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National Institute of Diabetes & Digestive & Kidney Diseases

National Heart, Lung, & Blood Institute

Workshop on Cardiovascular Disease in Chronic Kidney Disease:

Options for Intervention

MARCH 10-11, 2003

→ → Crystal Gateway Marriott
Arlington, Virginia

The burden of cardiovascular disease (CVD) among patients with kidney failure is substantial. For example, across most of the age spectrum the rates of cardiovascular mortality in patients treated by dialysis range from 10 to 100 times that of the general U.S. population. This combined with the increasing prevalence of kidney failure has resulted in CVD being a major medical concern. To address our shortcomings in available interventions and to reduce the burden of CVD in these patients the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute is sponsoring this two-day workshop.

The major goal of this workshop is to design and prioritize possible interventions to be evaluated in randomized clinical trials in patients with kidney failure and earlier stages of chronic kidney disease, including kidney transplant recipients, diabetic kidney disease, and non-diabetic kidney disease. The need for epidemiological studies to better identify risk factors will also be considered. Break-out sessions are designed to obtain broad input on study designs for clinical trials. Workshop participants will prioritize their ideas. To put these proposals into context, internationally recognized scientists will critically evaluate recent clinical trials and the latest information concerning ongoing studies will be presented. The workshop will be highlighted by state-of-the art lectures on the burden of cardiovascular disease in chronic kidney disease, atherosclerosis, and cardiomyopathy.

THE WORKSHOP PLANNING COMMITTEE

Andrew S. Levey, MD (Chairman)
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Mark Sarnak, MD
New England Medical Center
Boston, Massachusetts

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AGENDA

DAY 1 MONDAY, MARCH 10, 2003

8:00 – 8:05 AM	**Welcome**	Josephine P. Briggs *Director, Division of Kidney, Urologic and Hematologic Diseases, NIDDK;* Claude Lenfant *Director, NHLBI*
8:05 – 8:15 AM	**Purpose**	Andrew Levey
	STATE-OF-THE-ART LECTURES	Alfred Cheung *(Moderator)*
8:15 – 8:45 AM	**Cardiovascular Disease in Chronic Kidney Disease**	Eberhard Ritz
8:45 – 8:55 AM	**Discussion**	
8:55 – 9:25 AM	**Atherogenesis**	Valentin Fuster
9:25 – 9:35 AM	**Discussion**	
9:35 – 10:05 AM	**Heart Failure**	Michael Bristow
10:05 – 10:15 AM	**Discussion**	
10:15 – 10:30 AM	COFFEE BREAK	
	CRITICAL EVALUATION OF RECENT CLINICAL TRIALS	Patrick Parfrey *(Moderator)*
10:30 – 11:00 AM	**Treatment of Anemia**	Marc Pfeffer
11:00 – 11:30 AM	**Treatment of Hypertension**	Rob Califf
11:30 – 12:00 PM	**Trials to Prevent Illness in Chronic Kidney Disease**	Brendan Barrett

DAY 1 MONDAY, MARCH 10, 2003

12:00 – 12:30 PM	**Trials of Different Dialysis Doses**	David Churchill
12:30 – 1:30 PM	LUNCH PROVIDED	
	CRITICAL EVALUATION OF ONGOING CLINICAL TRIALS AND LONGITUDINAL STUDIES	Mark Sarnak *(Moderator)*
1:30 – 1:45 PM	**Chronic Renal Insufficiency Cohort Study**	Harold Feldman
1:45 – 2:00 PM	**Studies of daily/nocturnal dialysis**	Philip McFarlane
2:00 – 2:15 PM	**Cohort studies in progress at the USRDS**	Charles Herzog
2:15 – 2:30 PM	**The SHARP Trial**	Colin Baigent
2:30 –2:45 PM	**The PREVENT Trial**	Adeera Levin
2:45 – 3:00 PM	**The 4D Trial**	Christoph Wanner
3:00 – 3:15 PM	**The ALERT Trial**	Hallvard Holdaas
3:15 – 3:30 PM	**The FAVORIT Trial**	Andrew Bostom
3:30 – 3:40 PM	**Instructions to the Break-out Groups**	Bert Kasiske
3:40 – 4:00 PM	COFFEE BREAK IN BREAKOUT ROOMS	
4:00 – 6:00 PM	**BREAK-OUT SESSIONS** **Group 1: Diabetic Kidney Disease** **Group 2: Non-Diabetic Kidney Disease & Unspecified** **Group 3: Kidney Transplant** **Group 4: Dialysis**	
6:00 PM	ADJOURN	

DAY 2 TUESDAY, MARCH 11, 2003

8:00 – 10:00 AM	PRESENTATION OF CONCEPTS FROM BREAK-OUT GROUPS	Chairs, Break-out Groups
10:00 – 10:15 AM	COFFEE BREAK IN BREAKOUT ROOMS	
10:15 – 12:15 PM	PRIORITIZATION OF CONCEPTS	Chairs, Break-out Groups
12:15 – 1:15 PM	FINAL DISCUSSION OF CONCEPTS	Chairs, Break-out Groups
1:15 – 1:45 PM	WORKSHOP SUMMARY AND CONCLUDING REMARKS	Andrew Levey
1:45 PM	ADJOURN	

PROCEDURE FOR PRODUCING A PRIORITY LIST OF RESEARCH PROPOSALS

BREAKOUT SESSION 1 (MONDAY AFTERNOON/EVENING)

Groups: 1. CKD from diabetes
2. CKD from other causes
3. Hemodialysis and peritoneal dialysis
4. Transplantation

Duration: ~ 2 1/2 hours

Support: Each group will have a moderator, a secretary (who can be a participant with typing skills), a laptop computer, a flip chart, markers, post it notes, and wall space for taping the pages of the flip chart on the walls.

COLLECT IDEAS FOR PROPOSED STUDIES FROM EACH PARTICIPANT

The moderator asks each participant if he or she has an idea for a clinical trial or observational study. The participant can decline or can make a proposal in the form of a one-sentence/phrase statement. In the case of a clinical trial proposal, the statement should include the population to be studied, the intervention, and the endpoint (e.g. "randomized controlled trial of a statin in hemodialysis patients, with ischemic heart disease as the primary endpoint"). In the case of an observational study, the statement should include the basic study design, the population to be studied, and the primary endpoint (e.g. " a prospective cohort study in hemodialysis patients to examine risk factors for ischemic heart disease"). There will be no discussion at this point, so it should take only ~1 minute for each statement to be made and recorded on the flip chart. The moderator must strictly prohibit discussion and keep things moving.

After each participant has been polled, the moderator begins again with the first participant and asks for a second proposal. The participant can decline or make another proposal, as long as the proposal is different in some way from the proposals that have already been made. The moderator continues the process until no one has any new proposals to make.

PROCEDURE FOR PRODUCING A PRIORITY LIST OF RESEARCH PROPOSALS

ADD DETAILS, DISCUSS, AMEND AND/OR WITHDRAW PROPOSALS

The moderator begins with the first proposal. The person making the proposal briefly describes and defends it (~1-2 minutes). This should include statements about the significance and feasibility of the proposal. The group secretary records these statements. The proposal is then open for discussion and critique. At the end of this discussion (~5-10 minutes), the presenter can agree to withdraw the proposal, modify the proposal, merge it with another proposal, or leave the original proposal intact. The group secretary records major discussion points or criticisms.

The moderator continues down the list until all proposals have been discussed. In instances where there are 2 similar proposals, the moderator (or someone else) may suggest to the authors of these proposals that they consider merging them. Merging proposals will be in the interest of the authors and their proposals, as it will improve the chances of collecting more votes in the end.

VOTE

The remaining, modified proposals are taped to the walls around the room. Participants are each given "n" post it notes (votes) and asked to walk around the room and place one vote on each proposal that they favor (where n=the total number of proposals divided by 3 and rounded to the nearest integer). For example, if there are 10 proposals, each participant is allocated 3 votes, and if there are 20 proposals, each participant is given 7 votes. Participants cannot place more than 1 vote on any proposal.

At the end of the session, the moderator and secretary add and record the votes, and rank the proposals, accordingly. The moderator presents the top 5 proposals to the whole group the next morning. The secretary will give the moderator a diskette with the comments and discussion points for each proposal, to help the moderator organize and present these proposals the next morning.

PROCEDURE FOR PRODUCING A PRIORITY LIST OF RESEARCH PROPOSALS

PLENARY SESSION (TUESDAY MORNING)

Duration: ~2 hours

Each of the 4 section chairs is allocated 30 minutes (6 minutes for each of the 5 proposals) for presentation and discussion. The section chairs present each proposal in 1-2 minutes, briefly explaining the proposal and major discussion points that were brought up in the group (e.g. the group thought that this was a particularly strong proposal because….Major weaknesses to overcome would be….). The proposal would then be open to the whole group for questions and discussion 4-5 minutes. The original author of the proposal may wish to comment.

BREAK

BREAKOUT SESSION 2 (LATE MORNING)

Groups: Roughly equal numbers of participants from each of the first breakout session groups are randomly allocated to each of 4 new "combined" groups.

Duration: ~2 hours

Support: Each group will have a moderator, a secretary (who can be a participant with typing skills), a laptop computer, a flip chart, post it notes, and wall space for taping the pages of the flip chart on the wall.

PROCEDURE FOR PRODUCING A PRIORITY LIST OF RESEARCH PROPOSALS

DISCUSS PROPOSALS

Each of the 20 proposals will be discussed (~5 minutes for each proposal). Members of the breakout groups that originated the proposals can help lead the discussion for each proposal. The secretary records any notable discussion points regarding strengths and weakness of each proposal. Proposals cannot be modified, but amendments may be noted and subsequently presented for discussion in the final session.

VOTE

The proposals are taped to the walls around the room. Participants are each given 7 post it notes (votes) and asked to walk around the room and place one vote on any proposal that they favor. Participants cannot place more than 1 vote on any proposal.

BREAK

Votes are tabulated and an overall rank order is generated. This is done by combining the rank order in each of the 4 combined breakout groups. Specifically, each group assigns a 1, 2, 3, 4, etc. to each proposal. The mean score (for all 4 groups) for each proposal is used to assign the overall rank.

PLENARY SESSION (LATE MORNING OR EARLY AFTERNOON)

Duration: ~1 hour

The final combined rank order is presented and discussed (focusing on the 5 top "vote getters"). Final modification can be made from the floor, and approved by a vote of all present.

Speaker Abstracts ← ←

Andrew S. Levey, MD *Tufts New England Medical Center*

Chronic kidney disease (CKD) is a public health problem. 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 US Renal Data System (USRDS) *(Figure 1)*.

The primary cause of death in kidney failure is cardiovascular disease (CVD) mortality is 10-100 times greater than in the age-matched general population (NCHS) *(Figure 2)*. The high mortality rate reflects a high prevalence of CVD, as well as a high case fatality rate.

Figure 1

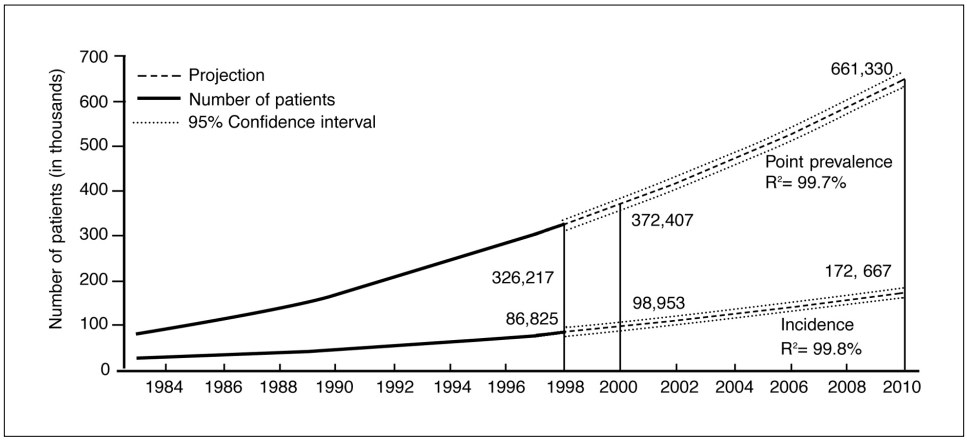
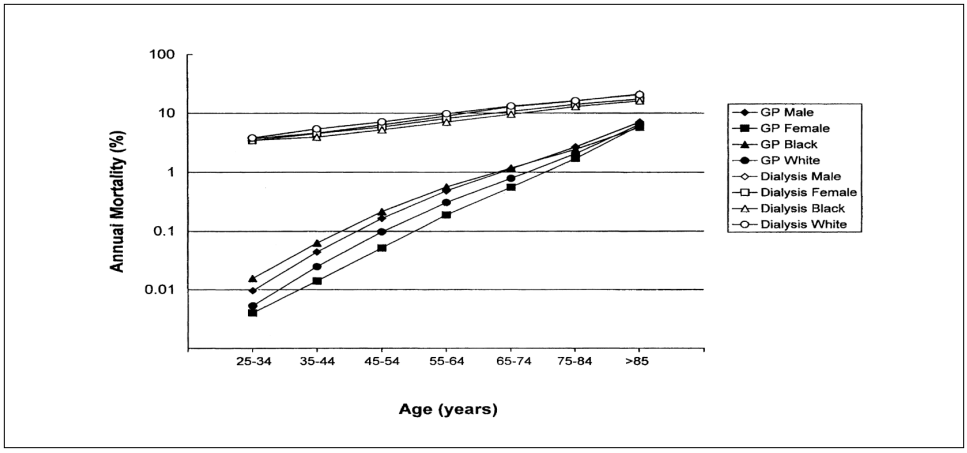


Figure 2



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 has provided an operational definition of CKD, irrespective of cause *(Table 1)*

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

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

Table 2: NKF-K/DOQI Classification, Prevalence and Action Plan for Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)	Prevalence* N (1000s)	Prevalence* %	Action**
	At increased risk	≥90 (with CKD risk factors)	–	–	Screening, CKD risk reduction
1	Kidney damage with normal or ↑ GFR	≥90	5,900	3.3	Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60–89	5,300	3.0	Estimating progression
3	Moderate ↓ GFR	30–59	7,600	4.3	Evaluating and treating complications
4	Severe ↓ GFR	15–29	400	0.2	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	300	0.1	Replacement (if uremia present)

Table 3 gives a simple classification of causes of kidney disease, which is useful in clinical practice, and in observational studies and clinical trials.

The high prevalence of CVD at the onset of kidney failure indicates that the onset of CVD occurs during or before the earlier stages of CKD. *Figures 3-4* are models of the stages progression of CKD and CVD, emphasizing the similarities in stages of disease, as well as in factors (horizontal arrows) related to susceptibility (black), initiation (dark gray), progression (light gray) and death (white).

There are several possible explanations for the increased risk of CVD in CKD *(Table 4)*.

Table 3: Classification of Chronic Kidney Disease by Diagnosis and Prevalence among Patients with Kidney Failure

Disease	Major Types (Examples*)	Prevalence **
Diabetic kidney disease	Type 1 and type 2 diabetes	33%
Nondiabetic kidney diseases	Glomerular diseases (autoimmune diseases, systemic infections, drugs, neoplasia)	19%
	Vascular diseases (hypertension, microangiopathy)	21%
	Tubulointerstitial diseases (urinary tract infection, stones, obstruction, drug toxicity)	4%
	Cystic diseases (polycystic kidney disease)	6%
Diseases in the transplant	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.

