers to the use of recommended medications.
4. RCT of spironolactone v. placebo in Stage 3-4 CKD with outcomes of both CVD and CKD.
5. Observational study of micro-inflammation and malnutrition in Stage 2-4 CKD. Outcomes: muscle mass, bicarbonate, biomarkers of inflammation, etc.

Other proposals that did not receive enough votes to be prioritized:

a. RCT of spirinolactone v. placebo in patients with heart failure and CKD.
b. RCT of coumadin v. antiplatelet agent for atrial fibrillation in stages IV and V CKD.
c. RCT (2 by 2 factorial design) of antioxidant and nitric oxide donor v. placebo.
d. Validation of different measures of kidney function.

GROUP 3. Kidney transplantation.

1. Prospective, observational study of living kidney donors, examining CVD risk factors over time and comparing the results in two-kidney, sibling controls.
2. RCT with a 2 x 3 factorial design to examine two blood pressure goals (e.g., ≤ 140 mm Hg systolic v. ≤ 125 mm Hg systolic) and compare a) a thiazide v. b) a angiotensin-converting enzyme inhibitor v. c) a dihydropyridine calcium antagonist as first line treatment. Outcome: composite CVD endpoint.
3. Prospective multicenter observational cohort study of CVD risk factors, including immunosuppressive agents, traditional and non-traditional CVD risk factors. Endpoint: composite CVD.
4. RCT at the time of evaluation for kidney transplantation comparing: a) usual management of CVD risk with b) screening with stress testing, angiography (and annual follow-up stress testing while on the waiting list) and revascularization of critical lesions. Endpoint: composite CVD after initial transplant evaluation.
5. Prospective observational study of outcomes after placement on the transplant waiting list to compare dialysis with transplantation.

Other proposals not receiving enough votes to be prioritized:

a. RCT of transplant recipients without prior CVD, comparing a) aerobic exercise with b) usual care. Endpoint: carotid internal medial thickness.
b. RCT of a peroxisome proliferator-activated receptor agonist (PPAR) v. placebo. Endpoints: post-transplant diabetes and composite CVD. RCT of usual care v. intensive risk factor management (using the Canadian multi-center randomized control trial, to determine the ability to PREVENT cardiovascular and kidney outcomes (CAN PREVENT) model.
c. Prospective observational study of young adults and children examining markers of oxidative stress and inflammation. Endpoint: endothelial function assessed by brachial artery vaso-reactivity.
d. Ancillary study to the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial to examine congestive heart failure hospitalizations and deaths.
e. RCT of vitamin E v. placebo. Primary endpoint: composite CVD. Secondary endpoints: markers of oxidative stress.
f. RCT in children of a) standard care, b) low-dose statin, and c) high-dose statin. Endpoints: markers of oxidative stress and inflammation.
g. RCT of high-risk (but no prior CVD) patients comparing a) moderate alcohol consumption in beer v. b) alcohol-free beer. Endpoint: carotid internal medial thickness after 2 years. RCT of diabetics who are C-peptide negative to pancreas transplantation v. no pancreas transplantation. Endpoint: composite CVD.

GROUP 4. Hemodialysis and peritoneal dialysis.

1. RCT of a beta blocker v. placebo. Outcomes: all-cause mortality and CVD.
2. RCT of a statin and converting enzyme inhibitor or angiotensin receptor blocker in a 2 x 2 factorial design. Outcomes: all-cause mortality and CVD deaths and events.
3. RCT of a converting enzyme inhibitor or angiotensin receptor blocker or aldosterone antagonist and two blood pressure targets in a 2 x 2 factorial design. Outcomes: all-cause mortality and CVD deaths and events.
4. RCT of coronary artery bypass grafting v. coated stents v. medical therapy. Outcomes: all-cause mortality and CVD deaths and events.
5. RCT of very high-flux hemodialysis or hemodiafiltration v. high flux hemodialysis. Outcomes: all-cause mortality and CVD deaths and events.

Other proposals not receiving enough votes to be prioritized:

a. RCT of an implantable defibrillator v. usual care. Outcomes: all-cause mortality and CVD deaths and events.
b. RCT of calcium v. non-calcium based phosphate binders. Outcomes: all-cause mortality and CVD deaths and events.
c. RCT of an anti-oxidant v. placebo. Outcomes: all-cause mortality and CVD deaths and events.

Appendix III ← ←

RESULTS OF THE PRIORITIZATION VOTES IN EACH GROUP AND OVERALL

APPENDIX III
Results of the Prioritization Votes in Each Group and Overall

Proposal[a]	Group 1	Group 2	Group 3	Group 4	Overall
Group 1: #1	3	2	3	1	1
Group 1: #2	5	3,4[b]		5	4,5[b]
Group 1: #3					
Group 1: #4			4,5,6[b]		
Group 2: #1			4,5,6[b]	4	
Group 2: #2			4,5,6[b]		
Group 2: #3					
Group 2: #4		1			
Group 2: #5		5,6[b]			
Group 3: #1	2			2	2
Group 3: #2		3,4[b]			
Group 3: #3			2		
Group 3: #4					
Group 3: #5					
Group 4: #1	1	5,6[b]			4,5[b]
Group 4: #2				3	
Group 4: #3					
Group 4: #4	4		1		3
Group 4: #5					

[a] Details of each proposal are provided in Appendix II.
[b] Proposals with more than one ranking indicate "ties."


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