Figure 3

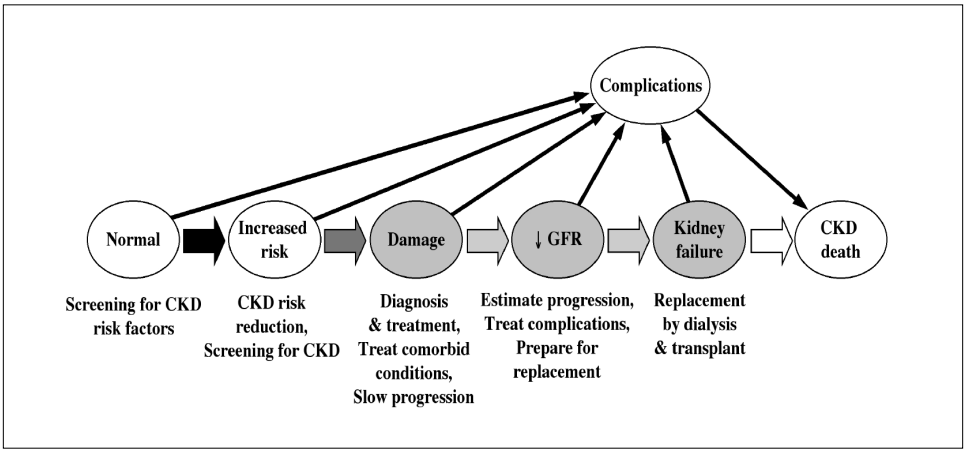


Figure 4

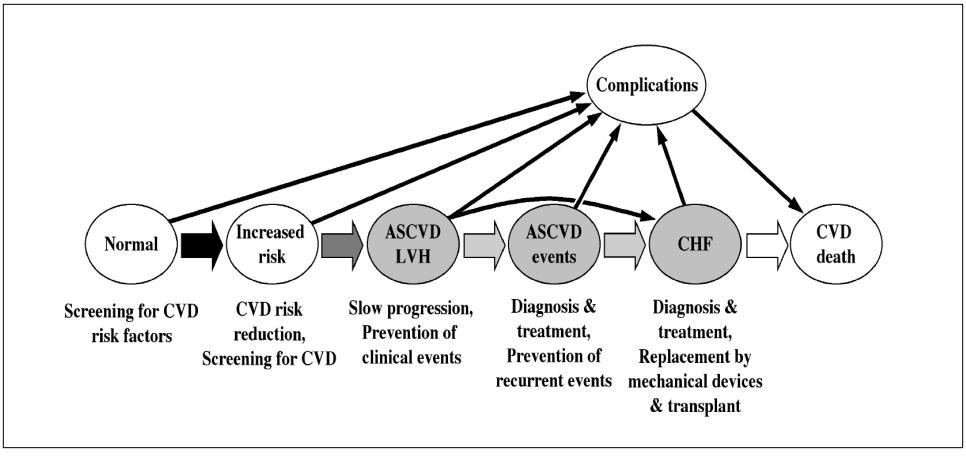


Table 4: Possible Explanations for the Increased Risk of CVD in CKD

Increased prevalence of CVD risk factors • Shared risk factors for development of CKD and CVD • CVD causes CKD (atherosclerosis, heart failure) • CKD causes CVD risk factor levels to rise
CKD is an independent risk factor for CVD • Proteinuria • Decreased GFR

Goal for this Workshop is to identify and prioritize possible interventions for CVD in CKD

1. Randomized clinical trials
2. Observational studies

Formats

1. Break-out sessions (kidney failure, kidney transplant recipients, diabetic kidney disease, non-diabetic kidney disease).
2. State-of-the-art lectures
3. Critical evaluation of evaluate recent clinical trials
4. Updates on ongoing studies

References

1. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske RL, Klag MJ, Maillous LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NL, Wilson PWF, Wright JT. Controlling the Epidemic of Cardiovascular Disease in Chronic Renal Disease: What Do We Know? What Do We Need to Learn? Where Do We Go From Here? American Journal of Kidney Diseases 1998; 32: 853-906.
2. Levey AS (guest editor). Controlling the Epidemic of Cardiovascular Disease in Chronic Renal Disease: What Do We Know? What Do We Need to Learn? Where Do We Go From Here? Special Report from the National Kidney Foundation Task Force on Cardiovascular Disease. American Journal of Kidney Diseases 1998; 32 (Suppl 3): S1-S199.
3, Levey AS (Work Group Chair). National Kidney Foundation. K/DOQI Clinical Practice guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39: S1-S266, 2002 (suppl 1).

Eberhard Ritz

Ruperto Carola University
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Because of the frequency of cardiovascular death in renal patients, the issue of CV disease has recently attracted considerable interest. Novel perspectives are available in 3 areas:

1. the recognition of excessive frequency of CV events and higher letality of cardiac ischemic event in patients with even minor renal dysfunction
2. progress in the understanding of cardiac risk, particularly of non-classical risk factors and cardiac dysfunction unrelated to CHD in patients, in endstage renal disease and
3. the recognition of excess sympathetic activity and its implications on blood pressure as well as cardiac arrhythmia.

The Framingham study and subsequent epidemiological investigations defined a number of risk factors predicting CV events, but it has only recently been recognised that renal dysfunction (either borderline decrease of estimated Ccr or microalbuminuria) is a powerful predictor of cardiovascular risk as well. This is true in the general population (JASN 2002; 13: 745; KI 2002; 61: 1486) and as in populations at high risk of atherosclerosis (Annals Int Med 2001; 134: 629; JASN 2001; 12: 218), particularly in diabetic patients, and the same has also been found in patients with heart failure and acute coronary syndromes (Circulation 2000; 102: 203; Circulation 2002; 106: 974; JACC 2000; 36: 679; KI 2003; 63: 696). From a public heath point of view it is important that the same elevation of CV risk with minor renal dysfunction applies to the large population of hypertensive individuals (Hypertension 1989; 123: I80; JASN 2001 12: 218; Arch Int Med 2001; 161: 688; AJKD 1993; 21: 31).

In patients with cardiac ischemic events, it has been clearly documented that the letality of acute MI was increased in patients with even minor renal dysfunction and increases progressively with more advanced renal dysfunction (Ann Int Med 2002; 137: 555; Ann Int Med 2002; 137: 563). Although this is in part caused by less aggressive intervention, there is almost certainly also a biological explanation. This is suggested by recent unpublished observations that under standard conditions the region of total myocardial infarction is greater in standard models of MI in subtotally nephrectomised rats. Furthermore, in a paper in press (JASN) we could show that in apo E knock out mice aortic staining for nitrotyrosine is increased (as an index of peroxinitrite formation) and the growth of atherosclerotic plaques accelerated even in animals which are only uninephrectomised.

There is good evidence that sympathetic activity is increased in renal disease and this was shown both in experimental studies (Hypertension 1995; 25: 878) and in clinical observations (NEJM 1992; 327: 1912). Increased sympathetic activity has recently been documented even in renal patients with normal GFR (JASN 2001; 12: 2427). In renal failure sympathetic overactivity contributes to hypertension (Hypertension 1995; 25: 878), progression of renal failure (KI 2001; 60: 1309) and presumably also arrhythmia. It had been argued sometime ago (NDT 1997; 12: 2497) that betablockers should be used aggressively based amongst others on the observation (Diabetologia 1993; 36: 1113) that use of betablockers was more frequent in surviving diabetic patients on

HD than in patients succumbing to CV death. Only limited further observational evidence is available, but it indicates a beneficial effect of betablockade on survival (DOPPS study) and prediction of survival by norepinephrin concentration (Circulation 2002; 105: 1354). Interventional controlled trials show improved cardiac function in HD patients with CHF on betablockade (JACC 12001; 37: 407).

In endstage renal failure it has been recognised that apart from the obvious and well known CV risk factors, non-classical risk factors, particularly anemia and hyperphosphatemia, are relevant as well. Hyperphosphatemia aggravates hyperparathyroidism and accelerates vascular calcification, but it would be wrong to attribute the increased CV risk exclusively to these factors. Our recent experimental studies show that high dietary phosphate aggravates cardiac fibrosis and arterial wall thickening in subtotally nephrectomised rats (in press).

It is striking that the cardiac risk is much higher in patients with systolic dysfunction (pump failure) than in patients with ischemic heart disease. The issue why the heart fails has not been very well explored. Past (J Clin Invest 1993; 92: 2934) and more recent studies (JASN 2003; 14: 90) documented instability of energy-rich nucleotides and abnormal cycling of intracelluular Ca^{++} in cardiomyocytes. An important observation may be the recent demonstration of cardiomyocyte drop out (in press), presumably in uremic animals as a result of apoptosis. Clarification of the mechanisms leading to heart failure, presumably going beyond IHD, are of high priority.

Much recent progress has been made concerning interventions. Coronary angioplasty, coronary artery stenting and coronary artery bypass surgery have been retrospectively compared (Circulation 2002; 106: 2207; JASN 2002; 13: 55a) and, cutting a long story short, show that CABG has higher short-term mortality, but in the long run yields somewhat better survival, at least if IMA grafts are used.

What are the highest investigational priorities? The DIGAMI study clearly documented a dramatic improvement of survival of diabetic patients with acute coronary syndromes, if normoglycemia was maintained by administration of glucose + insulin (Circulation 1999; 99: 2626). The underlying abnormality in diabetes is presumably diminished glucose uptake by cardiomyoctes; when under ischemic conditions ATP has to be generated by glycolysis rather than by mitochondrial oxidation, more glucose substrate is required and such uptake is limited because of reduced expression of glut-4 transporter. The same abnormality was found in the heart of uremic animals. Because insulin resistance occurs very early in renal disease (KI 1998; 53: 1343; JASN 2003; 14: 469) it would be logical, although unproven, that the DIGAMI protocol might be useful in uremic patients as well.

The second most urgent consideration would be to provide controlled prospective evidence for the postulate (NDT 1997; 12: 2497) to administer betablockers to abrogate the deadly combination of increased sympathetic nerve activity and increased catecholamine responsiveness as a result of patchy cardiac denervation from polyneuropathy denervation suprasensitivity (with upregulation of catecholamine receptors).

RENAL FUNCTION AND RISK FOR CV EVENTS

Marc A. Pfeffer, MD, PhD *Brigham and Women's Hospital*

Dialysis patients have a multifold increased risk of cardiovascular deaths and other nonfatal events that cannot be accounted for by standard cardiovascular risk factors. It is also apparent that the risk of death after an MI is greatly increased in the end-stage renal disease population. Emerging data has indicated that less severe impairments of renal function are also associated with heightened cardiovascular risks out of proportion to co-morbidity and conventional cardiovascular risk factors.

This presentation will focus on chronic kidney disease non-dialysis patients and cardiovascular risks. Data from the Survival and Ventricular Enlargement (SAVE) trial will be presented with the population stratified by baseline GFR. Increased risk for death, recurrent MI, heart failure and the combination of CV mortality and morbidity in the impaired GFR group will be illustrated along with the benefits of randomization to an ACE inhibitor in both the preserved and depressed renal function groups.

TRIALS TO PREVENT ILLNESS IN CHRONIC KIDNEY DISEASE

Brendan Barrett *Memorial University of Newfoundland*

Objectives

This presentation will critically appraise evidence of the impact of therapies on cardiovascular outcomes in people with chronic kidney disease (CKD) from trials in recent years. The impact of anemia management and blood pressure control per se will be considered in other presentations.

General Limitations in the Evidence Base

Few large clinical trials aimed at treating or preventing cardiovascular disease in general include large numbers of people with CKD, particularly of advanced degree (e.g. BHS-HPS, HOPE, ALLHAT, HOT, SYST-EUR). Therefore conclusions about the impact of the therapies studied for those with CKD are based on analyses, sometimes post-hoc, of small subgroups. Cardiovascular end-points have been included in some trials specifically in CKD populations, but they have generally been secondary outcome measures as the trials were focused largely on impacting the progression of the underlying kidney disease (E.g. RENAAL, IDNT, AASK). As a result, these latter trials also tended to include people selected for their higher risk of kidney disease progression and to exclude those at higher risk of competing cardiovascular events. The power of these trials in relation to CV outcomes is therefore limited.

Pathogenetic Considerations Relevant to Interpreting Existing Trial Data

Current understanding of the pathogenesis of CV disease in CKD suggests a variety of therapies that might be relevant for trials in populations with CKD. It is relevant to note that the pathogenesis of CV disease in CKD is complex and multifactorial. Some pathogenetic factors may vary in their impact at different stages of CKD. Many people with CKD have concomitant cardiovascular disease. In the general population, particularly with lesser degrees of reduction in GFR, there may be a higher burden of atherosclerotic cardiovascular disease. Treatments known to have positive impact on such processes, such as lipid lowering, may be expected to have similar impacts in those with concomitant early stage CKD. However, those with more advanced CKD may also be more heavily exposed to the variety of "uremia-related" pathogenetic factors that include, but are not limited to, anemia, disorders of mineral metabolism and parathyroid function, elevations of homocysteine levels, and progressive alterations of molecules and tissues as a result of oxidation and inflammatory processes. These emerging pathogenetic processes interact with therapy induced CV stresses, such as increased cardiac output related to AV fistulae. All of these latter factors promote the development of forms of CV disease somewhat dissimilar to those seen in populations without CKD. The vascular wall remodelling and cardiomyopathy seen in advanced CKD contribute to the high burden of heart failure in this population.

The implications of all this are that therapies shown to reduce the impact of atherothrombotic disease may or may not have the same relative benefit in populations with advanced kidney disease, and by contrast other therapeutic approaches, such as those aimed at mineral metabolism, may become more important as GFR declines. Existing trial data are insufficient to fully assess the relevance of the above considerations.

Lipid Lowering Therapy

Various lipid profile abnormalities have been associated with worsening of kidney function in CKD. No adequate treatment trials have been completed to indicate that this risk can be modified. A post-hoc subgroup analysis of the CARE trial indicated that pravastatin therapy was effective and safe for the secondary prevention of cardiovascular events in those with calculated GFR < 75 ml/min. People with serum creatinine levels of > 200 μmol/L (2.2 mg%) were excluded from the MRC/BHF Heart Protection Study of simvastatin for people with vascular disease or diabetes. However, in a sub-group analysis, men with creatinine values ≥ 130 μmol/L and women with values ≥ 110 μmol/L at baseline had at least as great a reduction in the risk of a first major vascular event with simvastatin as those with lower levels of creatinine. In fact the absolute rate of such events was 39.2% with placebo and 28.2% with simvastatin over 5 years in those with elevated creatinine levels. There are very limited data to guide use of lipid lowering therapy in people with CKD, but without manifest coronary heart disease. The SHARP study, to be discussed separately by Dr. Baigent, addresses this issue. Current guidelines for care of CKD patients extrapolate from the lipid levels used to initiate and target therapy in non-CKD populations. It is not known whether the pleiotropic anti-inflammatory effects of statins would have beneficial clinical effects in CKD independent of any lipid lowering effects.

Renin-Angiotensin System Interruption

Interruption of the renin-angiotensin system by either ACE inhibitors or angiotensin AT_1 receptor blockers has been shown to delay the progression of diabetic and non-diabetic kidney diseases in a number of randomized trials. Whether use of these agents specifically reduces the incidence of cardiovascular events in those with CKD has been less thoroughly established.

The HOPE investigators randomized patients at high risk of cardiovascular events to ramipril or placebo. Results of the trial were in favour of ramipril, with some debate about the mechanism of benefit, given a slight difference in blood pressure between the groups. A sub-group analysis of 980 patients with baseline serum creatinine in the range 124 to 199 μmol/L was reported. The absolute rate of events in this subgroup was higher than in those with lower creatinine concentrations (adjusted hazard ratio 1.4), but the relative risk reduction (0.8) with ramipril was independent of baseline serum creatinine category for the primary composite of cardiovascular death, myocardial infarction and stroke. Similarly among those with higher creatinine, cardiovascular death (6.6% versus 11.4%) and total mortality (10.6% versus 17.8%) were less frequent in the ramipril group.

The AASK trial randomized African-Americans with presumed hypertensive nephrosclerosis to one of two blood pressure goals and to metoprolol, amlodipine or ramipril based therapy. The amlodipine arm was stopped about one year early based on an unfavourable comparison to ramipril or metoprolol in terms of GFR decline in proteinuric subjects. The 1094 subjects were not diabetic or suffering heart failure at trial entry, however about 50% gave a history of some prior heart disease. Over the 4 years or so of follow-up, there were no statistically significant differences between the BP target, or drug type groups with respect to overall mortality, cardiovascular mortality, or the composite of first hospitalization for a cardiovascular event or CV death.

The angiotensin receptor blockers losartan (RENAAL) and irbesartan (IDNT) have both been compared to placebo and irbesartan to amlodipine in patients with Type 2 diabetes and advanced diabetic nephropathy. These trials were intended to primarily examine renoprotective effects, but cardiovascular events were studied as secondary outcomes. Patients with recently (3-6 months) unstable cardiovascular disease were excluded by design, as was concomitant therapy with ACE inhibitors. Blood pressure was treated to target in each trial group using other drugs and interventions permitted by the protocols. With fewer than 600 patients per arm, less than 30% of subjects with a prior history of cardiovascular disease at baseline, and a mean follow-up of about 2.5 years, the irbesartan trial did not have high power to detect differences in cardiovascular outcomes. There was no statistically significant difference between the irbesartan, amlodipine and placebo groups with regard to the composite of cardiovascular death, MI, CVA, leg amputation or hospitalization for heart failure. The trend was to about a 10% relative risk reduction with either active agent against placebo. Similarly the losartan trial had about 750 patients per group, probably less than 20% with prior cardiovascular disease at baseline and a mean follow-up time of 3.4 years. The composite of cardiovascular death, MI, CVA, leg amputation, revascularization, or hospitalization for heart failure or unstable angina occurred in 32.9% assigned to losartan versus 35.2% assigned to placebo (p=0.26). Further sub-analysis of both trials suggested a lower frequency of first hospitalization for heart failure with losartan and irbesartan compared to placebo, while amlodipine had a lower observed frequency of non-fatal MI than placebo.

Treatment Affecting Calcium, Phosphate or PTH

Epidemiologic data from cross-sectional, retrospective and some historical prospective cohort studies link elevated levels of serum calcium, phosphorus and calcium x phosphate product with vascular calcification and death. Limited data from small prospective studies associate higher cumulative prescribed oral calcium intake with vascular calcification. In a recently reported clinical trial comparing sevelamer with calcium-based phosphate binders in hemodialysis patients, the incidence of hypercalcemia and progression of vascular calcification was greater with calcium-based phosphate binders. Currently there is at best suggestive evidence that an impact on vascular calcification progression might provide clinical benefit. There are no trials to date indicating that specific management strategies for mineral and parathyroid metabolism change the incidence of clinical cardiovascular events or death.

Anti-Platelet Therapy

Anti-platelet therapy (largely aspirin) has been shown to reduce the incidence of cardiovascular events in high-risk populations by about 25%. Few studies have been carried out specifically in those with CKD. A recently reported meta-analysis of randomized trials up to 1997 demonstrated a 41% reduction in the odds of a cardiovascular event with the use of anti-platelet therapy in hemodialysis patients. The trials analyzed were largely short-term and the risk of major bleeding could not be reliably determined.

Anti-Oxidant Therapy

A randomized double-blind trial has been reported comparing 800 IU Vitamin E daily to placebo in 196 hemodialysis patients with existing cardiovascular disease (specifically not including heart failure) over a median follow-up of less than 2 years. The active treatment group had a statistically significant reduction (18.6% v. 34.3%) in the composite of fatal or non-fatal MI, ischemic CVA, new peripheral disease and unstable angina. Most of this was due to a difference in MI rates. This trial requires replication as most large trials with Vitamin E in non-CKD populations have failed to demonstrate reduction in cardiovascular events.

Therapy Aimed at Homocysteine Lowering

Epidemiologic data link the level of homocysteine in blood to cardiovascular risk. Renal failure is associated with increasing levels of this aminoacid and patients on dialysis can have substantially increased plasma concentrations. Many studies have used folic acid, pyridoxine, vitamin B_{12} alone, or in combination, at a variety of doses in an effort to reduce homocysteine levels in patients with CKD. To date no trial has been reported addressing whether these therapies can reduce adverse cardiovascular events. Even if such a trial were positive, caution would be needed about the mechanism of benefit, as these vitamin therapies have been shown to simultaneously affect the levels of homocysteine, fibrinogen and Lp_a, all of which have been linked to cardiovascular disease.

Effect of Arterio-Venous Fistula Closure

The degree to which AV access contributes to the long term cardiovascular outcomes in dialysis populations generally is not known at this time. There are no comparative trials of arterio-venous versus other access for hemodialysis and data are lacking to clearly identify those who might be better not having an AV access created. Case reports exist of improvement in heart failure after closure of fistulae. Studies in pre-dialysis patients before and after creation of a fistula have shown changes in ventricular performance within 3 months. Prospective studies in patients undergoing AV fistula closure after successful transplantation documented a reduction of LV diastolic diameter and calculated mass by 3 to 10 weeks after closure.

Conclusions

There is an acute need for good quality trials of therapies aimed at reducing cardiovascular disease in CKD. Extrapolation from evidence in non-CKD populations could overestimate the net benefit of therapies aimed at traditional atherothrombotic events. Therapies aimed at uremia related cardiovascular risk factors are also needed.

TRIALS OF DIFFERENT DIALYSIS DOSES ADEMEX AND HEMO; IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH DIRECTIONS

David N. Churchill *St. Joseph's Hospital McMaster University*

Objectives

1. to review recent randomized controlled trials addressing adequacy of dialysis;
2. to evaluate their validity;
3. to compare and contrast the findings and
4. to consider the clinical and research implications of the results.

The ADEMEX study (JASN 2002) evaluated adequacy of dialysis in 965 Mexican CAPD patients randomly allocated to conventional treatment with 4 two liter exchanges daily to one in which the volume and frequency of exchanges were adjusted to achieve a target peritoneal creatinine clearance (Ccr > 60 L/wk/1.73 m^2). The mean residual GFR was < 1.0 ml/min. The mean achieved total Ccr was 54.1 L and 62.9 L for the control and intervention groups respectively. The corresponding Kt/V values were 1.80 and 2.27. The intention to treat analysis demonstrated no survival differences between groups over a 28 month follow-up.

The HEMO study (NEJM 2002) used a factorial design to simultaneously evaluate the effect of increased urea clearance and high flux dialysis membranes on all-cause mortality in 1846 prevalent hemodialysis patients in the USA. The high urea clearance group had a target equilibrated Kt/V of 1.45 compared to 1.05 for the standard clearance group. The high flux group had a beta-2-microglobulin clearance > 20 ml/min and a UF coefficient >14. There was no difference in all-cause mortality between the high and standard Kt/V groups nor between the high and low flux groups during a mean follow-up of 2.84 years.

The internal validity of ADEMEX is threatened by the inclusion of prevalent patients (58%) who probably have a disproportionately increased prevalence of low and low average peritoneal membrane transporters. These patients are expected to have better outcomes than those with high and high average transport. Although the HEMO study subjects are prevalent, the survivor cohort is less likely biased to the same degree as ADEMEX.

The external validity of ADEMEX is diminished by the exclusion of patients with heart disease and by the low body weight compared to North American populations. The external validity of the HEMO study may be threatened by the high proportion of African-Americans (62.3%) and by the exclusion of patients with greater body weight. The relatively short dialysis times (190- 219 min) may limit generalizability to other countries.

The similarities between the studies are the use of the RCT design and that neither showed a difference in all-cause mortality between control and intervention groups. However, in sub-group analysis, both show increased cardiovascular disease in the control group. In the ADEMEX study, there was a statistically significant increase in death due to congestive heart failure in the low Kt/V group. In the HEMO study, there was a trend to increased cardiac death in those treated with low flux.

The differences between the studies are that ADEMEX study compared current KDOQI guidelines for weekly Ccr and Kt/V to lower targets while HEMO compared existing guidelines to higher targets. ADEMEX used conventional glucose based dialysate in CAPD while HEMO used bicarbonate dialysate and 50% received dialysis with high flux membranes.

The research implications of the ADEMEX study include the need to study more physiologic solutions at defined and controlled levels of adequacy and with greater attention paid to fluid balance, blood pressure and nutrition. The research implications of the HEMO study include the need to focus on different dialysis schedules (frequency and length) and on early treatment of cardiovascular risk factors and disease. The clinical implications will be dependent on the perceived validity of these studies.

THE CHRONIC RENAL INSUFFICIENCY COHORT STUDY

Harold Feldman *University of Pennsylvania*

The Chronic Renal Insufficiency Cohort Study is a national longitudinal study of renal insufficiency and cardiovascular disease.
The aims of CRIC are to establish the necessary infrastructure:

- To evaluate the patterns of progression of CRI and CVD
- To evaluate why some but not all individuals progress to ESRD
- To evaluate why CVD is accelerated in CRI
- To develop predictive models of progressive CRI and CVD
- To evaluate the resources consumed in caring for individuals with CRI
- To identify potential prevention strategies

The Study Addresses Five Broad Hypotheses

1. A set of non-traditional risk factors is associated with both progression of CRI and the development of ESRD.
2. A set of non traditional risk factors is associated with CVD events and measures of CVD progression in the setting of CRI
3. The risk factors for CRI progression and CVD in the setting of CRI vary by demographic characteristics (age/gender, race/ethnicity) and diabetes status
4. The morbidity and complications associated with CRI and its progression diminish global and disease specific quality of life, impair functional status, and increase health resource utilization.
5. Progression of CRI as estimated by serum creatinine. And currently available serum creatinine based formulae may yield biased estimates of the rate of progression of CRI

Research Methods

A prospective cohort study of 3000 patients recruited from 7 Clinical Centers nationwide will be followed for up to 6 years. The CRIC study population will include a racially and ethnically diverse group of adult patients with mild to moderate CRI, approximately half of whom have diabetes. The entry age range will be 21-74 years and the upper limit of acceptable estimated GFR at entry will vary by age.

Study data will include a broad array of information on sociodemographic, comorbidity, treatment, anthropometric, psychosocial, diet, body composition, quality of life, health care resource utilization, biochemical measures, and cardiovascular disease (including electrocardiography, echocardiography, ankle-brachial indices, and coronary calcification). A subcohort of one-third of study participants will have serial iothalamate clearance studies during follow-up to measure GFR. Patients will be contacted every 6 months including yearly visits for ascertainment of new cardiovascular events, evaluation of progression of renal and cardiovascular disease, and collection of other study data. Blood and urine specimens also will be obtained for storage and later analysis.

Primary outcomes focus on progression of renal disease as measured by progressive reductions in GFR and increases in the level of proteinuria, as well as the occurrence of clinically relevant declines in renal function. Primary outcomes regarding CVD will be clinical events indicative of ischemic vascular disease and progression of subclinical cardiovascular disease.

Summary

The CRIC study is designed to identify risk factors for CRI and CVD events among patients with varying severity of CRI and to develop predictive models that will identify high-risk subgroups with CRI. Improved recognition of etiological factors will permit development of future clinical trials designed to test strategies to reduce the burden of advanced renal failure.

HOME NOCTURNAL HEMODIALYSIS: THE GREAT CARDIOVASCULAR EQUALIZER

Phil McFarlane *University of Toronto*

The development of kidney failure is a potentially devastating event, reducing both quality and length of life. Much of this excess morbidity and mortality is related to cardiovascular disease, as 80% of deaths on dialysis are related to cardiovascular events. Dialysis patients younger than 40 face an annual cardiovascular mortality that is increased ten fold compared to the healthy population. This risk is twenty times higher in older dialysis patients. Broad ranges of factors contribute to this increased cardiovascular risk. In a dialysis population left ventricular hypertrophy is present in 75% of patients. Other associated cardiac abnormalities include left ventricular dilatation, arterial calcification, stiffening of the major arteries, and atherosclerotic coronary artery disease. Biochemical abnormalities such as elevated calcium-phosphate products, glycemic and lipid abnormalities, and hyperhomocysteinemia may also contribute. In new dialysis patients, one third have heart failure, one quarter have angina and there is a history of myocardial infarction in 10%. Clinicians have looked for a "great equalizer"; an intervention capable of reducing cardiovascular risk close to the range seen in individuals free of renal disease.

Dialysis dose has been suggested as a good candidate for broadly reducing cardiovascular events. Many epidemiologic studies have related delivered dialysis dose with cardiovascular events and mortality. However, the HEMO study clearly demonstrated that a moderate increase of dialysis dose fails to improve patient outcomes. When even higher doses of dialysis have been studied the results are more encouraging. The Tassan group in France have demonstrated superior blood pressure control and better than expected patient survival in those receiving dialysis for eight hours thrice weekly. This has led to a hope that even more intensive dialysis will improve outcomes further.

Home nocturnal hemodialysis (HNHD) was developed in Toronto, Canada in 1993, combining home treatments delivered in high frequency (five to seven nights a week), and long duration (six to ten hours). Studies now being reported demonstrate that markers of cardiovascular disease are improving with this therapy. It has been shown that conversion from conventional dialysis to HNHD leads to normalization of blood pressure without the need for antihypertensives, improvements in (and in many cases normalization of) left ventricular hypertrophy, reduced peripheral vascular disease, and improvements in ejection fraction in those patients with pre-existing congestive heart failure. Patient survival in those performing HNHD in Toronto has been better than expected. However, studies directly demonstrating that conversion to HNHD leads to fewer cardiovascular events or better long-term survival have yet to be performed.

Studies in this population suffer from several practical and methodologic barriers. Home hemodialysis accounts for approximately 1% of the dialysis population, with HNHD representing a fraction of these patients. It has been estimated that less than 300 patients are performing this modality worldwide. Many of the studies reported to date represent resampling of the same small population, and hard endpoint trials in this small population will likely require lengthy follow-up. Strong selection biases are present in these trials. The Toronto group of HNHD patients are on average younger, less likely to have diabetes, and have been on dialysis longer than seen typically. Attempts can be made to select appropriate controls and adjust for baseline demographics and comorbidities, but there are unmeasurable factors that lead to a person performing home dialysis rather than a hospital-based modality. Currently funding for home hemodialysis in the United States and Canada is less than the cost of HNHD, making it impossible for most programs to offer HNHD and restricting the availability in those programs that do offer this modality. This restricts the opportunity to recruit for future trials, as well as the ability to confirm published results, increasing the likelihood of centre-effect bias. In the short-term, overcoming these issues will require close coordination of research efforts between the programs that offer HNHD.

Looking to the future, most centres performing HNHD are currently collecting a broad range of tests profiling cardiovascular risk factors and disease in both incident and prevalent patients. These will advance the understanding of the progression of cardiovascular disease over time in these patients, and in some cases will allow an understanding of the changes seen in those converted to HNHD from other forms of dialysis. Some mechanistic studies are also underway. Unfortunately, large scale, hard endpoint studies have yet to be initiated.

THE CARDIOVASCULAR SPECIAL STUDIES CENTER (CVSSC) OF THE UNITED STATES RENAL DATA SYSTEM (USRDS): PROJECTS USING EXISTING USRDS DATA

Charles A. Herzog *USRDS*

The CVSSC of USRDS was created by NIDDK to perform research on cardiovascular disease in ESRD patients using the USRDS database (and to create special studies incorporating new data). CVSSC studies using existing USRDS data have included studies on comparative survival of coronary revascularization with PTCA, Coronary stents, and coronary artery bypass surgery in dialysis patients (Circulation 2002), cardiac valvular surgery (mechanical versus bioprosthetic valve outcome) in dialysis patients (Circulation 2002), cardiovascular disease in pediatric ESRD patients (Kidney International 2002), blood pressure and survival of dialysis patients (Kidney International 2002), the impact of smoking on survival of dialysis patients (Kidney International, in press), and outcome of coronary revascularization in renal transplant recipients (submitted). Recent preliminary projects have included survival studies on bacterial endocarditis in dialysis patients, CHF in dialysis patients and renal transplant recipients, stroke and atrial fibrillation in dialysis patients, temporal trends in cardiovascular disease in dialysis patients, and cardiac arrest ESRD patients and the general Medicare population.

Oberservational studies by the CVSSC using existing USRDS (and general Medicare) data should be useful in the formulation of clinical hypotheses and design of clinical trials.

CLINICAL CHARACTERISTICS OF DIALYSIS PATIENTS HOSPITALIZED WITH ACUTE MYOCARDIAL INFARCTION (AMI) IN THE UNITED STATES: A COLLABORATIVE NIDDK/NRMI STUDY (USRDS CVSSC SPECIAL STUDY)

Charles A. Herzog *USRDS*

Background

Dialysis patients with AMI suffer dismal long-term survival, with a two-year mortality of 73% (Herzog et al, NEJM, 1998). This outcome has not changed in the "era of reperfusion". We speculate that this partly reflects under-utilization of effective therapies and delayed diagnosis of AMI due to "atypical" clinical presentations.

Purpose

To Identify the Clinical Characteristics of Dialysis Patients Hospitalized with AMI in the United States, Treatment, and Impact of Clinical Variables on Outcome.

Study Design Retrospective cohort

Dialysis patients hospitalized 4/98-6/2000 identified from USRDS database and matched to NRMI 3 (National Registry of Myocardial Infarction) registry database (HIPAA rules prevented use of NRMI 4 registry). A geographically balanced (by state) randomly drawn subset (reflecting the overall distribution of dialysis patients with AMI nationally in the USRDS database) of patients (n=2000) will be studied. A unique dataset will be created for each patient comprising: 1. Pre-hospitalization dialysis facility data obtained by chart abstraction (medical history, dialysis characteristics, lab tests, prescription drugs); 2. NRMI 3 data; and 3. Post-hospitalization events from USRDS database.

STUDY OF HEART AND RENAL PROTECTION (SHARP)

Colin Baigent *Oxford University*

Among patients with pre-existing coronary heart disease (CHD), large-scale randomized trials have demonstrated that lowering LDL-cholesterol concentration by about 1 mmol/l (40mg/dl) for 4-5 years reduces the risk of coronary events and strokes by about 25%. However, it remains uncertain whether patients with CKD but no known CHD would derive net benefit from cholesterol-lowering treatment: vasculopathic changes distinct from atherosclerosis (including cardiomyopathy, arterial stiffness, and calcification) are highly prevalent in CKD patients, and their aetiology may not be related to blood cholesterol; observational studies among dialysis patients have consistently failed to demonstrate a positive relation between blood total cholesterol and mortality; and, as patients with CKD have been systematically excluded from previous trials, the long-term safety of cholesterol reduction among patients with CKD is unknown.

The Study of Heart and Renal Protection (SHARP) aims to assess the effects of cholesterol-lowering therapy with a combination of simvastatin and the cholesterol-absorption inhibitor ezetimibe among around 9,000 patients with CKD but no CHD. Such large-scale recruitment will allow reliable assessment of effects of lowering blood LDL-cholesterol on the risk of major vascular events and on the rate of loss of renal function in patients with various degrees of renal impairment.

CAN- CARE AND CAN- PREVENT: CANADIAN STUDIES IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Adeera Levin, MD, FRCPC *University of British Columbia, Canada*

There are a paucity of well designed observational and prospective trials that accurately characterize the population referred to nephrologists, the treatment strategies and outcomes of those patients, and which test different health care delivery systems in a rigorous manner. The 2 Canadian studies described here attempt to address these important outcome and health care delivery questions, while ensuring appropriate and extensive data which may be used to improve understanding of kidney disease and CVD disease progression.

These 2 studies are designed to examine specific questions in the Chronic Kidney Disease population. Both are Canadian multi-center studies but they examine different populations (referrd and un referred) and have different study designs(prospective observational and randomized control trial).

CAN CARE is a prospective observational study. This **Can**adian Study of **Care** prior to dialysis examines a cohort of 500 patients referred to Canadian nephrologists between 2000 and 2003, with 3 key objectives The first objective is to describe the cardiovascular morbidity/risk factors and level of kidney function at which patients are being referred to nephrologists in the current era. The second key objective is describe the change over time in parameters and treatments known to impact on CVD and CKD outcomes after exposure to nephrology care: namely, blood pressure control, use of drugs that interrupt the rennin angiotensin system, reduction in proteinuria, treatment of anemia and correction of metabolic abnormalities including calcium, phosphate, hyperparathyroidism, and acidosis. The 3rd objective is to describe the elements of care to which patients are exposed such as multidisciplinary interventions, formalized protocols for evaluation or care, and educational programs. Elements of care are classified and categorized into formal and informal, and patients followed for up to 4 years. The goal is to demonstrate that there is an improvement in factors known to be associated with adverse outcomes after referral to nephrology, and to determine which specific elements of care leads to improved outcomes in general, irrespective of referral to nephrology teams. Baseline data collected thus far reveal a high prevalence of CVD in patients referred to nephrologists, and baseline GFR < 30 ml/ min/ 1.73 m^2, representing stage 4 CKD.

CAN PREVENT is a **Can**adian multi-centre randomized control trial, to determine the ability to **PREVENT** cardiovascular and kidney outcomes, in a cohort of patients identified early in the course of CKD. The study examines the impact of protocol driven care, managed by a nurse and supervised by a nephrologist, versus standard care, in a cohort of patients identified as having kidney disease through a laboratory finding technique. This study compliments the CAN CARE study in that it focuses on a cohort of patients with early CKD, who may not have been referred to a nephrologist, and determines if intensive intervention at early stages of CKD (estimated using equations(stage 2-4)), impacts on CVD and/or CKD outcomes. Sample size calculations for this study, using a combined end point of CVD events or kidney events is estimated at 2400 patients, with a planned 5 year follow up. All end points will be blinded. This unique study includes patients between 18- 75 years of age, and uses laboratory facilities to find the cases (based on creatinine levels above the upper limit) and has 3 strata: 50% of the population will have diabetes and CKD, 20% will have no DM, but CKD and proteinuria, and 30% will have CKD, no DM, and no proteinuria.

Thus this study will facilitate the understanding of the progression of CVD and CKD in an unselected population, and the impact of a specific health care delivery system (protocol driven nurse co-ordinated) care. A number of sub-studies and ancillary studies are planned to facilitate understanding of physiology as well as sociology of this process.

Together these studies will provide a more extensive understanding of the relationship between CVD and CKD, as well as the impact of different care delivery systems and treatment methods. The large number of patients, from varying ethnic and geographical backgrounds, will permit generalizability of these findings, and generate new hypotheses to be tested in additional clinical trials.

The studies are made possible by funding support from Kidney Foundation of Canada, Canadian Institute of Health Research, and matched funding from multiple industry partners.

THE 4D TRIAL: A STUDY IN 1252 TYPE 2 DIABETIC PATIENTS ADMITTED FOR HEMODIALYSIS (HD)

Christoph Wanner *Departments of Internal Medicine Würzburg*

Whether lipid lowering therapy with statines improves survival in uremic diabetic patients is currently unknown. Because of the potential action of non-classical risk factors in renal patients, this issue is currently addressed in a German multicenter prospective controlled study comparing atorvastatin (20 mg/d) with placebo. Until 8/2002 1252 incident type 2 diabetic patients were randomized and so far followed for a maximum of 4 years. The data provide an opportunity to characterise baseline morbidity and overall follow up survival in this cohort (54.8% males; 45.2 % females; mean age 65.8 (33-80) years, average diabetes duration 17.8 years, BMI 27 kg/m2). Retinopathy was present in 73.6% and 10% were blind. Gangrene (amputation) was present in 14.4%. 17.3% had a history of MI, 17.7% a history of stroke and 41.4% had peripheral arterial disease. Coronarography with a positive result had been performed in 18.2%, CABG in 6.9% and PTCA in 5.6%. A native AV fistula could be established in 83.7%, a PTFE graft was used in 10.5% and a central catheter in 5.4%. Mean baseline systolic BP was 147 and diastolic 76 mm Hg; HbA1c 6.8%; Lipid values: TC 221 $\pm$ 4, TG 257 $\pm$ 157, LDL-C 128 $\pm$ 30, HDL-C 37 $\pm$ 18 mg/dl (data are from 826 patients). As of January 2003, 437 patients had died (35%). The data document (i) the catastrophic co-morbidity in type 2 diabetics entering HD and (ii) show better survival than in past national studies (Koch et al., NDT 1997).

Co-Investigators
Vera Krane, *Departments of Internal Medicine Würzburg - Germany;* Winfried März, *Clinical Chemistry Graz - Austria;* Günther Ruf, *Pfizer Ltd., Karlsruhe, Germany;* Manfred Olschewski, *Biostatistics, Freiburg, Germany;* Eberhard Ritz, *Departments of Internal Medicine Heidelberg - Germany*

RANDOMIZED DOUBLE BLIND TRIAL OF FLUVASTATIN FOR HYPERCHOLESTEROLEMIA IN RENAL TRANSPLANT RECIPIENTS.

Hallvard Holdaas *National Hospital, Oslo, Norway*

Background

Hyperlipidemia might be a risk factor for cardiovascular (CV) morbidity and mortality and long-term renal transplant dysfunction. However, no studies have demonstrated that lipid-lowering strategies significantly reduce CV or renal events in this population. We therefore conducted the first large-scale, randomized, double-blind controlled trial comparing the effects of a statin vs placebo on CV and renal outcomes.

Methods

ALERT (Assessment of Lescol in Renal Transplantation) was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial conducted to assess the effect of fluvastatin in renal transplant recipients with mild-to-moderate hypercholesterolemia (total cholesterol 4.0–9.0 mmol/L [155–348 mg/dL]). Eligible patients were aged 30-75 years who had received a renal transplant more than 6 months before enrolment and currently were receiving cyclosporine. Between June 1996 and October 1997, a total of 2102 patients were randomised.

The primary endpoint of the study was time to first major adverse cardiac event (MACE), defined as cardiac death, nonfatal myocardial infarction, or intervention procedure (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty), with fluvastatin 80 mg/d, compared with that of placebo, over a minimum of 5 years and a maximum of 6 years follow-up. The secondary endpoints included death, hospitalization for angina, stroke, limb amputation; and the combined renal endpoints: death or graft loss or doubling of serum creatinine.

Results

About 250 MACEs and 300 renal events had occurred by Oct 31, 2002, when a minimum of 5 years follow-up was attained.

FOLIC ACID FOR VASCULAR OUTCOME REDUCTION IN TRANSPLANTATION

Andrew G. Bostom, MD, MS *Rhode Island Hospital*

FAVORIT (*Folic Acid for Vascular Outcome Reduction in Transplantation*) is a multicenter, randomized, double-blind controlled clinical trial has been designed to determine whether total homocysteine (tHcy)-lowering treatment with a standard multivitamin augmented by a high dose combination of folic acid, vitamin B12, and vitamin B6, versus treatment with an identical multivitamin containing no folic acid, and Estimated Average Requirement (EAR) amounts of vitamin B6 and vitamin B12., reduces the pooled rate of recurrent and de novo cardiovascular disease [CVD] outcomes (i.e., pooled occurrence of non-fatal and fatal arteriosclerotic outcomes, including coronary heart, cerebrovascular, and peripheral vascular disease events = primary outcome), among clinically stable renal transplant recipients (RTRs) who have mild to moderately elevated tHcy levels. The basic eligibility criteria are age 35 to 75 years old, functioning renal allograft for ≥ 6-months with serum creatinine based glomerular filtration rate (GFR) ≥ 30 mL/min, and a screening random/non-fasting tHcy level ≥ 11 μmol/L for women, or ≥ 12 μmol/L for men. Patients will be stratified by clinic, and randomly assigned to treatment with a standard multivitamin containing a high dose combination of folic acid, vitamin B6, and vitamin B12, or an identical multivitamin containing no folic acid, and Estimated Average Requirement (EAR) amounts of vitamin B6 and vitamin B12. All patients will receive standard clinical management for traditional CVD risk factor reduction. The study is designed to recruit 4000 patients (2000 in each group; 30%-35% in each group will have diabetes) over a 2-year period for *83 to 87% power to detect a 19.0 to 20.0 % treatment effect during 5-years of follow-up.* Preceded by a careful chart review, study eligibility is further determined in conjunction with a routine renal transplant clinic visit, with the addition of random/non-fasting tHcy and creatinine determinations. Appropriately processed and stored EDTA plasma and serum aliquots will be shipped to the central lab for tHcy and creatinine analysis each week. Only women with a random/non-fasting tHcy level ≥ 11 μmol/L, or men with a random/non-fasting tHcy level ≥ 12 μmol/L, as well as a serum creatinine based GFR ≥ 30 mL/min, will be eligible to be randomized. All data required for randomization will be made available to the clinical sites within ≤ 2-3 weeks of a potential participants screening visit. The baseline/randomization examination requires: informed consent; medical history & detailed current medication review; intake of folic acid, vitamin B12, and vitamin B6 from supplements; basic physical activity data collection; fasting blood

collection for tHcy, folate, vitamin B12, pyridoxal 5'-phosphate (PLP), lipid profile, creatinine, & glucose determinations. Patients will be stratified by clinic, and randomly assigned to receive a daily multivitamin devoid of folic acid, vitamin B12, or vitamin B6, or a multivitamin containing, in addition to other standard multivitamins, a high dose of folic acid, vitamin B6, and vitamin B12. *Follow-up clinic visits each 12-months for evaluation* will include general medical histories focusing on hospitalizations, emergency room , and physician's office visits; full medication inventories; intake of folic acid, vitamin B12, and vitamin B6 from supplements; pill counts; and blood tests. In addition, questionnaires regarding hospitalizations, & intake of folic acid, vitamin B12, and vitamin B6 from supplements, will be administered *at 6-month intervals after each of these clinic visits, during telephone follow-up. Follow-up continues until death or a maximum of 5- years. For the primary analysis of the primary pooled CVD endpoint, participants with allograft failure requiring initiation/re-initiation of chronic maintenance dialysis will be censored at 3-months post-dialysis. A secondary analysis of the same endpoint will be performed without censoring.* Data analysis will be performed on the basis of original randomization (intention to treat) using the log-rank test of difference in survival-without-endpoint curves.

GROUP 1: DIABETIC KIDNEY DISEASE

DO VITAMINS FOR HOMOCYSTEINE SLOW THE PROGRESSION OF DIABETIC NEPHROPATHY?

Group 1

Principal Investigator: J David Spence
Co-Investigators: DN Churchill, M Eliasziw, D Cattran, House A

Funding: Canadian Institute for Health Research
Study Design: Clinical Trial – Randomized Parallel
Type of Disease: Diabetic Kidney Disease

Submitted by: David Churchill

This is a randomized placebo controlled double blind study, in 3 Canadian centres, to evaluate the efficacy of vitamin therapy on progression of diabetic nephropathy and the incidence of cardiovascular disease in diabetic patients. The hypothesis is that diabetic microvascular disease is, in part, due to hyperhomocysteinemia and that the combination of vitamins chosen for this study will reduce these levels and result in improved renal and cardiovascular outcomes. The inclusion criteria are diabetes mellitus, either type I or II with urine albumin excretion > 300 mg/day or protein excretion > 500 mg/day. Exclusion criteria include creatinine clearance < 30 ml/min and severe co-morbidity predictive of survival < 3years. The intervention is folic acid 2.5 mg, pyridoxine 25mg and Vitamin B12 1 mg daily in a single capsule compared to a placebo capsule. The primary outcome is the change in glomerular filtration rate over 3 years, measured by DTPA annually and by timed cimetidine creatinine clearance every 6 months. The secondary outcomes will include change in proteinuria, and two composite cardiovascular outcomes, the first of which is stroke, MI, amputation for peripheral vascular disease or death. The sample size, calculated on the basis of the primary outcome, is 150 patients per group. There is an 80% statistical power to detect a 25% difference in the rate of change in GFR between the intervention and control groups. The study was initiated in 2000 with the planned completion date in 2005.

ANGIOTENSIN II ANTAGONISM OF TGF-β_1: A CANDESARTAN DOSE – TGF-β_1 RESPONSE RELATIONSHIP STUDY

Group 1

Investigators: G. Dennis Clifton, PhD and Katherine R. Tuttle, MD
Funding: Astrazeneca

Study Design: Clinical Trial – Sequential
Type of Disease: Diabetic Kidney Disease

Submitted by: Dennis Clifton

Background

TGF-β_1 has been associated with the occurrence of diabetic micro- and macrovascular complications including nephropathy. Independent of their antihypertensive effects, ACE inhibitors and angiotensin II (AT-II) receptor antagonists decrease the synthesis and secretion of renal TGF-β_1 and slow progressive renal dysfunction. Clinical and experimental data exist suggesting that differences in AT-II receptor antagonist dose-response relationships exist between blood pressure reduction and TGF-β_1 suppression. Pharmacodynamic information regarding AT-II receptor antagonist dose, TGF-β_1 suppression and changes in renal function would be valuable in enhancing our understanding of the optimal use of agents that modulate the renin-angiotensin system.

Objective

To assess pharmacodynamic relationships between chronic candesartan dose and serum concentration with the parameters of blood pressure, serum and urine TGF-β_1, serum AT-II, and urinary albumin.

Study Design

Open-label, dose escalation study of candesartan in patients with diabetes, nephropathy and hypertension.

Study Population

Twelve patients with Type 2 diabetes, nephropathy, and hypertension. Matched controls (normal volunteers and patients with diabetes, hypertension but no nephropathy) provide comparative baseline biochemical values.

Intervention

Following a 2-week washout period from ACE-inhibitors or AT-II antagonists, study patients receive candesartan 8 mg for 3 weeks followed by escalations to daily doses of 16, 32 and then 64 mg each for 3 weeks. Antihypertensive control is maintained as needed by antihypertensive agents that do not suppress TGF-β_1.

Main outcome measures

Following the end of each 3-week dosing interval the blood pressure, serum creatinine, urinary protein, serum and urine TGF-β_1, serum AT-II, and serum candesartan data are collected.

OPTIMIZING VITAMIN E PROTECTION IN THE DIABETIC POPULATION: EFFECT ON RENAL HEMODYNAMICS IN TYPE 1 DIABETES

Group 1

Investigators: G. Dennis Clifton, PhD, Marc W. Fariss, PhD, Katherine R. Tuttle, MD, William Dittman, MD

Funding: Washington Attorney Generals Office
Study Design: Clinical Trial – Non-Randomized-Parallel
Type of Disease: Diabetic Kidney Disease

Submitted by: Dennis Clifton

Background

Mitochondria serve as an important source of reactive oxygen species (ROS) and are a key target of ROS damage. Hyperglycemia-induced mitochondrial overproduction of superoxide has been shown to serve as a casual link between elevated glucose and the major pathways responsible for hyperglycemic vascular damage. Data strongly support the enrichment of mitochondrial membranes with tocopherol as a critical event in preventing oxidative stress-mediated cell injury and death and a number of experimental and clinical studies have suggested that vitamin E may be effective in preventing DM-induced renal dysfunction. Platelets provide a readily available source of mitochondria, which may be useful as surrogates for determination of optimal vitamin E dosing regimens in patients with DM and/or DM nephropathy.

Objectives

To determine the relationship between vitamin E succinate dose, tocopherol serum concentration, and tocopherol content of platelets, platelet mitochondria and inner mitochondria membrane. To correlate improvement in biochemical markers of renal function and oxidative stress with the resistance of platelet mitochondria to lipid and cardiolipin peroxidation.

Study Design

Prospective, open label dose ranging study of vitamin E in diabetic subjects and healthy volunteers.

Study Population

12 adult individuals with Type 1 diabetes and 12 gender and age matched controls.

Intervention

Following baseline data collections subjects are placed on an oral regimen of d-alpha-tocopherol succinate (d-α-TS) 1200 IU and then 2400 IU for a total of 180 days each followed by repeat data collection.

Main outcome measures

At baseline and following each of the dosing periods plasma tocopherol content, total antioxidant capacity, creatinine, and coagulation studies are collected along with urine for creatinine and albumin. Plateletpheresis is performed to collect platelets for determination of tocopherol and cardiolipin content in platelet fractions and the resistance of platelet mitochondria to lipid and cardiolipin peroxidation.

PREVALENCE OF CARDIOVASCULAR CALCIFICATION (CVC) IN PREDIALYSIS PATIENTS WITH CHRONIC RENAL FAILURE (CRF) DUE TO TYPE 2 DIABETIC NEPHROPATHY (DN)

Group 1

Investigators: Qunibi WY, Abouzahr F, Mizani M, Nolan CR

Type of Disease: Diabetic Kidney Disease

Submitted by: Wajeh Qunibi

Cardiovascular calcification is common in dialysis patients. The pathogenesis is multifactorial and includes both traditional and dialysis-related risk factors such as hyperphosphatemia and high calcium phosphorus product. Less well established is the role of calcium-based phosphate binders (CBPB) and vitamin D therapy (VD). Diabetes mellitus is a known risk factor for CVC and is the main cause of CRF in the United States, particularly in Hispanic Americans. Predialysis patients with CRF are not subjected to many of the dialysis-related factors. The prevalence of CVC in these patients is not well established.

The aim of this pilot study was to compare the prevalence and factors associated with CVC in a homogeneous group of 30 Hispanic predialysis patients with CRF due to type 2 DN to that found in a control group of 30 diabetic patients with normal renal function and microalbuminuria (MA).

Patients were included if they are adults, Hispanic, have GFR < 20 ml/min. Control subjects were included if they are adults, Hispanic, have microalbuminuria and normal renal function. Patients who received CBPB, VD or had CABG were excluded from the study. Results from this pilot study will be used to design a larger prospective randomized study.

THE EFFECT OF LY333531 ON ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES

Group 1

Principal Investigator: Katherine Tuttle
Funding: Lilly Corporation

Study Design: Clinical Trial – Randomized- Parallel
Type of Disease: Diabetic Kidney Disease

Submitted by: Katherine Tuttle

Treatment strategies for the prevention or treatment of diabetic nephropathy are limited. Good control of hypertension with the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) has been shown to be effective in treatment of established nephropathy. However, despite the widespread use of these agents, many patients progress to end-stage renal disease. Protein kinase C (PKC)-β activation in renal tissue is involved in the pathogenesis and progression of nephropathy. Therefore, a selective PKC-β inhibitor could be beneficial in reducing the progression of nephropathy.

Primary Objective

To determine if the specific PKC-β inhibitor, LY333531, given orally at 32 mg/day for 12 months, significantly reduces the urinary albumin-to-creatinine ratio compared to placebo treatment in adult patients with type 2 diabetes, persistent albuminuria (albumin-to-creatinine ratio 200-2000 mg/g after taking an ACEI or ARB at a therapeutic dose ≥6 months), and relatively preserved renal function (serum creatinine ≤2.0 mg/dL in men and ≤1.7 mg/dL in women). Enrollment goal is 120 patients.

GROUP 2: NON-DIABETIC KIDNEY DISEASE AND UNSPECIFIED

EPO-CAN-10: A STUDY TO DETERMINE THE IMPACT OF HEMOGLOBIN MAINTENANCE AND OTHER INTERVENTIONAL STRATEGIES TO PREVENT OR DELAY THE PROGRESSION OF LEFT VENTRICULAR MASS GROWTH IN SUBJECTS WITH EARLY RENAL INSUFFICINECY

Group 2

Principal Investigator: Adeera Levin
Funding: Janssen Ortho Canada

Study Design: Clinical Trial – Randomized – Parallel
Type of Disease: Diabetic and Non-Diabetic Kidney Disease

Submitted by: Brendan Barret

A randomized parallel 2 group trial in people with CKD, not on dialysis, attending nephrology clinics in Canada. The general objective is to determine whether preventing anemia development (maintaining hemoglobin about 130 g/L) by timely initiation of Eprex and/or iron prevents the development of LV hypertrophy documented by serial echocardiography when compared to treating anemia only when the hemoglobin falls below 100 g/L. The trial was initially designed to run for 2 years, but follow-up has been extended. Approximately 150 subjects are to be studied. Enrollment is complete and final data should be available during 2003.

CARDIOVASCULAR DISEASE AND CHRONIC RENAL DISEASE IN A VA POPULATION

Group 2

Principal Investigator: Linda Fried
Co-Investigators: Steve Weisbord, Michael Fine, Jeff Whittle

Funding: Local VA funds
Study Design: Observational – Cohort
Type of Disease: Diabetic and Non-Diabetic Kidney Disease

Submitted by: Linda Fried

Background

Those with end-stage renal disease have a cardiovascular mortality rate that is 10 to 20 times that of the general population. However, the natural history of those with mild renal disease is poorly defined.

Objective

We aim in this study to: to analyze overall and cardiovascular mortality rates in patients with renal insufficiency and to analyze the epidemiology of MI and revascularization procedures in those with chronic renal disease. A secondary aim is to compare the outcomes and use of renal and cardiac protective medications in African Americans and Caucasians.

Research Plan/Methods

We will use the VISTA database to search for patients with 2 measured serum creatinines at least 30 days apart. The study sample will include all patients with a creatinine > 1.4 mg/dl and a sample of those with a creatinine <1.2. Data on the subjects will be obtained from Vista and Austin databases on demographics, laboratory values, cardiovascular procedures, hospitalizations and mortality.

The primary outcome is mortality. Secondary outcomes are hospitalization for myocardial infarction, ischemia, congestive heart failure, and cerebrovascular disease; revascularization procedures, and use of ACEI and cardioprotective medications. The data will be analyzed by multivariate regression (Poisson for rates and Cox for time to event analyses).

Group 2

Principal Investigator: Andrew Levey and Mark Sarnak
Funding: Amgen

Study Design: Observational Study – Cohort (Secondary Analysis)
Type of Disease: Non-Diabetic Kidney Disease

Submitted by: Andrew Levey

The prevalence, incidence and risk factors for CVD in CKD are not well defined. Past cohort studies by NHLBI included only a small number of participants with elevated serum creatinine, but may have included a large number of participants with decreased GFR. We plan secondary analysis of pooled data from these cohort studies, including estimating the level of GFR from serum creatinine using the MDRD Study equation (after calibration to the MDRD Study laboratory). Outcome variables will include total mortality, cause-specific mortality, prevalent CVD, and incident CVD. Predictor variables will include level of GFR as well as known risk factors for CVD. We anticipate that the large number of subjects will allow determination of

1. prevalence of CVD according to level of GFR,
2. incidence of CVD according to level of GFR,
3. whether decreased GFR is risk factor for CVD independent of know CVD risk factors,
4. interactions of known risk factors for CVD with the level of GFR,
5. and possible nonlinear relationships between risk factor levels and CVD risk in CKD.

NATIONAL KIDNEY FOUNDATION'S KIDNEY EARLY EVALUATION AND PROGRAM (KEEP 3.0 STUDY)

Group 2

Principal Investigator: John Flack, MD, MPH
Funding: NIH

Study Design: Clinical Trial – Randomized – Parallel
Type of Disease: Diabetic and Non-Diabetic Kidney Disease

Submitted by: Peter A. McCullough

The KEEP 3.0 Study (prospective longitudinal with embedded randomized trial) has the following aims

1. To determine the prevalence of kidney disease and risk factors for kidney disease in a high-risk cohort
2. To determine the cross-sectional association of kidney disease and CVD-kidney risk factors
3. To determine the rate of change in kidney disease and risk factors that determine this progression
4. To determine the long-term morbidity and mortality of individuals (e.g., CVD, Chronic Kidney failure), with evidence of kidney disease
5. To determine different methods for providing treatment information to patients and physicians that optimally influence process of care measures and clinical outcomes

Adult men and women aged 18 and older with one or more of the following: 1. hypertension, 2. diabetes mellitus, 3. first degree family member [mother, father, brother, sister, and/or children] with hypertension, diabetes mellitus, or kidney disease. In persons without diabetes mellitus, reduced kidney function, or heart failure, hypertension will be defined ad SBP $\geq$ 140 or DBP $\geq$ 90 mm Hg or taking BP medication. Amongst individuals with diabetes mellitus or reduced kidney function, hypertension will be defined as SBP $\geq$ 130 or DBP $\geq$ 80 mm Hg or taking BP medication. Diabetes mellitus will be defined as fasting plasma glucose $\geq$ 126 mg/dl or non-fasting glucose > 200mg/dl or taking insulin and/or oral hypoglycemia agents. KEEP 3.0 participants will be recruited during the initial 2 study years. Aggregate annual recruitment goals at each of the 15 centers will be established so that approximately one-half of the total sample size of 6900 participants will be recruited each year. Patients, providers, and centers will participate in a randomized trail of graded levels of educational materials and interventions with respect to chronic kidney disease. These interventions are expected to have an impact on a variety of outcomes including rate of decline in eGFR, microalbuminuria, and usage of renal-protective medications.

Group 2

Principal Investigator: Mark Mitsnefes
Funding: NIH

Study Design: Observational Study – Cohort
Type of Disease: Non-Diabetic Kidney Disease

Submitted by: Mark Mitsnefes

Hypothesis

Cardiovascular changes occur in children with relatively mild CRI, and progress as end-stage disease approaches.

Design

Cohort study f 48 children with measured GFR 25-75 ml/min/1.73m^2.

Methods

1. Cardiac structure by evaluation of LV mass, LV geometry; 2. LV systolic and diastolic function using rest and stress echocardiography; 3. Vascular structure by assessment of carotid artery intima-media thickness (IMT); 4. Vascular function by assessment of endothelium-mediated vasodilatation of the brachial artery using high-resolution B-mode ultrasound. In addition, we will determine the role of blood pressure by ambulatory blood pressure monitoring, anemia, etiology and rate of progression of CRI, hyperlipidemia and hyperhomocysteinemia and other variables as possible risk factors for cardiac or vascular abnormalities.

Follow up

To assess the changes of cardiovascular structure and function by repeating the evaluation 1 and 2 years after initial examination.

IMPROVING DRUG USE IN PATIENTS WITH HYPERTENSION

Group 2

Principal Investigator: Michael Murray
Funding: NHLBI

Study Design: Clinical Trial – Randomized Parallel
Type of Disease: Non-Diabetic Kidney Disease

Submitted by: Michael Murray

Optimal use of medications in patients with hypertension prevents adverse health outcomes. Because hypertension is asymptomatic and antihypertensive drugs have intolerable side effects, patients often feel better when they are not taking their medication as opposed to when they are carefully adhering to their physician's prescribed regimen. Innovative strategies are needed to educate patients and improve their adherence to a complicated regimen often involving many drugs. Minority patients often may not have access to the resources needed to assist them with their medications and as such they are especially vulnerable. This study aims to develop and test, in a randomized controlled trial, a multileveled pharmacy-based program to improve adherence in minority patients incorporating patient education materials and medication packaging designed for patients with low-literacy.

Patients with uncomplicated (n=264) or complicated hypertension (n=224) are randomly assigned to a pharmacist intervention or usual care. Study participation for the patients in the intervention group concludes after 12 months of active intervention followed by six months of post-intervention follow up. Medication adherence is monitored electronically. Clinical endpoints include blood pressure, cardiovascular events, serum creatinine, health related quality of life, cognitive function, costs, and satisfaction with care.

AN OBSERVATIONAL STUDY OF AUTONOMIC FUNCTION CHANGE AS MEASURED BY HEART RATE VARIABILITY IN SUBJECTS WITH CHRONIC KIDNEY DISEASE

Group 2

Principal Investigator: Sriram S. Narsipur, MD
Funding: Dialysis Clinics Incorporated

Study Design: Observational Study – Cross-Sectional
Type of Disease: Non-Diabetic Kidney Disease

Submitted by: Sriram Narsipur

We have discovered profound deviations from normal in heart rate variability (HRV) among subjects with End Stage Renal Disease (ESRD) during a pilot study of pharmacologic effects on autonomic function in that population. HRV has been documented to be a reliable indicator of autonomic neuropathy, which we know to be common in ESRD. In addition, HRV is a strong marker for sympathetic hyperactivity, a risk factor for sudden cardiac death in the general population. We are testing the hypothesis that autonomic dysfunction is a function of the degree of renal failure, such that the greater the extent of renal failure the worse the autonomic dysfunction. We are also collecting HRV data on children with CKD as no information is available in this sub- population. Patients will be stratified into one of four groups (n=30 in each group) depending on degree of renal dysfunction based upon a creatinine clearance (CrCl) calculated using a formula described by Levy, et. al. [130] for adults or using the standard Schwartz formula for children under the age of 18: Normal > 75 ml/min (the "control group"), mild = 75-50 ml/min, moderate = 49-25 ml/min, and severe = <24 ml/min but pre-dialysis. This data will help provide normative baselines for future interventional studies among patients with CKD and ESRD. Identification of a threshold response of HRV dependant on creatinine clearance will also be explored.

THE PREVALENCE OF REDUCED GLOMERULAR FILTRATION RATE (GFR) IN OLDER HYPERTENSIVE PATIENTS AND ITS ASSOCIATION WITH CARDIOVASCULAR DISEASE: A REPORT FROM THE ALLHAT STUDY

Group 2

Principal Investigator: Mahboob Rahman MD, MS
Co-Investigators: Clinton D. Brown, MD; Josef Coresh MD, PhD; Barry R. Davis, MD; John H. Eckfeldt, MD, PhD; Nelson Kopyt, DO; Andrew S. Levey, MD; Chuke Nwachuku, MA, MPH; Sara Pressel, MS; Efrain Reisin, MD; and Candace Walworth, MD

Submitted by: Mahboob Rahman

Background

The prevalence of reduced glomerular filtration rate (GFR) in older hypertensive patients, and the relationship between level of GFR and cardiovascular disease (CVD) and its risk factors is not well known.

Methods

We evaluated baseline renal function in 40,193 hypertensive patients, aged ≥55 years enrolled in the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). The simplified Modification of Diet in Renal Disease study equation was used to estimate GFR, and the prevalence of CVD in patients with different levels of GFR examined.

Results

Fifty six percent of patients had mild (60-89 ml/min/1.73m^2), 17.1% had moderate (30-59), and 0.5% had severe reduction in GFR (≤29). Patients with moderate or severe reduction in GFR were more likely to have had a prior myocardial infarction or stroke (28.7% and 27.3%), have ischemic changes on electrocardiogram (ECG) (24.6% and 33.1%), and have left ventricular hypertrophy on ECG(ECG-LVH) (6.0% and 10.7%) than patients with mild reduction or normal GFR. A decrease in GFR of 10ml/min/1.73m^2 was independently associated with 6% higher risk of CVD (OR 1.06/10ml/min/1.73m^2, p<0.0001), and 15% higher risk of ECG-LVH (OR 1.15/10ml/min/1.73m^2, p<0.0001). The increase in risk was marked at a GFR of approximately 60-70ml/min/1.73m^2.

Conclusions

The prevalence of reduced GFR is high in older hypertensive patients. Patients with moderate or severe reduction in GFR are more likely to have a history of CVD and ECG-LVH. Even modest reductions in GFR are independently associated with a higher prevalence of CVD and ECG-LVH.

Group 2

Principal Investigators: Donal Reddan, Ajay Singh
Funding: Ortho Biotech

Study Design: Clinical Trial – Randomized – Parallel
Type of Disease: Diabetic and Non-Diabetic Kidney Disease

Submitted by: Donal Reddan

Major complications and death risk in end-stage renal disease (ESRD) develop early in the course of chronic kidney disease (CKD). Cardiovascular disease is the main cause of death in patients with ESRD, and the majority of new dialysis patients have pre-existing cardiac disease. In patients with CKD, anemia is associated with decreased cardiac function, exercise capacity, quality of life (QOL), and cognitive function. Correction of anemia with recombinant human erythropoietin (r-HuEPO, epoetin alfa) may improve these outcome measures.

This large, prospective, randomized, open-label, multicenter trial will compare cardiovascular and mortality outcomes in patients with CKD who are randomly assigned to 1 of 2 groups: those treated to reach a target hemoglobin (Hb) of 13.0–13.5 g/dL (Group A), and those treated to reach a target Hb of 10.5–11.0 g/dL (Group B). Group A patients receive PROCRIT® (epoetin alfa) 10,000 U subcutaneously once weekly (QW) for 4 weeks; Group B patients receive the same dose when Hb falls below 10.5 g/dL. After 4 weeks, the dose is adjusted based on response. The trial will examine the effects of the degree of anemia correction with QW dosing of PROCRIT® in patients with CKD on cardiovascular and mortality outcomes. Target enrollment is 2,000 CKD patients across 150 sites with baseline criteria of Hb <11 g/dL, and glomerular filtration rate (GFR) ϒ⇑15 mL/min and ϒ⇐ 50 mL/min.

The primary outcome measure will be a composite comprising mortality (all-cause), myocardial infarction (MI), stroke, and hospitalization for congestive heart failure (CHF). All MI, stroke, and CHF outcomes will be adjudicated by an independent clinical events committee. Secondary outcomes will include rate of deterioration in GFR, QOL, and time to initiation of renal replacement therapy. Each patient will be followed for 36 months, or until renal replacement therapy is initiated.

GLUCOSE METABOLISM IN CHRONIC KIDNEY DISEASE (CKD)

Group 2

Principal Investigator: Bruce M. Robinson, MD
Funding: NIH through the Penn GCRC

Study Design: Observational – Cross Study
Type of Disease: Non-Diabetic Kidney Disease

Submitted by: Bruce Robinson

In both non-diabetics and those with type 2 diabetes mellitus, insulin resistance has been independently linked with atherosclerotic cardiovascular disease (CVD), and it commonly clusters with other risk factors for CVD as part of the insulin resistance syndrome. However, because most epidemiologic studies of insulin resistance have excluded patients with CKD, the associations in CKD of insulin resistance and the metabolic syndrome with CVD are largely unknown. In this General Clinical Research Center (GCRC) study of 34 subjects, we will determine the validity across a range of CKD severity of steady state indices of insulin sensitivity, such as the homeostasis model assessment (HOMA), compared to an index of insulin sensitivity from the frequently sampled intravenous glucose tolerance test (FSIGTT). We hypothesize that the correlation of the HOMA or other steady state measure of insulin sensitivity with insulin sensitivity measured by the FSIGTT will be within an acceptable range for its use in epidemiologic studies of CKD patients. This study will serve as a prelude to our future proposed investigation in the Chronic Renal Insufficiency (CRIC) Study of the relationships of insulin resistance and the metabolic syndrome to incident CVD and other outcomes.

CARDIOVASCULAR RISK FACTORS IN CHRONIC RENAL INSUFFICIENCY: FOLLOW-UP FROM THE MODIFICATION OF DIET IN RENAL DISEASE STUDY

Group 2

Principal Investigators: Mark J. Sarnak and Andrew S. Levey

Funding: NIDDK
Study Design: Observational study
Type of Disease: Non-Diabetic Kidney Disease

Submitted by: Mark J. Sarnak

The incidence and risk factors for development of cardiovascular disease (CVD) in subjects with chronic kidney disease (CKD) are not well defined. The Modification of Diet in Renal Disease (MDRD) Study was a randomized controlled trial, conducted between 1988 and 1993, to study the effects of strict blood pressure control and dietary protein restriction on the progression of kidney disease. Mean glomerular filtration rate at baseline was ~32 ml/ml/1.73 m^2 (range 13-55 ml/min/1.73 m^2). A total of 840 participants were randomized into the trial. The goal of the current proposal is to obtain follow up data on this cohort and to ascertain ESRD and mortality outcomes. We will measure rates of all-cause and CVD specific mortality pre and post ESRD. Subsequently using both baseline data collected during the study as well as data utilizing frozen samples, we will evaluate risk factors for both all-cause mortality and CVD specific mortality.

HEART FAILURE DETECTION AND PROGRESSION IN RENAL DISEASE: THE CRIC HEART FAILURE ANCILLARY STUDY

Group 2

Principal Investigator: Michael G. Shlipak, MD, MPH
Co-Principal Investigator: Alan S. Go, MD

Funding: NIDDK (pending)
Study Design: Observational Study – Cohort
Type of Disease: Diabetic and Non-Diabetic Kidney Disease

Submitted by: Michael G. Shlipak

The Chronic Renal Insufficiency Cohort (CRIC) is a multi-center, longitudinal study funded by the National Institute for Diabetes, Digestive and Kidney diseases to investigate the mechanisms for kidney disease progression and cardiovascular disease events in 3,000 persons with CRI. The CRIC Heart Failure Ancillary study was proposed to comprehensively investigate the development and progression of heart failure in this high-risk population. This grant application was submitted to the NIH in February, 2003.

ELUCIDATING THE KIDNEY'S ROLE IN CARDIOVASCULAR RISK: AN ANCILLARY STUDY FROM THE CARDIOVASCULAR HEALTH STUDY'S RENAL WORKING GROUP

Group 2

Principal Investigator: Michael G. Shlipak, MD, MPH
Co-Investigator: Linda F. Fried, MD, MPH; Catherine Stehman-Breen, MD, MS; Dan Gillen, MS; David Siscovick, MD, MPH; Bruce Psaty, MD, PhD

Funding: NHLBI (pending funding for supplemental analysis)
Study Design: Observational Study – Cohort
Type of Disease: Diabetic and Non-Diabetic Kidney Disease

Submitted by: Michael G. Shlipak

Although CRI is associated with a higher risk for myocardial infarction, stroke, heart failure, and cardiovascular mortality, independent of traditional cardiovascular risk factors, such as age, diabetes, hypertension, dyslipidemia, and tobacco use, the mechanisms are poorly defined. The relative contributions of traditional and novel risk factors for predicting cardiovascular events among persons with CRI have not been evaluated. In particular, levels of certain novel cardiovascular risk factors – including inflammatory and hemostatic factors, homocysteine, and lipoprotein(a) are elevated in patients with CRI and may mediate the association of CRI with cardiovascular morbidity.

Serum cystatin-C is an innovative and promising measure of renal function that is more sensitive than creatinine for detecting CRI and is not affected by age, sex, race, or muscle mass. To that end, we propose to use data from the Cardiovascular Health Study (CHS), an NHLBI-funded longitudinal cohort study to determine which individual cardiovascular risk factors appear most responsible for the association between CRI and cardiovascular events, and to determine the utility of cystatin-C levels as a marker for increased cardiovascular risk in the elderly. The results of this study will lead to a greater understanding of the relationship between CRI and cardiovascular disease in the elderly, and will foster the design of future intervention studies to decrease the burden of cardiovascular disease.

Group 2

Principal Investigator: Katherine Tuttle
Funding: Attorney General of Washington Vitamins Settlement Grant

Study Design: Clinical Trial – Randomized – Parallel
Type of Disease: Diabetic and Non-Diabetic Kidney Disease

Submitted by: Katherine Tuttle

Dietary factors contribute greatly to development of cardiovascular diseases. However, the effect of nutritional intervention on cardiovascular outcomes has not been determined. Heart attack survivors will be randomized to a "heart-healthy" diet, either Mediterranean style or American Heart Association Step 2. The primary difference between them is higher monounsaturated and omega-3 fats in the Mediterranean diet. For each diet group, effects on the composite of total and cardiac mortality and recurrent heart attacks will be evaluated and compared to a database control group.

Goals

a. To compare a Mediterranean diet to the AHA Step 2 diet, versus no nutritional intervention, among people who have survived a first heart attack for effects on survival and recurrent cardiovascular events.
b. To evaluate effects of monounsaturated and omega-3 polyunsaturated fats, and of antioxidant vitamins or those that lower homocysteine, on cardiovascular outcomes and risk factors (including renal function and albuminuria).

Statistical Considerations

a. *Sample Size*
Specific Aim 1 is based on the Lyon Heart study. After 24 months, the proportion of patients free of cardiovascular events was 0.97 in the Mediterranean diet group and 0.85 in the "prudent Western diet" group. We assume the dropout rate will be 40%. For power of 0.80 and alpha of 0.05, recruitment of 90 patients per group would permit a two-tailed, log-rank test to detect a difference in the 24-month primary outcome rate. To estimate conservatively and ensure adequate data to achieve the goals, we plan to enroll 100 patients per group (200 total).
b. *Diabetes Subgroup*
Type 2 diabetes has been designated as a prespecified subgroup because of the markedly increased risk of MI and higher death rates. Randomization is stratified by diabetes status to achieve equal proportions (about 30%) of participants with diabetes.

MICROALBUMINURIA AS A PREDICTOR OF CORONARY ARTERY DISEASE

Group 2

Principal Investigator: Katherine Tuttle
Funding: The Heart Institute of Spokane: Eagles

Study Design: Observational Study – Cohort
Type of Disease: Diabetic and Non-Diabetic Kidney Disease

Submitted by: Katherine Tuttle

Microalbuminuria is an independent risk factor for cardiovascular disease (CVD). We have previously shown that microalbuminuria levels predict angiographic coronary artery disease (CAD) severity. Similarly, serum uric acid (UA) levels correlate with CAD, particularly in females. A cross-sectional study (1996-1997) established these observations. We now are evaluating prospective data on mortality and CVD events for the subsequent 5-7 years.

Goal

To determine if albuminuria and uric acid predict CVD events, independent of CAD severity.

Patients (n=316) referred for elective coronary angiography provided blood and urine for measurement of albuminuria, UA, creatinine, insulin, glucose, hemoglobin A1C, lipids, and hematocrit. Histories were obtained by interview and review of medical records. Height, weight, and blood pressure were also measured. Patients were contacted annually to evaluate vital status and events. Medical records were obtained to verify patient reports and to identify unreported events. Death records for states of WA and ID were searched to verify causes of death.

Preliminary analyses have shown UA, lipids, and severity of CAD independently contribute to the prediction of later events.

Further, data analysis is in progress. Primary outcomes are CVD mortality and events (myocardial infarction, stroke, amputations, renal failure requiring dialysis or transplantation). Levels of albuminuria and UA, along with other risk factors, including kidney function and anemia, will be correlated with outcomes. If the bivariate correlation meets a level of significance <0.10, the variable will be included in multivariate analysis. Kaplan-Meier plots and Cox proportional hazards modelling will be used to assess predictors.

THE VALUE TRIAL (DIOVAN ANTIHYPERTENSIVE LONG-TERM USE EVALUATION)

Group 2

Principal Investigator: Stevo Julius
Co-Investigator: Katherine Tuttle

Funding: Novartis Pharmaceuticals
Study Design: Clinical Trial – Randomized – Parallel
Type of Disease: Diabetic and Non-Diabetic Kidney Disease

Submitted by: Katherine Tuttle

The renin angiotensin system (RAS) has negative cardiovascular effects, in addition to its effects on blood pressure. By antagonizing the RAS with an angiotensin II blocker, it is hypothesized that an added beneficial cardiovascular effect beyond that with lowering blood pressure alone may be attained.

Primary Objective

To determine the efficacy of the angiotensin II receptor antagonist, valsartan, in reducing mortality and morbidity as compared to the calcium channel blocker, amlodipine.

This is a six-year prospective, multinational, multicenter, double-blind, randomized, active controlled, two-arm parallel group trial comparing the efficacy and tolerability of valsartan alone and in combination with HCTZ to amlodipine alone and in combination with HCTZ. Patients will be titrated, dependent on their blood pressure response. The patient population includes those with stable hypertension, 50 years of age or older, and at high risk of having cardiovascular events. Primary efficacy outcome measure will consist of time to cardiac mortality or the first event of cardiac morbidity, defined as new or chronic CHF requiring hospitalization, non-fatal MI, or interrupted MI by thrombolysis and/or emergency angioplasty/CABG. Secondary endpoints include all-cause mortality, cardiovascular morbidity; new, worsening, or unstable angina requiring hospitalization; routine PTCA and/or CABG; potentially fatal arrhythmia; stroke; silent MI; end-stage renal failure or worsening of renal disease (serum creatinine increasing 50% above baseline). The VALUE trial also includes a microalbuminuria sub-study. Study-wide the enrollment is about 4000; at our site, we have 12 patients enrolled.

GROUP 3: KIDNEY TRANSPLANT

MAINTENANCE IMMUNOSUPPRESSION USE AND ACUTE CORONARY SYNDROMES AFTER RENAL TRANSPLANTATION IN THE UNITED STATES

Group 3

Investigators: Kevin C. Abbott, MD, Christina M. Yuan, MD, David Cruess, PhD, Allen J. Taylor, MD, Lawrence Y.C. Agodoa, MD

Funding: NIDDK
Study Design: Observational Study – Cohort
Type of Disease: Transplant

Submitted by: Kevin Abbott

Although some of the side-effects of transplant immunosuppressive agents (IA) might be expected to contribute to the development of coronary heart disease, none has yet been shown to be associated with increased rates of acute coronary syndromes (ACS) in the national population of renal transplant (RT) recipients. Using the United States Renal Data System (USRDS) database, we studied 35,196 patients who received solitary RT from 1 January 1996-30 March 1999 and followed until 31 December 1999. Cox proportional hazards regression models were used to calculate the adjusted relative risk for first hospitalization for ACS (ICD9 Code 410.x or 411.x) after RT associated with maintenance immunosuppression use. The one-year incidence of ACS was 0.7% each for patients using cyclosporine, tacrolimus, and mycophenolate, respectively; 0.9% in patients using azathioprine; and 1.8% in patients using sirolimus. In adjusted analysis, no individual IA was independently associated with ACS. There was also no significant difference in all cause mortality between IA. 95% of patients taking sirolimus also used cyclosporine, so comparison with combined sirolimus/tacrolimus use was not possible. We conclude that despite the differing cardiovascular risk profiles between IA, their risk for acute coronary syndromes and mortality early after RT is not different.

STUDY OF HEART AND RENAL PROTECTION (SHARP)

Group 3

Principal Investigator: Colin Baigent
Co-Investigator: Bert Kasiske
Funding: Merck Sehering Plough

Study Design: Clinical Trial – Randomized – Parallel
Type of Disease: Dialysis, Diabetic and Non-Diabetic Kidney Disease

Submitted by: Colin Baigent

Among patients with pre-existing coronary heart disease (CHD), large-scale randomized trials have demonstrated that lowering LDL-cholesterol concentration by about 1 mmol/l (40 mg/dl) for 4-5 years reduces the risk of coronary events and of strokes by about 25%. However, it remains uncertain whether patients with CKD but no known CHD would derive net benefit from cholesterol-lowering treatment: vasculopathic changes distinct from atherosclerosis (including cardiomyopathy, arterial stiffness, and calcification) are highly prevalent in CKD patients, and their aetiology may not be related to blood cholesterol; observational studies among dialysis patients have consistently failed to demonstrate a positive relation between blood total cholesterol and mortality; and, as patients with CKD have been systematically excluded from previous trials, the long-term safety of cholesterol reduction among patients with CKD is unknown.

The Study of Heart and Renal Protection (SHARP) aims to assess the effects of cholesterol-lowering therapy with a combination of simvastatin and the cholesterol-absorption inhibitor ezetimibe among around 9,000 patients with CKD but no CHD. Such large-scale recruitment will allow reliable assessment of the effects of lowering blood LDL-cholesterol on the risk of major vascular events and on the rate of loss of renal function in patients with various degrees of renal impairment.

CARDIOVASCULAR ABNORMALITIES IN CHILDREN AND ADOLESCENTS WITH RENAL TRANSPLANTATION

Group 3

Principal Investigator: Mark Mitsnefes
Funding: American Heart Association

Study Design: Observational Study – Cross-sectional
Type of Disease: Transplant

Submitted by: Mark Mitsnefes

Primary Goal

To assess cardiac structure and function as well as vascular structure and function in pediatric patients with successful renal transplantation.

Hypothesis

Pediatric patients with successful renal transplantation will have a high prevalence of LVH and LV dysfunction as well as vascular abnormalities.

Design

Cross-sectional study of 48 children with renal transplantation and measured GFR > 40/ml/min/1.73m^2.

Methods

1. Rest echocardiography to evaluate LV mass and LV geometry
2. Rest and stress echo to examine LV systolic and diastolic function
3. High-resolution B-mode ultrasound to assess carotid artery intima-media thickness (IMT) and endothelium-mediated vasodilatation of the brachial artery
4. Ambulatory blood pressure monitoring

PAMIDRONATE THERAPY FOR THE BONE DISEASE OF RENAL AND CARDIAC TRANSPLANTATION

Group 3

Principal Investigator: Katherine Tuttle, Jill Lindberg, Don Sherrard

Funding: The Heart Institute of Spokane and Ochsner Clinic
Study Design: Clinical Trial – Sequential
Type of Disease: Transplant

Submitted by: Katherine Tuttle

Pamidronate has been clearly shown to improve bone mass in numerous disorders of bone. Other bisphosphonates, as well as pamidronate, have been proven to be beneficial in steroid-related bone disorders. It is most likely that steroid treatment is the cause of osteopenia in organ transplant recipients. Preliminary studies in both cardiac and renal transplant recipients document the effectiveness of pamidronate. While other studies have described the benefits of other bisphosphonates in protecting bone mass or reversing bone loss, only pamidronate is approved for use in renal failure. This would obviously limit the usefulness of these oral agents in renal transplant recipients. Cardiac transplant recipients might also present a risk because of the common occurrence of decreased renal function or acute renal failure following transplantation.

Goal
To determine if intravenous pamidronate administered every 6 months for 2 years will reduce bone loss and fractures in recipients of kidney or heart transplants.

Primary outcomes
Bone density (DEXA) and fracture rates.

Kidney (n=47) and heart recipients (n=19) have recently completed the protocol and data analysis is in process.

GROUP 4: DIALYSIS

HEART FAILURE AS AN ETIOLOGY FOR HOSPITALIZATION IN CHRONIC DIALYSIS PATIENTS

Group 4

Investigators: Fernando C. Trespalacios, MD; Allen J. Taylor, MD; Lawrence Y. Agodoa, MD; George L. Bakris, MD; Kevin C. Abbott, MD

Study Design: Observational Study – Cohort
Type of Disease: Dialysis

Submitted by: Kevin Abbott

Background

Risk factors for heart failure (HF) have not been previously reported in a nationally representative sample of dialysis patients.

Methods

We conducted a historical cohort study 1995 patients enrolled in the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Study (DMMS) Wave II who were Medicare eligible at the study start, followed until December 31 1999 or receipt of renal transplant. Cox Regression analysis was used to model associations with time to first hospitalization for both recurrent and *de novo* HF (ICD9 code 428.x), defined as patients with and without a prior history of HF, respectively.

Results

The incidence density of HF was 71/1000 person years. Angiotensin converting enzyme inhibitors and beta-blockers were each used in less than 25% of patients with a known history of HF. A prior history of coronary heart disease (CHD) was associated with an increased total risk of HF, as were hemodialysis (HD, vs. peritoneal dialysis), aspirin use, and a history of diabetes. However, HD and aspirin use were the only factors associated with both de novo and recurrent HF. Widened pulse pressure was associated with de novo HF. Mortality after HF was 83% at three years (adjusted hazard ratio for mortality, 2.10; 95% CI 1.80, 2.45, $p<0.0001$).

Conclusions

In chronic dialysis patients, HD and aspirin use were associated with increased risk of both recurrent and *de novo* HF. Hospitalized HF was associated with a significantly increased risk of death.

PREDICTORS OF CORONARY ARTERY DISEASE IN HEMODIALYSIS PATIENTS

Group 4

Principal Investigator: Vinod K. Bansal MD
Funding: Loyola University Medical Center

Study Design: Observational Study – Cohort
Type of Disease: Dialysis

Submitted by: Vinod Bansal

Goal of the study

1. To observe the incidence of coronary artery disease in a cohort of hemodialysis patients over a 5-year period (2000-2005) and determine if correlation exists with standard cardiovascular risk variables;
2. To observe the incidence of coronary artery disease in a cohort of CKD patients followed in our pre-ESRD clinic in a similar manner

Number of patients

1. All patients within one hospital-owned urban dialysis unit are followed within a central database, approximately 120-150 annually. Demographics at start of study: mean age 58 $\pm$ 15.7 years, 51% male, 48% black, 16% Hispanic, 42% diabetic;
2. all patients within a pre-ESRD clinic

Primary interventions

None, standard of care

Primary outcomes

CAD event or change from absence to presence of CAD by clinical assessment of coronary angiogram, 2D echo, stress tests and/or ECG.

Data collected

Tracked data includes HCT, TIBC, age, gender, albumin, serum lipids (cholesterol, HDL, LDL, triglycerides), c-reactive protein. Patient data also collected on history of smoking, diabetes, hypertension, clinical assessment of PVD and CAD. Calculated variables include Framingham score, body mass index, calcium-phosphorus product, dialysis adequacy.

Initial one year assessment divided hemodialysis cohort group into presence or absence of CAD using established criteria. Differences between groups were found statistically for Framingham score, HCT, TIBC, evidence of PVD, and age. No correlation found with non-fasting serum lipids. Observational study continues on both populations.

ALTERATIONS IN WHOLE BLOOD VISCOSITY DURING HEMODIALYSIS IN CHILDREN: EVALUATION OF DYNAMIC CHANGES IN VISCOSITY USING A STEPPED SODIUM GRADIENT

Group 4

Investigators: Craig B. Langman, MD; Ellen R. Brooks, PhD; Sahar Fathallah-Shaykh, MD; Heather Price, MS
Funding: Sponsor holds patent on the Capillary Scanning Viscometer

Study Design: Observational Study – Case-control (with repeated measures)
Type of Disease: Dialysis, Non-Diabetic Kidney Disease

Submitted by: Ellen Brooks

Patients with ESKD, undergoing hemodialysis (HD), are prime candidates for dynamic evaluation of their whole blood viscosity (WBV) status as hyperviscosity is observed immediately post-HD. Furthermore, post-HD hypotension often occurs due to a decline in intravascular fluid volume, in conjunction with impaired peripheral vascular resistance. Arterio-venous fistula and graft thrombosis occurs frequently in HD patients and have been attributed to hyperviscosity, hypercoagulability, and stenotic lesion formation in the venous side of the fistula. In addition, increased whole blood and plasma viscosity are associated with a higher risk for cardiovascular and cerebrovascular disease, with a significantly higher incidence of thrombogenic-related events. Atherosclerosis is also exacerbated in ESKD and serves as an additive problem to altered rheological conditions in this patient population. This repeated measures pilot study will evaluate the utility of intermittent monitoring of WBV, using a capillary scanning viscometer, throughout HD in response to three different stepped sodium gradients in 11 subjects immediately pre-HD, 1, 2, and 3 hours intra-HD, and within 10 minutes post-HD during recovery. HD sessions will be received in random order at mid-week and one week apart. In addition, total body water (TBW) will be measured by bioelectric impedance, in conjunction with hematocrit and blood volume. We will also measure blood pressure; heart rate and subject symptoms to evaluate to what extent these variables are explained by on-line dynamic change in WBV.

Group 4

Principal Investigator: Liam Casserly
Funding: Boston Medical Center

Study Design: Clinical Trial – Randomized Parallel
Type of Disease: Dialysis

Submitted by: Liam Casserly

This study will assess the effect of routine administration with intravenous iron on endothelial function as well as inflammatory markers in ESRD using a randomized non-controlled design. Patients and principal investigator will not be blinded to the treatment since the measurement of out-comes by laboratory personnel can be blinded from the study investigators. The study will enroll 0 patients with ESRD undergoing chronic, outpatient hemodialysis and peritoneal dialysis at Boston Medical Center. These patients routinely receive intravenous iron treatment approximately one to two times a year, based on established clinical criteria. These criteria include transferrin saturation below 30%, or serum ferritin less that 200. Endothelial function and markers of inflammation will be measured at two time points before and after a routine infusion course of iron (eight 125mg treatments with ferrilecit) in the active treatment arm.
In the "non-treatment arm", delivery of iron will be withheld until fur identical sets of studies have been performed. Primary outcome analysis will be performed by comparing endothelial function tested after study 3 in each treatment arm (i.e. immediately after receiving iron). Adjustment will be made for changes in hematocrit, erythropoietin dose and blood pressure.

Group 4

Principal Investigator: Leticia Castillo
Co-Investigator: Ajay Singh
Funding: NIH

Study Design: Observational Study – Cohort
Type of Disease: Dialysis, Diabetic and Non-Diabetic Kidney Disease

Submitted by: Leticia Castillo

Cardiovascular disease (CVD) is a major cause of death among End Stage Renal Disease (ESRD) patients. CVD is caused in part by endothelial dysfunction. Three metabolic pathways have a major role in the regulation of endothelial function: the L-arginine-Nitric Oxide (NO) pathway, the methionine-homocysteine cycle and the asymmetric dimethylarginine (ADMA). This application is a comprehensive study, aimed at integrating metabolic, nutritional, physiologic and genetic aspects of endothelial dysfunction in renal patients. We will conduct a randomized, controlled, mechanistic study on the *in vivo* homeostasis of these metabolic pathways, and their influence on endothelial dysfunction of renal patients, and in healthy controls. The influence of dietary supplementation with arginine and folic acid on these metabolic pathways will also be explored. Relevant enzymatic genotype (MTHFR and DDAH), will be correlated with the metabolic phenotype. We hypothesize that dysregulation of the metabolism of the L-arginine-NO pathway, the methionine-homocysteine cycle and ADMA kinetics contributes to endothelial dysfunction and that arginine and folic acid supplementation will improve homeostais of these pathways.

The aims are

1. To assess NO bioavailability in CRD and ESRD patients and in healthy controls in relation to:
   1a. Whole body rates of NO and arginine synthesis, methionine transmethylation, homocysteine re-methylation and transulfuration, cysteine oxidation and the rates of synthesis of whole blood glutathione, by conducting primed, constant intravenous infusions of the stable isotope tracers L-[guanidino $^{15}N_2$] arginine, L-[$^{2}H_3$-methyl]methionine and L-[1-^{13}C]methionine;L-[^{13}Cureido]citrulline and L-[^{13}C]cysteine
   1b. The plasma concentrations of the asymmetric dimethyl arginine (ADMA) and activity of DDAH.
   1c. The differences of these metabolic parameters across the three groups. And
2. To explore the regulatory effects of a 4 week dietary supplementation with a) arginine or b) folic acid on the homeostasis of these pathways. The primary endpoint is NO bioavailability and the predictor variables are the kinetic parameters. State of the art mass spectrometric techniques and vascular imaging will be used. The long term objective is to gain new and relevant knowledge about the mechanisms of these processes and to eventually improve the outcome of CVD in these patients.

Group 4

Principal Investigator: Kamyar Kalantar-Zadeh, MD, MPH
Co-Investigators: Joel D. Kopple, MD; Gladys Block, PhD; Michael H Humphreys, MD

Study Design: Observational Study – Cohort
Type of Disease: Dialysis

Submitted by: Kamyar Kalantar-Zadeh

Over a quarter of a million maintenance hemodialysis (MHD) patients in the US have an increased rate of malnutrition and inflammation, which are felt to be major risk factors for their high morbidity and mortality. The risk of cardiovascular death appears to be especially high among those MHD patients who have a low, and not a high, body mass index, serum cholesterol level and blood pressure. This paradoxically reversed correlation between conventional cardiovascular risk factors and outcome in MHD patients has been referred to as "reverse epidemiology". Although a single hypothesis might not fully explain this paradoxical phenomenon, the so-called "Malnutrition-Inflammation Complex Syndrome" (MICS) appears to be the most plausible etiology of the reverse epidemiology.

The goals of this prospective cohort study are to determine whether the nutritional and inflammatory states in MHD population affect the mortality, morbidity, and other clinical outcomes in a predictable way and to ascertain how the deterioration of these indices over time is associated with poor outcome and paradoxical reversal of risk factor-outcome relationship. To achieve these goals, we have been studying a cohort of 360 MHD patients prospectively (October 2001-Sept 2006), from a pool of 1,500 MHD patients from 8 outpatient DaVita dialysis clinics in Los Angeles area. Nutritional and inflammatory measurements including pro-inflammatory cytokines are obtained semi-annually and food intake is measured annually by means of a "food frequency questionnaire" (FFQ) as well as diet records. A convenient but reliable nutritional scoring system known as "Malnutrition-Inflammation Score" (MIS) that have been used to predict mortality and clinical outcome in the MHD patients will be further evolved and validated.

The following specific questions will be answered:

1. Are the dialysis associated mortality and risk of cardiovascular disease and death correlated with malnutrition and/or inflammation or a combination of both known as MICS?
2. Do malnutrition and/or inflammation and their deterioration over time reverse the conventional epidemiology and/or have measurable and distinct impact on relevant clinical outcomes in dialysis patients such as hospitalization, dialysis access failure, and erythropoietin resistance?
3. Can a numerical result of a uniform nutritional scoring system, currently known as MIS, be a reliable indicator of MICS and a predictor of dialysis associated morbidity and mortality?
4. Can an FFQ reliably detect deficient nutrient intake in MHD patients?

SUDDEN DEATH AND DYSAUTONOMIA IN HEMODIALYSIS PATIENTS

Group 4

Principal Investigator: Sriram S. Narsipur, MD
Funding: National Kidney Foundation

Study Design: Clinical Trial – Randomized Parallel
Type of Disease: Dialysis

Submitted by: Sriram S. Narsipur

Nearly two thirds of patients with End Stage Renal Disease (ESRD) will die prematurely from cardiovascular causes. Understanding pathologic mechanisms and developing tools for evaluation of cardiac function in dialysis patients is necessary for developing preventive strategies and therapeutic intervention. The research program will examine a potential cause of sudden cardiac death in patients with CKD and ESRD. Patients with ESRD and CKD commonly demonstrate an autonomic neuropathy. Measurement of heart rate beat-to-beat variability permits an accurate assessment of sympatho-vagal tone affecting cardiac electrical conduction. This study proposes to address the working hypothesis that autonomic dysfunction, as measured by the time domain SDNN of heart rate variability, is unaffected by dihydropyridine calcium channel blocker treatment (active control) in hemodialysis patients but worsened with selective beta-blocker treatment. Hemodialysis patients will serve as their own controls in a repeated-measures design clinical trial comparing the effects of two months of treatment with metoprolol, a beta-blocker (BB) that our preliminary data suggests worsens HRV, versus amlodipine, a calcium channel blocker (CCB) that does not affect HRV and will serve as our active control. We will cross two repeated-measures conditions; active control CCB versus BB treatment with three time points; pre-intervention, 8 weeks post-intervention, 2 weeks washout following intervention, resulting in a 2(condition) x 3 (time) crossover design. We will submit our primary outcome variable, SDNN, to a 2x3 Repeated Measures Analysis of Variance (ANOVA), setting alpha=.05 for tests of statistical significance. We anticipate a significant Condition by Time interaction illustrating the worsening of HRV in the BB condition from Pre- to Post- intervention, returning to Pre- values after the 2-week washout period, relative to essentially no change in HRV in the Active Control CCB condition over the three time points. Based on our previous studies on changes in HRV following kidney transplantation in patients with ESRD [89], we anticipate a difference of 20% in the mean SDNN time domain of heart rate variability from baseline to post therapy, returning to baseline values after a 2 week washout. We anticipate no change in the Active Control condition over time. A minimum of 19 subjects would be necessary in order to achieve 90% power to detect this effect. Given typical subject attrition of 10-20% and the possibility for wider SDNN variability (as we observed in our pilot study), we will recruit 25 subjects for this study.

Group 4

Principal Investigator: Daniel Ornt
Funding: NIH

Study Design: Clinical Trial – Randomized – Parallel
Type of Disease: Dialysis

Submitted by: Daniel Ornt

Background
The effects of the dose of dialysis and the level of flux of the dialyzer membrane on mortality and morbidity among patients undergoing maintenance hemodialysis are uncertain.

Methods
We undertook a randomized clinical trial in 1846 patients undergoing thrice-weekly dialysis, using a two-by-two factorial design to assign patients randomly to a standard or high dose of dialysis and to a low-flux or high-flux dialyzer.

Results
In the standard-dose group, the mean (±SD) urea-reduction ratio was 66.3±2.5 percent, the single-pool Kt/V was 1.32±0.09, and the equilibrated Kt/V was 1.16±0.08; in the high-dose group, the values were 75.2±2.5 percent, 1.71±0.11, and 1.53±0.09, respectively. Flux, estimated on the basis of beta2-microglobulin clearance, was 3±7 ml per minute in the lowflux group and 34±11 ml per minute in the high-flux group. The primary outcome, death from any cause, was not significantly influenced by the dose or flux assignment: the relative risk of death in the high-dosegroup as compared with the standard-dose group was 0.96 (95 percent confidence interval, 0.84 to 1.10; P= 0.53), and the relative risk of death in the high-flux group as compared with the low-flux group was 0.92 (95 percent confidence interval, 0.81 to 1.05; P=0.23). The main secondary outcomes (first hospitalization for cardiac causes or death from any cause, first hospitalization for infection or death from any cause, first 15 percent decrease in the serum albumin level or death from any cause, and all hospitalizations not related to vascular access) also did not differ significantly between either the dose groups or the flux groups. Possible benefits of the dose or flux interventions were suggested in two of seven prespecified subgroups of patients.

Conclusions
Patients undergoing hemodialysis thrice weekly appear to have no major benefit from a higher dialysis dose than that recommended by current U.S. guidelines or from the use of a high-flux membrane. (N Engl J Med 2002; 347:2010-9.)

DOUBLE BLIND STUDY TO ASSESS THE IMPACT OF NORMALIZATION OF HEMOGLOBIN COMPARED TO PARTIAL CORRECTION OF HEMOGLOBIN WITH EPREX®/ERYPO ® ON LEFT VENTRICULAR STRUCTURE IN EARLY HEMODIALYSIS PATIENTS.

Group 4

Principal Investigators: P. Parfrey, R. Foley
Funding: Johnson and Johnson

Study Design: Clinical Trial – Randomized – Parallel
Type of Disease: Dialysis, Diabetic and Non-Diabetic Kidney Disease

Submitted by: P. Parfrey

This study is a randomized multicenter, clinical trial to assess the effect of hemoglobin (Hgb) normalization (14 ± 0.5g/dL = Higher group) compared to partial correction of anemia ($10 \pm 0.5 - 11 \pm 0.5$ g/dL = lower group) using epoetin alfa, on left ventricular (LV) structure in early hemodialysis (HD) patients (3-18 months on HD) without symptomatic cardiac disease who have normal left ventricular cavity volume.

N=554 subjects will be enrolled (277/treatment group) for a study duration of 96 weeks. The intent to treat principle will be used. The study will be double blinded on the primary efficacy criteria to percent change in LC volume and also on secondary efficacy criteria of percent change in LV mass. Echocardiograph studies will be done at baseline, Wk 24 and Wk 96. Other secondary endpoints include development of de novo heart failure, correlation between change in LV indices and average maintenance Hgb level, six minute walking test, and quality of life using KDQOL and FACIT questionnaires. Safety evaluations will include clinical laboratory tests, vital signs and adverse event reporting. An independent Data Safety Monitoring Board will review safety information on an ongoing basis. (Subject enrollment completed June 2001/last subject to finish May 2003).

IMMUNOLOGICAL RESPONSES TO PNEUMOCOCCAL CAPSULAR POLYSACCHARIDE VACCINE IN HEMODIALYISIS (HD) PATIENTS

Group 4

Principal Investigator: Sushil Sagar
Funding: Albert Einstein College of Medicine

Study Design: Observational Study – Cohort
Type of Disease: Dialysis

Submitted by: Sushil Sagar

HD Patients have immunologic abnormalities which contribute to their increased susceptibility to infections. We evaluated the antigen-specific B cells and AB response a PPV in 22 HD patients (M:F 11:11, 64.2 ± 9.8 years). The circulating antigen-specific B cells and the pre and post-vaccination AB to different pneumococcal capsular polysaccharides included in the PPV (3, 4, 8, 14, 19F and 23F) were quantified by an antigen capture ELISA.

Although both the antigen-specific cells and the 1-month post-vaccination AB levels were increased, they were lower than the ones previously reported in normal volunteers.

The results reveal significant variability in the response. We concluded that the AB response to PPV is blunted in ESRD patients on HD and is associated with a decreased number of circulating antigen-specific B cells.

Pre-PPV & 1 month Post-PPV AB (ug/ml. N=22, *p <0.01 others NS)

Serotype	Pre	Post*	Serotype	Pre	Post*
3IgA	0.70	2.5	4 IgG	1.65	3.38
4IgA	0.26	0.97	8 IgG	1.09	3.29
8IgA	0.69	3.29	23F IgG	2.11	7.54
19F IgA	0.56	1.64	8 IgM	16	32.07

Mean Number of AB secreting cells/10^6 PBMCs at day 7 post-PPV

	Serotype: 4	8	19F	23F
IgA	72.4	97.1	23.0	19.6
IgG	19.2	89.5	8.5	22.3
IgM	1.5	4.6	2.0	2.0

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